

PATENT SPECIFICATION

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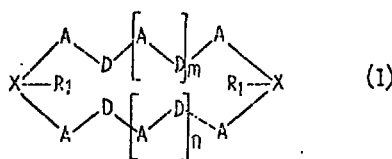
(72) Inventor JEAN-MARIE LEHN

(54) NEW MACROCYCLIC HETEROCYCLIC COMPOUNDS AND COMPLEXES THEREOF

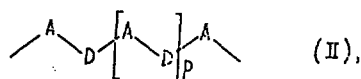
(71) We, SCHERICO LTD., of Topferstrasse 5, 6000 Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel macrocyclic heterocyclic compounds, to processes for their preparation, to complexes formed from the novel macrocyclic compounds and to processes for the preparation of such complexes.

The novel macrocyclic compounds of this invention may be illustrated by the general formula I



where each R_1 is hydrogen, a hydrocarbon group having up to 12 carbon atoms or an alkoxy-carbonyl group having up to 10 carbon atoms, or both R_1 form together a grouping of the general formula II



(i.e. providing a bridge between the two X-groupings in the molecule);

each A is a hydrocarbon group having up to 12 carbon atoms;

each X is nitrogen or phosphorus;

each D is oxygen, sulfur, $>\text{N}\text{---}\text{R}$ (R being hydrogen or a hydrocarbon group having up to 12 carbon atoms) or a hydrocarbon group having up to 12 carbon atoms, with the proviso that, at least two of the groups or atoms represented by D are selected from oxygen, sulfur and $>\text{N}\text{---}\text{R}$, and that when each R_1 is hydrogen, hydrocarbon or alkoxy-carbonyl and both X are nitrogen, then one of these two groups or atoms

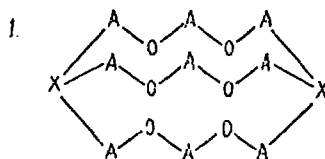
represented by D is oxygen or sulfur and the other is oxygen or $>N-R$; and each of m, n and p is a whole number from 0 to 5 inclusive.

Included amongst the compounds of this invention are the phosphonium and/or ammonium salts of the compounds of general formula I, the nitrogen and/or phosphorous oxides of the compounds of general formula I having tertiary nitrogen and/or phosphorus and complexes formed from the compounds of general formula I and from the N- and/or P-oxides, with organic or inorganic cations.

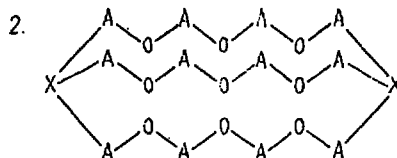
The hydrocarbon groups represented by A and D preferably have at least 2 carbon atoms. Preferred are: straight and branched chained alkylene and alkenylene groups having from 2 to 8 carbon atoms such as ethylene, propylene, butylene and hexylene and their unsaturated analogs; cycloalkylene and cycloalkenylene groups such as cyclopropylene, cyclobutylene, cyclohexylene and cycloheptylene and their unsaturated analogs; the corresponding cycloalkylene-di-alkyl groups such as cyclohexylene-dimethyl and aromatic groups such as phenylene and phenylene-di-alkyl, preferably phenylene-di-methyl. The groupings A which are adjacent to X preferably have an aliphatic moiety attached to X.

The hydrocarbon groups represented by R_i preferably have from 1 to 8 carbon atoms. Preferred are straight and branched alkyl groups having from 1 to 8 carbon atoms and straight or branched alkenyl groups having from 2 to 8 carbon atoms. Other typical representatives are cycloalkyl, aralkyl and aryl groups. The preferred alkoxy carbonyl groups represented by R_i are those having up to eight carbon atoms.

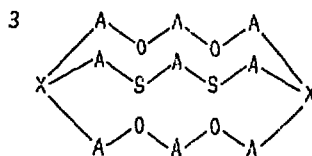
Preferred groups of compounds of this invention are those in which m, n and p are integers from 0 to 2 and in which both X are the same and compounds in which each X is nitrogen, each O is oxygen and m, n and p are other than zero. Typical configurations are listed below:



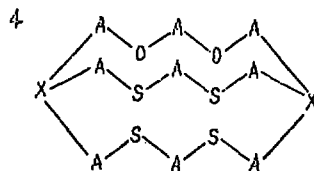
a) $X=N$
b) $X=P$



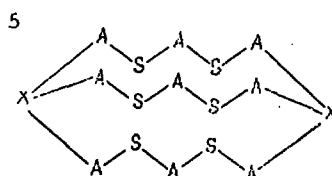
a) $X=N$
b) $X=P$



a) $X=N$
b) $X=P$

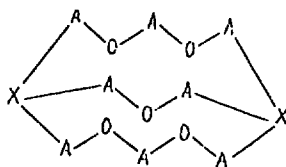


a) $X=N$
b) $X=P$



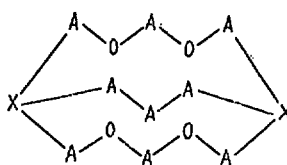
a) $X=N$
b) $X=P$

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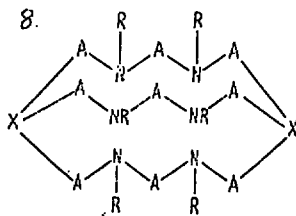
- a) $X=N$
b) $X=P$

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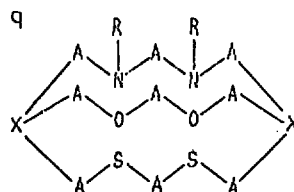
- a) $X=N$
b) $X=P$

8.



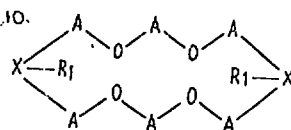
- a) $X=N$
b) $X=P$

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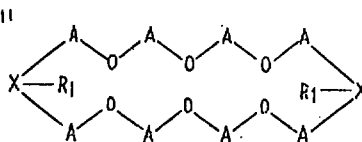
- a) $X=N$
b) $X=P$

10.



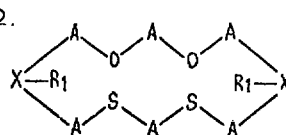
- a) $X=N$
b) $X=P$

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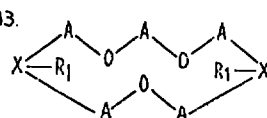
- a) $X=N$
b) $X=P$

12.

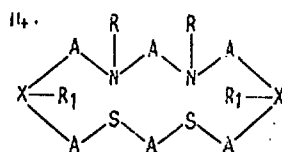


- a) $X=N$
b) $X=P$

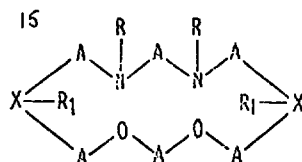
13.



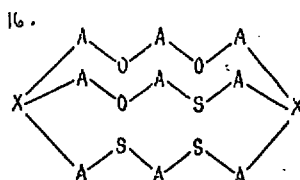
- a) $X=N$
b) $X=P$



- a) $X=N$
b) $X=P$



- a) $X=N$
b) $X=P$



- a) $X=N$
b) $X=P$

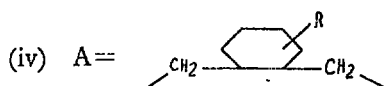
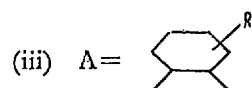
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The typical representatives of the compounds of this invention may be illustrated by inserting various groups for A and R_1 in the above formulae:

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- (i) $A = -CH_2-CH(R)-$
(ii) $A = -CH_2-CH(R)-CH_2-$ or $-CH(R)-CH_2-CH_2-$

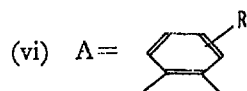


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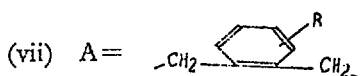
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- (v) $A =$ unsaturated analogs of the groupings (i) to (iv)

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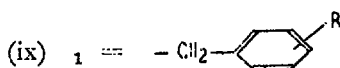


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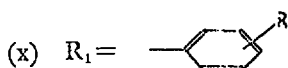


- (viii) $R_1 = -CH_3$; $-CH_2-CH_2R$; $-CH_2-CH(R)-CH_3$; and unsaturated analogs

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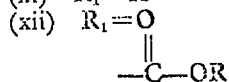


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- (xi) $R_1 = H$



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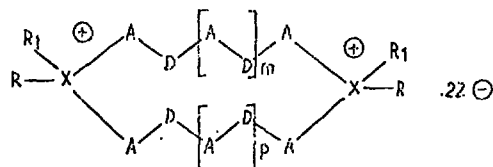
wherein in formulae (i) to (xi) R is a hydrogen atom or a hydrocarbon group (with the proviso that the total number of carbon atoms in groups A and R_1 does not exceed 12) and in formula (xii) R is a hydrocarbon group having from 1 to 9 carbon atoms.

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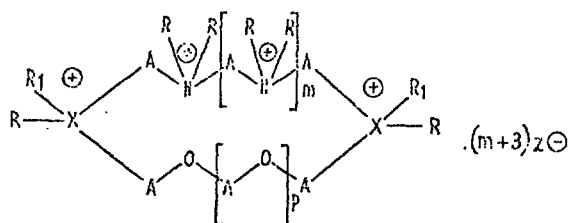
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The phosphonium and/or ammonium salts may be illustrated by the following general formulae:

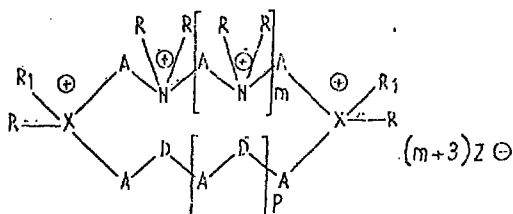
A:



B:



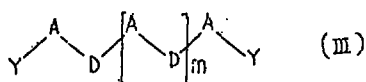
C:



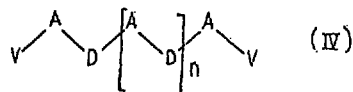
wherein A, D, R, R₁, X, m and p are as previously defined and Z is an inorganic or organic anion. It is obvious to one skilled in the art that several other configurations are possible.

The compounds of this invention may be prepared by using known chemical reactions. The principle of the processes is to condense two linear compounds to form a cyclic compound or to introduce a bridge into a cyclic starting compound, whereby the desired bicyclic compound may be obtained.

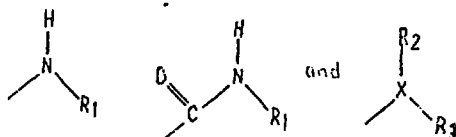
A suitable process for the preparation of the compounds of this invention is characterized in that a compound of the general formula III



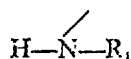
is condensed with a compound of the general formula IV



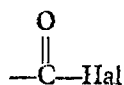
wherein A, D, m and n are as previously defined and either Y is selected from the groupings



R₁ and X being as previously defined R₂ being a hydrogenolysable group and R₃ being the same as R₁ or R₂, and V is a leaving group (as hereinafter defined) which is sufficiently labile to be displaced by Y; or Y is the grouping



and V is the grouping



R₁ being as above defined and Hal representing a halogen atom, the condensation being performed using high dilution techniques; that any carbonyl groups in a so-obtained compound is reduced to CH₂ and that, if desired, a compound obtained by any of the previous steps is subjected to one or more of the following finishing steps:

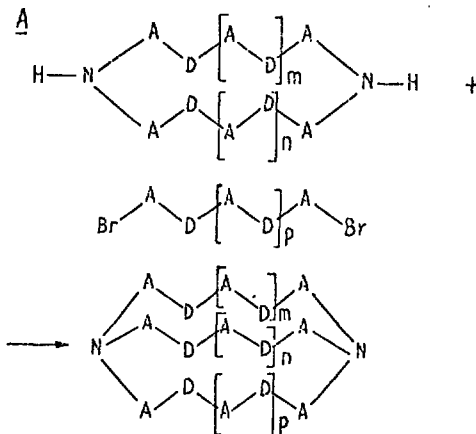
- (a) hydrogenolysis of any hydrogenolysable groups represented by R₂ and/or R₃;
- (b) transformation into a phosphonium and/or ammonium salt;
- (c) transformation of any phosphonium and/or ammonium salt into the free compound;
- (d) transformation into a N- and/or P-oxide;
- (e) transformation into a complex containing an organic or inorganic cation and
- (f) transformation of a complex into the free compound, for example, by treatment with an acid.

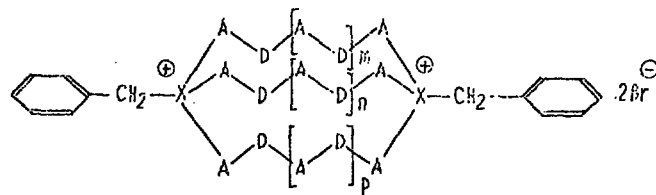
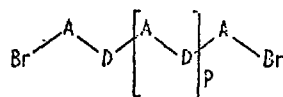
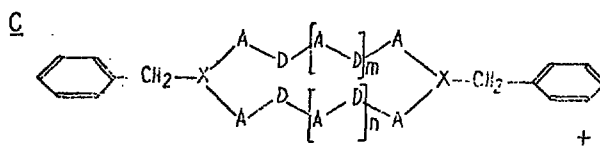
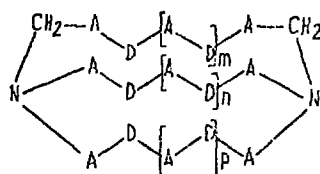
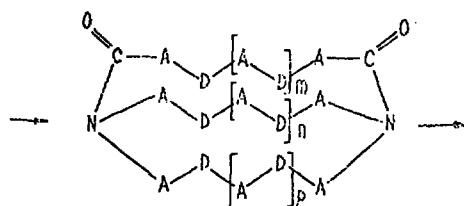
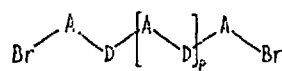
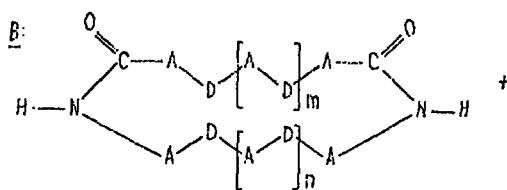
By the term "leaving group" as used herein is meant a group bound to a carbon atom by a single bond and capable of leaving the bonded site together with the electrons by which it was bound to the carbon atom.

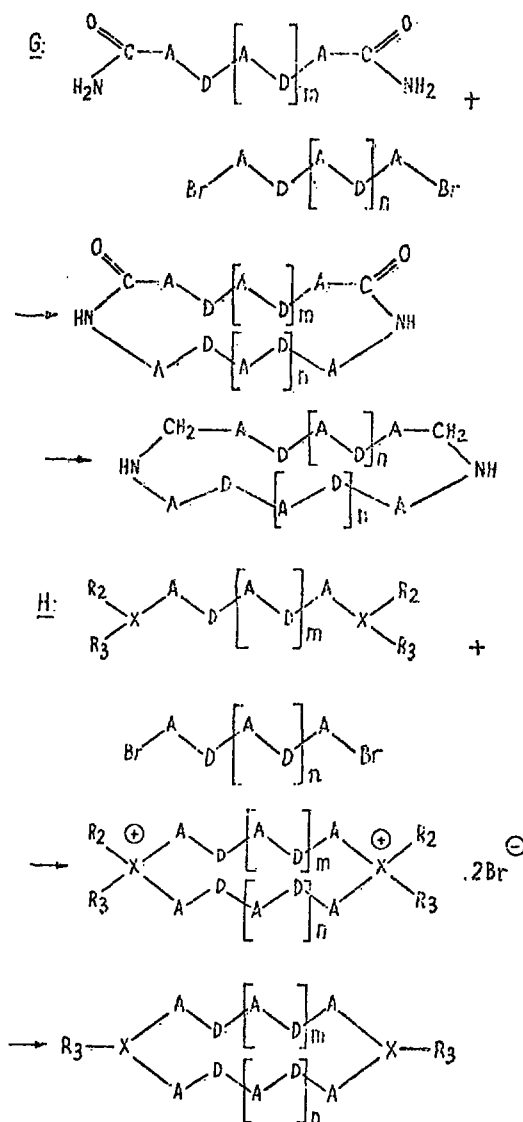
Examples of leaving groups which are sufficiently labile to be displaced by Y include halogen atoms and methane-sulfonate or *p*-toluene-sulfonate groups.

The most preferred halogen atom in the above reaction is bromine and the preferred hydrogenolysable group is the benzyl group. Other examples of hydrogenolysable groups are —CH₂OH, —CH₂—CH=CH₂ and —CH₂—CH₂—CN.

Various embodiments of the above process may be illustrated by the reaction schemes A to H below:







In order to prevent the formation of polymers, the condensation in the first step of the above described reactions is carried out using high dilution techniques. Any inert solvent may be used, but benzene is preferred. The acid formed during the reaction must be neutralized. This may be accomplished by using two moles of the diamine to each mole of the halide, or by adding a further base, particularly a tertiary amine such as a trialkylamine or pyridine, preferably triethylamine.

The reduction of the carbonyl groups in the second step of the reactions B, D, F and G is preferably carried out by means of LiAlH_4 or B_2H_6 in tetrahydrofuran. Other possible reducing agents are mixed metal hydrides such as for example NaBH_4 , $\text{LiAlH}_4(\text{OCH}_3)$, $\text{LiAlH}_4/\text{AlCl}_3$ and $\text{NaBH}_4/\text{BF}_3$.

For the preparation of cyclic lactams according to the process indicated in reactions B and G preferably the disalt of the amide group (preferably the di-alkali metal salt) is used.

The transformation of a compound of formula I into a phosphonium and/or ammonium salt may be accomplished by using standard methods such as reaction with suitable quaternizing agents; for example alkylhalides such as methyl iodide.

Similarly any hydrogenolysable groups may be removed by using standard techniques such as catalytic or electrolytic reduction. Examples of catalysts which may be used are platinum, palladium, rhodium and ruthenium. Preferably the reduction is performed by means of LiAlH_4 . Thus the immediate product of reaction scheme C (a phosphonium and/or ammonium salt) may, if desired, subsequently be transformed into the free macrocycle by reduction in presence of LiAlH_4 .

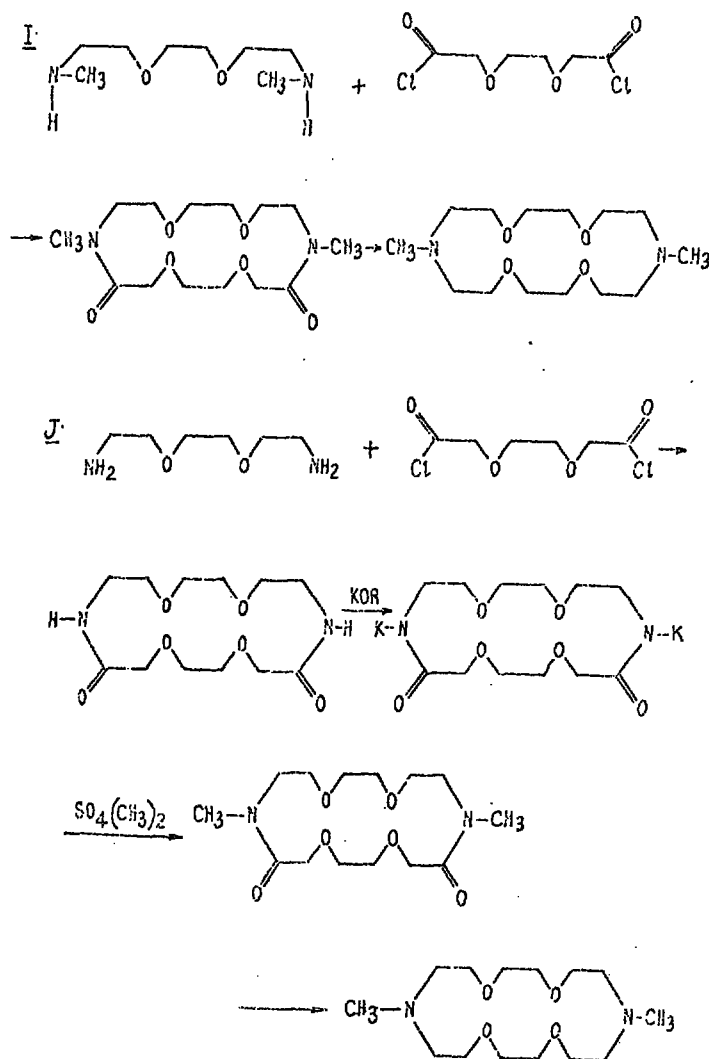
Also the transformation of a compound of formula I into its phosphorus and/or nitrogen oxide may be accomplished by applying standard oxidation procedures such as treatment with excess dilute hydrogen peroxide in water or with perchthalic acid in ether.

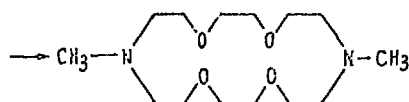
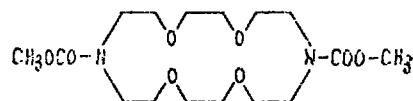
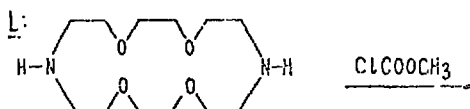
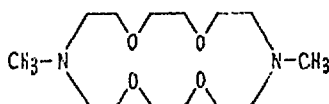
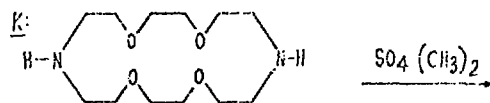
Often the immediate product of the above reaction is not the free macrocyclic compound but rather a derivative thereof additionally containing part or all of the structural elements of other constituents of the reaction mixture; in such a case, the macrocyclic compound is subsequently liberated from such derivatives, by standard procedures such as for example treatment with dilute acid whereby the acid addition salt of the macrocycle is formed, or with other hydrolyzing agents.

Any such salt may be dissolved in water and treated with an anion exchange resin. The so-obtained aqueous solution of the free macrocycle may then be isolated by evaporation to dryness.

For the preparation of those compounds in which R_1 is a hydrocarbon or alkoxy-carbonyl group, it is also possible to use a starting compound of formula III in which R_1 in the definition of Y is hydrogen, and to introduce the desired substituents at any stage of the process. The introduction of these substituents may be accomplished by means of known methods.

Thus as an example the 4,13-dimethyl-1,7,10,16-tetraoxa-4,13-diaza-cycloocta-decane may be obtained according to the following reaction schemes:





In the above reactions the reagents mentioned may be replaced by any other suitable reagents. If the methylation agents or reagents are replaced by other alkylating agents, compounds in which R_1 represents higher hydrocarbon groups are obtained.

The compounds in which R_1 represents alkenyl groups may be obtained following the same procedures.

The starting compounds of the general formulae III and IV may be obtained according to known methods. Some of the most convenient methods are illustrated by the Examples.

The compounds of this invention are readily soluble in most common organic solvents and in water.

The novel macrocyclic compounds have an unusual ability to form stable complexes with compatible cations. In the monocyclic compounds, i.e. those compounds of formula I in which R_1 is hydrogen, alkyl, alkenyl or alkoxy-carbonyl, the cation presumably is held in the centre of the macrocycle. In the bicyclic compounds, i.e. those compounds of formula I wherein both R_1 together form a third bridge between the two nitrogen atoms, the bridges between the two nitrogen atoms probably form a "cage" in which the cation is situated. The ability to form complexes and the stability of the complexes formed seem to depend on the arrangement of the hetero atoms or groups surrounding the cation and on the relative diameters of the ring(s) and the cation. Complexes of the monocyclic compounds are much less stable than the complexes formed from the same cation with bicyclic compounds, and macrocyclic compounds forming stable complexes with cations of a certain diameter are not able to form complexes with cations having much larger diameters.

Each macrocyclic molecule is able to form a complex with one cation. The magnitude of the charge on the cation has no influence. The cations may be inorganic or organic.

The complexes formed are generally readily soluble in water, CHCl_3 , CH_2Cl_2 , and in acetone or other polar solvents, whereas they are slightly soluble or essentially insoluble in non polar organic solvents. They dissociate at a more or less acid pH. Protonation of the free diamine hinders complex formation and leads to the dissociation of the complex by displacement of the equilibrium. The same dissociation is accomplished by treatment with any acid including Lewis acids. Release of the cation may also be accomplished by treating the complex with a quaternizing agent.

The complexes are normally formed by dissolving the macrocyclic compound and the cation yielding compound in a common solvent, such as for example acetone, methanol or water. The mixture normally is heated approximately to the boiling point of the solvent. If the complex formed is insoluble in the solvent used, the complex

will crystallize and may be separated by filtration. If the complex formed is soluble in the solvent used, it may be isolated by evaporating the solution to dryness. The complexes may be purified by recrystallization.

Complexes may also be formed when the cation yielding compound (e.g. the salt) is insoluble in the solvent used. It is sufficient to bring a solution of the macrocyclic compound together with the crystalline salt and agitate the mixture with or without heating.

The formation of complexes is possible even if the cation yielding compound and the complex are insoluble in the medium used. In this case the macrocycle and the cation yielding compound are mixed in the presence of a medium which is then agitated and heated, whereby the crystalline macrocycle gradually changes into the crystalline complex.

The presence of a complex in solution can be determined by spectroscopic analysis, as the addition of the cation causes changes in the spectral patterns of the macrocycle in solution.

The novel complexes make it possible to use certain chemical reagents in solvents where they are normally insoluble. For example potassium fluoride is insoluble in chloroform, whereas a complex of the salt with 4,7,13,16,21,24-hexaoxa-1, 10-diazabicyclo[8,8,8]hexacosane is readily soluble.

The cation complexing properties of the macrocyclic compounds of this invention make them of value for use in much the same way and for the same purposes as chelating agents. Thus, the cation complexing properties of the compounds render them of value in processes directed to the desalination of brines or to the separation of metals, for example to the separation of metals such as the transition metals and the actinides from low grade sources of these metals and to subsequently obtaining such metals in high purity form. In this connection, the compounds are considered to be particularly useful in the separation of high cost metals such as those of the platinum group. In the separation of uranium from crude ores, the uranium may be complexed with the macrocycle compound and the resulting complex subsequently separated in aqueous solution. The compounds of the invention may also advantageously be used for cation transport and for the preparation of ion selective membranes and electrodes.

The compounds are also of use in chemical syntheses, e.g. in polypeptide and protein syntheses, wherein the compounds advantageously selectively protect ammonium cation groups derived from amino groups in the amino acid. Additionally, the compounds may be used as a catalyst for ionic reactions in a polar organic media wherein the macrocyclic compounds activate the reaction via an "agent-separated ion pair" mechanism.

When incorporated in pharmaceutical compositions the compounds of this invention "tie-up" trace metals and thus prevent the occurrence of catalytic oxidation due to the presence of trace metals. Additionally, when administered to an animal, e.g. mammals, the compound has an action on biological cation mechanisms such as nervous conduction, sodium-potassium pump, and calcium metabolism of muscle and bone. These compounds are thus useful in conditions in animals requiring the regulation of cation exchange within the host.

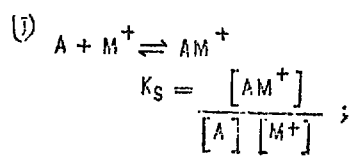
In addition to the foregoing macrocyclic compounds of this invention have been found to possess pharmacological activity. For example, the N-alkylated compounds of the invention, e.g. 4,13-dimethyl-1,7,10,16-tetraoxa-4,13-diazacyclooctadecane, demonstrate antiviral activity against A₂ influenza when measured by a modification of the well recognized *in vitro* methods of Hermann in chick fibroblast tissue culture.

Additionally, the bicyclic macrocyclic compounds of this invention, e.g. 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane, have been found to inhibit catechol amine induced free fatty acid mobilization when tested *in vitro* with isolated adipose tissue. These compounds are therefore of use in the treatment of diabetes and hyperlipemia.

Stability constants of macrocycle complexes in aqueous solution

General

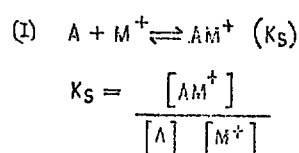
We have determined by measuring the pH, in water, the equilibrium constants for reactions of the following type, the type being illustrated by bicyclic amine macrocycles: —



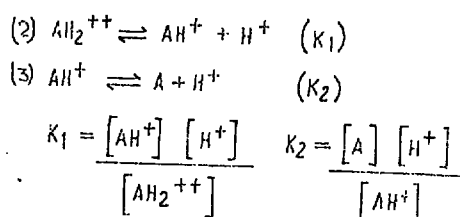
where

K_s = law of mass action constant;
 A = bicyclic amine under consideration;
 AM^+ = macrocycle complex;
 M^+ = cation;
 $[]$ = activity of the ionic species.

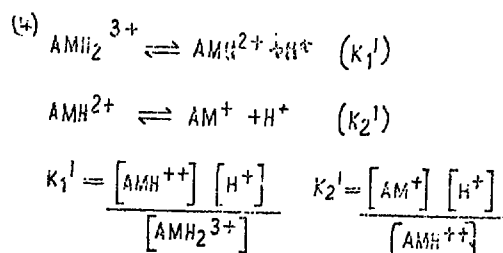
Equilibria present
Complexation



Protonation of the diamine



Protonation of the macrocycle complex



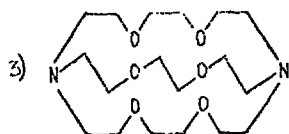
We have verified that the last two equilibria of protonation of the macrocycle complex, remain comparatively negligible and have established a formula relating K_s to the pH and all constants of the mixture:

$$K_s = \frac{bC_A - aC}{bC_M - (bC_A - aC)} \cdot \frac{b}{C}$$

$$\text{where: } C = C_H + [OH^-] - [H^+]$$

$$a = 1 + \frac{[H^+]}{K_2} + \frac{[H^+]^2}{K_1 K_2}$$

$$b = \frac{[H^+]}{K_2} + 2 \frac{[H^+]^2}{K_1 K_2}$$



Reference salt = NMe₄ Br $\left(\frac{N}{10}\right)$

Cation	K _s	pK _s
Li ⁺	<10 ^{1.5}	<1.5
Na ⁺	5.6 × 10 ³	3.75
K ⁺	1.5 × 10 ⁵	5.17
Rb ⁺	1.6 × 10 ⁴	4.20
Cs ⁺	<10 ^{1.5}	<1.5

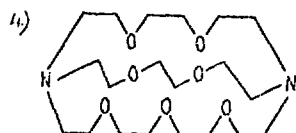
Protonation of the amine
—8

K₁ = 5.2 × 10; pK₁ = 7.28

—10

K₂ = 2.5 × 10; pK₂ = 9.60

ΔpK_s ≈ 0.10



Reference salt = LiCl

$\left(\frac{N}{10}\right)$

Cation	K _s	pK _s
Li ⁺	} <10 ^{1.5}	<1.5
Na ⁺		
K ⁺		
Rb ⁺	4 × 10 ²	2.60
Cs ⁺	1.5 × 10 ²	2.18

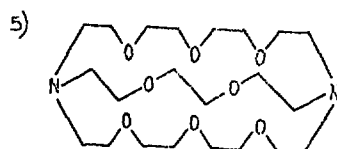
Protonation of the amine
—8

K₁ = 4.7 × 10; pK₁ = 7.33

—9

K₂ = 3.2 × 10; pK₂ = 8.50

Δ(pK_s) ≈ 0.10



Reference salt = LiCl

$\left(\frac{N}{10}\right)$

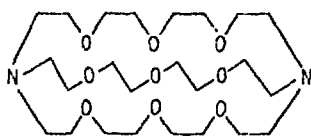
pK₁ = 7.31

pK₂ = 8.15

For Li, Na, K, Rb : K_s < 10^{1.5}

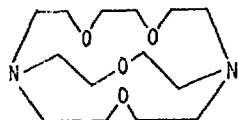
Cs⁺ : K_s ≈ 60 pK_s ≈ 1.7 (±0.5)

6)

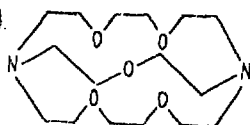
Reference salt = $\text{LiCl} \left(\frac{\text{N}}{10} \right)$ $\text{pK}_1 = 6.96$ $\text{pK}_2 = 7.70$ For the alkali metals $K_s < 10^{1.5}$

(B) Alkaline — Earth Metals

1).

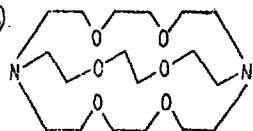
Reference salt = $\text{NMe}_4 \text{Br} \left(\frac{\text{N}}{10} \right)$ For all the alkaline earths $K_s < 10^3$

2).

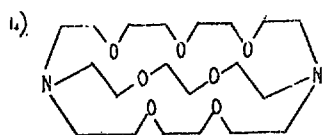
Reference salt = $\text{NMe}_4 \text{Br} \left(\frac{\text{N}}{10} \right)$ $\Delta(\text{pK}_s) = \pm 0.10$

Cation	K_s	$-\text{pK}_s$
Mg^{++}	$< 10^3$	$<^2$
Ca^{++}	5.0×10^3	6.70
Sr^{++}	1.2×10^7	7.07
Ba^{++}		

3).

Reference salt = $\text{NMe}_4 \text{Br} \left(\frac{\text{N}}{10} \right)$ $\Delta(\text{pK}_s) = \pm 0.10$

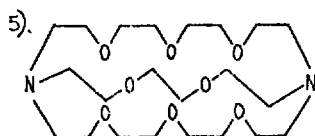
Cation	K_s	$-\text{pK}_s$
Mg^{++}	$< 10^3$	$<^2$
Ca^{++}	1.74×10^1	4.24
Sr^{++}	1.02×10^3	8.01
Ba^{++}	3.0×10^3	9.48



Reference salt = $\text{LiCl} \left(\frac{\text{N}}{10} \right)$

$$\Delta(\text{pK}_s) = \pm 0.10$$

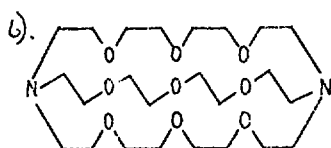
Cation	K_s	$-\text{pK}_s$
Mg^{++}	$\left. \begin{array}{c} \text{ } \\ \text{ } \end{array} \right\} < 10^2$	$\left. \begin{array}{c} \text{ } \\ \text{ } \end{array} \right\} < 2$
Ca^{++}		
Sr^{++}	2×10^3	2.30
Ba^{++}	5.6×10^5	5.75



Reference salt = $\text{LiCl} \left(\frac{\text{N}}{10} \right)$

$$\Delta(\text{pK}_s) = \pm 0.20$$

Cation	K_s	$-\text{pK}_s$
Mg^{++}	$\left. \begin{array}{c} \text{ } \\ \text{ } \\ \text{ } \end{array} \right\} < 10^2$	$\left. \begin{array}{c} \text{ } \\ \text{ } \\ \text{ } \end{array} \right\} < 2$
Ca^{++}		
Sr^{++}		
Ba^{++}	3×10^3	3.48



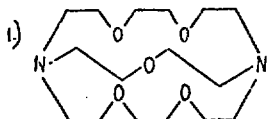
Reference salt = $\text{LiCl} \left(\frac{\text{N}}{10} \right)$

For Mg , Ca , Sr : $\text{pK}_s < 2$

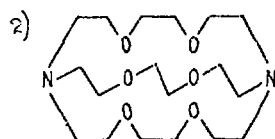
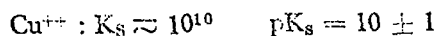
For Ba^{++} : $K_s = 5.1 \times 10^4$

$$\text{pK}_s = 4.71 \pm 0.20$$

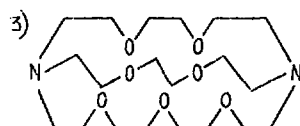
(C) Other cations studied



Reference salt = $\text{NMe}^+ + \text{Br}^- \left(\frac{\text{N}}{10} \right)$



Cation	K_s	$-pK_s$	ΔpK_s	Reference Salt
Ag^+	4.1×10^9	9.61	± 0.20	Without reference salt
Tl^+	2.1×10^6	6.32	± 0.20	Without reference salt
Pb^{++}	1.13×10^{12}	12.05	± 0.10	$\text{NMe}_4\text{Br} \left(\frac{\text{N}}{10} \right)$



Reference salt = $\text{LiCl} \left(\frac{\text{N}}{10} \right)$

$\text{Tl}^+ : K_s = 3.10^1 \quad pK_s = 4.48 \pm 0.10$
 $\text{Pb}^{++} : K_s = 1.3 \times 10^8 \quad pK_s = 8.11 \pm 0.10$

The invention will now be illustrated by way of the following examples:

Example 1

Preparation of Triglycolyl Chloride

A. Preparation of Triglycolic Acid

100 g. of nitric acid (density=1.38) are heated to 45° C. 20 g. of triethylene glycol are added in small portions so as to keep the temperature at about 45° C to 50° C. After this step the mixture is agitated for about 20 minutes at 45° C and then for one hour at about 80° C. The solution is evaporated under vacuum at 70° C for 2 to 3 hours. A viscous paste of a brownish colour is obtained. 100—120 ml of benzene are added and water is distilled off. Upon cooling, the diacid crystallizes and is recrystallized from a mixture of acetone and benzene. The solid is dried under a vacuum of 0.1 mm. Hg and the acid obtained has m.p.=74° C—75° C.

PMR (in D_2O): 3.80 ppm (singlet); 4.25 ppm (singlet)

B. Preparation of Triglycolyl Chloride

15 g. of the acid obtained above, 30 g. of oxalyl chloride, 100 ml. anhydrous benzene and three drops of pyridine are mixed and agitated for 24 hours. Petroleum ether is added and the product is decanted. The mixture is filtered and the benzene and the excess of oxalyl chloride is evaporated on a rotatory evaporator without heating. The evaporation is repeated twice, each time with 100 ml. of benzene. The product obtained is a yellow oil. The oil is diluted with a mixture of ethyl ether and petroleum ether and after cooling to a temperature between room temperature and -70° C, the product crystallizes out. The crystals are then washed with petroleum ether, care being taken that the product does not come into contact with moisture in the air. After recrystallizing twice and washing twice with ether, the product is dried under a vacuum of 0.1 mm. Hg. m.p.=20° C—30° C (crude product). PMR (CDCl_3): 3.85 ppm (singlet); 4.52 ppm (singlet).

Example 2

Preparation of 1,8 - Diamino - 3,6 - dioxaoctane

A. Preparation of Trichylene Glycol Dibromide

66 g. of triethylene glycol and 13.3 g. of anhydrous pyridine are slowly added to 100 g. of phosphorous tribromide while agitating and cooling the mixture. After standing overnight at room temperature, the mixture is poured on to ice and the organic phase is decanted, washed with water and dilute hydrochloric acid and dried over sodium sulphate. After distillation under vacuum (95° C and 0.5 mm. Hg) the title compound is obtained.

Yield: 60—70%.

PMR (CDCl₃): 3.4—4.0 ppm (multiplet); 3.70 ppm (singlet)

B. Preparation of Trichylene Glycol Diphtalimide

161 g. of phthalimide are mixed with 50 g. of potassium hydroxide in 500 ml. ethanol. The mixture is agitated for 24 hours and filtered and potassium phthalimide is obtained. 7.5 g. of the dibromide obtained in part A of this example is mixed with 30 ml. dimethylformamide and 9 g. of the potassium phthalimide obtained above, and the mixture is heated for one hour at 100° C. After cooling, 50 ml. water and 50 ml. chloroform are added. After decantation, the organic layer is washed with dilute potassium hydroxide, then with water and is dried over potassium sulphate and evaporated. The title compound crystallizes out and is recrystallized from acetic acid.

Yield 95%, m.p.: 175° C.

PMR (CDCl₃): 3.5—3.85 ppm (multiplet); 3.60 ppm (singlet); 7.80 (multiplet).

C. Preparation of 1,8 - Diamino - 3,6 - dioxaoctane

22.4 g. of the product obtained in step B are suspended in 250 ml. ethanol and heated under reflux. 19 ml. of N₂H₄ and water (50%) are added and the heating under reflux is continued for 2 hours. After this time, the reaction is practically finished. 25 ml. of 10N hydrochloric acid is added and the mixture is heated under reflux for an additional half hour. The majority of the alcohol is distilled off, and the residual solution is filtered and saturated with potassium hydroxide. The mixture is poured into a liquid-liquid extractor and extracted with benzene. The benzene solution is evaporated, and the diamine distilled under a vacuum of 0.5 mm. Hg at 88° C. Yield = 70%.

PMR (CDCl₃): CH₂—N: 2.85 ppm (triplet); CH₂—O: 3.50 ppm (triplet) and 3.60 ppm (singlet).

Example 3

Preparation of 5,12 - Dioxo - 1,7,10,16 - tetraoxa - 4,13 - diazacyclooctadecane

This reaction is carried out applying a high dilution technique. A solution of 14.8 g. of the diamine obtained in Example 2 (0.1 mole) in 500 ml. anhydrous benzene and a solution of 11.2 g. of the dichloride obtained in Example 1 in 500 ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of 8 hours under vigorous agitation and under a nitrogen atmosphere. On termination, the benzene solution is filtered and evaporated to dryness. The crystalline residue is dissolved in anhydrous benzene and passed through a column of aluminium oxide. The polymers formed during the reaction are retained and a pure solution of the desired compound is obtained. After recrystallization from a mixture of benzene and heptane, the title product is produced.

m.p. = 111° C. Yield = 70%.

PMR (CDCl₃): —CO—CH₂—O: 4.00 ppm (singlet); —CH₂—N and —CH₂—O: 3.6 ppm (multiplet)

Example 4

Preparation of 1,7,10,16 - Tetraoxa - 4,13 - diazacyclooctadecane

A solution of 18.5 g. of the diamide obtained in Example 3 in 450 ml. anhydrous tetrahydrofuran is slowly added to a mixture of 150 ml. anhydrous tetrahydrofuran and 12 g. LiAlH₄ while stirring and heating at the reflux temperature. After the addition is completed, the mixture is stirred under reflux and under a nitrogen atmosphere for 24 hours. After cooling to room temperature the excess reagent is destroyed by adding a mixture of water and THF (1:2). The mixture is filtered and the filtrate is evaporated to dryness. The residue is dissolved in benzene and the solution is passed through a column of Al₂O₃ with benzene as eluant. The solution is evaporated to dryness and after recrystallization from benzene/petrol ether 13.5 g. of the desired product is obtained.

m.p. = 115° C—116° C. Yield: 80%.

PMR (CDCl₃): —CH₂—O: 3.58 ppm (singlet+triplet); —CH₂—N: 2.78 ppm (triplet)

Example 5

5 Preparation of 2,9 - Dioxo - 4,7,13,16,21,24 - hexaoxa - 1,10 - diazabicyclo[8,8,8]-hexacosane

The reaction is carried out applying the high dilution technique.

10 A solution of 5.24 g. of the cyclic diamine obtained in Example 4 and 4.4 g. of triethylamine in 500 ml. anhydrous benzene and a solution of the dichloride (4.4 g. in 500 ml. anhydrous benzene) obtained in Example 1B is added to 1000 ml. anhydrous benzene during 10 hours under nitrogen atmosphere and under agitation. The salt of triethylamine and the hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al₂O₃ using benzene as an eluant. The product is crystallized from a hexane-benzene mixture.

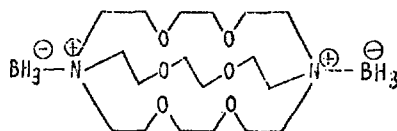
15 m.p. = 114° C. Yield 50%.

PMR (CDCl₃): several peaks between 3.3 and 4.6 ppm

Example 6

20 Preparation of 4,7,13,16,21,24 - hexaoxa - 1,10 - diazabicyclo[8,8,8]hexacosane
B₂H₆ is prepared according to the process described in "Org. Reactions" 13, 31—32 (1963).

25 A solution of 1 g. of the bicyclic diamide obtained in Example 5 in 20 ml. tetrahydrofuran is slowly added to 15 ml. of the fresh prepared B₂H₆ solution under nitrogen atmosphere and at a temperature of 0° C. The mixture is agitated at this temperature for 30 minutes and thereafter 1 hour at reflux temperature. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. 1 g. of the diborane of the title compound is obtained:



30 This compound is hydrolysed by adding 20 ml. 6N hydrochloric acid under heating and a solution is obtained. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The residue is dissolved in 10 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1) ("DOWEX" is a Registered Trade Mark). The column is washed with water until there is no basic reaction. The water is evaporated. The residue is recrystallized from hexane and dried in vacuum (0.1 mm. Hg). 890 mg. of the desired product is obtained.

35 m.p. = 68° C—69° C. Yield 95%.

PMR (CDCl₃): —CH₂—N: 2.65 ppm (triplet); —CH₂—O: 3.65 ppm (singlet+triplet)

Example 7

40 Preparation of 4,13 - Dimethoxycarbonyl - 1,7,10,16 - tetraoxa - 4,13 - diazacyclo-octadecane

45 3.6 g. of the diamine obtained in Example 4 are dissolved in 30 ml. methanol and 3 ml. water. A solution of 3.6 g. ClCO₂CH₃ in 15 ml. methanol is added while cooling and agitating. The agitation is maintained for 24 hours. The mixture is filtered and the filtrate evaporated to dryness. The residue is recrystallized from CHCl₃/petroleum ether.

m.p. = 104° C. Yield 80%.

PMR (CDCl₃): Signals at about 3.65 ppm.

Example 8

50 Preparation of 4,13 - Dimethyl - 1,7,10,16 - tetraoxa - 4,13 - diazacyclooctadecane
A: 3 g. of the compound of Example 7 dissolved in 20 ml. dry ether are slowly added to 3 g. LiAlH₄ in 5 ml. dry ether. The mixture is agitated for 24 hours. Then 3 g. KOH in 6 ml. H₂O is added followed by 10 ml. H₂O. The mixture is filtered and

	20	21	1,304,367	21
on			evaporated to dryness. The residue is extracted with ether and benzene. The solution is evaporated to dryness and an oil which boils at 97° C at a pressure of 0.05 mm. lig is obtained.	
]-	5	5	PMR (CDCl ₃): —CH ₂ —N: 2.70 ppm (triplet); N—CH ₂ : 2.32 ppm (singlet); —CH ₂ —O: 3.65 ppm (singlet+triplet)	5
of			B: Alternatively this compound may be obtained by reacting N,N'-dimethyl-1,8-diamino-3,6-dioxaoctane with triglycolyl chloride following the procedure of Examples 3 and 4.	
g-	10	10	Example 9 Preparation of the KSCN - Complex of 1,7,10,16 - Tetraoxa - 4,13 - diaza - cyclo-octadecane	10
he			524 mg. of the macrocyclic compound and 194 mg. of KSCN are refluxed in 20 ml. of acetone for 5 minutes. The acetone is then removed under vacuum, and the residue is recrystallized from CHCl ₃ /Petroleum ether. The crystalline complex melts at 167° C—168° C.	
ed	15	15		15
ed			Example 10 Preparation of the CuCl ₂ - Complex of 1,7,10,16 - Tetraoxa - 4,13 - diaza - cyclo-octadecane	
3,	20	20	A solution of 2.62 g. of the macrocyclic compound in 10 ml. CH ₃ OH is mixed with a solution of 1.70 g. of CuCl ₂ ·2H ₂ O in 10 ml. CH ₃ OH. The blue complex is immediately formed and precipitates. After filtration and recrystallization from CHCl ₃ /CH ₃ OH the pure complex is obtained.	20
el-			Example 11 Preparation of the RbSCN - Complex of 4,7,13,16,21,24 - hexaoxa - 1,10 - diaza-bicyclo[8,8,8]hexacosane	
er	25	25	130 mg. amine and 35 mg. RbSCN are mixed in a flask. 20 ml. acetone are added. The mixture is heated to the boiling point until all solid material has dissolved. After evaporation to dryness the residue is extracted with chloroform, which dissolves the complex. The chloroform solution is also evaporated to dryness, yielding the crystalline complex. The complex may be recrystallized from acetone-heptane. It melts at 163° C—164° C.	25
is			PMR (CDCl ₃): —CH ₂ —N: 2.56 ppm (triplet)	
ss			Example 12 Preparation of the BaCl ₂ - Complex of 4,7,13,16,21,24 - hexaoxa - 1,10 - diazabicyclo-[8,8,8]hexacosane	
a	30	35	37.6 mg. amine and 21 mg. BaCl ₂ ·2H ₂ O are dissolved in 10 ml. water. The solution is then evaporated to dryness. The solid residue is extracted with methylene chloride. After filtration of the solution, ether is added until crystallization sets in. The crystalline complex does not melt but darkens at about 200° C.	35
is	35	40	PMR (CDCl ₃): —CH ₂ —N: 2.80 ppm (triplet)	40
ed			Example 13 Preparation of Tetraglycolyl Chloride	
is	40	45	A: Preparation of Tetraglycolic Acid 100 g. of nitric acid (density=1.38) are heated to 45° C 20 g. of tetraethylene glycol are added in small portions so as to keep the temperature at about 45° C—50° C. After this step the mixture is agitated for about 20 minutes at 45° C and then for one hour about 80° C. The solution is evaporated under vacuum at 70° C for 2 to 3 hours. A viscous paste of a brownish colour is obtained. 100 to 120 ml. of benzene are added and water is distilled off. The diacid is a viscous oil which does not crystallize.	45
is	45	50	PMR (D ₂ O): 3.75 ppm (singlet); 4.22 ppm (singlet)	50
m			B: Preparation of Tetraglycolyl Chloride 28 g. of the acid obtained above, 50 g. of oxalyl chloride, 200 ml. anhydrous benzene and six drops of pyridine are mixed and agitated for 6 hours. The mixture is filtered and the benzene and the excess of oxalyl chloride is evaporated on a rotatory evaporator without heating. The evaporation is repeated twice, each time with 100 ml. of benzene. The product obtained is a yellow oil, which does not crystallize.	
to	50	55	PMR (CDCl ₃): 3.75 ppm (multiplet); 4.52 ppm (singlet)	55
ve				
n				
g				

Example 14

Preparation of 1,11 - Diamino - 3,6,9 - trioxaundecane

A: Preparation of Tetrathylene Glycol Dibromide

300 g. of tetrathylene glycol and 100 g. of anhydrous pyridine are slowly added to 727 g. of phosphorus tribromide, while agitating and cooling the mixture. After cooling to room temperature, the mixture is poured on to ice and the organic phase is decanted, washed with water and dilute hydrochloric acid and dried over sodium sulphate. After distillation under vacuum (123° C—125° C and 0.4 mm. Hg) the title compound is obtained.

Yield: 60%.

PMR (CDCl₃): 3.70 ppm (multiplet)

B: Preparation of Tetrathylene Glycol Diphthalimide

161 g. of diphthalimide are mixed with 50 g. of potassium hydroxide in 500 ml. ethanol. The mixture is agitated for 24 hours and filtered and potassium phthalimide is obtained. 217 g. of the dibromide obtained in part A of this example is mixed with 1000 ml. dimethylformamide and 260 g. of the potassium phthalimide obtained above, and the mixture is heated for eight hours at 100° C. After cooling, the mixture is poured into 3 liters of cold water. The precipitate is filtered, washed with water and acetone and dried under vacuum. The title compound is recrystallized from ethanol.

Yield 85%, m.p. 108° C—109° C.

PMR (CDCl₃): 3.60 ppm (singlet); 3.80 ppm (multiplet); 7.80 (multiplet)

C: Preparation of 1,11 - Diamino - 3,6,9 - trioxaundecane

254 g. of the product obtained in step B are suspended in 1000 ethanol and heated under reflux. 90 g. of N₂H₄ in 90 g. water is added and the heating under reflux is continued for 3 hours. After this time, the reaction is practically finished. 10N hydrochloric acid is added until pH 1 is obtained and the mixture is heated under reflux for an additional half hour. The residual mixture is filtered; the solution is evaporated to dryness. 250 ml. water are added and the solution is saturated with potassium hydroxide. The mixture is again filtered to remove precipitated KCl and is poured into a liquid-liquid extractor and extracted with benzene. The benzene solution is evaporated, and the diamine distilled under a vacuum of 0.2 mm Hg is 114° C—116° C. Yield=72%.

PMR (CDCl₃): —NH₂: 1.30 ppm (singlet); CH₂—N: 2.85 ppm (triplet); —CH₂—O: 3.48 ppm (triplet) and 3.60 ppm (singlet).

Example 15

Preparation of 5,15 - Dioxo - 1,7,10,13,19,22 - hexaoxa - 4,16 - diaza - cyclo-tetracosane

This reaction is carried out applying a high dilution technique. A solution of 15.4 g. of the diamine obtained in Example 14 in 500 ml. anhydrous benzene and a solution of 10.4 g. of the dichloride obtained in Example 13 in 500 ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of 10 hours under vigorous agitation and under a nitrogen atmosphere. On termination, the benzene solution is filtered and evaporated to dryness. The oily residue is dissolved in anhydrous benzene and passed through a column of aluminium oxide. The polymers formed during the reaction are retained and a pure solution of the desired compound is obtained. After evaporation of the benzene, the title product is produced as a viscous oil.

Yield=68%.

PMR (CDCl₃): —CH₂—O and —CH₂—N: 3.60 ppm (three peaks)
—CO—CH₂—O: 3.85 ppm (singlet)

Example 16

Preparation of 1,7,10,13,19,22 Hexaoxa - 4,16 - diazacyclopentacosane

A solution of 30 g. of the diamine obtained in Example 15 in 200 ml. anhydrous tetrahydrofuran is slowly added to a mixture of 50 ml. anhydrous tetrahydrofuran and 18 g. LiAlH₄ while stirring and heating at the reflux temperature. After the addition is completed, the mixture is stirred under reflux and under a nitrogen atmosphere for 24 hours. After cooling to room temperature the reducing agent is destroyed by adding a mixture of water and TiCl₃ (1:2). The mixture is filtered and the filtrate is evaporated to dryness. The residue is dissolved in benzene and the solution

	22	23	1,304,367	23
			is passed through a column of Al_2O_3 with benzene as eluant. The solution is evaporated to dryness and the desired product is obtained as a colourless oil which crystallizes at low temperatures. m.p. = 15°C Yield 95%.	
added After case is odium e title	5	5	PMR (CDCl_3): NH: 2.10 ppm (singlet); $\text{CH}_2\text{--N}$: 2.80 ppm (triplet); $\text{CH}_2\text{O--}$: 3.60 ppm (singlet and triplet).	5
			Example 17 Preparation of 2,12 - dioxo - 4,7,10,16,19,22,27,30,33 - nonaoxa - 1,13 - diazabicyclo-[11,11,11]pentatriacontane	
	10	10	The reaction is carried out applying the high dilution technique. A solution of 7.0 g. of the cyclic diamine obtained in Example 16 and 4.4 g. of triethylamine in 500 ml. anhydrous benzene and a solution of the dichloride (5.2 g. in 500 ml. anhydrous benzene) obtained in Example 13B is added to 1200 ml anhydrous benzene during ten hours under nitrogen atmosphere and under agitation. The salt of triethylamine and the hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al_2O_3 using benzene as an eluant. The product is a colourless oil which crystallizes on standing. m.p. $72^\circ\text{--}74^\circ\text{C}$ Yield = 65%.	10
0 ml. amide with above, re is and anol.	15	15	PMR (CDCl_3): 3.4—3.8 ppm (broad peaks); $\text{--CO--CH}_2\text{--N}$: 4.33 ppm (broad peak).	15
	20	20	Example 18 Preparation of 4,7,10,16,19,22,27,30,33 - nonaoxa - 1,13 - diaza - bicyclo[11,11,11]-pentatriacontane	20
and nder hed. ated tion with and ene g is et);	25	25	B_2H_6 is prepared according to the process described in 'Org. Reactions' 13, 31—32 (1963). A solution of 1.3 g. of the bicyclic diamide obtained in Example 17 in 20 ml. tetrahydrofuran is slowly added to 15 ml. of the fresh prepared B_2H_6 solution (1.6 mole) under nitrogen atmosphere and at a temperature of 0°C . The mixture is agitated at this temperature for 30 minutes and thereafter 2 hours at reflux temperature. After cooling to room temperature the excess reagent is destroyed by adding 10 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. The bis-amine-borane of the title compound is obtained by extraction of the residue with chloroform.	25
	30	30	This compound is hydrolysed by adding 25 ml. 6N hydrochloric acid under heating to reflux for 3 hours and a solution is obtained. The mixture is evaporated under vacuum on a rotatory evaporator. The residue is dissolved in 10 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1). The column is washed with water until there is no basic reaction. The water is evaporated. The residue is the desired product, obtained as a colourless oil. Yield 95%.	30
do-	35	35	PMR (CDCl_3): $\text{--CH}_2\text{--N}$: 2.85 ppm (triplet); $\text{--CH}_2\text{--O}$: 3.65 ppm (singlet and triplet)	35
of d a ous der me amers and ous	40	40	Example 19 Preparation of 5,12 - Dioxo - 1,7,10,16,19 - pentaaoxa - 4,13 - diaza - cycloeneicosane	40
ks)	45	45	This reaction is carried out applying a high dilution technique. A solution of 31.8 g. of the diamine obtained in Example 14 in 1000 ml. anhydrous benzene and a solution of 17.8 g. of the dichloride obtained in Example 1 in 1000 ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of 14 hours under vigorous agitation and under a nitrogen atmosphere. On termination, the benzene solution is filtered and evaporated to dryness. The crystalline residue (25 g.) is dissolved in anhydrous benzene and passed through a column of aluminium oxide. The polymers formed during the reaction are retained and a pure solution of the desired compound is obtained. After recrystallization from a mixture of benzene and heptane, the title product is produced. m.p. = $90^\circ\text{C--}91^\circ\text{C}$. Yield 75%.	45
	50	50	PMR (CDCl_3): $\text{--CH}_2\text{--O--}$ and $\text{--CH}_2\text{--N}$: 3.5 to 3.9 ppm (complex multiplet); $\text{--CO--CH}_2\text{--O}$: 4.05 ppm (singlet).	50
a- e. n is e n	55	55	Example 20 Preparation of 1,7,10,16,19 - Pentaaoxa - 4,13 - diazacycloeneicosane	55
	60	60	A solution of 6.7 g. of the diamide obtained in Example 19 in 100 ml. anhydrous	60

- 5 tetrahydrofuran is slowly added to a mixture of 50 ml. anhydrous tetrahydrofuran and 3.8 g. LiAlH₄, while stirring. After the addition is complete, the mixture is stirred under reflux and under a nitrogen atmosphere for 11 hours. After cooling to room temperature, the reagent is destroyed by adding 10 ml. water in 25 ml. THF, followed by 10 ml. NaOH (15% in water) and then 20 ml. water. The mixture is filtered and the filtrate is evaporated to dryness. The residue is dissolved in benzene and the solution is passed through a column of Al₂O₃ with benzene as eluant. The solution is evaporated to dryness and the desired product is obtained as a colourless oil which crystallizes at low temperature.
- 10 m.p. about 0°C Yield 70%
 PMR (CDCl₃): NH: 2.50 ppm (singlet); —CH₂—N: 2.80 ppm (triplet); —CH₂—O: 3.5—3.7 ppm (two singlets+triplet).

Example 21

- 15 Preparation of 14,21,Dioxo - 4,7,10,16,19,24,27 - heptaoxa - 1,13 - diazabicyclo-[8,8,11]nonacosane

- The reaction is carried out applying the high dilution technique. A solution of 2.45 g. of the cyclic diamine obtained in Example 20 and 2 g. of triethylamine in 200 ml. anhydrous benzene and a solution of the dichloride (1.8 g. in 200 ml. anhydrous benzene) obtained in Example 1B is added to 1200 ml. benzene during 5 hours under nitrogen atmosphere and under agitation. The salt of triethylamine and hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al₂O₃ using benzene as an eluant. After evaporation of the solvent, the residue crystallizes on standing. The product obtained is the desired compound.
- 20 m.p. 97° C—98° C. Yield 65%.
- 25 PMR (CDCl₃): CH₂—N and CH₂—O: 3.5—3.9 ppm (broad peaks); CO—CH₂—O: 4.0—4.3 ppm (very broad peaks).

Example 22

- 30 Preparation of 4,7,10,16,19,24,27 - heptaoxa - 1,13 - diazabicyclo[8,8,11]nonacosane B₂H₆ is prepared according to the process described in "Org. Reactions", 13, 31—32 (1963).

- A solution of 1.5 g. of the bicyclic diamide obtained in Example 21 in 15 ml. anhydrous tetrahydrofuran is slowly added to 15 ml. of the fresh prepared B₂H₆ solution (1.2 M) under nitrogen atmosphere and at a temperature of 0° C. The mixture is agitated at this temperature for 30 minutes and thereafter 2 hours at reflux temperature. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. The bis-amine-borane of the title compound is obtained.

- This compound is hydrolysed by adding 30 ml. 6N hydrochloric acid under heating at reflux for 2 hours and a solution is obtained. The mixture is evaporated under vacuum on a rotatory evaporator. The residue is dissolved in 10 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1). The column is washed with water until there is no basic reaction. The water is evaporated. The residue is dried in vacuum (0.1 mm. Hg). 1 g. of the desired product is obtained as a colourless liquid.

- 45 Yield 75%.
- PMR (CDCl₃): —CH₂—N: 2.75 ppm (triplet); —CH₂—O: 3.70 ppm (singlet); 3.65 ppm (triplet).

Example 23

- 50 Preparation of 2,12 - Dioxo - 4,7,10,16,19,22,27,30 - octaoxa - 1,13 - diazabicyclo-[8,11,11]dotriacontane

- The reaction is carried out applying the high dilution technique.
- A solution of 1.67 g. of the cyclic diamine obtained in Example 20 and 1.2 g. of the triethylamine in 100 ml. anhydrous benzene and a solution of the dichloride (1.30 g. in 100 ml. anhydrous benzene) obtained in Example 13B is added to 1000 ml. benzene during 2 hours under nitrogen atmosphere and under agitation. The salt of triethylamine and the hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al₂O₃ using benzene as an eluant. The desired product is obtained as a colourless viscous oil.

- 60 Yield 50%.
- PMR (CDCl₃): 3.4—3.8 ppm (broad peaks); —CO—CH₂—O: 4.35 ppm (broad peak)

24	25	1,304,367	25
		Example 24	
		Preparation of 4,7,10,16,19,22,27,30 - octaoxa - 1,13 - diazabicyclo[8,11,11]dotriacontane	
	5	B_2H_6 is prepared according to the process described in "Org. Reactions" 12, 31—32 (1963).	5
	10	A solution of 1.2 g. of the bicyclic diamide obtained in Example 23 in 20 ml. tetrahydrofuran is slowly added to 10 ml. of the fresh prepared B_2H_6 solution (1.6 M) under nitrogen atmosphere and at a temperature of 0° C. The mixture is agitated at this temperature for 30 minutes and thereafter 2 hours at reflux temperature. The excess reagent is destroyed by adding 3 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. 1.13 g. of the bis-amine-borane of the title compound is obtained by extracting the residue with chloroform.	10
	15	This compound is hydrolysed by adding 40 ml. 6N hydrochloric acid under heating for 2 hours and a solution is obtained. The mixture is evaporated under vacuum on a rotatory evaporator. The residue is dissolved in 10 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1). The column is washed with water until there is no basic reaction. The water is evaporated. The residue is the desired product, obtained as a colourless liquid.	15
	20	Yield 95%. PMR ($CDCl_3$): $—CH_2—N$: 2.80 ppm (triplet); $—CH_2—O—$: 3.4—3.8 ppm (singlet and triplet)	20
		Example 25	
	25	Preparation of the $CsSCN$ complex of 4,7,10,16,19,22,27,30,33 - nonaoxa - 1,13 - diazabicyclo[11,11,11]pentatriacontane	25
	30	100 mg. of the macrocyclic compound obtained in Example 18 and 45 mg. of $CsSCN$ are refluxed in 20 ml. of acetone for 5 minutes. After filtration, the solvent is evaporated. The residue is extracted with chloroform, filtered again and evaporated to dryness. The complex is crystallized from acetone/ethyl acetate.	30
	30	m.p. = 155° C—156° C. PMR ($CDCl_3$): $—CH_2—N$: 2.60 ppm (triplet); $—CH_2—O$: 3.55 ppm (triplet) and 3.62 ppm (singlet)	30
		Example 26	
		Preparation of Ethylene - bithioglycolic acid dichloride	
	35	A. Preparation of Ethylene - bithioglycolic acid Thioglycolic acid (20 g.), water (20 ml.), ethanol (20 ml.), and a solution of sodium hydroxide (17.6 g.) in water (30 ml.) are mixed in a flask and heated at reflux temperature. 1,2-Dibromocethane (18.5 g.) is added with strong agitation over a period of three hours. The mixture is refluxed for another two hours. After filtration, the filtrate is evaporated to dryness and taken up in a mixture of water (100 ml.) and 12 N hydrochloric acid (60 ml.). The mixture is extracted with ether (50 ml. three times). The organic layer is separated, dried over sodium sulfate and evaporated to dryness to give the crystalline sub-title compound which is then recrystallized from toluene.	35
	40	m.p. = 107° C (Yield 80%) PMR (D_2O): $S—CH_2—CH_2—S$: 3.0 ppm (singlet; 4H); $S—CH_2—CO$: 3.55 ppm (singlet; 4H).	40
	45	B. Preparation of the dichloride of the preceding acid 15 g. of the above diacid are added to a mixture of 100 ml. anhydrous benzene and 100 ml. anhydrous ether. Then 30 g. oxalyl chloride are added the flask being protected by a calcium chloride tube. The mixture is stirred for 36 hours and the diacid progressively dissolves as it is being transformed into the corresponding dichloride. The solution is then evaporated to dryness (without heating) leaving a brownish solid residue which is recrystallized from a mixture of anhydrous ether and petroleum ether by cooling at $-70^{\circ}C$ in a dry ice-acetone mixture.	45
	50	The solid yellowish dichloride is obtained in a nearly quantitative yield. m.p. = approx. 30° C (crude product) PMR ($CDCl_3$): $S—CH_2—CH_2—S$: 2.92 ppm (singlet; 4H); $S—CH_2—CO$: 3.55 ppm (singlet; 4H)	50
	55		55
	60	Example 27	60
		Preparation of 3,6-dithia-1,8-diamino-octane	
		8.5 g. potassium metal are dissolved in 100 ml. anhydrous tertiary-butanol (heav-	

- ing at 60° C accelerates the process). When the metal is entirely dissolved 15.4 g. cysteamine are added at once. The mixture is stirred for one hour until all the solid has dissolved. 18.8 g. 1,2-dibromosthane are then added slowly (over approx. thirty minutes); the reaction is exothermic. The mixture is stirred overnight at room temperature, then filtered through a sintered glass funnel; the solid residue is washed with benzene. The combined organic layers are evaporated to dryness. A viscous brownish oil is obtained. This oil is taken up into benzene (100 ml.) and filtered through a short column of alumina (approx. 20 g.) The column is washed with an additional 250 ml. of benzene. The benzene solutions are evaporated to dryness. The yellowish residue crystallizes to yield the title compound.
- 5
- 10
- m.p. = approx. 35° C—40° C (Yield: 85%)
 PMR (CDCl₃): —NH₂: 1.32 ppm (singlet: 4H); S—CH₂—CH₂—S: 2.72 ppm (singlet: 4H); N—CH₂—CH₂—S: 2.75 ppm (multiplet: 8H)

Example 28

- 15 Preparation of 3,14 - Dioxo - 1,16 - dioxo - 7,10 - dithia - 4,13 - diaza - cyclooctadecane

This reaction is carried out applying a high dilution technique. A solution of 10.2 g. of the diamine obtained in Example 27 in 500 ml. anhydrous benzene and a solution of 6.1 g. of the dichloride obtained in Example 1B in 500 ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of ten hours under vigorous agitation and under a nitrogen atmosphere. On termination, the benzene solution is filtered, the residue is washed with benzene and the combined benzene solutions are evaporated to dryness. The residue is dissolved in anhydrous benzene and passed through a short column of alumina (30 g.) The polymers formed during the reaction are retained and a pure solution of the desired compound is obtained. After recrystallization from a mixture of benzene and heptane, the title product is produced.

20

25

m.p. = 145° C Yield = 60%

- 30 PMR (CDCl₃): S—CH₂—CH₂—S: 2.80 ppm (singlet: 4H); S—CH₂—: 2.80 ppm (multiplet: 4H); N—CH₂: 3.45 ppm (multiplet: 4H); O—CH₂—CH₂—O: 3.72 ppm (singlet: 4H); O—CH₂—CO: 4.0 ppm (singlet: 4H)

Example 29

Preparation of 1,16 - dioxo - 7,10 - dithia - 4,13 - diaza cyclooctadecane

A solution of 7 g. of the cyclic diamide obtained in Example 28 in 100 ml. anhydrous tetrahydrofuran is added slowly to 50 ml. of a freshly prepared solution (1.5 M) of diborane in anhydrous tetrahydrofuran under nitrogen atmosphere and at a temperature of 0° C. The mixture is then heated to reflux for two hours. The excess reagent is destroyed by adding 10 ml. of water and the solution is evaporated to dryness on a rotatory evaporator under vacuum. 100 ml. 6N hydrochloric acid are added to the residue and the mixture is refluxed for two hours; a clear solution is obtained. This solution is then evaporated to dryness under vacuum. The residue is dissolved in 30 ml. water and the solution is pressed through a column of an anion exchange resin (Dowex 1, Trade Mark). The column is washed with water until there is no basic reaction. The combined water solutions obtained are evaporated to dryness under vacuum on a water bath (80° C—100° C). The residue is recrystallized.

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Yield = 70% m.p. = 45° C

PMR (CDCl₃): CH₂—N+CH₂—S: 2.77 ppm (complex band: 16H); CH₂—O: 3.59 ppm (singlet: 4H; triplet: 4H)

Example 30

- 50 Preparation of 2,9 - Dioxo - 4,7,13,16 - tetraoxa - 21,24 - dithia - 1,10 - diazabicyclo-[8,8,8]hexacosane

The reaction is carried out applying the high dilution technique. A solution of 3.5 g. of the cyclic diamine obtained in Example 29 and 1.3 g. of triethylamine in 400 ml. anhydrous benzene and a solution of the dichloride (2.7 g. in 400 ml. anhydrous benzene) obtained in Example 1B are added to 1000 ml. benzene during eight hours under nitrogen atmosphere and under agitation. The triethylamine hydrochloride precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al₂O₃ (20 g.) using benzene as an eluant. The solutions are evaporated to dryness. The product is a viscous oil.

55

Yield 50%

- 60 PMR: —CH₂—S—CH₂—CH₂—S—CH₂: 2.8 ppm (complex broad band: 8H); CH₂—O+CO—N—CH₂: 3.6 ppm (broad signals: 20H); CO—CH₂—O—: 4.0 ppm (broad signals: 4H).

Example 31

Preparation of 4,7,13 - 16 - tetrathia - 21,24 - dithia - 1,10 - diazabicyclo[8,8,8]-hexacosane

A solution of 1.6 g. of the bicyclic diamide obtained in Example 30 in 30 ml. anhydrous tetrahydrofuran is slowly added to 20 ml. of the fresh prepared diborane solution (1.5 N) under nitrogen atmosphere and a temperature of 0° C. The mixture is stirred two hours at reflux temperature. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. This residue is treated with 50 ml. 6 N hydrochloric acid under heating at reflux for two hours and a solution is obtained. The mixture is evaporated under vacuum on a rotatory evaporator (water bath 80°—100° C). The residue is dissolved in 50 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1, Trade Mark). The column is washed with water until there is no basic reaction. The water is evaporated. The residue is dried in vacuum (0.1 mm. Hg) and recrystallized from a benzene and heptane mixture, yielding the desired compound.

m.p. = 78° C—80° C (Yield: 95%)

PMR (CDCl₃): N—CH₂—CH₂—S+N—CH₂: 2.65 ppm (multiplet: 16H); S—CH₂—CH₂—S: 2.90 ppm (singlet: 4H); O—CH₂—: 3.60 ppm (triplet: 8H); 3.65 ppm (singlet: 8H)

Example 32

Preparation of 5,12 - dioxo - 1,7,10,16 - tetrathia - 4,13 - diaza - cyclooctadecane

This reaction is carried out applying a high dilution technique. A solution of 18 g. of the diamine obtained in Example 27 (0.1 mole) in 500 ml. anhydrous benzene and a solution of 12.4 g. of the dichloride obtained in Example 26 in 500 ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of eight hours under vigorous agitation and under a nitrogen atmosphere. Most of the desired amide precipitates during the course of the reaction. On termination, the benzene solution is filtered and evaporated to dryness. A small amount (2 g.) of solid residue is obtained. The solid precipitates formed during the high dilution reaction are extracted three times with 250 ml. boiling chloroform. The residue obtained from the benzene layer is added to the combined chloroform extracts. This solution is then filtered through a short column of alumina (30 g.), the column being washed with an additional 1,000 ml. of chloroform. The solution obtained is concentrated and the desired diamide crystallizes out.

m.p. = 148° C—149° C (Yield = 85%)

PMR (CDCl₃): —CH₂—S—: 2.65—2.90 ppm (complex band: 12H); —CO—CH₂—S: 3.25 ppm (singlet: 4H); —N—CH₂—: 3.52 ppm (multiplet: 4H)

Example 33

Preparation of 1,7,10,16 - tetrathia - 4,13 - diazacyclooctadecane

A solution of diborane (20 ml.; 1.5 N) in anhydrous tetrahydrofuran is added dropwise to a suspension of 2 g. of the diamide obtained in Example 32 in 50 ml. anhydrous tetrahydrofuran under nitrogen at room temperature. The solid dissolves giving a clear solution. After the addition is completed the mixture is refluxed during four hours and a solid precipitate is formed. After cooling to room temperature, the excess reagent is destroyed by adding carefully 10 ml. of water. The solvents are evaporated to dryness and 6 N hydrochloric acid (50 ml.) is added to the solid residue. The mixture is refluxed for three hours; the solid does not dissolve, the mixture remaining heterogeneous. The mixture is evaporated to dryness and a solution of 10% sodium hydroxide in water (50 ml.) is added to the residue.

The heterogeneous mixture is extracted three times with chloroform (50 ml.) The combined chloroform layers are dried over sodium sulfate and filtered through a short alumina (20 g.) column. The solvent is removed and the solid product is recrystallized from ethanol.

m.p. = 125° C Yield 50%

PMR (CDCl₃): one complex band from 2.75 to 2.83 ppm.

Example 34

Preparation of 2,9 - dioxo - 4,7 - dioxo - 13,16,21,24 - tetrathia - 1,10 - diazabicyclo[8,8,8]hexacosane

The reaction is carried out applying the high dilution technique. A solution of 1.0 g. of the cyclic diamine obtained in Example 33 and 0.3 g. of trichloramine in 100 ml.

anhydrous benzene and a solution of the dichloride (0.8 g. in 100 ml. anhydrous benzene) obtained in Example 1B are added to 1,000 ml. anhydrous benzene during two hours under nitrogen atmosphere and under vigorous agitation. The salt of triethylamine and the hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and filtered through a column of Al_2O_3 (20 g.) followed by 500 ml. of chloroform.

The solvents are evaporated, leaving the title compound as a viscous oil which may crystallize on standing.

Yield: 40%

PMR ($CDCl_3$): CH_2-S : 2.75 ppm (broad band: 16H); CH_2-N and CH_2-O : 3.65 ppm (broad bands: singlet+triplet: 12H); $CO-CH_2-O$: around 4 ppm (several broad peaks: 4H)

Example 35

Preparation of 4,7 - dioxo - 13,16,21,24 - tetrathia - 1,10 - diazabicyclo[8,8,8]hexacosane

A solution of 0.6 g. of the bicyclic diamide obtained in Example 34 in 10 ml. tetrahydrofuran is slowly added to 10 ml. of the freshly prepared B_2H_6 solution (1.5 M) under nitrogen atmosphere and at a temperature of $0^\circ C$. The mixture is refluxed for two hours. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. The solid residue is treated with 50 ml. 6 N hydrochloric acid under reflux for two hours. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The residue is treated with a solution of tetraethylammonium hydroxide until a basic reaction is obtained. The mixture containing a precipitate, is extracted several times with chloroform. The solutions are filtered through alumina and evaporated to dryness leaving the title compound as a crystalline residue.

The solid residue is recrystallized from a benzene-hexane mixture and dried in vacuum (0.1 mm Hg.)

m.p. = $86^\circ C$ - $87^\circ C$ (Yield = 95%)

PMR ($CDCl_3$): $N-CH_2-CH_2-S+N-CH_2$: 2.70 ppm (multiplet: 20H); $S-CH_2-CH_2-S$: 2.90 ppm (broad band: 8H); CH_2-O : 3.60 ppm (triplet: 4H); 3.68 ppm (singlet: 4H).

Example 36

Preparation of 2,9 - dioxo - 4,7,13,16,21,24 - hexathia - 1,10 - diazabicyclo[8,8,8]hexacosane

The reaction is carried out applying the high dilution technique. A solution of 4.5 g. of the cyclic diamine obtained in Example 33 and 1.5 g. of triethylamine in 500 ml. hot anhydrous benzene (maintained at approx. $60^\circ C$ during the addition) or in 400 ml. anhydrous chloroform and a solution of the dichloride (3.5 g. in 400 ml. anhydrous benzene) obtained in Example 26B is added to 1000 ml. anhydrous benzene during six hours under nitrogen atmosphere and under vigorous agitation. The salt of triethylamine and the hydrochloric acid and the product precipitate and are filtered off. The benzene layer contains only a very small amount of product. The solid is extracted three times with hot chloroform. The combined chloroform solutions are filtered through an alumina column. The bicyclic amide is eluted with methanol. After evaporation to dryness the title product is obtained as a viscous oil.

Yield 20%

PMR ($CDCl_3$): CH_2-S : several broad peaks between 2.5 and 3.1 ppm (20H); $COCH_2-S+CH_2-N$: several broad peaks between 3.2 and 3.8 ppm (12H).

Example 37

Preparation of 4,7,13,16,21,24 - hexathia - 1,10 - diazabicyclo[8,8,8]hexacosane

20 ml. of the fresh prepared B_2H_6 solution is added to a suspension of 1 g. of the bicyclic diamide obtained in Example 36 in 20 ml. tetrahydrofuran under nitrogen atmosphere and at a temperature of $0^\circ C$. The mixture is agitated at this temperature for thirty minutes and thereafter four hours at reflux temperature. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. 50 ml. 6 N hydrochloric acid are added and the mixture is heated under reflux for four hours. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The mixture is made alkaline with NaOH N/10 and is ex-

28					
ben		29	1,304,367		29
two			tracted three times with chloroform. The chloroform solutions are filtered through		
ethyl-			alumina and evaporated to dryness. The residue is recrystallized from a chloroform/		
para-			hexane mixture leading to the title compound.		
on of	5		m.p. = 172° C Yield = 80%		
which		5	PMR (CDCl ₃): N—CH ₂ —CH ₂ —S: 2.68 ppm (singlet: 24H); S—CH ₂ —CH ₂ —S:	5	
			2.90 ppm (singlet: 12H)		
			Example 38		
—O:	10		Preparation of 1,5 - dioxino - 3 - oxapentane		
ppm		10	1,5-Dichloro-3-oxapentane is treated with potassium phthalimide, followed by	10	
			hydrazinolysis of the resulting diphtalimide-derivative and consecutive acidification		
			whereby the bis-hydrochloride of the title compound is obtained.		
exa-			The bis-hydrochloride is treated with a very concentrated (approx. 10N) solution		
	15	15	of potassium hydroxide in water and continuously extracted with benzene in a liquid-	15	
ml.			liquid extractor for several (three to five) days. The solvent is evaporated and the liquid		
(1.5			residue is distilled under reduced pressure giving the desired compound.		
and			b.p.: 48°—50°/1mm Hg: Yield 30% (from the initial 1,5-dichloro-3-oxapentane).		
olu-			PMR (CDCl ₃): —NH ₂ : 1.30 ppm (singlet: 4H); —CH ₂ —N 2.90 ppm (triplet: 4H);		
ated			—CH ₂ —O: 3.50 ppm (triplet: 4H).		
ara-	20	20	Example 39	20	
ch a			Preparation of diglycolic acid dichloride		
mixture			To 13.4 g. of diglycolic acid covered with chloroform (150 ml.), 45 g. phosphorus		
ions			pentachloride are added in one aliquot.		
as	25	25	After standing for ten minutes at room temperature the mixture is heated slowly	25	
in			to reflux temperature over a period of one hour and is then left under reflux for 1.5		
			hours. The solvent is then evaporated at room temperature under reduced pressure		
(H);			(water pump). Then, the phosphorus oxychloride formed during the reaction is taken		
er:	30	30	off at room temperature under 0.5 mm Hg pressure (oil pump). The remaining oil is	30	
			distilled (oil bath below 80° C) giving 14.8 g. of the desired dichloride.		
			b.p. = 56°—57°/0.5 mm Hg. Yield = 86%.		
			PMR (CDCl ₃): O—CH ₂ —CO: 4.65 ppm (singlet).		
			The dichloride is unstable to heat and must be distilled at low temperature at		
			sufficiently low pressure.		
			Example 40		
4]-			Preparation of 5,9 - dioxo - 1,7,13 - trioxa - 4,10 - diazacyclopentadecane		
1.5	35	35	This reaction is carried out applying a high dilution technique. A solution of 29.6	35	
ml.			g. of the diamine obtained in Example 2 (0.2 mole) in 1000 ml. anhydrous benzene		
20			and a solution of 17.2 g. (0.1 mole) of the dichloride obtained in Example 39 in 1000		
us			ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of		
ex	40	40	eighteen hours under vigorous agitation and under a nitrogen atmosphere. On termina-	40	
1.			tion, the benzene solution is filtered and evaporated to dryness. The crude solid residue		
he			is almost pure (m.p. 147°—148° C). It is recrystallized from a hot mixture of tetra-		
ed			hydrofuran and heptane giving the title product.		
ed			m.p. = 149°—150° C Yield = 75%		
	45	45	PMR (CDCl ₃): N—CH ₂ —CH ₂ —O: 3.60 ppm (multiplet: 8H); O—CH ₂ —CH ₂ —O:	45	
			3.67 ppm (singlet: 4H); —CO—CH ₂ —O: 4.08 ppm (singlet: 4H); NH: 7.15		
			ppm (broad band: 2H).		
			Example 41		
			Preparation of 1,7,13 - Trioxa - 4,10 - diazacyclopentadecane		
			A solution of 15.7 g. of the diamide obtained in Example 40 in 300 ml. hot an-		
	50	50	hydrous tetrahydrofuran is slowly added to a mixture of 50 ml. anhydrous tetrahydro-	50	
			furan and 15 g. LiAlH ₄ , while stirring over a period of 1.5 hours. After the addition		
			is completed, the mixture is stirred under reflux and under a nitrogen atmosphere for		
			twenty hours. After cooling to room temperature the excess reagent is destroyed by		
	55	55	adding a mixture (45 ml.) of water and THF (1:2), followed by 15 ml. NaOH 15%	55	
			and 45 ml. water. The mixture is filtered and the filtrate is evaporated to dryness. The		
			residue is dissolved in benzene and the solution is passed through a column of Al ₂ O ₃		
	55		with benzene as eluant. The solution is evaporated to dryness and a semicrystalline pro-		
			duct is obtained (mixture of crystals and an oil) which proves to be the desired product.		
			Yield = 89%		
			PMR (CDCl ₃): CH ₂ —N: 2.75 ppm (triplet: 8H); CH ₂ —O: 3.60 ppm (triplet+		
			singlet: 12H)		
	60	60		60	

Example 42

Preparation of 2,9 - dioxo - 4,7,13,16,21 - penta-oxa - 1,10 - diazabicyclo[8,8,5]tricosane

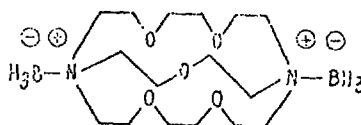
The reaction is carried out applying the high dilution technique. A solution of 8.72 g. of the cyclic diamine obtained in Example 41 and 8.8 g. of triethylamine in 500 ml. anhydrous benzene and a solution of the dichloride (8.6 g. in 500 ml. anhydrous benzene) obtained in Example 1B is added to 1000 ml. anhydrous benzene during ten hours under nitrogen atmosphere and under agitation. The salt of triethylamine and the hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al_2O_3 (100 g.) using benzene as an eluant. The title compound is obtained as an oil which crystallizes on standing. The product is recrystallized from a hexane-benzene mixture. m.p. = 105° C Yield 45%

PMR ($CDCl_3$): several peaks between 3.3 and 4.6 ppm.

Example 43

Preparation of 4,7,13,16,21 - penta-oxa - 1,10 - diazabicyclo[8,8,5]tricosane

A solution of 5 g. of the bicyclic diamide obtained in Example 42 in 50 ml. anhydrous tetrahydrofuran is slowly added to 50 ml. of the fresh prepared B_2H_6 solution (1.0M) under nitrogen atmosphere and at a temperature of 0° C. The mixture is agitated at this temperature for thirty minutes and thereafter 1.5 hours at reflux temperature. The excess reagent is destroyed by adding 10 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. 3.5 g. of the diborane of the title compound is obtained (m.p. = 205°—209° C).



This compound is hydrolysed by adding 50 ml. 6N hydrochloric acid under heating and a solution is obtained. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The residue is dissolved in 30 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1, Trade Mark). The column is washed with water until there is no basic reaction. The water is evaporated. The title compound is obtained as a colourless oil (3 g.)

Yield = 95%

PMR ($CDCl_3$): $-CH_2-N$: 2.65 ppm (triplet: 12H); $-CH_2-O$: 3.60 ppm (triplet: 12H); 3.70 ppm (singlet: 8H).

Example 44

Preparation of 5,9 - dioxo - 1,7 - dioxo - 4,10 - diaza - cyclododecane

This reaction is carried out applying the high dilution technique. A solution of 10.4 g. of the diamine obtained in Example 38 (0.1 mole) in 100 ml. anhydrous benzene and a solution of 8.6 g. (0.05 mole) of the dichloride obtained in Example 39 in 100 ml. anhydrous benzene are added to 1000 ml. anhydrous benzene over a period of 50 minutes under vigorous agitation. The reaction mixture is filtered and the residue is washed with hot chloroform (3×500 ml.) The combined solutions are evaporated to dryness leaving a crystalline residue (m.p. = 180°—181° C) which is recrystallized from a hot mixture of chloroform and heptane giving the desired product. m.p. = 182°—183° C Yield = 65%

PMR ($CDCl_3$): $N-CH_2-CH_2-O$: 3.60 ppm (broad multiplet: 8H); $CO-CH_2-O$: 4.15 ppm (singlet: 4H); NH: 7.65 ppm (broad band: 2H)

Example 45

Preparation of 1,7 - dioxo - 4,10 - diazacyclododecane

A suspension of 5.0 g. of the diamide obtained in Example 44 in 100 ml. hot anhydrous tetrahydrofuran and 4.8 g. $LiAlH_4$ while stirring over a period of one hour. After the addition is completed, the mixture is stirred under reflux and under a nitrogen atmosphere for eighteen hours. After cooling to room temperature the excess reagent is destroyed by adding a mixture (15 ml.) of water and THF (1:2) followed by 5 ml. NaOH 15% and 15 ml. water. The mixture is filtered and the filtrate is evaporated to dryness. The residue is dissolved in benzene and the solution is passed through

a column of Al_2O_3 with benzene as eluant. The solution is evaporated to dryness and after recrystallization from hot benzene/heptane the desired product is obtained.

m.p. = 83° — 84° C Yield = 70%

PMR ($CDCl_3$): NH: 2.40 ppm (singlet: 2H); $-CH_2-N$: 2.80 ppm (triplet: 8H); $-CH_2-O$: 3.66 ppm (triplet: 8H).

Example 46

Strongly basic solutions

When solid potassium hydroxide is added to a solution of 4,7,13,16,21,24 - hexaoxa - 1,10 - diaza - bicyclo[8,8,8] - hexacosane (obtained in Example 6) in anhydrous tetrahydrofuran, a very strongly basic solution is obtained as KOH dissolves in the solvent under complex formation with the bicyclic diamine.

The strong basicity may be shown by adding some fluorene: an intense red colour, due to the formation of the fluorenyl anion, develops immediately. By treating this strongly basic solution with air the fluorenone is obtained. When no bicyclic amine is present the anion is not formed and the solution remains colourless.

The same observations may be made when KOH is replaced by another base such as sodamide.

Example 47

Purification of Tetraglycolic acid

A. Preparation of tetraglycolic acid dianilide

Tetraglycolic acid dichloride is prepared as described in Example 13. 22 g. of this dichloride in 50 ml. anhydrous benzene are treated at 0° C (ice bath) with 35g. aniline in 50 ml. anhydrous benzene. The mixture is heated to 60° C for ten minutes and is poured into a separation funnel; 200 ml. water and 200 ml. chloroform are then added. The organic layer is separated and washed with 200 ml. 5% hydrochloric acid and then with 200 ml. water.

The solution is dried over sodium sulfate and the solvents are evaporated. The dianilide is thus obtained as an oil crystals of the dianilide may be obtained by crystallization:

- 1) first from acetone-water (dissolved in hot acetone; water added until the mixture becomes cloudy);
- 2) then from acetone-hexane (dissolved in hot acetone; hexane added until cloudy) using a crystal from (1) to initiate crystallization (m.p. 56° C)
- 3) finally again from acetone-water; a white crystalline product (19 g.) containing one mole of water, is thus obtained, m.p. 58° C Yield = 60%

PMR ($CDCl_3$): $O-CH_2-CH_2-O$: 3.75 ppm (singlet: 8H); $O-CH_2-CO$: 4.06 ppm (singlet: 4H); aromatic protons: 7.0—7.6 ppm (multiplet: 10H).

All signals are sharp; no impurities present.

B. Hydrolysis of the dianilide

19 g. Of the dianilide obtained previously are suspended in 200 ml. 15% sodium hydroxide in water. The mixture is refluxed for approx. twenty hours. After cooling to room temperature, the liquid mixture (the aniline formed forms an upper layer) is washed three times with 150 ml. benzene. The water layer is then brought to pH 1 using 10% hydrochloric acid and evaporated first at the water pump and then at the oil pump while heating on the steam bath. The residue ($NaCl$ +tetraglycolic acid) is washed with acetone, filtered and the solid on the funnel is washed two times with acetone. The acetone solution is evaporated to dryness. The oily residue obtained is pure tetraglycolic acid; PMR spectrum as described in Example 13A; small peaks due to contaminating compounds have completely disappeared (purity approx. 99%) Yield = 90%

Example 48

Preparation of 19,26 - dioxo - 4,7,13,16 - tetraoxa - 1,10 - diazabicyclo[8,8,8]hexacosane

The reaction is carried out applying the high dilution technique. A solution of 10.48 g. of the cyclic diamine obtained in Example 4 and 8.8 g. of triethylamine in 300 ml. anhydrous benzene and a solution of the dichloride of octane-1,8-dicarboxylic acid (8.44 g. in 500 ml. anhydrous benzene) is added to 1200 ml. anhydrous benzene during ten hours under nitrogen atmosphere and under agitation. The salt of triethylamine and the hydrochloric acid precipitates and is filtered off. The filtrate is evaporated to dryness.

The product is an oil which crystallizes on standing.
 m.p. = 96° — 93° C. Yield = 45%
 PMR (CDCl_3): $-(\text{CH}_2)_6-$: 1.4—2.0 ppm (broad peaks: 12H); CH_2-N and CH_2-O : several peaks between 3.3 and 4.6 ppm.

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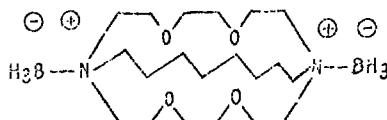
Example 49

5

Preparation of 4,7,13,16 - tetraoxa - 1,10 - diazabicyclo[8,8,8]hexacosane

A solution of 7 g. of the bicyclic diamide obtained in Example 48 in 80 ml. anhydrous tetrahydrofuran is slowly added to 70 ml. of the fresh prepared B_2H_6 solution (1.0M) under nitrogen atmosphere and at a temperature of 0° C. The mixture is agitated at this temperature for thirty minutes and thereafter 1.5 hour at reflux temperature. The excess reagent is destroyed by adding 20 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. 6 g. of the diborane of the title compound is obtained (m.p. = 139° C)

15



15

This compound is hydrolysed by adding 100 ml. 5N hydrochloric acid under heating and a solution is obtained. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The residue is dissolved in 20 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1, Trade Mark). The column is washed with water until there is no basic reaction. The water is evaporated. The title compound is obtained as a white crystalline solid.

20

m.p. = 90° — 91° C Yield = 85%
 PMR (CDCl_3): $-(\text{CH}_2)_6-$: 1.4 ppm (broad peak: 12H); $-\text{CH}_2-\text{N}$: 2.40 ppm (broad peak: 4H); 2.65 ppm (triplet: 8H); $-\text{CH}_2-\text{O}$: 3.53 ppm (triplet: 8H); 3.70 ppm (singlet: 8H).

25

25

Example 50

Preparation of the KSCN-complex of 4,7,13,16,21 - pentaoxa - 1,10 - diazabicyclo[8,8,5]tricosane.

30

100 mg. Of the macrocyclic compound are dissolved in chloroform and an excess solid KSCN is added. After standing overnight at room temperature the mixture is filtered and the solution is evaporated to dryness. The residue is crystallized from an ether-acetone mixture. The crystalline complex melts at 131° — 132° C.

30

Example 51

Preparation of the $\text{Ba}(\text{SCN})_2$ -complex of 4,7,19,16,19,24,27 - heptaoxa - 1,13 - diazabicyclo[8,8,11]nonacosane

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35

70 mg. Of the macrocyclic compound and 70 mg. solid $\text{Ba}(\text{SCN})_2 \cdot \text{H}_2\text{O}$ are refluxed in 20 ml. acetone for five minutes. The acetone is then removed under vacuum and the residue is treated with 25 ml. chloroform. After filtration, the chloroform is evaporated and the residue is crystallized from a chloroform-benzene-ether mixture. A crystalline complex is obtained. m.p. = above 260° C.

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40

Example 52

Further complexes of 4,7,13,16,21,24 - hexaoxa - 1,10 - diazabicyclo[8,8,8]hexacosane

45

The following complexes have been obtained by the method already described in Example 11, or else their formation has been observed by spectroscopic methods:

45

TiHCOO complex (m.p. = 50° — 52° C)
 $\text{Ca}(\text{SCN})_2$ complex (m.p. = above 260° C)
 $\text{Zn}(\text{BF}_4)_2$
 $\text{Pb}(\text{SCN})_2$

50

50

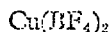
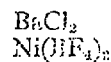
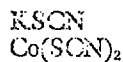
Example 53

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Complexes of 4,7,13,16,21 - pentaoxa - 1,10 - diazabicyclo[8,8,5]tricosane

This compound, obtained in Example 43, gives stable complexes with various metal salts in particular it readily forms complexes with transition metal salts. The

complexes of the following salts have been prepared by mixing methanol solutions of the salt and of the complexing agent and letting the complex crystallize out, or else their formation has been observed by spectroscopic methods:



Example 54

Preparation of 2,9 - dioxo - 4,7,13,18 - tetraoxa - 1,10 - diazabicyclo[5,5,8]cicosane

The reaction is carried out applying the high dilution technique. A solution of 8.7 g. of the cyclic diamine obtained in Example 45 and 11 g. of triethylamine in 200 ml. anhydrous chloroform and 300 ml. anhydrous benzene and a solution of the dichloride (10.8 g. in 500 ml. anhydrous benzene) obtained in Example 1B is added to 1000 ml. anhydrous benzene during eight hours under nitrogen atmosphere and under agitation. The solution is filtered and the solid residues are washed several times with benzene. The combined organic layers are evaporated to dryness leaving an oily residue which is then extracted three times with hot benzene (3×200 ml.) Evaporation of the benzene layers give a solid residue which is filtered in benzene solution through a column of alumina.

The solid obtained after evaporation of the solvent, is recrystallized from a benzene-heptane mixture. The desired product is obtained.

m.p. = 151°—152° C Yield = 45%

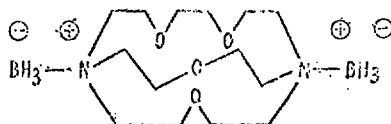
PMR (CDCl₃): two very complex multiplets between 2.6—3.2 ppm (4H) and 3.4—4.8 ppm (20H).

Example 55

Preparation of 4,7,13,18 - tetraoxa - 1,10 - diazabicyclo[5,5,8]cicosane

22 ml. of a freshly prepared B₂H₆ solution (0.8 M) are added with a syringe to a suspension of 2.9 g. of the bicyclic diamine obtained in Example 54 in 20 ml. anhydrous tetrahydrofuran under nitrogen atmosphere and at a temperature of 0° C. The mixture is agitated at this temperature for thirty minutes and thereafter three hours at reflux temperature. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. The residue is extracted several times with chloroform and the solution obtained is evaporated to dryness. 1.9 g. Of the diborane of the title compound is obtained.

m.p. = 121°—122° C Yield = 98%



This compound (1.7 g.) is hydrolysed by adding 20 ml. 6N hydrochloric acid under heating (2.5 hours) and a solution is obtained. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The residue is dissolved in 10 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1, Trade Mark). The column is washed with water until there is no basic reaction. The water is evaporated. The title compound is obtained as a colourless oil.

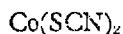
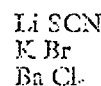
Overall yield = 95%

PMR (CDCl₃): —CH₂—N: 2.75 ppm (triplet: 12H); —CH₂—O: 3.4—3.8 ppm (multiplet: 12H); 3.70 ppm (singlet: 4H).

Example 56

Complexes of 4,7,13,18 - tetraoxa - 1,10 - diazabicyclo[5,5,8]cicosane

Complex formation with the title compound (obtained in Example 55) has been observed spectrometrically (NMR) for the following salts:



Some of these complexes are unstable in water.

Strongly basic solutions have also been obtained by following the procedure of Example 46. Also here the formation of the fluorenyl anion has been observed when adding fluorene to an anhydrous tetrahydrofuran solution of the complex formed with KOH.

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Example 57

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A. Preparation of 2-chloroethyl-chloromethyl ether

322 g. of $\text{ClCH}_2\text{CH}_2\text{OH}$, cooled in ice-water, was saturated with gaseous HCl , and 120 g. of trioxymethylene was added, after which the solution was again saturated with HCl . The lower layer was separated, dried over CaCl_2 , and dry CO_2 passed through the solution to remove excess HCl . Upon fractionation at reduced pressure the major portion boils at $65\text{--}73^\circ\text{C}/23\text{--}27\text{ mm}$. A small amount of trioxymethylene appears in the forerun. The yield is approx. 330 g.

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B. Preparation of 2-chloroethoxy acetonitrile

Mixing of 315 g. of the product obtained in Example A and 250 g. copper cyanide $\text{Cu}_2(\text{CN})_2$, followed by gentle heating, gives rise to a reaction which is controlled by cooling the flask with water. The reaction is finally completed by heating on a water bath for two hours. The reaction product is distilled at reduced pressure without removal of the $\text{Cu}_2(\text{CN})_2$, yielding 250 g. of the title compound. b.p. $55\text{--}58^\circ/0.8\text{ mm}$. Yield = 85%.

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15

C. Preparation of 2-chloroethoxy acetic acid

This compound was prepared by treating 120 g. of the product obtained in Example 57B with 250 ml. of concentrated HCl . Reaction sets in after a short time, and it is necessary to cool the flask to control the reaction, which is finally completed by heating on a steam bath for two hours. The mixture is diluted with an equal volume of water, and extracted four times with 50 cc portions of ether. The ether is evaporated and the product is distilled in vacuum, b.p. $130^\circ/3\text{--}5\text{ mm}$.

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20

D. Preparation of monothio-triglycolic acid

9.2 g. (0.1 mole) of thioglycolic acid are dissolved in a solution of 12 g. NaOH in 100 ml. water. 13.8 g. of the product obtained in Example 57C are added slowly (over approx. fifteen minutes) and the mixture is heated to 80°C for two hours. After cooling the solution is acidified with concentrated HCl and extracted three times with ether (3x50 ml.). The ether layers are combined, dried over sodium sulfate and evaporated to dryness. The sub-title product (14.5 g.) is obtained as a very viscous oil.

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Yield = 85%

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PMR (D_2O): $-\text{S}-\text{CH}_2-$: 2.85 ppm (triplet; 2H); $-\text{S}-\text{CH}_2-\text{CO}-$: 3.4 ppm (singlet; 2H); $-\text{O}-\text{CH}_2-$: 3.85 ppm (triplet; 2H); $-\text{O}-\text{CH}_2-\text{CO}-$: 4.2 ppm (singlet; 2H).

E. Preparation of monothio-triglycolic acid dichloride

The dichloride of the diacid obtained in Example 57D is prepared using oxalyl chloride in the same way as described in Example 28B. The product is a viscous oil. Yield = quantitative.

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40

PMR (CDCl_3): $-\text{S}-\text{CH}_2-$: 2.85 ppm (triplet; 2H); $-\text{S}-\text{CH}_2-\text{CO}-$: 3.3 ppm (singlet; 2H); $-\text{O}-\text{CH}_2-$: 3.8 ppm (triplet; 2H); $-\text{O}-\text{CH}_2-\text{OH}$: 4.45 ppm (singlet; 2H).

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45

Example 58

Preparation of 2,9 - dioxo - 4,12,16 - trioxa - 7,21,24 - trithia - 1,10 - diazabicyclo-[8,8,8]hexacosane

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This reaction is carried out applying the high dilution technique. A solution of 4.5 g. of the diamine obtained in Example 29 and 2 g. triethylamine in 200 ml. anhydrous benzene and a solution of 3.8 g. of the dichloride obtained in Example 57E in 200 ml. anhydrous benzene are added to 1,200 ml. anhydrous benzene over a period of 2.5 hours under vigorous agitation and under a nitrogen atmosphere. On termination, the benzene solution is filtered and evaporated to dryness.

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The oily residue is redissolved in benzene (100 ml.) and is filtered through a column of aluminium oxide (50 g.). The product is eluted with a mixture of chloroform and benzene (30%/70%). The solution is evaporated to dryness leaving a viscous oil, which is the desired compound (yield approx. 50%).

55

55

PMR (CDCl_3): very complex spectrum from 2.5 to 4.0 ppm; $\text{S}-\text{CH}_2+\text{NCH}_2$: from 2.5 to 2.9 ppm; $\text{O}-\text{CH}_2$: from 3.5 to 4.0 ppm.

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60

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Example 59

Preparation of 4,13,16 - trioxa - 7,21,24 - triithia - 1,10 - diazabicyclo[8,8,8]hexacosane

20 ml. of a solution (1.2 M) of a dibromide in anhydrous tetrahydrofuran are added to a solution of 1.5 g. of the bicyclic diiodide obtained in Example 58 in 20 ml. anhydrous tetrahydrofuran, under nitrogen atmosphere and at 0° C. The mixture is refluxed for two hours. The excess reagent is destroyed by adding 5 ml. of water and the solution is evaporated on a rotatory evaporator under vacuum. The residue is treated with 40 ml. 6N hydrochloric acid under reflux for two hours. The mixture is evaporated to dryness under vacuum on a rotatory evaporator. The residue is treated with a solution of triethylammonium hydroxide until a basic reaction is obtained. The mixture is extracted with benzene (3X50 ml.) and the organic layers are dried and filtered over a column of aluminium oxide. The solution is evaporated to dryness, leaving a viscous oil (1.4 g.), which is the desired compound.

Yield = 95%

PMR (CDCl₃): (—S—CH₂—) + (—N—CH₂—): 2.4—2.9 ppm (complex band: 24H; the —S—CH₂—CH₂—S group gives a singlet at 2.9 ppm); —O—CH₂—: 3.4—3.7 ppm (complex band: 12H)

Example 60

21,24-Dimethyl-4,7,13,16-tetraoxa-1,10,21,24-tetraazabicyclo[8,8,8]hexacosane

A. Following the procedure of Example 3, 3,6-dimethyl-3,6-diaza-1,8-octane-diamine is reacted with the dichloride obtained in Example 1B, to give 10,13-dimethyl-6,17-dioxo-1,4-dioxo-7,10,13,16-tetraaza-cyclooctadecane.

B. The product of step A is reduced at the oxo-groups, following the procedure of Example 4 to give 10,13-dimethyl-1,4-dioxo-7,10,13,16-tetraaza-cyclooctadecane.

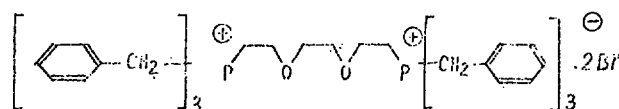
C. Following the procedure of Example 5 the product of step B is condensed with the dichloride of Example 1B to give 21,24-dimethyl-2,9-dioxo-4,7,13,16-tetraoxa-1,10,21,24-tetraaza-bicyclo[8,8,8]hexacosane.

D. Reduction of the oxo-groups following the procedure of Example 6 gives the title compound.

Example 61

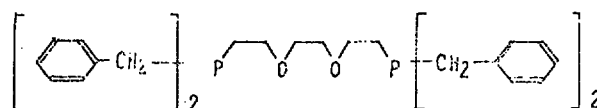
Preparation of 4,7,13,16,21,24 - hexaoxa - 1,10 - diphosphabicyclo[8,8,8]hexacosane

A. A mixture of 27.6 g. of triethylene glycol dibromide obtained according to Example 2A and 60.8 g. of tribenzylphosphine is heated on a steam bath for three to four hours under nitrogen atmosphere. The diphosphonium dibromide of the formula



[3,6-dioxo-1,8-bis(tribenzylphosphonium)-octane dibromide] is obtained.

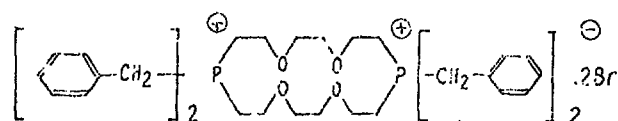
B. Two equivalents of lithium aluminium hydride are added to a suspension of the phosphonium salt obtained according to step A in dry tetrahydrofuran. The mixture is refluxed for several hours and the excess LiAlH₄ is destroyed by adding wet ether followed by aqueous NaOH. The ether layer is separated off and the solvent is evaporated. The diphosphine of the formula



[3,6-dioxo-1,8-bis(dibenzylphosphine)-octane] is obtained.

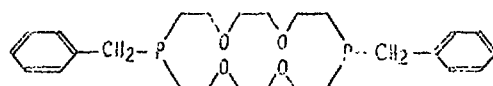
C. A mixture of the diphosphine obtained according to step B and one equivalent of triethylene glycol dibromide obtained according to Example 2A in dimethyl formamide are slowly added drop-wise over a period of several hours to hot dimethyl formamide (high dilution) under vigorous stirring and under nitrogen. After the evaporation of the

solvent and purification of the residue the monocyclic diphosphonium salt of the formula:



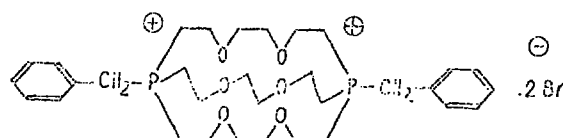
5 [1,7,10,16 - tetraoxa - 4,4,13,13 - tetrabenzyl - 4,13 - diphosphonium - cyclooctadecane dibromide] is obtained. 5

10 D. The diphosphonium salt obtained according to step C is transformed into the diphosphine of the formula 10



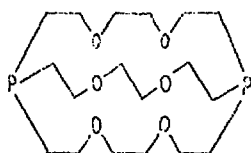
10 [4,13 - dibenzyl - 1,7,10,16 - tetraoxa - 4,13 - diphosphacyclooctadecane] by treating the salt with LiAlH_4 in tetrahydrofuran according to the process of step B above. 10

E. The product of step D is further reacted with triethylene glycol dibromide according to the process of step C and the bicyclic diphosphonium salt of the formula 20



15 [4,7,13,16,21,24 - hexaoxa - 1,10 - dibenzyl - 1,10 - diphosphonium - bicyclo[8,8,8]-hexacosane dibromide] is obtained. 15 20

F. The benzyl groups are removed following the process of step B and the title compound of the formula 35



[4,7,13,16,21,24 - hexaoxa - 1,10 - diphosphabicyclo[8,8,8]hexacosane] is obtained. 40

20

Example 62

Preparation of 1,2-di-(chlorocarbonyl-methoxy)-benzene. 20

A) 1,2-di-(carbonylmethoxy)-benzene.

200 g sodium hydroxide (5 mol) in 200 ml water and 110 g pyrocatechol (1 mole) are mixed in a 1 l. flask. 189 g of monochloroacetic acid (2 mol) are added slowly over a period of 3 hours. The mixture is heated to 100° over a period of 2 hours. After cooling, hydrochloric acid (100 ml) are added, the acid precipitates and is recrystallized in water. 25

M.P.: 177°C

Yield: 50%

PMR (basic $(\text{NaOH})\text{D}_2\text{O}$) 30

$-\text{O}-\text{CH}_2-$: 4.40 ppm (singlet; 4H)

aromatic portions: 6.9 ppm (multiplet; 4H) 30

E) Acid dichloride.

35 30 g of the above acid are added to a mixture of 200 ml anhydrous benzene. Then 35 g oxalyl chloride are added, the flask being protected by a calcium chloride tube. The mixture is stirred for four days and the diacid progressively dissolves as it is being transformed into the corresponding dichloride. The solution is then evaporated to dry-

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ness (without heating) leaving a brownish solid residue which is recrystallized from a mixture of chloroform-benzene giving white crystals.

m.p.: -50°C

Yield: 80%

5 $\text{PMR (CDCl}_3\text{): } \text{---O---CH}_2\text{---COCl---: 5 ppm (singlet 4H) aromatic protons: 7 ppm (singlet: 4H).}$ 5

decane

5

By reacting this dichloride with the diamine obtained in Example 2, following the procedure of Examples 3 and 4, 2,8,11,17-tetraoxa-5,14-diaza-bicyclo[16,4,0]docosa-18,20,22-triene is obtained.

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Example 63

Preparation of 2,13 - dioxo - 4,11,17,20,25,28 - hexaoxa - 1,14 - diaza - tricyclo-[12,8,8,0¹⁰⁻¹⁰] - triacont - 5,7,9 - triene

10

This reaction is carried out applying the high dilution technique. A solution of 5.2 g. of the diamine obtained in Example 4 and 5 g. of triethylamine in 300 ml. anhydrous benzene; and a solution of 5.4 g. of the dichloride obtained in Example 62 in 300 ml. anhydrous benzene, are added to 1000 ml. benzene during six hours under nitrogen atmosphere and under agitation. The triethylamine hydrochloride precipitates and is filtered off. The filtrate is evaporated to dryness. The residue is dissolved in benzene and passed through a column of Al_2O_3 (20 g.) using benzene as an eluant. The solutions are evaporated to dryness. The product is viscous oil.

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Yield: 50%
 $\text{PMR (CDCl}_3\text{): CH}_2\text{---N and CH}_2\text{O: 2.5 to 4.5 ppm (complex multiplet: 24H):}$
 $\text{O---CH}_2\text{---CO: 5.0 ppm (AB system) aromatic protons: 7.0 ppm (singlet: 4H)}$

20

Example 64

25 Preparation of 4,11,17,20,25,28 - hexaoxa - 1,14 - diazatriacyclo[12,8,8,0¹⁰⁻¹⁰] - triacont-5,7,9 - triene

25

35 ml. of a freshly prepared solution (1.2 M) of diborane are added slowly to a solution of 3 g. of the amide obtained in Example 63 in 20 ml. anhydrous tetrahydrofuran under nitrogen atmosphere and at a temperature of 0°C . The mixture is then heated to reflux for two hours. The excess reagent is destroyed by slowly adding 5 ml. of water. The solution is evaporated to dryness on a rotatory evaporator under vacuum.

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60 ml. 6N Hydrochloric acid are added to the residue and the mixture is refluxed for two hours. The solution is then evaporated to dryness under vacuum. The residue dissolved in 30 ml. water and the solution is passed through a column of an anion exchange resin (Dowex 1, Trade Mark). The column is washed with water until there is no basic reaction. The combined water solutions obtained are evaporated to dryness under vacuum on a water bath. The residue is a viscous oil.

30

35

Yield: 80%
 $\text{PMR (CDCl}_3\text{): } \text{---CH}_2\text{---N: 2.72 ppm (triplet: 8H), 2.90 ppm (triplet: 4H):}$
 $\text{---CH}_2\text{---O: 3.55 ppm (singlet: 8H and triplet 8H): } \text{---CH}_2\text{---O (phenolic): 4.10 ppm (triplet: 4H): aromatic protons: 6.85 ppm (singlet: 4H)}$

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d.

Listed below are some representatives of compounds from which complexes have been formed with the macrocyclic compounds of this invention:

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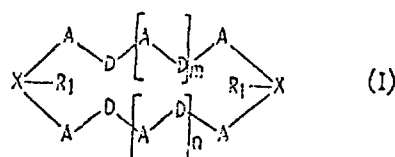
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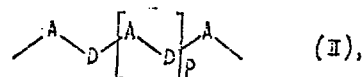
KF	NaCl	CaBr ₂	TlCl
KCl	NaI	CaCl ₂	AgNO ₃
KBr	NaSCN	SrBr ₂	Mg(OAc) ₂
KI	Na ₂ SO ₄	SrCl ₂	LiSCN
KOH	Na ₂ (COO) ₂	BaCl ₂	TlHCOO
KMnO ₄	RbCl	BaBr ₂	Zn(BF ₄) ₂
KBH ₄	NH ₄ SCN	BaSO ₄	Pb(SCN) ₂
KSCN	RbSCN	CuCl ₂	Co(SCN) ₂
K ₂ (COO) ₂	CsSCN		TiNO ₃
	NH ₄ I		

WHAT WE CLAIM IS:—

1. A macrocyclic compound of the general formula I



5 wherein each of R₁ is hydrogen, a hydrocarbon group having up to 12 carbon atoms or an alkoxy-carbonyl group having up to 10 carbon atoms, or both R₁ form together a grouping of the general formula II



10 (i.e. providing a bridge between the two X-groupings in the molecule); each A is a hydrocarbon group having up to 12 carbon atoms; each X is nitrogen or phosphorus; each D is oxygen, sulfur, >N—R (R being hydrogen or a hydrocarbon group having up to 12 carbon atoms) or a hydrocarbon group having up to 12 carbon atoms, with the proviso that at least two of the groups or atoms represented by D are selected from oxygen, sulfur and >N—R, and that when each R₁ is hydrogen, hydrocarbon or alkoxy-carbonyl and both X are nitrogen, then one of these two groups or atoms represented by D is oxygen or sulfur and the other is oxygen or >N—R; and each of m, n and p is a whole number from 0 to 5 inclusive.

15 2. A compound according to claim 1, wherein each R₁ is hydrogen, a hydrocarbon group or an alkoxy-carbonyl group.

20 3. A compound according to claim 2, wherein any hydrocarbon or alkoxy-carbonyl group represented by R₁ has from 1 to 8 carbon atoms.

4. A compound according to claim 2 or claim 3 wherein, m and n are each independently 0, 1 or 2 and both X are the same.

5. A compound according to claim 1, wherein both R₁ together form the grouping

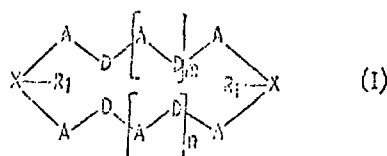


25 providing a bridge between the two X-groupings of the molecule.

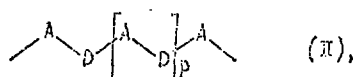
KF	NaCl	CoBr ₂	TiCl
KCl	NaI	CaCl ₂	AgNO ₃
KBr	NaSCN	SrBr ₂	Mg(OAc) ₂
KI	Na ₂ SO ₄	ScCl ₂	LiSCN
KOH	Na ₂ (COO) ₂	BaCl ₂	TiHCOO
KMnO ₄	RbCl	BaBr ₂	Zn(BF ₄) ₂
KBH ₄	NH ₄ SCN	LaSO ₄	Pb(SCN) ₂
KSCN	RbSCN	CuCl ₂	Co(SCN) ₂
K ₂ (COO) ₂	CsSCN		TiNO ₃
	NH ₄ I		

WHAT WE CLAIM IS:—

1. A macrocyclic compound of the general formula I



5 wherein each of R₁ is hydrogen, a hydrocarbon group having up to 12 carbon atoms or an alkoxy-carbonyl group having up to 10 carbon atoms, or both R₁ form together a grouping of the general formula II



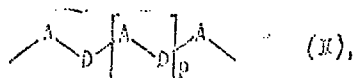
10 (i.e. providing a bridge between the two X-groupings in the molecule); each A is a hydrocarbon group having up to 12 carbon atoms; each X is nitrogen or phosphorus; each D is oxygen, sulfur, >N—R (R being hydrogen or a hydrocarbon group having up to 12 carbon atoms) or a hydrocarbon group having up to 12 carbon atoms, with the proviso that at least two of the groups or atoms represented by D are selected from oxygen, sulfur and >N—R, and that when each R₁ is hydrogen, hydrocarbon or alkoxy-carbonyl and both R₁ are nitrogen, then one of these two groups or atoms represented by D is oxygen or sulfur and the other is oxygen or >N—R; and each of m, n and p is a whole number from 0 to 5 inclusive.

2. A compound according to claim 1, wherein each R₁ is hydrogen, a hydrocarbon group or an alkoxy-carbonyl group.

20 3. A compound according to claim 2, wherein any hydrocarbon or alkoxy-carbonyl group represented by R₁ has from 1 to 8 carbon atoms.

4. A compound according to claim 2 or claim 3 wherein, m and n are each independently 0, 1 or 2 and both X are the same.

5. A compound according to claim 1, wherein both R₁ together form the grouping



providing a bridge between the two X-groupings of the molecule.



6. A compound according to claim 5 wherein m, n and p are each independently 0, 1 or 2 and both X are the same.

7. A compound according to any one of claims 1 to 6, wherein the hydrocarbon groups represented by A and any hydrocarbon groups represented by D have at least 2 carbon atoms.

8. A compound according to claim 7, wherein the hydrocarbon groups represented by A and any hydrocarbon groups represented by D have from 2 to 8 carbon atoms.

9. A compound according to claim 7 or claim 8, wherein the hydrocarbon groups represented by A and any hydrocarbon groups represented by D are alkylene, alkenylene, cycloalkylene, cycloalkenylene, cycloalkylene-di-alkyl, phenylene or phenylene-di-alkyl.

10. An N- and/or P- oxide of a compound as claimed in any preceding claim having tertiary nitrogen and/or phosphorus.

11. An ammonium and/or phosphonium salt of a compound as claimed in any one of claims 1 to 9.

12. A compound according to any one of claims 1 to 9, wherein both X are nitrogen.

13. A compound according to claim 12, wherein each D is oxygen and m, n and p are other than zero.

14. A compound according to claim 1, wherein each X is nitrogen, each D is oxygen and m, n and p are other than zero.

15. An N-oxide of a compound as claimed in any one of claims 12 to 14 having tertiary nitrogen.

16. An ammonium salt of a compound as claimed in any one of claims 12 to 14.

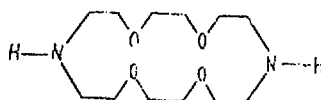
17. A compound according to any one of claims 1 to 9, wherein both X are phosphorus.

18. A P-oxide of a compound as claimed in claim 17 having tertiary phosphorus.

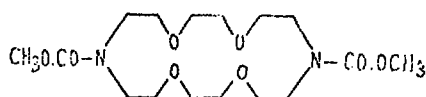
19. A phosphonium salt of a compound as claimed in claim 17.

20. A complex formed from a compound as claimed in any one of claims 1 to 9, 12 to 14 and 17 or from an N- or P- oxide claimed in any one of claims 10, 15 and 18 with an organic or inorganic cation.

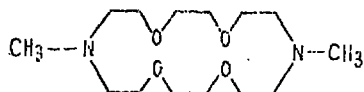
21. The compound of the formula



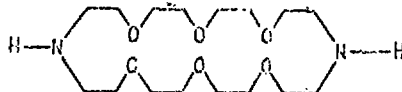
22. The compound of the formula



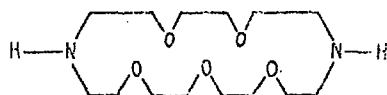
23. The compound of the formula



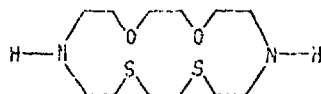
24. The compound of the formula



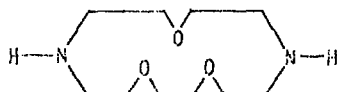
25. The compound of the formula



26. The compound of the formula



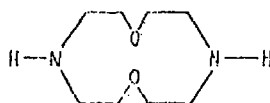
27. The compound of the formula



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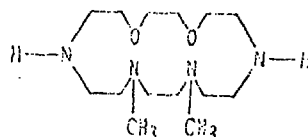
28. The compound of the formula

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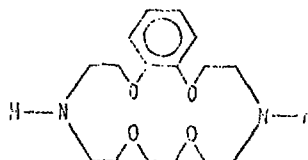
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29. The compound of the formula



30. The compound of the formula

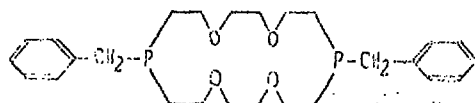
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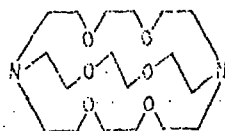
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31. The compound of the formula



32. The compound of the formula

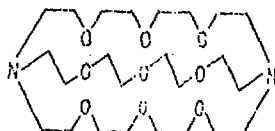


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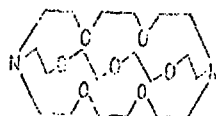
33. The compound of the formula

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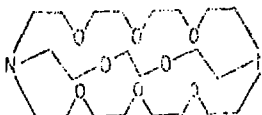
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34. The compound of the formula



35. The compound of the formula

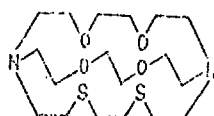


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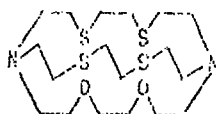
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36. The compound of the formula

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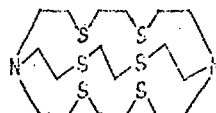
37. The compound of the formula



38. The compound of the formula

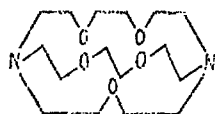
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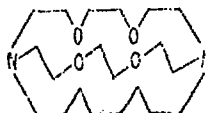


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39. The compound of the formula



40. The compound of the formula

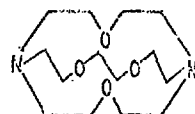


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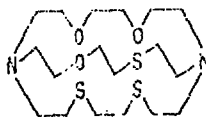
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41. The compound of the formula

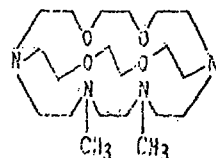
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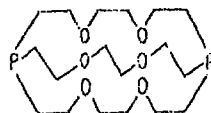
42. The compound of the formula



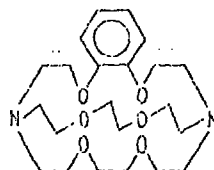
43. The compound of the formula



44. The compound of the formula



45. The compound of the formula

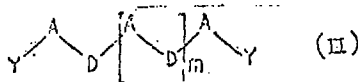


46. An N-oxide of a compound claimed in anyone of claims 22, 23 and 32 to 45.

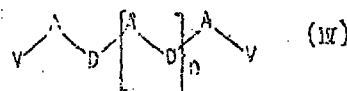
47. A P-oxide of a compound claimed in claim 31 or claim 34.

48. A complex formed from a compound as defined in any one of claims 21 to 47 with an inorganic or organic cation.

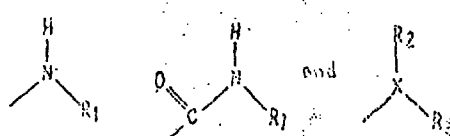
49. A process for the preparation of a compound of general formula I defined in claim 1; or of an N- or P-oxide of such a compound of general formula I having tertiary nitrogen or phosphorus; or of a complex formed from such a compound of general formula I or from such an N- or P-oxide; or of an ammonium and/or phosphonium salt of such a compound of general formula I, characterised in that a compound of the general formula III



is condensed with a compound of the general formula IV:

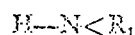


wherein A, D, m and n are as defined in claim 1 and either Y is selected from the groupings



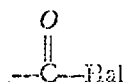
R_1 and X being as defined in claim 1, R_2 being a hydrogenolysable group and R_3 being the same as R_1 or R_2 , and V is a leaving group (as defined herein) which is sufficiently labile to be displaced by Y ; or Y is the grouping

5



5

and V is the grouping



R_1 being as above defined and Hal representing a halogen atom; the condensation being performed using high dilution techniques; that any carbonyl groups in a so-obtained compound are reduced to CH_2 and that, if desired, a compound obtained by any of the previous steps is subjected to one or more of the following finishing steps:

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- (a) hydrogenolysis of any hydrogenolysable groups represented by R_2 and/or R_3 ;
- (b) transformation into phosphonium and/or ammonium salt;
- (c) transformation of any phosphonium and/or ammonium salt into the free compound;
- (d) transformation into a N- and/or P-oxide;
- (e) transformation into a complex containing an organic or inorganic cation and
- (f) transformation of a complex into the free compound.

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50. A process according to claim 49 in which V is a halogen atom or a methanesulfonate or *p*-toluenesulfonate group.

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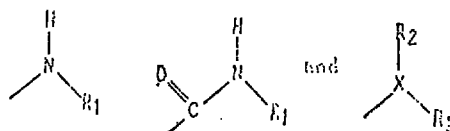
51. A process according to claim 49, characterised in that V in the general formula



IV is halogen or the grouping $-C(Hal)$, where Hal represents halogen, and when V is halogen then Y in the general formula III is selected from the groupings

45.

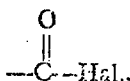
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and when V is the grouping

25

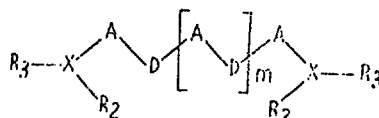


then Y is the grouping $N-H<R_1$, the groups R_1 , R_2 , R_3 and X being as defined in claim 49.

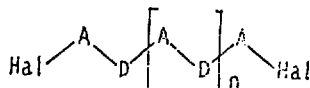
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52. A process according to claim 49, characterised in that a compound of the general formula

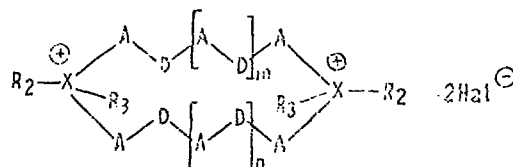
30



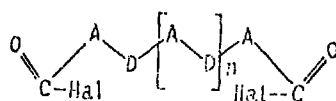
is condensed with a compound of the general formula



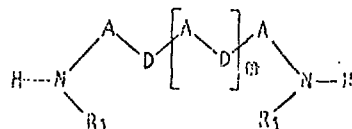
A, D, R₂, R₃, X, m and n being as defined in claim 49 and Hal being a halogen atom, followed, if desired, by hydrogenolysis of the hydrogenolysable groups in the so-obtained quaternary salt of the general formula



53. A process according to claim 49 for the preparation of compounds in which both X are nitrogen characterized in that a compound of the general formula



is condensed with a compound of the general formula



- A, D, R₁, m, n and Hal being as defined in claim 49.
54. A process according to any one of claims 49 to 53 characterised in that the complex is transformed into the free compound by treatment with acid.
55. A process according to any one of claims 49 to 53 characterised in that the transformation into a complex containing an organic or inorganic cation is accomplished by admixing the macrocycle with a cation-containing compound.
56. A process according to claim 55 characterised in that the components are admixed in a liquid medium.
57. A process according to claim 49 and substantially as hereinbefore described.
58. A compound of general formula I defined in claim 1; or an N- or P-oxide of such a compound of general formula I having tertiary nitrogen or phosphorus; or a complex formed from such a compound of general formula I or from such an N- or P-oxide; or an ammonium and/or phosphonium salt of such a compound of general formula I, whenever prepared by a process as claimed in any one of claims 49 to 57.

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