UNIVERSITY OF SOUTHAMPTON

SYNTHETIC AND NATURALLY OCCURRING IONOPHORES

A Thesis submitted for the Degree of
Doctor of Philosophy

by

Keith Whiston

February 1989

To MUM and DAD

and

for my late brother

CLIVE

ACKNOWLEDGEMENTS

I am very grateful to Dr. John Mellor for his diligent supervision and encouraging support throughout my stay at Southampton University. Without his friendly guidance none of this work would have been possible.

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

SYNTHETIC AND NATURALLY OCCURRING IONOPHORES

by Keith Whiston

The importance of host guest interactions involving the binding of metal ions is discussed. The diversity of synthetic compounds capable of hosting metal ions and the applications to which they have been put are reviewed. The possibility of preparing macrocyclic compounds containing 3,6-diaminoacridine units, and the methods for synthesising macrocyclic compounds containing nitrogen as part of the ring are discussed.

By reaction of various 1,ω-dibromoalkanes and 3,6-diaminoacridine the synthesis is described of a number of acridinophanes, protected as the tetra p-toluene sulphonamides, containing macrocyclic rings of between 24 and 30 atoms. The deprotection of two of these macrocycles to give the free amine acridinophanes is reported. These acridinophanes are shown not to exhibit ionophoric properties with Cu (II), Ni (II), Mn (II) and Zn (II) ions, but the idea of preparing further macrocycles containing additional binding sites in order to encourage such properties is suggested. The synthesis is described of some acridinophanes protected as the tetra p-toluene sulphonamides from 3,6-diaminoacridine and various alkylating agents such as 1,5-dihalooxapentane containing oxygen, sulphur or nitrogen in the chain. The deprotection by hydrolytic cleavage of the toluene sulphonyl groups of one of these macrocycles is described. The synthesis of some other alkylating agents containing different nitrogen protecting groups is described.

The properties of naturally occurring ionophores in general and the polyethers in particular are reviewed. The concept of a chromoionophore is discussed and the possibility of synthesising molecules of this type from monensin A is introduced.

Some studies involving the modification of monensin A by acylation, oxidation and alkylation are described. The synthesis of two monensin derivatives containing appended anthracene moieties is described. Sodium ions are not found to change significantly the electronic spectral properties of these derivatives and reasons for this are suggested. The preparation of some anthraquinone and anthracene carboxylic acids is described and attempts to couple these with monensin A are reported.

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PART ONE

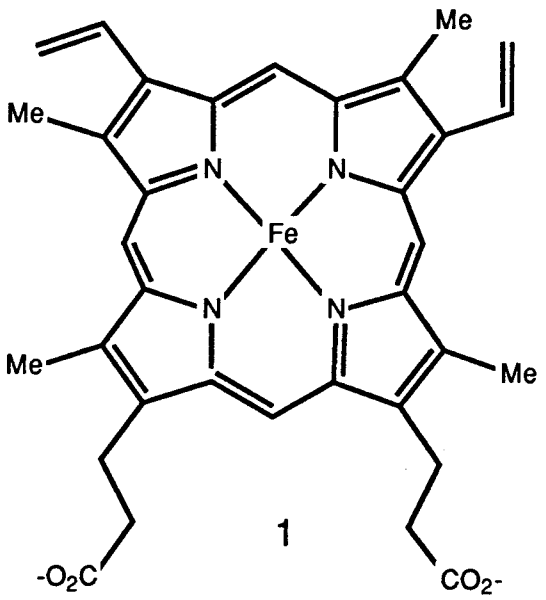
SYNTHETIC IONOPHORES

C H A P T E R
O N E

INTRODUCTION

1.1 General Introduction and Background

The physical properties and chemical reactions of organic molecules containing bound metal ions are of vital importance, both in the chemical sciences and in the biological world. Much of the chemistry which makes life itself possible occurs through interactions and reactions at metal cations bound in enzymes and proteins. For example, the reversible oxygenation of the iron (II) porphine complex heme (1) within haemoglobin provides the method by which oxygen is distributed throughout the body via the bloodstream.[1]



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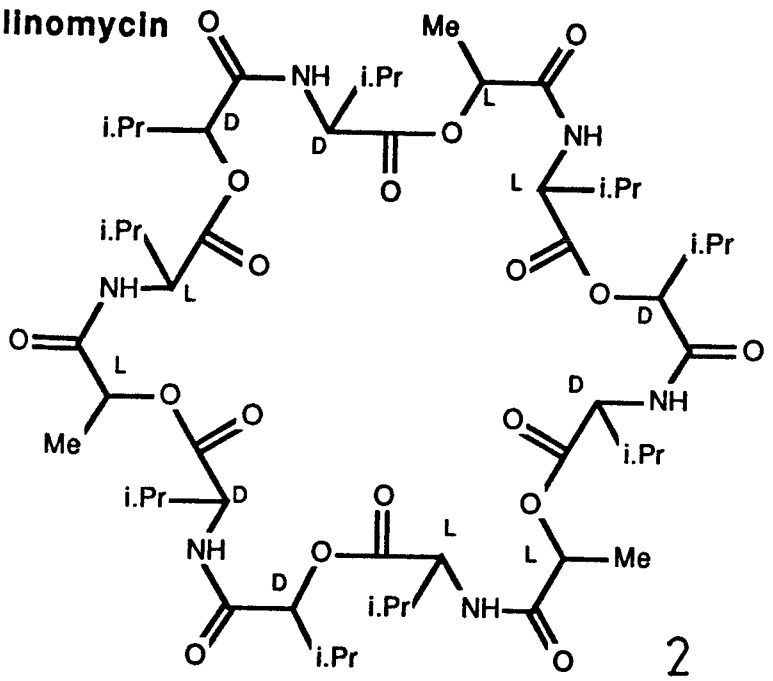
Many smaller naturally occurring molecules, known as ionophores also bind metal ions. These systems include the macrotetrolides [2], the polyethers[3] and some cyclic peptides[4]. These molecules are very often capable of discriminating

Valinomycin



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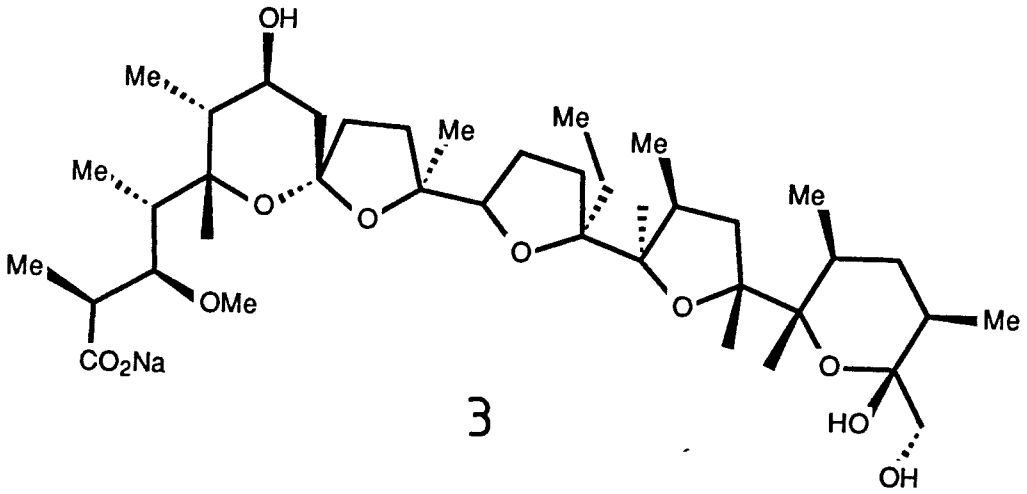

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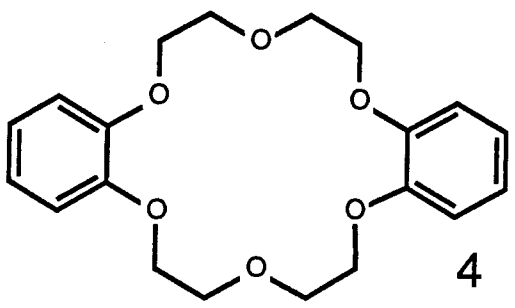
between different metal ions accurately. For example, the cyclic dodecadepsipeptide valinomycin (2)[4] is a highly selective ionophore for potassium cations, showing a typical selectivity of 4×10^3 for potassium over sodium ions in aqueous methanol.[5] The physical chemistry of naturally occurring ionophores and their metal complexes gives rise to interesting biochemical, and biological properties. A further discussion of this and other aspects of naturally occurring ionophore chemistry, particularly that of the polyethers and monensin A (3)[6] more specifically, is given within Chapter 5 of this thesis.

In the scientific world, interest in the preparation and properties of synthetic compounds capable of complexing metal ions was started by the discovery in 1962 by Pederson[7] that a cyclic ether compound (4) which he had accidentally made was capable of solubilising certain inorganic metal salts in organic solvents.



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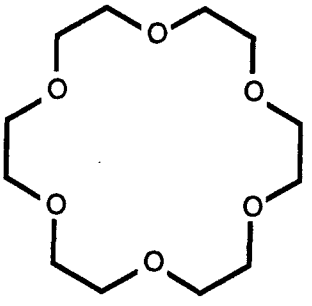
It was this observation which began the extensive interest that now exists in the chemistry of synthetic macrocyclic compounds capable of complexing or encapsulating metal ions.

1.2 Introduction to synthetic macrocyclic chemistry

Pederson synthesised dibenzo-18-crown-6 (4) as well as a range of other cyclic polyether compounds such as 18-crown-6 (5) and cyclohexyl-15-crown-5 (6)[7]. He recognised that many of them were able to form stable salts with alkali and alkaline earth metal ions, a previously unobserved phenomenon for a synthetic molecule.



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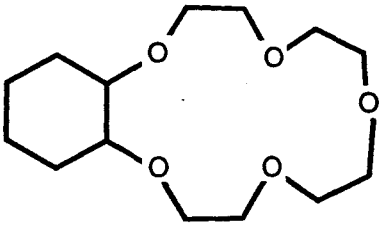

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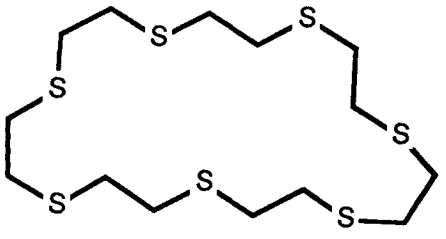
Subsequent work in this area has resulted in the synthesis of a great variety of synthetic host compounds capable of binding not only metal cations of all sorts, but anions[8], nucleotide bases[9], aliphatic ammonium cations[10], and other organic substrates[11,12,13].

Molecules containing atoms other than oxygen as binding sites have been synthesised. For example, sulphur containing

macrocycles such as (7)[14] form complexes with a variety of transition metal ions, as do nitrogen containing cycles such as (8)[15].

Sulphur and nitrogen are both softer Lewis base donor atoms than oxygen, thus preferring to co-ordinate to transition metal ions rather than the harder alkali or alkaline earth ions.



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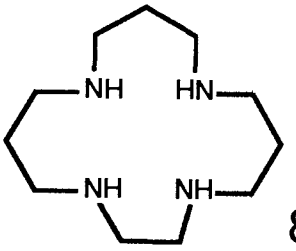

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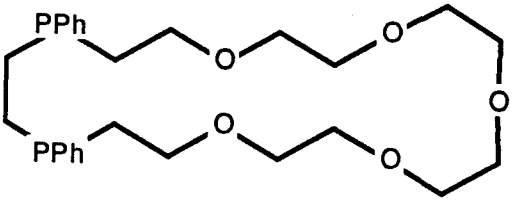
More recently, other elements have been used in host compounds such as phosphorus in the oxaphosphand (9) which binds palladium (II) and other metals[16], and silicon in the macrocycle (10) which transports chloride and bromide anions across a lipophilic methylene chloride barrier[17].



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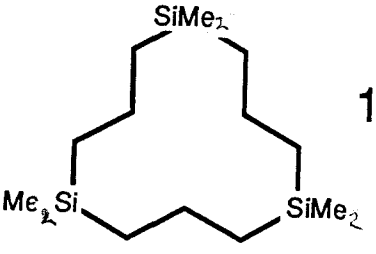

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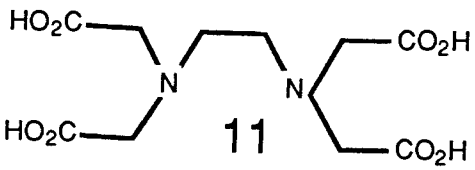
Reviews exist on synthetic compounds capable of hosting metal ions and other positively charged species[18-22] as well as the more general area of hosting organic molecules[23]. Some examples of the more important types of host compound which have been found to bind one or more metal ions are shown in Scheme (1).

It is not essential, of course, for a host compound to be cyclic for it to bind metal ions effectively. The co-ordination chemistry of nitrogen ligands such as E.D.T.A. (11) with transition metals for instance, is well known[24]. However, a number of acyclic ligands have been prepared which will form crystallizable complexes even with alkali metals. For example, Vogtle et al have synthesised (12)[25] which binds Na^+, K^+ and Rb^+.

Lariat crowns, of which (13) is an example[26], are synthesised by attaching a side arm or "lariat" to a macrocycle usually through the third valence of nitrogen. The effect of the side arm is mainly to provide an additional binding site above the crown ring. Systems of this sort are usually found to bind metal ions more effectively than the simple crowns from which they are derived. Many different side arms have been used, for example the dipyridine system (14)[27] was found to transport Cu^{2+}, Co^{2+} and Zn^{2+} across a lipophilic barrier effectively.

Further geometrical constraints may be placed on the cation binding site by forming a three dimensional cage into

SCHEME 1



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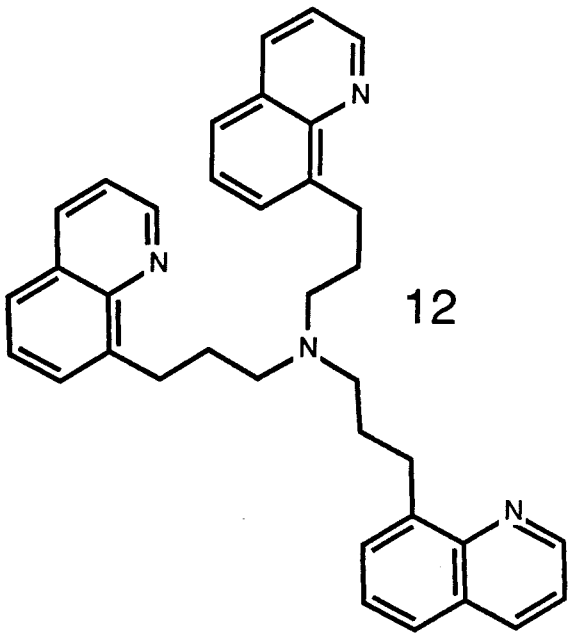

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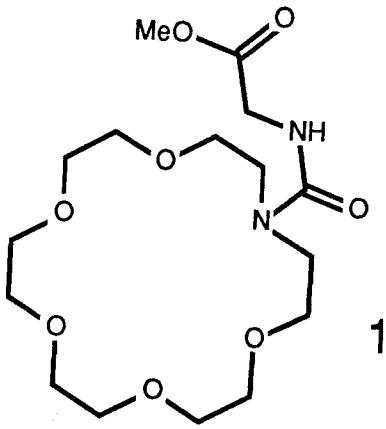

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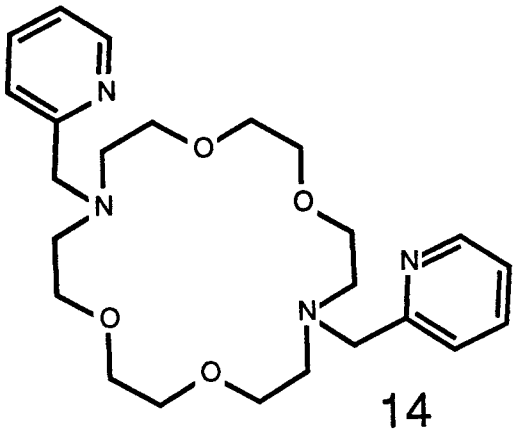

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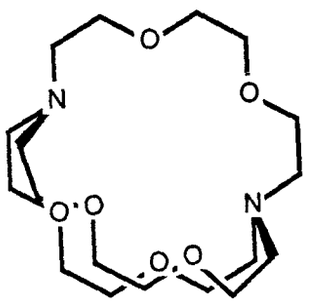
SCHEME 1 continued



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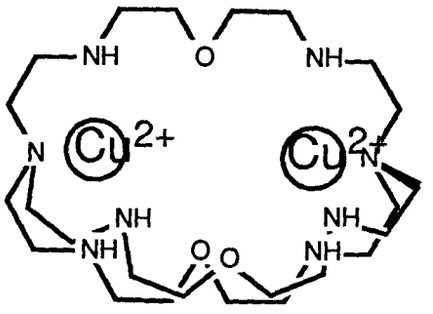

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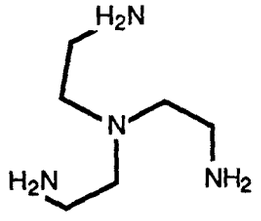

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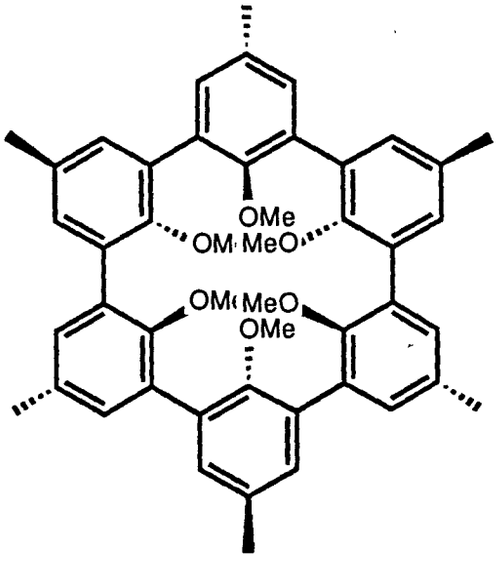

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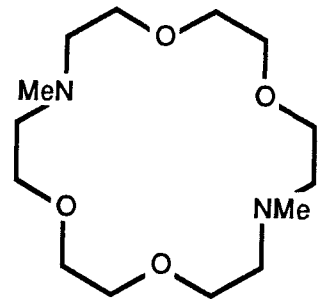
which a potential guest must fit. Lehn has done this by joining two sides of an azacrown together with a polyether bridge, forming cryptate molecules of which (15) is an example[28]. These strikingly symmetrical molecules can form very stable metal complexes. For example (15) has a binding constant for K^+ in methanol/water around 10^5 greater than the analogous methylated azacrown (16)[29].



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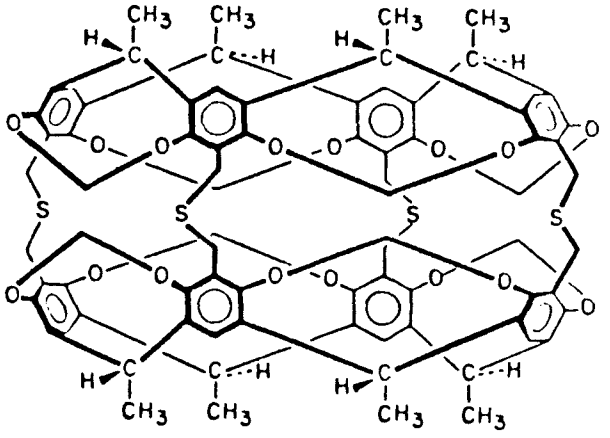
The increased stability of the cryptate complex can be attributed to a macrobicyclic effect where the polyether bridge lends a greater degree of pre-organisation to the molecule.

Larger cryptates have been prepared which are capable of hosting two metal ions within the same cage. For example, cryptate (17)[30] makes use of the high affinity for transition metal ions which the tren ligand (18) possesses. The central cavity can encapsulate two Cu^{2+} ions simultaneously.

Host systems with even greater rigidity around the cation binding site have been prepared. The spherand (19) contains six octahedrally arranged oxygen atoms around a central

binding cavity[31]. This molecule binds Li^+ and Na^+ very strongly but completely rejects cations of larger radius which are unable to get into the binding pocket.

The molecular container (20) has recently been synthesised[11]. This molecule is capable of permanently incarcerating molecules or ions within its central cavity. Solvent molecules and inorganic salts present during the final cage formation step cannot be released without destroying the framework of the host, for example by pyrolysis.



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1.3 Applications of macrocyclic host guest chemistry

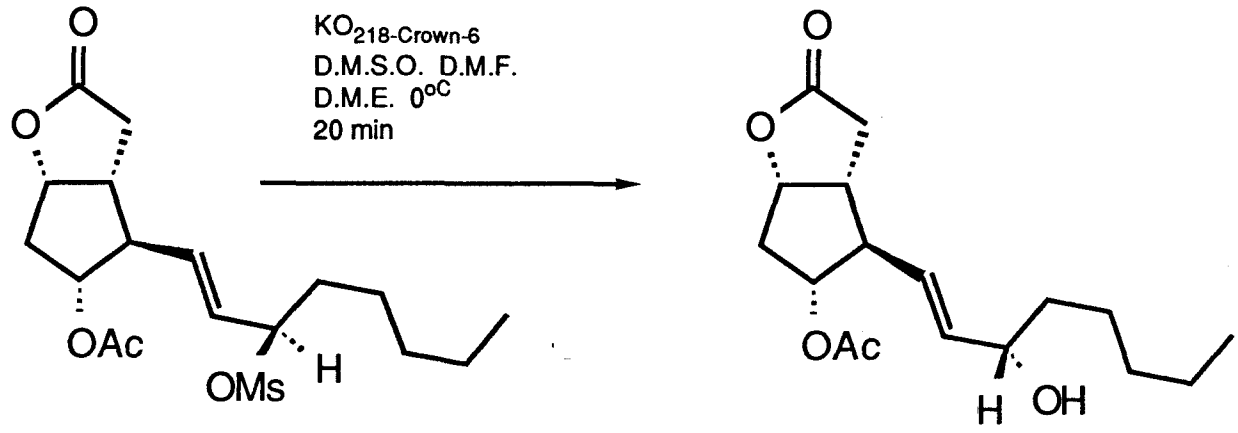
Crown ethers, cryptates and other host compounds have been put to a wide range of uses across different branches of

chemistry[32,22]. Some of the principle applications which have been found for these molecules are in the fields of organic synthesis[32], analytical chemistry[34], as ion transport and extraction agents[35], and in the area of catalysis[36].

1.3.1 Organic Synthesis

In organic synthesis the ability of many crown ethers to solubilise inorganic salts in organic solvents, and their ability to thereby activate anions, has been used many times. For example, potassium superoxide is activated in organic solutions by 18-*crown*-6, and can be used to invert stereochemistry by SN2 displacement of a leaving group. Scheme 2 shows one application[37] of this methodology.

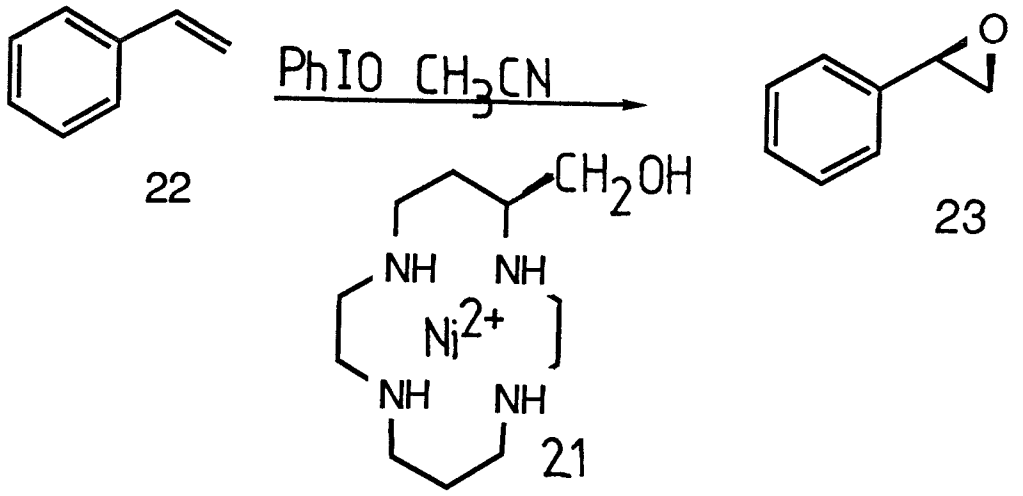
SCHEME 2



Another example of the use of macrocycles as catalysts in organic synthesis is the use of Ni^{2+} cyclam complexes as epoxidation catalysts[38]. Nickel cyclam (21) catalyses epoxidation of the alkene (22) to the epoxide (23) in the manner

shown in Scheme 3.

SCHEME 3



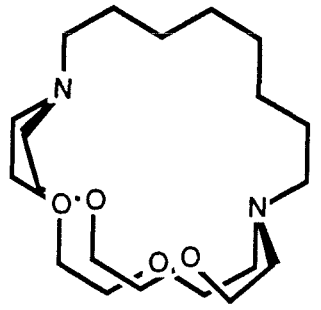
1.3.2 Analytical Chemistry

In the field of analytical chemistry, host systems have found application in sensor devices for the detection of metal ions[39]. Analysis for the physiologically important alkali metal ions Na^+ and K^+ in blood samples can now be carried out with the aid of field effect transistor devices coated with ionophore doped polymers[34]. A discussion of this area appears in Chapter 5.

1.3.3 Ion Transport and Extraction

The ability of host compounds to reversibly complex cations has led to their use in cation transport systems[35]. Molecules such as the cryptate (24) which forms moderately stable complexes with K^+ ions efficiently transports these ions

across a lipophilic chloroform barrier with a selectivity over Na^+ of about 2:1[40].



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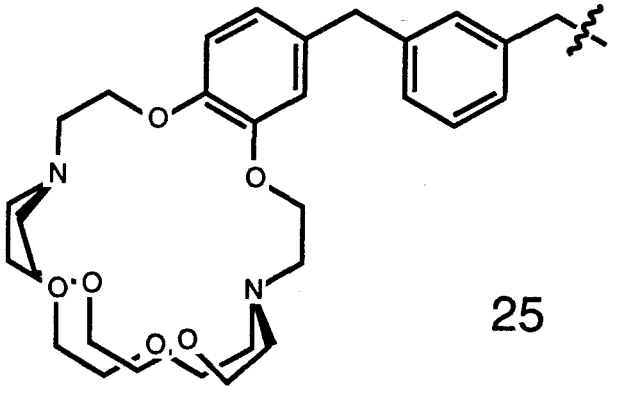
Molecules which form highly stable complexes with metal cations such as the cryptate (15) with K^+ do not function efficiently as transport agents since the rate of ion transfer is then limited by the rate of heterogeneous reaction at the barrier water interface[40]. However, molecules of this sort can be used efficiently as selective ion extraction agents, for example, in the removal of metal ions from industrial wastes. Extraction agents are particularly convenient if polymer bound, for example the resin bound cryptate (25)[41] has been used for selective potassium ion extraction.



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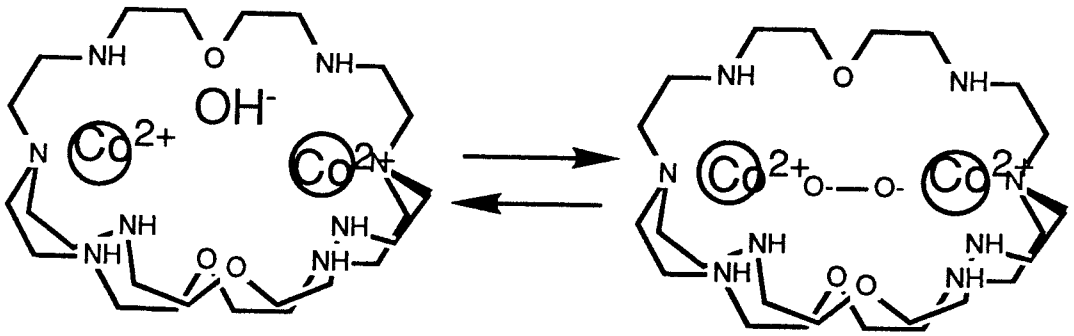
More recently, it has been shown that metal complexes themselves are capable of fulfilling a transport role. For example, the dicobalt cryptate complex (26) can function as an oxygen carrier by co-ordinating dioxygen reversibly[42].

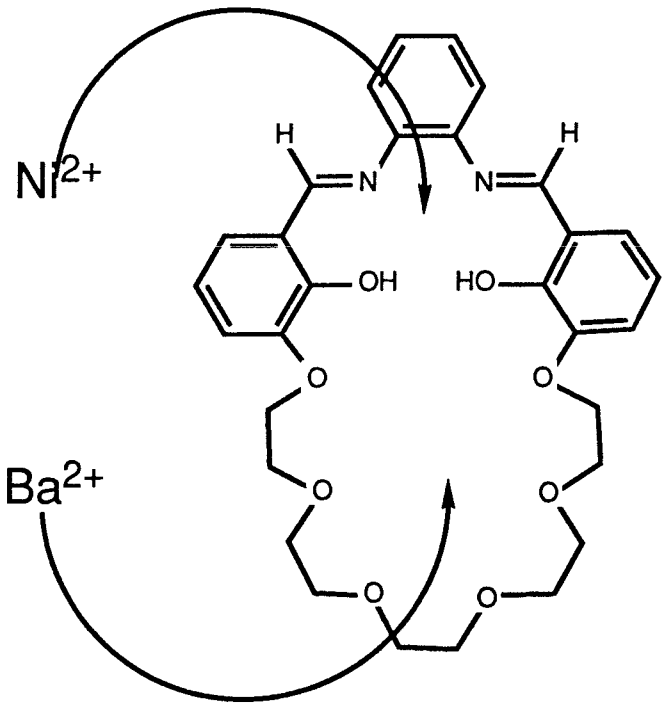


26 27

The complex formed (27) is much less stable than other cobalt dioxygen complexes having polyamine ligands. This makes the system potentially useful for the chemical separation of oxygen from gaseous mixtures.

1.3.4 Catalysis

The preparation of host compounds capable of binding two metal ions simultaneously has led to the suggestion that such systems may prove useful as models for metallo-proteins, for example, superoxide dismutase[43], providing the opportunity to examine cation-cation catalytic interactions at near bonding distance. Particularly interesting are molecules such as (28)[44] and (29)[36] which are heterobinucleating, being able to bind two different metal cations simultaneously.



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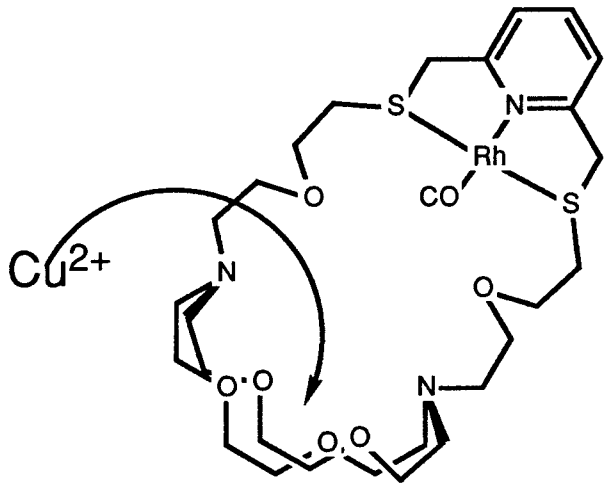

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1.4 Synthesis of macrocycles and crown compounds

The preparation of any synthetic macrocyclic host compound involves the cyclisation of a linear precursor, or the simultaneous coupling and cyclisation of a number of pieces to produce the final ring or cage. Methods for the preparation of simple crown compounds principally involve the displacement of leaving groups by oxygen anions,and these have been reviewed[32,22]. Other host compounds have been prepared using a range of condensation and nucleophilic displacement reactions. Cyclisations are typically carried out at relatively high dilution to minimise polymerisation via intermolecular reaction, although this is not always the case[22]. The comparatively high yields of macrocycles obtained in many cyclisations has frequently been accounted for in terms of a template effect from metal cations present during ring closure[22].

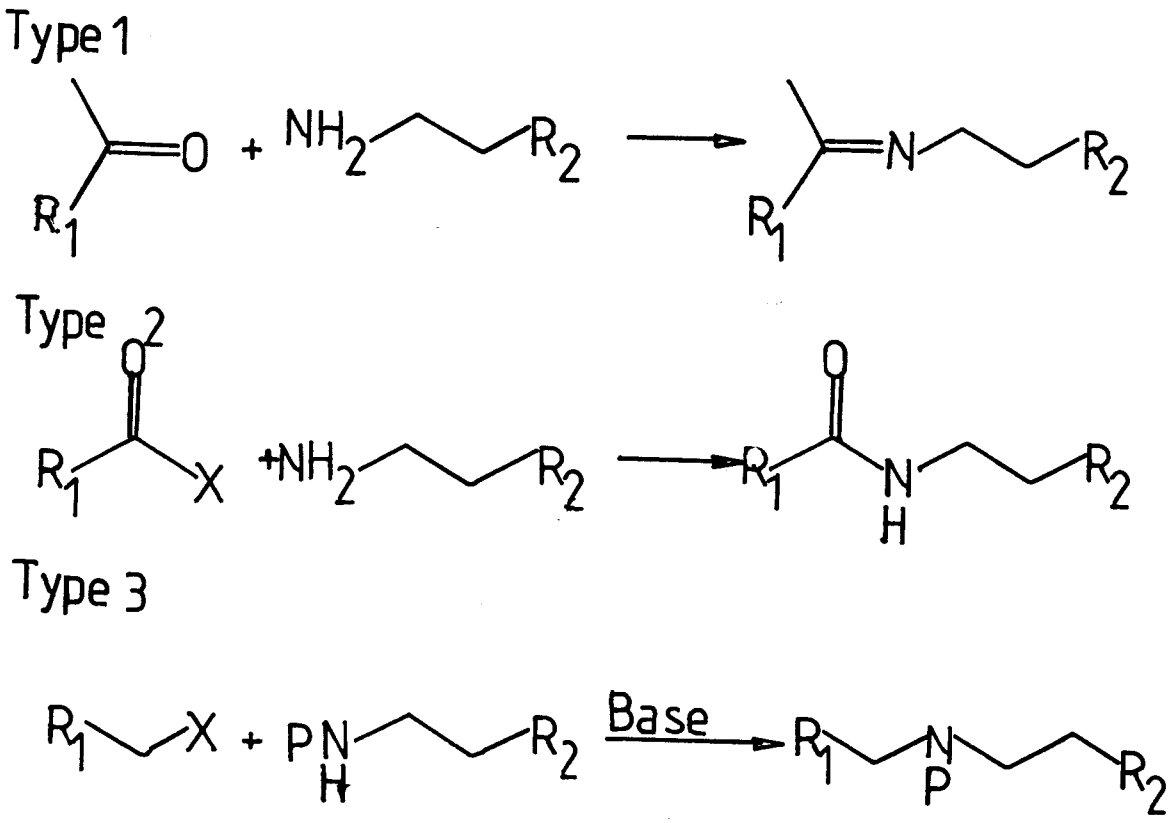
1.5 Synthetic Methods for the Preparation of Nitrogen Containing Macrocycles

Since the first part of this thesis deals with the preparation of nitrogen containing macrocycles, the discussion of cyclisation methodology will be restricted to the preparation of rings or cages where the crucial bond forming step is between carbon and nitrogen.

In these cases, methods can be divided generally into

three groups according to Scheme 4 . Type (1) methods involve the formation of an imine or Schiff's base by the condensation of a ketone or an aldehyde with an amine. Type (2) methods involve the formation of an amide from an activated ester, acid chloride or anhydride. Type (3) methods involve the Sn2 displacement of a leaving group, for example halide or mesylate, by the anion of a protected amine, usually a sulphonamide.

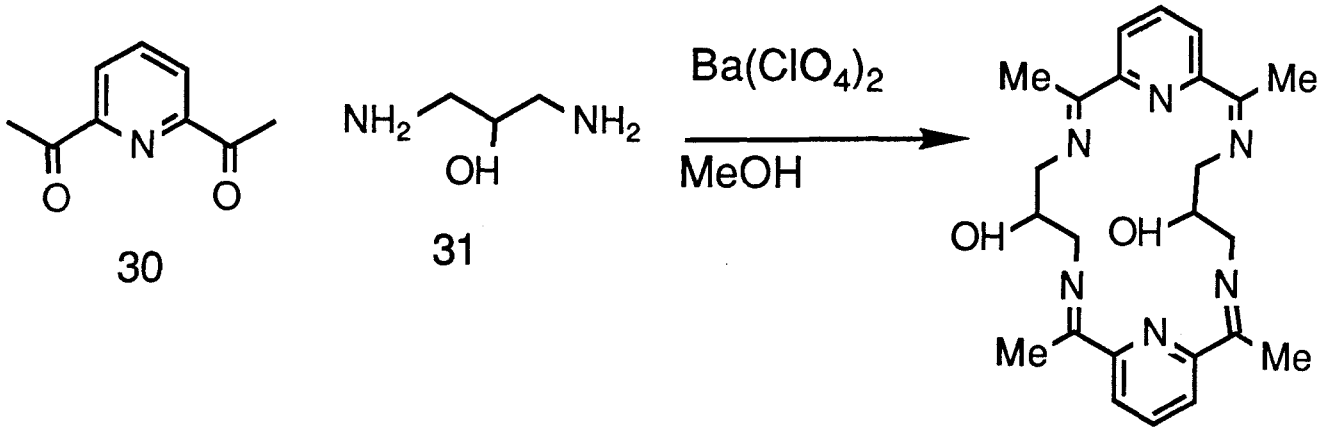
Scheme 4



1.5.1 Methods involving Imine Formation

This method can be illustrated by the preparation of the macrocycle (32) from the diketone (30) and the diamine (31) according to Scheme 5[33]. In this case the macrocycle is synthesised in the presence of barium ions which act as a template for the cyclisation. The metal ion co-ordinates to the reactants during the reaction, and the product is formed as the mononuclear barium complex.

SCHEME 5

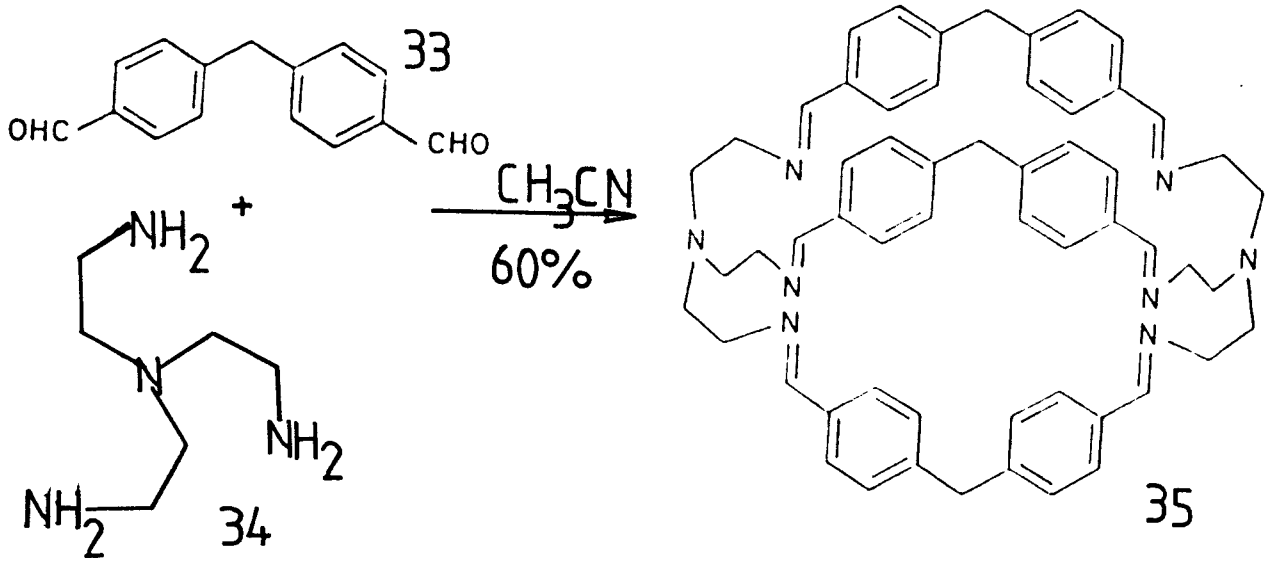


30 31 32

Lehn has prepared the cryptate (35) using a similar condensation methodology shown in Scheme 6. Dropwise addition of dialdehyde (33) to an acetonitrile solution of tren (34) at room temperature,

yields the desired hexaimine in 60% yield[45].

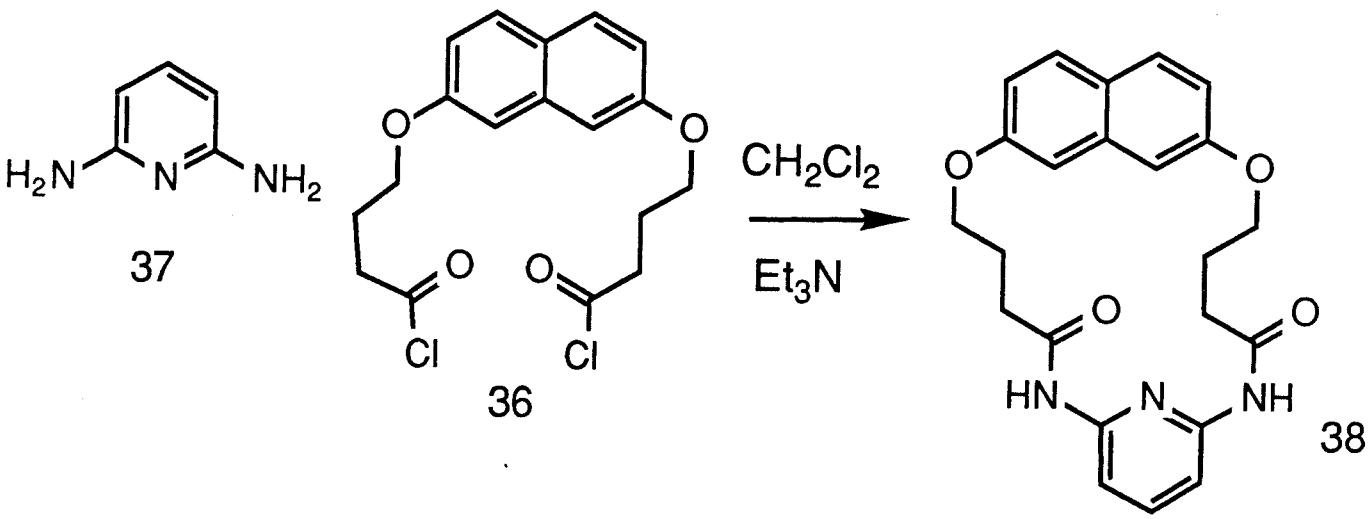
SCHEME 6



1.5.2 Methods involving Amide Formation

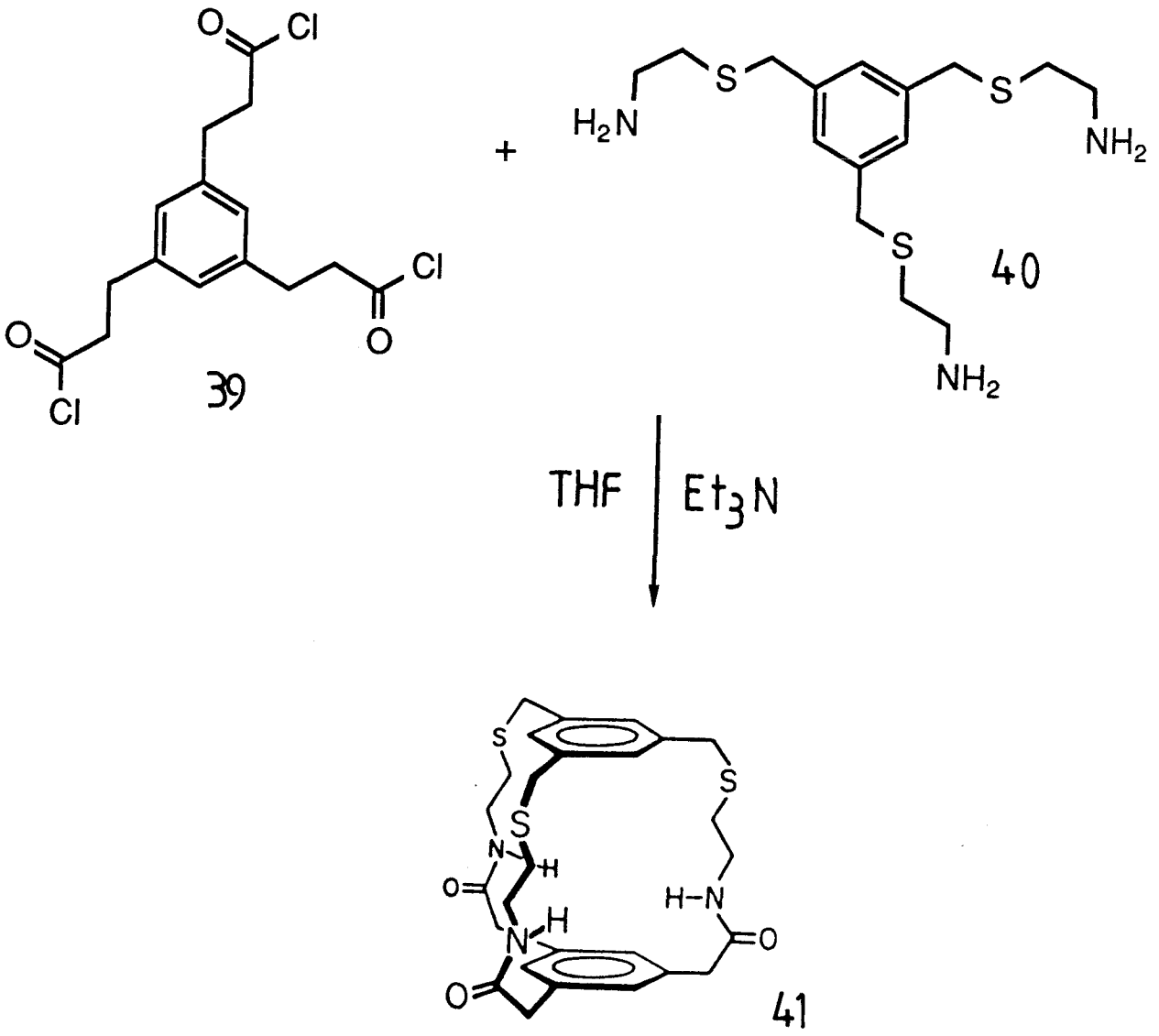
Hamilton et al have prepared the macrocyclic naphthalene derivative (38) according to Scheme 7[46]. High dilution condensation in dichloromethane of the diacid chloride (36) with 2,5-diaminopyridine (37) yielded the desired product in 26% yield. Typically, acid chloride couplings of this sort must be done at low concentration in order to favour the intramolecular cyclisation reaction over the intermolecular polymerisation.

SCHEME 7



This methodology has also been used to prepare cage systems. For example, Pascal et al have prepared the cyclophane (41) in one reaction from the triacidchloride (39) and the triamine (40), forming three bonds at the same time, as in Scheme 8 [47].

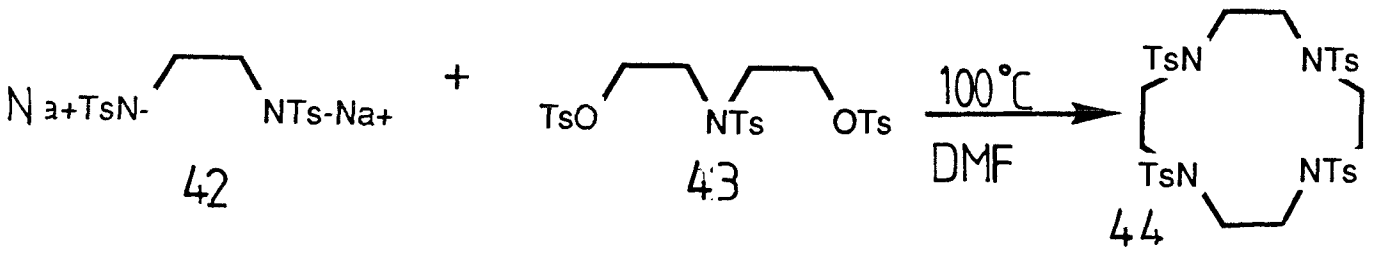
SCHEME 8



1.5.3 Methods Involving Nucleophilic Displacement Reactions

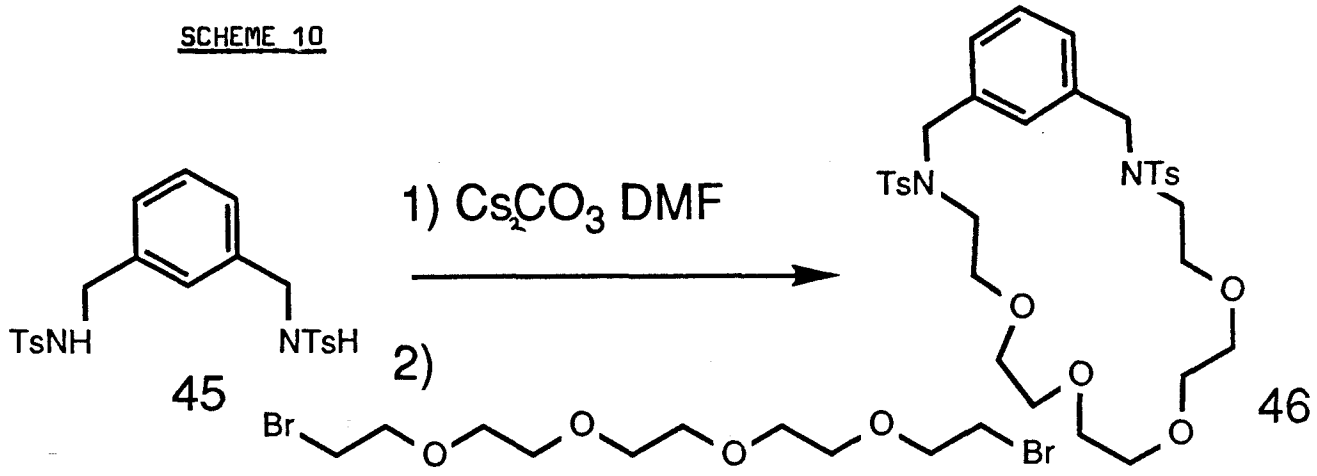
The macrocyclic polyamine (44) was synthesised from the disulphonamide (42) and the tritosylate (43) in D.M.F. as shown in Scheme 9 [48]. The preformed anion of the sulphonamide displaces tosylate in each of the bond forming steps. The reaction proceeds in high yield and does not require high dilution.

SCHEME 9



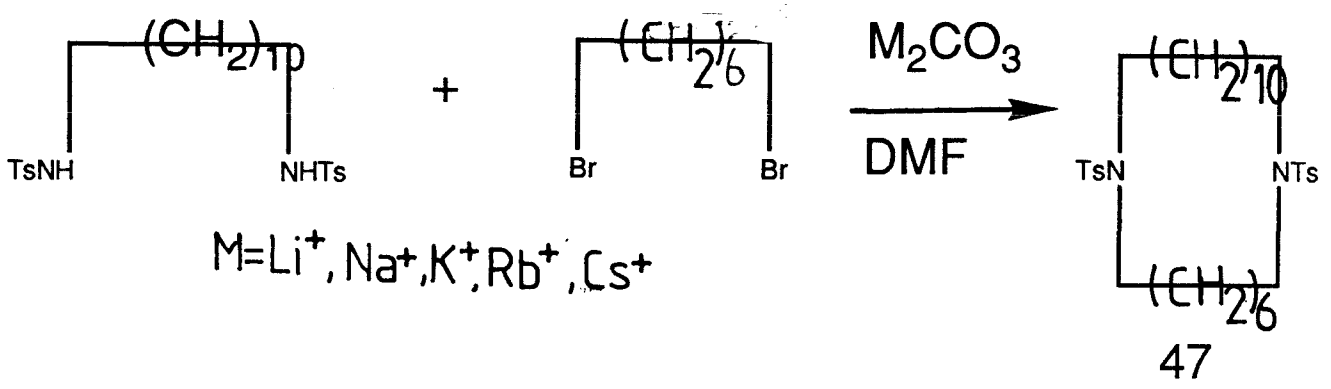
Kellogg et al have used an analogous method for the preparation of (46) using cesium carbonate to deprotonate the disulphonamide (45) in situ[49]. In this case, bromide ion is the leaving group, see Scheme 10.

SCHEME 10



The related cyclisation shown in Scheme 11 has been carried out[49] using a number of different alkali metal carbonates to deprotonate the sulphonamide, in order to examine the effect of the counter ion on the yield of this step.

Scheme 11

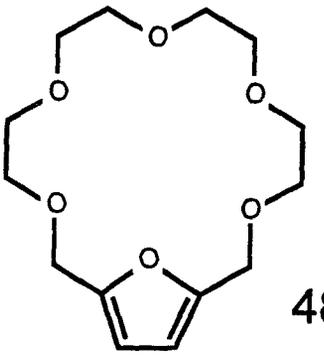


Cesium was found to give a 95% yield of (47), rubidium a 70% yield, and the other cations much poorer results. This effect was rationalised in terms of the greater basicity of the cesium carbonate which more efficiently deprotonates the amide, not because of a template effect.

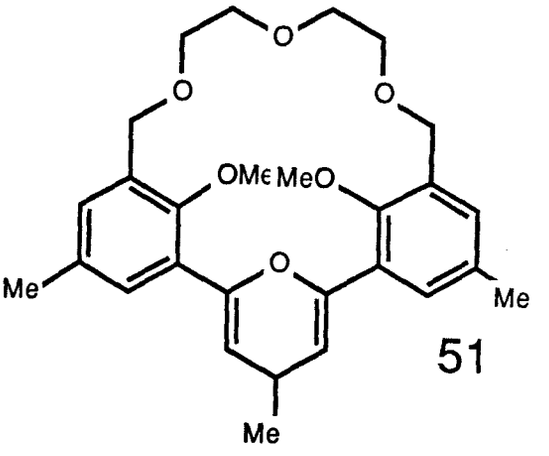
1.6 Diversity of Crown Compounds

Since Pederson's original syntheses of crown compounds[7], a very large variety of closely related compounds have been prepared, and their properties as host compounds examined. Many of these systems have included aromatic residues, or heterocyclic groups as part of the ring or crown. A few examples of such systems are shown in Scheme12 including furan (48)[50], binaphthyl (49)[51], biphenyl (50)[51], 4H-pyran (51)[52] and thiadiazole (52)[53] as part of crown ring systems.

SCHEME 12



48



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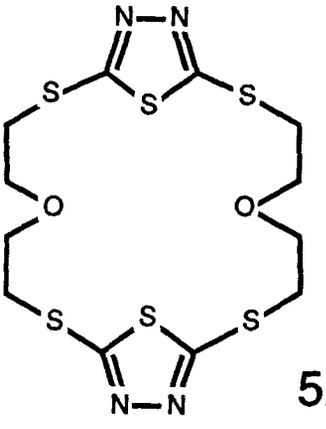
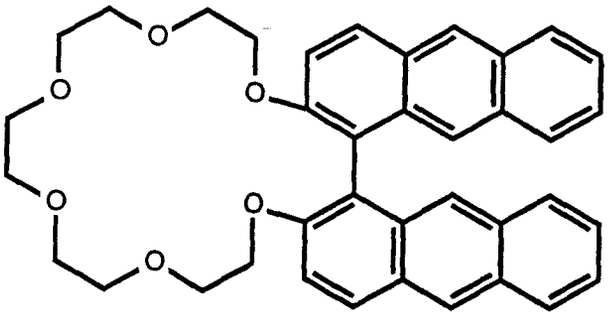


52



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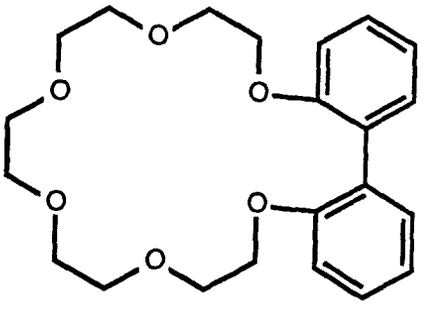
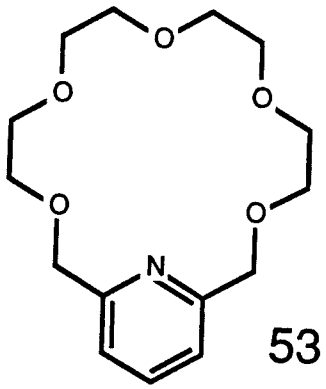


50

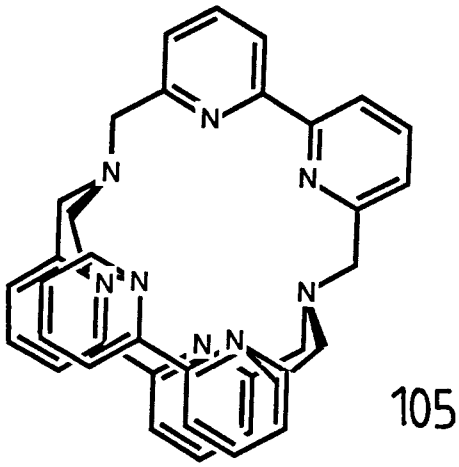
1.7 Present Study

Many host systems based on heterocyclic nitrogen bases have been prepared. Early examples such as the simple pyridine crown (53)[54], have been followed by binucleating systems such as (29)[36].



53

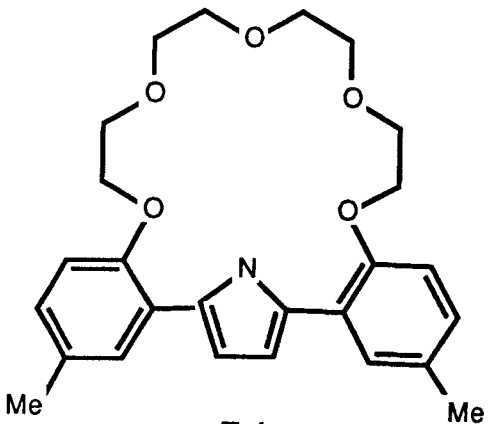
In a fully developed system, Lehn et al have shown that the bipyridine based cryptate (105) forms complexes with lanthanide metal ions and that these systems exhibit unusual physical properties[55].



105

The europium (III) and terbium (III) complexes of (105) are capable of energy transfer luminescence in aqueous solution. The ligand groups absorb u.v. light, which by energy transfer to the metal ion is then re-emitted in visible form.

Many other nitrogen heterocycles have been used in host macrocycles, for example pyrroles[56] in compound (54), and 1,10-phenanthroline[57] in (55).



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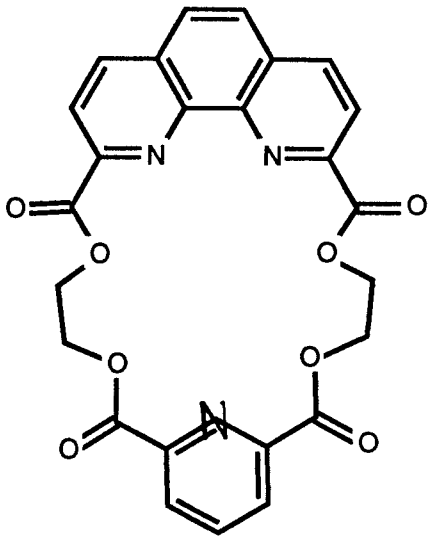
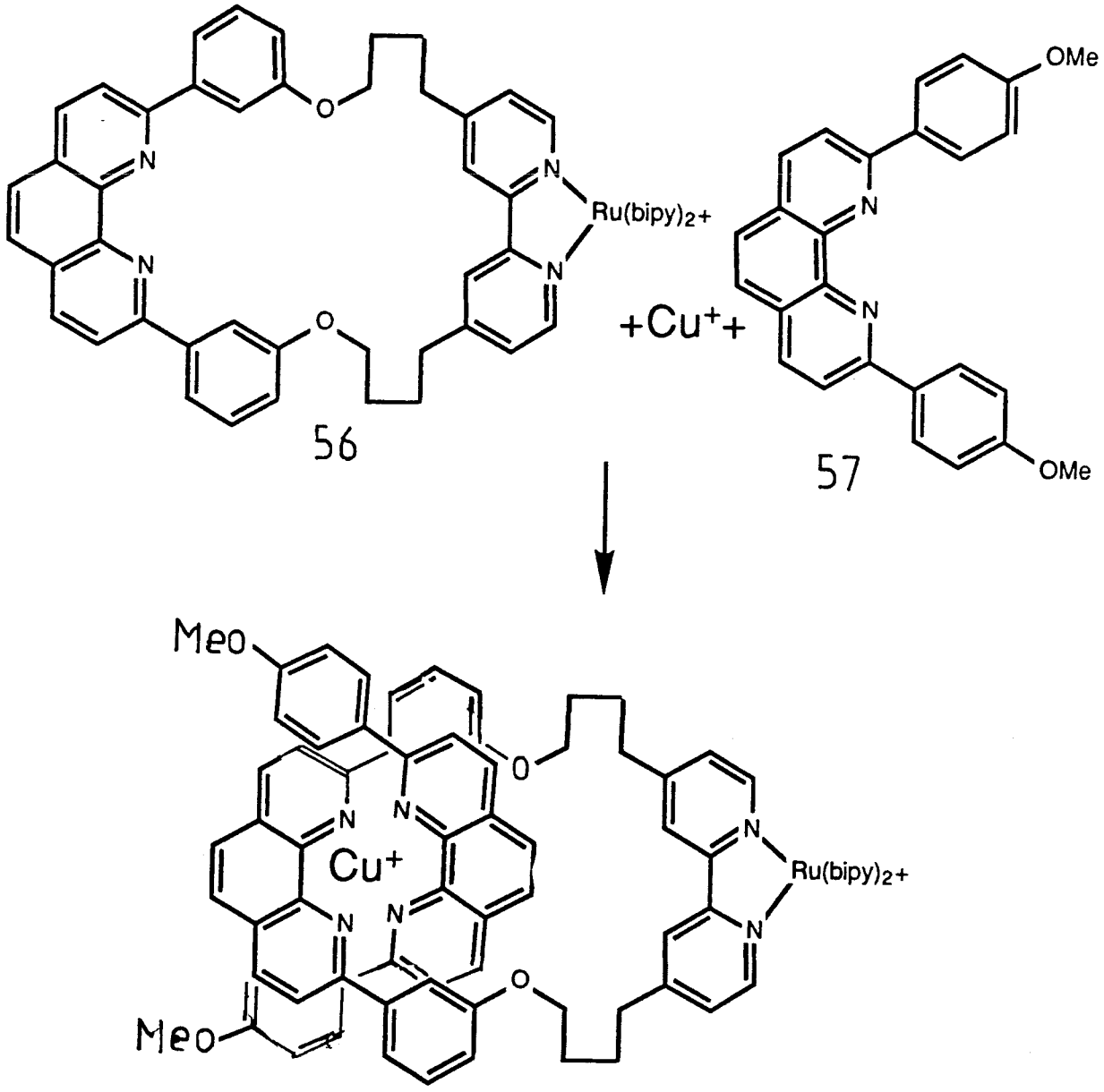


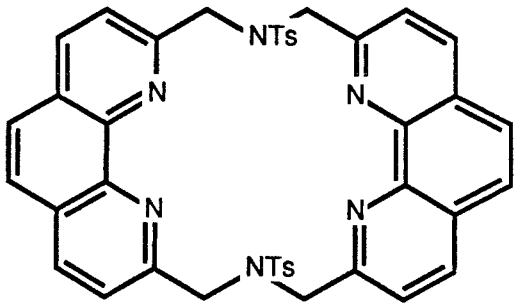
55

Sauvage et al have shown that the 1,10-phenanthrene bipyridyl macrocycle (56) will bind Copper (I) and Ruthenium (II) in the presence of the derivative (57) according to Scheme 13.[58]

SCHEME 13



Cram et al have shown[59] that the 1,10-phenanthrene based macrocycle (58) binds a variety of alkali metal and transition metal ions.

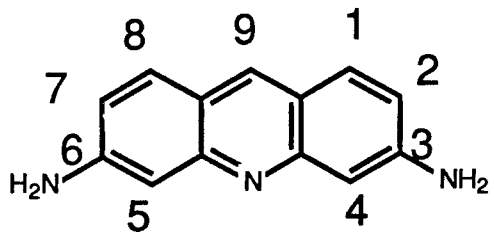


58

1.8 Aims

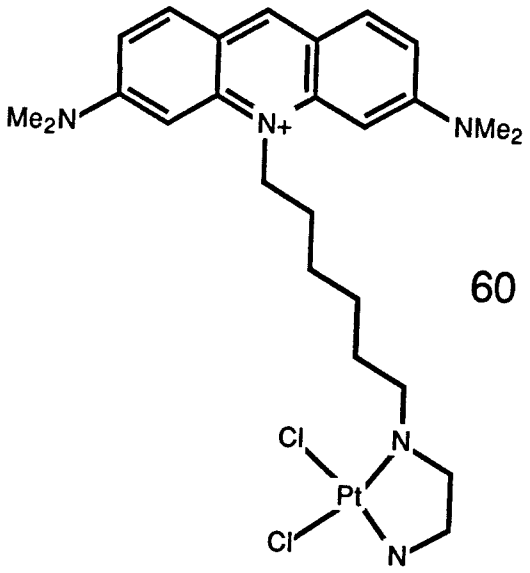
The aims during this part of the project have been to prepare a series of macrocyclic molecules structurally related to the systems described above containing a new nitrogen heterocycle as part of the ring system. It was decided to prepare some potential host systems, based on proflavine.

3,6-Diaminoacridine (59), or proflavine, which is its trivial name, is a flat tricyclic aromatic molecule containing three nitrogen atoms. The first published synthesis appeared in 1912[60] and the molecule is now commercially available as its hydrochloride and hydrosulphate salts. The presently accepted nomenclature for the acridine ring system is shown in (59).



59

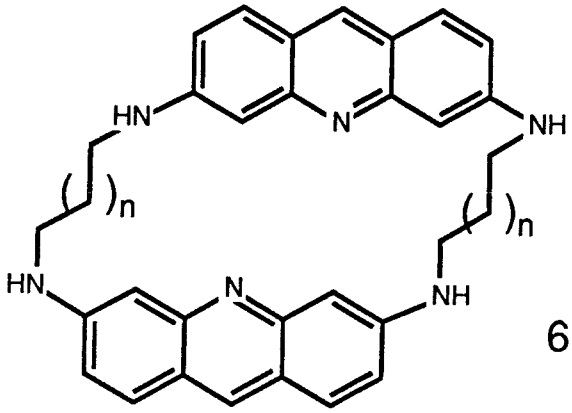
The molecule was used during the First World War as an antibacterial agent[61], being applied to open wounds to suppress or destroy infection. A further interest in the system has centred on the ability of the acridine ring system to interchelate into D.N.A.[62]. The cisplatin derivative (60) has been used to investigate the mechanism of action of platinum anticancer drugs[63,64].



60

The acridine ring disrupts the D.N.A. structure by interchelating and unwinding the duplex and effectively increases the platinum concentration where this occurs.

The aim of this part of the project was to build up a series of macrocyclic compounds based on the proflavine ring system, initially by coupling two rings together with methylene chains to give compounds of the general formula (61).



61

It was hoped to examine the physical chemistry of these derivatives in order to determine whether they exhibit the ability to co-ordinate with metal ions in particular.

Further, it was hoped to prepare other systems containing additional binding sites, for example, other nitrogen or sulphur atoms, and to examine the physical properties of these systems.

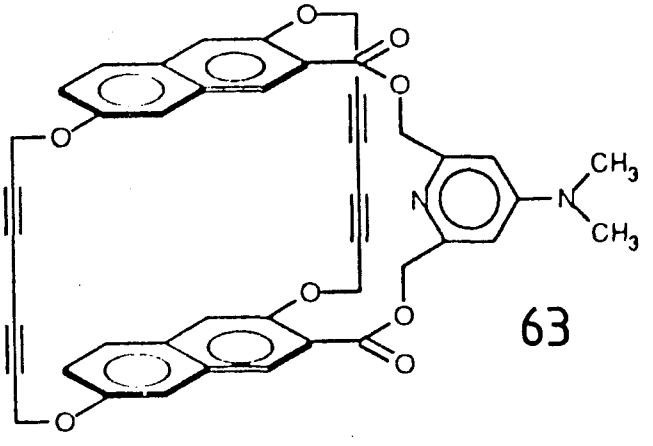
C H A P T E R
T W O

CARBOCYCLIC FRAMEWORKS

2.1 Introduction

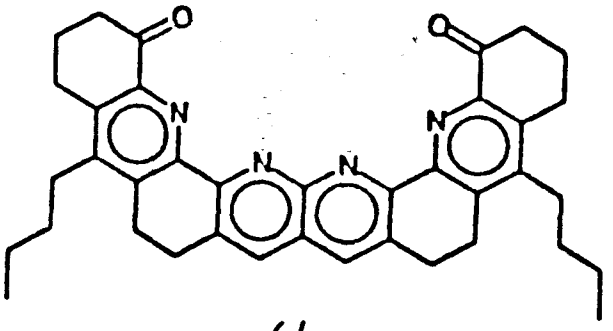
The preparation of macrocyclic acridine derivatives of the general structure (61) opens up the possibility of binding other organic molecules in addition to metal ions, because of the large cavity size within the macroring, and the hydrogen bonding which is possible to the nitrogen atoms of the proflavine moiety. The hosting of small biologically important molecules by synthetic host compounds has become an important area of research in recent years[23]. Because many biological processes occur via the binding of organic molecules at receptor sites, the design and synthesis of artificial host molecules becomes important as a means of mimicking such biological processes, and gaining a greater understanding of the electrostatic and steric factors influencing them.

For example, the recently synthesised cyclophane type host (63) shows a very high affinity for binding phenols[65]. The phenol is held rigidly between the two naphthalene rings and is bound by a single hydrogen bond to the pyridine nitrogen.



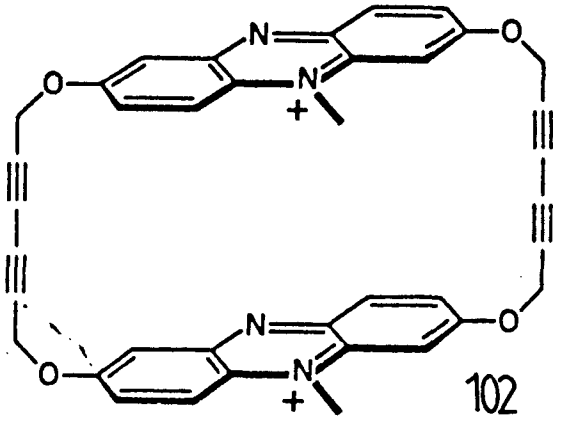
63

Bell and Liu have shown[66] that the rigid receptor molecule (64) is a good host for urea forming highly stable complexes with the amide. Host (64) will dissolve urea in organic solvents such as chloroform, in which the guest would normally be insoluble. The complex is held together by a network of four hydrogen bonds between the urea nitrogen and the heterocyclic nitrogen atoms of the host.



64

Lehn et al[81] have also synthesised a cyclo-bis-intercaland structure (102) from two phenazine residues. The macrocycle exhibits stacking interactions with paraphthalate dianion, as shown by ultra violet spectroscopy.



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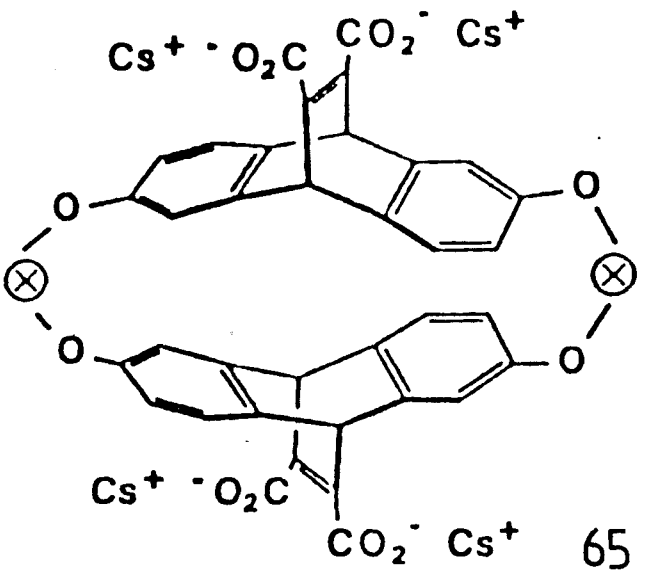
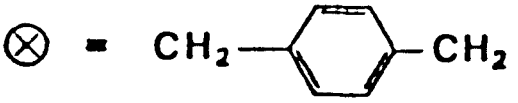


65



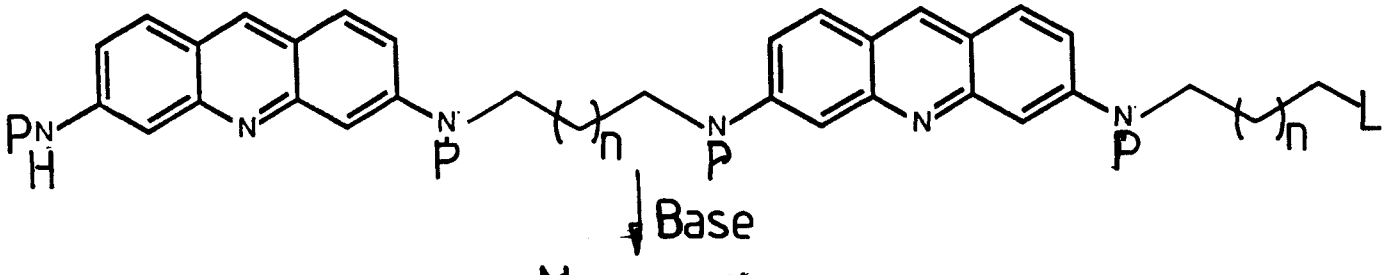
The cyclophane type host (65) is found to bind a series of aromatic nitrogen bases in aqueous solution[67]. It is argued that hydrophobic, electrostatic and donor acceptor π- stacking interactions all contribute to the host's ability to bind quinoline systems.

Macrocyclic compounds of the general structure (61) have the potential to exhibit binding interactions of the type shown above.

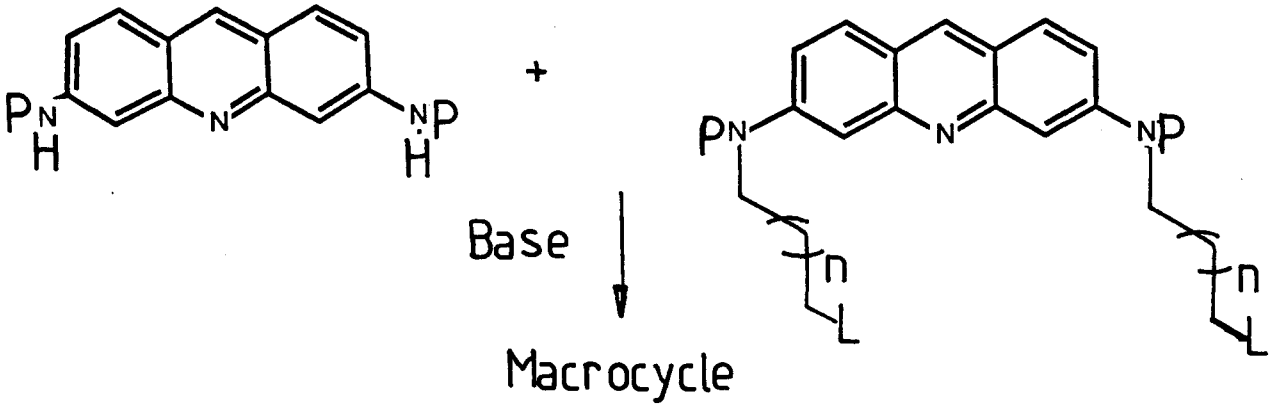
2.2 Synthetic Strategy

The synthesis of macrocyclic molecules of structure (61) involves as the key step cyclisation of a linear precursor. Two ways in which this process can be approached are shown in Scheme 14.

Type I SCHEME 14



Type II

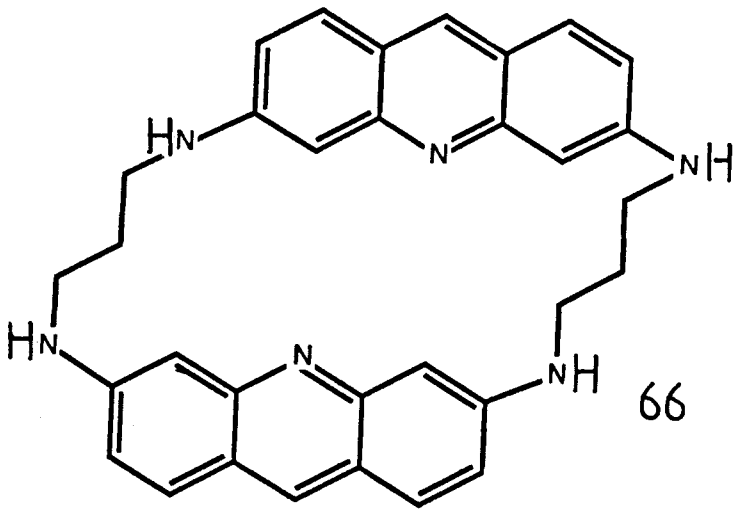


A cyclisation procedure of type I involves the preparation of one linear precursor containing a leaving group L, and a protected nitrogen centre which, in the presence of base, will form a sufficiently nucleophilic anion to displace

the leaving group using the general method described in Section 1.5.3. A cyclisation of Type II would involve the coupling and cyclisation in one reaction of two precursors, with two bond forming steps of the same nucleophilic displacement type. Initially a Type II cyclisation method was adopted.

As has been previously discussed in Section 1.5.3, a number of different leaving groups have been used in Sn2 displacement macrocyclisations and studies of their relative merits have been published. In this case, it was decided for convenience to use bromide as the leaving group in our macrocyclisation,

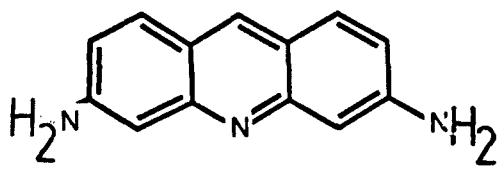
Examination of CPK models of (61) with different methylene spacers between the two rings, led us to the conclusion that synthesising a system with n = 3 would be possible without introducing undue strain into the molecule. A smaller spacer led to a system containing significant steric interference between the two aromatic systems. It was therefore decided initially to synthesise (66) as a relatively strain free target which contained the smallest ring of which models could be constructed.



66

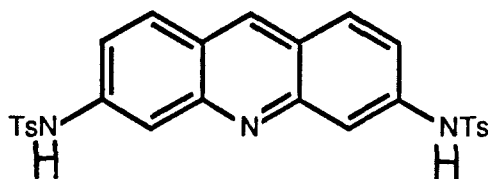
2.3 Synthesis of Cyclisation Precursors

In order to facilitate the attachment of a suitable alkyl side chain to the proflavine nucleus, it was necessary to protect both of the amine groups of proflavine (59). A suitable protecting group would be capable of rendering the remaining NH protons acidic enough to be removed by a mild base such as carbonate. The paratoluene sulphonyl (tosyl) group was chosen as a good candidate.



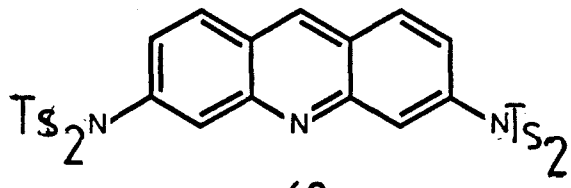
59

Reaction of (59) in its free base form with five equivalents of paratoluenesulphonyl chloride at 0°C in pyridine yielded, after recrystallisation from the reaction mixture, a red hygroscopic powder corresponding to the diamide derivative (67) as the major product. The reaction was carried out in the presence of triethylamine to prevent the starting material precipitating out of solution as the hydrochloride salt, when acylation proceeded.



67

Compound (67) was characterised by ^{1}H and ^{13}C nmr, as well as microanalysis as its hemihydrate. The diamide was found to gain weight on standing as it absorbed atmospheric moisture. Chromatography over silica gel of the material remaining after recrystallisation of (67), yielded a smaller quantity of a brown oil consisting of the tetraamide (68).

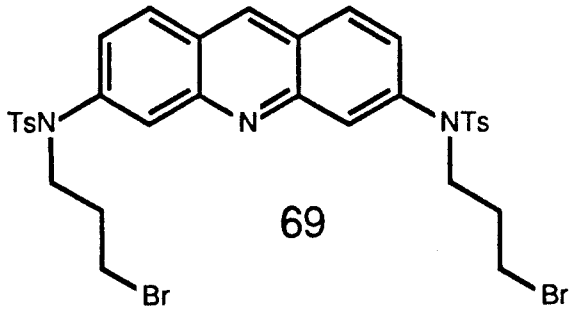


68

Conversion of the unwanted tetraamide (68) to the desired diamide was achieved in quantitative yield by heating under reflux in aqueous dimethyl formamide containing potassium carbonate. The product isolated from this reaction had identical spectroscopic and physical properties to those of (67) isolated from the original protection reaction.

Studies of mechanical molecular models led us to synthesise (66) initially, containing three methylene units between each of the proflavine groups as the final macrocyclic target. Towards this end it was necessary to prepare the cyclisation precursor (69) which was achieved by reacting the diamide (67) with potassium carbonate and 1,3-dibromopropane

in dimethyl formamide. The alkylating agent was used in large excess to minimise the formation of intermolecular polymers rather than the desired dialkylated product. Column chromatography over silica gel yielded light yellow crystals of the dialkylated cyclisation precursor (69).



69

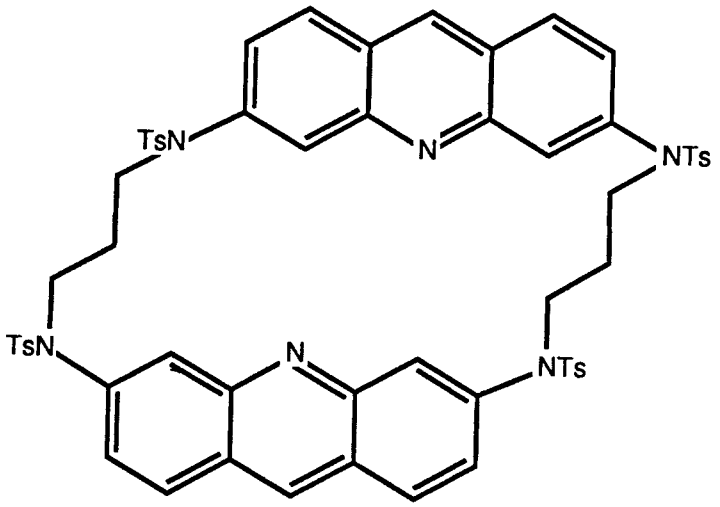
Compound (69) was characterised by ^{1}H nmr, ^{13}C nmr and microanalysis. The ^{1}H nmr spectrum was characterised by two clear triplets in the aliphatic region of the spectrum corresponding to the methylene groups next to nitrogen and bromine, and the ^{13}C nmr spectrum clearly showed that the molecule had retained a plane of symmetry.

2.4 Cyclisation

Having synthesised the two precursor parts (69) and (67) to the target macrocycle, we attempted to couple and cyclise them. Because of the low solubility of (67) in organic solvents such as chloroform, ether and tetrahydrofuran,

it was found necessary to perform the cyclisation reaction in dimethyl formamide, a sufficiently polar solvent to solubilise all the organic reactants.

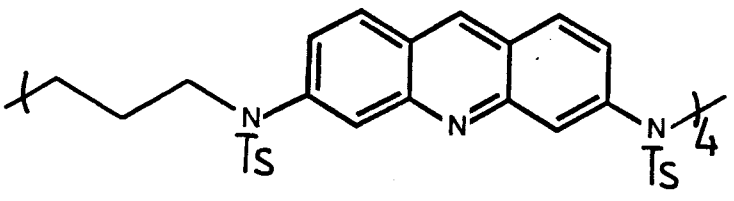
Reaction of an equimolar mixture of (69) and (67) in dimethyl formamide containing an excess of potassium carbonate as the base yielded the desired cyclised product (70) as a cream coloured solid which proved insoluble in most organic solvents.



70

The macrocycle (70) showed a characteristically simple ^{13}C nmr spectrum, containing only 14 signals, indicating that the product contained a plane of symmetry. The ^{1}H nmr spectrum was characterised by only three signals in the aliphatic region of the spectrum, a singlet at 2.34 ppm corresponding to the methylene groups adjacent to the sulphonamide nitrogens, and a triplet integrating for 4 protons corresponding to the other two methylene groups. The macrocycle was also characterised

by microanalysis; the recrystallised product was found to contain one molecule of water. The possibility of the product being a larger symmetrical polymer of proflavine moieties linked with propyl chains, such as the tetramer (103) was ruled out by mass spectroscopy. The F.A.B. mass spectrum showed a highest mass peak, which was also the base peak, at 1115 corresponding to MH^+, and showed other strong peaks at 961 and 805 corresponding to sequential loss of tosyl groups from the macrocycle.

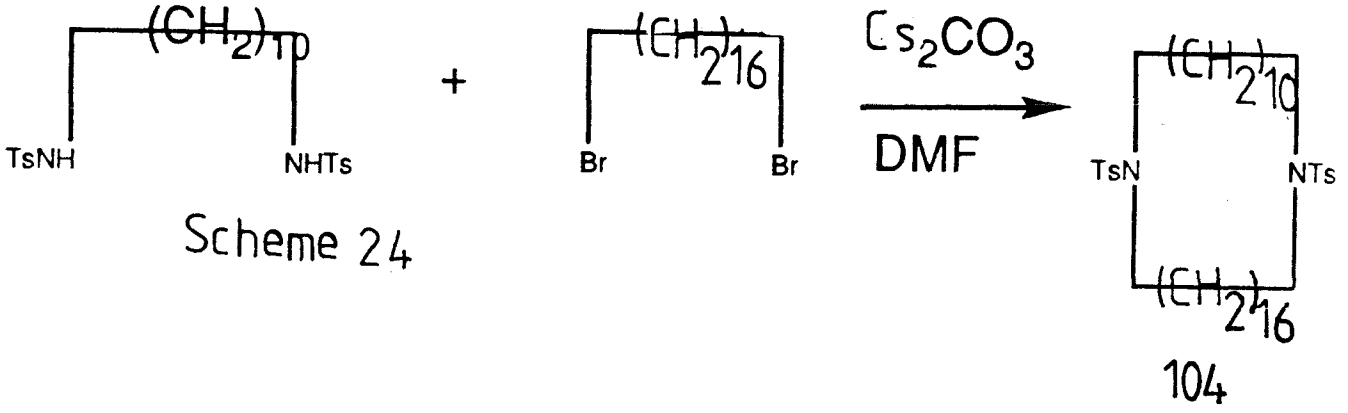


103

The cyclisation reaction was found to proceed slowly at room temperature, reaching completion in 24h, or slightly faster at 60°C reaching completion in 16h. The highest yield of the 24 membered ring was obtained at a total organic substrate concentration of 0.02 Molar, that is to say, a moderately high dilution, and at 60°C under an inert atmosphere. Under these conditions a 59% yield was obtained.

Kellogg et al have prepared[49] the simpler aliphatic 28 membered macrocycle (104) using an analogous method to that which was employed, in 60% yield according to Scheme 24

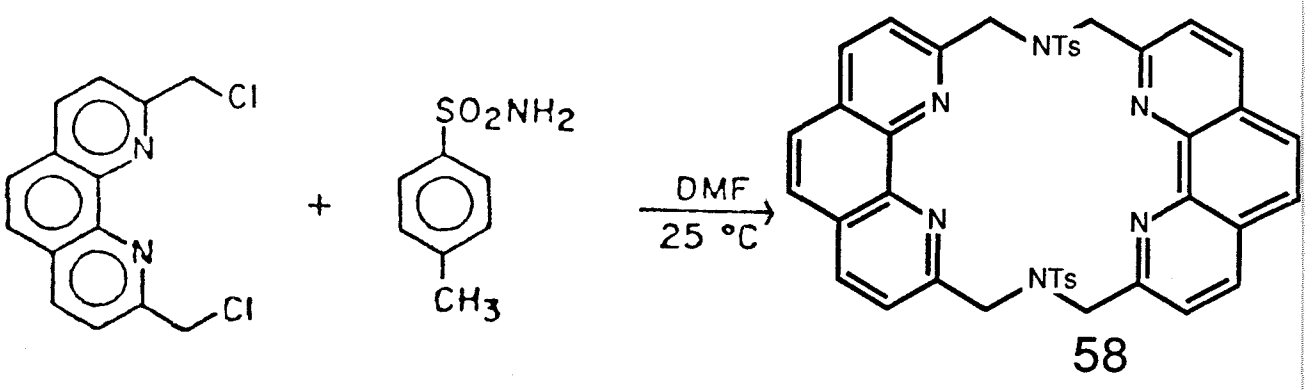
using cesium carbonate as the base at 10^{-2} Molar substrate concentration.



Scheme 24

Cram et al have synthesised[59] the phenanthralene macrocycle (58), an 18 membered ring, at high dilution, in dimethyl formamide in 21% yield according to Scheme 15.

SCHEME 15



The yield which we have obtained in the synthesis of

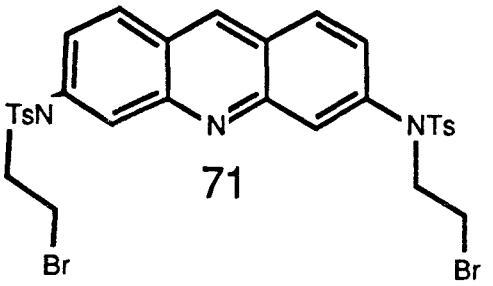
(70) is thus comparable with, and in some cases superior to, analogous preparations in the literature. Higher molecular weight cyclic oligomers are sometimes isolated from cyclisation reactions of the type illustrated above. For example, in the preparation of (58) a small quantity of the cyclic trimeric material was isolated in addition to the main dimer product[59]. However, no higher molecular weight cyclic oligomers were isolated during the preparation[49] of (104) which is consistent with observations made during the preparation of (70).

2.5 Further Cyclisation Studies

Having synthesised the 24 membered macrocycle (70), and shown that the coupling and cyclisation reaction worked for this particular case, it was decided to investigate the reaction further, and establish whether we might prepare other systems containing different lengths of methylene spacer between the two proflavine systems.

Towards this end the dialkylated cyclisation precursors (71), (72), (73) and (74) were prepared from (67) using the same method used for the preparation of (69), and respectively 1,2-dibromoethane, 1,4-dibromobutane, 1,5-dibromopentane and 1,6-dibromohexane as the alkylating agents. In each case the alkylating agent was used in large excess to prevent inter-molecular coupling before alkylation was complete. The products were identified by NMR as having the correct structure; in each

case the ^{13}C nmr spectrum displayed 11 aromatic signals.



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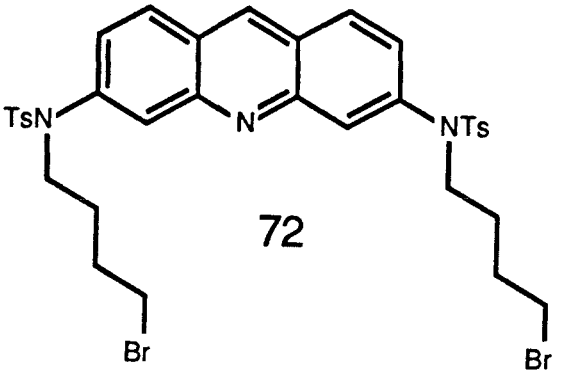

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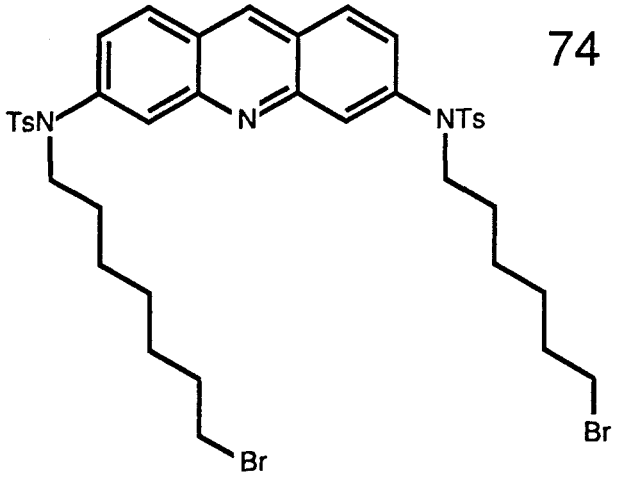

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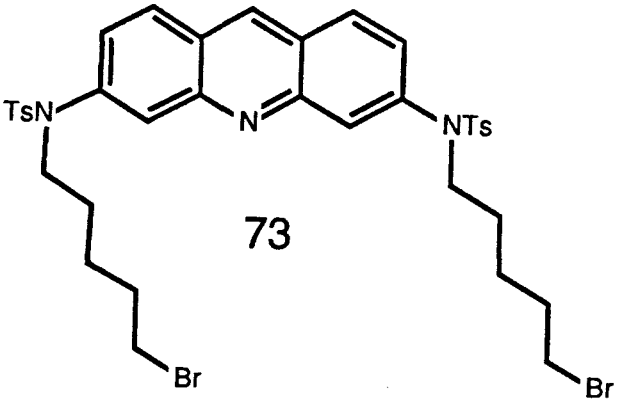


73

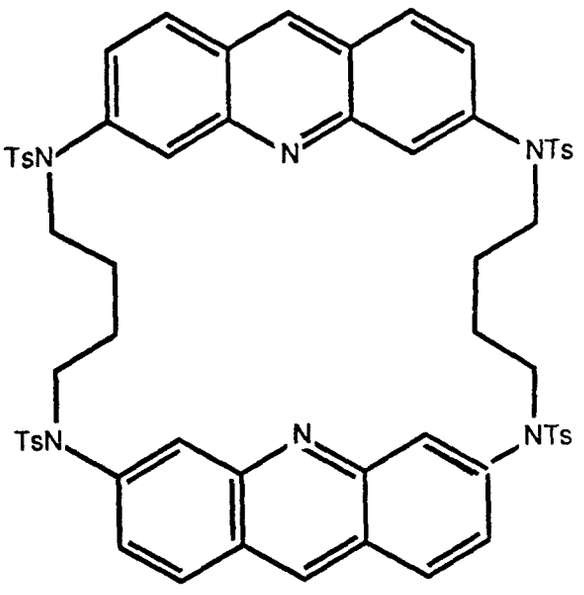
In each case cyclisation was attempted between (67) and one of the dialkylated precursors. Attempts to cyclise (72) at 60°C under the same conditions used for (69) proved unsuccessful, only polymeric material was recovered from the reaction. However (72) was successfully cyclised at room temperature and 0.02 Molar total substrate concentration over a period of 24 hours, and these conditions were adopted for each of the subsequent cyclisation attempts.

Table 1 shows the yield in each of the cyclisation reactions, together with the yield of the proceeding alkylation

TABLE 1

No. CH_2 Groups	Macrocycle	Yield of Cyclisation %	Conversion of Cyclisation %	Time h	Temperature ^oC	Ring Size	Dialkylated precursor	Yield of alkylation %
2	—	—	—	24	RT	22	(71)	86
3	(70)	59	59	24	60	24	(69)	47
4	(75)	40	42	24	RT	26	(72)	55
5	(76)	32	38	24	RT	28	(73)	74
6	(77)	18	20	24	RT	30	(74)	61

RT = Room Temperature



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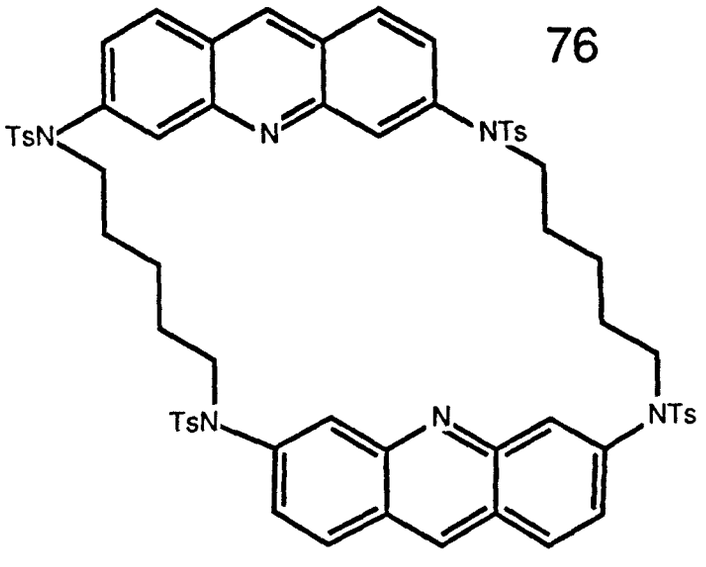

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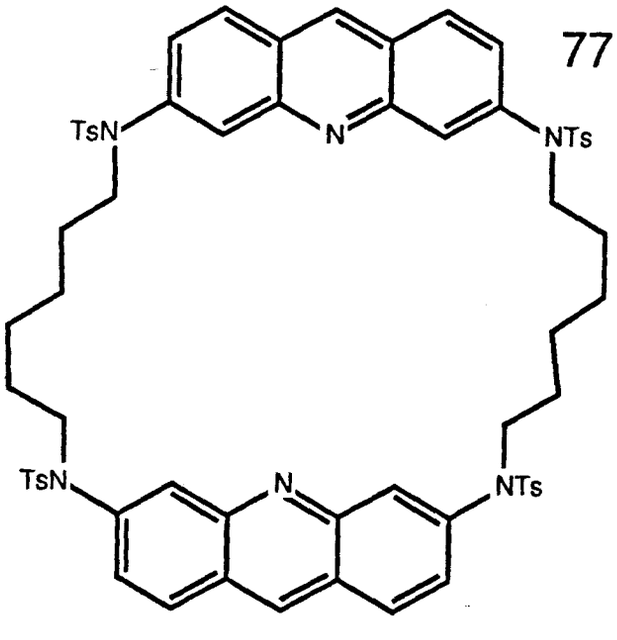


77

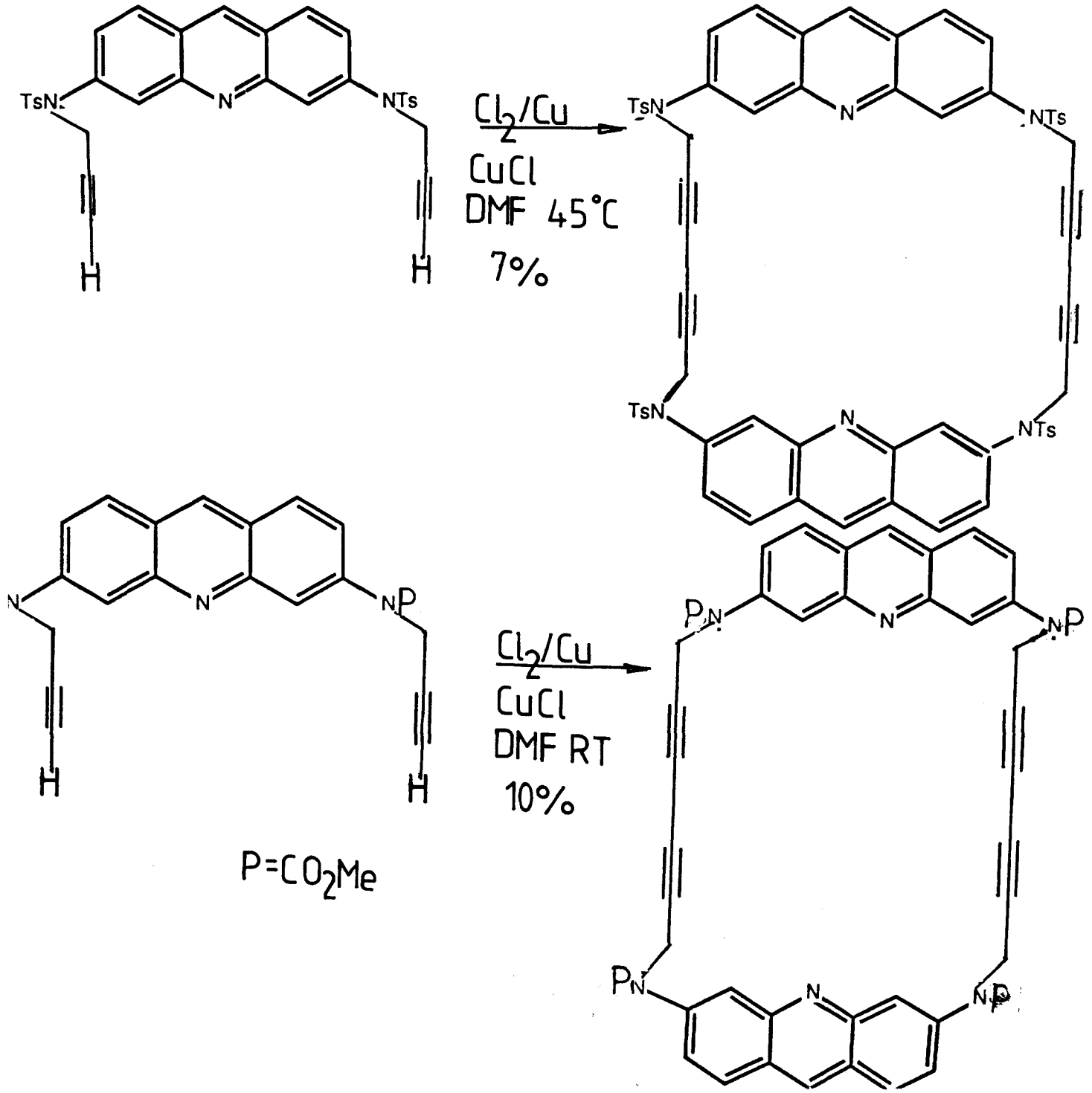
step. Not all of the cyclisation reactions went to completion after 24 hours at room temperature, and Table 1 also contains a conversion percentage which takes account of the starting materials recovered from the reaction mixture after that time. There are two main observations which arise from Table 1. Firstly, CPK models suggest that the cyclisation of (71) failed because the corresponding macrocycle product is too strained and contains significant interference between the two aromatic ring systems. Secondly, the yield in the macrocyclisation is at its highest for (70), the smallest system which can be prepared by this route, and reduces with increasing chain length. The decrease in yield can be explained in terms of an entropic effect where the larger the ring size being formed, the smaller the chance of the intramolecular reaction occurring in preference to the intermolecular polymerisation. Each of the macrocyclic products was crystallised as an off white or cream powder and, with the exception of (77), were insoluble in chloroform, ether and most other organic solvents. The compounds showed characteristically simple ^{13}C nmr spectra consistent with their cyclic symmetry, containing in each case 11 aromatic signals. Table 2 contains a compilation of physical data for the macrocyclic products.

TABLE 2 Physical Data for Carbocyclic Tolwene Sulphonyl Protected Acridinophanes

Structure	Ring Size	M.P. ^{o}C	I.R. λ max cm^{-1}	^{13}C N.M.R. P.P.M.
70	24	305 - 308	1630, 1465, 1360	147.19 (C9 & C21), 20.83(Tosyl CH_3)
75	26	300 - 302	1630, 1465, 1361	147.92 (C9 & C22), 20.80(Tosyl CH_3)
76	28	176 - 179	1618, 1460, 1361	148 (C9 & C23), 20(Tosyl CH_3)
77	30	172 - 174	1626, 1458, 1359	148.14 (C9 & C24), 20.77(Tosyl CH_3)

In a closely related study Lehn et al[68] have coupled two proflavine ring systems together using an acetylenic coupling to produce macrocyclic derivatives. The results of their study are shown in Scheme 16. The yields obtained for macrocyclisation using a copper catalysed coupling are markedly poorer than our own results using a base catalysed Sn2 process.

Scheme 16

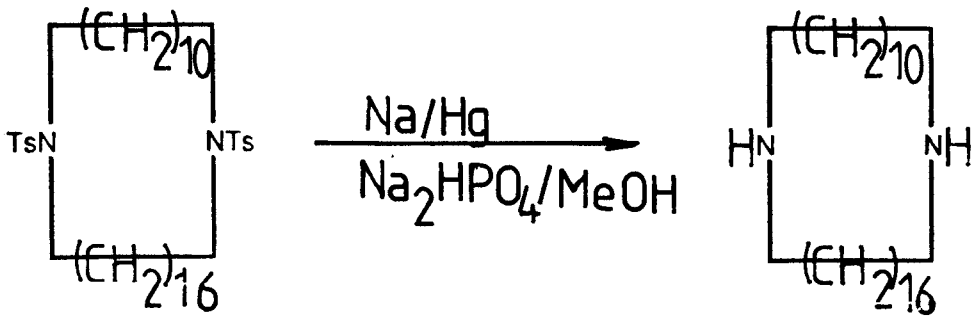


2.6 Deprotection of the Macrocycle

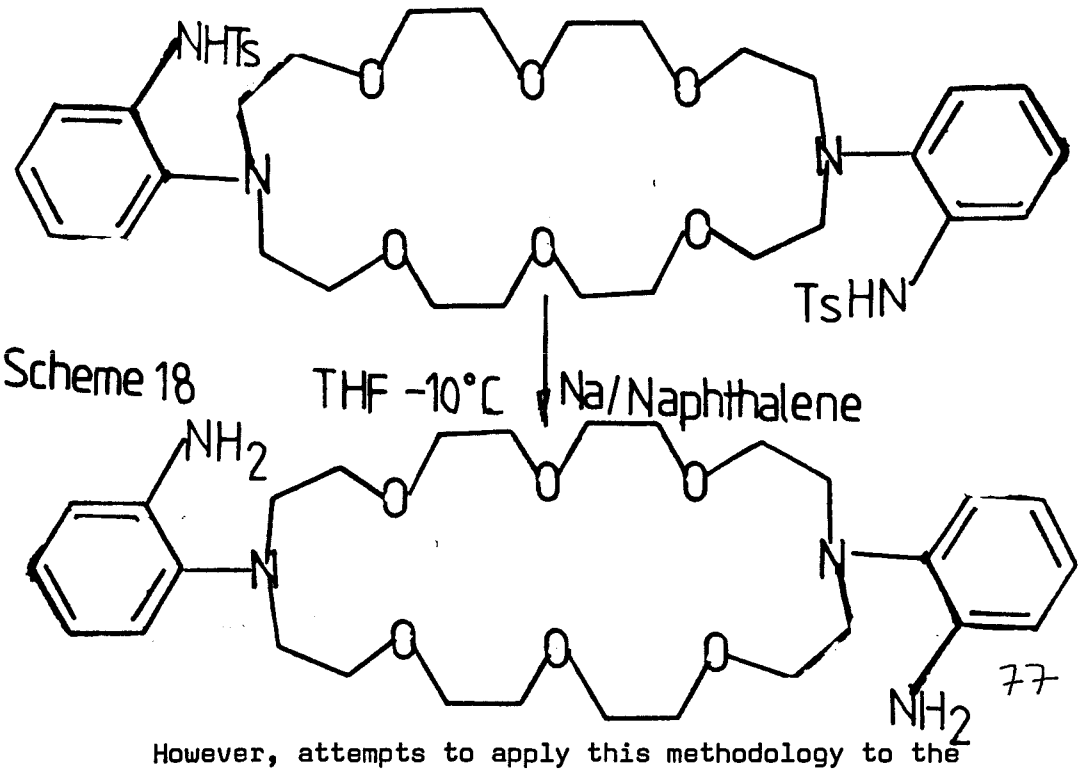
Before being able to assess the physical properties and binding ability of the macrocyclic proflavine derivatives, it was necessary to deprotect the systems by removing the paratoluene sulphonyl protecting groups. Attempts were made initially at deprotecting (70) since this was the most readily available material.

The use of sodium metal as a reagent for the reductive elimination of tosyl groups is well established[69] and has been applied successfully to the synthesis of macrocycle and crown compounds. Kellogg et al[49] have used Trost's method[77] for this reaction, deprotecting a series of aliphatic macrocycles as shown in Scheme 17 .

SCHEME 17



Sonveaux et al have applied the method of reduction with sodium and naphthalene in tetrahydrofuran for the preparation of (77) shown in Scheme 18[70].



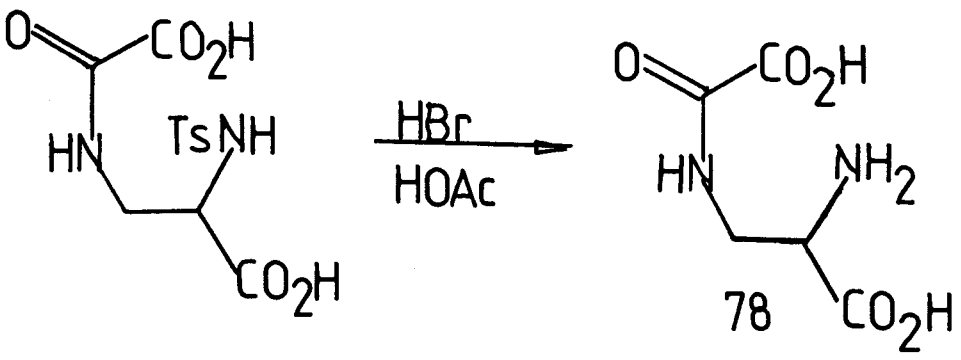
Scheme 18

77

However, attempts to apply this methodology to the reductive deprotection of (70) led to mixtures of partially reduced material which, because of the high polarity and insolubility of the products, proved impossible to separate.

Hydrogen bromide in acetic acid has been used successfully as a hydrolytic method for the removal of tosyl groups[71]. For example, Haskell et al have used this method in the synthesis of (78) according to Scheme 19 [72].

SCHEME 19



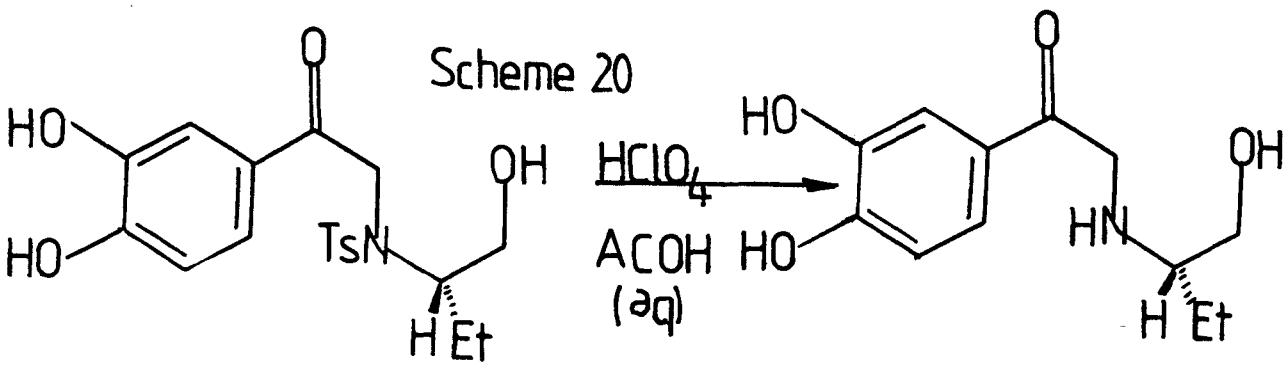
78

However, treatment of the macrocycle (70) with this reagent system for a prolonged length of time led again to mixtures of products which could not be effectively purified.

Three other hydrolytic methods of deprotection were attempted with little success. Aqueous 4 Molar hydrochloric acid and sodium hydroxide in ethanol both failed to react with (70), only starting material was recovered from both reactions. Potassium hydroxide in dimethyl sulphoxide on the other hand reacted to produce uncharacterisable material of uncertain composition.

Recently, however, Hosangadi et al have shown[73] that conditions employing perchloric acid in aqueous acetic acid at 60°C are effective for tosyl group hydrolysis. Scheme 20 gives one example of this method.

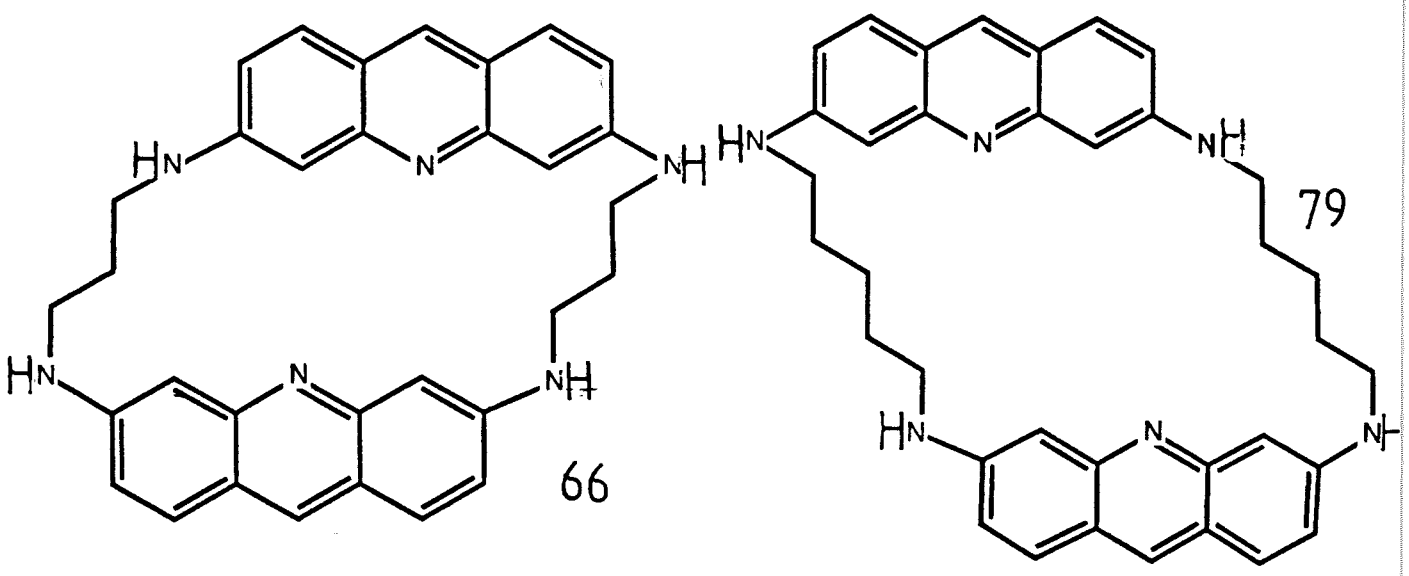
Scheme 20



Treatment of macrocycle (70) with 50 % perchloric acid in aqueous acetic acid at 80°C for 1 hour gave a quantitative yield of the deprotected macrocycle (66) as an orange powder which was insoluble in most organic solvents. Macrocycle (66)

gave a very simple ^{13}C nmr spectrum containing only 9 signals establishing that the material was symmetrical. The mass spectrum of (66) contained a highest mass molecular ion peak at 499, representing MH^+.

The use of perchloric acid in acetic acid was also successfully applied to the deprotection of (75) under identical conditions. The deprotected macrocycle (79) was prepared again in virtually quantitative yield as an orange powder, without the need for any chromatographic separation. The product (79) was again characterised principally by ^{13}C nmr and mass spectrometry.



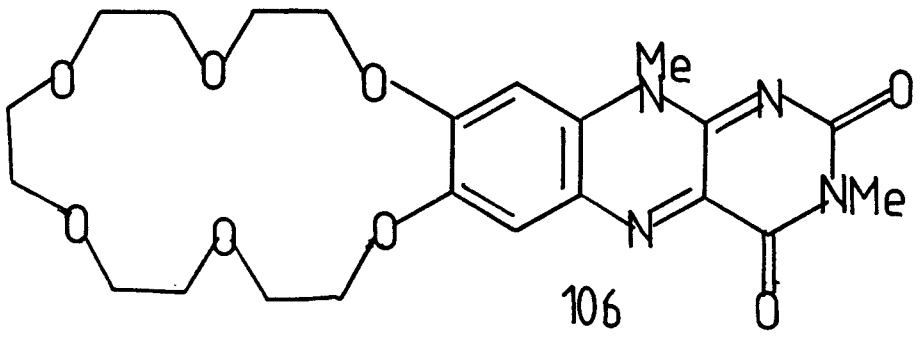
2.7 Physical Chemistry

Having successfully synthesised a number of new macrocyclic derivatives of proflavine, and developed a methodology for deprotecting them to produce the free

tetraamines, it was decided to investigate the physical chemistry of the derivatives which we had prepared, to establish whether either showed potential as host molecules.

NMR is a technique which has frequently been applied to the examination of the phenomenon of host guest complexation. For example, Cram et al have used ^{1}H nmr to establish ΔG^o values for the complexation of various metal ions with the phenanthrolene macrocycle (58)[59]. Addition of metal ions to a dimethyl sulphoxide solution of the macrocycle (58) led to significant changes in the chemical shift of the aromatic protons around the phenanthrolene rings, enabling an estimate to be made of the percentage of macrocycle in complexed form. However, since both the macrocycles (66) and (79) proved to be highly insoluble in all solvents suitable for nmr measurements except dimethyl sulphoxide, and even in this solvent poor resolution characterised the spectra because of the instability and haziness of the solutions, ^{1}H nmr was not used as the primary technique for testing for ion binding. The protected macrocycles (70), (75), (76) and (77) proved to be somewhat more soluble in dimethyl sulphoxide and gave normal ^{1}H nmr spectra. No abnormal coupling constants were noted between any of the methylene protons in the aliphatic side chains, an observation which suggests that even in the case of macrocycle (70), conformational mobility is maintained with rotational freedom of the methylene groups within the side chains.

Electronic absorption spectroscopy is a particularly sensitive technique for following ion binding of macrocyclic host compounds if the host compound contains a conjugated or aromatic chromophore adjacent to the binding cavity. The metal ion within a macrocyclic complex will interact electrostatically with any conjugated system nearby, and thus alter its electronic absorption characteristics. For example, Shinkai et al[80] have used this method to examine the binding interaction of the crown ether flavin derivatives (106) with a number of alkali metal ions.



106

Addition of alkali metal ions to a methanolic solution of (106) resulted in a sharp reduction in intensity of the 460 nm absorption maximum. This effect was particularly marked for potassium ion which exhibits the highest association constant with the 18-crown-6-ring.

The electronic spectrum of proflavine (59) in its free base form consists of three peaks at 263 nm, 285 nm and 405 nm in ethanol. This spectrum changes radically when acid is added to the solution, as first the monoprotonated and then the

TABLE 3 Electronic Spectra in Ethanol at 30°C Range 250 - 600 n.m.

Structure	Concentration	Conditions	λ_{max} (ε_{max})
	M.		n.m.
59	2.29×10^{-5}	10^{-3} M KOH	263 (41,000), 235 (28,000), 405 (14,000)
"	"	10^{-3} M H_2SO_4	262 (47,000), 284 (20,500), 460 (35,000)
"	"	1M H_2SO_4	264 (25,000), 348 (6,100), 362 (7,000) 460 (19,200)
66	1.84×10^{-5}	10^{-3} M KOH	261 (56,000), 292 (35,000), 419 (20,500)
		10^{-3} M H_2SO_4	261 (62,000), 290 (24,000), 448 (52,000)
		1M H_2SO_4	261 (68,000), 290 (35,000), 448 (52,000)
79	1.58×10^{-5}	10^{-3} M KOH	264 (40,000), 292 (40,000), 301 (38,000) 420 (20,000)
		10^{-3} M H_2SO_4	264 (54,000), 294 (23,000), 451 (39,000) 469 (42,000)
		1M H_2SO_4	264 (54,000), 294 (23,000), 451 (39,000) 469 (42,000)

diprotonated cations are formed. Somewhat different behaviour is observed for the macrocycle (66), which at neutral and basic pH displays three peaks at 262 nm, 292 nm and 420 nm due to the unprotonated free base tetraamine. At lower pH, however, only one new change in the spectrum is observed. Presumably at acid pH the macrocycle (66) forms a diprotonated species which does not readily protonate further. Similar behaviour is observed for the macrocycle (79). The results of these protonation experiments are shown in Table 3 .

In order to determine the effect of transition metal ions on the electronic spectra of (79) and (66), spectra were determined in 80% aqueous ethanol containing a phosphate buffer to remove spectroscopic changes due to pH variation. Spectra were obtained in the presence of copper (II), manganese (II), zinc (II) and nickel (II) ions as their respective acetates, at concentrations varying in each case between half that of the macrocycle and twenty times that of the macrocycle. For comparison, spectra were run under identical conditions with proflavine (59). However with neither (66) or (79) were any significant changes observed upon introducing any of the transition metal ions listed above.

In Section 2.1 the possibility of binding small molecules within a host macrocycle was discussed. In this context it is interesting to note that the tetraamides (70), (75) and (76) all gave analytical data consistent with

hydrated or partly hydrated structures. It is possible that in these compounds the macrocyclic ring is acting as a host cavity for water molecules.

2.8 Conclusions

The principle achievements of this section of our studies are

1) An entirely new range of macrocyclic proflavine derivatives (70), (75), (76) and (77) containing ring sizes of between 24 and 30 atoms, were synthesised using a simple procedure in good yield.

2) A methodology for the deprotection of these macrocycles was developed, producing the tetraamines (66) and (79) in excellent yield.

Neither of the two macrocycles which were tested showed promise as an ionophore or novel metal host molecule. Examination of C.P.K. models led to the belief that the preparation of analogous cyclic proflavine derivatives containing additional metal binding sites as part of the linking side chains between the ring systems, might improve ion binding. Additional heteroatom binding sites present as part of the flexible side chains, would enable the system to adopt a conformation containing a tetrahedral array of binding sites within which a

guest ion might sit. Chapter 3 deals with our synthetic efforts in this area.

CHAPTER THREE

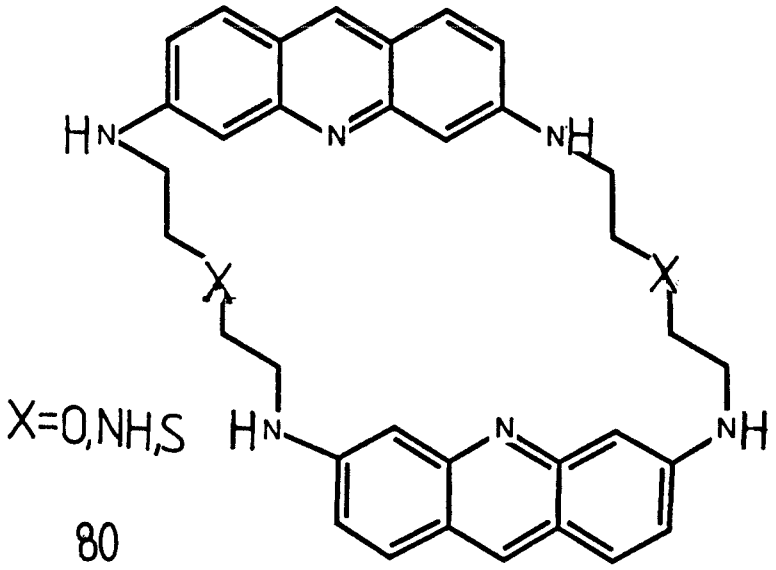
HETEROATOMIC FRAMEWORKS

3.1 Introduction

The chemical literature contains a large range of different crown ether[5] and cryptate compounds containing different heteroatoms as binding sites. Section 1.6 describes some of the diversity which exists among such compounds. However, by far the most common atoms used as binding sites in host compounds are oxygen[7], nitrogen[15], and sulphur[14]. Pederson's initial work on crown ethers concerns compounds which bind hard alkali metal ions exclusively through co-ordination to oxygen[7] and the host guest chemistry of the polyether antibiotics dealt with more thoroughly in the second part of this thesis, occurs again through co-ordination of oxygen atoms[3]. The chemisty of azo crowns[15], and cyptates[29] is well known. Compounds containing sulphur as the main donor atom tend to bind transition metal ions very much more strongly than alkali metal ions because of their soft base donor characteristics. Compounds containing nitrogen as the main donor atom generally bind both alkali metal and transition metal ions, since nitrogen is intermediate in character between oxygen and sulphur.

It was decided to investigate the possibility of synthesising macrocyclic proflavine derivatives containing oxygen, sulphur and nitrogen as additional donor heteroatoms, within the side chains linking the two acridine ring systems together. Examination of CPK models led to the conclusion that a side chain length of five atoms between the two proflavine

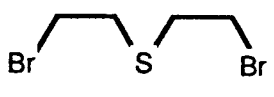
nitrogens would provide a system capable of adopting a conformation containing a square planar or tetrahedral array of binding sites. The objective was therefore to prepare compounds of the general formula (80).



80

3.2 Sulphur containing Acridinophane

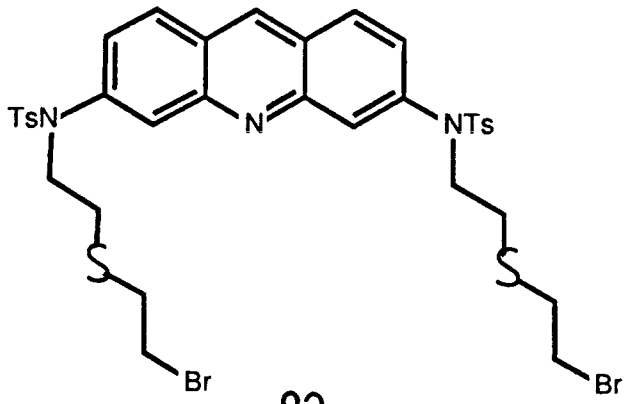
In order to prepare a sulphur containing macrocycle (80) using the method adopted for the preparation of the analogous carbocyclic framework, it was necessary to prepare a suitable alkylating agent. Towards this end, thiodiethanol was treated with phosphorous tribromide using the method of Steinkopf et al[74], which yielded the dibromide (81) as a low melting point solid.



81

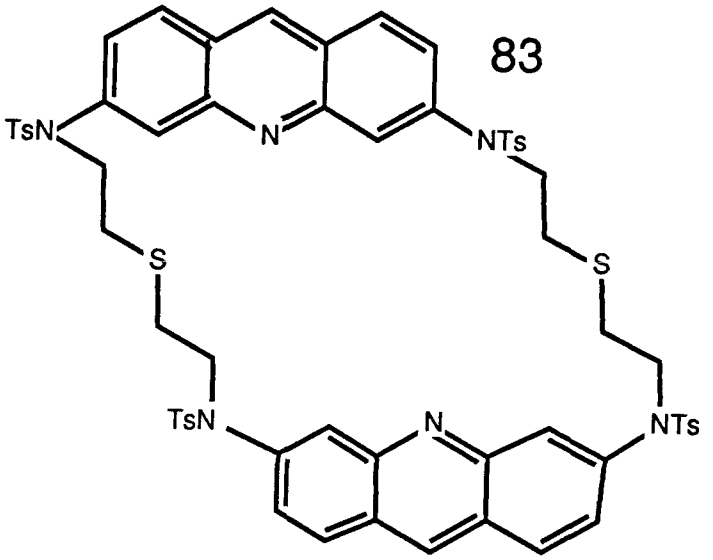
Alkylation of the proflavine diamide (67) with (81) proceeded under the conditions employed for the preparation

of (69) furnishing the product (82) in 48% yield which was characterised by NMR and microanalysis.



82

Coupling and cyclisation of (82) and (67) occurred slowly at room temperature with potassium carbonate in dimethyl formamide. The reaction appeared complete after 4 days and the cyclised product (83) was obtained as a light yellow solid in 27% yield. The product had a ^{1}H NMR spectrum which contained only three signals in the aliphatic region, a triplet at 3.75 ppm corresponding to the methylene groups adjacent to nitrogen, a triplet at 2.48 ppm corresponding to the methylene groups adjacent to sulphur and a singlet at 2.36 ppm corresponding to the toluene methyl groups. The ^{13}C NMR spectrum gave 11 signals in the aromatic region and 3 in the aliphatic region indicating the high level of symmetry in the product. The product also gave correct microanalytical data and had a mass spectrum consistent with the ascribed structure.



83

Having prepared the 28 membered ring macrocycle (83) we proceeded to attempt to deprotect it by removal of the toluene sulphonyl groups. However, exposure of (83) to 30% perchloric acid in aqueous acetic acid, the conditions used previously to successfully deprotect macrocycles (70) and (76), resulted in decomposition of the starting material. Only a red powder whose ^{13}C NMR spectrum showed no aliphatic signals, was isolated from the reaction mixture. Perchloric acid is a powerful oxidant and it is probable that oxidation of the sulphur atoms in the aliphatic side chains occurred together with hydrolysis of the tosyl protecting groups.

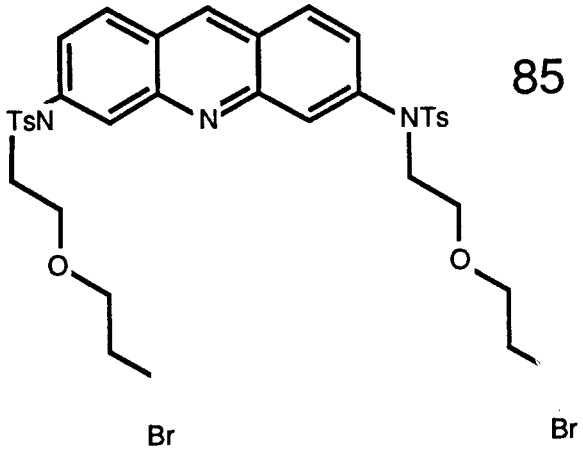
3.3 Oxygen containing Acridinophane

In order to prepare a suitable alkylating agent for the synthesis of a macrocycle of the general structure (80) containing oxygen as part of the cycle, diethylene glycol was

brominated with phosphorous tribromide according to the method of Luttringhaus et al [75] affording 1,5-dibromo-3-oxopentane (84) as an oil.

84

Treatment of the proflavine diamide (67) under the previously employed conditions with (84) led smoothly to the preparation of the desired dialkylated cyclisation precursor (85).

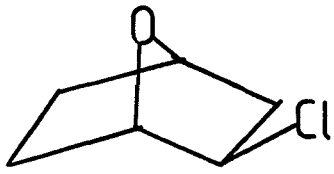


85

Coupling and cyclisation of (85) and (67) was attempted at room temperature in dimethyl formamide at 0.02 Molar substrate concentration. However, none of the desired cyclised product was isolated from the reaction mixture even after prolonged reaction times. The starting materials were predominantly recovered unchanged. Operation of the reaction at 60^{o}C made little change to the result, however a small amount of material whose NMR spectra suggested it was an elimination product of the starting material was isolated under these conditions. The presence of

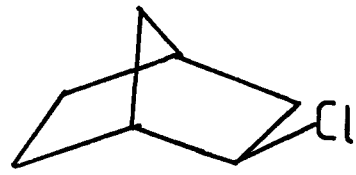
an oxygen atom β to the site of SN2 substitution in (85) was deactivating that site towards reaction, and thus the materials were failing to cyclise effectively. Another example of this effect is provided by the work of Martin et al[79] on the solvolysis of 2-halo-1,4-endoxycyclohexanes. The calculated rate constant for the hydrolysis of the oxo bridged exocyclohexyl chloride (108) at 85°C in 80% ethanol is 2×10^3 smaller than that of the all carbon analogue (109) under the same conditions as shown in Scheme 23. The presence of the oxygen atom β to the site of nucleophilic attack is thus retarding the reaction rate.

SCHEME 23



108

$k = 2 \times 10^{-8} s^{-1}$



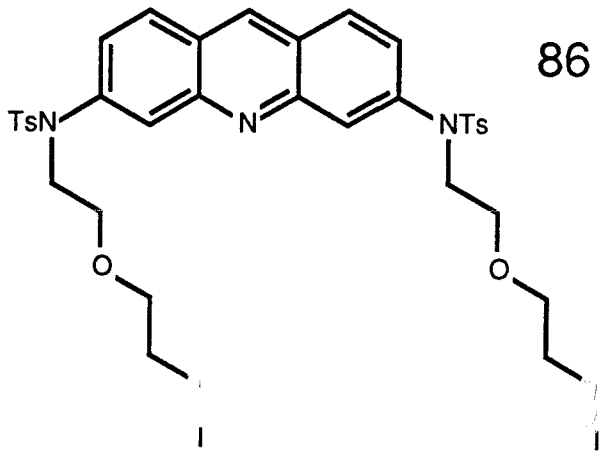
109

$4 \times 10^{-5} s^{-1}$

In order to improve the chances of the cyclisation proceeding, it should be possible to increase the nucleophilicity of the attacking sulphonamide anion. To explore this possibility, the coupling and cyclisation of (67) and (85) were repeated with dimethyl sulphoxide as the solvent. Dimethyl sulphoxide is a somewhat more polar solvent than dimethyl formamide, and this should serve to increase the reactivity of any anion in solution. However, no improvement to the result occurred in our case, with starting materials being mostly recovered from the reaction mixture, together with some polymeric

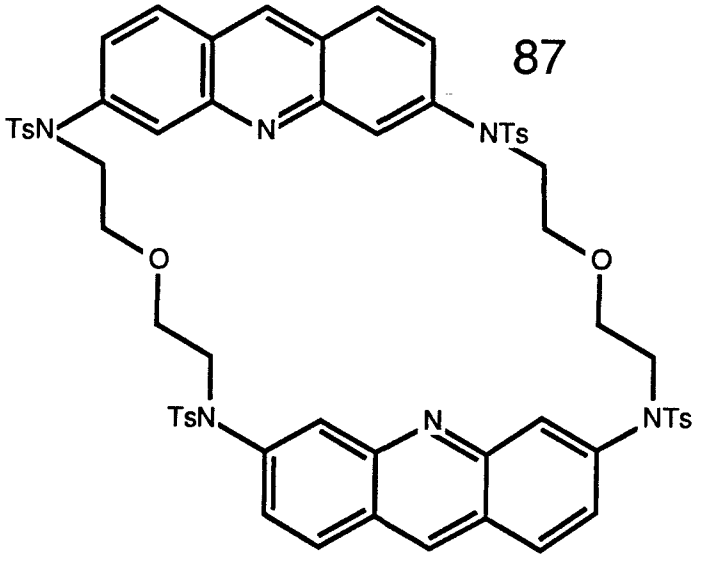
material. Kellogg et al[49] have noted the ability of cesium carbonate to improve the yield in SN2 sulphonamide ring closure reactions by acting as a better base than either sodium or potassium carbonate. Since cesium is a larger alkali metal cation than sodium or potassium, this renders the anion which results from the deprotonation of the sulphonamide nitrogen more nucleophilic because of the weaker ion pairing which occurs between a large metal cation and its counter anion. We attempted to couple and cyclise (67) and (85) in dimethyl formamide and dimethyl sulphoxide using cesium carbonate as the base; however, no cyclised product was isolated in either case from the reaction mixtures.

An alternative approach to improving the chances of success in the cyclisation reaction would be to improve the leaving group efficiency. Therefore the cyclisation was attempted using the diiododerivative (86) rather than the previously used dibromoderivative (85), since iodide should be a better leaving group than bromide. The alkylating agent 1,5-diiodo-3-oxapentane was prepared according to the method of Kulstad and Malmsten[76] using the Finkelstein reaction. The cyclisation precursor (86) was prepared smoothly from the proflavine diamide (67) at room temperature. The reaction proceeded relatively quickly reaching completion in 16 hours. The product had a characteristically simple ^{13}C NMR spectrum including a signal at 2.43 ppm corresponding to the methylene groups adjacent to iodine, and was characterised by microanalysis.



86

The cyclisation of (67) and (86) was attempted in dimethyl formamide with potassium carbonate as the base at room temperature over 4 days. The cyclised product (87) was isolated in a low yield of 9% as a cream coloured solid by chromatography. The acridinophane product showed only three signals in the aliphatic region of the ^{1}H NMR spectrum, two triplets at 3.75 ppm and 3.28 ppm corresponding to the protons next to nitrogen and oxygen respectively, and a singlet at 2.36 ppm corresponding to the methyl groups of the tosyl moiety.



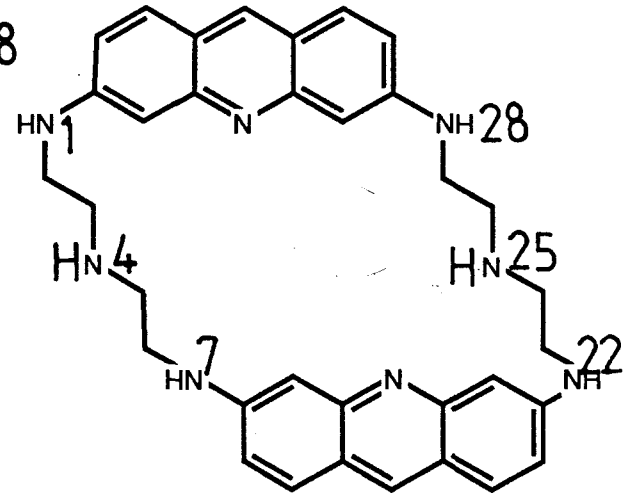
87

Although the approach of changing to a better leaving group enabled the preparation of the desired macrocycle, the reaction proceeded in a low yield which was not synthetically useful. Because of the inability to improve the yield of the cyclisation step, and because of the small amounts of cyclic product which we were able to prepare, further synthesis along this path was discontinued.

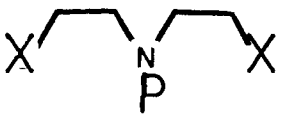
3.4 Acridinophane containing further Nitrogen atoms within the ring

The preparation of an acridinophane containing additional nitrogen functionality in the side chains joining the two acridine ring systems together, such as structure (88), is of particular interest because it opens up the possibility of a further functionalisation of the macrocycle through the third valence of nitrogen. It should be possible to prepare a side armed or "lariat" macrocycle by functionalising (88) at positions 4 and 25 through the third valence of nitrogen. It might eventually be possible to link the two sides of the macrocycle together, thus producing a cage molecule containing a more strictly defined internal cavity of the sort which is present in Lehn's cryptate compounds[29].

88



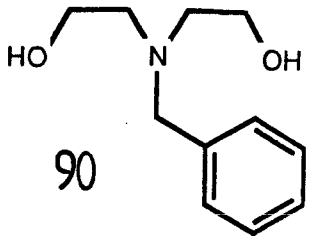
In order to prepare an acridinophane such as (88) using the method which we have employed so far for the synthesis of analogous compounds, it is necessary to prepare a fragment of the general structure (89) where P is a protecting group and X is a good leaving group, as the side chain section of the eventual macrocycle.



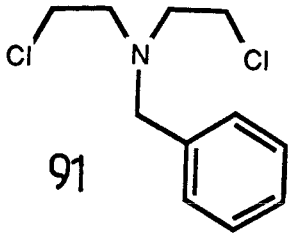
89

The protecting group is necessary not only to prevent interference from the central nitrogen atom during nucleophilic substitution reactions, but also because compounds of structure (89) where P is H are highly toxic, and tend to decompose to polymer on standing.

Initially, it was decided to use benzyl protection on the nitrogen atom of the side chain since this should be selectively removed by catalytic hydrogenation, leaving the toluene sulphonyl groups on the macrocycle intact. Diethanolamine was thus treated with benzyl chloride and potassium carbonate in xylene to produce the benzyl protected diol (90). The protected diol was then treated with thionyl chloride in benzene for 3 hours to yield the dichloro derivatives (91) as its hydrochloride salt[80]. The free NN -di(2-chloroethyl)benzylamine was obtained from the hydrochloride salt by treatment with sodium hydroxide solution, and was used directly in the next step.

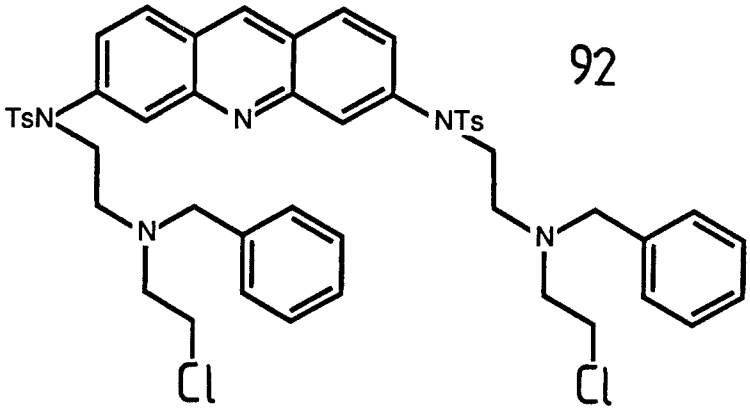


90



91

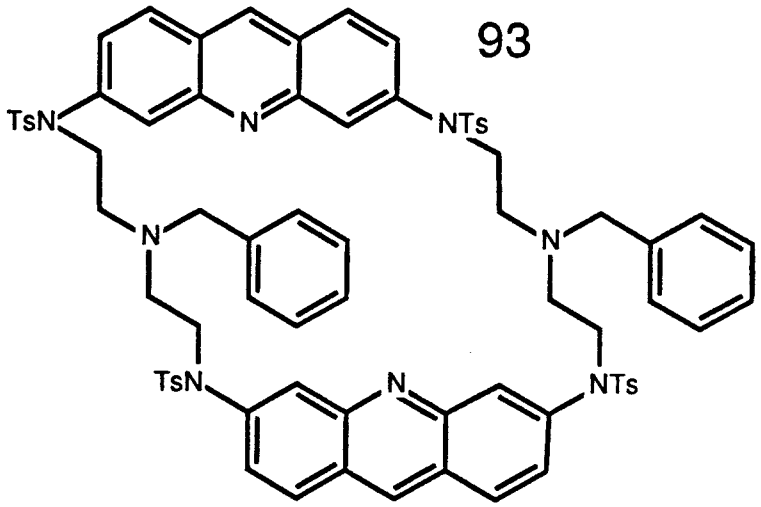
Alkylation of the proflavine diamide (67) with (91) under the previously employed conditions led to the isolation in modest yield of the cyclisation precursor (92) after 24 hours. The lower yield of this reaction is due to the poorer leaving group ability of chloride compared with the previously used bromide and iodide



92

Attempts to cyclise (92) and (67) in dimethyl formamide with potassium carbonate, failed even after prolonged reaction times. Only starting materials were recovered from the reaction mixture each time, and it can be assumed that chloride is too poor a leaving group to allow cyclisation to proceed under the conditions employed.

Repetition of the cyclisation conditions previously attempted for (67) and (92) in dimethyl formamide in the presence of 2 equivalents of potassium iodide, led to the isolation of a small amount of the cyclised product (93) after 4 days at room temperature. Execution of the same reaction at 60°C for 16 hours yielded 52% of the 28 membered macrocycle as pale orange crystals. The product gave a ^{1}H NMR spectrum containing only four signals in the aliphatic region, a singlet at 3.84 ppm due to the benzyl methylene, a triplet at 3.50 ppm corresponding to the methylenes next to the sulphonamide nitrogens, a triplet at 2.56 ppm due to the side chain methylene groups adjacent to the benzylated nitrogens, and a singlet at 2.37 ppm corresponding to the tosyl methyl groups. The compound also gave a simple ^{13}C NMR, and microanalytical data in accord with its monohydrate.



The preparation was successful, in protected form, of each of the three macrocycles which we targeted. Table 4 contains

TABLE 4 Physical Data for Heteroatomic Tolvene Sulphonyl Protected Acridinophanes

Structure No.	Ring Size	M.P. ^{o}C	IR λmax cm^{-1}	^{13}C NMR ppm
83	28	249 - 251	1625, 1450, 1372	147.80 (CH9 & 23), 21.01 (Tosyl Me)
87	28	308 - 309	1610, 1390	147.7 (CH9 & 23), 20.8 (Tosyl Me)
93	28	145 - 147	1610, 1350	148.63 (CH9 & 23), 21.62 (Tosyl Me)

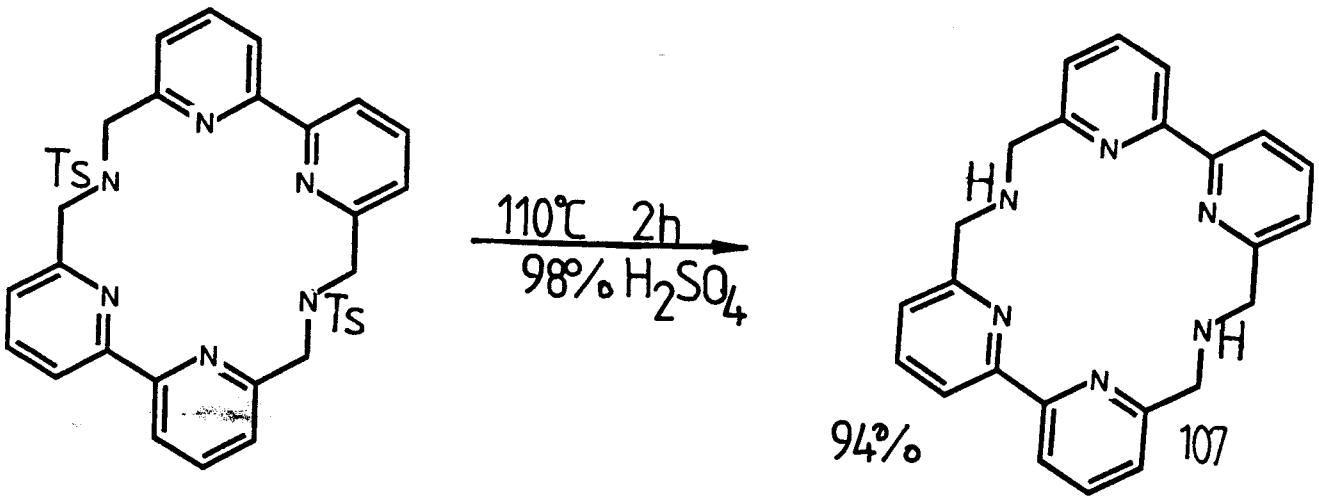
physical data and cyclisation yields for the heteroatomic macrocycles prepared above. One point of interest is the considerably lower melting point of (93) relative to the other two compounds. The aromatic rings of the benzyl protecting groups may disrupt the otherwise flat packing of the linked acridine rings and thus lower the melting point.

3.5 Deprotection and Physical Chemistry of the Acridinophane (93)

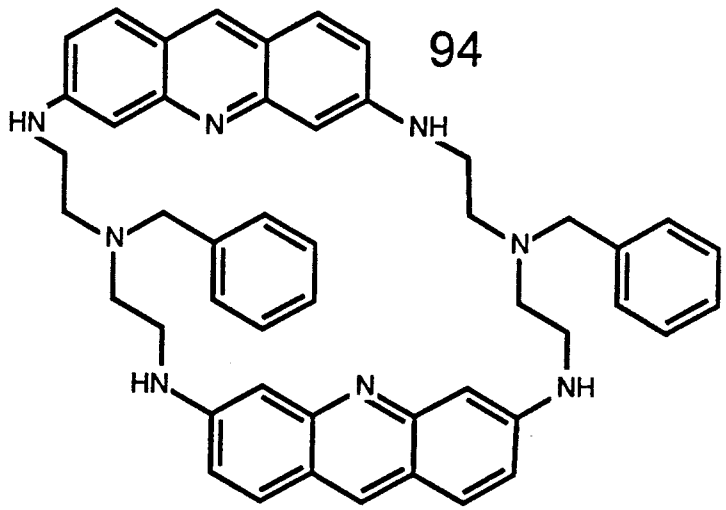
Having prepared the N-benzyl acridinophane (93), we attempted to remove the protecting groups from the macrocycle.

Because of the problems encountered when using perchloric acid as a detosylating agent for (83), we attempted instead to use sulphuric acid as the reagent of choice for the same reaction on (93). Concentrated sulphuric acid has been used effectively for the detosylation of a number of macrocyclic sulphonamides, for example Lehn et al[79] have used this method for the preparation of the tetrapyridine derivative (107) according to Scheme 21.

SCHEME 21



Reaction of (93) in 98% sulphuric acid for 6 hours at 60°C furnished the desired detosylated macrocycle (94) in 70% yield as an orange powder, which proved to be insoluble in most organic solvents. The product was identified principally by NMR, the ^{13}C NMR spectrum contained only 14 signals of which only three were in the aliphatic region of the spectrum at 58.7, 52.2 and 41.1 ppm corresponding to the three types of methylene group within the molecule. The ^{1}H NMR spectrum showed a singlet at 3.71 ppm corresponding to the benzyl methylene groups, and two multiplets at 3.29 ppm and 2.79 ppm corresponding to the other two aliphatic proton environments.



94

Macrocycle (94) is a good candidate for a host compound, since it contains an array of nitrogen atoms within the ring which could act as binding sites for a guest metal cation. Accordingly the electronic spectral properties of (94) were examined at basic pH and in the presence of manganese (II),

TABLE 5 Acridinophane (94)

Electronic Spectra at 30°C in 50% aqueous Ethanol Range 250–600 nm

1.312×10^{-5} Molar

Conditions	λ_{max} nm (ε max)
10^{-3} M KOH	256 (46,000), 286 (33,500), 402 (17,000)
10^{-3} M H_2SO_4	258 (50,000), 431 (42,500)
1 M H_2SO_4	258 (58,000), 447 (42,500)

TABLE 6 Acridinophane (94)

Electronic Spectra at 30°C in Acetontrile Range 300–550 nm

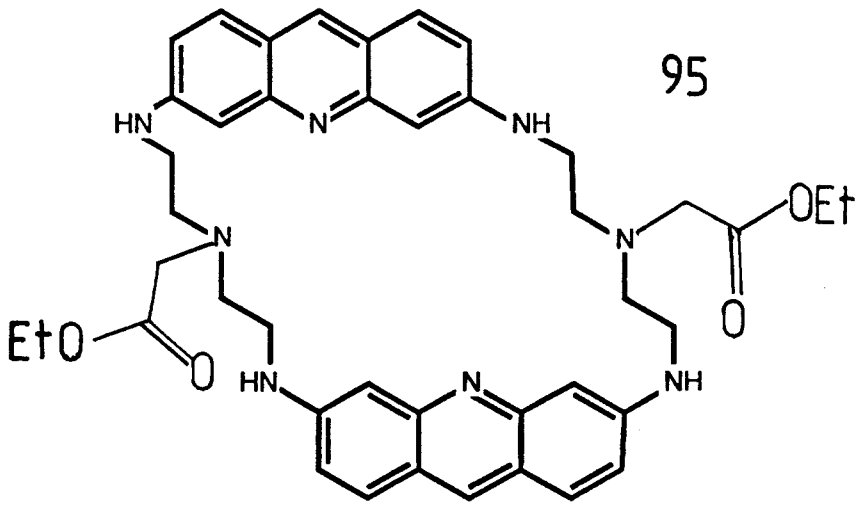
1.312×10^{-5} Molar

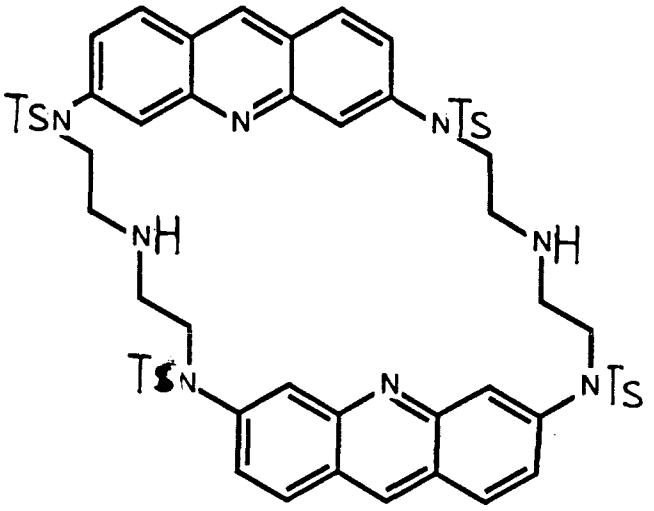
Conditions	λ_{max} nm (ε max)
10 eq Et_3N	404 (50,000)
10 eq Et_3N 1 eq $Cu(OAc)_2$	410 (41,000)
10 eq Et_3N 10eq $Cu(OAc)_2$	410 (33,500)

nickel (II), zinc (II) and copper (II) ions as well as examining changes in λ_{max} and extinction coefficient at different pH values. The spectra which had been treated with metal ions were determined at constant basic pH to avoid effects due to protonation of any of the nitrogen atoms. Under these conditions, addition of an excess of copper (II) ions gave a λ_{max} shift of about 10nm, and a slight decrease in extinction coefficient, which is an indication that metal binding is taking place. Tables 5 and 6 give details of the conditions used for these tests together with the λ_{max} and ε_{max} values obtained.

Encouraged by evidence that the macrocycle (94) was showing ionophore properties, it was decided to continue with the synthesis of compounds, such as (95), containing lariats or side arms providing further sites for metal ion co-ordination, thus hopefully producing a better host compound. In order to facilitate this, it was necessary to remove the benzyl groups from (93) and functionalise the resultant macrocycle (96) and the selectively deprotected nitrogen atoms.

95





96

Removal of the benzyl protecting groups from (94) was attempted using hydrogenation under 1 atmosphere of hydrogen in ethanol, using 5% palladium on charcoal or platinum dioxide as catalysts. However, neither of these experiments yielded a helpful result with starting materials being recovered on both occasions. The use of glacial acetic acid as the solvent with 10% palladium on charcoal as the catalyst, led to the isolation of an orange powder on work up which proved not to be the desired product. Examination of the NMR spectra of the product showed that although the benzyl groups had been successfully removed, the product did not have spectral characteristics consistent with the desired compound. The ^{13}C NMR contained too many peaks with the wrong proton carbon connectivity for the structure (95). Hydrogenation of the acridine aromatic system at the 9 position is also a relatively low energy process and it is possible that this reaction is occurring along with the

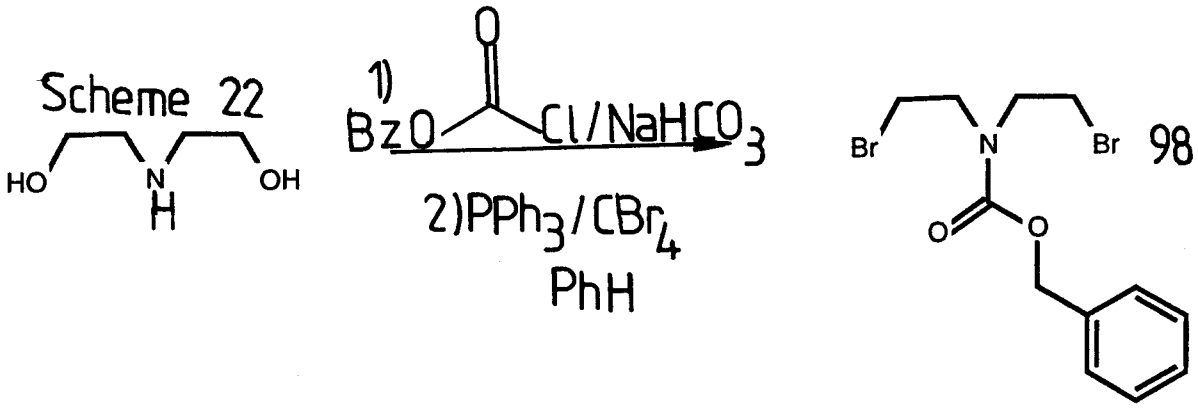
reductive hydrogenolysis of the benzyl groups.

3.6 Synthesis involving other Protecting Groups

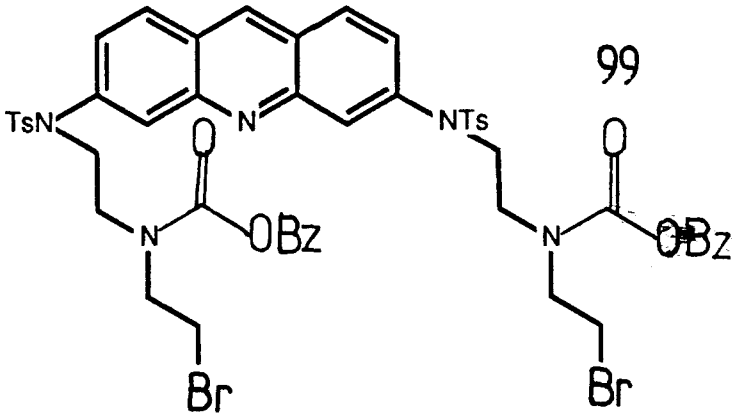
The difficulties which we encountered in debenzylating the macrocycle (93) led us to attempt alternative strategies for the preparation of lariat macrocycles such as (95), which did not involve the use of benzyl protection. The two alternative possibilities using the synthetic method previously employed for macrocyclisation were either to alter the protecting group on the side chain nitrogen atoms, or to synthesise the side chain, and eventually, the macrocycle, with the lariat side arm already in place.

Initially, it was decided to adopt the former approach and attempt the synthesis of side chain synthons containing alternative nitrogen protecting groups. The benzyloxycarbonyl group is an extensively used nitrogen protecting group which is stable under basic conditions but is removed with strong acid smoothly. Treatment of diethanolamine with benzyl chloroformate in aqueous sodium bicarbonate yielded the benzyloxycarbonyl protected amine. This was treated with triphenyl phosphine and carbon tetrabromide to yield the dibromo protected amine (98) as shown in Scheme 22.

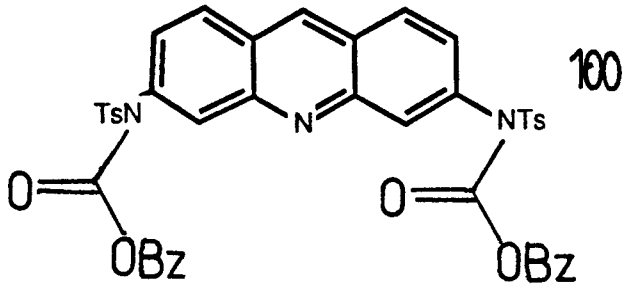
Scheme 22



However, attempts to use the alkylating agent (98) with the acridine diamide (67) in the hope of producing the cyclisation precursor (99), resulted instead in the preparation of an acyl transfer product (100) as the major product. Compound (100) was identified by ^{13}C and ^{1}H NMR as well as IR.

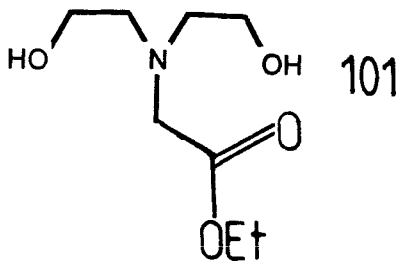


99



100

Having experienced difficulties in trying to use alternative nitrogen protecting groups, the synthesis of a lariat acridine macrocycle by incorporating the lariat arm into the side chain precursor used for alkylation and cyclisation was attempted. Thus we reacted ethyl bromoacetate with diethanolamine to produce the coupled aminoester (101).



101

In order to prepare a suitable alkylating agent from (101), the compound was reacted initially with thionyl chloride in acetonitrile, however no useful product was isolated from the reaction mixture. Attempts to brominate (101) with carbon tetrabromide and triphenyl phosphine also proved inadequate, with only a brown material of uncertain composition being isolated from the reaction mixture. Finally, (101) was treated with methanesulphonyl chloride in dichloromethane to generate the corresponding dimesylate, however attempts to couple this material with proflavine diamide (87) proved unsuccessful with only starting materials being recovered. Table 7 gives relevant physical data relating to various five atom alkylating agents which have been employed in the syntheses of various macrocycle compounds, together with the same data relating to the compounds of this type which we have prepared.

3.7 Conclusions

The significant results in this section of studies are as follows:

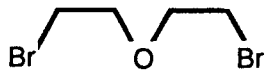
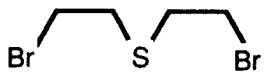
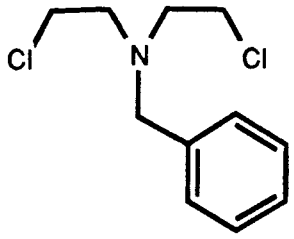
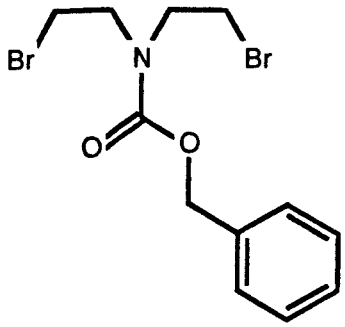
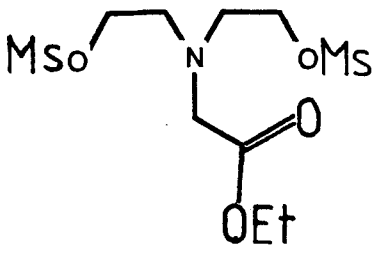
1) A series of novel 28-membered ring acridinophane structures containing different heteratoms in the side chains between the two aromatic systems, have been synthesised. In the synthesis of the azomacrocycle (93), an iodide ion catalysed ring closure reaction was effectively employed.

2) The azoacridinophane (93) was detosylated with concentrated sulphuric acid to produce the partially deprotected structure (94) in good yield.

3) Some evidence was gathered which suggested that (94) can act as a host compound for Cu^{2+} ions.

4) Several novel five atom side chain synthons of general structure (89) were prepared.

TABLE 7

Species	Ref.	mp/b.p.	IR cm^{-1}
	75	b.p. 115°C (32mm Hg)	3050(s), 1460(m), 1360(s)
	82	mp 31 - 34°C	3000(s), 1450(m), 1355 (s)
	80	mp (H Cl salt) 138-140°C	3050(s), 1460(m), 1395(s)
	-	-	3050(m), 1705(vs), 1490(s)
	-	-	3000(s), 1750(vs), 1680(s), 1480(s)

CHAPTER FOUR

EXPERIMENTAL

4. Experimental

4.1 General Procedures

Solvents were dried by distillation under an atmosphere of nitrogen from the following drying agents:

Calcium hydride	:	Pyridine, Triethylamine, Dimethylformamide, Pentane.
Sodium	:	Xylene, Benzene, Tetrahydrofuran, Diethyl ether.
Phosphorous pentoxide	:	Dichloromethane
Potassium carbonate	:	Acetone, Acetonitrile

Light petroleum refers to petroleum ether, boiling range 40 - 60°C (distilled prior to use).

Analytical thin-layer chromatography was carried out on precoated silica plates (Merck, type 25 UV254), and compounds were visualised using U.V. fluorescence, iodine vapour, vanilin solution or potassium permanganate solution.

Silica chromatography refers to the method of Still et al[84], and was performed using Machery-Nagel Kieselgel 60 230 - 400mesh with the eluant stated.

4.2 Instrumentation

Melting points (mp) were measured using an Electrothermal hotplate melting point apparatus and are uncorrected.

^{1}H nuclear magentic resonance (NMR)

spectra were recorded in deuterated solvents as stated,
at 60 MHz on a Perkin-Elmer R-24B,
at 270 MHz on a Jeol FX 270, or
at 360 MHz on a Bruker WH-360 spectrometer.
Tetramethylsilane was used as internal standard (0). Chemical shifts are quoted as δ - values and the following abbreviations apply: s - singlet; d - doublet; t - triplet; q - quartet; m - multiplet; and J - coupling constant.

^{13}C nuclear magnetic resonance (NMR)

spectra were recorded in deuterated solvent as stated,
at 67.9 MHz on a Jeol FX270 spectrometer or
at 90.6 MHz on a Bruker WH-360 spectrometer, using tetramethylsilane as an internal standard. Chemical shifts are quoted as δ values. The number of protons attached to each carbon atom was determined unambiguously by DEPT (distortionless enhancement by polarisation transfer) experiments.

Infrared (IR) spectra were recorded as dichloromethane solutions, thin film, potassium bromide pressed discs or nujol mulls on a Perkin-Elmer 157G grating spectrometer and were

calibrated using the 1601 and 1028 cm^{-1} lines of polystyrene. Only the most important absorptions are reported and the following abbreviations apply: w - weak; m - medium; s - strong; vs - very strong.

Ultra violet/visible spectroscopy - these spectra were recorded on a Unicam SP1800 Ultraviolet spectrophotometer using matched silica cells. A discussion of these appears where appropriate in preceding chapters, not in the following experimental section.

Mass spectra (MS) were recorded on either a Kratos MS30 spectrometer or a V.G. Analytical 11-250J spectrometer. Spectra were run by electron impact (EI), chemical ionisation (CI), or fast atom bombardment (FAB) from a matrix of stated composition. The molecular ion is given in each case together with other significant peaks, intensity is stated as a percentage in brackets after each value.

Elemental analyses were carried out at University College, London.

4.3 Experimental Procedures

The following compounds were prepared using methods described in the literature:

1,5-Dibromo-3-oxapentane[75], 1,5-diiodo-3-oxapentane[75], 1,5-dibromo-3-thiapentane[82], N-(t-butoxy carbonyl)-3-aza pentane-1,5-diol[83].

N-Benzyloxycarbonyl-diethanolamine

To a stirred solution of diethanolamine (4.0g, 38.0mmol) in water (20ml) containing sodium bicarbonate (3.2g, 38.0mmol) was added benzyl chloroformate (6.5g, 38 mmol) at room temperature. After 10 min an exothermic reaction occurred evolving carbon dioxide.

The reaction mixture was allowed to stir for 3 hours before being extracted with dichloromethane. The extracts were washed with water before being dried ($MgSO_4$). Removal of the solvent at reduced pressure furnished N-benzyloxycarbonyl-diethanolamine (8.1g, 90%) as a clear oil.

^1H NMR ($CDCl_3$, 60MHz) :	7.3 (5H,s), 5.1 (2H,S), 4.5 (2H,s), 3.8 (4H,m), 3.5 (4H,m)
^{13}C NMR ($CDCl_3$) :	156.92 (C), 136.52 (C), 128.56 (CH), 128.11 (CH), 127.85 (CH), 67.41 (CH_2), 61.46 (CH_2), 52.73 (CH_2), 51.95 (CH_2)
IR (Liquid Film) ν_{max} cm^{-1}:	3600-3100 (broad), 2950 (s), 1700 (vs), 1480 (s), 1420 (s), 1380 (m)
Found :	C,60.1; H,7.0; N,5.8%
$C_{12}H_{17}NO_4$ requires	C,60.2; H,7.2; N,5.8%

N-Benzyloxycarbonyl-1, 5-dibromo-3-azapentane

To a stirred mixture of carbon tetrabromide (26.4g, 0.080mol) and triphenyl phosphine (20.9g, 0.080mol) in benzene (70ml) at room temperature under an atmosphere of nitrogen was added N-benzyloxycarbonyl-diethanolamine (6.8g, 0.028 mol) in benzene (10ml). The reaction proceeded exothermically and the initial brown colouration of the mixture discharged within 5 min. After 2 hours the reaction mixture was filtered and the solid residue washed with benzene. The combined filtrate was concentrated under reduced pressure yielding a crude oil (31.9g). Chromatography over silica gel with dichloromethane : light petroleum (1 : 1) as eluant yielded N-benzyloxycarbonyl-1, 5-dibromo-3-azapentane (3.8g, 37%) as a clear oil.

^{1}H NMR ($CDCl_3$, 360MHz) : 7.35 (5H,m), 5.12 (2H,s), 3.68 (4H,m), 3.50 (2H,t,J7.3Hz), 3.39 (2H,t,J7.3Hz)

^{13}C NMR ($CDCl_3$) : 155.4 (C), 136.1 (C), 128.5 (CH), 128.1 (CH), 127.8 (CH), 67.5 (CH_2), 50.8 (CH_2), 50.3 (CH_2), 29.3 (CH_2)

IR (Thin Film) ν max cm^{-1} : 3050 (m), 1705 (vs), 1490 (s), 1420 (s), 1375 (m)

N-Benzyl diethanolamine (90)

To a vigorously stirred solution of diethanolamine (50g, 0.47 mol) in xylene (100ml) at 100°C containing potassium carbonate (120g, 0.86mol) was added benzyl chloride (70g, 0.55mol) dropwise over 25 min. The resulting mixture was heated under reflux for 6 hours. The reaction was then allowed to cool before filtering off the solid. The solid was washed with toluene and the combined filtrate was concentrated under reduced pressure to yield the crude product. Distillation under reduced pressure yielded N-benzyl diethanolamine (90) (72g, 79%) as a clear liquid. bp 176-178°C at 3mm Hg (lit[5] 176-178°C, 4mmHg)

^{1}H NMR ($CDCl_3$, 360MHz) : 7.30 (5H,m), 4.31 (2H,s), 3.71-3.40 (4H, complex), 2.60 (4H,m)

^{13}C NMR ($CDCl_3$) : 138.32 (C), 128.77 (CH), 128.10 (CH), 126.90 (CH), 59.39 (CH_2), 55.74 (CH_2), 50.87 (CH_2)

IR (CH_2Cl_2) ν_{max} cm^{-1} : 3600-3000 (broad), 2900 (s), 1975 (w), 1885 (w), 1455 (m)

NN'-Di(2-chloroethyl) benzylamine (91)

To a stirred solution of N-benzyldiethanolamine (5.0g, 0.025mol) in benzene (10ml) was added thionyl chloride (5.95g, 0.05mol) dropwise over 15min. The resulting mixture was heated to 55°C for 3 hours. After the reaction had cooled, ethanol (3ml) was added and the mixture was heated under reflux for a further 15min. After cooling, the reaction was concentrated under reduced pressure to yield a brown oil. Trituration with acetone, followed by refrigeration at -5°C yielded NN'-di (2 chloroethyl) benzylamine hydrochloride salt (4.86g, 72%) as a white powder.

m.p. 138-140°C (lit [80] 148-150°C)

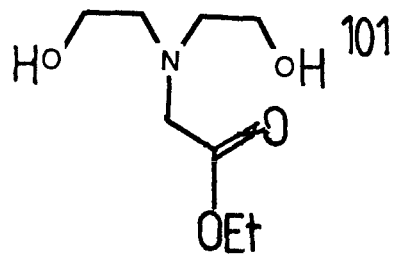
The solid was treated with sodium hydroxide solution (10%), and extracted with ether. The extracts were washed with water before drying ($MgSO_4$), and removal of the solvent at reduced pressure furnished NN'-di (2-chloroethyl) benzylamine (91) as a liquid.

^1H NMR ($CDCl_3$, 360MHz) : 7.40-7.15 (5H,m), 3.68 (2H,s), 3.40 (4H,t, J6.7Hz), 2.85 (4H,t, J6.7Hz)

^{13}C NMR ($CDCl_3$) : 136.92 (C), 128.58 (CH), 128.44 (CH), 127.36 (CH), 59.24 (CH_2), 56.47 (CH_2)

IR (Thin Film) ν max cm^{-1} : 3050-2850 (s), 1460 (m), 1395 (s), 1260 (m), 1210 (s)

Ethyl NN-di (2-hydroxyethyl)amino acetate (101)



101

A mixture of diethanolamine (5.0g, 47.6mmol), ethylbromoacetate (8.0g, 48.0mmol) and sodium carbonate (10.0g, 94.3mmol) was heated under reflux in acetonitrile (50ml) under an atmosphere of nitrogen. After 4 hours the mixture was allowed to cool, before the solid was filtered, and washed with acetonitrile (50ml) and ethyl acetate (50ml). The combined extracts were evaporated under reduced pressure to yield the product ethyl NN-di (2-hydroxethyl)aminoacetate (101) (3.1g, 34%) as an oil.

^{1}H NMR ($CDCl_3$, 60MHz) : 4.35 (4H,m), 3.95-2.70 (10H,complex), 1.20 (3H,t,J7Hz)

IR (Liquid Film) ν_{max} cm^{-1} : 3700-3250 (broad), 1750 (vs), 1480 (s)

N-Tertiary butoxy carbonyl - 1,5-dimethanesulphonyl oxy-3-azapentane

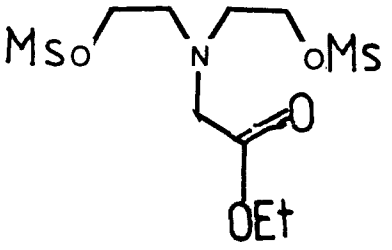
To a stirred solution of N-tertiary butoxy carbonyl diethanolamine (1.6g, 7.7mmol) in dichloromethane (10ml) containing triethylamine (1.7g, 16.3mmol) at 0^{o}C under an

atmosphere of nitrogen, was added methane sulphonyl chloride (1.9g, 16.3mmol) in dichloromethane (10ml) dropwise over 30 min. The mixture was stirred at $0^{o}C$ for a further 3 hours before being added to ice water and being extracted with dichloromethane. The extracts were washed with water, before drying ($MgSO_4$), when removal of the solvent under reduced pressure yielded N-tertiary butoxy carbonyl-1, 5-dimethane sulphonyloxy-3-azapentane (2.5g, 90%) as a yellowish oil.

^1H NMR ($CDCl_3$, 60MHz) : 4.3 (4H,t,J7Hz), 3.6 (4H,t,J7Hz), 3.1 (6H,s), 1.5 (12H,s)

IR (Liquid Film) max cm^{-1}: 3000 (s), 1770 (s), 1700 (vs), 1480 (s), 1380 (s)

Ethyl NN-di (2-methane sulphonyloxyethyl) amino acetate (103)

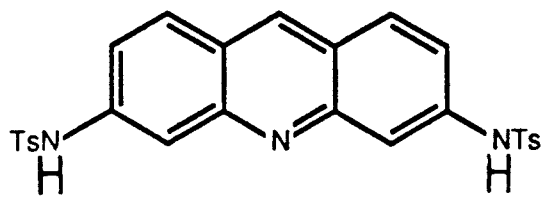


103

From ethyl NN-di(2-hydroxyethyl) amino acetate (101) using the previously described method, as an oil (92%)

^1H NMR ($CDCl_3$, 60MHz) : 4.30 (4H,m), 4.00-2.72 (14H,complex), 1.20 (3H,t,J7Hz)

IR (Liquid Film) ν max cm^{-1} : 3000 (s), 1750 (vs), 1680 (s), 1480 (s)



67

NN´-Ditoluene sulphonyl-3, 6-diaminoacridine (67)

Method 1:

To a stirred solution of 3,6-diaminoacridine free base (3.50g, 0.017mol) in pyridine (65ml) and triethylamine (5ml) at 0°C on an ice bath was slowly added paratoluene sulphonyl chloride (16.5g, 0.087mol) as a solution in pyridine (20ml). After 3 hours the red mixture was allowed to warm slowly to room temperature and was stirred for a further 10 hours. The solution was then added to dilute hydrochloric acid to afford an orange precipitate (14g), which was collected and dried. The solid was dissolved in methanol triethylamine (9:1) and ethyl acetate was added. Refridgeration of the resulting red solution yielded triethylamine hydrochloride as the first crop of crystals. Further crops consisted of NN´-ditoluenesulphonyl-3, 6-diamino acridine (67) (5.73g, 65%) as bright red crystals which proved to be hygroscopic .

mp 173-176°C (ethyl acetate)

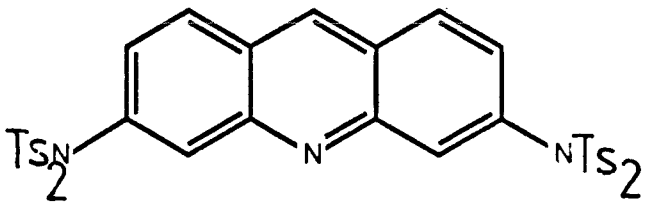
^{1}H NMR (DMSOd_6, 360MHz) : 9.12 (1H,s), 8.52-8.23 (8H,complex), 8.10-7.82 (6H,m), 2.85 (6H,s)

^{13}C NMR (DMSO-d_6) : 149.02 (C), 143.48 (C), 140.50 (C), 136.68 (CH), 136.17 (C), 129.93 (CH), 129.75 (CH), 126.67 (CH), 122.13 (CH), 119.90 (CH), 112.40 (C), 20.80 (CH_3)

IR (Nujol) ν max cm^{-1} : 1625 (s), 1320 (m), 1249 (m), 1177 (vs)

Found: C, 61.3; H, 4.6; N, 8.0; S, 11.9%

$C_{27}H_{23}N_3O_4S_2 . \frac{1}{2}H_2O$ requires C,61.6; H, 4.8; N, 8.0; S, 12.2%



The residual mother liquor was evaporated under reduced pressure to yield a brown oil. Chromatography over silica gel with dichloromethane/ethyl acetate (9:1) as eluant yielded tetratoluenesulphonyl-3, 6-diaminoacridine (68) (4.20g, 30%) as a yellow oil.

^1H NMR ($CDCl_3$, 360MHz) : 8.50 (1H,s), 8.40-7.65 (16H,complex), 7.40-6.95 (6H,m), 2.80 (12H,s)

^{13}C NMR ($CDCl_3$) : 145.46 (C), 144.15 (C), 137.53 (C), 136.43 (CH), 136.21 (C), 130.03(CH), 129.81 (CH), 129.06 (CH), 128.62 (CH), 127.58 (CH), 122.03 (C), 21.62 (CH_3)

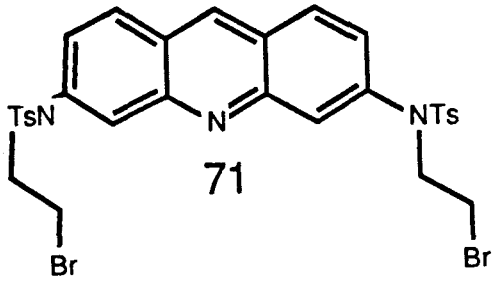
IR (CH_2Cl_2) ν max cm^{-1} : 1635 (vs), 1610 (s), 1375 (s), 1177 (vs)

NN - Ditoluenesulphonyl-3, 6-diaminoacridine (67)

Method 2:

Tetratoluenesulphonyl-3, 6-diaminoacridine (103) (4.0g, 4.85mmol) as a solution in dimethyl formamide:water (6:1) (50ml)

containing potassium carbonate (4.0g, 28.9mmol) was heated under reflux under an atmosphere of nitrogen. After 16 hours the solution was allowed to cool before being filtered. The filtrate was concentrated under reduced pressure yielding a red oil. Chromatography over silica gel with dichloromethane/ethylacetate (8:2) as eluant yielded NN' - ditoluenesulphonyl-3,6-diaminoacridine (67) 2.44mmol, 98%) as a red powder with physical properties identical to those listed under method 1.



71

NN'-Ditoluene sulphonyl-NN'-di(2-bromoethyl)-3,6-diaminoacridine (71)

To a stirred solution of NN'-ditoluene sulphonyl-3,6-diaminoacridine (67) (206mg, 0.40mmol) in dimethyl formamide (1.5ml) at room temperature under an atmosphere of nitrogen, was added 1,2-dibromoethane (750mg, 4.03mmol) and potassium carbonate (300mg, 2.17mmol). After 24 hours the mixture was filtered to remove inorganic solid, and the solvent removed under reduced pressure to yield the crude product (536mg). Chromatography over silica gel using a solvent gradient of dichloromethane to dichloromethane/ethyl acetate (8:2) as eluant, yielded

NN′-ditoluene sulphonyl-NN′-di(2-bromoethyl)-3, 6 diamino acridine (71) (251mg, 86%) as light yellow crystals.

mp 91-94°C (ethylacetate)

^{1}H NMR ($CDCl_3$, 360MHz) : 8.75 (1H,s), 8.00 (2H,d, J9Hz), 7.72 (2H,s) 7.58-7.46 (6H,complex) 7.25 (4H,m), 4.05 (4H,t, J7Hz), 3.48 (4H,t,J7Hz), 2.40 (6H,s)

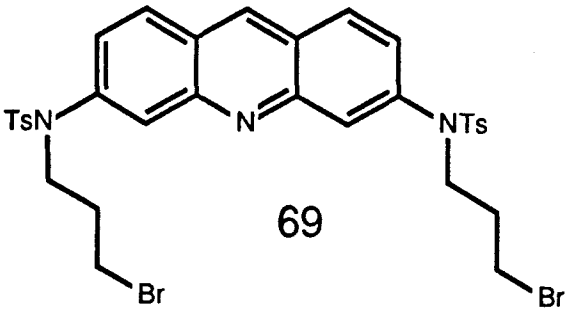
^{13}C NMR ($CDCl_3$) : 149.15 (C), 144.28 (C), 141.88 (C), 135.90 (CH), 135.00 (C), 129.86 (CH), 129.31 (CH), 128.21 (CH), 127.72 (CH), 126.97 (CH), 125.96 (C), 52.50 (CH_2), 29.86 (CH_2), 21.60 (CH_3)

IR (CH_2Cl_2) ν max cm^{-1} : 2980 (w), 1620 (m), 1600 (w), 1460 (m), 1360 (s)

Found : C, 51.2; H, 4.2; N, 5.5; S, 8.9%

$C_{31}H_{29}N_3Br_2O_4S_2$ requires C, 51.1; H, 4.0; N, 5.8; S, 8.8%

The following NN′-dialkylated-3, 6-diaminoacridines were prepared by analogous experimental procedures:



69

NN'-Ditoluene sulphonyl-NN'-di (3 bromopropyl)-3, 6-diamino acridine (69) as light yellow crystals in 47% yield from NN'-ditoluene sulphonyl proflavine (67) and 1,3-dibromo propane by stirring at room temperature for 24 hours.

mp 97-98°C (ether-dichloromethane-pentane)

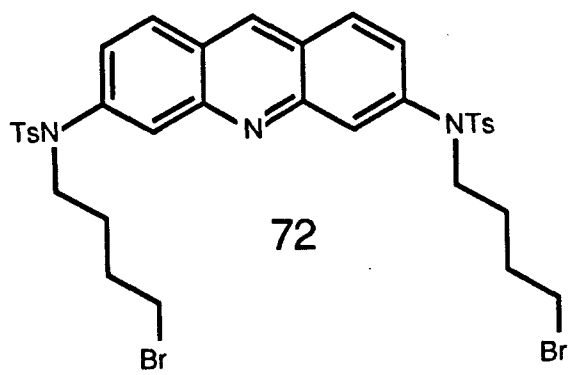
^{1}H NMR ($CDCl_3$, 360MHz) : 8.75 (1H,s), 8.02 (2H,d,J9Hz), 7.66 (2H,s), 7.55-7.42 (6H,m), 7.25 (4H,d,J9Hz), 3.81 (4H,t,J7Hz), 3.42 (4H,t,J7Hz), 2.39 (6H,s), 2.07 (4H,m)

^{13}C NMR ($CDCl_3$) : 149.24 (C), 144.09 (C), 142.00 (C), 135.79 (CH), 134.84 (C), 129.80 (CH), 129.12 (CH), 128.07 (CH), 127.80 (CH), 126.59 (CH), 125.86 (C), 49.21 (CH_2), 31.76 (CH_2), 29.73 (CH_2), 21.60 (CH_3)

IR (CH_2Cl_2) ν max cm^{-1} : 2950 (m), 1623 (m), 1613 (m), 1455 (m), 1362 (s)

Found : C, 52.2; H, 4.8; N, 5.0; S, 8.7%

$C_{33}H_{33}N_3Br_2O_4S_2$ requires C, 52.2; H, 4.4; N, 5.5; S, 8.4%



72

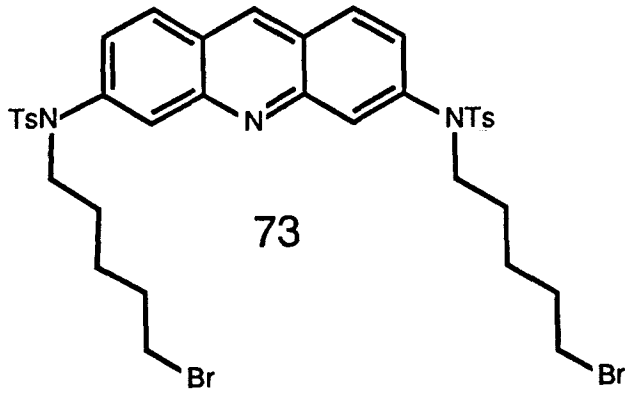
NN´-Ditoluene sulphonyl-NN´-di(4-bromobutyl)-3,6-diaminoacridine (72) as cream coloured crystals in 55% yield from NN´-ditoluene sulphonyl proflavine (67) and 1,4-dibromobutane by stirring at room temperature for 24 hours.

mp 167-168°C (dichloromethane-pentane)

^{1}H NMR ($CDCl_3$, 360MHz) : 8.78 (1H,s), 7.98 (2H,m), 7.64 (2H,s), 7.55-7.40 (6H,complex), 7.20 (4H,m), 3.70 (4H,t, J7Hz), 3.36 (4H,m), 2.39 (6H,s), 1.93 (4H,m), 1.61 (4H,m)

^{13}C NMR ($CDCl_3$) : 149.19 (C), 143.98 (C), 141.70 (C), 135.81 (CH), 134.92 (C), 129.77 (CH), 129.01 (CH), 128.30 (CH), 127.75 (CH), 126.39 (CH), 125.86 (C), 49.29 (CH_2), 32.88 (CH_2), 29.49 (CH_2), 26.51 (CH_2) 21.61 (CH_3)

IR (CH_2Cl_2) ν_{max} cm^{-1} : 2950 (w), 1620 (m), 1610 (w), 1460 (m), 1360 (s),



73

NN´-Ditoluene sulphonyl-NN´-di(5-bromopentyl)-3, 6-diaminoacridine (73)

as cream coloured crystals in 74% yield from NN' - ditoluene sulphonyl-3,6-diaminoacridine (67) and 1,5-dibromopentane by stirring at room temperature for 24 hours.

mp 148-149°C (ethyl acetate-ether)

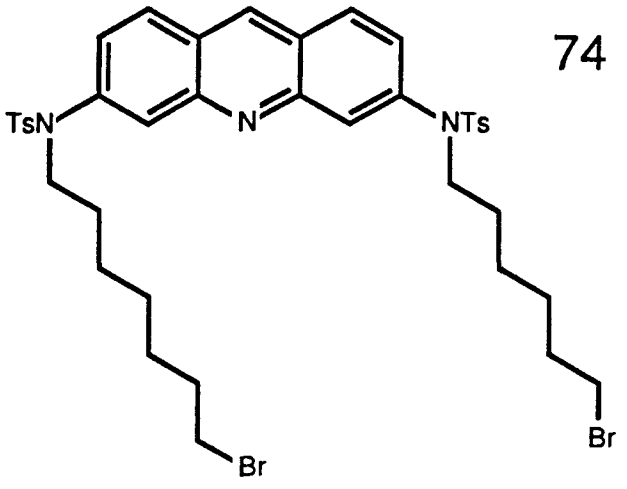
^{1}H NMR ($CDCl_3$, 360MHz) : 8.81 (1H,s), 8.02 (2H,d,J9Hz), 7.65 (2H,s), 7.58-7.45 (6H, complex), 7.23 (4H,m), 3.70 (4H,t,J7Hz), 3.32 (4H,t,J7Hz), 2.40 (6H,s), 1.79 (4H,m), 1.50 (8H,m).

^{13}C NMR ($CDCl_3$) : 149.02 (C), 143.74 (C), 141.83 (C), 135.67 (CH), 134.86 (C), 129.59 (CH), 128.83 (CH), 128.09 (CH), 127.55 (CH), 126.23 (CH), 125.64 (C), 49.91 (CH_2), 33.26 (CH_2), 32.01 (CH_2), 27.15 (CH_2), 24.96 (CH_2), 21.47 (CH_3) .

IR (CH_2Cl_2) ν max cm^{-1} : 2950 (w), 1620 (m), 1600 (w), 1430 (m), 1360 (m)

Found : C, 54.5; H, 5.0; N, 5.0; S, 7.6%

$C_{37}H_{41}N_3Br_2O_4S_2$ requires C, 54.5; H, 5.1; N, 5.2; S, 7.9%



74

NN'-Ditoluene sulphonyl-NN'-di(6-bromohexyl)-3,6-diaminoacridine (74) as a light yellow powder in 61% yield from NN'-ditoluene sulphonyl-3,6-diaminoacridine (67) and 1,6-dibromohexane by stirring at room temperature for 24 hours.

mp 143-144°C (ethyl acetate-pentane)

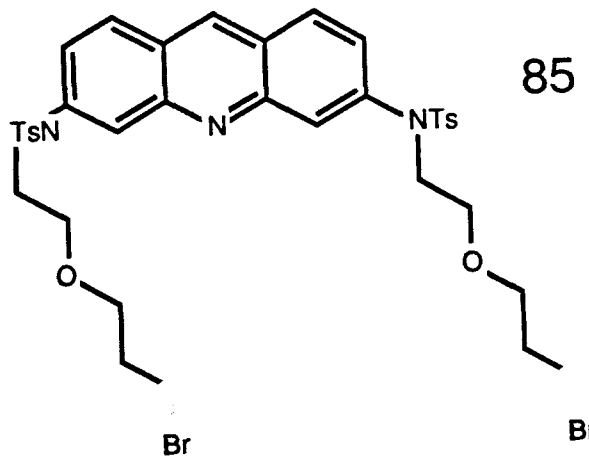
^{1}H NMR ($CDCl_3$, 270MHz) : 8.80 (1H,s), 8.00 (2H,d,J9Hz), 7.65 (2H,s), 7.60-7.42 (6H, complex), 7.22 (4H,m), 3.70 (4H,t,J7Hz), 3.34 (4H,t,J7Hz), 2.41 (6H,s), 1.77 (4H,m), 1.50-1.22 (12H,complex).

^{13}C NMR ($CDCl_3$) : 149.06 (C), 143.85 (C), 141.80 (C), 135.84 (CH), 134.68 (C), 129.72 (CH), 128.87 (CH), 128.53 (CH), 127.76 (CH), 125.97 (CH), 125.75 (CH), 50.04 (CH_2), 33.74 (CH_2), 32.60 (CH_2), 27.81 (CH_2), 27.65 (CH_2), 25.66 (CH_2), 21.68 (CH_3).

IR (CH_2Cl_2)) max cm^{-1} : 2950 (w), 1620 (m), 1600 (w), 1460 (m), 1350 (s)

Found : C, 55.7; H, 5.4; N, 4.7; S, 7.9%

$C_{39}H_{45}N_3Br_2O_4S_2$ requires C, 55.5; H, 5.4; N, 5.0; s, 7.6%



85

NN' - Ditoluene sulphonyl-NN' -di (5-bromo-3-oxapentyl)-3,6-diaminoacridine (85)

To a stirred solution of NN' -ditoluene sulphonyl-3,6-diaminoacridine (67) (300mg, 0.58mmol) in dimethyl formamide (2ml) at room temperature under an atmosphere of nitrogen were added 1,5-dibromo-3-oxapentane (3.4g, 15.4mmol) and potassium carbonate (400mg, 2.89mmol). After 24 hours the reaction mixture was added to water and extracted with dichloromethane. The extracts were washed with water before being dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded an oil (3.8g). Chromatography over silica gel using a solvent gradient of dichloromethane to dichloromethane/ethyl acetate (8:2) as eluant yielded NN' -ditoluene sulphonyl-N,N' -di (5-bromo-3-oxapentyl)-3,6-diaminoacridine (85) (367mg, 77%) as cream coloured needles.

mp 149-150°C (diethyl ether-pentane)

^1H NMR (360MH_3, $CDCl_3$) : 8.75 (1H,s), 7.96 (2H,d,J9Hz), 7.71 (2H,s), 7.60-7.45 (6H,complex), 7.23 (4H,m), 3.90 (4H,t,J5.7Hz), 3.65 (8m,m), 3.30 (4H,t,J5.9Hz), 2.38 (6H,s),

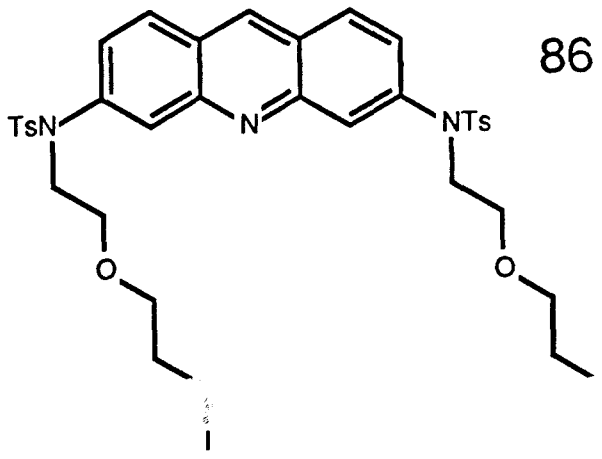
^{13}C NMR ($CDCl_3$) : 149.21 (C), 143.94 (C), 142.37 (C), 135.64 (CH), 129.74 (CH), 128.93 (CH), 128.33 (CH), 127.74 (CH), 126.90 (CH),

125.82 (C), 70.99 (CH_2), 69.03 (CH_2), 50.53 (CH_2), 30.04 (CH_2), 21.58 (CH_3).

IR (CH_2Cl_2) ν_{max} cm^{-1} : 2890 (w), 1920 (w), 1820 (w), 1630 (s), 1460 (s), 1360 (vs)

Found : C, 51.3; H, 4.5; N, 5.0; S, 8.0%

$C_{35}H_{27}N_3Br_2O_6S_2$ requires C,51.4; H, 4.6; N, 5.1; S, 7.8%



86

NN'-Ditoluene sulphonyl-NN'-di(5-iodo-3-oxapentyl)-3,6-diamino acridine (86) as light yellow crystals in 47% yield from NN'-ditoluene sulphonyl-3,6-diaminoacridine (67) and 1,5-diiodo-3-oxapentane by stirring at room temperature for 16 hours.

mp 147-148°C (ether-dichloromethane-pentane)

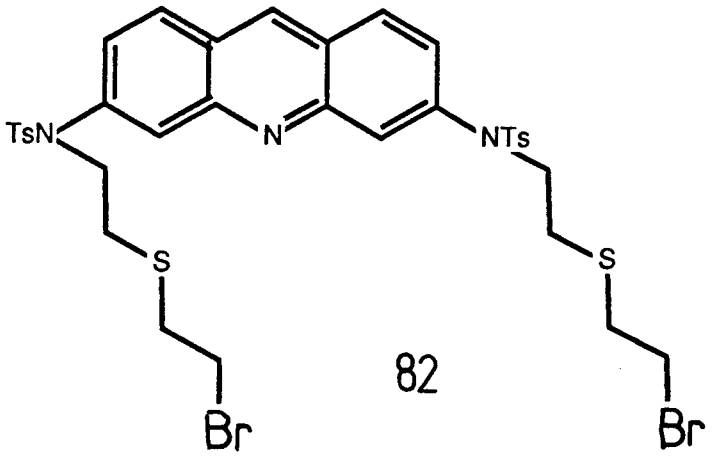
^1H NMR ($CDCl_3$, 360MHz) : 8.78 (1H,s), 7.99 (2H,d,J9Hz), 7.73 (2H,s), 7.57-7.50 (6H,complex), 7.24 (4H,m), 3.90 (4H,t,J5.8Hz), 3.68-3.57 (8H,complex), 3.08 (4H,t, J6.7Hz), 2.40 (6H,s)

^{13}C NMR ($CDCl_3$) : 149.07 (C), 143.83 (C), 142.21 (C), 135.59 (CH), 135.22 (C), 129.65 (CH), 128.87 (CH), 128.21 (CH), 127.62 (CH), 126.75 (CH), 125.70 (C), 71.56 (CH_2), 68.56 (CH_2), 50.42 (CH_2), 21.53 (CH_3), 2.43 (CH_2I).

IR (CH_2Cl_2)) max cm^{-1}: 2890 (w), 1930 (w), 1730 (w), 1620 (m). 1605 (m), 1455 (s),

Found : C, 45.7; H, 4.0: N, 4.4; S, 7.0%

$C_{35}H_{37}N_3I_2O_6S_2$ requires C, 46.0; H, 4.1; N, 4.6; S, 7.0%



82

NN´-Ditoluene sulphonyl-NN´-di (5-bromo-3-thiapentyl)-3,6-diaminoacridine (82) as light orange crystals in 48% yield from NN´-ditoluene sulphonyl proflavine (67) and 1,5-dibromo-3-thiapentane by stirring at room temperature for 24 hours.

mp 155-157°C (dichloromethane-pentane)

^1H NMR($CDCl_3$, 360MHz) : 8.80 (1H,s), 8.05 (2H,m), 7.75-7.46 (8H, complex), 7.20 (4H,m),

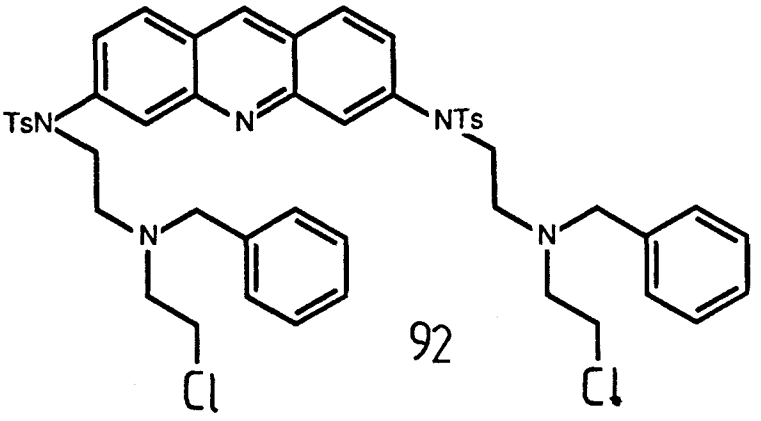
3.74 (4H,t,J7.3Hz), 3.38 (4H,m),
2.90 (4H,m), 2.74 (4H,t,J7.1Hz),
2.40 (6H,s),

^{13}C NMR ($CDCl_3$) : 149.10 (C), 144.18 (C), 141.88 (C), 135.90 (C), 134.97 (CH), 129.84 (CH), 129.19 (CH), 128.27 (CH), 127.69 (CH), 125.49 (CH), 124.87 (C), 50.76 (CH_2), 34.30 (CH_2), 31.19 (CH_2), 30.32 (CH_2), 21.61 (CH_3)

IR (CH_2Cl_2) ν max cm^{-1} : 2950 (w), 1620 (m), 1455 (m), 1360 (s), 1170 (vs)

Found : C, 49.3; H, 4.3; N, 4.9; S, 15.4%

$C_{35}H_{37}N_3Br_2O_4S_4$ requires C, 49.2; H, 4.6; N, 4.9; S, 15.0%



92

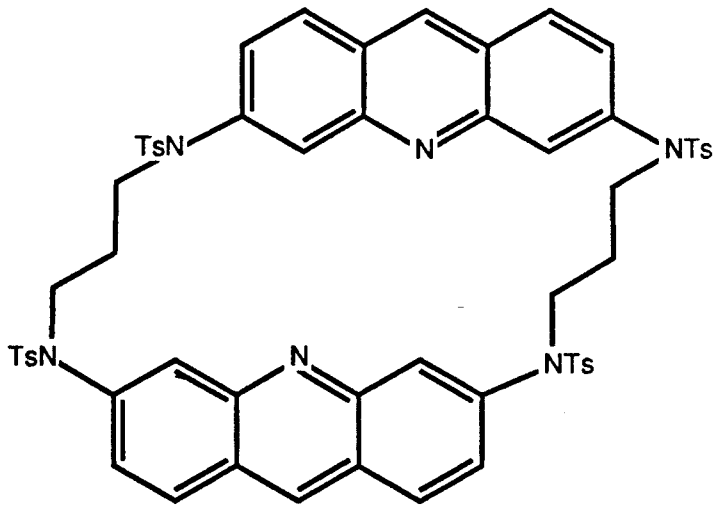
NN´-Ditoluene sulphonyl-NN´-di(5-chloro-3-(N-benzyl) azapentyl)-3-6-diaminoacridine (92) as a light yellow oil in 28% yield from NN-ditoluene sulphonyl-3,6-diaminoacridine (67) and NN-di(2-chloroethyl) benzylamine (91) by stirring at room temperature for 24 hours.

^{1}H NMR ($CDCl_3$, 360MHz) : 8.76 (1H,s), 7.94 (2H,m), 7.60 (2H,s), 7.52 (2H,d,J8.8Hz), 7.42 (4H,m), 7.34-7.03 (14H,complex), 3.75 (4H,t,J7.0Hz), 3.61 (4H,s), 3.35 (4H,t,J7.0Hz), 2.78 (8H,m), 2.37 (6H,s),

^{13}C NMR ($CDCl_3$) : 143.95 (C), 142.39 (C), 138.82 (C), 135.63 (CH), 135.00 (C), 129.78 (CH), 129.03 (C), 128.80 (CH), 128.51 (CH), 128.44 (CH), 128.37 (CH), 127.77 (CH), 127.23 (CH), 126.14 (CH), 125.78 (C), 56.26 (CH_2), 53.14 (CH_2), 49.11 (CH_2), 41.89 (CH_2), 21.64 (CH_3).

IR (CH_2Cl_2) ν_{max} cm^{-1} 2950 (w), 1620 (m), 1500 (w), 1460 (m), 1360 (s)

1,5,20,24 - Tetraaza - 1,5,20,24-tetratoluene sulphonyl(5,5)-3,6-acridinophane (70)



70

A solution of NN′-ditoluene sulphonyl-NN′-di(3-bromo propyl)- 3,6 -diaminoacridine (69) (111mg, 0.146mmol) in dimethyl formamide (15ml) was stirred with NN′-ditoluene sulphonyl-3,6-diaminoacridine (67) (75mg, 0.15mmol) and potassium carbonate (100mg, 0.13mmol) at 60°C under an atmosphere of nitrogen. After 16 hours the mixture was filtered, and the solvent removed under reduced pressure to yield an oil. Chromatography over silica gel with dichloromethane/ethyl acetate (97:3) as eluant yielded 1,5,20,24-tetraaza-1,5,20,24-tetratoluene sulphonyl (5,5) (3,6) acridinophane (70) (99mg, 59%) as an off white solid.

mp 305-308°C (dec.) (methanol-ether-ethylacetate)

^{1}H NMR (DMSO-d_6, 360MHz) : 8.59 (2H,s), 7.76 (4H,d,J9Hz), 7.41-7.30 (16H,complex), 7.11 (4H,s), 7.02 (4H,m), 3.72 (8H,t,J7Hz), 2.34 (12H,s), 1.66 (4H, quintet z)

^{13}C NMR (DMSO-d_6) : 147.19 (C), 143.61 (C), 139.80 (C), 135.35 (CH), 134.53 (C), 129.63 (CH), 129.19 (CH), 127.11 (CH), 126.28 (CH), 126.15 (CH), 124.06 (C), 46.56 (CH_2), 25.93 (CH_2), 20.83 (CH_3)

IR (KBr press)ν_{max} cm^{-1} : 2950 (m), 1630 (s), 1465 (s), 1360 (vs), 1175 (vs)

MS (FAB,3-nitrobenzyl alcohol matrix) : 1115 (MH^+, 100%)

961(MH_2^+ - $SO_2C_6H_4Me$, 44%)

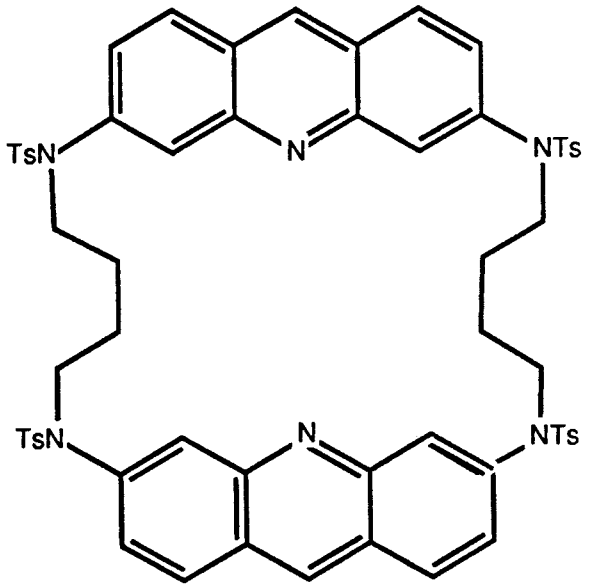
805(MH^+-$2SO_2C_6H_4Me$, 55%)

Found : C, 63.4; H, 4.9: N, 7.1; S, 11.1%

$C_{60}H_{54}N_6O_8S_4$ H_2O requires C,63.6; H, 5.0; N, 7.4; S,11.3%

The following acridinophanes were prepared by analogous experimental procedures.

1,6,21,26 - Tetraaza - 1,6,21,26-tetratoluene sulphonyl (6,6) - 3,6- acridinophane (75)



75

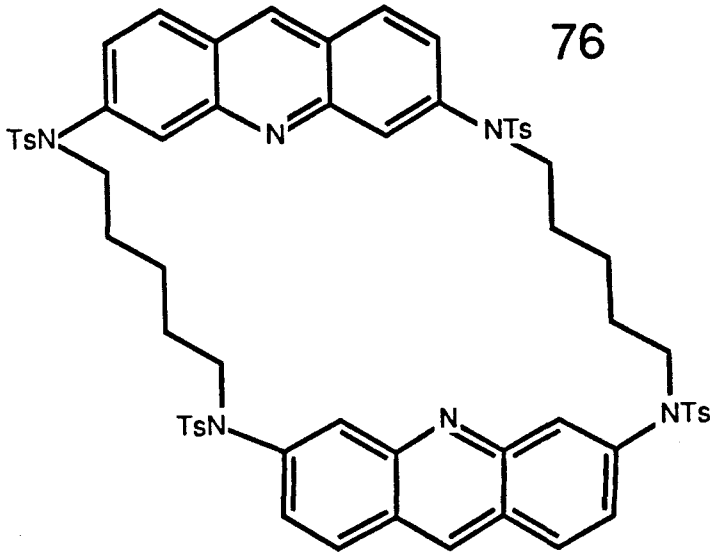
as an off white solid in 40% yield from NN′-ditoluene sulphonyl-NN′-di(4-bromobutyl)-3,6-diaminoacridine (72) and NN′-ditoluene sulphonyl-3,6-diaminoacridine (67), by stirring at room temperature for 24 hours.

mp 300-302°C (dec) (acetonitrile)

^{1}H NMR (DMSO-d_6, 360MHz) : 9.05 (2H,s), 8.07 (4H,d,J9.1Hz), 7.45-7.10 (24H,complex), 3.66 (8H,t,J7.0Hz), 2.32 (12H,s), 1.42 (8H,m).

^{13}C NMR (DMSO-d_6) : 147.92 (C), 143.50 (C), 140.71 (C), 135.90 (CH), 134.72 (C), 129.98 (CH), 129.14 (CH), 127.03 (CH), 126.17 (CH), 126.09 (CH), 124.70 (C), 48.68 (CH_2) 25.10 (CH_2), 20.80 (CH_3)

IR (CH_2Cl_2) max cm^{-1} : 2950 (w), 1630 (m), 1465 (m), 1361 (s), 1178 (vs).



76

1,7,22,28-Tetraaza - 1,7,22,28-tetratoluene sulphonyl (7,7) -3, 6-acridinophane (76) as a cream coloured powder in 32% yield from NN´-ditoluene sulphonyl-NN´-di(5-bromopentyl)-3,6-diaminoacridine (73) and NN´-ditoluene sulphonyl-3,6-

diaminoacridine (67), by stirring at room temperature for 24 hours.

mp 176-179°C (acetonitrile)

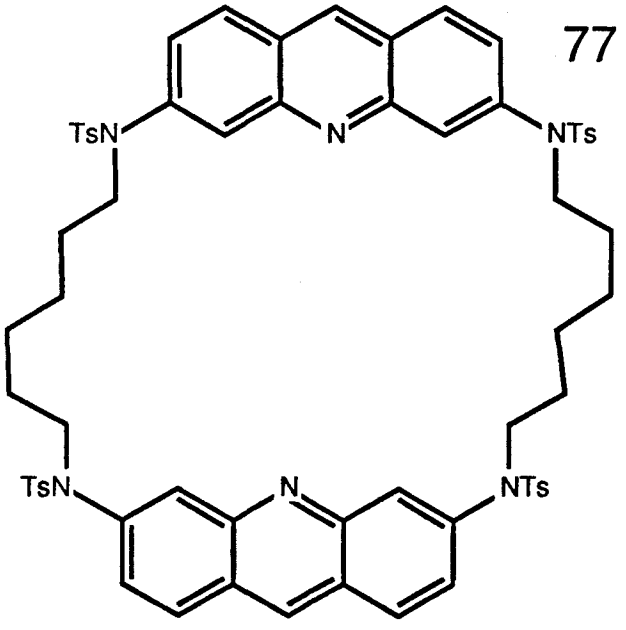
^{1}H NMR (DMSO-d_6, 360MHz) : 8.94 (2H,s), 8.01 (4h,d,J9Hz), 7.51-7.21 (24H, complex), 3.65 (8H,t,J7.1Hz), 2.35 (12H,s), 1.30 (4H,m), 1.21 (8H,m),

^{13}C NMR (DMSO-d_6) : 148 (C), 143 (C), 140 (C), 135 (CH), 134 (C), 130 (CH), 129 (CH), 127 (CH), 126 (CH), 125 (CH), 124 (C), 49 (CH_2), 27 (CH_2), 23 (CH_2), 20 (CH_3) .

IR (CH_2Cl_2) νmax cm^{-1} : 2950 (w), 1618 (m), 1460 (m), 1361 (s), 1179 (vs)

Found : C, 64.8; H, 5.7; N, 6.7; S, 10.7%

$C_{64}H_{62}N_6O_8S_4.H_2O$ requires C,64.6; H, 5.4; N, 7.1; S, 10.8%



77

1,8,23,30 - Tetraaza - 1,8,23,30 - tetra toluene sulphonyl (8,8) -3,6-diaminoacridinophane (77) as a cream coloured solid in 18% yield from NN'-ditoluene sulphonyl-NN'-di(6-bromohexyl)3,6-diamino acridine (74) and NN'-ditoluene sulphonyl-3,6-diaminoacridine (67), by stirring at room temperature for 24 hours.

mp 172-174°C (acetonitrile)

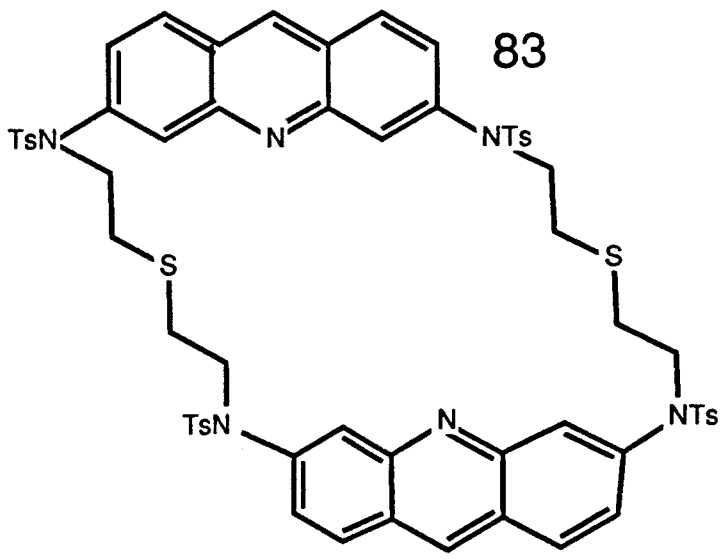
^{1}H NMR (DMSO-d_6, 360MHz) : 9.06 (2H,s), 8.11 (4H,d,J9z), 7.60-7.20 (24H, complex), 3.62 (8H,t,J7.2Hz), 2.30 (12H,s), 1.25-1.10 (16H, complex).

^{13}C NMR (DMSO-d_6) : 148.14 (C), 143.43 (C), 140.63 (C), 135.75 (CH), 134.60 (C), 129.56 (CH), 128.93 (CH), 127.01 (CH), 126.34 (CH), 125.64 (C), 124.67 (CH), 49.25 (CH_2), 27.27 (CH_2), 25.60 (CH_2), 20.77 (CH_3).

IR (CH_2Cl_2) max cm^{-1} : 2950 (w), 1626 (m), 1458 (m), 1359 (s), 1172 (vs).

Found : C,66.3; H, 5.9; N, 6.5; S, 10.4%

$C_{66}H_{66}N_6O_8S_4$ requires C, 66.1; H, 5.6; N, 7.0; S, 10.7%



1,7,22,28-Tetraaza-1,7,22,28-tetratoluene sulphonyl-4,25,-dithia (7,7)-3,6-acridinophane (83) as a light yellow solid in 27% yield from NN′-ditoluene sulphonyl-NN′-di(5-bromo-3-thiapentyl)-3,6-diaminoacridine (82) and NN′-ditoluene sulphonyl-3,6-diaminoacridine (67) by stirring at room temperature for 4 days.

mp 249-251°C (dichloromethane-pentane)

^{1}H NMR (DMSO-d_6, 270MHz) : 8.95 (2H,s), 8.05 (4H,d,J9.8Hz), 7.42-7.30 (24H, complex), 3.75 (8H,t,J6.7Hz), 2.48 (8H,t,J6.7Hz), 2.36 (12H,s).

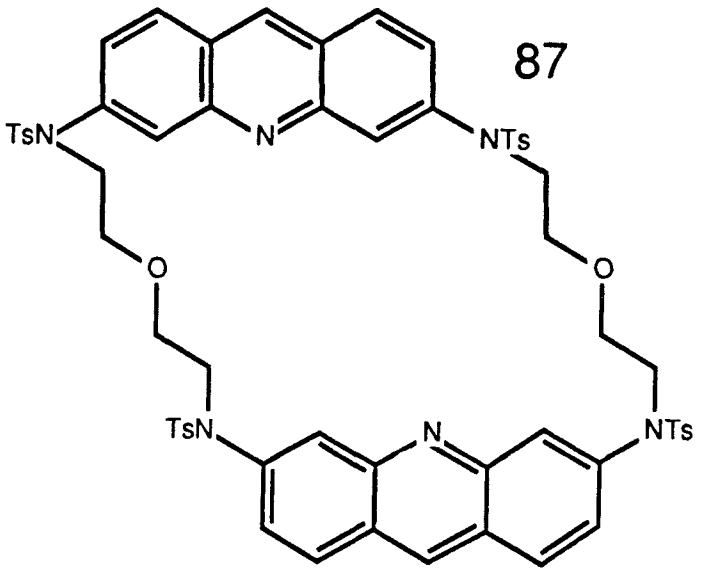
^{13}C NMR (DMSO-d_6) : 147.80 (C), 143.80 (C), 140.63 (C), 135.99 (C), 134.26 (CH), 129.80 (CH), 129.27 (CH), 127.24 (CH), 126.66 (CH), 125.71 (CH), 124.53 (C), 50.14 (CH_2), 30.78 (CH_2), 21.01 (CH_3).

IR (CH_2Cl_2) max cm^{-1} : 2980 (w), 1625 (w), 1599 (w), 1450 (m), 1372 (s), 1170 (vs)

MS (FAB,3-Nitrobenzyl alcohol matrix): 1207 (MH^+, 100%), 1051 (37%), 979 (9%), 897 (38%).

Found : C, 61.5; H, 4.8; N, 6.8; S, 15.8%

$C_{62}H_{58}N_6O_8S_6$ requires C, 61.7; H, 4.8; N, 7.0; S, 16.0%



1,7,22,28-Tetraaza-1,7,22,28-tetratoluene sulphonyl-4,25-dioxa-(7,7)-3,6-acridinophane (87) as a cream coloured solid in 9% yield from NN´-ditoluene sulphonyl-NN´-di (5-iodo-3-oxapentyl) -3,6-diaminoacridine and NN´-ditoluene sulphonyl 3,6-diamino acridine (67) by stirring at room temperature for 4 days.

mp 308-309°C (acetonitrile-ether)

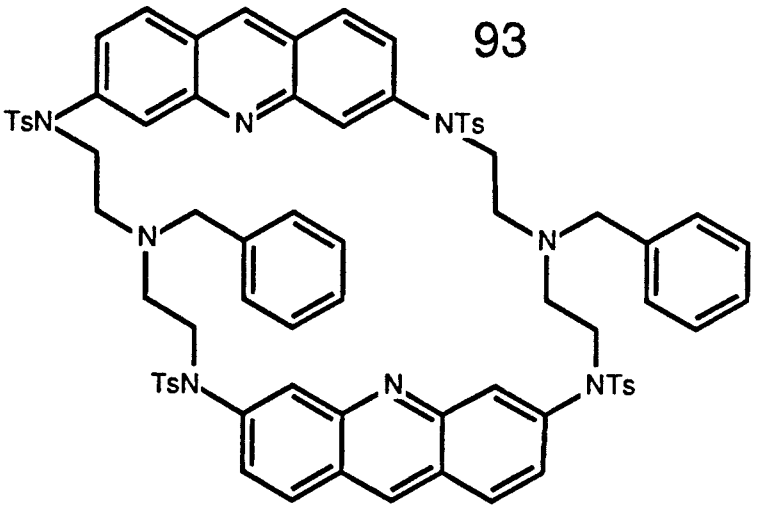
^{1}H NMR (DMSO-d_6, 360MHz) : 8.70 (2H,s), 7.98 (4H,d,J9Hz), 7.42 (8H,m), 7.34 (8H,m), 7.22 (8H,m), 3.75 (8H,t,J5.1Hz), 3.28 (8H,t,5.1Hz), 2.36 (12H,s).

^{13}C NMR (DMSO-d_6) : 147.7 (C), 143.5 (C), 140.7 (C), 135.6 (CH), 134.7 (C), 129.6 (CH), 128.9 (CH), 127.0 (CH), 126.2 (CH), 125.9 (CH), 124.3 (C), 67.9 (CH_2), 49.7 (CH_2), 20.8 (CH_3).

IR (CH_2Cl_2) ν max cm^{-1} : 2950 (w), 1700 (m), 1610 (m), 1390 (s), 1280 (s)

Found : C, 62.5; H, 4.9; N, 6.9%

$C_{62}H_{58}N_6O_{10}S_4$ H_2O requires C, 62.4; H, 5.1; N, 7.0%



1,4,7,22,25,28-Hexaaza-1,7,22,28-tetratoluene sulphonyl-4,25-dibenzyl (7,7)-3,6-acridinophane (93)

To a stirred solution of NN´-ditoluene sulphonyl-NN´-di (5-chloro-3-(N benzyl)azapentyl)-3,6-diaminoacridine (92) (78mg, 0.086mmol) and NN´-ditoluene sulphonyl-3,6-diaminoacridine (67) (48mg, 0.094mmol) in dimethyl formamide (10ml) at 60°C under an atmosphere of nitrogen, were added anhydrous potassium carbonate (87mg, 0.63mmol) and anhydrous potassium iodide (31mg, 0.19mmol). After 16 hours the solution was allowed to cool before the solvent was removed under reduced pressure. The resultant solid was thoroughly triturated with dichloromethane. The extracts

were filtered and the solvents removed under reduced pressure, yielding the crude product. Chromatography over silica gel with dichloromethane/ethyl acetate (8:2) as eluant yielded 1,4,7,22,25,28-hexaaza-1,7,22,28-tetratoluene sulphonyl-4, 25-dibenzyl (7,7)-3,6-acridinophane (93) (60mg, 52%) as pale orange crystals.

mp 145-147°C (dichloromethane-ether)

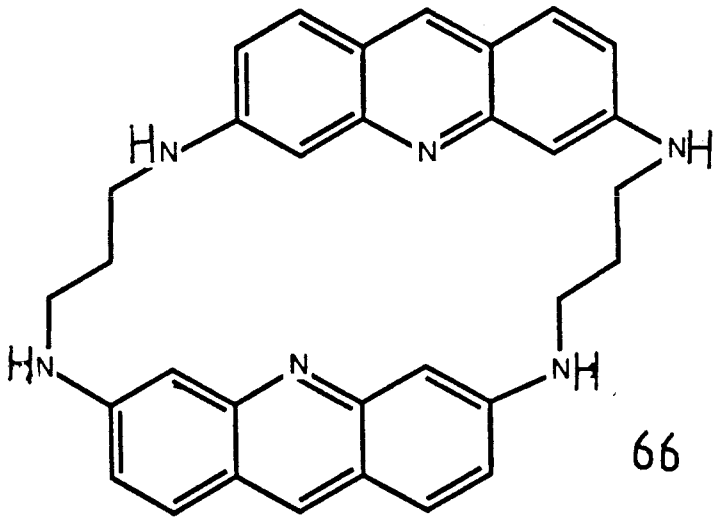
^{1}H NMR ($CDCl_3$, 360MHz) : 8.40 (2H,s), 7.70(4H,d,J9.1Hz), 7.41-7.24 (28H, complex), 7.22-7.10 (6H, complex), 3.84 (4H,s), 3.50 (8H,t,J6.4Hz), 2.56 (8H,t,J6.4Hz), 2.37 (12H,s)

^{13}C NMR ($CDCl_3$) : 148.63 (C), 143.87 (C), 141.64 (C), 139.16 (C), 135.02 (CH), 134.82 (C), 129.72 (CH), 129.06 (CH), 128.52 (CH), 128.38 (CH), 128.19 (CH), 127.67 (CH), 125.61 (CH), 125.11 (C), 56.91 (CH_2), 53.30 (CH_2), 48.34 (CH_2), 21.62 (CH_3) .

IR (CH_2Cl_2) ν max cm^{-1} : 2950 (w), 1700 (w), 1610 (m), 1350 (s), 1175 (vs) .

Found : C, 66.7; H, 5.3; N, 8.1

$C_{76}H_{72}N_8O_8S_4$ H_2O requires C, 66.6; H, 5.4; N, 8.2



66

1,5,20,24-Tetraaza (5,5)-3,6-acridinophane (66). To a stirred solution of 1,5,20,24-tetraaza-1,5,20,24-tetratoluene sulphonyl (5,5)-3,6-acridinophane (70) (54mg, 0.048mmol) in glacial acetic acid (1.5ml) at room temperature under an atmosphere of nitrogen was added aqueous perchloric acid (70%, 3ml). The mixture was heated to 80°C, and the solid dissolved to give an orange brown solution. After 1 hour the solution was added to ice water, and the resulting mixture was made neutral with sodium hydroxide solution (25%). The precipitate was collected, washed with water and dried to yield 1,5,20,24-tetraaza (5,5)-3,6-acridinophane (66) (24mg, 100%) as an orange powder.

mp 309-311°C (dec.) (methanol)

^{1}H NMR (DMSO-d_6, 360MHz) : 8.70 (2H,s), 8.20-7.60 (6H,m), 7.10-6.55 (6H,m), 3.40 (8H,m), 1.93 (4H,m)

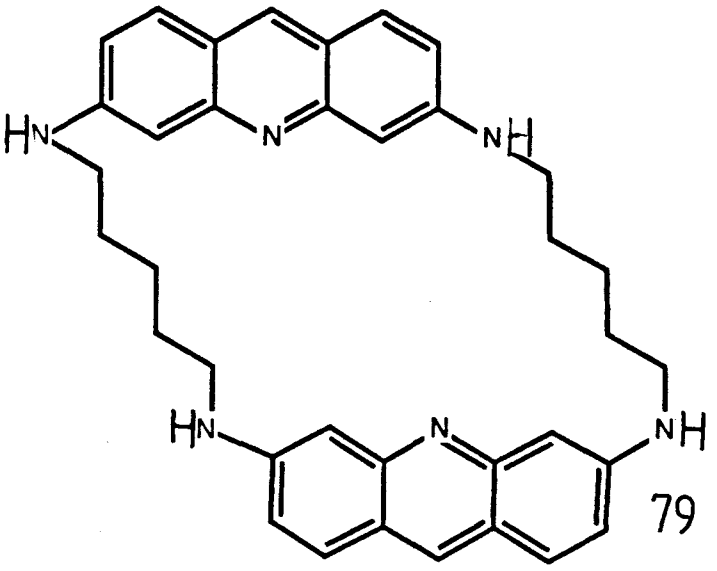
^{13}C NMR (DMSO-d_6) : 154.25 (C), 142.37 (C), 141.89 (C), 130.69 (CH), 118.14 (CH), 116.37 (CH), 89.59 (CH), 38.82 (CH_2), 29.21 (CH_2)

IR (KBr press) ν max cm^{-1} : 3500-3200 (broad), 2950 (w), 1655 (vs), 1618 (s), 1540 (m)

MS (FAB, glycerol-thioglycerol-trifluoroacetic acid matrix):

499(MH^+, 5%), 309(10%), 293(10%)

The following acridinophane was also prepared by an analogous experimental procedure:



79

1,7,22,28-Tetraaza (7,7)-3,6-acridinophane (79) as an orange powder in 98% yield from 1,7,22,28-tetraaza-1,7,22,28-tetra toluene sulphonyl (7,7)-3,6-acridinophane (76) at 80°C for 1 hour.

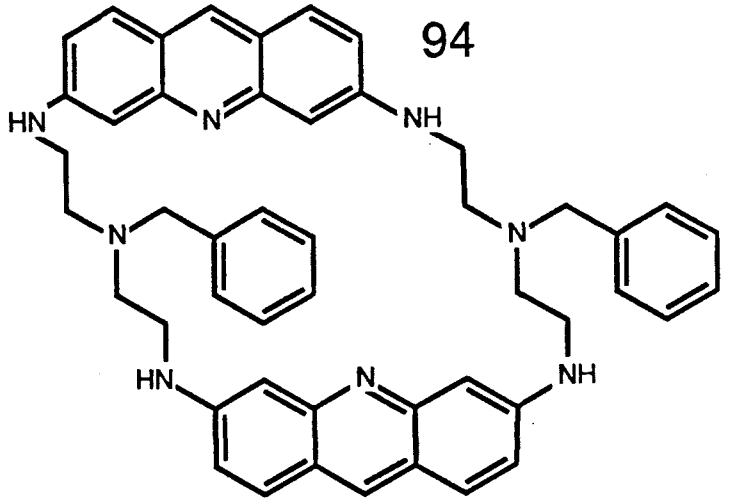
mp 266-268°C (dec.) (methanol)

^{1}H NMR (DMSO-d_6, 360MHz) : 8.32 2H,s), 7.60 (4H,m), 6.90-6.55 (8H,m), 3.25 (8H,m), 1.64 (8H,m), 1.43 (4H,m)

^{13}C NMR (DMSO-d_6) : 150.16 (C), 149.28 (C), 135.71 (C), 129.12 (CH), 118.06 (CH), 117.74 (CH), 96.62 (CH), 42.53 (CH_2), 27.70 (CH_2), 24.22 (CH_2).

IR (KBr press) ν max cm^{-1} : 3500-3200 (broad), 2950 (w), 1655 (s), 1618 (vs), 1550 (s)

MS (FAB, Glycerol - thio glycerol - trifluoroacetic acid matrix): 555 (MH^+, 8%), 307 (4%), 277 (9%)



94

1,4,7,22,25,28-Hexaaza-4,25-dibenzyl-(7,7)-3,6-acridinophane (94).

1,4,7,22,25,28-Hexaaza-1,7,22,28-tetratoluene sulphonyl-4,25-dibenzyl (7,7)-3,6-acridinophane (93) (126mg, 0.9mmol) was stirred in sulphuric acid (98%, 2.5ml) under an atmosphere of nitrogen, and warmed to 60°C. After 6 hours the brown mixture

was added dropwise to ice water and rendered basic with aqueous sodium hydroxide (10%). The resulting orange solid was collected and dried. Recrystallisation from acetonitrile yielded 1,4,7,22,25,28-hexaaza-4,25-dibenzyl (7,7)-3,6-acridinophane (94) (48mg, 70%) as an orange powder.

mp 235-236°C (dec.) (acetonitrile)

^{1}H NMR (DMSO-d_6, 360MHz) : 8.30 (2H,s), 7.83-7.05 (16H,complex), 6.85-6.50 (6H,complex), 3.71 (4H,s), 3.29 (8H,m), 2.79 (8H,m),

^{13}C NMR (DMSO-d_6) : 150.28 (C), 139.30 (C), 134.45 (C), 129.17 (CH), 128.61 (CH), 128.03 (CH), 126.74 (CH), 118.26 (C), 117.92 (CH), 117.72 (CH), 102.93 (CH), 58.71 (CH_2), 52.23 (CH_2), 41.11 (CH_2)

IR (Nujol) ν_{max} cm^{-1} : 1650 (m), 1621 (m), 1210 (s), 1180 (s)

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PART TWO

NATURALLY OCCURRING IONOPHORES

C H A P T E R
F I V E

INTRODUCTION

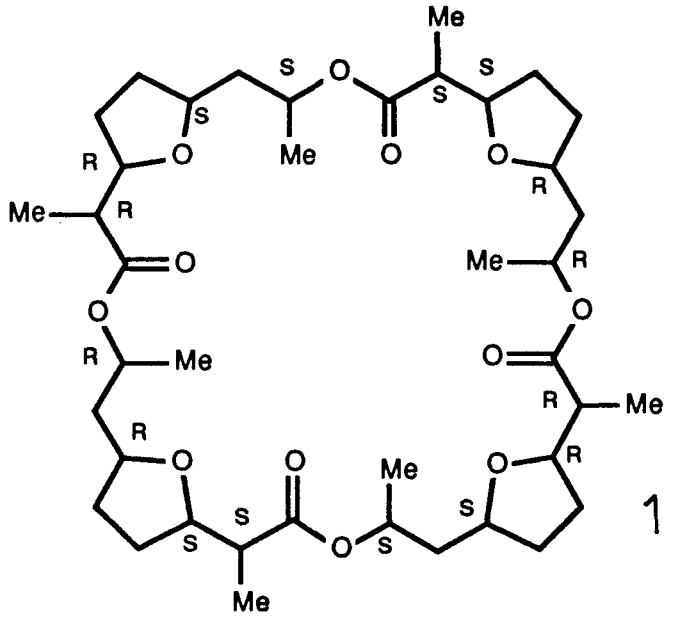
5.1 Naturally Occurring Ionophores

Naturally occurring ionophores are compounds found in nature, capable of forming stable complexes with metal ions. They can generally be divided into three groups of structurally related systems.

5.1.1 Macrotetrolides

The macrotetrolides are a group of cyclic neutral molecules containing the same basic ring structure. Nonactin (1) is a cyclic tetramer of both enantiomers of nonactic acid (2) alternating (+) (-) (+) (-) around the ring.[1]

Nonactin



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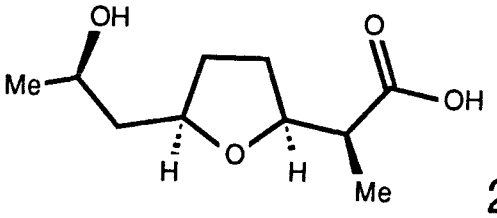
Nonactin forms stable complexes with the physiologically important alkali metal ions Na^+ and K^+, and exhibits antiobiotic

effects by acting as a transmembrane ion carrier[2].



+Nonactic Acid

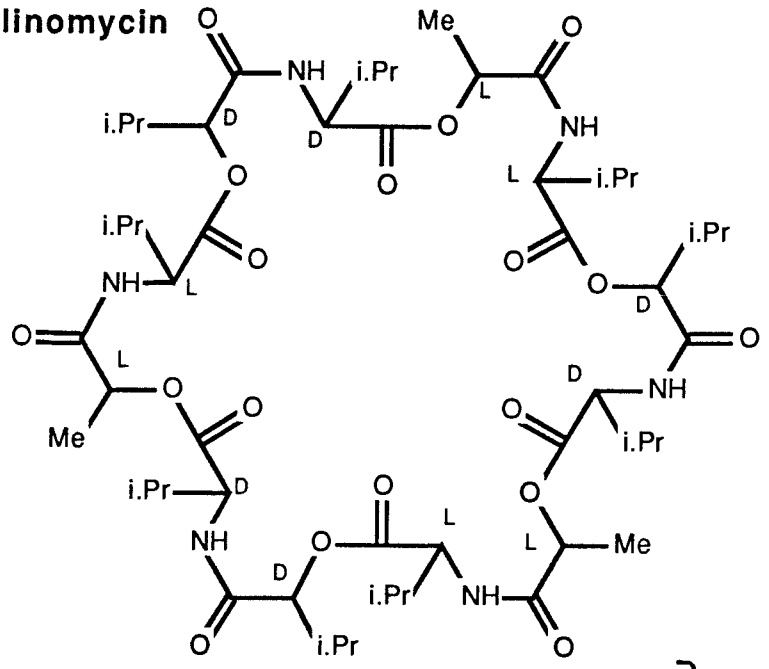
2

Antibiotic action is an effect common to many naturally occurring ionophores.

5.1.2 Cyclic Peptides

A number of cyclic peptides have been found to act as ion carriers, for example the cyclic dodecadepsipeptide, valinomycin (3)[3] is a highly selective ionophore for the potassium ion[4]. The molecule is capable of encapsulating a cation in a central cavity of restricted dimensions, by forming a bracelet-like conformation shown schematically as (4). The complex is held together by hydrogen bonding between amide protons and carbonyl groups around the macrocycle[5]. The valinomycin potassium salt has a highly lipophilic exterior which is capable of passing through cell walls.

Valinomycin



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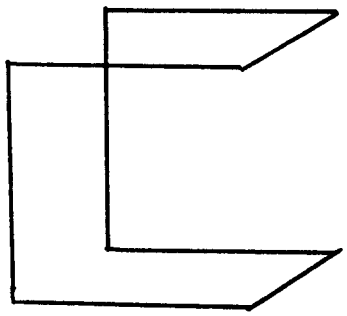

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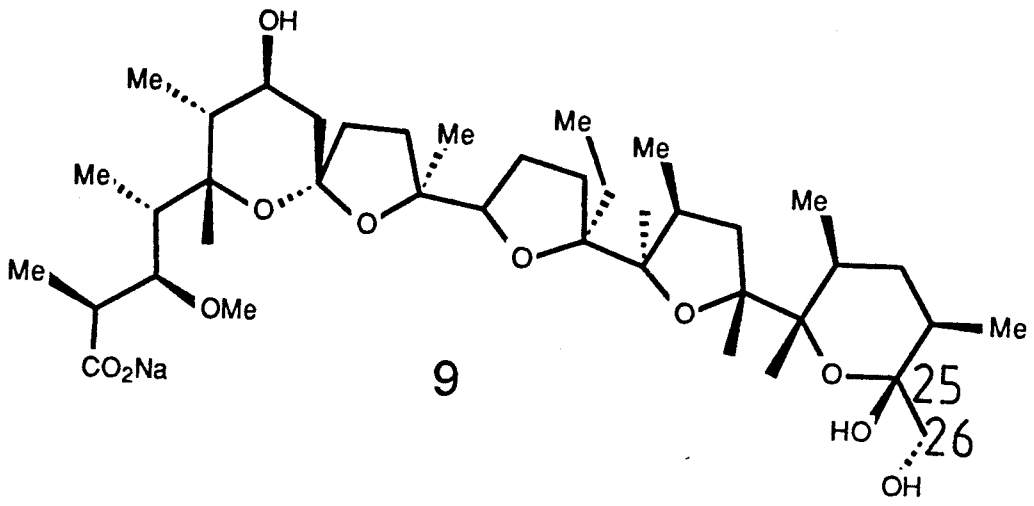
Other cyclic peptides have been found to act as ionophores, for example the enniatins and beauvericin, but none are as selective or form such highly stable complexes as valinomycin[6].

5.1.3 The Polyether Antibiotics

The polyether antibiotics are a large class of naturally occurring ionophores[7]. Members of this group include lasalocid (5)[8], dianemycin (6)[9], grisorixin(7)[10] and lysocellin (8)[11]. These molecules are all capable of forming complexes with alkali and alkaline earth metal ions, and Na^+ and K^+ in particular. They do so by forming pseudocyclic structures held together by hydrogen bonding between the ionised carboxylate function at one end of the molecule, and a hydroxyl group at the other. The central metal ion is then surrounded by co-ordinating oxygen functionality while the exterior of the complex is predominantly lipophilic in character. Thus the antibiotics themselves and their metal salts are rather insoluble in water but highly soluble in non polar organic solvents.

5.2 Monensin

Monensin A (9) is an important polyether antibiotic isolated from cultures of streptomyces cinnamonensis[12]. It was found to form stable metal salts, and has found veterinary applications, along with lasalocid (5), as an agent for the control of coccidosis in poultry and to improve feed utilisation in ruminant livestock[7].



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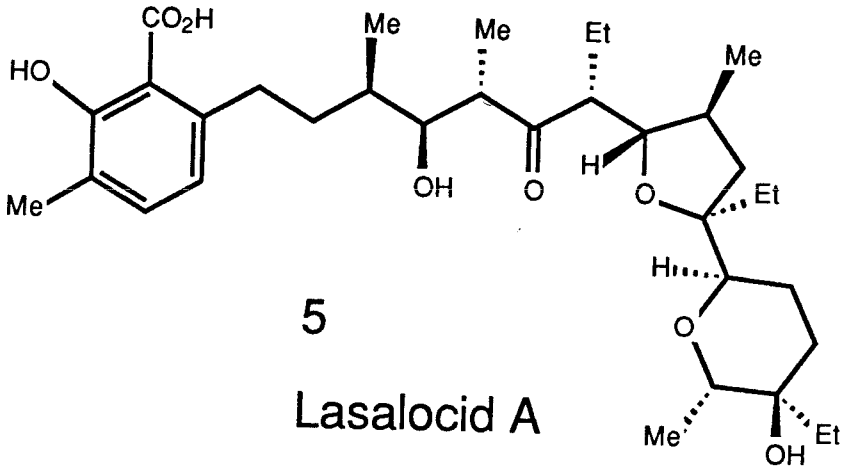

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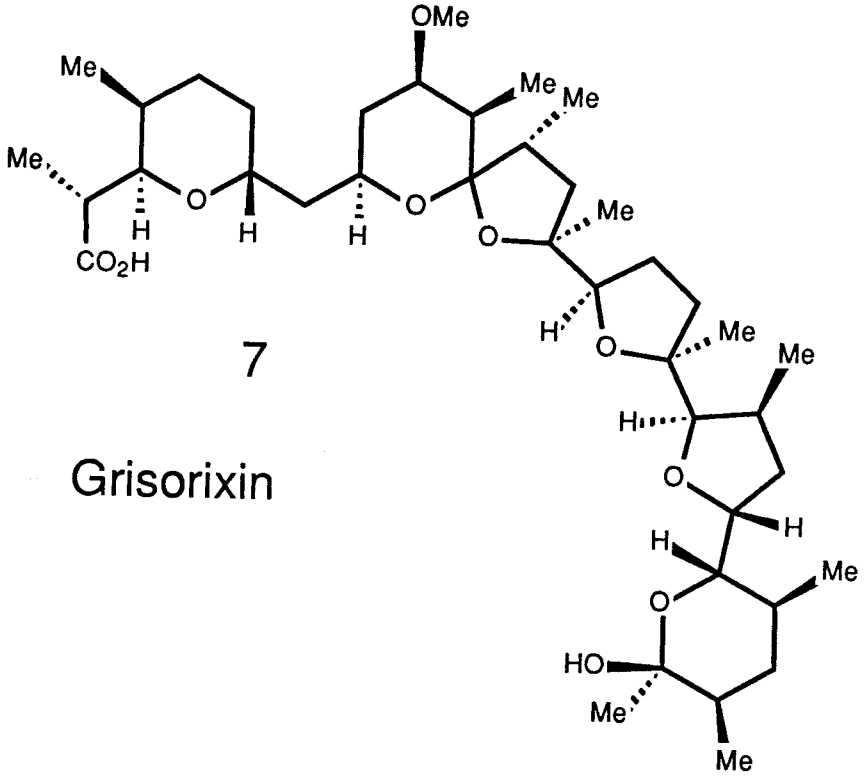
Lasalocid A



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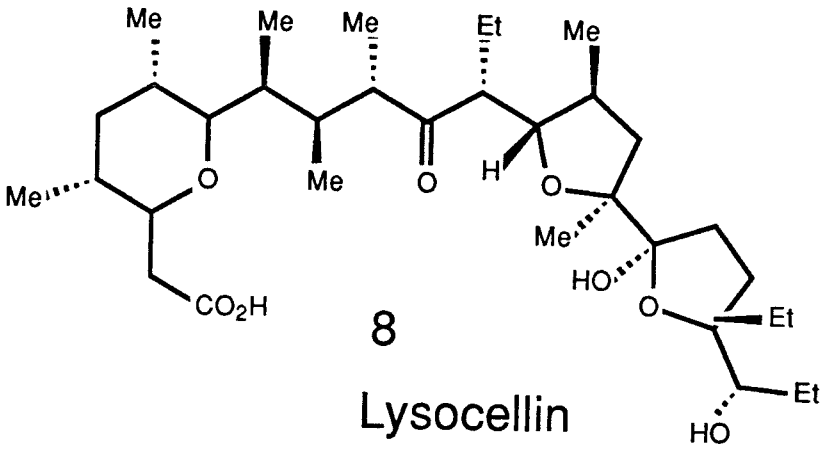
Grisorixin



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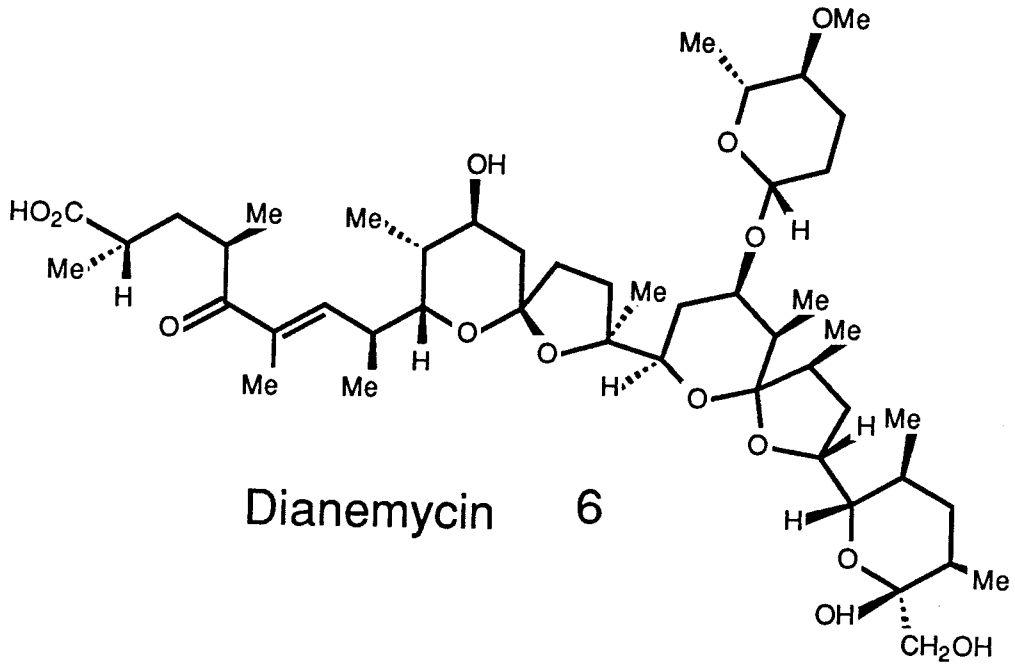
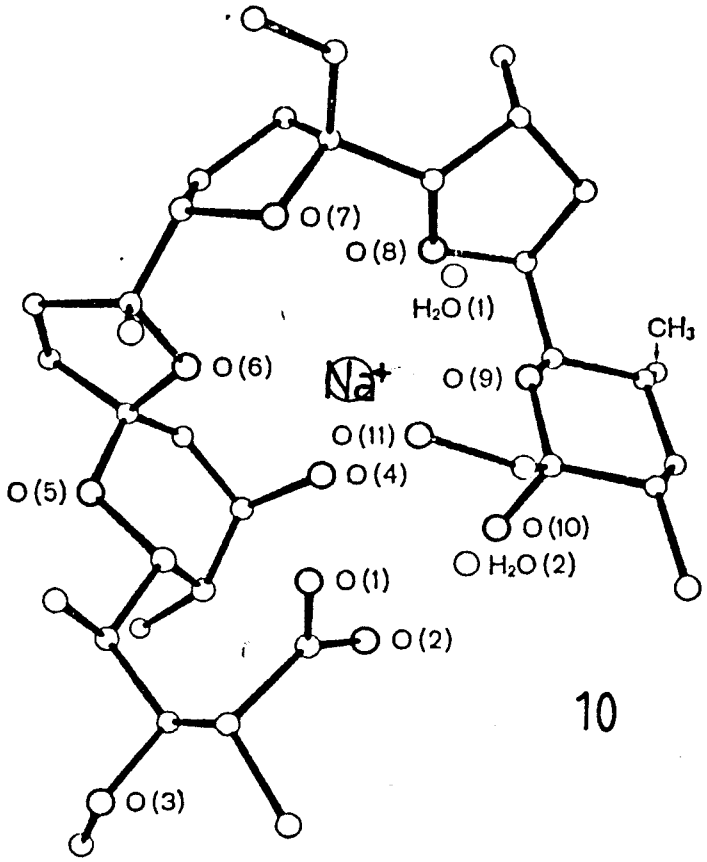
Lysocellin



Dianemycin 6

The structure of the monensin A sodium complex (10)[12] shows that the central sodium ion is held in an octahedral array of oxygen atoms, with the ionophore wrapped around and held together by terminal hydrogen bonding between the carboxylate anion and the two hydroxyl functions at C25 and C26.



10

Monensin is of particular interest because it is selective for Na^+ over K^+ in both complexation and ion transport[13,14]. This is a property which is quite rare, particularly among the polyether antibiotics. This selectivity can be rationalised in terms of the hole size within the pseudocyclic bound complex. It is argued that the conformational energy of the K^+ complex is higher than that of the Na^+ complex[14] because of the extra strain which the larger cation introduces.

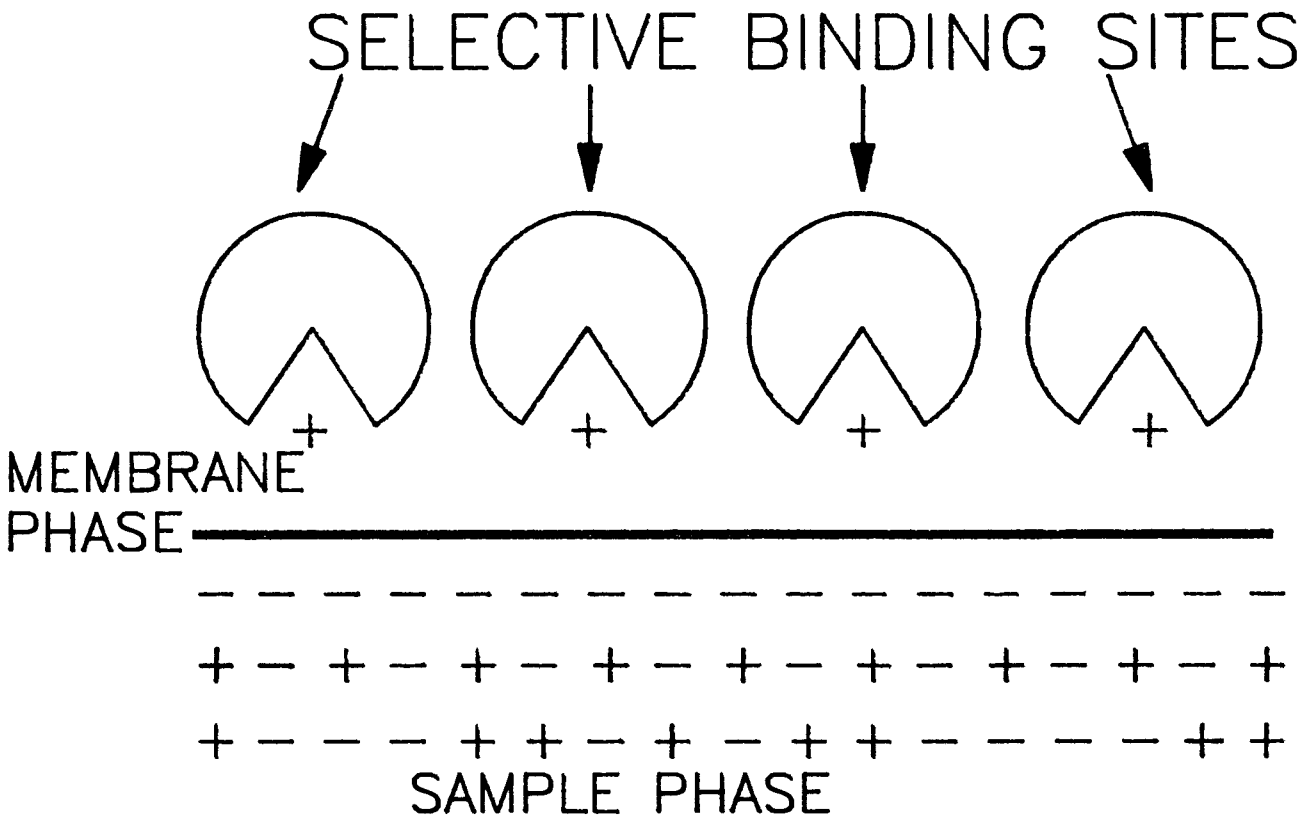
Monensin has also been used in ion transport experiments with heavy metal ions[15]. It was found to transport Ag^+ and Pb^{2+} as well as ammonium ion much more efficiently than Cu^{2+}, Ni^{2+}, or other transition metal ions. The authors explained this result in terms of the match between ionic radius and cavity size.

5.3 The Use of Ionophores in Sensing and Detection Systems

The need for quantitative methods of analysis for metal ions, particularly alkali metal ions, is great. For example, in medicine, analysis of blood and urine samples for K^+ and Na^+ is a routine operation. In the past these analyses have been carried out using flame photometric methods[16], but more recently ion selective electrodes have been developed which, in many cases, make use of selective ionophores capable of discriminating between different cations[16,17,18].

An ion selective electrode can be represented at the most simple level as shown in Figure 1[16].

FIGURE 1

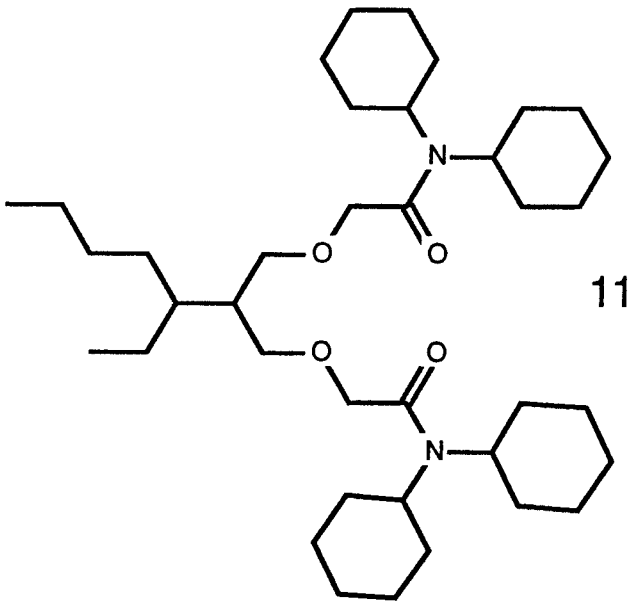


Selective binding of cations from the sample in the membrane phase causes a charge separation across the sample/medium interface. This can then be measured potentiometrically. If the system is suitably calibrated, thie then provides a measurement of cation concentration within the original sample eolution. A key problem when designing any electrochemical sensing system of this sort is to produce an accurate enough charge separation proportional to the concentration of the desired cation without any interference from other ions within the solution. For example, when analysing a

clinical sample for K^+ ion, the Na^+ concentration within the solution may be 10^3 times greater than that of the desired cation. This problem is overcome by the use of highly selective ionophores.

Valinomycin (1) has been used successfully in this way as part of an electrochemical sensor for potassium ion[4]. Its high selectivity for potassium ion over sodium ion of at least 4×10^3 make it ideal for this purpose, since sodium is usually the principle interfering ion.

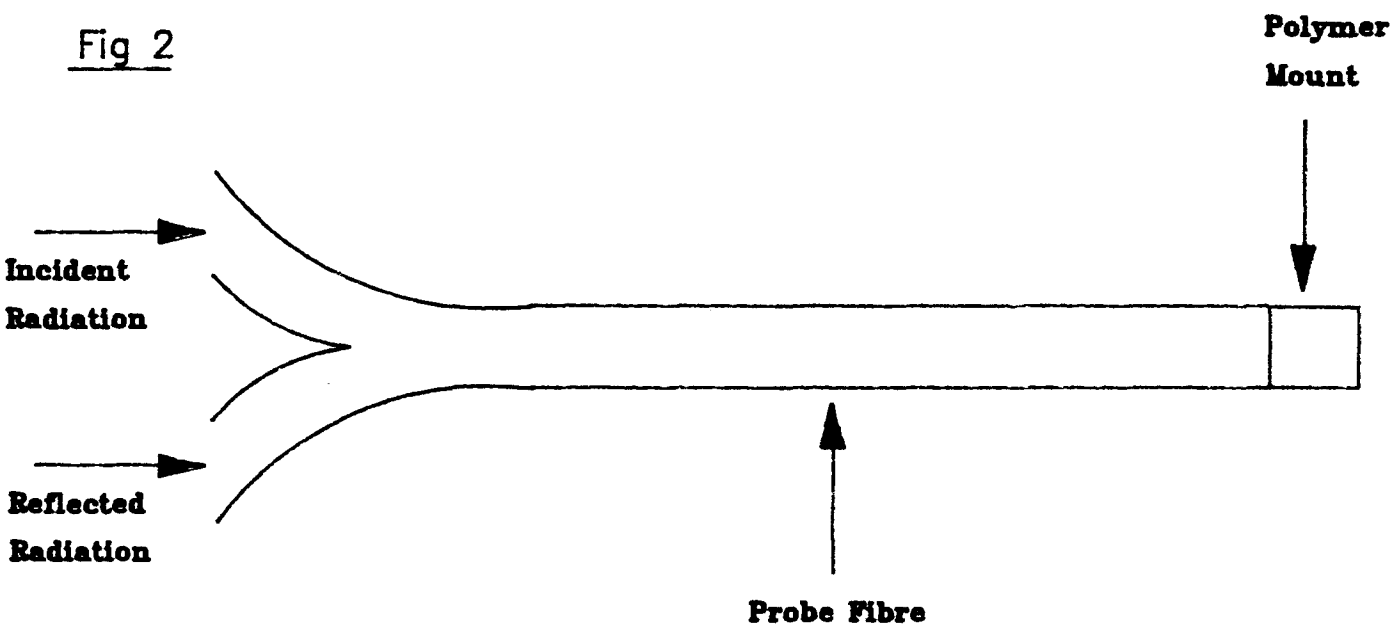
Synthetic ionophores have also been used in ion selective electrodes. For example (11) which is a highly selective host for Lithium ion has been used in a membrane electrode[19]. Lithium ion is an important analyte since it is used in the treatment of certain mental disorders, but is toxic in high concentrations.



11

More recently the concept of optical detection systems based on optical fibre technology has been outlined[20]. In such a system, a polymer mounted compound whose optical properties, either absorbance or fluorescence, are changed by the analyte, is mounted on the end of an optical fibre, as shown in Figure 2[20]. When the fibre is introduced into the sample solution, a change in optical property is measured by detecting the reflected radiation returning down the fibre.

Fig 2



If the change in optical property is proportional to the concentration of the analyte, and the system is suitably calibrated, this then provides the basis for a quantitative sensing device.

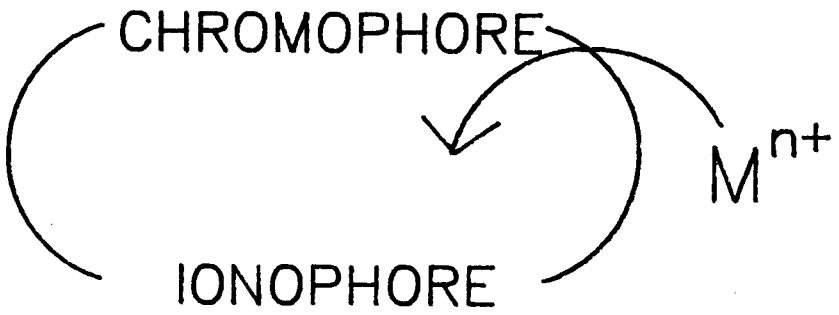
The application of optrode sensing technology to the

monitoring of metal ion concentration relies on the development of ionophore systems containing an optically active chromophore, whose electronic spectrum will change when the ionophore complexes a guest cation.

5.4 Chromoionophores

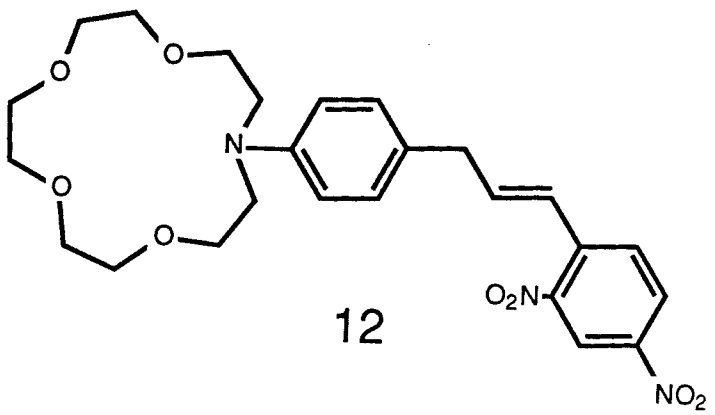
During his original work on crown ethers, Pederson[21] noticed salt dependent changes in U.V. spectra for some crown compounds containing aromatic rings. However, it is only more recently that host systems have been designed and synthesised specifically containing both an ionophore and a chromophoric group. Molecules of this type which have been called chromoionophores[22] possess the general structure shown in Figure 3.

FIGURE 3



Many systems of this type rely on the effect which co-ordination of a metal cation has on a donor heteroatom. Such co-ordination results in changes in the electronic surroundings of the donor atom via an ion dipole interaction. If the heteroatom is part of a mesomeric system, the electronic perturbation should spread throughout the whole (n +π) system. This in turn should influence the ground and photoexcited states of the chromophore, giving rise to changes in absorption spectra.

A good example of a system based on this principle is (12)[23]. In this case the donor heteroatom is nitrogen, and the aromatic system to which it is conjugated is a substituted stilbene moiety.

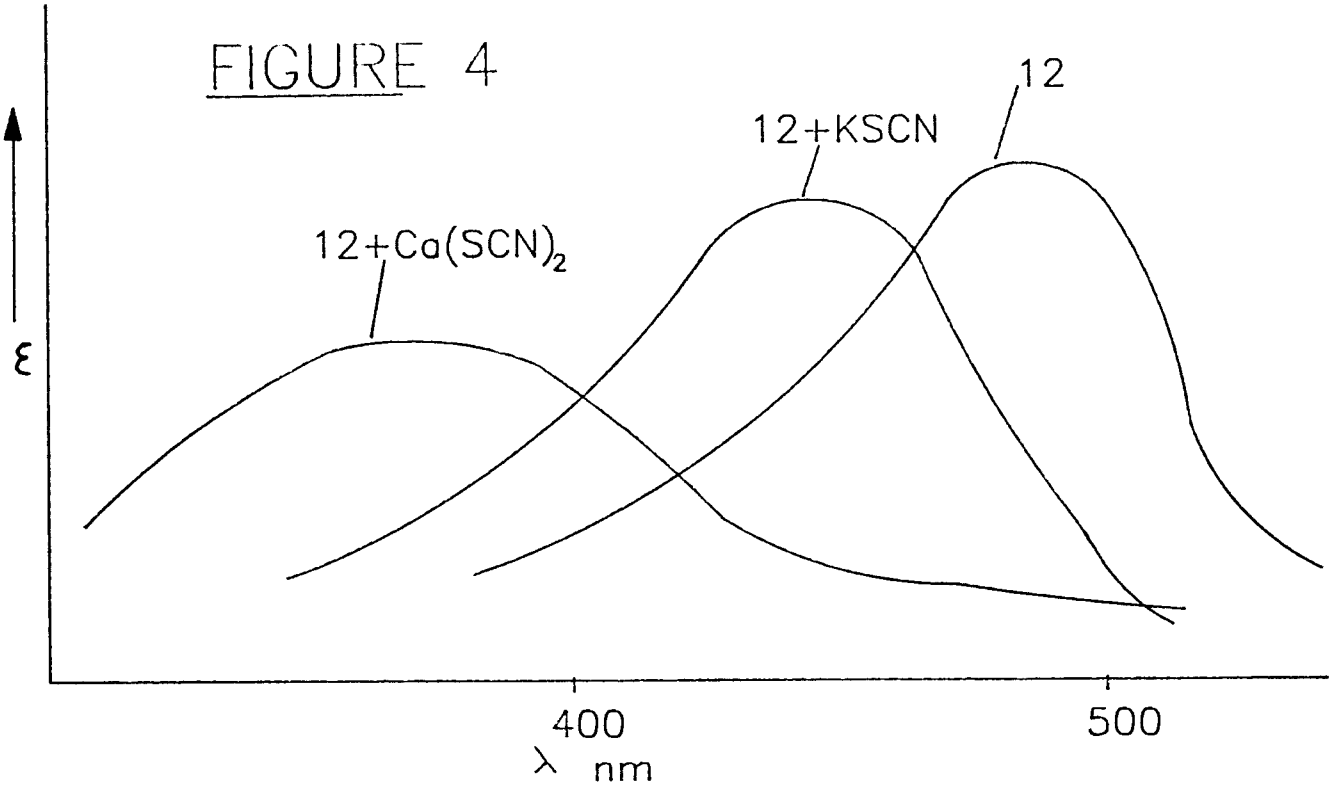


12

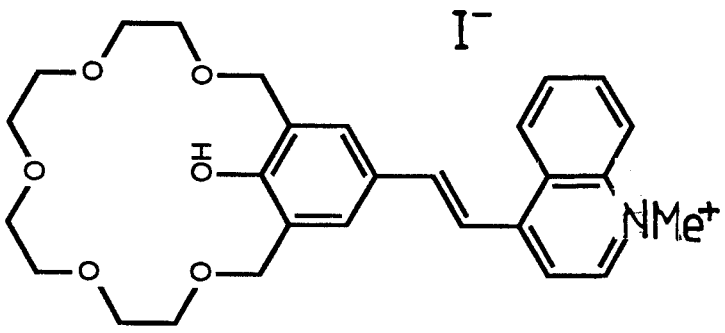
When an acetonitrile solution of (12) is treated with various metal salts, substantial changes are observed in the electronic absorption spectrum. Figure 4 shows that the

whole spectrum is shifted hypsochromically by metal ions, and that both λmox and ε mox values change.

FIGURE 4

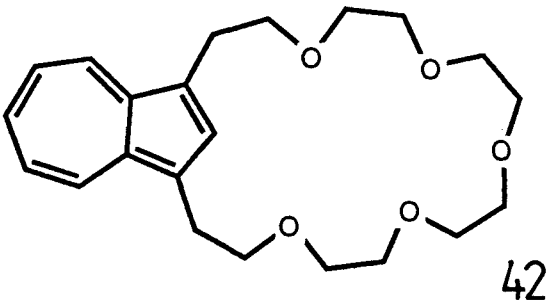


Similar effects have been observed when the aromatic chromophore is a charged species. The methyl quinolinium iodide crown (13) shows considerable changes in its electronic spectrum in the presence of a range of alkali and alkaline earth metal ions[24]. In this case the co-ordinated cation interacts with the aromatic system via the phenolic oxygen atom.



13

In some cases co-ordinated metal ions have been shown to interact directly with aromatic systems. For example, the azulene crown (42) has an electronic spectrum which shows considerable changes in λ max and extinction coefficient in the presence of Ba^{2+} and Ca^{2+} ions. In this case no intermediate heteroatom is present, and the effect must derive from direct influence of the cation on the azulene π system[25].



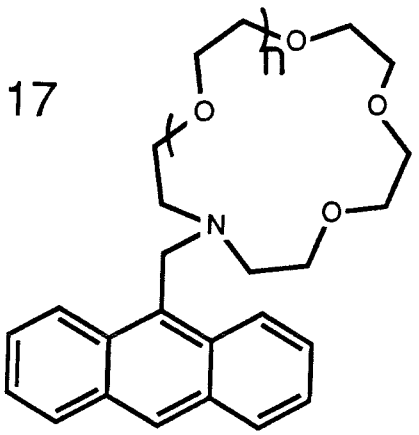
42

5.5 Present Study

All the published literature on chromoionophores and photoreactive host compounds is based on coupling a synthetic ionophore, usually a crown or azacrown, with a photoreactive chromophore as shown in Section 5.4. We hoped to extend this idea by coupling monensin A, a naturally occurring ionophore, with a chromophoric tag, with the aim of producing a chromoionophore possessing the selectivity of the antiobiotic.

There are in the chemical literature four examples of anthracene crown derivatives[26-29].

Vogtle et al have used the anthracene cryptand (14) as a



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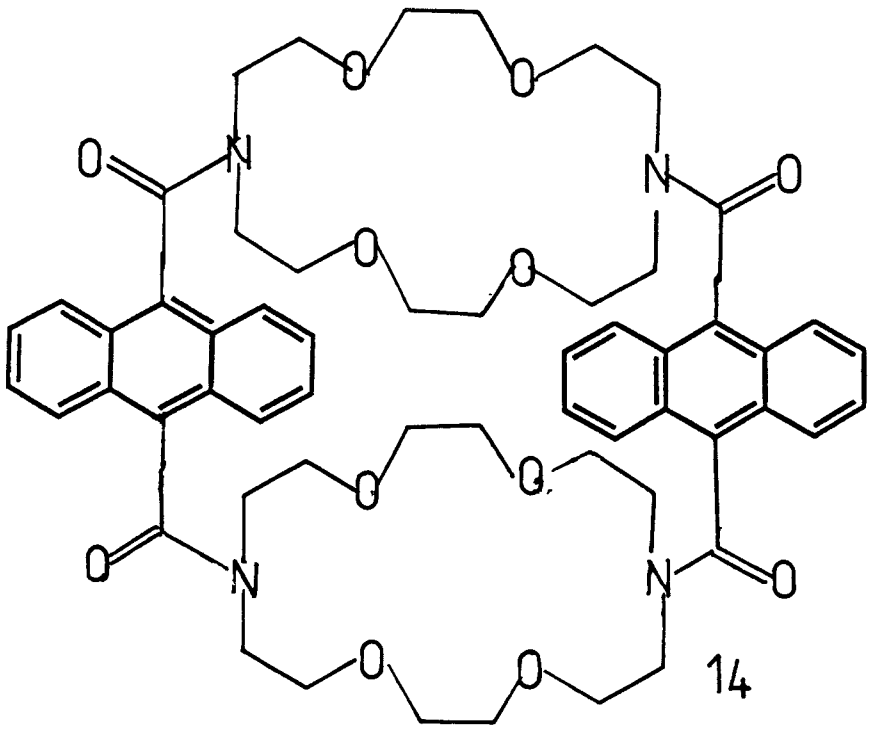
n = 1,2



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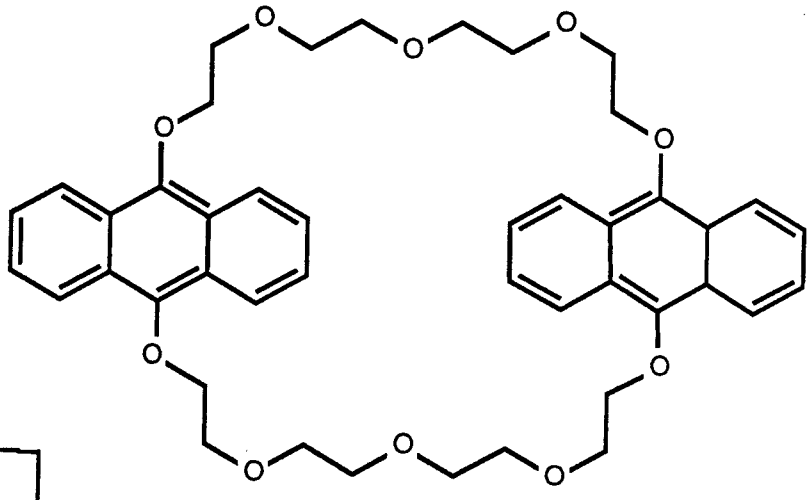

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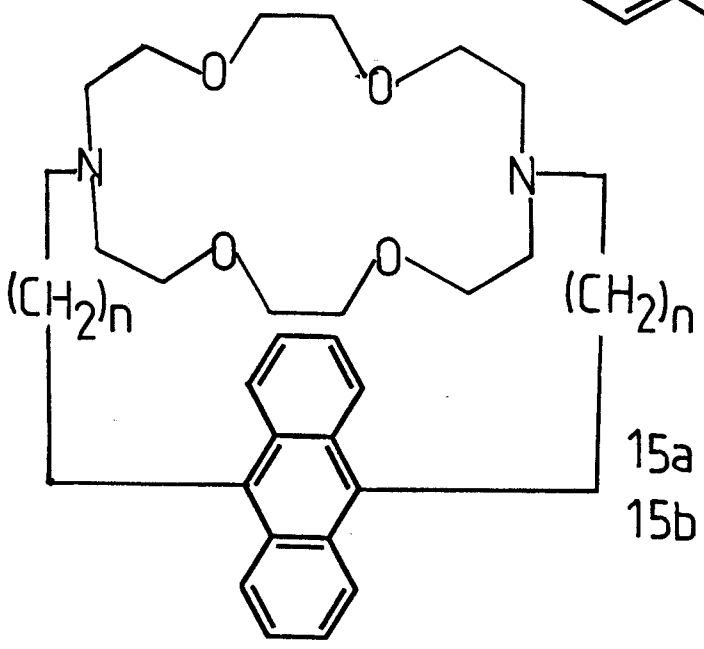


15a n=2

15b n=3

fluorescent probe in the detection of the solid-phase transition of phosphatidylcholines.[26]

Lehn et al have investigated the absorption and emission spectra of (15)[27], and found that addition of salts produced modifications of the absorption spectra. They also established that for (15)b participation of the nitrogen lone pairs in ion co-ordination, or protonation prevents formation of amine-anthracene exiplexes.

Similar observations about fluorescence quenching and to a lesser extent electronic absorption spectral modifications have been made for the derivatives (16)[28] and (17)[29]. In the case of (17) the disodium complex was shown to have a significantly different photochemistry to that of the free ligand, forming a different intramolecular dimer.

We hoped therefore to use anthracene as a suitable chromophore to link with monensin A.

5.6 Aims

The aims of this project were to examine the chemistry of the polyether antibiotic monensin A, in order to establish how the molecule might be modified or functionalised with a chromophoric tag.

We hoped to combine monensin's selectivity for sodium ions with the proximity of an anthracene residue to produce a sensing molecule or chromoionophore.

C H A P T E R
S I X

MONENSIN CHEMISTRY

6.1 Introduction

In order to achieve our aim of synthesising derivatives of monensin containing a chromophoric anthracene residue, we needed to explore some of the chemistry of the antibiotic. It was necessary to establish how monensin could be modified to incorporate a chromophore. This could be done either by attaching one directly to the antibiotic, or by degrading the structure in some way, so as to facilitate the later introduction of an anthracene residue. The following section describes our efforts in this area.

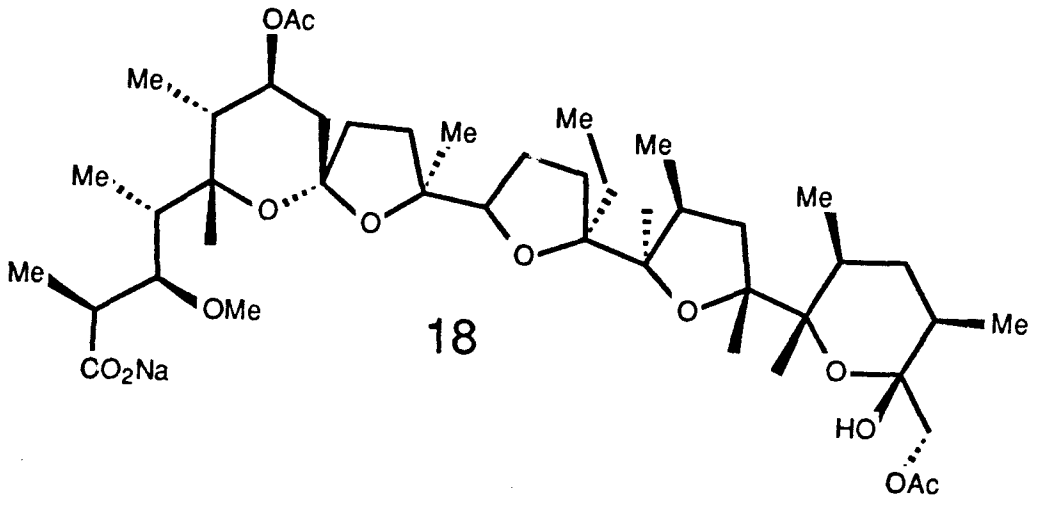
6.2 Monensin Modification Studies

Our investigations into the chemistry of monensin can be divided into three parts. Firstly we investigated the possibility of attaching new sections to the antibiotic by forming ester bonds between the hydroxyl functionality of monensin and a carboxylic acid derivative. There are a number of studies in the literature based around this idea[31,32]. Secondly we investigated some oxidation reactions to establish how the carbon framework of the antibiotic might be altered[33,34]. Thirdly we investigated some organometallic reactions of the derivatives we had prepared, in order to establish whether we might prepare a labelled monensin derivative by using a suitable organometallic nucleophile derived from an anthracene residue.

6.2.1 Esterification of Monensin

Treatment of monensin A sodium salt with a large excess of

acetic anhydride in pyridine yields the diacetate (18) in our hands, as the sole product. This confirms the work of Agtarap et al[30] during their original characterisation of the antibiotic. The product shows a characteristically strong acetate carbonyl absorption in the infrared spectrum at 1722cm^{-1}, quite different to the parent antibiotic where the carbonyl group of the carboxylate anion absorbs at 1565cm^{-1}.



18

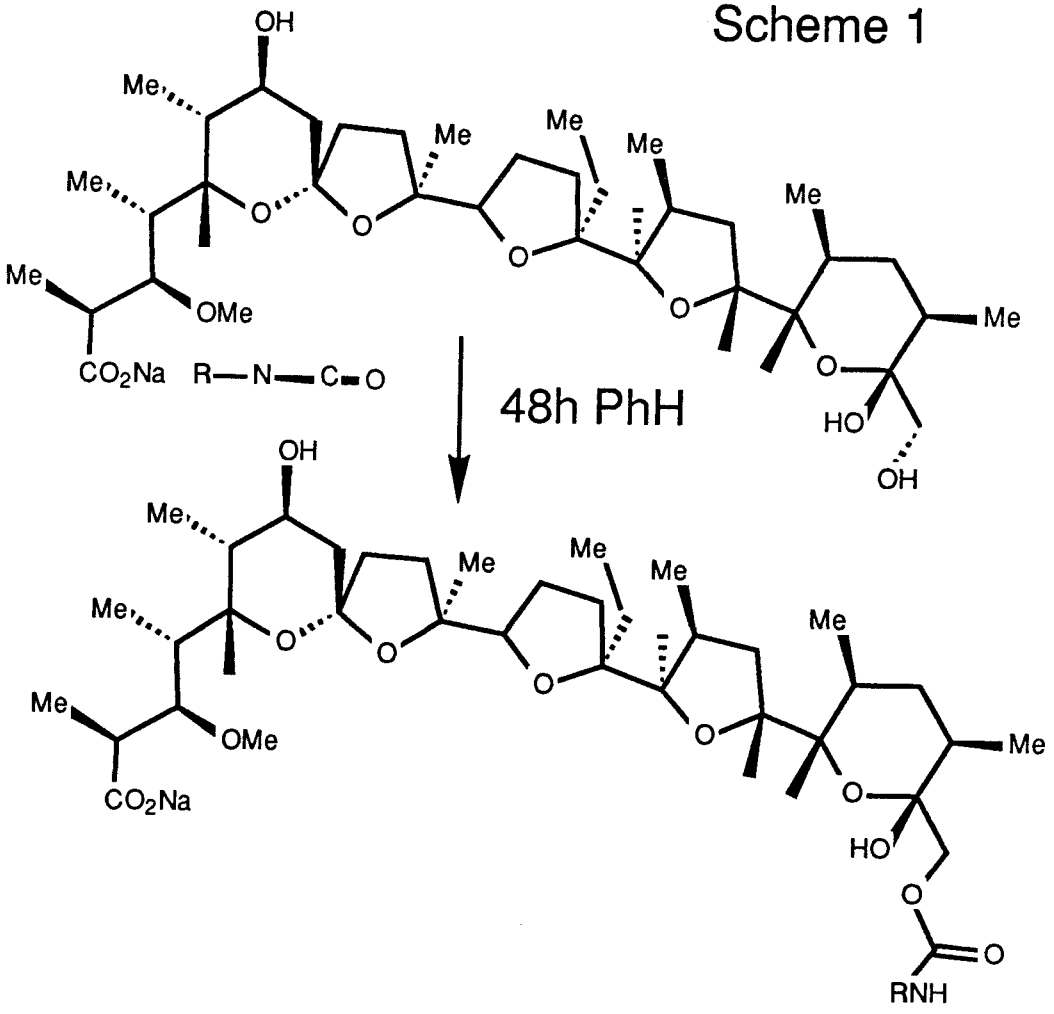
The fact that only two of monensin's three hydroxyl groups have been acetylated is shown by the compounds mass spectrum, which has a peak for the molecular ion at 776, and by the appearance of only four new signals in the ^{13}C nmr spectrum. The two acetate carbonyls show signals at 171.24 and 170.83 ppm and the two methyl groups at 21.60 and 20.93 ppm. The ^{1}H nmr spectrum shows that the methine proton at C7 adjacent to the secondary acetylated hydroxyl has been shifted down field

relative to monensin, by 0.5 ppm to 4.8 ppm. The signal corresponding to the methylene protons at C26 has also been shifted downfield in the ^{1}H nmr by 0.4 ppm again because of the presence of the acetate function. Under the conditions employed for this reaction the tertiary hydroxyl group at C25 is too sterically hindered to undergo acetylation.

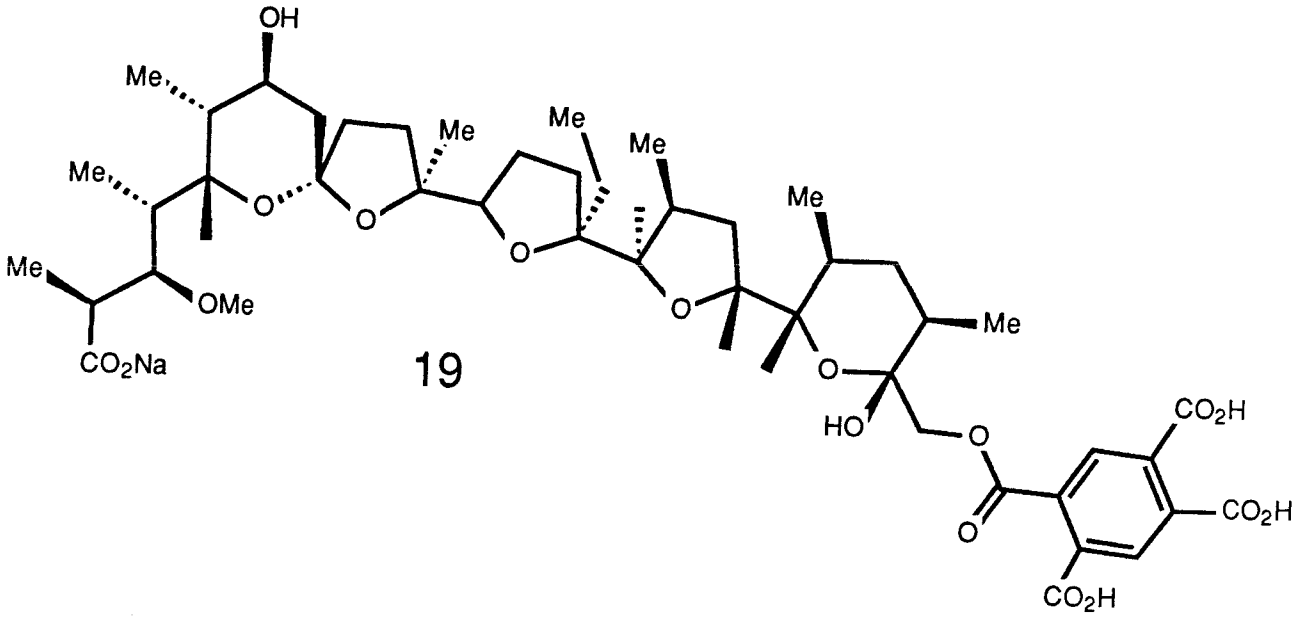
The preparation of (18) involves reaction of a primary and a secondary hydroxyl group, with differing steric environments. It should be possible to functionalise monensin solely at the C26 primary hydroxyl group, since this should be considerably more accessible than the secondary site.

Westley et al[31] were able to prepare a series of urethane derivatives of monensin by reaction selectively at the C26 hydroxyl group using the method shown in Scheme 1.

Scheme 1



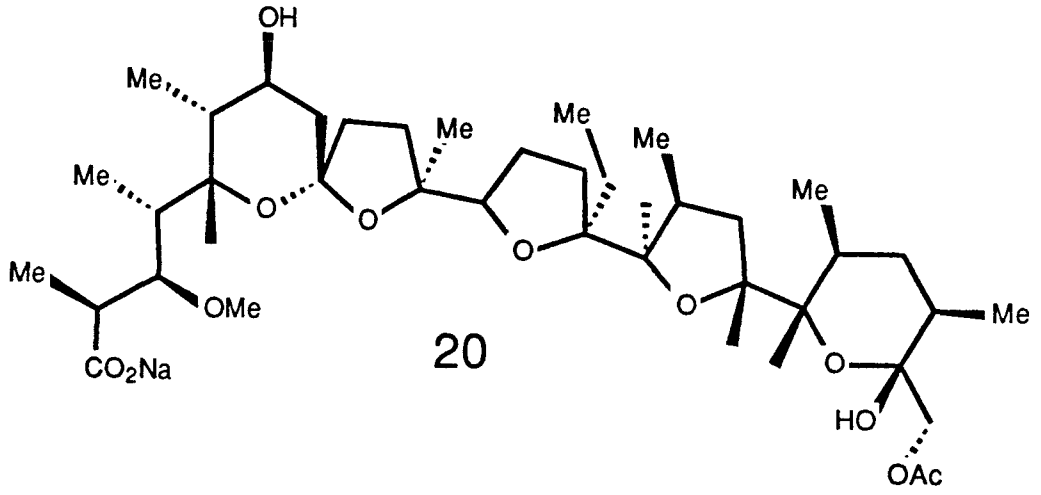
Fuhrop et al[32] prepared the monensin 26 pyromellitate derivative (19) from pyromellitic dianhydride and monensin A in pyridine. Reaction was again selective at C26.



19

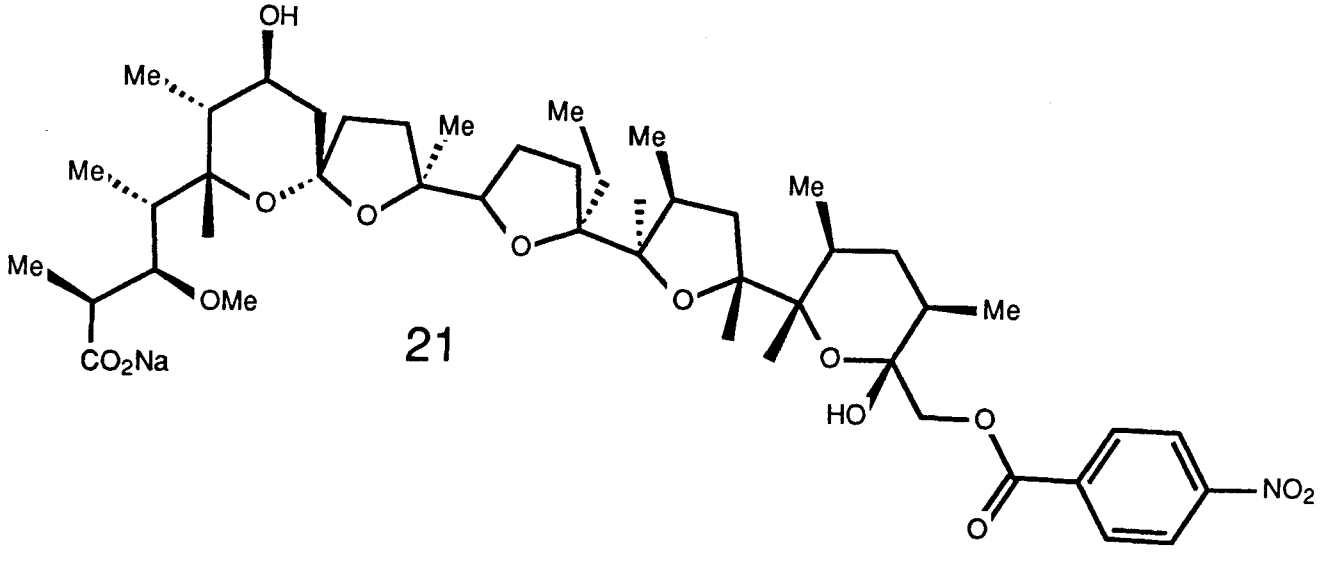
Accordingly we reacted monensin with 1.1 equivalents of acetic anhydride in pyridine and were able to isolate a compound of slightly higher polarity than (18) by column chromatography as a colourless foam. Spectroscopic evidence indicated that the structure was the novel monensin monoacetate (20).
Compound (20) again shows acetate carbonyl absorption in the infrared at 1728cm^{-1}, and shows a molecular ion at 734 in the mass spectrum indicating that one acetate group has been appended. The methylene protons at C26 have again been shifted downfield by 0.4 ppm in the ^{1}H nmr spectrum indicating that this is the point of attachment of the acetate group. In the ^{13}C nmr spectrum two new signals are present in (20), relative to

monensin, a quarternary acetate carbonyl at 170.88 ppm and a methyl group at 21.06 ppm.



20

Monensin was then reacted with paranitro benzoyl chloride in pyridine to form the paranitro benzoate ester by acylation of the hydroxyl function at C26. The compound isolated from the reaction by column chromatography was the primary paranitro benzoate ester (21), a previously unknown compound.



21

This ester again shows characteristic absorption in the infrared spectrum consistent with an ester carbonyl. The mass spectrum shows a peak for the molecular ion at 843, the correct value for the ester sodium salt. In the ^{13}C nmr spectrum the signal for C26, at 64.98 ppm in monensin, is shifted downfield by 3.3 ppm to 68.26 ppm in (21) indicating that it is this site which has been esterified.

Attempts to react monensin with a large excess of paranitrobenzoyl chloride yielded only (21) as the product. No product resulting from reaction at C7 was isolated, and it can be concluded that this site is too hindered for reaction under the conditions employed. Consistent with this idea is the fact that attempts to react the monoacetylated derivative (20) with paranitrobenzoyl chloride gave rise merely to recovery of starting material.

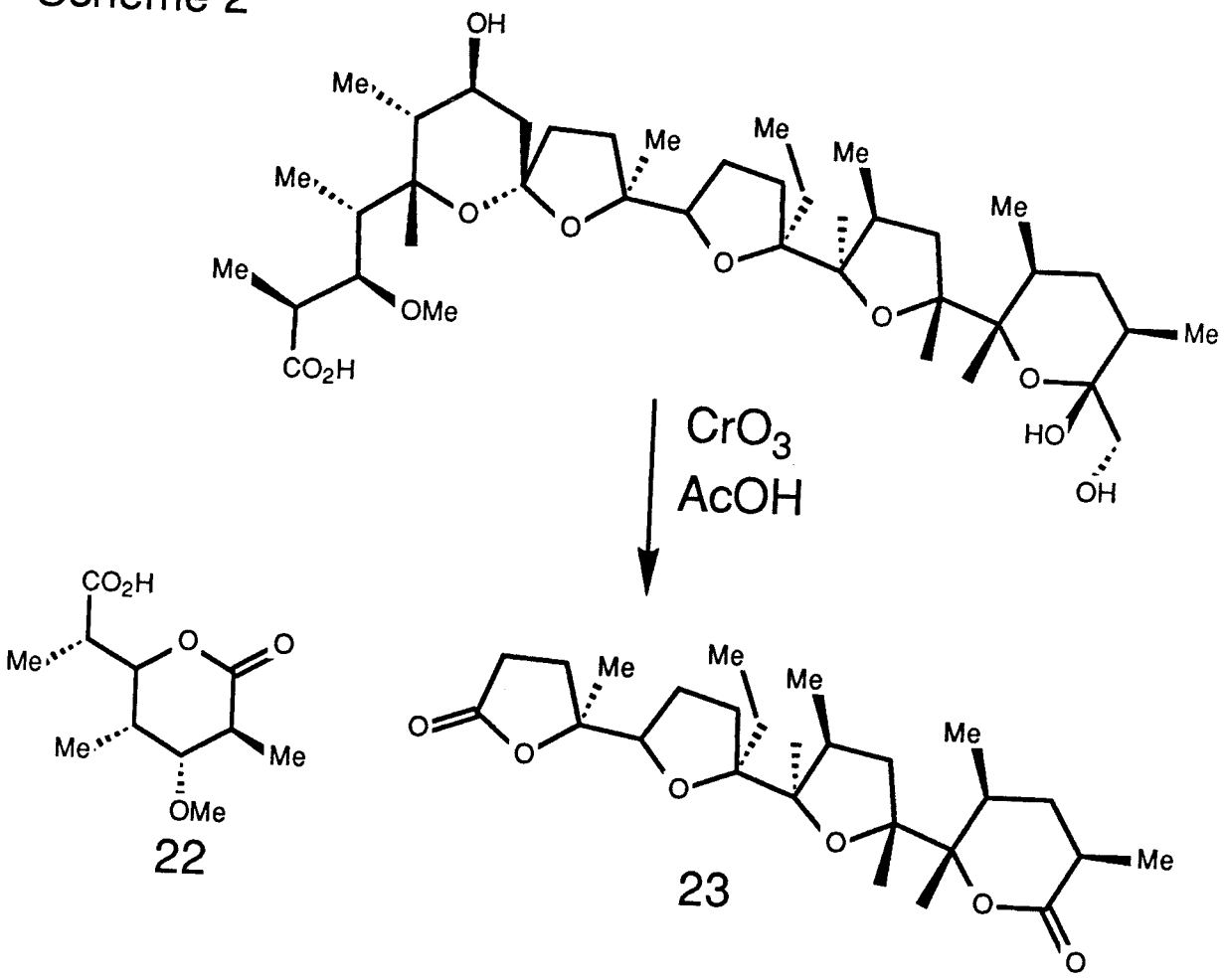
We have confirmed in the above reactions that it is possible to selectively functionalise monensin A by esterifying the primary hydroxyl group.

6.2.2 Oxidation Reactions of Monensin

It was decided to explore some more fundamental modifications of the antibiotic involving fragmentation of the carbon framework by oxidation. Day et al reported[33] that oxidation of monensin A with chromium trioxide in acetic acid at room temperature, gave as the major products the lactonic acid (22), and the tetracyclic dilactone (23). This reaction

is illustrated in Scheme 2.

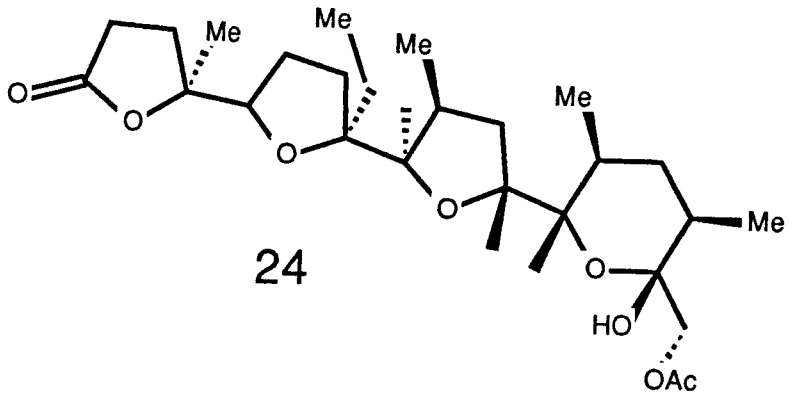
Scheme 2



In this reaction both the vicinal diol function at C25 and C26, and the spiro ketal centre C9 are oxidised in a series of steps. Attempts to repeat this reaction failed in our hands. The reaction gave rise to a large number of products which

could not be separated by chromatography.

However, oxidation of monensin diacetate sodium salt (18) with chromium trioxide in acetic acid, under the same conditions used for the reaction in Scheme 2, yielded one major product after column chromatography. Examination of the spectroscopic properties led to the conclusion that the product had the novel structure (24).



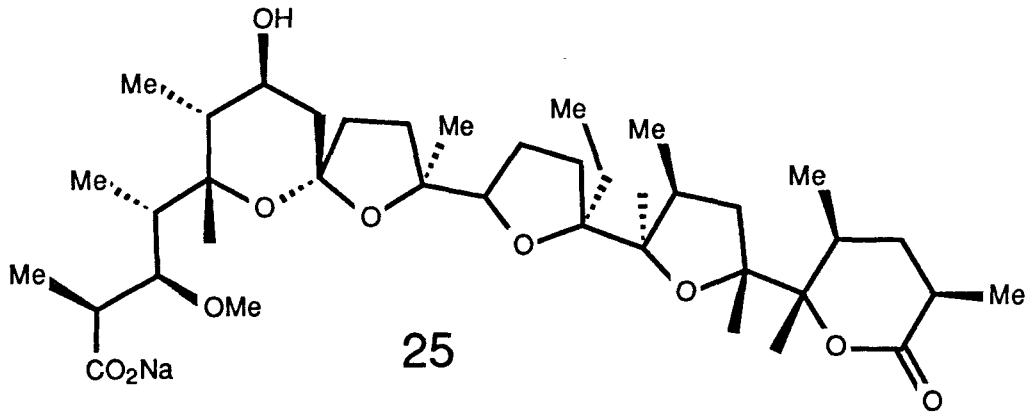
24

The rationale for ascribing this structure comes principally from the following observations. The mass spectrum contains a highest mass molecular ion peak at 482 which has an exact mass consistent with the proposed structure. The ^{13}Cnmr spectrum contains two carbonyl signals, and clearly the peak previously ascribed to the methylene group at C26 in monensin is still present at 67.85 ppm in (24). The ^{13}C nmr is completely consistent with the proposed structure, in that it contains the

correct number of resonances of the correct multiplicity. The proposed structure is closely related to (23) obtained by Day et al[33], and represents oxidation of the spiroketal moiety, with retention of the partly acetylated vicinal diol function.

In order to investigate this reaction further, we undertook a series of experiments varying the stoichiometry of the oxidant, the scale of the reaction, and the duration of the reaction. The results of this study are presented in Table 1. The general conclusions which can be drawn from this study are that the reaction does not proceed with fewer than 2 equivalents of chromium trioxide, and that prolonged reaction times have a detrimental effect on the product yield.

Treatment of monensin A sodium salt with sodium periodate in isobutyl alcohol and aqueous methanol, resulted in the oxidative removal of the vicinal diol function at C25 and C26 of monensin, furnishing the γ lactone (25) as the only product. This result confirms that of Cane et al[34] who also isolated this material.



25

TABLE 1 Chromium Trioxide Oxidation of Diacetylated Monensin (18)

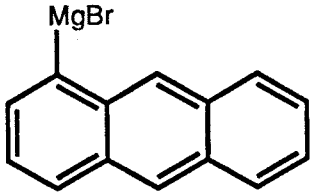
M Mols Diacetate	M Mols Chromium Trioxide	Equivalents Chromium Trioxide	Reaction Time h	Yield of γ Lactone %
0.65	0.98	1.5	2	0
1.28	5.12	4.0	12	11
1.31	9.30	7.1	12	4
0.62	1.24	2.0	2	15
0.66	1.65	2.5	2	32
0.66	1.98	3.0	3	34
0.63	2.58	4.1	3	40

Reactions carried out at room temperature in acetic acid/water

The structure of this compound is confirmed by the ^{13}C nmr spectrum. The signal corresponding to the methylene group at C26 in monensin is absent in the spectrum of (25), and the peak corresponding to the quaternary centre at C25 in monensin is moved downfield by 75 ppm in (25) to 174.28 ppm. The infrared spectrum also shows a clear carbonyl absorption at 1735cm^{-1} consistent with the presence of a δ lactone. By preparing the novel degradation product (24) and the δ lactone (25), it has been shown that monensin A can be oxidised selectively at either end of the carbon framework. The lactonic products of the degradative reactions should be amenable to further functionalisation by nucleophilic attack at the newly formed carbonyl groups.

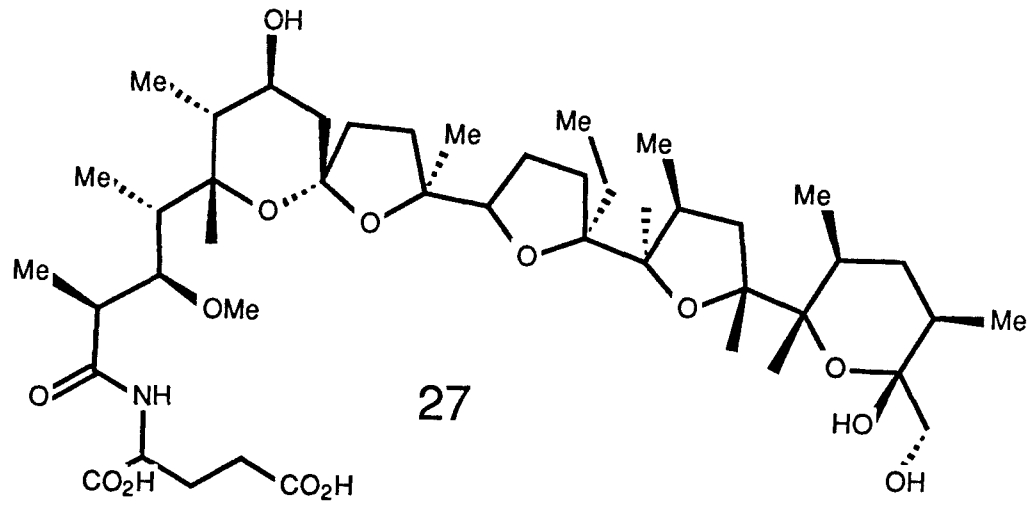
6.2.3 Methylation and Organometallic Reactions of Monensin and Derivatives

An alternative approach for introducing a chromophore into the structure of monensin would be to employ a suitable organometallic nucleophile to alkylate the antibiotic at the C1 carbonyl group. A reagent such as anthracene-1-magnesium bromide (26) might react with the methyl ester of monensin to produce a labelled product.



26

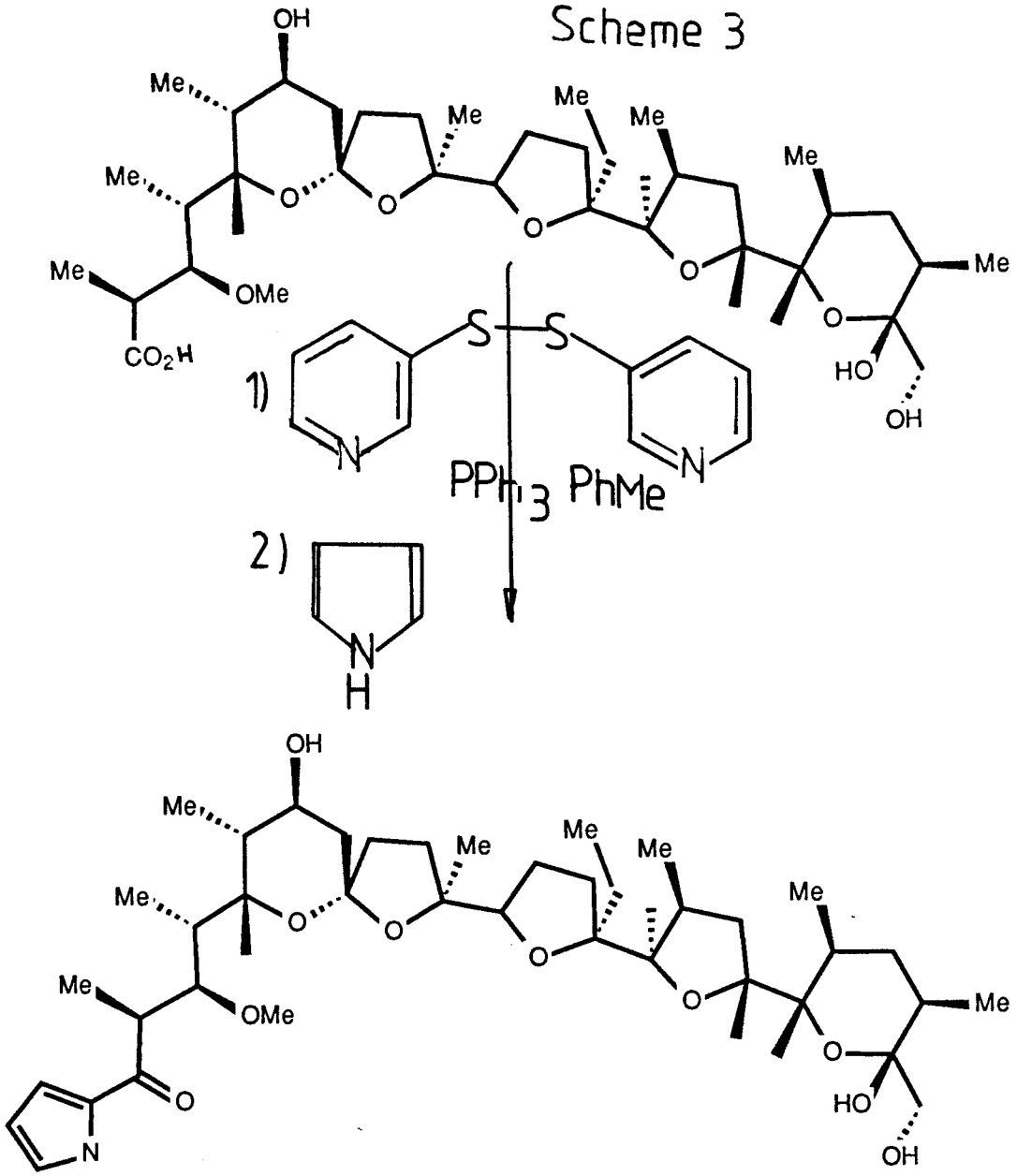
A number of studies have been carried out involving manipulations of the carboxylic acid group of monensin. Maruyama et al[35] have prepared a number of amide derivatives such as (27) at this end of the antibiotic.



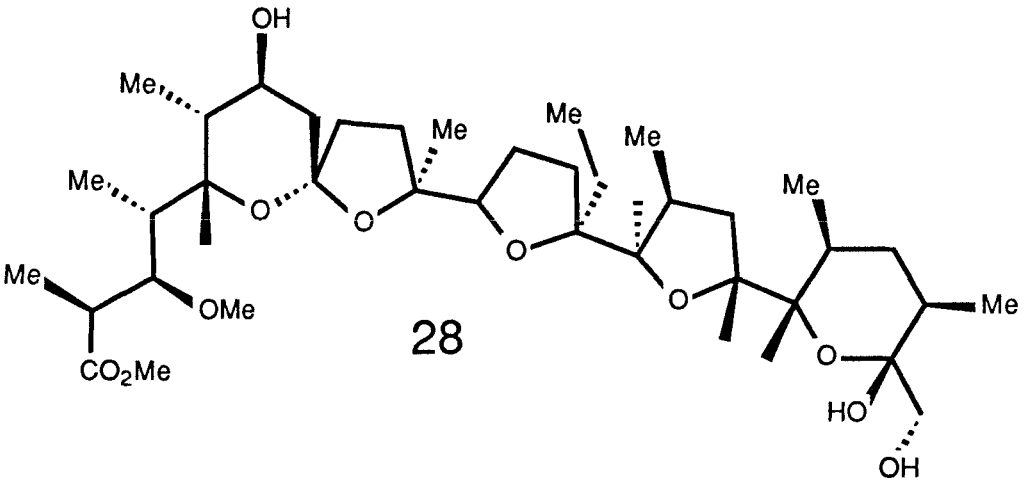
27

Nicolaou et al[36] have successfully applied a methodology for the synthesis of 2 - ketopyrroles from the carboxylic acid of monensin as shown in Scheme 3.

Scheme 3



Reaction of monensin A free acid with excess diazomethane for 1h afforded the known methyl ester (28)[41] after column chromatography.



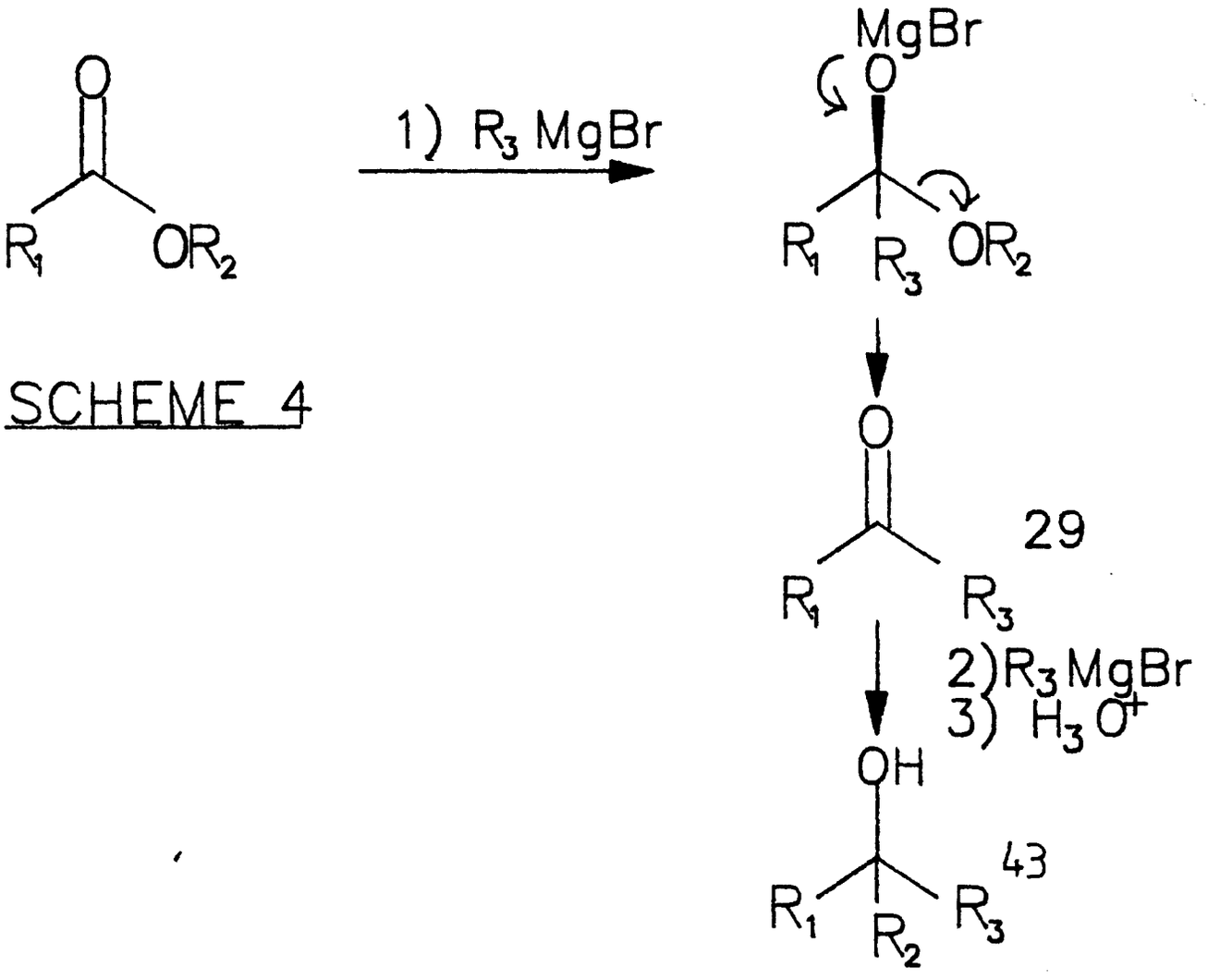
28

The ^{13}C nmr spectrum of (28) shows a new peak for the methyl group at 51.42 ppm and the infrared spectrum shows a sharp absorption at 1735cm^{-1} consistent with an ester.

We proceeded to examine the reaction of monensin methyl ester (28), the δ lactone (25) and the γ lactone (24) with a model Grignard reagent, phenyl magnesium bromide, in order to establish whether this route provided a viable way of introducing a chromophore into the polyether structure.

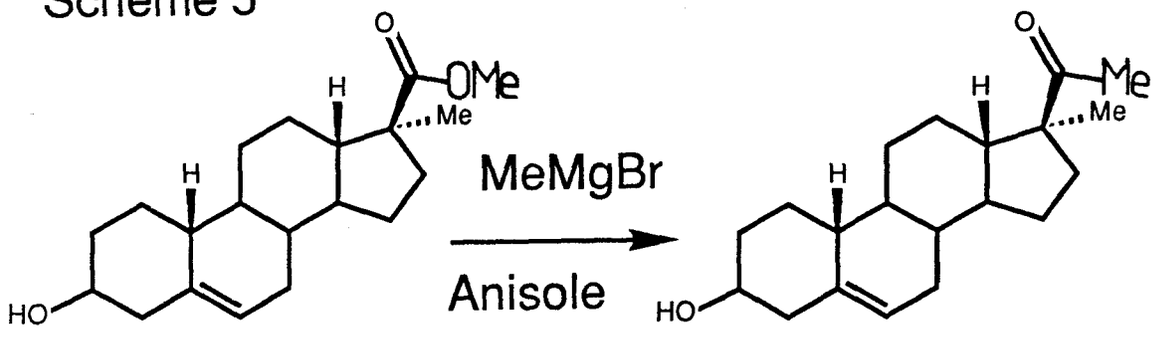
The general reaction of a Grignard reagent with a lactone or an ester is illustrated in Scheme 4. The reaction usually gives rise to a tertiary alcohol (43) as the product resulting from addition of 2 equivalents of the Grignard reagent. However under certain circumstances, the intermediate ketone (29)

resulting from the addition of 1 equivalent of Grignard reagent, may be isolated. Scheme 5 gives one example of the isolation of a ketone from the reaction of a Grignard reagent with an ester[37]. In this example the ketone is formed as the principal product because of steric hindrance from the methyl group β to the ketone carbonyl preventing further attack on the initially formed ketone.



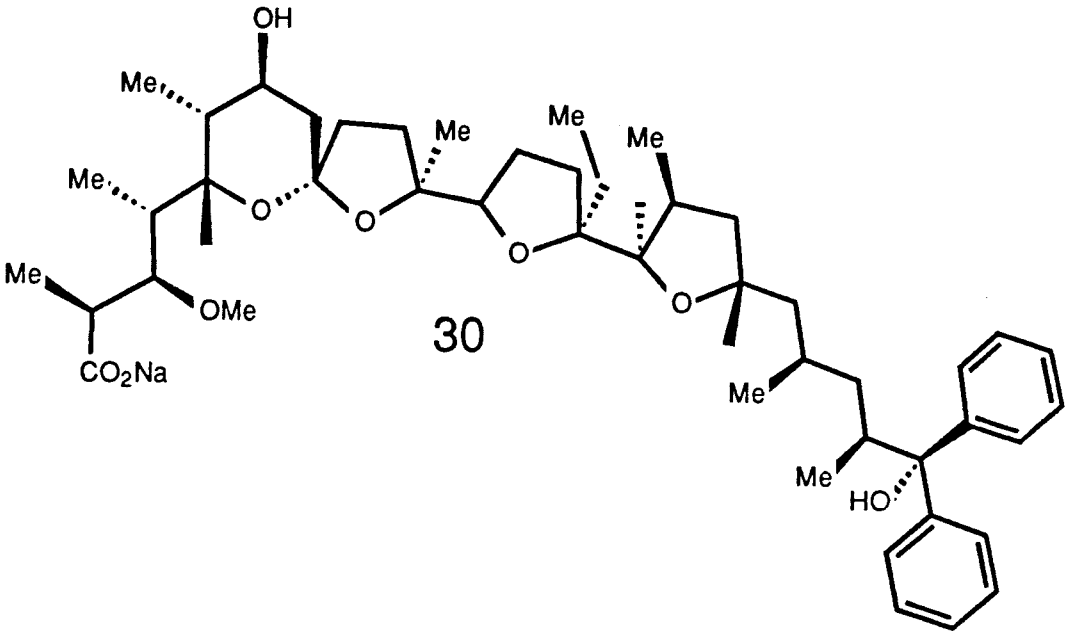
SCHEME 4

Scheme 5



We hoped to isolate chromophorically labelled monensin derivatives at the level of a ketone, from the Grignard reaction. Systems of this type containing a carbonyl group which is in conjugation with the anthracene π system, could provide a direct link between a bound metal ion and the chromophore.

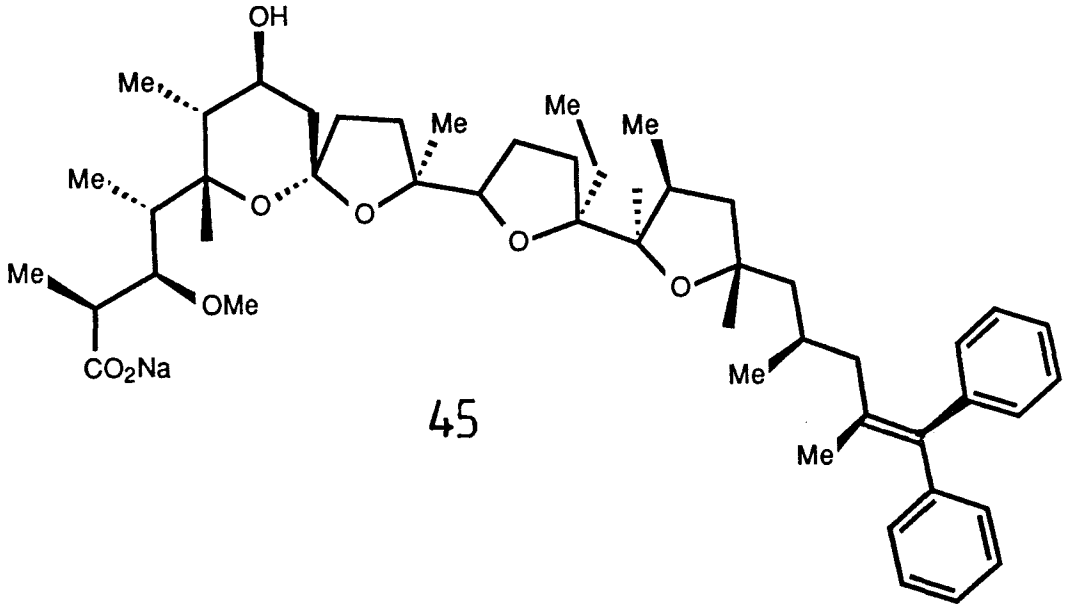
When the δ lactone (25) was treated with five equivalents of phenyl magnesium bromide the novel triol (30) was isolated as an oil in 44% yield after column chromatography.



30

Compound (30) has a mass spectrum containing a highest mass molecular ion consistent with the assigned structure, together with a ^1H nmr spectrum having the correct integrated

peak areas for the alcohol (30). The use of fewer than five equivalents of phenyl magnesium bromide in the above reaction resulted in either partial conversion of the δ lactone (25) to the alcohol (30), or in no reaction at all. No intermediate ketone was isolated from the reaction mixture. In our case there is no special reason for the reaction to stop at the stage of an intermediate ketone, since there is no obvious source of steric hindrance preventing further reaction to the product alcohol (30). However the product alcohol (30) which was isolated from the reaction mixture is an interesting compound which could be further functionalised. For example, dehydration of (30) by elimination of the tertiary hydroxyl group would lead to a styrene product (45), containing a highly conjugated chromophore adjacent to a potential metal binding site.



45

In our case the relative lack of steric interaction accords well with the absence of a ketonic product and preferential formation of the alcohol (30).

Reactions of the γ lactone (24) with phenyl magnesium bromide proved less successful. No useful product was isolated when (24) was treated with 6 equivalents of phenyl magnesium bromide. The reaction is complicated in this case by the presence of the acetate function as well as the γ lactone.

Reaction of the methyl ester (28) with the same Grignard reagent proved equally fruitless with no useful product being isolated from the reaction mixture.

6.2.4 Conclusions

The principle achievements of our studies of the modification of monensin are:

1) It was established that the antibiotic can be effectively acetylated at two sites C26 and C7, and that this can be done selectively at C26 under appropriate conditions.

2) This selective acylation methodology was extended to the attachment of an aromatic residue to the C26 end of the antibiotic.

3) It was shown that monensin can be oxidised selectively at either end, and by modification of the carbon framework produce lactonic

products. The novel γ lactone (24) was produced in good yield using a simple procedure at room temperature. It also proved possible to prepare the δ lactone (25).

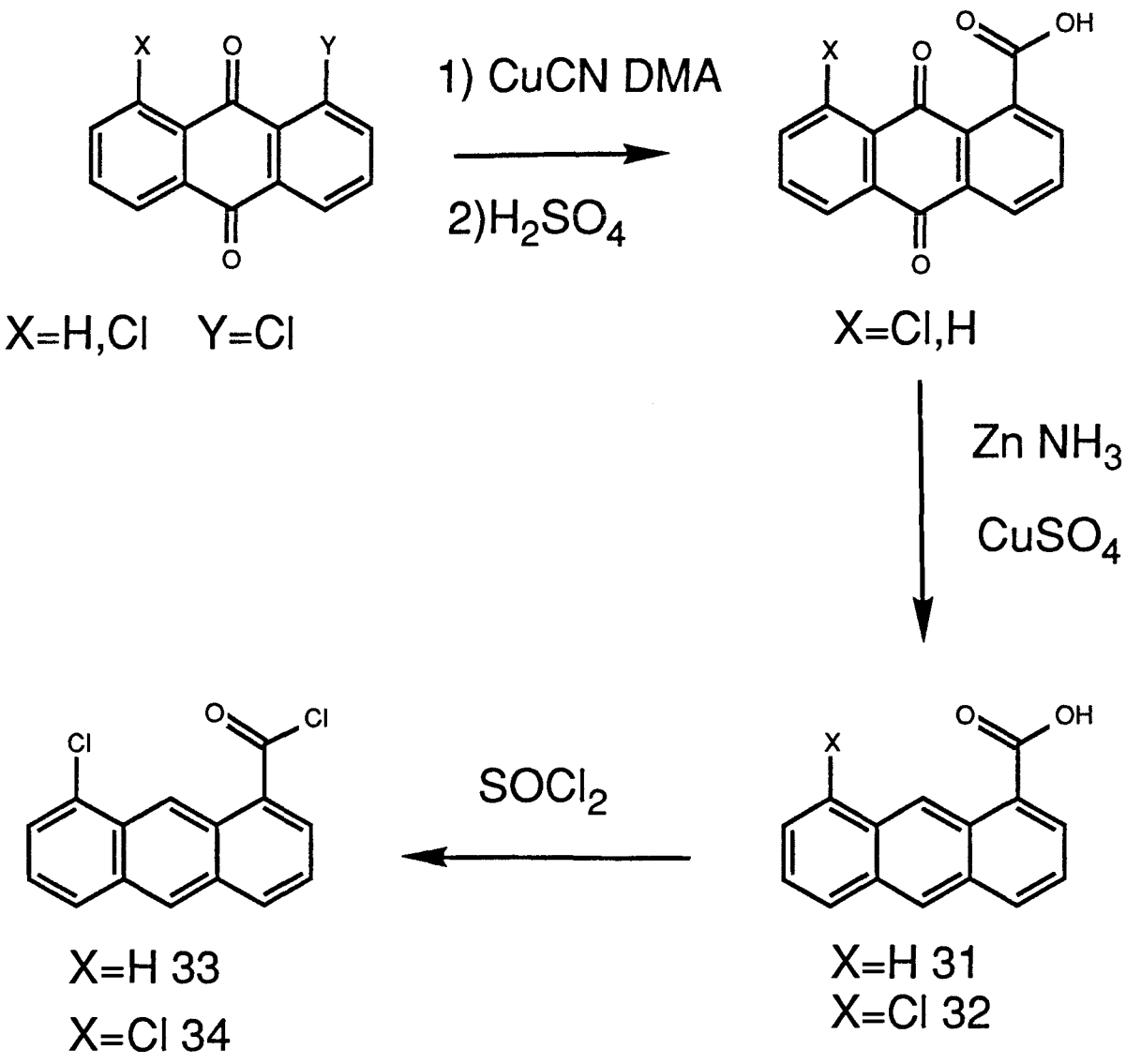
4) The triol (30) was also prepared from the ester (25) in reasonable yield using phenyl magnesium bromide.

6.3 Preparation of Chromophores and Coupling

The results of our study on the degradative and functionalisation chemistry of monensin presented above led us to the conclusion that the most profitable approach to synthesising a chromophoric derivative of monensin would be esterification of the C26 primary hydroxyl group with a suitable anthracene carboxylic acid derivative. Since we had successfully accomplished such a coupling reaction with paranitrobenzoyl chloride, we decided to react an acid chloride to form the ester bond.

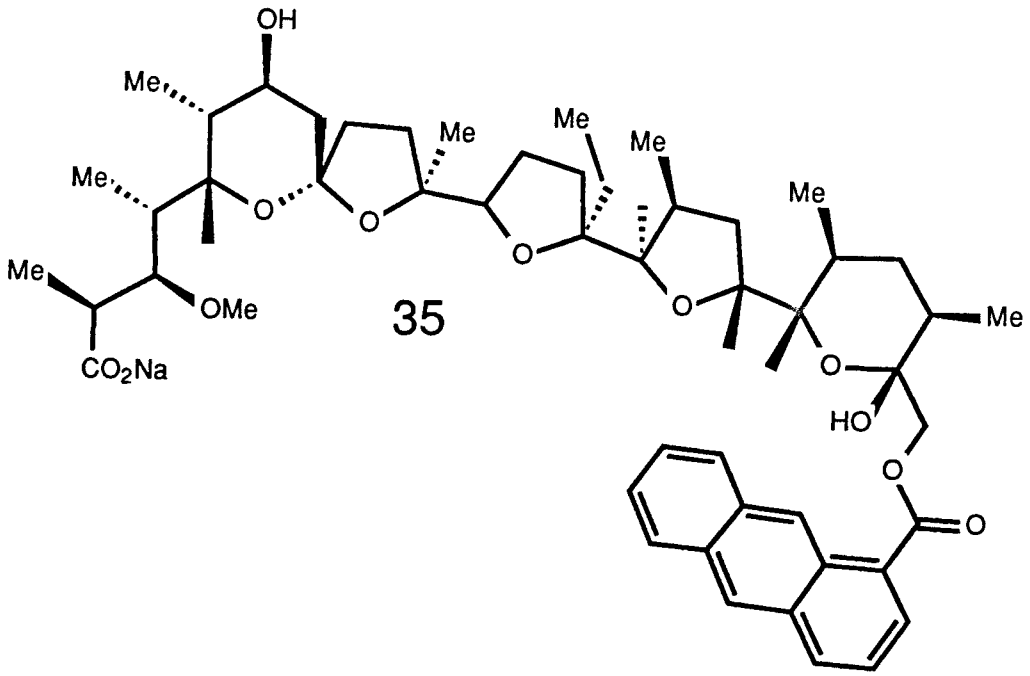
Initially we chose anthracene-1-carboxylic acid (31) and 8-chloroanthracene-1-carboxylic acid (32) as suitable groups with which to label monensin. Anthracene-1-carboxylic acid was prepared according to the method of Stock et al[48] as shown in Scheme 6. 1-Chloroanthraquinone was treated with copper (I) cyanide in dimethylacetamide to yield 1-cyanoanthraquinone, which was hydrolysed with sulphuric acid. The resulting anthraquinone-1-carboxylic acid was reduced using zinc dust in aqueous ammonia with a copper (II) sulphate catalyst to yield anthracene-1-carboxylic acid (31). 8-chloroanthracene-1-carboxylic acid (32) was prepared from 1,8-dichloroanthraquinone using analogous methods.

Scheme 6



Compound (31) was converted to the acid chloride derivatives (33) by the action of thionyl chloride. Initial attempts to couple (33) with monensin were unsuccessful

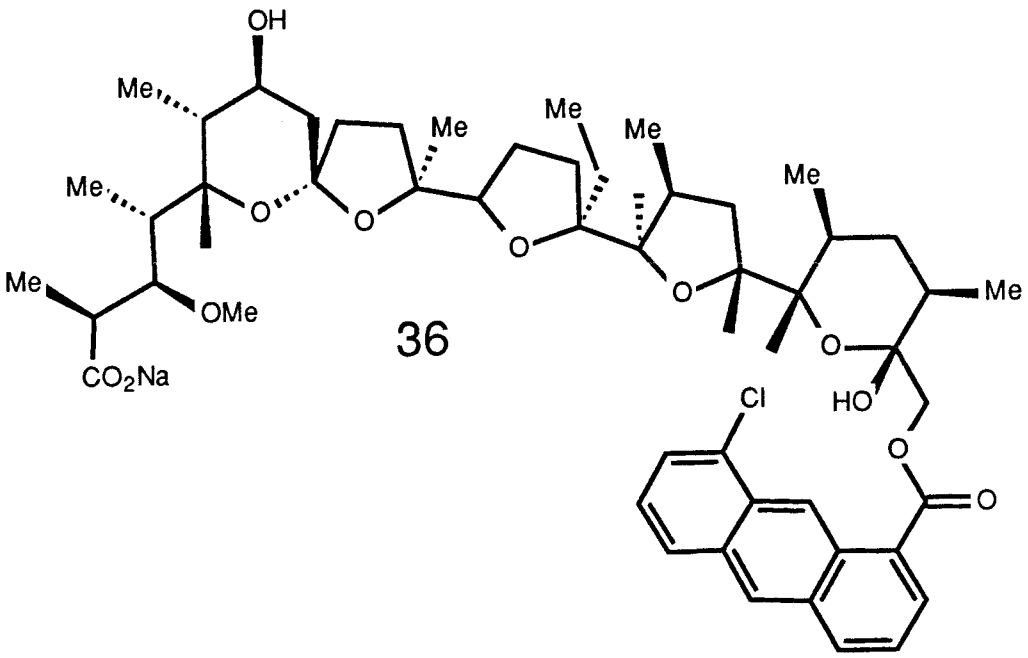
because of the presence of water in the monensin sodium salt hydrate. Thorough drying at reduced pressure alleviated this problem, and the coupled monensin derivative (35) was isolated as a yellow foam in subsequent attempts.



35

The ^{1}H nmr spectrum of (35) shows that the C26 methylene protons have been shifted downfield by 0.6 ppm relative to the parent antibiotic, and in the ^{13}C nmr the signal for C26 has been shifted downfield by 2.5 ppm again relative to monensin.

Under identical experimental conditions coupling was achieved between monensin A sodium salt and 8 chloroanthracene-1-carbonyl chloride (34) yielding the labelled derivative (36).



36

The fact that monensin had again been effectively esterified at C26 was established by nmr evidence. The C26 methylene protons were shifted downfield by 0.66 ppm in the ^{1}H nmr, and the corresponding carbon signal was also shifted downfield by 3.0 ppm in the ^{13}C nmr. The infrared spectrum of derivative (36) also showed a strong carbonyl absorption at 1730cm^{-1} consistent with this structure.

Having succeeded in synthesising two labelled monensin derivatives containing an ultraviolet chromophore, it was decided to examine the electronic spectra of these compounds to establish whether either showed changes in extinction coefficient of λ max value when sodium ions were introduced.

6.4 Electronic Spectral Studies

Still et al have shown[49] that for the polyether antibiotic lasalocid A (5) it is possible to calculate binding constants for various antibiotic salt complexes from observation of the absorbance and fluorescence emission spectra of the antibiotic. The binding of a metal ion to the ionophore produces a direct and highly significant effect on the electronic spectral properties of the host, by ion induced perturbation of the aromatic π system, and this can be used to give a quantitative indication of the extent of ion association.

The electronic spectrum of monensin derivative (35) was determined as the free acid form in methanol and then, in the presence of an excess of sodium fluoride, as the sodium salt. No significant changes in absorption properties in λ max or ε max values were observed. The procedure was repeated in dichloromethane, acetonitrile and cyclohexane as the solvent with a similar result in each case. The spectra of anthracene-1-carboxylic acid methyl ester were determined in methanol under identical conditions to those used for (35) as a reference.

The electronic spectrum of monensin derivative (36) was also determined in methanol with and without sodium ion present. Again no changes in absorption characteristics were observed.

The electronic spectral characteristics of (35) and (36) together with those of anthracene-1-carboxylic acid methyl ester are shown in Table 2.

In the case of the work of Still [49] on lasalocid A (5), antibiotic salt association results in the formation of a carboxylate anion directly attached to the aromatic chromophore whose electronic spectrum is being observed. Examination of the crystal structure of lasalocid metal ion complexes reveals that the guest metal cation is held close to the benzene chromophore of the host. Both these factors contribute to the observation of large variations in electronic spectral properties which occur in lasalocid A (5) when a metal cation is bound.

Observation of the ^{13}C nmr spectra of the chromophoric monensin derivatives (35) and (36) indicate clearly that these compounds are forming sodium salts. The signal for the C1 carboxylate anion at 181 ppm in monensin A sodium salt is present at 177 ppm in (35) and at the same chemical shift in (36), that is at considerably higher chemical shift than would be expected for the free acid form of the antibiotic or its derivatives. Thus the failure to observe marked changes in the electronic spectra of the derivatives (35) and (36) must be due to a failure to produce direct electrostatic interactions between bound ion and aromatic chromophore which clearly do occur in the case of lasalocid A. Whether the absence of electronic perturbation of the chromophoric π system in our case is due to a failure of the derivatives to adopt a wrap around conformation such as (10), or whether such a conformation

is adopted but does not produce an intimate enough link between the metal ion and the anthracene group is not clear from our results.

6.5 Further Chromophore Synthesis

The failure of our initial labelled monensin derivatives to show significant ion induced changes in electronic spectra led us to question the design of the aromatic chromophores.

A study of the mode of binding of monensin to metal ions both in the crystalline state[42,43] and in solution[44,45], shows that one of the crucial factors affecting the ability of monensin to bind alkali metal ions is the strong hydrogen bonding interaction which exists between the carboxylate anion at one end of the molecule, and the vicinal diol function at C25 and C26 at the other. This bonding interaction which secures the wrap around polyether structure as it binds metal ions, is crucial not only for monensin, but for many ionophore antibiotics[7]. In the labelled monensin derivatives (35) and (36), no such hydrogen bonding can exist, because the crucial C26 hydroxyl group has been esterified.

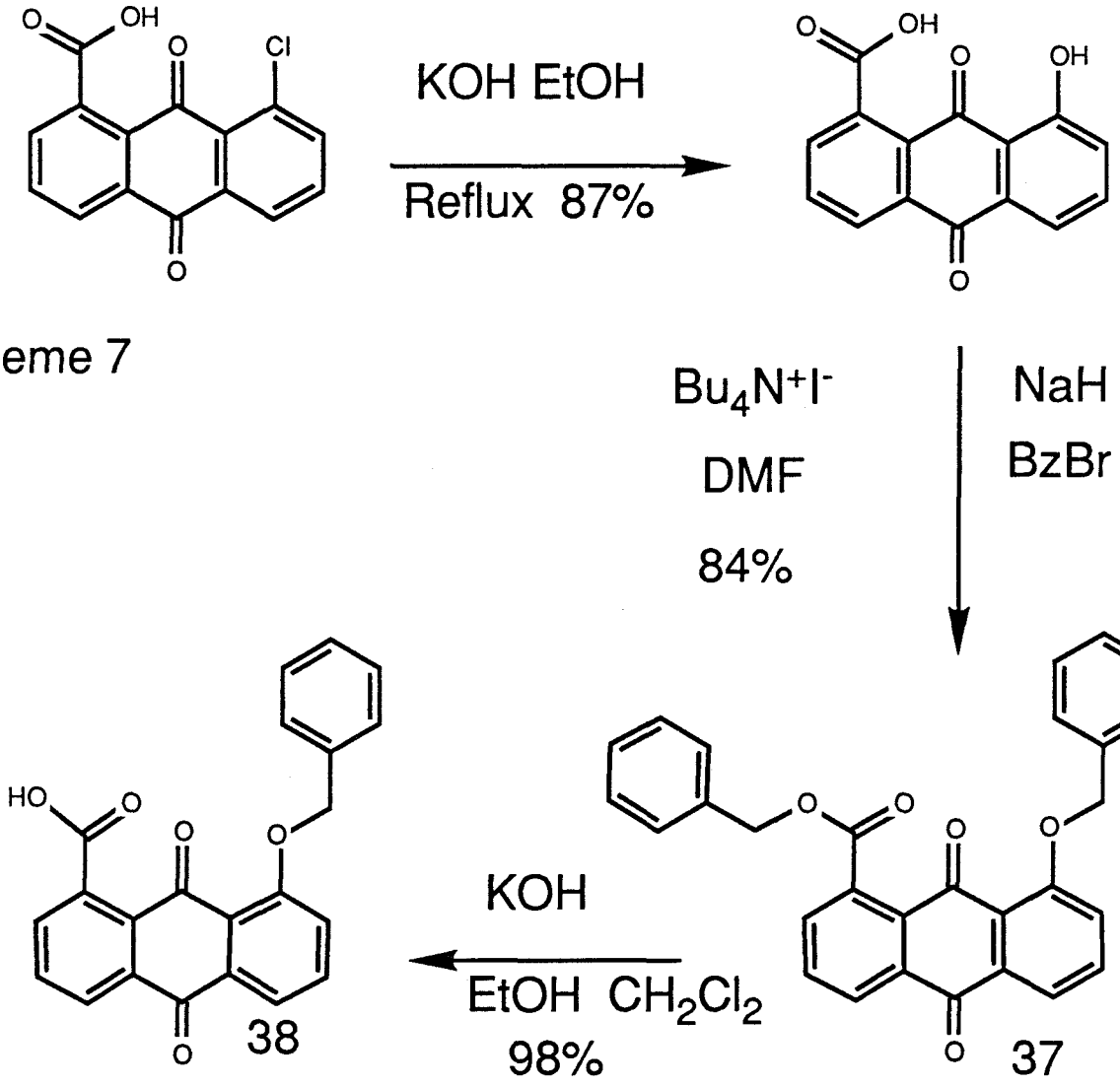
We hypothesised that if we were able to synthesise a chromophoric label containing a hydroxyl group, and couple this with monensin, we might restore the favourable interaction between the two ends of the antibiotic and bring the aromatic π system closer to the alkali metal ion bound within the complex. This should help to create an interaction between the

Table 2 Electronic Spectra at 25°C 300 - 430 nm

Substrate	Solvent	λ_{max} nm ($\varepsilon_{max} \times 10^3$)				
34	Methanol	331(1.23),	347(2.30),	364(3.25),	382(3.36),	402(1.90)
34	Dichloromethane	331(0.96),	348(1.66),	365(2.38),	381(2.60),	396(1.90)
34	Acetonitrile	330(1.08),	348(1.75),	355(2.00),	366(2.45),	380(2.59)
34	Cyclohexane	331(1.8),	348(3.1),	365(4.8),	383(5.3),	397(3.9)
35	Methanol	348(1.54),	359(2.04),	366(2.29),	378(2.62),	398(2.11)
Anthracene-1-carboxylic acid methyl ester	Methanol	330(0.4),	347(0.9),	356(1.1),	365(1.4),	380(1.4)

chromophore and the bound cation, and therefore a change in electronic spectral properties.

The benzyl protected anthraquinone derivative (38) was therefore synthesised from 8-chloroanthraquinone-1-carboxylic acid using the method described in Scheme 7.



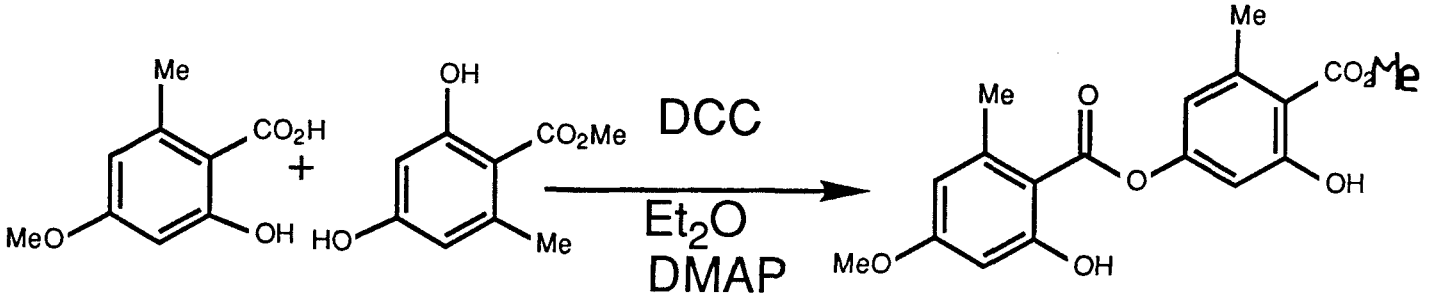
Scheme 7

8-chloroanthraquinone-1-carboxylic acid was hydrolysed with potassium hydroxide in ethanol to yield 8-hydroxyanthraquinone-1-carboxylic acid. Selective protection of the hydroxyl group was

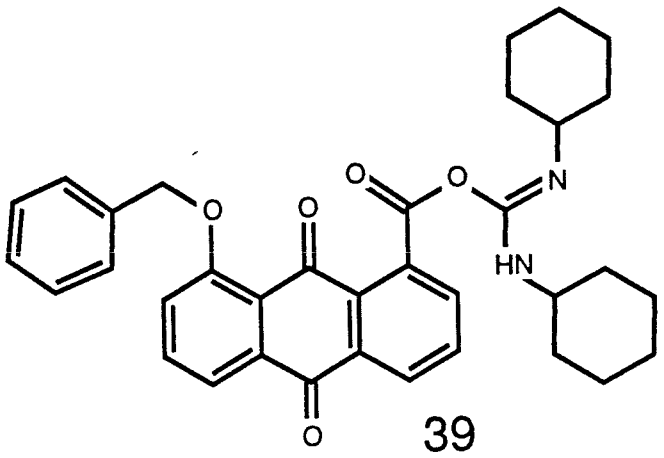
achieved by synthesising the dibenzylated derivative (37) using sodium hydride and benzyl bromide in dimethyl formamide, followed by hydrolysis of the benzyl ester with potassium hydroxide in ethanol and dichloromethane. Attempts to couple the protected anthraquinone (38) with monensin using the previously adopted acid chloride condensation method proved consistently unsuccessful. The starting materials were recovered from the reaction mixture each time.

Dicyclohexylcarbodiimide has been used successfully as a reagent for effecting esterification of a carboxylic acid[39]. For example, Scheme 8 shows one application of this method[46].

Scheme 8



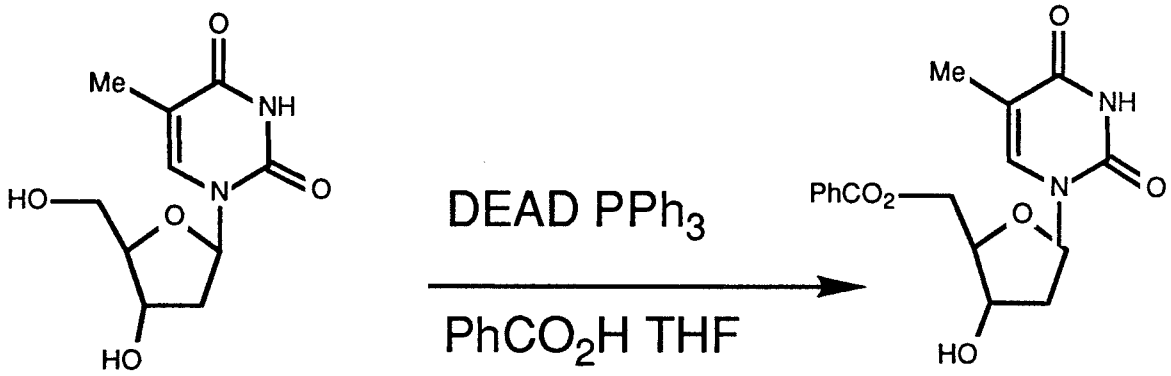
However, we were unsuccessful in applying this method to our system. Treatment of (38) with dicyclohexyl carbodiimide and dimethylamino pyridine in the presence of monensin yielded no coupled product, only the dicyclohexyl derivative (39) as the major product which had failed to react with the monensin alcohol.



39

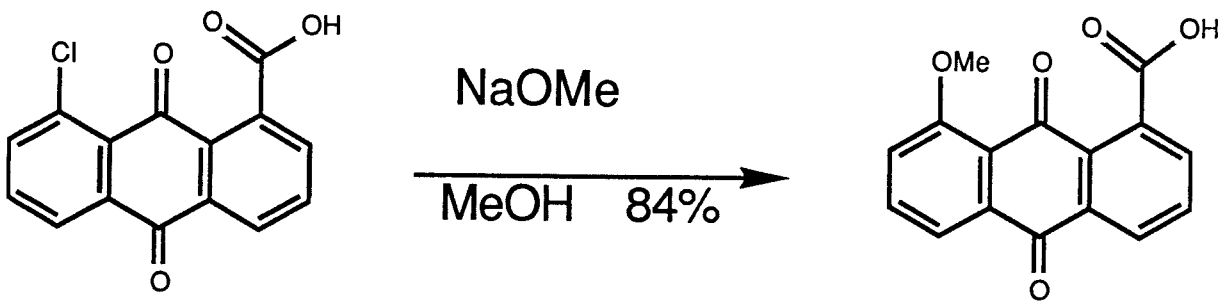
Another, more recently developed method for the preparation of carboxylic esters, is the Mitsonobu reaction[40]. Scheme 9 shows one example of its use in this context[47].

Scheme 9

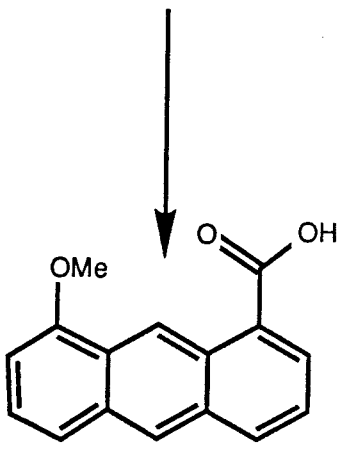


However, we were unable to couple (38) with monensin using this method.

In order to establish whether the benzyl protecting group in (38) was hindering coupling by steric interference, 8-methoxy anthracene-1-carboxylic acid (40) was synthesised from 8-chloroanthraquinone-1-carboxylic acid using the method in Scheme 10[38].



Scheme 10



40

However, attempts to couple (40) with monensin A sodium salt using the acid chloride condensation methodology failed.

Again starting materials were recovered even after prolonged reaction times.

A number of other attempts were made to couple a variety of anthracene and anthraquinone carboxylic acids with monensin, and a list of these appears in Table 3. In addition to the esterification methods mentioned previously, methods involving ethyl chloroformate/triethylamine[41] and trifluoroacetic anhydride/triethylamine[42] were attempted. Both these methods rely on the nucleophilic attack of an alcohol on a mixed anhydride formed between the carboxylic acid and the reagent.

6.6 Conclusions

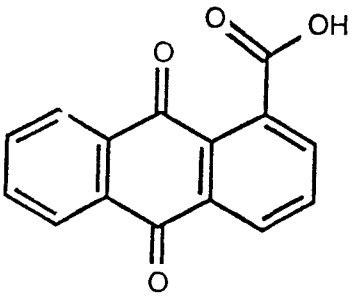
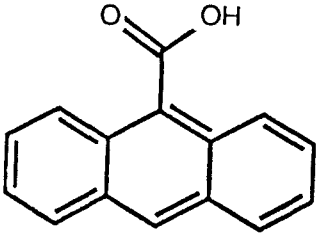
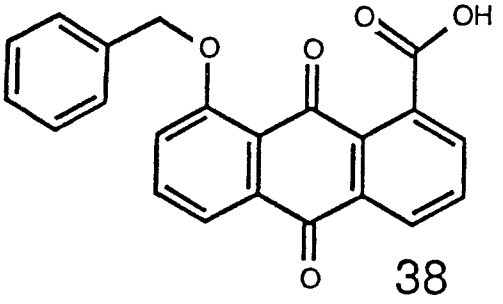
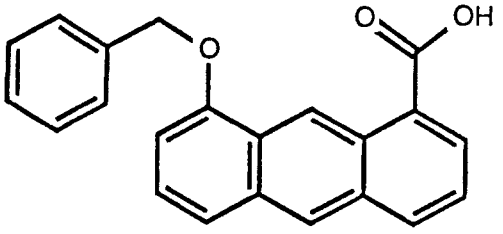
The principle achievements of our studies on labelled monensin derivatives are:

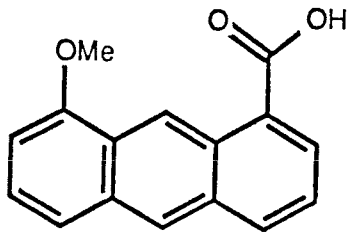
1) It was possible to extend the selective acylation methodology previously applied to the preparation of (21), to the synthesis of the monensin derivatives (35) and (36) in reasonable yield.

2) It proved possible to synthesise a suitably protected chromophore containing a latent hydroxyl group which we hoped would be a more suitable chromophore with which to label monensin.

However, because of our inability to prepare more highly functionalised chromophoric monensin derivatives, and because those derivatives which were prepared, although clearly capable

TABLE 3 Attempted Couplings between Monensin A Sodium and Anthraquinone/Anthracene Carboxylic acids

Substrate	Method
	1 2 3 4 5
	1 2 3 4 5
 38	1 2 3
 41	1

Substrate	Method
 40	1

Methods

1. Acid Chloride condensation.
2. Mitsonobu conditions.
3. Triethylamine/ethyl chloroformate mixed anhydride.
4. Triethylamine/trifluoroacetic anhydride mixed anhydride method.
5. DCC/DMAP

of forming sodium salts, did not display effects in their electronic spectra resulting from electrostatic interactions between bound sodium ions and the anthracene π-system, this area of research was curtailed.

CHAPTER SEVEN

EXPERIMENTAL

7.1 General Procedures and Instrumentation

Details of general procedures adopted and of instruments used to obtain spectral data are given in Section 4.1.

7.2 Anthraquinone and Anthracene Derivatives

The following compounds were all prepared using the methods of Golden and Stock[48].

Anthraquinone-1-carboxylic acid from
1-chloroanthraquinone as a yellow powder
in 73% yield.
mp 291°C, lit[48] 293-294°C (chlorobenzene)
IR (Nujol) ν_{max} cm^{-1} : 1690 (m), 1580 (m), 1330 (m)

8-Chloroanthraquinone-1-carboxylic acid from
1,8-dichloroanthraquinone as a yellow powder
in 50% yield.
mp 243-244°C, lit[4] 245-246°C (chlorobenzene)
IR (nujol) ν_{max} cm^{-1} : 1710 (m), 1680 (s)
1375 (m), 1330 (m)
MS : 286.0005 (M^+, 4%), 242 (20%)
214 (15%)

$C_{15}H_7O_4{}^{35}Cl$ require 286.0033

8-Hydroxyanthraquinone-1-carboxylic acid from
8-chloroanthraquinone-1-carboxylic acid as an
orange powder in 87% yield.
mp 253-254°C, lit [48] 253°C (chlorobenzene)
IR (Nujol) ν_{max} cm^{-1} : 1710 (m), 1675 (s),
1580 (m)
MS : 268.0387 (M^+, 7%), 250 (8%)
222 (7%)

$C_{15}H_8O_5$ require 268.0372

8-Methoxyanthraquinone-1-carboxylic acid from 8-chloroanthraquinone-1-carboxylic acid as yellow crystals in 84% yield.

mp 274°C, lit[46] 288°C (chlorobenzene)

IR (nujol) ν_{max} cm^{-1} : 3500 - 2600 (broad), 1720 (m), 1680 (s), 1580 (s).

Found : C, 68.4; H, 3.5%

$C_{16}H_{10}O_5$ requires : C, 68.1; H, 3.6%

Anthracene-1-carboxylic acid from anthraquinone 1-carboxylic acid as yellow crystals in 28% yield.

mp 248-249°C, lit[48] 249°C (ethyl acetate)

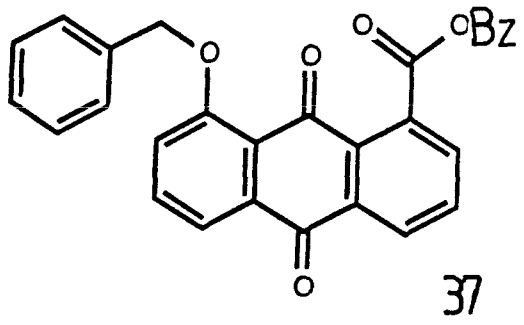
8 Chloroanthracene-1-carboxylic acid from 8 chloroanthraquinone-1-carboxylic acid as an orange powder in 74% yield.

mp 265-266°C, lit[40] 267°C (chlorobenzene)

8-Methoxanthracene-1-carboxylic acid from 8-methoxyanthraquinone-1-carboxylic acid as orange needles in 61% yield

mp 266°C, lit[48] 271°C (chlorobenzene)

8-Benzyloxyanthraquinone-1-carboxylic acid benzyl ester (37)



37

To a stirred suspension of sodium hydride (60mg, 2.51mmol) in dimethylformamide (3ml) at room temperature, under an atmosphere of nitrogen, was added 8-hydroxyanthraquinone-1-carboxylic acid (217mg, 0.81mmol) in dimethylformamide (2ml). The mixture was left for 20 minutes until all hydrogen evolution had ceased. Benzyl bromide (0.41g, 2.4mmol) and tetra-n-butyl ammonium iodide (10mg, 0.03mmol) were then added as a solution in dimethylformamide (2ml). The resulting purple mixture was warmed to 60°C on an oil bath. After 3 hours the mixture was allowed to cool before being added to dilute hydrochloric acid. The resulting mixture was extracted with dichloromethane and the extracts washed with water, before drying ($MgSO_4$), and removal of the solvent under reduced pressure yielded a brown oil (830mg). Chromatography over silica gel with ether/toluene (1.1) as eluant yielded 8-benzyloxyanthraquinone-1-carboxylic acid benzyl ester (37) (295mg, 84%) as an orange solid

mp 124 - 125°C (dichloromethane-pentane)

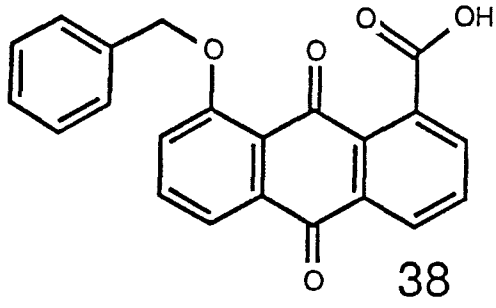
^1H NMR ($CDCl_3$, 360MH_z) : 8.29 (1H,m), 7.87 (1H,d, J 7.7 Hz), 7.80 - 7.21 (14H, complex), 5.43 (2H,s), 5.26 (2H,s).

IR (CH_2Cl_2) ν max cm^{-1} : 3020 (w), 1735 (s), 1680 (vs), 1590 (s)

Found : C, 77.2; H, 4.5

$C_{29}H_{20}O_5$ requires : C, 77.7; H, 4.5

8-Benzyloxy anthraquinone-1-carboxylic acid (38)



38

8-Benzyloxyanthraquinone-1-carboxylic acid benzyl ester (89mg, 0.21mmol) was stirred in ethanol/dichloromethane (2:1) (5ml) containing potassium hydroxide (0.5g) at room temperature. After

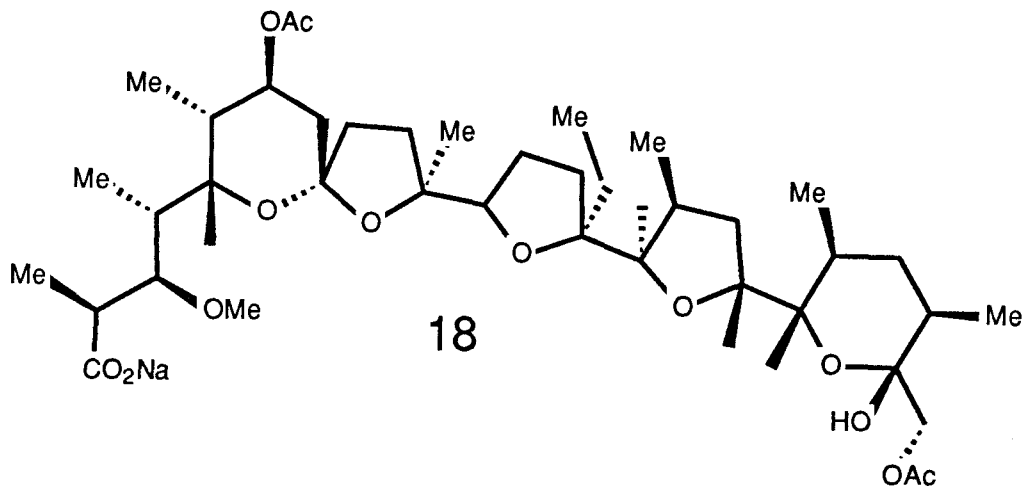
16h the solvent was removed under reduced pressure and the residue mixed with dichloromethane. The mixture was extracted with aqueous potassium hydroxide (10%). The extracts were washed with dichloromethane before acidification with hydrochloric acid (35%). The resulting yellow mixture was extracted with dichloromethane. The extracts were washed with water before drying ($MgSO_4$) and removal of the solvents at reduced pressure yielded 8-benzyloxyanthraquinone-1-carboxylic acid (38) (72mg, 98%) as an orange powder.

mp 208 - 210°C (ethyl acetate)

^{1}H NMR (DMSO d6, 360MHz)	:	8.40 - 7.23 (11H, complex), 5.39 (2H,s)
IR (CH_2Cl_2) ν max cm^{-1}	:	3050 (w), 2950 (w), 1715 (s), 1680 (vs), 1590 (s)
MS	:	358 (M^+, 0.1%), 340.0714 (M^+-H_2O, 4.5%), 250 (4.4%)
$C_{22}H_{14}O_5 - H_2O$ requires		340.0736
Found :		C, 73.4; H, 3.9%
$C_{22}H_{14}O_5$ requires		C, 73.7; H, 3.9%

7.3 Monensin Derivatives

7,26 - Diacetoxy monensin A sodium salt (18)



18

To a stirred solution of monensin A sodium salt (1.00g, 1.37mmol) in pyridine (6ml) was added acetic anhydride (5ml) at room temperature. After 12h, the mixture was poured into ice water and extracted with dichloromethane. The extracts were washed with dilute hydrochloric acid, dried (Na_2SO_4) and concentrated under reduced pressure to yield 7,26 - diacetoxy monensin A sodium salt (18) as a colourless foam (1.02g, 96%)

^1H NMR ($CDCl_3$, 360MHz) : 4.76 (1H,m), 4.28 - 3.41 (8H, complex), 3.36 (3H, s), 2.62 (1H, m), 2.27 - 0.80 (52H, complex)

^{13}C NMR ($CDCl_3$) : 178.37 (C), 171.24 (C), 170.83(C), 106.56 (C), 96.39 (C), 86.12 (C), 84.45 (CH), 82.12 (CH),

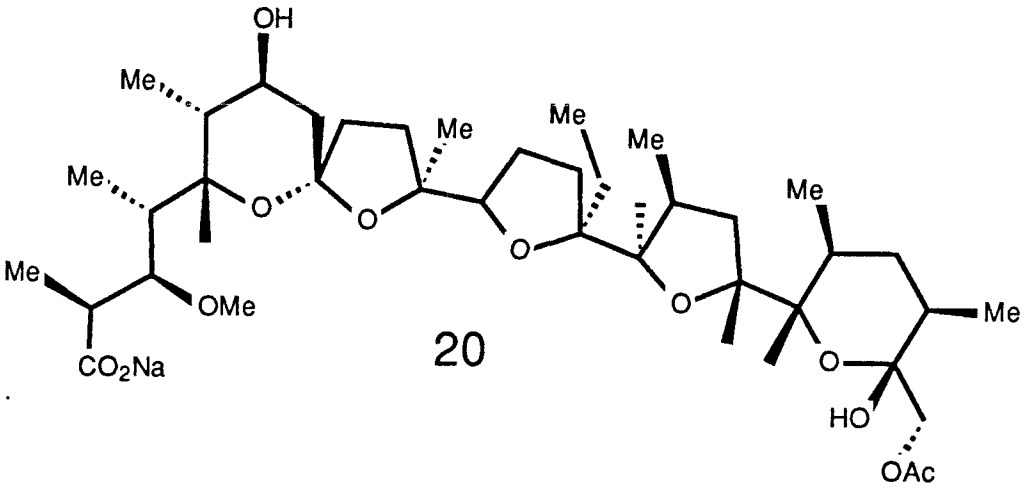
76.62 (CH), 76.48 (CH), 73.05 (CH), 70.03 (CH), 68.36 (CH), 67.85 (CH_2), 58.37 (OCH_3), 40.46 (CH), 39.49 (CH), 37.28 (CH), 36.98 (CH_2), 35.24 (CH), 35.10 (CH), 33.59 (CH_2) 33.28 (CH_2), 33.09 (CH), 32.97 (CH_2), 32.61 (CH), 30.76 (CH_2), 28.79 (CH_2), 27.06 (CH_2), 24.69 (CH_3), 21.56 (CH_3), 20.89 (CH_3), 17.29 (CH_3), 16.14 (CH_3), 15.88 (CH_3), 12.63 (CH_3), 11.79 (CH_3), 10.41 (CH_3), 7.78 (CH_3).

IR (CH_2Cl_2) ν max cm^{-1} : 3550 - 3200 (broad), 2960 (s), 1725 (vs), 1450 (m), 1390 (m)

MS (FAB, glycerol) : 779 (MH^+,2.1%), 737 (6.0%) 694 (4.2%)

$C_{40}H_{67}O_{13}Na$ requires 778

26-Acetoxy monensin A sodium salt (20)



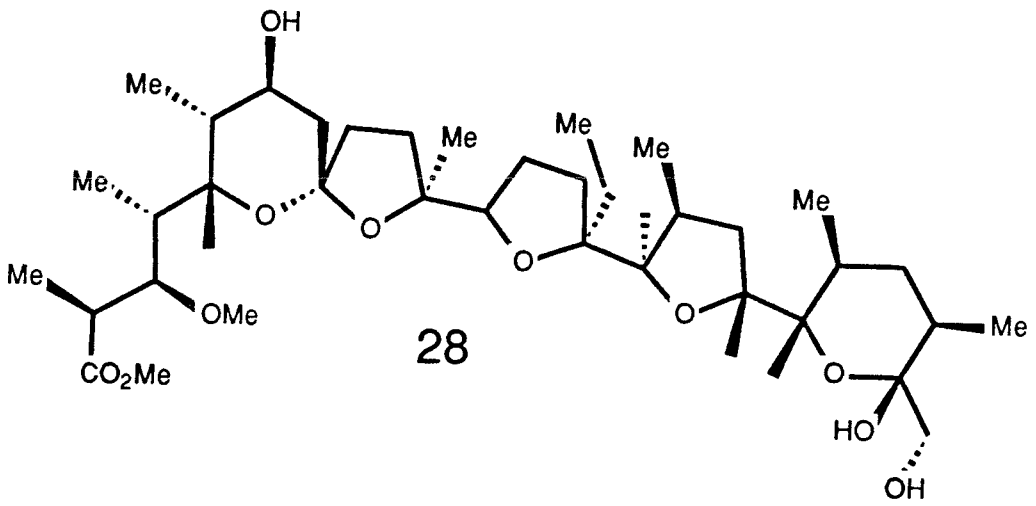
20

To a stirred solution of monensin A sodium salt (5.00g, 6.89mmol) in pyridine (18ml) was added acetic anhydride (0.72g, 7.05mmol) at room temperature. After 12h. the mixture was poured into ice water and extracted with dichloromethane. The extracts were washed with dilute hydrochloric acid, dried (Na_2SO_4) and concentrated under reduced pressure to yield a foam (5.1g). Chromatography over silica gel with ethyl acetate/ light petroleum (1:4) as eluant yielded 26-acetoxy monensin A sodium salt (20) (1.53g, 30%) as a colourless foam

^1H NMR ($CDCl_3$, 360MHz) : 4.25(2H,m), 4.16(2H,m), 4.02(2H,m), 3.80(1H,m), 3.51(1H,m), 3.34(3H,s), 3.30(2H,m), 2.62(1H,m), 2.30 - 0.78(49H, complex)

^{13}C NMR ($CDCl_3$)	:	177.18(C), 170.88(C), 107.84(C), 96.72(C), 86.42(C), 85.12(CH), 83.33(CH), 82.01(CH), 77.01(CH), 75.68(CH), 71.23(CH), 67.74(CH_2), 67.55(CH), 58.15(OCH_3), 40.98(CH), 38.94(CH_2), 37.19(CH), 36.63(CH_2), 35.42(CH), 35.31(CH), 34.99(CH), 34.55(CH_2), 33.29(CH_2), 33.11(CH_2), 32.85(CH), 31.28(CH_2), 30.47(CH_2), 27.96(CH_2), 26.67(CH_3), 21.06(CH_3), 17.55(CH_3), 16.22(CH_3), 15.99(CH_3), 14.09(CH_3), 11.28(CH_3), 10.79(CH_3), 8.29(CH_3).
IR (CH_2Cl_2) ν max cm^{-1}	:	3450 - 3050 (broad), 2950 (m), 1725 (m), 1400 (w), 1380 (m).
MS (FAB, glycerol)	:	735(MH^+, 3.7%), 697 (3.0%), 696 (11.1%)
$C_{38}H_{63}O_{12}Na$ requires		734

Monensin A methyl ester (28)



28

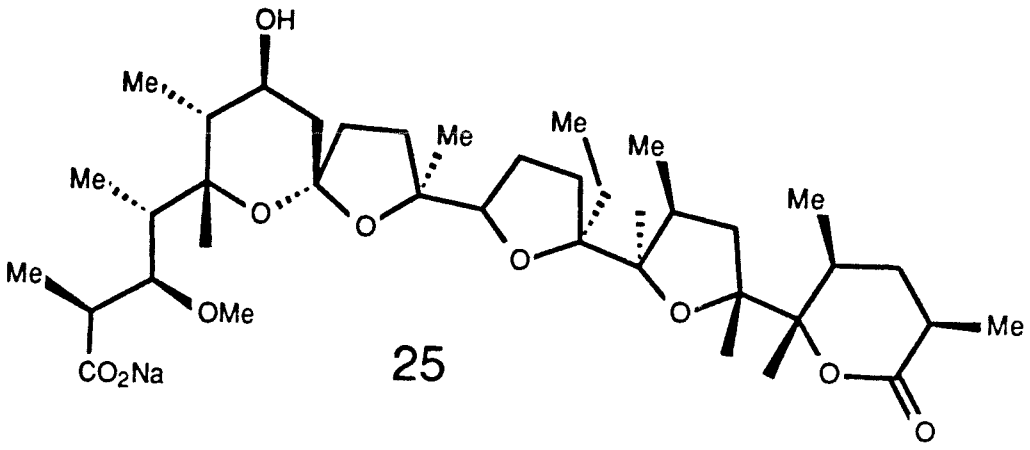
To a stirred solution of monensin A free acid (5.5g, 7.55mmol) in diethyl ether (50ml) at 0°C under an atmosphere of nitrogen was added diazomethane (1.0g, 23mmol) as a solution in ether (50ml). After 1h. the yellow solution was treated with glacial acetic acid (1ml) to destroy the residual diazomethane. The reaction mixture was then concentrated under reduced pressure, furnishing a clear oil (5.7g). Chromatography over silica gel with ethyl acetate/light petroleum (1:1) as eluant yielded monensin A methyl ester (28) (3.2g, 62%) as a clear oil.

^{1}H NMR ($CDCl_3$, 360MHz) : 4.30(1H,m), 4.1-3.85(4H, complex), 3.76(3H,s), 3.68-3.42(5H, complex), 3.33(3H,s), 2.70(1H,m), 2.30-1.15(22H, complex), 1.03-0.73 (24H, complex)

^{13}C NMR ($CDCl_3$) : 175.50(C), 107.40(C), 96.80(C), 87.01(C), 86.15(C), 85.37(CH), 83.46(CH), 81.66(CH), 76.72(CH), 76.00(CH), 71.07(CH), 67.66(CH), 67.08(CH_2), 57.95(OCH_3), 51.42(OCH_3), 40.71(CH), 38.87(CH_2), 37.03(CH), 36.74(CH_2), 35.83(CH), 34.93(CH), 34.55(CH), 34.23(CH_2), 33.64(CH_2), 32.84(CH), 32.09(CH_2), 31.06(CH_2), 29.29(CH_2), 27.59(CH_2), 25.36(CH_3), 17.12(CH_3), 15.84(CH_3), 15.46(CH_3), 12.08(CH_3), 11.86(CH_3), 10.78(CH_3), 7.69(CH_3).

IR (CH_2Cl_2) ν max cm^{-1} : 3550 - 3050 (broad), 2950 (s), 1735 (s), 1455 (m), 1390 (m)

25-De(hydoxymethyl)-25-deoxy-25-oxomonensin A (25)



25

To a stirred solution of monensin A sodium salt (5.00g, 6.89mmol) in isobutyl alcohol/methanol (3:1) (100ml) under an atmosphere of nitrogen at room temperature was added a solution of sodium periodate (3.7g, 17.3mmol) in water (33ml). After 48h. the mixture was diluted with water, filtered and the filtrate extracted with dichloromethane. The extracts were washed with water and dried (Na_2SO_4) before removal of the solvent under reduced pressure to yield a foam (5.7g). Chromatography over silica gel with ethyl acetate/light petroleum (1:1) as eluant yielded 25-de(hydroxymethyl)-25-deoxy-25-oxomonensin A (25) (4.02g, 89%) as a white foam.

^1H NMR ($CDCl_3$, 360MHz) : 4.23 (1H,m), 4.11 (1H,m), 4.04 (1H,m), 4.00 (1H,m), 3.75 (1H,m), 3.66 (1H,m),

3.53 (1H,m), 3.46 (1H,m), 3.34 (3H,s), 2.61 (1H,m), 2.41 (1H,m), 2.28 (1H,m), 2.15–1.44 (17H, complex), 1.37 (2H,m), 1.29–0.85 (24H, complex).

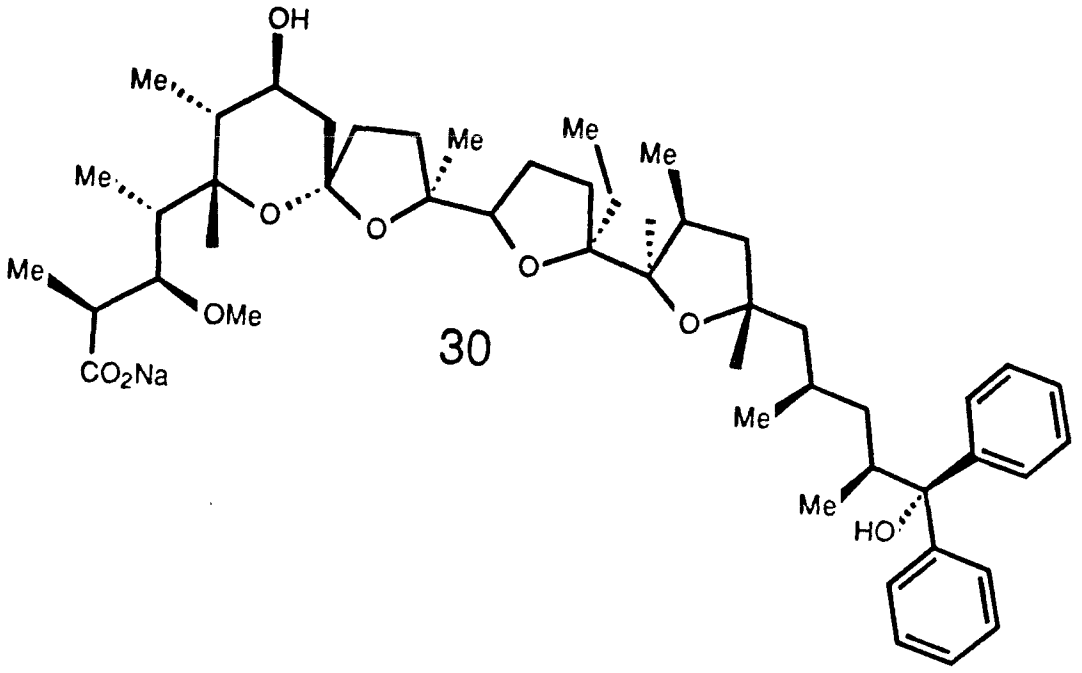
^{13}C NMR ($CDCl_3$) : 178.64 (C), 174.26 (C), 107.6(C), 88.37 (C), 88.15 (CH), 86.54 (C), 85.94 (C), 83.25 (CH), 81.71 (CH), 77.62 (CH), 71.66 (CH), 67.92 (CH), 58.17 (CH_3), 40.97 (CH), 39.51 (CH_2), 37.50 (CH_2), 37.17 (CH), 36.05 (CH), 35.92 (CH), 35.42 (CH_2), 35.05 (CH), 34.66 (CH_2), 31.73 (CH), 31.38 (CH_2), 31.07 (CH_2), 29.72 (CH_2), 28.63 (CH_2) 24.72 (CH_3), 18.34 (CH_3), 17.16 (CH_3), 15.81 (CH_3), 12.55 (CH_3), 11.94 (CH_3), 10.99 (CH_3), 8.05 (CH_3).

IR (CH_2Cl_2) ν_{max} cm^{-1} : 3550 - 3100 (broad), 2950 (s), 1730 (vs), 1462 (m), 1385 (m).

MS (FAB, glycerol matrix): 661(MH^+, 48.9%), 639 (8.0%), 621 (7.3%)

$C_{35}H_{57}O_{10}Na$ requires 660

The Triol sodium salt (30)



30

To a stirred solution of the lactone (25) (200mg, 0.30mmol) in tetrahydrofuran (2ml) at room temperature under an atmosphere of nitrogen was added phenyl magnesium bromide (270mg, 1.50mmol) in tetrahydrofuran (2.6ml). After 12h. the solution was added dropwise to ice water before being acidified with dilute hydrochloric acid. The mixture was extracted with ether, and the extracts were washed with water, before being dried ($MgSO_4$). Removal of the solvents at reduced pressure yielded an oil (350mg). Chromatography over silica gel with ethyl acetate/light petroleum (1:1) as eluant yielded the triol sodium salt (30) (104mg, 44%) as an oil.

^{1}H NMR ($CDCl_3$, 360MHz) : 7.55 (4H,m), 7.23 (4H,m), 7.11 (2H,m), 5.50-4.60 (3H, broad), 4.02 (2H,m), 3.95 (1H,m), 3.80-3.60 (4H,m), 3.41 (1H,m), 3.35 (3H,s), 3.00(1H,m), 2.61 (2H,m), 2.30-1.12 (33H, complex), 1.10-0.79 (12H, complex)

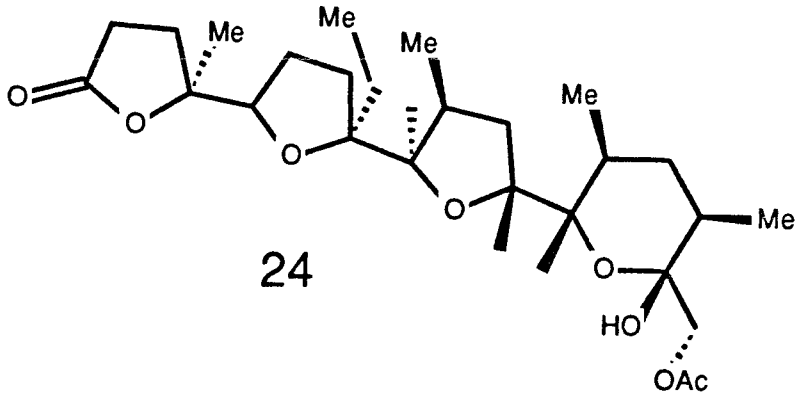
^{13}C NMR ($CDCl_3$) : 178.10 (C), 147.10(C), 146.73(C), 127.94 (CH), 127.83 (CH), 126.28 (CH), 126.23 (CH). 126.15 (CH), 126.11 (CH), 116.59 (C), 107.62 (C), 86.71 (CH), 85.96 (C), 83.38 (CH), 81.72 (CH), 81.40 (C), 77.80 (CH), 76.66 (CH), 71.47 (CH), 67.83 (CH), 58.09 (OCH_3), 41.05 (CH), 39.39 (CH), 39.19 (CH_2), 37.07 (CH_2), 36.99 (CH), 35.47 (CH), 35.21 (CH), 34.46 (CH_2), 34.07 (CH_3), 33.62(CH_2), 32.28 (CH_2), 30.18 (CH_2), 28.53 (CH_2), 25.70 (CH_3), 22,27 (CH_2), 18.06 (CH_3), 15,63 (CH_3), 13.48 (CH_3), 11.59 (CH_3), 10.82 (CH_3), 8.12 (CH_3),

IR (CH_2Cl_2) ν max cm^{-1} 3600 - 3100 (broad), 2980 (s), 1590 (s), 1465 (m), 1380 (m)

MS (FAB, glycerol matrix) : 817 (MH^+, 3.74%), 777 (1.1%), 755 (3.8%)

$C_{47}H_{69}O_{19}Na$ requires 816.5

Lactone (24)



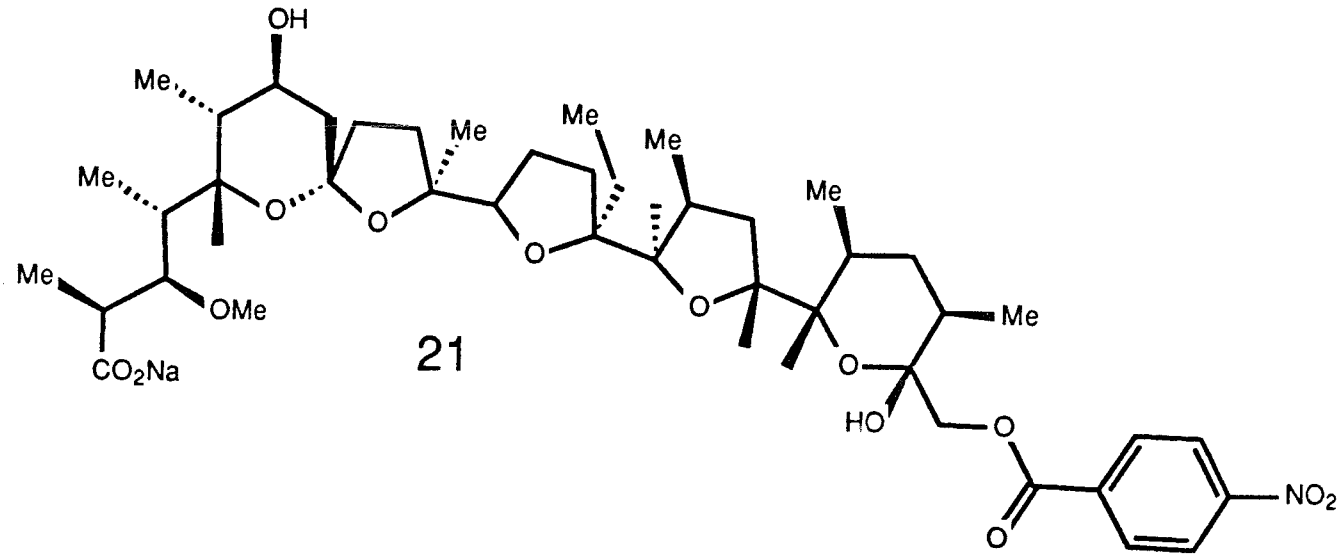
24

To a stirred solution of 7,26-diacetoxy monensin A (467mg, 0.62mmol) in glacial acetic acid (5ml) at room temperature was added chromium trioxide (120mg, 1.2mmol) in acetic acid/water (1:1) (12ml). After 12h. the solution was added to ice water and extracted with dichloromethane. The extracts were washed with sodium chloride solution and water before drying (Na_2SO_4). Removal of the solvent under reduced pressure yielded a foam (550mg). Chromatography over silica gel with ethyl acetate /light petroleum (1:2) as eluant yielded the lactone (24) (42mg,14%) as a clear oil.

^1H NMR ($CDCl_3$, 360MHz) : 4.26 (2H,m), 4.10 (3H, complex), 3.80 (1H,m), 3.65 (1H,m), 2.45-2.05 (10H, complex), 1.75 (1H,m), 1.65 (2H,m), 1.55-1.22 (11H, complex), 1.0-0.78 (12H, complex)

^{13}C NMR ($CDCl_3$)	:	179.49 (C), 171.26 (C), 96.25 (C), 88.99 (C), 87.69 (C), 83.61 (CH), 81.28 (CH), 77.46 (CH), 75,23 (CH), 67.85 (CH_2), 36.98 (CH_2), 35.50 (CH), 34.86 (CH), 32.59 (CH_2), 32.19 (CH_2), 30.42 (CH_2), 29.65 (CH_2), 29.04 (CH_2), 28.44 (CH_2), 28.09 (CH_2), 24.60 (CH_3), 20.91 (CH_3), 17.29 (CH_3), 16.50 (CH_3), 15.76 (CH_3), 7.99 (CH_3).
IR (CH_2Cl_2) νmax cm^{-1}	:	3550 - 3200 (broad), 2950 (s), 1755 (vs), 1740 (vs), 1460 (m)
MS	:	482.2820
$C_{26}H_{42}O_8$ requirss		482.2868

Monensin A 26-4-nitrobenzoate sodium salt (21)

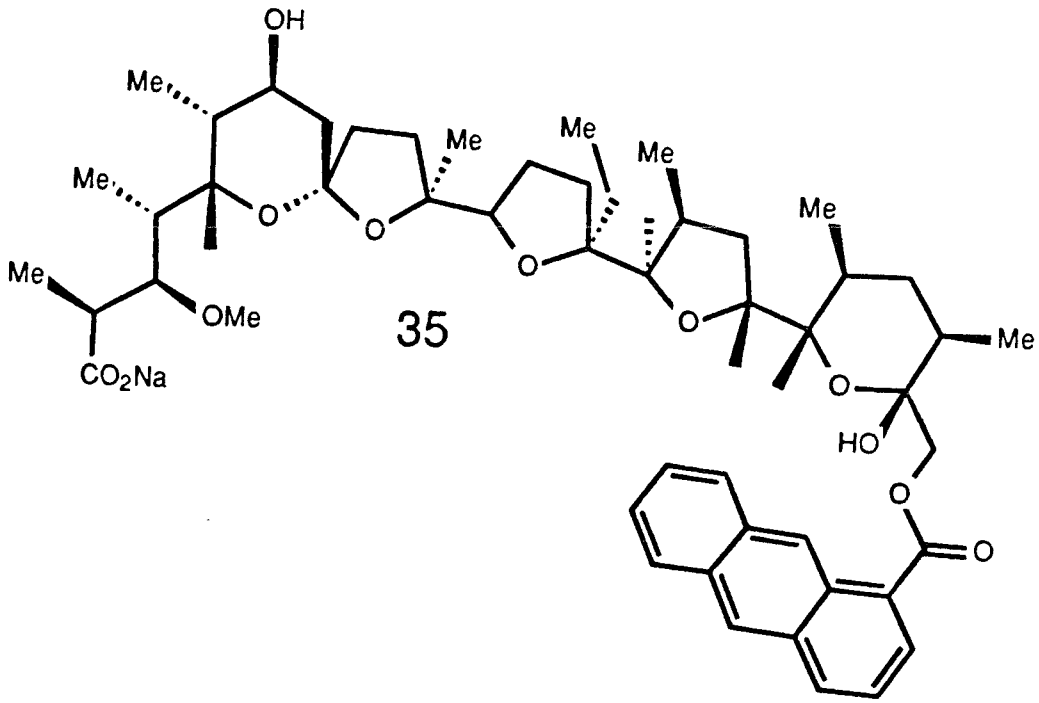


21

To a stirred solution of monensin A sodium salt (481mg, 0.66mmol) in pyridine (3ml) at room temperature under an atmosphere of nitrogen was added 4-nitro benzoyl chloride (357mg, 1.92mmol) in pyridine (4ml). After 12h. the solution was added to ice water and extracted with dichloromethane. The extracts were washed with dilute hydrochloric acid and water before being dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded a yellow foam (721mg). Chromatography over silica gel with ethyl acetate/light petroleum (1:3) as eluant yielded the 4-nitrobenzoate (21) (461mg, 83%) as a yellow foam.

^1H NMR ($CDCl_3$, 360MHz)	:	8.35-8.15 (4H,m), 4.50 (3H,m), 4.31 (1H,m), 4.12 (2H,m), 4.90 (1H,m), 3.78 (1H,m), 3.52 (1H,m), 3,38 (3H,s), 3.30 (1H,m), 2.62 (1H,m), 2.25-0.81 (46H, complex)
^{13}C NMR ($CDCl_3$)	:	177.02 (C), 164.29 (C), 150.66 (C), 136.14 (C), 130.85 (C), 123.57 (CH), 107.95 (C), 97.12 (C), 86.44 (C), 85.99 (C), 85.03 (CH), 83.49 (CH), 82.08 (CH), 76.91 (CH), 75.42 (CH). 71.20 (CH), 68.26 (CH_2), 67.22 (CH), 58.12 (OCH_3), 40.66 (CH), 38.76 (CH_2), 36.95 (CH), 36.38 (CH_2), 35.30 (CH), 35.11 (CH), 34.74 (CH), 34.48 (CH_2), 33.50 (CH_2), 32.97 (CH_2), 32.78 (CH), 31.16 (CH_2), 30.44 (CH_2), 27.63 (CH_2), 27.19 (CH_3), 17.52 (CH_3), 16.32 (CH_3), 17.52 (CH_3), 16.32 (CH_3), 15.87 (CH_3), 14.56 (CH_3), 11.00 (CH_3), 10.72 (CH_3), 8.27 (CH_3).
IR (CH_2Cl_2) ν max cm^{-1}	:	3550 - 3050 (broad),2950 (s), 1735 (v s) 1540 (s), 1450 (m)
MS (FAB, glycerol matrix)	:	844 (MH^+,0.25%), 827 (0.53%), 812 (0.47%)
$C_{43}H_{66}O_{14}N$ Na requires		843

26(Anthracene-1-carboxylic acid) Monensin A sodium salt (35)



35

To a stirred solution of anthracene-1-carboxylic acid (200mg, 0.90mmol) in benzene (2ml) at 40°C was added oxaloyl chloride (0.25ml, 2.8mmol). After 2h. the solution was allowed to cool before removal of the solvent at reduced pressure. The resulting yellow anthracene-1-carbonyl chloride was used directly without further purification.

To a stirred solution of dried monensin A sodium salt (439mg, 0.60mmol) in pyridine (2ml) at room temperature under an atmosphere of nitrogen was added the anthracene-1-carbonyl chloride as a solution in pyridine (2ml). After 3h. the solvent was removed under reduced pressure and the residue chromatographed

over silica gel with ethyl acetate/light petroleum/glacial acetic acid (49:49:2) as eluant. The product 26(anthracene-1-carboxylic acid) monensin A sodium salt (35) (146mg, 27%) was a yellow foam.

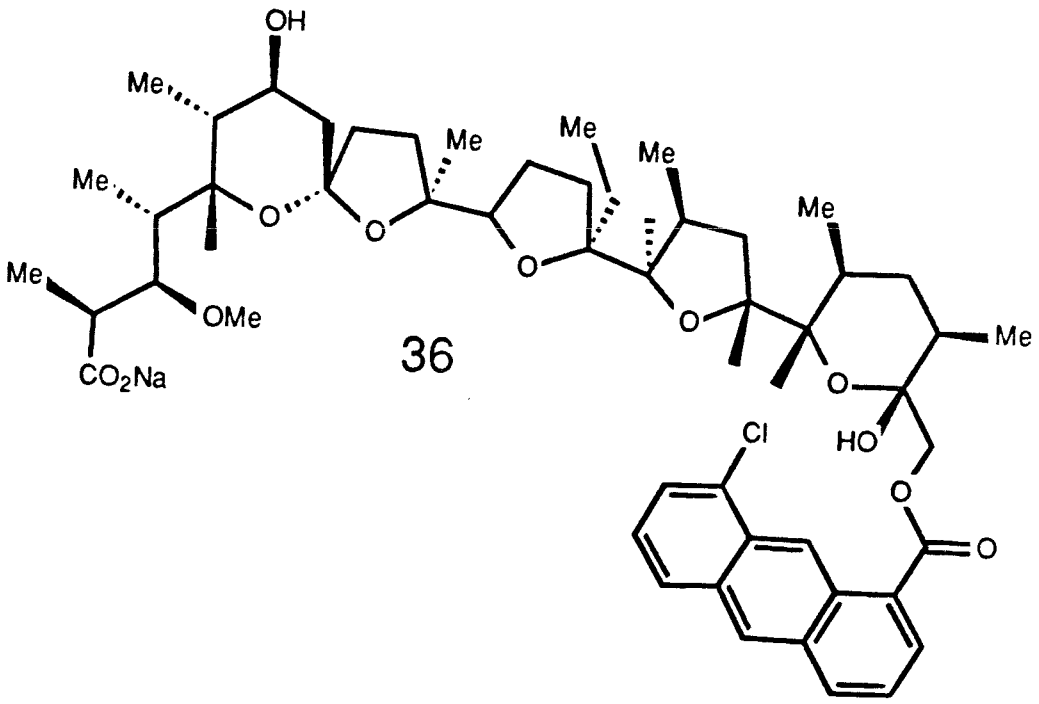
^{1}H NMR ($CDCl_3$, 360MHz) : 9.61 (1H,s), 8.41 (1H,s), 8.24 (2H,m), 8.05 (2H,m), 7.47 (3H,m), 4.60 (2H,m), 4.31 (1H,m), 4.14 (2H,m), 4.03 (1H,m), 3.79 (1H,m), 3.49 (1H,m), 3.36 (3H,s), 3.31 (2H,mO, 2.67 (1H,m), 2.27-1.02 (34H, complex), 1.00-0.80 (12H, complex).

^{13}C NMR ($CDCl_3$) : 177.37 (c), 166.92 (C), 134.02 (CH), 132.87 (C), 132.00 (C), 131.54 (C), 130.98 (CH), 129.27 (CH), 128.93 (C), 127.76 (CH), 127.08 (C), 126.97 (CH), 126.02 (CH), 125.89 (CH), 125.68 (CH), 123.71 (CH), 107.89 (C), 97.40 (C), 86.46 (C), 86.32 (C), 85.03 (CH), 83.47 (CH), 82.05 (CH), 77.06 (CH), 75.67 (CH), 71.26 (CH), 67.51 (CH_2), 67.30 (CH), 58.12 (OCH_3), 40.74 (CH), 38.89 (CH_2), 37.05 (CH), 36.55 (CH_2), 35.21 (2CH), 34.72 (CH), 34.57 (CH), 33.23 (CH_2), 33.14 (CH_2), 32.96 (CH), 31.17 (CH), 30.21 (CH_2), 27.69 (CH_2),

26.92 (CH_3), 17.54 (CH_3), 16.39 (CH_3), 15.79 (CH_3), 14.45 (CH_3), 11.05 (CH_3), 10.74 (CH_3), 8.16 (CH_3).

IR (CH_2Cl_2) ν_{max} cm^{-1} : 3550 - 3100 (broad), 2950 (s), 1710 (s), 1601 (m), 1450 (m)

26-(8-Chloroanthracene-1-carboxylic acid)Monensin A sodium salt (36)



36

(95%) from 8-chloroanthracene carboxylic acid and monensin A sodium as a yellow foam.

^{1}H NMR ($CDCl_3$, 360MHz) : 10.09 (1H,s). 8.43 (1H,s), 8.34 (1H,m), 8.16 (1H,d, J 8.6 Hz), 7.88 (1H,d, J 8.6Hz), 7.59 (1H,d, J7.0Hz), 7.51 (1H,m), 7.36 (1H,m), 4.61 (2H,m), 4.30 (1H,m), 4.10 (2H,m), 3.98 (1H,m), 3.78 (1H,m), 3.47 (2H,m), 3.34 (3H,s), 3.31 (1H,m), 2.65 (1H,m), 2.22-0.98 (34H, complex), 0.95-0.76 (12H, complex).

^{13}C NMR ($CDCl_3$) : 177.20 (c), 165.50 (C), 133.57 (CH), 131.50 (CH), 127.55 (CH), 127.09 (CH), 125.89 (CH), 125.47 (CH), 124.59 (H), 122.97 (CH), 107.76 (C), 97.18 (C), 86.50 (2C), 85.20 (CH), 83.44 CH), 81.90 (CH), 76.96 (CH), 76.66 (CH), 71.23 (CH), 67.86 (CH_2), 67.34 (CH), 58.08 (OCH_3), 40.66 (CH), 38.87 (CH_2), 37.06 (CH), 36.59 (CH_2), 35.21 (2CH), 34.75 (CH), 34.48 (CH_2), 33.23 (CH_2), 32.94 (CH_2), 32.88 (CH), 31.12 (CH_2), 30.17 (CH_2), 27.76 (CH_2), 26.67 (CH_3), 17.51 (CH_3), 16.37 (CH_3), 15.79 (CH_3), 14.16 (CH_3), 11.12 (CH_3), 10.74 (CH_3), 8.06 (CH_3),

IR (CH_2Cl_2) ν max cm^{-1} : 3600 - 3050 (broad), 2950 (vs), 1725 (s), 1460 (m), 1380 (m)

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