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☒	Claim(s)	: paged to paged
☐	Drawing(s)	: paged to paged
☐	Abstract	: paged to paged
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PROCESS FOR PREPARING MONO-N-ALKYLATED POLYAZAMACROCYCLES

The present invention concerns a process for preparing mono-N-alkylated polyazamacrocycles.

T. A. Kaden, *Top.Curr.Chem.* 121, 157-75 (1984) has shown that simple alkylative techniques using electrophiles and polyazamacrocycles for the production of mono-N-functionalized polyazamacrocycles result in the formation of a mixture of mono, bis, and tris alkylated products which are difficult to separate and purify. To overcome this problem, large excesses of macrocycle, for example 5-10 equivalents relative to electrophile, have been employed by M. Studer et al., *Helv.Chim.Acta*, 69, 2081-86 (1986) and by E. Kimura et al., *J.Chem.Soc.Chem.Comm.* 1158-59 (1986). Additionally, auxiliary bases have used together with large excesses of macrocycle to obtain the mono-N-alkylation product by M. Studer et al., *supra*. Purification of the desired mono-N-alkylated product from the large excess of starting material and inorganic salt is a major problem associated with these methods. Additionally, the cost associated with employing a large excess of expensive reagent is prohibitive.

Other mono-N-alkylation attempts by F. Wagner et al., *Inorg.Chem.* 15, 408 (1976) involve selective deprotonation of a transition metal complex of a polyazamacrocycle with strong base followed by alkylation with methyl iodide. Further synthetic manipulation of this compound necessitates metal removal and purification which can be tedious.

Additional synthetic routes which afford mono-N-functional polyazamacrocycles involve lengthy, protection, functionalization, deprotection schemes which are divergent and not always general. For example, see P. S. Pallavicini et al., *J.Amer.Chem.Soc.* 109, 5139-44 (1987) and published European patent application 0 232 751 (1984).

In light of these limitations on mono-N-alkylation techniques existing in the art, it would be desirable to employ a direct alkylation approach which would not be reliant upon the use of excess macrocycle and an auxiliary base and yet would be selective for the desired mono-N-alkylated product.

Surprisingly, the present invention provides such a process for preparing selectively the mono-N-alkylated products without the use of large excesses of macrocycle and auxiliary base. The present invention is directed to a novel process for preparing a mono-N-alkylated polyazamacrocycle which comprises reacting an electrophile with between one to five equivalents of a polyazamacrocycle in a solvent which will not promote a proton transfer. This process results in a greater selectivity for the desired mono-N-alkylated product compared to the bis, tris, tetra or higher N-alkylated products.

The present invention concerns the reaction of an appropriate electrophile (E) with a free base polyazamacrocycle (M) in a relatively non-polar, preferably relatively aprotic solvent. The ratio of E to M is about one E to about five M equivalents, preferably from about one E to about three M equivalents, more preferably from about one E to about two M equivalents, and most preferably from about one E to about one M equivalent.

The present process is very general and can produce selective mono-N-alkylation products with various polyazamacrocycles and electrophiles. A slight excess of polyazamacrocycle is preferred to insure complete conversion of the electrophile; however, only small differences in isolated yield occur when larger excesses of the polyazamacrocycle are used.

The polyazamacrocycles used in the present invention must contain at least two nitrogen atoms. However, the polyazamacrocycles can also contain other hetero moieties such as oxygen atoms (polyoxazamacrocycles) or sulfur atoms (polythioazamacrocycles). Also included in the term polyazamacrocycles are any symmetrical rings such as polyazamacrocycle, azaoxamacrocycle or bicyclopolyazamacrocycle (i.e. bridged moieties or fused rings, but the mono-N-alkylation reaction occurs on the nitrogen atom of a saturated ring) which bears secondary amines capable of mono-N-alkylation. Preferably the secondary amines are all chemically equivalent. The macrocycle preferably has a plane of symmetry and the total number of hetero atoms (O, S, N) should preferably total an even integer. The final macrocycle also contains a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms. The term "polyazamacrocycles" means all of these heterocyclic possibilities and includes, for example, 1,4-diazacyclohexane, 1,3,7-triazacyclononane, 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane, 1,4,7,10,13-pentaazacyclopentadecane, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,7,13-triaza-4,10,16-trioxacyclooctadecane, 1,7-diaza-4,11-dithiacyclododecane and the like.

The electrophile (RX) used in the present process is one capable of accepting a pair of electrons from one of the nitrogen atoms in the polyazamacrocycle. A covalent bond results from the reaction between the electrophile and polyazamacrocycle and selective mono-N-alkylation results. In the term RX, the R term is a moiety which will yield the desired mono-N-alkylated product, particularly any alkyl, alkylaryl, or alkyl-heterocaryl functionality. Some examples of the R term are C₁-C₄ alkyl, cyano, pyridinyl, CO₂R¹ or CON(R¹)₂.



where R' is H, C₁-C₄ alkyl, C₁-C₄ alkaryl where the aryl portion can be a 5 or 6 member ring having carbon, sulfur, nitrogen or oxygen atoms. The X term is any leaving group. Such leaving groups are well known in the art such as, for example, chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo, brosylate and other similar known groups. Some suitable electrophiles are, for example, *d,l*-2-bromo-4-N-phthalamidobutanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester, 4-nitrocinnamyl bromide, 4-nitrophenethyl bromide, 4-nitrobenzyl bromide, benzyl bromide and other similar known groups.

Concentration of the reagents is not critical for the present process but for economic reasons and reasonable reaction times, the present process is preferably conducted under non-dilution conditions such as 1 X 10⁻³M to 2M in each reagent. Mono-N-alkylations conducted under these concentrations afford the desired product in good to excellent yield with unexpectedly high selectivities. The mono-N-alkylated polyazamacrocyclic is obtained in a selectivity of at least 40 percent, preferably from 50 to 98 percent, compared to the bis, tris and or tetra N-alkylated products.

The solvent used for the present process is one which will not promote a proton transfer. A suitable solvent is a relatively non-polar, relatively aprotic solvent such as, for example, chloroform (CHCl₃), carbon tetrachloride (CCl₄), methylene chloride (CH₂Cl₂), tetrahydrofuran, 1,4-dioxane, and acetonitrile, or a relatively non-polar, relatively aprotic hydrocarbon solvent such as, for example, benzene, cyclohexane, n-hexane, and toluene, or a relatively non-polar, protic alcohol such as, for example, n-butanol, t-butanol, isopropanol, n-hexanol and the like. The preferred solvents are the relatively non-polar, relatively aprotic solvents, especially chloroform. The term "relatively aprotic" means that the solvent does not donate a proton to the reaction under the process conditions. The term "relatively non-polar" means that the solvent has a relatively low dipole moment, as seen from the above listed examples of suitable solvents.

Temperature employed is in the range of from -78 to 100 °C, preferably from -25 to 40 °C, more preferably from 0 to 25 °C. The time of the reaction, at a temperature of from 0 to 25 °C, is from 10 to 24 hours. The time of the reaction will vary inversely with the temperature; however, the lower temperatures are preferred to aid in selectivity of the desired mono-N-alkylated product.

The absence of base from the displacement conditions of the reaction helps to prevent epimerization of chiral electrophilic reagents. Hence, optically active mono-N-alkylated adducts are potentially available by this present process. The product formed will possess the inverted optical form from the starting electrophile reagent. For example, the resulting mono-N-alkylated polyazamacrocyclic product has the opposite optical configuration from the optically active α-haloacid ester.

The present process does not require the presence of an auxiliary base. Although trace amounts of such bases may be used, the process is conducted in the substantial absence of an inorganic auxiliary base such as, for example, sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and the like, or of an organic auxiliary base such as, for example, triethylamine, trimethylamine, pyridine, 4-N,N-diethylaminopyridine, diazobicyclododecane, diazobicyclononane and the like.

Furthermore, the absence of strong base and a low temperature allows for incorporation of other latent functionalities into the periphery of the polyazamacrocyclic. For example, both ester and phthalamido functionalities are tolerant of the mild conditions of the present process. A procedure in the art [M. Studer et al., *Helv.Chim.Acta*, 69, 2081-86 (1986)] which employs lithium hydroxide in polar protic solvents such as aqueous ethanol or methanol may be expected to hydrolyze these groups.

The present process has been used to make valuable synthetic precursors to bifunctional chelator molecules for radioactive pharmaceuticals. [See for example, European Patent Application 89 111 497.7 and European published application 296,522, published December 28, 1989, by W. J. Kruper et al.] The brevity of the five step synthetic approach to these compounds, of which the present mono-N-alkylation step is critical, is superior to the nine step process for other pharmaceutical products by M. K. Moi et al., *J.Amer.Chem.Soc.* 110, 6266-27 (1988).

The mono-N-alkylation process of this invention depends upon the availability of the desired electrophile. In the case of substituted α-haloacid esters, commercially available acids may be brominated and converted to an ester in a one pot, two step procedure using N-bromosuccinimide [see D. N. Harpp et al., *J.Org.Chem.* 40, 3420-27 (1975)]. This ionic bromination procedure is superior to the standard Hell-Vollard-Zelinski process and allows for exclusive alpha halogenation of alkanolic acids which contain even reactive benzyl groups. Optically active α-haloacids are readily available from the corresponding amino acids using recent advances in diazotization chemistry [see B. Koppenhoefer et al., "Organic Synthesis", Vol. 66, Ed. C. Heathcock, Pub. Wiley-Interscience, N.Y., pp. 151-57 (1988)]. Other electrophiles used in this invention may be prepared by procedures known in the art or can be purchased commercially.

The polyazamacrocyclics such as 1,4,7,11-tetraazacyclododecane and similar cryptand ligands may be



prepared by well documented methods which utilize a template effect in a multi-step procedure. For example see T. S. Adkins et al., *J. Amer. Chem. Soc.* 96, 2268-70 (1974) and a review article by T. J. Adkins et al., *Organic Syntheses* 28, 86-97 (1978). With advent of this versatile procedure, a number of these symmetrical macrocycles are now commercially available.

The invention will be further clarified by consideration of the following examples, which are intended to be purely exemplary of the use of this invention.

General Experimental

In the following examples, the equipment used was as follows:

Mass spectra were obtained on either a Finnigan TSQ mass spectrometer or a VG ZAB-MS high resolution mass spectrometer;

^1H and ^{13}C NMR spectra were obtained using a Varian VXR-300 spectrometer; and

IR were recorded on a Nicolet SSX FT/IR instrument.

In the following examples, all solvents were Fisher HPLC grade materials. All preparative chromatography of organic compounds was performed using flash chromatography techniques by W. C. Still et al., *J. Org. Chem.* 43, 2923-2925 (1978) and employed the following solvent systems:

Solvent System 1 - $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$ 2:2:1 (V:V:V);

Solvent System 2 - $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$ 12:4:1 (V:V:V); and

Solvent System 3 - $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$ 16:4:1 (V:V:V).

R_f values are reported using these solvent systems and commercially available silica plates.

1,4,7,10-Tetraazacyclododecane and 1,4,7,10, 13-pentaazacyclopentadecane were purchased from Parrish Chemical Co.

1,4,8,11-Tetraazacyclotetradecane was purchased from Aldrich Chemical Co.

The following terms used in the examples are defined as follows:

conc. means concentrated;

dec means decomposition; and

% means percent.

Preparation of electrophiles

Example A

Preparation of *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester.

To a solution of 5 mL of carbon tetrachloride and 15 mL of thionyl chloride was added 10.46 g (0.05 mole) of 4-(4-nitrophenyl)butanoic acid under a nitrogen atmosphere. The solution was brought to reflux for one hour with initial rapid liberation of hydrogen chloride and sulfur dioxide. Following the gaseous liberation, 11.0 g (0.06 mole) of N-bromo-succinimide in 25 mL of carbon tetrachloride and 3 drops of 48% aqueous hydrogen bromide catalyst was added to the warm solution whereupon bromine liberation occurred. The dark red solution was refluxed for an additional 15 minutes, cooled and poured into 100 mL of methanol with stirring. TLC (60:40 ethyl acetate:n-hexane) indicated a product characterized by R_f = 0.69. The excess solvent was removed and the dark red oil was filtered through a flash silica gel pad 1 in. X 6 in. (2.5 cm X 15.2 cm) using methylene chloride as the eluent. Evaporation of solvent gave 14.5 g of a colorless oil which was an 85:15 mixture of the title product:methyl ester of the starting material and was further characterized by:

^1H NMR (CDCl_3)

δ 8.16(d), 7.38(d), 4.20(dd), 3.79(s), 2.88(m);

^{13}C NMR (CDCl_3)

δ 169.6, 147.5, 129.3, 123.7, 53.0, 44.4, 35.5, 33.0.

Example B



Preparation of *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid isopropyl ester.

The title ester was obtained as a clear oil in 50% yield after quenching the crude acid chloride with isopropanol and chromatographic purification. The product ($R_f = 0.73$, methylene chloride) was devoid of any unbrominated ester and was further characterized by:

^1H NMR (CDCl_3)

δ 8.16(d), 7.38(d), 5.05(septet), 4.14(dd), 2.88(m), 2.39(m), 1.29(d);

^{13}C NMR (CDCl_3)

δ 168.7, 147.7, 129.3, 123.8, 69.9, 45.1, 35.6, 33.0, 21.5, 21.2.

Example C

Preparation of *trans*-p-nitrocinnamyl bromide.

In 35 mL of dry acetonitrile under nitrogen atmosphere was added 7.3 g (27.9 mmole) of triphenylphosphine. To the solution was added dropwise over 15 minutes 4.31 g of bromine (27.0 mmole) while cooling the reaction mixture to maintain the temperature between 0-10 °C. The solution was allowed to warm to room temperature (about 22-25 °C) and 5.0 g (27.9 mmole) of p-nitrocinnamyl alcohol (Pfaltz & Bauer Chemical Co.) was added as a slurry in 50 mL of acetonitrile which caused an exothermic reaction, temperature about 45 °C. The resulting dark red solution was heated for one hour at 60 °C with stirring and then poured into 500 mL of ether. Triphenylphosphine oxide precipitated from the solution after standing overnight (about 16 hours). The solution was filtered and 15 g of flash silica gel was added to the solution, followed by solvent removal. The resulting powder matrix was applied to a 3 in. X 8 in. (7.6 cm X 20.3 cm) flash column and the desired product was eluted with hexane, followed by 20% ethyl acetate in hexane to yield 5.8 g (23.9 mmole) of the desired pure *trans* product in 86% yield (MP = 75-76 °C, $R_f = 0.81$, 60:40 ethyl acetate:n-hexane) and was further characterized by:

^1H NMR (CDCl_3)

δ 8.17(d), 7.51(d), 6.70(dd), 6.56(dt), 4.16(dd);

^{13}C NMR (CDCl_3)

δ 147.3, 142.1, 132.0, 129.8, 127.2, 123.9, 31.8.

Example D

Preparation of *d,l*-2-bromo-4-(N-phthalamido)butanoic acid isopropyl ester.

Into a flask equipped with a trap and water condensor was placed 14.8 g (100 mmole) of phthalic anhydride, 10.3 g (100 mmole) of γ -aminobutyric acid (Aldrich Chemical Co.), 1.3 mL of triethylamine and 150 mL of toluene. The mixture was brought to reflux and 1.75 mL of water was removed azeotropically over 1.5 hours. The solution was allowed to cool and stand overnight (about 16 hours). The resulting white crystals that formed were filtered, washed with hexane and dried. The crude crystals were then washed with 250 mL of 5% aqueous hydrogen chloride and 100 mL of cold water. After drying, 19.0 g (81.5 mmole) of 4-(N-phthalamido)butanoic acid was obtained in 82% yield (MP = 114.5-115.5 °C, recrystallized from 30% methanol in water) and further characterized by:

^1H NMR (CDCl_3)

δ 7.84(dd), 7.72(dd), 6.05(bs), 3.77(t), 2.42(t), 2.02(p);

^{13}C NMR (CDCl_3)

δ 177.9, 169.4, 134.0, 123.3, 37.1, 31.2, 23.6.

The above prepared 4-(N-phthalamido)butanoic acid was reacted by the procedure of Example A and B to obtain the title ester as a white solid, yield 68%, (MP = 72-74.5 °C, $R_f = 0.38$, chloroform) after flash silica gel chromatography using chloroform as an eluant, and further characterized by:

^1H NMR (CDCl_3)

δ 7.85(dd), 7.73(dd), 5.04(septet), 4.23(dd), 3.85(dt), 2.51(m), 2.36(m), 1.29(d), 1.26(d).



Process of the invention.

Example 1

Preparation of 1,4,7,10-tetraaza-1-[(4-nitrophenyl)methyl]cyclododecane.

The free base, 3.5 g (20.3 mmol), of 1,4,7,10-tetraazacyclododecane and 1.7 g (7.87 mmol) of p-nitrobenzyl bromide in 50 mL of chloroform were stirred under nitrogen for 24 hours at 25 °C. The chloroform slurry of hydrobromide salt was then applied to a 1 in. X 17 in. (2.5 cm X 43.2 cm) column of flash silica gel (Solvent System 3). The product, 2.13 g (6.93 mmol) was obtained as a pale yellow solid (MP = 128-29 °C, R_f = 0.58 Solvent System 3) in 88% yield and further characterized by:

¹H NMR (CDCl₃)

δ 8.18(d), 7.49(d), 3.69(s), 2.82(t), 2.70(t), 2.59(m);

¹³C NMR (CDCl₃)

δ 147.2, 128.4, 123.8, 58.8, 51.7, 47.1, 46.3, 45.1.

Example 2

Preparation of 1,4,7,10-tetraaza-1-[2-(4-nitrophenyl)ethyl]cyclododecane.

To a stirred solution of 3.5 g (20.3 mmol) of 1,4,7,10-tetraazacyclododecane in 50 mL of pentene stabilized chloroform was added dropwise over five minutes with vigorous stirring under a nitrogen atmosphere 4.0 g (17.4 mmol) of 1-bromo-2-(4-nitrophenyl)ethane (Aldrich Chemical Co.). The stirring was continued overnight at about 25 °C whereupon crystals of amine hydrobromide precipitated from solution. The contents of the flask were applied to a flash silica gel column 1 in. X 18 in. (2.5 cm X 45.7 cm) which had been pre-eluted with 5% methanol in chloroform and 200 mL of this solution was applied as an eluent, followed by elution with Solvent System 3. The p-nitrostyrene (1.45 g, 9.7 mmol, R_f = 0.98, Solvent System 2) was cleanly separated from 2.27 g (7.06 mmol) of the desired product as an orange yellow oil (yield 40.6%) which solidified upon standing (R_f = 0.73, Solvent System 2). A sample was recrystallized [MP = 146.5-148.5 °C (dec)] from chloroform/cyclohexane and was further characterized by:

¹H NMR (CDCl₃)

δ 8.14(d), 7.40(d), 2.91(t), 2.77(t), 2.72(t), 2.50(t), 2.60(s);

¹³C NMR (CDCl₃)

δ 148.5, 129.6, 123.4, 55.5, 51.4, 46.9, 45.9, 45.1, 33.7.

Example 3

Preparation of 1,4,7,10-tetraaza-1-[1-carbomethoxy-3-(4-nitrophenyl)propyl]cyclododecane.

To a stirred solution of 1.72 g (10.0 mmol) of 1,4,7,10-tetraazacyclododecane in 17 mL of pentene stabilized chloroform was added 2.07 g (5.82 mmol) of crude *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester (prepared by the procedure of Example A) over a five minute period under a nitrogen atmosphere. The reaction mixture was stirred for 48 hours at about 25 °C and TLC (Solvent System 2) indicated the conversion to the desired monoalkylation product (R_f = 0.73, ninhydrin, iodine, and UV active). The yellow chloroform solution was applied to a 1 in. X 16 in. (2.5 cm X 40.6 cm) flash silica gel column which had been preeluted with 5% methanolic chloroform, followed by elution with 250 mL of the preelution solvent system, and then elution with Solvent System 2. The fractions containing the desired product were combined and evaporated affording 2.15 g (5.46 mmol) of the desired product (MP = 156-159 °C, recrystallized from chloroform, ether) in 94% yield and further characterized by:

¹H NMR (CDCl₃)

δ 8.14(d), 7.39(d), 3.71(s), 3.39(dd), 2.5-3.0(m), 2.08(m), 2.01(m);

¹³C NMR (CDCl₃)



8172.7, 149.3, 146.4, 129.2, 123.6, 62.3, 51.2, 48.9, 47.2, 45.8, 45.4, 32.8, 30.9.

Example 4

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Preparation of 1,4,7,10,13-pentaaza-1-[1-carboisopropoxy-3-(4-nitrophenyl)propyl]cyclopentadecane.

The purified desired product was obtained as a light yellow oil in 77% yield after chromatography on
10 silica gel (R_f = 0.82, Solvent System 2) and further characterized by:

^1H NMR (CDCl_3)

δ 8.14(d), 7.49(d), 5.09(septet), 4.86(s), 3.38(dd,s), 2.5-3.0(m), 2.30(m), 2.11(m), 1.29(d);

^{13}C NMR (CDCl_3)

δ 171.9, 149.1, 146.5, 129.5, 123.6, 68.7, 61.9, 49.5, 46.8, 46.7, 45.5, 45.3, 32.9, 32.1, 22.1, 22.0;

15 IR (CDCl_3) cm^{-1}

3450, 2860, 1735, 1350, 915.

Example 5

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Yields of mono-N-alkylation of p-nitrobenzyl bromide (Aldrich Chemical Co.) with 1,4,7,10-tetraazacyclododecane.

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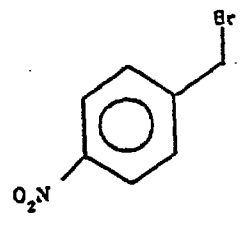
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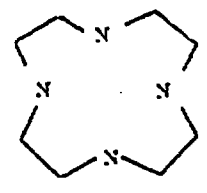
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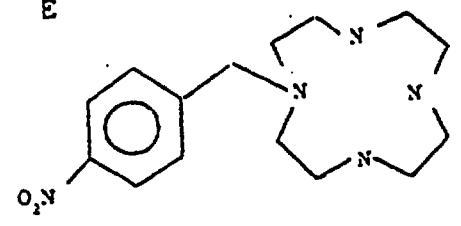
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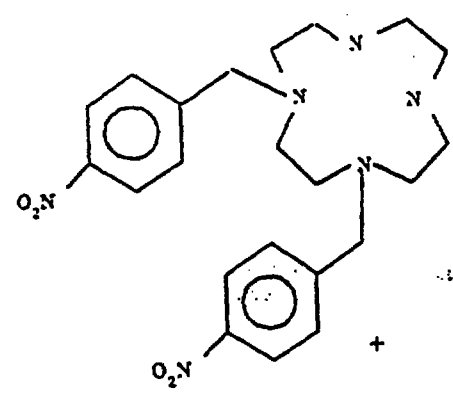
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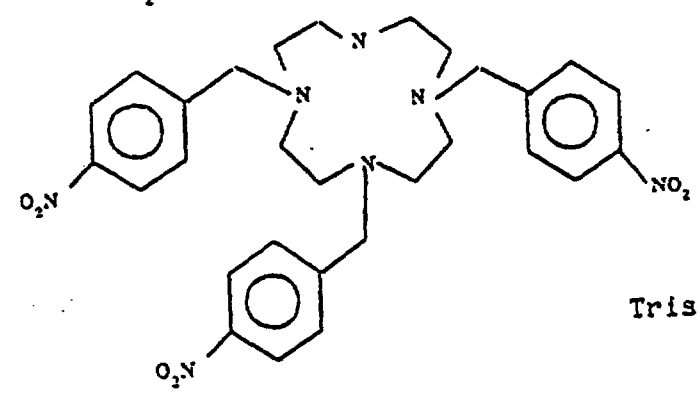
M



Mono



Bis



Tris



TABLE I

Ex. No.	M:E	[E] MOLARITY	SOLVENT	% ISOLATED YIELD **			MONO:BIS
				MONO	BIS	TRIS	
5A	1:1.0	1	CHCl ₃	49	11	5	4.5:1
5B	1:1.5	1	CHCl ₃	66	10	3	6.6:1
5C	1:1.5	4 x 10 ⁻²	CHCl ₃	73	9	2	7.4:1
5D	1:1.5	1	CH ₃ OH	39	16	3	2.4:1
5E	1:1.5	1	CH ₃ (CH ₂) ₃ OH	43	15	3	3.0:1
A*	1:1.5	1	CH ₃ OH***	34	19	7	1.8:1

*A is not a process of the invention.

**Isolated yield of product after flash chromatography; process at 25° C.

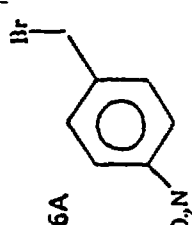
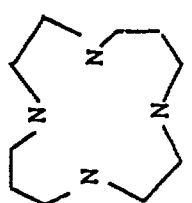
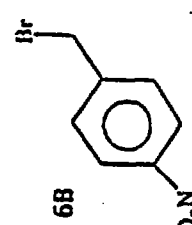
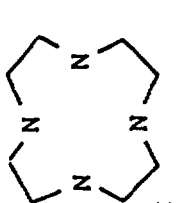
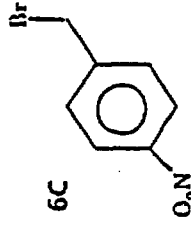
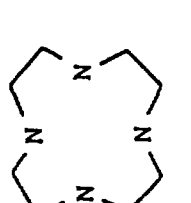
***1.0 equivalents of KCO₃ added relative to bromide.

Example 6

Preparation of various mono-N-alkylpolyazamacrocycles using the process of the invention.

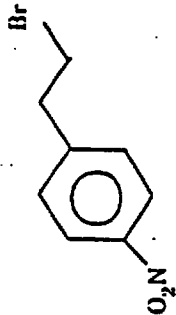
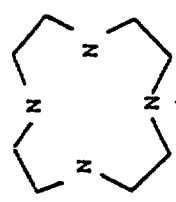
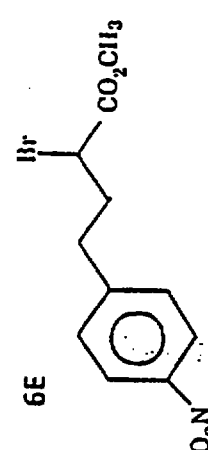
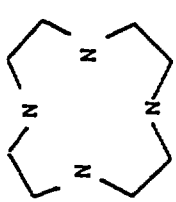
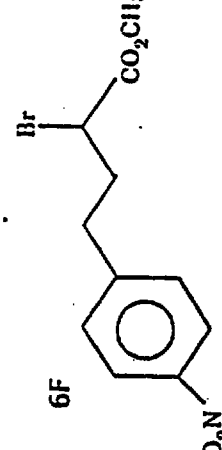
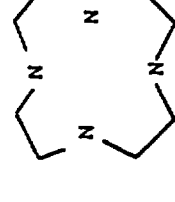
In Table II following, various electrophiles were reacted with polyazamacrocycles which gave yields greater than 40% selectivity for the desired mono-N-alkylpolyazamacrocycles, expressed as percent (%) isolated yield. The process was run using the equivalents and solvents given in Table II and by the procedure of Examples 1-4. Table III following indicates the structure of the desired mono-N-alkylpolyazamacrocycles formed by the reaction in Table II.



EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6A		 (2.0)	CHCl ₃	100	
6B		 (1.0)	CHCl ₃	50	4.5:1
6C		 (2.0)	CHCl ₃	87	10:1

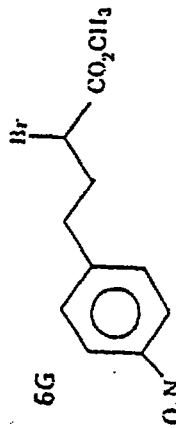
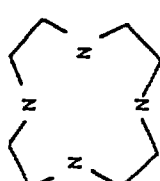
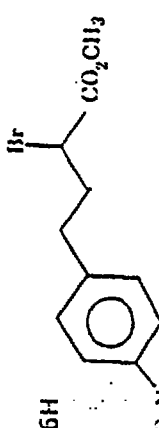
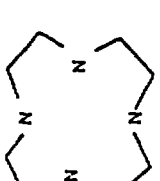
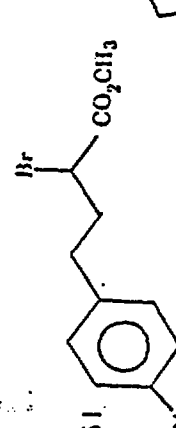
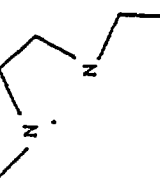
*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)



EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6D			CHCl ₃	43**	>20:1
6E			CHCl ₃	81	
6F			CHCl ₃	94	

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)
 **p-nitrostyrene isolated in 54% yield



EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6G			CCl ₄	70	
6H			THF	86	
6I			CHCl ₃	61	

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)



EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD	MONO:BIS
6J			CHCl3	64	
6K			CHCl3	58	

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)

EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6L			CHCl ₃	69	4.1:1
6M			CHCl ₃	83	34:1

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)



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TABLE III

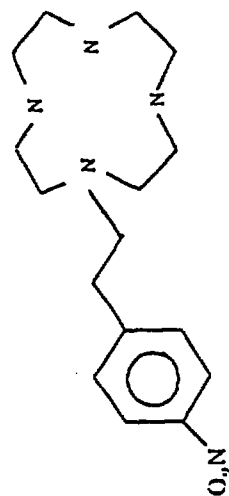
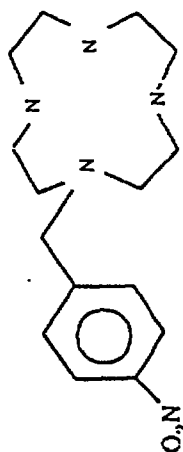
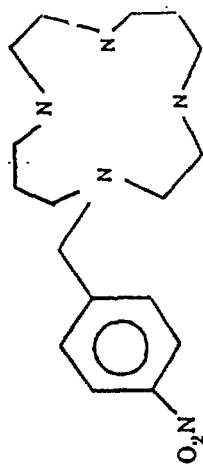
POLYAZAMACROCYCLE

EX.

6A

6B AND 6C

6D



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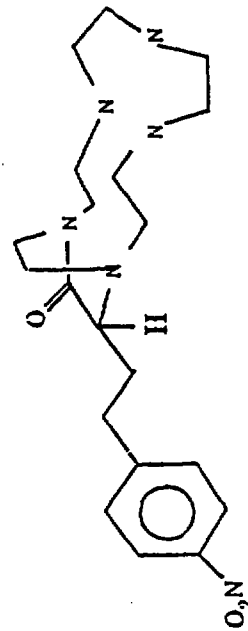
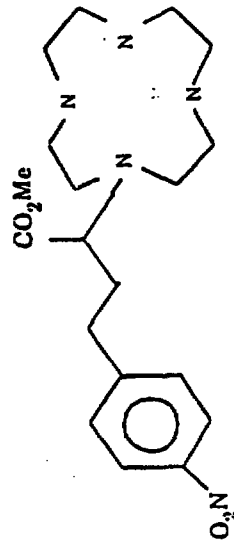
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TABLE III CONT'D

POLYAZAMACROCYCLE

EX.

6E, 6F, 6G AND 6H

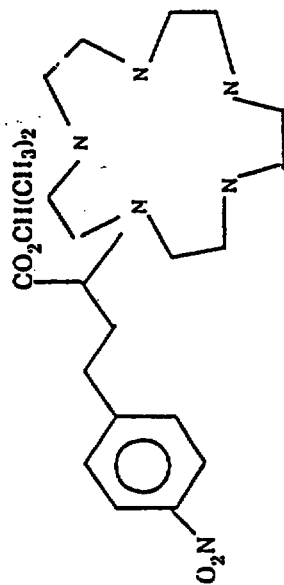


6I



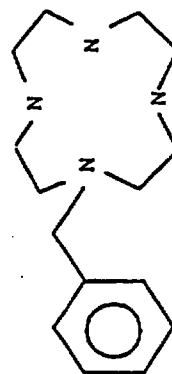
TABLE III CONT'D

POLYAZAMACROCYCLE



EX.

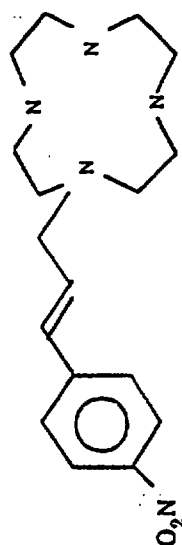
6J



6K

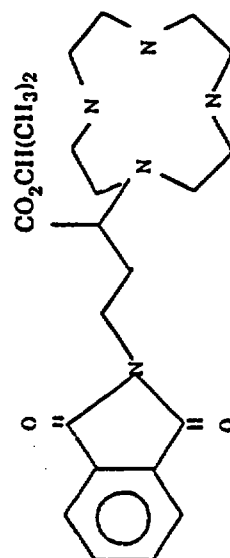
TABLE III CONT'D

POLYAZAMACROCYCLE



EX.

6L



6M





Other embodiments of the invention will be apparent to those skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims:

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Claims

1. A process for preparing a mono-N-alkylated polyazamacrocyclic which comprises reacting an
10 electrophile with between one to five equivalents of a polyazamacrocyclic in a solvent which will not promote a proton transfer.
2. The process of Claim 1 wherein the solvent is a relatively non-polar, relatively aprotic solvent.
3. The process of Claim 2 wherein the solvent is chloroform, carbon tetrachloride, methylene chloride, tetrahydrofuran, 1,4-dioxane or acetonitrile.
- 15 4. The process of Claim 2 or 3 wherein the solvent is chloroform.
5. The process of Claim 2 wherein the solvent is a hydrocarbon solvent.
6. The process of Claim 5 wherein the solvent is benzene, cyclohexane, n-hexane or toluene.
7. The process of Claim 1 wherein the solvent is a relatively non-polar, protic alcohol.
8. The process of Claim 7 wherein the solvent is n-butanol, t-butanol, isopropanol or n-hexanol.
- 20 9. The process of Claim 1 wherein the polyazamacrocyclic is symmetrical.
10. The process of Claim 9 wherein the polyazamacrocyclic has a methylene moiety containing from 2-4 carbon atoms between hetero atoms.
11. The process of Claim 10 wherein the polyazamacrocyclic is 1,4-diazacyclohexane, 1,3,7-triazacyclononane, 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane, 1,4,7,10, 13-pentaazacyclopentadecane, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,7,13-triaza-4,10,16-trioxacyclooctadecane or 1,7-diaza-4,11-dithiacyclododecane.
- 25 12. The process of Claim 1 wherein the electrophile is RX wherein R is a moiety which is any alkyl or alkylaryl functionality which will yield the desired mono-N-alkylated product, and X is any leaving group.
13. The process of Claim 12 wherein X is chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo or brosylate.
- 30 14. The process of Claim 13 wherein the electrophile is *d,l*-2-bromo-4-N-phthalamidobutanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)-butanoic acid methyl ester, 4-nitrocinnamyl bromide, 4-nitrophenethyl bromide, 4-nitrobenzyl bromide or benzyl bromide.
- 35 15. The process of Claim 12 wherein R is an optically active α -haloacid ester.
16. The process of Claim 15 wherein the resulting mono-N-alkylated polyazamacrocyclic product has the opposite optical configuration from the optically active α -haloacid ester.
17. The process of Claim 1 wherein the temperature is from -78 to 100° C.
18. The process of Claim 17 wherein the temperature is from -25 to 40° C.
- 40 19. The process of Claim 18 wherein the temperature is from 0 to 25° C.
20. The process of Claim 1 wherein between one to three equivalents of polyazamacrocyclic are used relative to the electrophile.
21. The process of Claim 1 wherein between one and two equivalents of polyazamacrocyclic are used relative to the electrophile.
- 45 22. The process of Claim 1 wherein about one equivalent of polyazamacrocyclic is used relative to the electrophile.
23. The process of Claim 1 wherein the mono-N-alkylated polyazamacrocyclic is obtained in a selectivity of at least 40 percent.
24. The process of Claim 1 wherein the mono-N-alkylated polyazamacrocyclic is obtained in a
50 selectivity of from 50 to 98 percent.

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PROCESS FOR PREPARING MONO-N-ALKYLATED POLYAZAMACROCYCLES

The present invention concerns a process for preparing mono-N-alkylated polyazamacrocycles.

T. A. Kaden, *Top. Curr. Chem.* 121, 157-75 (1984) has shown that simple alkylative techniques using electrophiles and polyazamacrocycles for the production of mono-N-functionalized polyazamacrocycles result in the formation of a mixture of mono, bis, and tris alkylated products which are difficult to separate and purify. To overcome this problem, large excesses of macrocycle, for example 5-10 equivalents relative to electrophile, have been employed by M. Studer et al., *Helv. Chim. Acta.* 69, 2081-86 (1986) and by E. Kimura et al., *J. Chem. Soc. Chem. Commun.* 1158-59 (1986). Additionally, auxiliary bases have used together with large excesses of macrocycle to obtain the mono-N-alkylation product by M. Studer et al., *supra*. Purification of the desired mono-N-alkylated product from the large excess of starting material and inorganic salt is a major problem associated with these methods. Additionally, the cost associated with employing a large excess of expensive reagent is prohibitive.

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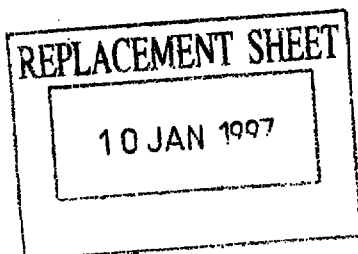
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Other mono-N-alkylation attempts by F. Wagner et al., *Inorg. Chem.* 15, 408 (1976) involve selective deprotonation of a transition metal complex of a polyazamacrocycle with strong base followed by alkylation with methyl iodide. Further synthetic manipulation of this compound necessitates metal removal and purification which can be tedious.

Additional synthetic routes which afford mono-N-functional polyazamacrocycles involve lengthy, protection, functionalization, deprotection schemes which are divergent and not always general. For example, see P. S. Pallavicini et al., *J. Amer. Chem. Soc.* 109, 5139-44 (1987) and published European patent application 0 232 751 (1984).

In light of these limitations on mono-N-alkylation techniques existing in the art, it would be desirable to employ a direct alkylation approach which would not be reliant upon the use of excess macrocycle and an auxiliary base and yet would be selective for the desired mono-N-alkylated product.

Surprisingly, the present invention provides such a process for preparing selectively the mono-N-alkylated products without the use of large excesses of macrocycle and auxiliary base. The present invention is directed to a novel process for preparing a mono-N-alkylated polyazamacrocycle which comprises reacting an electrophile with between one to five equivalents of a polyazamacrocycle in a solvent which will not promote a proton transfer. This process results in a greater selectivity for the desired mono-N-alkylated product



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compared to the bis, tris, tetra or higher N-alkylated products.

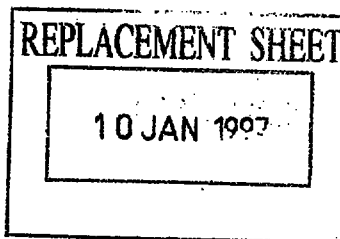
The present invention concerns the reaction of an appropriate electrophile (E) with a free base polyazamacrocycle (M) in a relatively non-polar, preferably relatively aprotic solvent. The ratio of E to M is about one E to about five M equivalents, preferably from about one E to about three M equivalents, more preferably from about one E to about two M equivalents, and most preferably from about one E to about one M equivalent.

The present process is very general and can produce selective mono-N-alkylation products with various polyazamacrocycles and electrophilies. A slight excess of polyazamacrocycle is preferred to insure complete conversion of the electrophile; however, only small differences in isolated yield occur when larger excesses of the polyazamacrocycle are used.

The polyazamacrocycles used in the present invention must contain at least two nitrogen atoms. However, the polyazamacrocycles can also contain other hetero moieties such as oxygen atoms (polyoxazamacrocycles) or sulfur atoms (polythioazamacrocycles). Also included in the term polyazamacrocycles are any symmetrical rings such as polyazamacrocycle, azaoxamacrocycle or bicyclopolyazamacrocycle (i.e. bridged moieties or fused rings, but the mono-N-alkylation reaction occurs on the nitrogen atom of a saturated ring) which bears secondary amines capable of mono-N-alkylation. Preferably the secondary amines are all chemically equivalent. The macrocycle preferably has a plane of symmetry and the

total number of hetero atoms (O, S, N) should preferably total an even integer. The final macrocycle also contains a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms. The term "polyazamacrocycles" means all of these heterocyclic possibilities and includes, for example, 1,4-diazacyclohexane, 1,3,7-triazacyclononane, 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane, 1,4,7,10,13-pentaazacyclopentadecane, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,7,13-triaza-4,10,16-trioxacyclooctadecane, 1,7-diaza-4,11-dithiacyclododecane and the like.

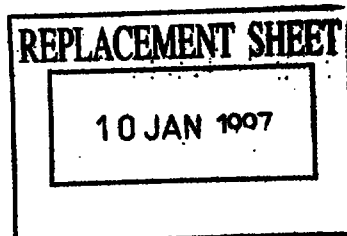
The electrophile (RX) used in the present process is one capable of accepting a pair of electrons from one of the nitrogen atoms in the polyazamacrocycle. A covalent bond results from the reaction between the electrophile and polyazamacrocycle and selective mono-N-alkylation results. In the term RX, the R term is a moiety which will yield the desired mono-N-alkylated product, particularly any alkyl, alkylaryl, or alkylheteroaryl functionality. Some examples of the R term are C_1-C_4 alkyl, cyano, pyridinyl, CO_2R^1 or $CON(R^1)_2$ where R^1 is H, C_1-C_4 alkyl, C_1-C_4 alkaryl where the aryl portion can be a 5 or 6 member ring having carbon, sulfur, nitrogen or oxygen atoms. The X term is any leaving group. Such leaving groups are well known in the art such as, for example, chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo, brosylate and other similar known groups. Some suitable electrophiles are, for example, *d,l*-2-bromo-4-N-phthalamidobutanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester, 4-



nitrocinnamyl bromide, 4-nitrophenethyl bromide, 4-nitrobenzyl bromide, benzyl bromide and other similar known groups.

Concentration of the reagents is not critical for the present process but for economic reasons and reasonable reaction times, the present process is preferably conducted under non-dilution conditions such as $1 \times 10^{-3}M$ to $2M$ in each reagent. Mono-N-alkylations conducted under these concentrations afford the desired product in good to excellent yield with unexpectedly high selectivities. The mono-N-alkylated polyazamacrocyclic is obtained in a selectivity of at least 40 percent, preferably from 50 to 98 percent, compared to the bis, tris and/or tetra N-alkylated products.

The solvent used for the present process is one which will not promote a proton transfer. A suitable solvent is a relatively non-polar, relatively aprotic solvent such as, for example, chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), methylene chloride (CH_2Cl_2), tetrahydrofuran, 1,4-dioxane, and acetonitrile, or a relatively non-polar, relatively aprotic hydrocarbon solvent such as, for example, benzene, cyclohexane, n-hexane, and toluene, or a relatively non-polar, protic alcohol such as, for example, n-butanol, t-butanol, isopropanol, n-hexanol and the like. The preferred solvents are the relatively non-polar, relatively aprotic solvents, especially chloroform. The term "relatively aprotic" means that the solvent does not donate a proton to the reaction under the process conditions. The term "relatively non-polar" means that



the solvent has a relatively low dipole moment, as seen from the above listed examples of suitable solvents.

Temperature employed is in the range of from -78 to 100°C, preferably from -25 to 40°C, more preferably from 0 to 25°C. The time of the reaction, at a temperature of from 0 to 25°C, is from 10 to 24 hours. The time of the reaction will vary inversely with the temperature; however, the lower temperatures are preferred to aid in selectivity of the desired mono-N-alkylated product.

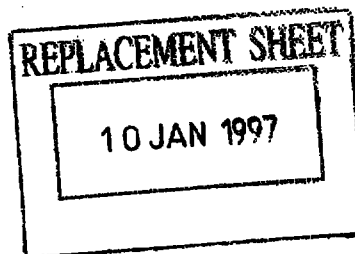
The absence of base from the displacement conditions of the reaction helps to prevent epimerization of chiral electrophilic reagents. Hence, optically active mono-N-alkylated adducts are potentially available by this present process. The product formed will possess the inverted optical form from the starting electrophile reagent. For example, the resulting mono-N-alkylated polyazamacrocyclic product has the opposite optical configuration from the optically active α -haloacid ester.

The present process does not require the presence of an auxiliary base. Although trace amounts of such bases may be used, the process is conducted in the substantial absence of an inorganic auxiliary base such as, for example, sodium hydroxide, lithium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and the like, or of an organic auxiliary base such as, for example, triethylamine, trimethylamine, pyridine, 4-N,N-diethylaminopyridine, diazobicyclododecane, diazobicyclononane and the like.

Futhermore, the absence of strong base and a low temperature allows for incorporation of other latent functionalities into the periphery of the polyazamacrocyclic. For example, both ester and phthalamido functionalities are tolerant of the mild conditions of the present process. A procedure in the art [M. Studer et al., *Helv. Chim. Acta.* 69, 2081-86 (1986)] which employs lithium hydroxide in polar protic solvents such as aqueous ethanol or methanol may be expected to hydrolyze these groups.

The present process has been used to make valuable synthetic precursors to bifunctional chelator molecules for radioactive pharmaceuticals. [See for example, European Patent Application 89 111 497.7 and European published application 296,522, published December 28, 1989, by W. J. Kruper et al.] The brevity of the five step synthetic approach to these compounds, of which the present mono-N-alkylation step is critical, is superior to the nine step process for other pharmaceutical products by M. K. Moi et al., *J. Amer. Chem. Soc.* 110, 6266-27 (1988).

The mono-N-alkylation process of this invention depends upon the availability of the desired electrophile. In the case of substituted α -haloacid esters, commercially available acids may be brominated and converted to an ester in a one pot, two step procedure using N-bromosuccinimide [see D. N. Harpp et al., *J. Org. Chem.* 40, 3420-27 (1975)]. This ionic bromination procedure is superior to the standard Hell-Vollard-Zelinski process and allows for exclusive alpha halogenation of alkanolic acids which contain even reactive benzyl groups. Optically active α -haloacids



are readily available from the corresponding amino acids using recent advances in diazotization chemistry [see B. Koppenhoefer et al., "Organic Synthesis", Vol. 66, Ed. C. Heathcock, Pub. Wiley-Interscience, N.Y., pp. 151-57 (1988)]. Other electrophiles used in this invention may be prepared by procedures known in the art or can be purchased commercially.

The polyazamacrocycles such as 1,4,7,11-tetraazacyclododecane and similar cryptand ligands may be prepared by well documented methods which utilize a template effect in a multi-step procedure. For example see T. S. Adkins et al., *J. Amer. Chem. Soc.* 96, 2268-70 (1974) and a review article by T. J. Adkins et al., *Organic Syntheses* 28, 86-97 (1978). With advent of this versatile procedure, a number of these symmetrical macrocycles are now commercially available.

The invention will be further clarified by consideration of the following examples, which are intended to be purely exemplary of the use of this invention.

General Experimental

In the following examples, the equipment used was as follows:

Mass spectra were obtained on either a Finnigan TSQ mass spectrometer or a VG ZAB-MS high resolution mass spectrometer;

^1H and ^{13}C NMR spectra were obtained using a Varian VXR-300 spectrometer; and

10 JAN 1997

IR were recorded on a Nicolet SSX FT/IR instrument.

In the following examples, all solvents were Fisher HPLC grade materials. All preparative chromatography of organic compounds was performed using flash chromatography techniques by W. C. Still et al., *J. Org. Chem.* 43, 2923-2925 (1978) and employed the following solvent systems:

Solvent System 1 - $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$
2:2:1 (V:V:V);

Solvent System 2 - $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$
12:4:1 (V:V:V); and

Solvent System 3 - $\text{CHCl}_3:\text{CH}_3\text{OH}:\text{conc. NH}_4\text{OH}$
16:4:1 (V:V:V).

R_f values are reported using these solvent systems and commercially available silica plates.

1,4,7,10-Tetraazacyclododecane and 1,4,7,10,13-pentaazacyclopentadecane were purchased from Parrish Chemical Co.

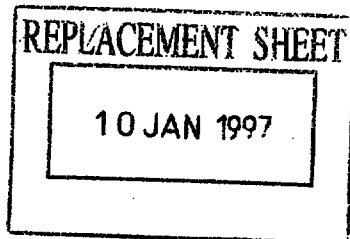
1,4,8,11-Tetraazacyclotetradecane was purchased from Aldrich Chemical Co.

The following terms used in the examples are defined as follows:

conc. means concentrated;

dec means decomposition; and

% means percent.



Preparation of electrophiles

Example A

Preparation of *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester.

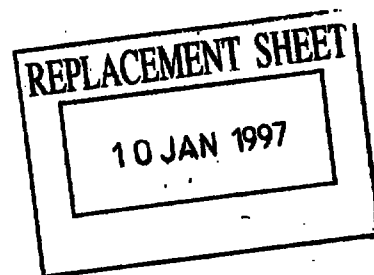
To a solution of 5 mL of carbon tetrachloride and 15 mL of thionyl chloride was added 10.46 g (0.05 mole) of 4-(4-nitrophenyl)butanoic acid under a nitrogen atmosphere. The solution was brought to reflux for one hour with initial rapid liberation of hydrogen chloride and sulfur dioxide. Following the gaseous liberation, 11.0 g (0.06 mole) of N-bromo-succinimide in 25 mL of carbon tetrachloride and 3 drops of 48% aqueous hydrogen bromide catalyst was added to the warm solution whereupon bromine liberation occurred. The dark red solution was refluxed for an additional 15 minutes, cooled and poured into 100 mL of methanol with stirring. TLC (60:40 ethyl acetate:n-hexane) indicated a product characterized by $R_f = 0.69$. The excess solvent was removed and the dark red oil was filtered through a flash silica gel pad 1 in. X 6 in. (2.5 cm X 15.2 cm) using methylene chloride as the eluent. Evaporation of solvent gave 14.5 g of a colorless oil which was an 85:15 mixture of the title product:methyl ester of the starting material and was further characterized by:

^1H NMR (CDCl_3)

8.16(d), 7.38(d), 4.20(dd), 3.79(s), 2.88(m);

^{13}C NMR (CDCl_3)

8169.6, 147.5, 129.3, 123.7, 53.0, 44.4, 35.5, 33.0.



Example B

Preparation of *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid isopropyl ester.

The title ester was obtained as a clear oil in 50% yield after quenching the crude acid chloride with isopropanol and chromatographic purification. The product ($R_f = 0.73$, methylene chloride) was devoid of any unbrominated ester and was further characterized by:

^1H NMR (CDCl_3)

δ 8.16(d), 7.38(d), 5.05(septet), 4.14(dd), 2.88(m), 2.39(m), 1.29(d);

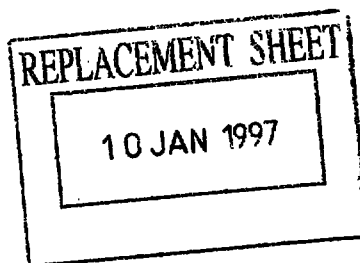
^{13}C NMR (CDCl_3)

δ 168.7, 147.7, 129.3, 123.8, 69.9, 45.1, 35.6, 33.0, 21.5, 21.2.

Example C

Preparation of *trans*-*p*-nitrocinnamyl bromide.

In 35 mL of dry acetonitrile under nitrogen atmosphere was added 7.3 g (27.9 mmole) of triphenylphosphine. To the solution was added dropwise over 15 minutes 4.31 g of bromine (27.0 mmole) while cooling the reaction mixture to maintain the temperature between 0-10°C. The solution was allowed to warm to room temperature (about 22-25°C) and 5.0 g (27.9 mmole) of *p*-nitrocinnamyl alcohol (Pfaltz & Bauer Chemical Co.) was added as a slurry in 50 mL of acetonitrile



which caused an exothermic reaction, temperature about 45°C. The resulting dark red solution was heated for one hour at 60°C with stirring and then poured into 500 mL of ether. Triphenylphosphine oxide precipitated from the solution after standing overnight (about 16 hours). The solution was filtered and 15 g of flash silica gel was added to the solution, followed by solvent removal. The resulting powder matrix was applied to a 3 in. X 8 in. (7.6 cm X 20.3 cm) flash column and the desired product was eluted with hexane, followed by 20% ethyl acetate in hexane to yield 5.8 g (23.9 mmole) of the desired pure *trans* product in 86% yield (MP = 75-76°C, R_f = 0.81, 60:40 ethyl acetate:n-hexane) and was further characterized by:

^1H NMR (CDCl_3)

8.17(d), 7.51(d), 6.70(dd), 6.56(dt), 4.16(dd);

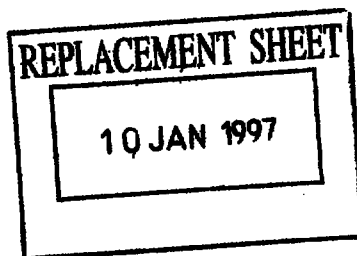
^{13}C NMR (CDCl_3)

8147.3, 142.1, 132.0, 129.8, 127.2, 123.9, 31.8.

Example D

Preparation of *d,l*-2-bromo-4-(*N*-phthalamido)butanoic acid isopropyl ester.

Into a flask equipped with a trap and water condensor was placed 14.8 g (100 mmole) of phthalic anhydride, 10.3 g (100 mmole) of γ -aminobutyric acid (Aldrich Chemical Co.), 1.3 mL of triethylamine and 150 mL of toluene. The mixture was brought to reflux and 1.75 mL of water was removed azeotropically over 1.5 hours. The solution was allowed to cool and stand



overnight (about 16 hours). The resulting white crystals that formed were filtered, washed with hexane and dried. The crude crystals were then washed with 250 mL of 5% aqueous hydrogen chloride and 100 mL of cold water. After drying, 19.0 g (81.5 mmole) of 4-(N-phthalamido)butanoic acid was obtained in 82% yield (MP = 114.5-115.5°C, recrystallized from 30% methanol in water) and further characterized by:

^1H NMR (CDCl_3)

δ 7.84(dd), 7.72(dd), 6.05(bs), 3.77(t), 2.42(t), 2.02(p);

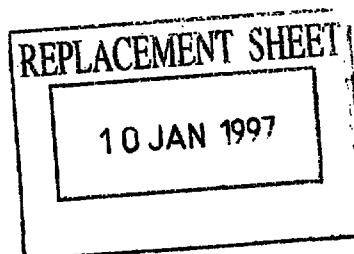
^{13}C NMR (CDCl_3)

δ 177.9, 169.4, 134.0, 123.3, 37.1, 31.2, 23.6.

The above prepared 4-(N-phthalamido)butanoic acid was reacted by the procedure of Example A and B to obtain the title ester as a white solid, yield 68%, (MP = 72-74.5°C, R_f = 0.38, chloroform) after flash silica gel chromatography using chloroform as an eluant, and further characterized by:

^1H NMR (CDCl_3)

δ 7.85(dd), 7.73(dd), 5.04(septet), 4.23(dd), 3.85(dt), 2.51(m), 2.36(m), 1.29(d), 1.26(d).



Process of the invention.

Example 1

Preparation of 1,4,7,10-tetraaza-1-[(4-nitrophenyl)methyl]cyclododecane.

The free base, 3.5 g (20.3 mmols), of 1,4,7,10-tetraazacyclododecane and 1.7 g (7.87 mmols) of p-nitrobenzyl bromide in 50mL of chloroform were stirred under nitrogen for 24 hours at 25°C. The chloroform slurry of hydrobromide salt was then applied to a 1 in. X 17 in. (2.5 cm X 43.2 cm) column of flash silica gel (Solvent System 3). The product, 2.13 g (6.93 mmols) was obtained as a pale yellow solid (MP = 128-29°C, R_f = 0.58 Solvent System 3) in 88% yield and further characterized by:

^1H NMR (CDCl_3)

8.18(d), 7.49(d), 3.69(s), 2.82(t), 2.70(t), 2.59(m);

^{13}C NMR (CDCl_3)

8147.2, 128.4, 123.8, 58.8, 51.7, 47.1, 46.3, 45.1.

Example 2

Preparation of 1,4,7,10-tetraaza-1-[2-(4-nitrophenyl)ethyl]cyclododecane.

To a stirred solution of 3.5 g (20.3 mmole) of 1,4,7,10-tetraazacyclododecane in 50 mL of pentene stabilized chloroform was added dropwise over five minutes with vigorous stirring under a nitrogen atmosphere 4.0 g (17.4 mmols) of 1-bromo-2-(4-

10 JAN 1997

nitrophenyl)ethane (Aldrich Chemical Co.). The stirring was continued overnight at about 25°C whereupon crystals of amine hydrobromide precipitated from solution. The contents of the flask were applied to a flash silica gel column 1 in. X 18 in. (2.5 cm X 45.7 cm) which had been pre-eluted with 5% methanol in chloroform and 200 mL of this solution was applied as an eluent, followed by elution with Solvent System 3. The p-nitrostyrene (1.45 g, 9.7 mmole, R_f = 0.98, Solvent System 2) was cleanly separated from 2.27 g (7.06 mmole) of the desired product as an orange yellow oil (yield 40.6%) which solidified upon standing (R_f = 0.73, Solvent System 2). A sample was recrystallized [MP = 146.5-148.5°C (dec)] from chloroform/cyclohexane and was further characterized by:

^1H NMR (CDCl_3)

8.14(d), 7.40(d), 2.91(t), 2.77(t), 2.72(t), 2.50(t), 2.60(s);

^{13}C NMR (CDCl_3)

8148.5, 129.6, 123.4, 55.5, 51.4, 46.9, 45.9, 45.1, 33.7.

Example 3

Preparation of 1,4,7,10-tetraaza-1-[1-carbomethoxy-3-(4-nitrophenyl)propyl]cyclododecane.

To a stirred solution of 1.72 g (10.0 mmole) of 1,4,7,10-tetraazacyclododecane in 17 mL of pentene stabilized chloroform was added 2.07 g (5.82 mmole) of crude *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl

10 JAN 1997

ester (prepared by the procedure of Example A) over a five minute period under a nitrogen atmosphere. The reaction mixture was stirred for 48 hours at about 25°C and TLC (Solvent System 2) indicated the conversion to the desired monoalkylation product ($R_f = 0.73$, ninhydrin, iodine, and UV active). The yellow chloroform solution was applied to a 1 in. X 16 in. (2.5 cm X 40.6 cm) flash silica gel column which had been preeluted with 5% methanolic chloroform, followed by elution with 250 mL of the preelution solvent system, and then elution with Solvent System 2. The fractions containing the desired product were combined and evaporated affording 2.15 g (5.46 mmole) of the desired product (MP = 156-159°C, recrystallized from chloroform, ether) in 94% yield and further characterized by:

^1H NMR (CDCl_3)

8.14(d), 7.39(d), 3.71(s), 3.39(dd), 2.5-3.0(m),
2.08(m), 2.01(m);

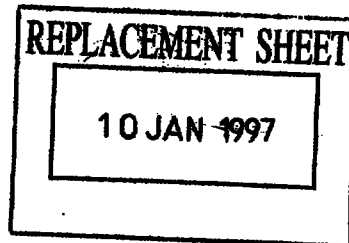
^{13}C NMR (CDCl_3)

8172.7, 149.3, 146.4, 129.2, 123.6, 62.3, 51.2, 48.9,
47.2, 45.8, 45.4, 32.8, 30.9.

Example 4

Preparation of 1,4,7,10,13-pentaaza-1-[1-carboisopropoxy-3-(4-nitrophenyl)propyl]-cyclopentadecane.

The purified desired product was obtained as a light yellow oil in 77% yield after chromatography on



silica gel ($R_f = 0.82$, Solvent System 2) and further characterized by:

^1H NMR (CDCl_3)

δ 8.14(d), 7.49(d), 5.09(septet), 4.86(s), 3.38(dd,s), 2.5-3.0(m), 2.30(m), 2.11(m), 1.29(d);

^{13}C NMR (CDCl_3)

δ 171.9, 149.1, 146.5, 129.5, 123.6, 68.7, 61.9, 49.5, 46.8, 46.7, 45.5, 45.3, 32.9, 32.1, 22.1, 22.0;

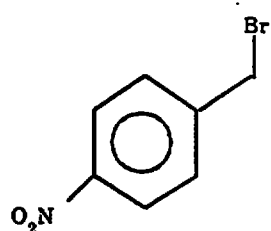
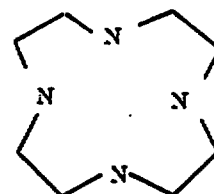
IR (CDCl_3) cm^{-1}

3450, 2860, 1735, 1350, 915.

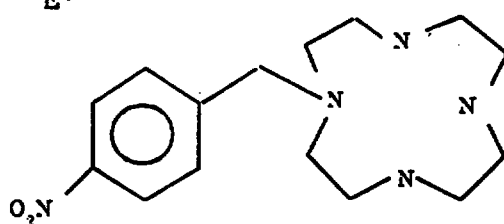
Example 5

Yields of mono-N-alkylation of p-nitrobenzyl bromide (Aldrich Chemical Co.) with 1,4,7,10-tetraazacyclododecane.

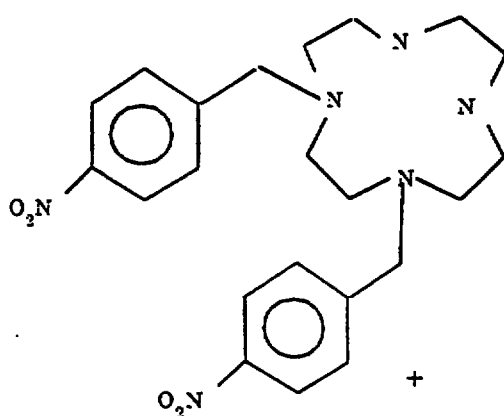
10 JAN 1997

**F**

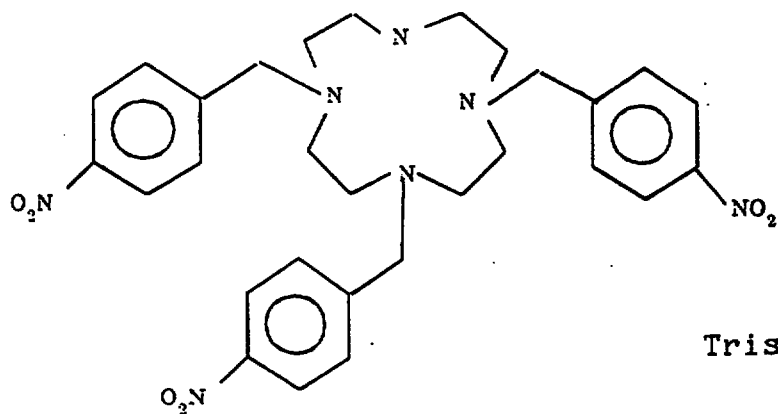
M



Mono



Bis



Tris

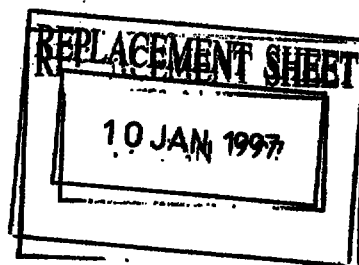


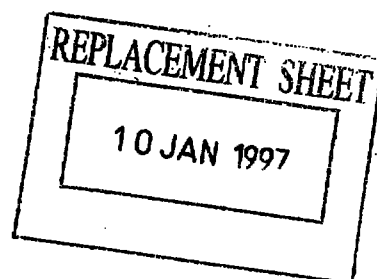
TABLE I

Ex. No.	M:E	[E] MOLARITY	SOLVENT	% ISOLATED YIELD **			MONO:BIS
				MONO	BIS	TRIS	
5A	1:1.0	1	CHCl ₃	49	11	5	4.5:1
5B	1:1.5	1	CHCl ₃	66	10	3	6.6:1
5C	1:1.5	4 x 10 ⁻²	CHCl ₃	73	9	2	7.4:1
5D	1:1.5	1	CH ₃ OH	39	16	3	2.4:1
5E	1:1.5	1	CH ₃ (CH ₂) ₃ OH	43	15	3	3.0:1
A*	1:1.5	1	CH ₃ OH***	34	19	7	1.8:1

*A is not a process of the invention.

**Isolated yield of product after flash chromatography; process at 25°C.

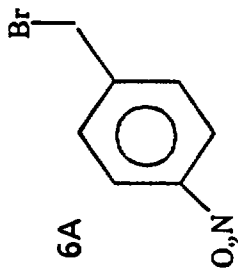
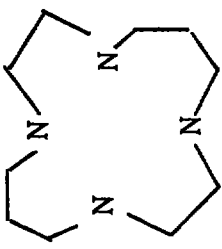
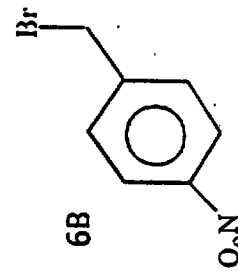
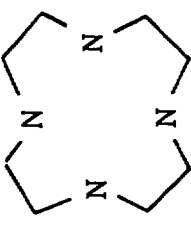
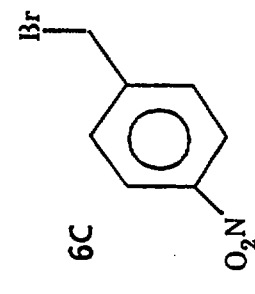
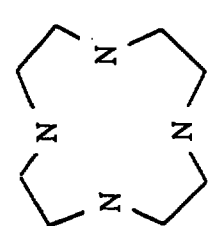
***1.0 equivalents of KCO₃ added relative to bromide.



Example 6

Preparation of various mono-N-alkylpolyazamacrocycles using the process of the invention.

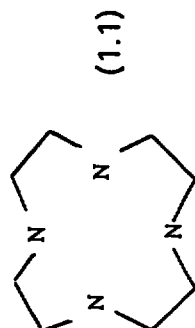
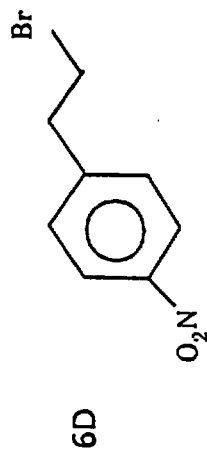
In Table II following, various electrophiles were reacted with polyazamacrocycles which gave yields greater than 40% selectivity for the desired mono-N-alkylpolyazamacrocycle, expressed as percent (%) isolated yield. The process was run using the equivalents and solvents given in Table II and by the procedure of Examples 1-4. Table III following indicates the structure of the desired mono-N-alkylpolyazamacrocycle formed by the reaction in Table II.

EX:	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6A		 (2.0)	CHCl ₃	100	
6B		 (1.0)	CHCl ₃	50	4.5:1
6C		 (2.0)	CHCl ₃	87	10:1

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)

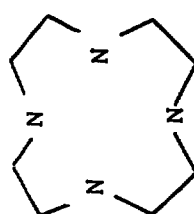
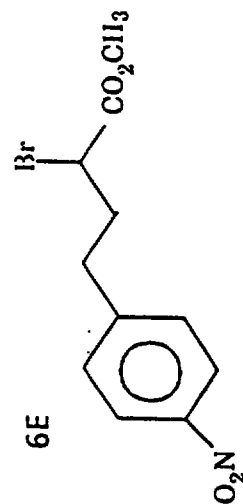
TABLE II CONT'D

EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
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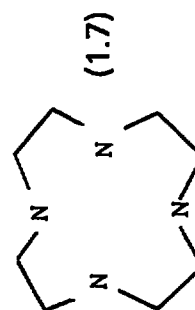
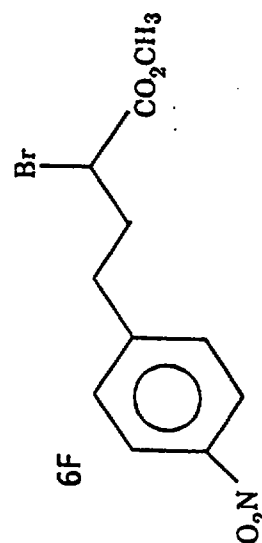


>20:1

43**

CHCl₃

81

CHCl₃

94

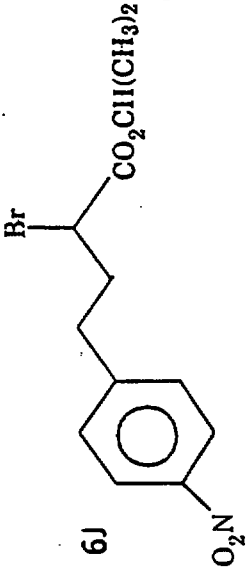
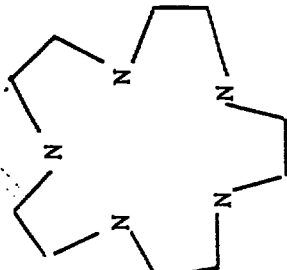
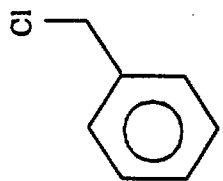
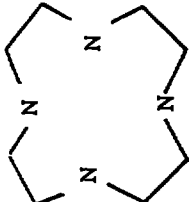
CHCl₃

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)
 **p-nitrostyrene isolated in 54% yield

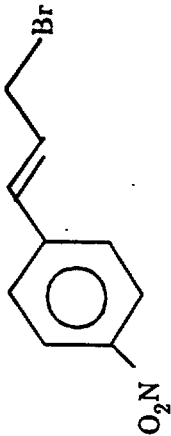
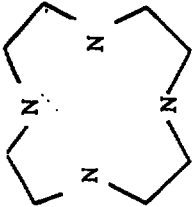
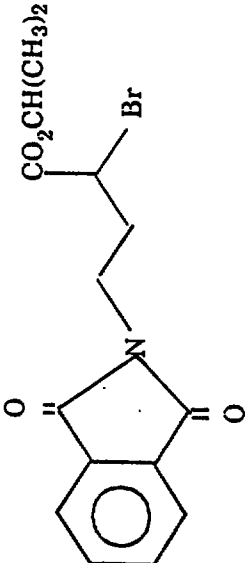
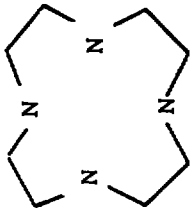
EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6G			CCl4	70	
6H			THF	86	
6I			CHCl3	61	

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)

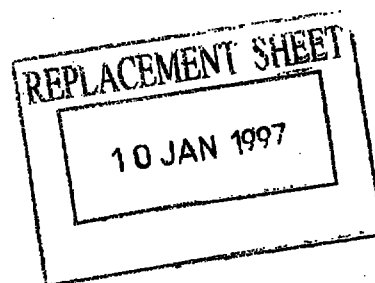
TABLE II CONT'D

EX.	ELECTROPHILE	MACROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6J			CHCl ₃	64	
6K			CHCl ₃	58	

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)

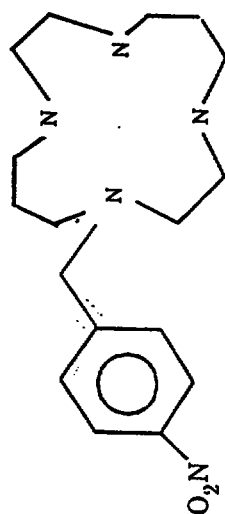
EX.	ELECTROPHILE	N. CROCYCLE (EQ)	SOLVENT	% ISOLATED YIELD *	MONO:BIS
6L		 (1.2)	CHCl ₃	69	4.1:1
6M		 (1.1)	CHCl ₃	83	34:1

*Flash chromatography purification based upon electrophile as limiting reagent (1.0 eq.)

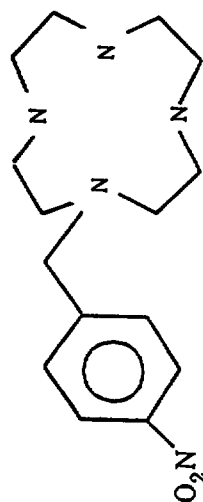


POLYAZAMACROCYCLE

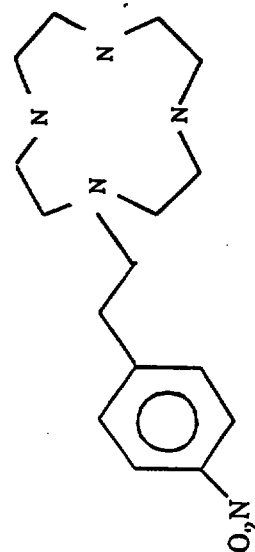
EX.



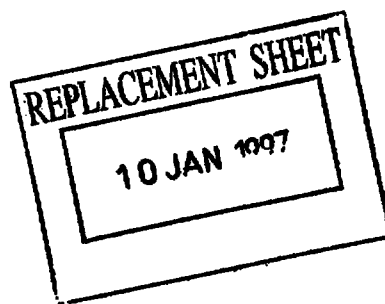
6A



6B AND 6C



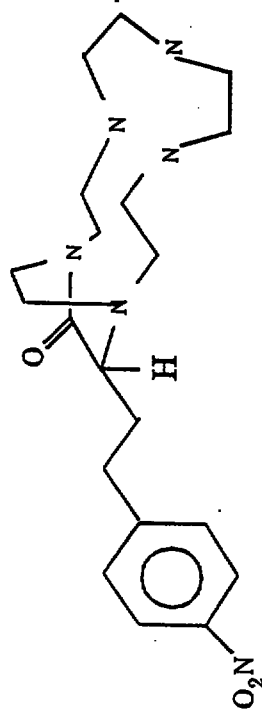
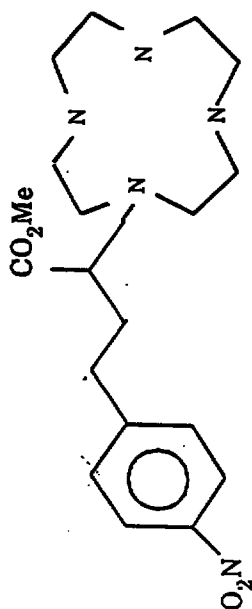
6D



POLYAZAMACROCYCLE

EX.

6E, 6F, 6G AND 6H



6I

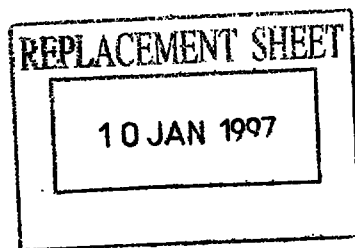
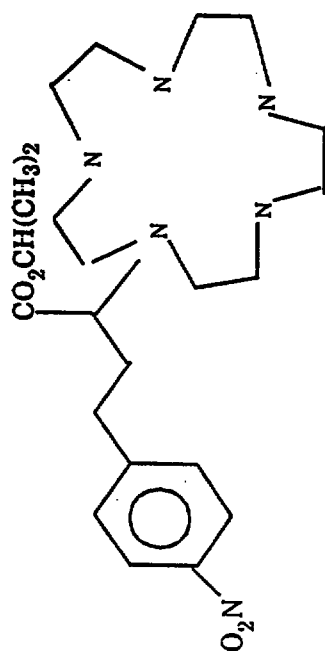


TABLE III CONT'D

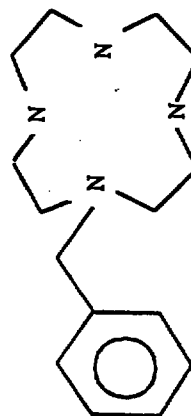
POLYAZAMACROCYCLE

EX.

6J

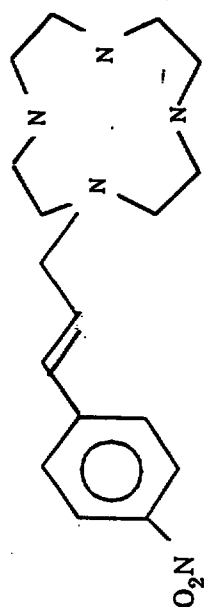


6K

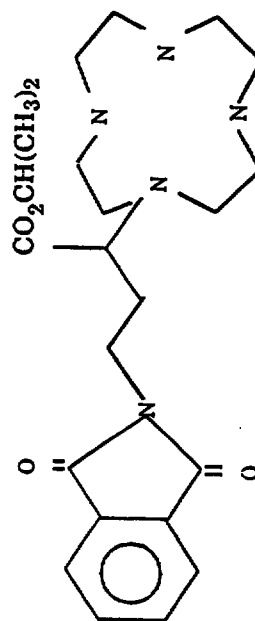


POLYAZAMACROCYCLE

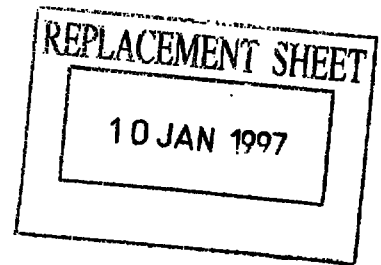
EX.



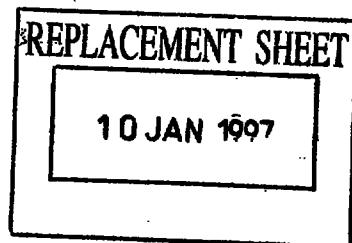
6L



6M



Other embodiments of the invention will be apparent to those skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims:



1. A process for preparing a mono-N-alkylated polyazamacrocyclic compound which comprises reacting an electrophile with between one to five equivalents of a polyazamacrocyclic compound in a solvent which will not promote a proton transfer.

2. The process of Claim 1 wherein the solvent is a relatively non-polar, relatively aprotic solvent.

3. The process of Claim 2 wherein the solvent is chloroform, carbon tetrachloride, methylene chloride, tetrahydrofuran, 1,4-dioxane or acetonitrile.

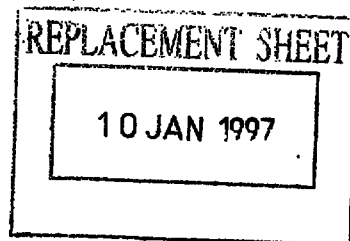
4. The process of Claim 2 or 3 wherein the solvent is chloroform.

5. The process of Claim 2 wherein the solvent is a hydrocarbon solvent.

6. The process of Claim 5 wherein the solvent is benzene, cyclohexane, n-hexane or toluene.

This Sheet Has Been Replaced





7. The process of Claim 1 wherein the solvent is a relatively non-polar, protic alcohol.

8. The process of Claim 7 wherein the solvent is n-butanol, t-butanol, isopropanol or n-hexanol.

9. The process of Claim 1 wherein the polyazamacrocyclic is symmetrical.

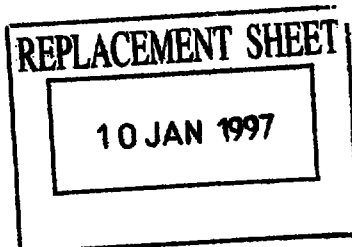
10. The process of Claim 9 wherein the polyazamacrocyclic has a methylene moiety containing from 2-4 carbon atoms between hetero atoms.

11. The process of Claim 10 wherein the polyazamacrocyclic is 1,4-diazacyclohexane, 1,3,7-triazacyclononane, 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane, 1,4,7,10,13-pentaazacyclopentadecane, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,7,13-triaza-4,10,16-trioxacyclooctadecane or 1,7-diaza-4,11-dithiacyclododecane.

12. The process of Claim 1 wherein the electrophile is RX wherein R is a moiety which is any alkyl or alkylaryl functionality which will yield the desired mono-N-alkylated product, and X is any leaving group.

13. The process of Claim 12 wherein X is chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo or brosylate.





14. The process of Claim 13 wherein the electrophile is *d,l*-2-bromo-4-*N*-phthalamidobutanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid isopropyl ester, *d,l*-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester, 4-nitrocinnamyl bromide, 4-nitrophenethyl bromide, 4-nitrobenzyl bromide or benzyl bromide.

15. The process of Claim 12 wherein R is an optically active α -haloacid ester.

16. The process of Claim 15 wherein the resulting mono-*N*-alkylated polyazamacrocyclic product has the opposite optical configuration from the optically active α -haloacid ester.

17. The process of Claim 1 wherein the temperature is from -78 to 100°C.

18. The process of Claim 17 wherein the temperature is from -25 to 40°C.

19. The process of Claim 18 wherein the temperature is from 0 to 25°C.

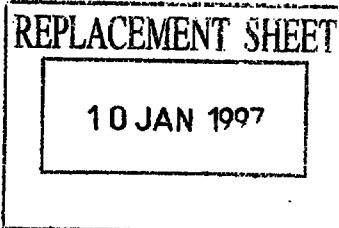
20. The process of Claim 1 wherein between one to three equivalents of polyazamacrocyclic are used relative to the electrophile.

21. The process of Claim 1 wherein between one and two equivalents of polyazamacrocyclic are used relative to the electrophile.





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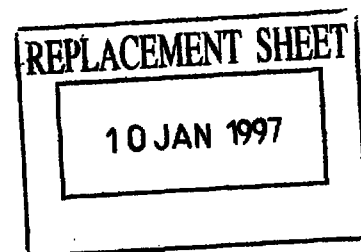
22. The process of Claim 1 wherein about one equivalent of polyazamacrocyclic is used relative to the electrophile.

23. The process of Claim 1 wherein the mono-N-alkylated polyazamacrocyclic is obtained in a selectivity of at least 40 percent.

24. The process of Claim 1 wherein the mono-N-alkylated polyazamacrocyclic is obtained in a selectivity of from 50 to 98 percent.

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35

PROCESS FOR PREPARING MONO-N-ALKYLATED POLYAZAMACROCYCLES

ABSTRACT

The invention relates to a novel process to prepare selectively mono-N-alkylated polyazamacrocycles which requires a electrophile with between one and five equivalents of a suitable macrocycle in a solvent which will not promote a proton transfer.

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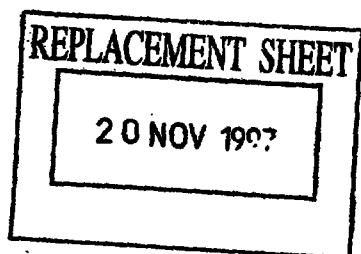
compared to the bis, tris, tetra or higher N-alkylated products.

The present invention concerns the reaction of an appropriate electrophile (E) with a free base polyazamacrocyclic (M) in a relatively non-polar, preferably relatively aprotic solvent. The ratio of E to M is about one E to about five M equivalents, preferably from about one E to about three M equivalents, more preferably from about one E to about two M equivalents, and most preferably from about one E to about one M equivalent.

The present process is very general and can produce selective mono-N-alkylation products with various polyazamacrocyclics and electrophilicities. A slight excess of polyazamacrocyclic is preferred to insure complete conversion of the electrophile; however, only small differences in isolated yield occur when larger excesses of the polyazamacrocyclic are used.

Accordingly, there is provided according to a broad form of the invention a process for preparing a mono-N-alkylated polyazamacrocyclic consisting essentially of reacting an electrophile with between about one and three equivalents of a polyazamacrocyclic in a solvent which will not promote a proton transfer and recovery of the thus prepared mono-N-alkylated polyazamacrocyclic; wherein the electrophile is represented by the formula RX wherein R is a C_1 - C_4 alkyl; a C_1 - C_4 alkyl which is substituted with a cyano, pyridinyl, CO_2R^1 or $CON(R^1)_2$ moiety where R^1 is H or C_1 - C_4 alkyl; or an alkylaryl where the alkyl portion is C_1 - C_4 and the aryl portion is a 5 or 6 member carbon ring or a 9 member ring containing carbon and one or more hetero atoms selected from sulfur, nitrogen or oxygen and X is chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo or brosylate; and wherein the polyazamacrocyclic contains at least two nitrogen atoms and at least one additional hetero atom selected from the group consisting of oxygen sulfur and nitrogen, and a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms such that the total carbon and hetero atoms in the polyazamacrocyclic is 12, 13 or 14.

The polyazamacrocyclics used in the present invention must contain at least two nitrogen atoms. However, the polyazamacrocyclics can also contain other hetero moieties such as oxygen atoms (polyoxazamacrocyclics) or sulfur atoms (polythioazamacrocyclics). Also included in the term polyazamacrocyclics are any symmetrical rings such as polyazamacrocyclic, azaoxamacrocyclic or bicyclopolyazamacrocyclic (i.e. bridged moieties or fused rings, but the mono-N-alkylation reaction occurs on the nitrogen atom of a saturated ring) which bears secondary amines capable of mono-N-alkylation. Preferably the secondary amines are all chemically equivalent. The macrocyclic preferably has a plane of symmetry and the



REPLACEMENT SHEETS		SG
☒	Description :	paged 31 to paged 32
☒	Drawings :	paged 31 to paged 32
☐	Figures :	paged 31 to paged 32
☒	Abstract :	paged 31 to paged 32
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CLAIMS

1. A process for preparing a mono-N-alkylated polyazamacrocycle consisting essentially of reacting an electrophile with between about one and three equivalents of a polyazamacrocycle in a solvent which will not promote a proton transfer and recovery of the thus prepared mono-N-alkylated polyazamacrocycle; wherein the electrophile is represented by the formula RX wherein R is a C_1-C_4 alkyl; a C_1-C_4 alkyl which is substituted with a cyano, pyridinyl, CO_2R^1 or $CON(R^1)_2$ moiety where R^1 is H or C_1-C_4 alkyl; or an alkylaryl where the alkyl portion is C_1-C_4 and the aryl portion is a 5 or 6 member carbon ring or a 9 member ring containing carbon and one or more hetero atoms selected from sulfur, nitrogen or oxygen and X is chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo or brosylate; and wherein the polyazamacrocycle contains at least two nitrogen atoms and at least one additional hetero atom selected from the group consisting of oxygen sulfur and nitrogen, and a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms such that the total carbon and hetero atoms in the polyazamacrocycle is 12, 13 or 14.
2. A process of claim 1 wherein the solvent is a non-polar, aprotic solvent; a polar, aprotic solvent; or a protic alcohol.
3. The process of claim 2 wherein the solvent is a non-polar, aprotic solvent.
4. The process of claim 3 wherein the solvent is carbon tetrachloride, toluene, benzene, cyclohexane or n-hexane.
5. The process of claim 2 wherein the solvent is a polar, aprotic solvent.
6. The process of claim 5 wherein the solvent is chloroform, methylene chloride, tetrahydrofuran, acetonitrile or 1,4-dioxane.
7. The process of claim 6 wherein the solvent is chloroform.
8. The process of claim 2 wherein the solvent is a protic alcohol.
9. The process of claim 8 wherein the solvent is n-butanol, t-butanol, isopropanol, or n-hexanol.
10. The process of claim 1 wherein the polyazamacrocycle contains at least two nitrogen atoms and at least one additional hetero atom and a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms.
11. The process of claim 1 wherein the polyazamacrocycle is symmetrical.
12. The process of claim 1 wherein the polyazamacrocycle is 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane, or 1,7-diaza-4,10-dithiacyclododecane.
13. The process of claim 1 wherein the electrophile is d,l,-2-bromo-4-N-phthalamidobutanoic acid isopropyl ester, d,l-2-bromo-4-(4-nitrophenyl) butanoic acid isopropyl ester, d,l-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester, 4-

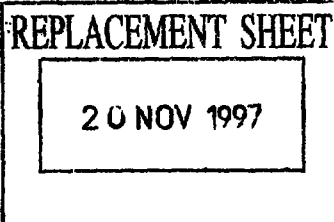
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nitrocinnamyl bromide, 4-nitrophenethyl bromide, 4-nitrobenzyl bromide, or benzyl bromide.

14. The process of claim 1 wherein R is an optically active α -haloacid ester.
15. The process of claim 14 wherein the resulting mono-N-alkylated polyazamacrocycle product has the opposite optical configuration from the optically active α -haloacid ester.
16. The process of claim 1 wherein the temperature is from about -78° to about 100° .
17. The process of claim 16 wherein the temperature is from about -25° to about 40° .
18. The process of claim 17 wherein the temperature is from about 0° to about 25° .
19. The process of claim 1 wherein between about one and about two equivalents of polyazamacrocycle are used relative to the electrophile.
20. The process of claim 1 wherein about one equivalent of polyazamacrocycle is used relative to the electrophile.
21. The process of claim 1 wherein the mono-N-alkylated polyazamacrocycle is obtained in a selectivity of at least 40%.
22. The process of claim 1 wherein the mono-N-alkylated polyazamacrocycle is obtained in a selectivity of from about 50 to about 98%.



PROCESS FOR PREPARING MONO-N-ALKYLATED POLYAZAMACROCYCLES**ABSTRACT**

The invention relates to a novel process to prepare selectively mono-N-alkylated polyazamacrocycles which requires a electrophile with between one and five equivalents of a suitable macrocycle in a solvent which will not promote a proton transfer.

