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㉒ Process for the isolation of 1,4,7,10,13,16-hexaoxacyclooctadecane.

㉒ Process for isolating 1,4,7,10,13,16- hexaoxacyclooctadecane (A) in high yield from a mixture also containing other macrocyclic polyethers, by reacting A with nitromethane in the presence of a solvent for these macrocyclic polyethers, to precipitate a complex of A and nitromethane, separating the complex from the reaction mixture and dissociating the separated complex into A and nitromethane.

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PROCESS FOR THE ISOLATION OF 1,4,7,10,13,16-
HEXAOXACYCLOOCTADECANE

The invention relates to a process for the isolation of 1,4,7,10,13,16-hexaoxacyclooctadecane from a mixture also containing one or more other macrocyclic polyethers.

Hereinafter 1,4,7,10,13,16-hexaoxacyclooctadecane will
5 also be referred to by its trivial name "18-crown-6". Its structural formula is shown on the Formula page (compound 9).

18-Crown-6 can be prepared by heating tetraethylene glycol and bis(2-chloroethyl) ether in the presence of tetrahydrofuran as a solvent and potassium hydroxide, see "Synthesis"
10 1976, 515-516. The reaction mixture thus formed contains 18-crown-6, potassium chloride, water and by-products, i.a. macrocyclic polyethers having a ring of larger size than 18-crown-6. The solvent was evaporated from the reaction mixture to give a brown slurry to which dichloromethane was
15 added. The potassium chloride was filtered off from the solution thus obtained, the filtrate was dried (MgSO_4), the solvent was evaporated from the dried filtrate to yield a residue of crude 18-crown-6. This residue was distilled to give a discoloured distillate containing 18-crown-6. This distillate
20 was dissolved in acetonitrile and the solution was cooled to -45°C . The resultant precipitate of 18-crown-6-acetonitrile complex was collected by filtration. Distillation of this complex gave a distillate of pure 18-crown-6.

A disadvantage of this procedure is that the 18-crown-6
25 is distilled twice and that expensive measures must be taken

to prevent the occurrence of powerful and destructive explosions during these distillations, see "Chemical & Engineering News", September 6, 1976, page 5 and December 13, 1976, page 5. Moreover the 18-crown-6 is obtained in a fairly
5 low yield.

The Applicants have found a process for the isolation of 18-crown-6 in which the 18-crown-6 is obtained in high yield and need not be distilled, thus avoiding the explosions mentioned hereinbefore.

10 Accordingly the invention provides a process for the isolation of 1,4,7,10,13,16-hexaoxacyclooctadecane from a mixture also containing one or more other macrocyclic polyethers, characterized by reacting the 1,4,7,10,13,16-hexaoxacyclooctadecane with nitromethane in the presence of a solvent
15 for the said macrocyclic polyethers, to precipitate a complex of 1,4,7,10,13,16-hexaoxacyclooctadecane and nitromethane, separating precipitated complex from the mixture containing the complex, dissociating separated complex and separating the components from each other.

20 Surprisingly, nitromethane is selective in that, when contacted with a mixture containing 18-crown-6 and one or more other macrocyclic polyethers, it only forms a complex with 18-crown-6. Hence, the 18-crown-6-nitromethane complex obtained according to the invention does not or hardly contain
25 macrocyclic polyethers other than 18-crown-6.

As the 18-crown-6-nitromethane complex gives off nitromethane vapour the complex can simply be dissociated into 18-crown-6 and nitromethane by allowing it to stand in the open air. The complex is rapidly dissociated by heating it at sub-
30 atmospheric pressure and removing the nitromethane vapour formed, leaving pure or almost pure 18-crown-6. Heating may take place at a temperature of, for example, 35°C to 125°C at a pressure of, for example, 5 to 1500 Pa.

The process according to the invention must be carried
35 out in a solvent for macrocyclic polyethers in which the

18-crown-6-nitromethane complex can be precipitated. Such a solvent may substantially consist of nitromethane. A solvent is taken to consist substantially of a specified compound when the content of this specified compound in the solvent is higher than 50 %w.

According to a feature of the invention the solvent substantially consists of an ether. Preferred ethers are dialkyl ethers and cyclic ethers. Examples of dialkyl ethers are diethyl ether, di-n-butyl ether and di-n-hexylether. The 18-crown-6-nitromethane complex is considerably less soluble in diethyl ether than in nitromethane at the same temperature, so that a considerably larger part of the 18-crown-6 present in the starting mixture can be isolated. Attractive examples of the cyclic ethers are 1,4-dioxane and tetrahydrofuran.

According to another feature of the invention the solvent substantially consists of an alkanol, a hydrocarbon (or a mixture of hydrocarbons) or water. Examples of suitable alkanols are those having in the range of from one to five carbon atoms, for example methanol, ethanol, 2-propanol and tert-butanol. Examples of suitable hydrocarbons are benzene, toluene, the three xylenes and heptane. Particularly attractive solvents are methanol and benzene. 18-Crown-6, dissolved in water may be removed therefrom by reaction with nitromethane to form a precipitate of the 18-crown-6-nitromethane complex in nitromethane-containing water. Mixtures of solvents may be used, for example of diethyl ether and ethanol.

The 18-crown-6-acetonitrile complex is very difficult to precipitate from the solvents mentioned in the last three paragraphs, if at all, as this complex is too highly soluble in these solvents.

The reaction between 18-crown-6 and nitromethane is preferably carried out at a temperature in the range of from -25°C to $+35^{\circ}\text{C}$, and, when the solvent substantially consists of nitromethane, of from 0°C to -25°C , so as to enable a very large part of the 18-crown-6 to be isolated. Where the

solvent substantially consists of an ether, an alkanol, a hydrocarbon (or a mixture of hydrocarbons) or water, the reaction between 18-crown-6 and nitromethane is very suitably carried out at a temperature in the range of from 0°C to +35°C.

5 Ambient temperature, for example, a temperature between 15°C and 25°C, is very suitable.

The 18-crown-6-nitromethane complex can easily be separated from the mixture containing the complex, for example by filtration, centrifugation or decantation.

10 The 18-crown-6-nitromethane complex contains two molecules of nitromethane per molecule of 18-crown-6. Accordingly, the 18-crown-6 is reacted with nitromethane using a molar ratio of nitromethane to 18-crown-6 of at least 2:1. Preferably, this molar ratio is not higher than 20:1. This range is not critical,
15 molar ratios of nitromethane to 18-crown-6 outside this range may be used, if desired.

The 18-crown-6-nitromethane complex may be precipitated in any suitable manner, for example by adding nitromethane to the starting mixture and, if desired, cooling the mixture
20 thus obtained to a suitable temperature, or by dissolving the starting mixture in diethyl ether and adding nitromethane at ambient temperature to the solution obtained, or by dissolving the starting mixture in any other of the above-mentioned solvents, for example methanol, adding nitro-
25 methane and, if desired, cooling the mixture obtained to a suitable temperature. The starting mixture may be solid or liquid at the temperature at which the 18-crown-6 is reacted with nitromethane.

The 18-crown-6 in the starting mixture may have been formed
30 by any process. Very good results have been obtained by reacting tetraethylene glycol with a bis(2-haloethyl)ether, halo representing chloro, bromo or iodo, in the presence of an alkali metal hydroxide. If desired, the alkali metal halide formed and solvent, if present, may be removed from the reaction
35 mixture obtained, leaving the 18-crown-6-containing starting

mixture. Other examples of processes for the preparation of 18-crown-6 are:

- (1) Elimination of hydrogen chloride from 17-chloro-3,6,9,12,15-pentaoxaheptadecanol, followed by ring closure, in the presence of potassium tert-butoxide, see British patent specification 1,285,367.
- (2) Catalytic oligomerization of ethylene oxide, see German Offenlegungsschrift 2,401,126.
- (3) Reaction of triethylene glycol with 3,6-dioxo-1,8-dichlorooctane in the presence of potassium hydroxide and 10% aqueous tetrahydrofuran, as described in J.Org.Chem. 39 (1974) 2445-2446.

The invention will now be illustrated by reference to the following Examples.

Preparation of crude 18-crown-6

A 3-litre three-necked round-bottomed flask, fitted with a mechanical stirrer, a reflux condenser and a 250 ml dropping funnel was charged with potassium hydroxide pellets (416 g. containing 6.3 mol KOH), tetraethylene glycol (1.25 mol) and tetrahydrofuran (1000 ml). The reaction vessel was placed in a heating mantle and gently heated. After 15 minutes a solution of bis(2-chloroethyl)ether (3.125 mol) in tetrahydrofuran (150 ml) was added in one stream from the dropping funnel to the vigorously stirred reactants. The reaction mixture was then heated under reflux, with stirring for 18 hours. Subsequently, the reaction mixture was cooled and the solvent was removed under a pressure of 1.9 kPa to give a brown slurry to which dichloromethane (750 ml) was added. The resulting suspension of potassium chloride was filtered and the potassium chloride filtered off was washed with dichloromethane (100 ml). The combined filtrate and washings were dried over anhydrous magnesium sulphate and the solvent was evaporated at a pressure of 1.9 kPa to give a residue of crude 18-crown-6 (396 g) containing 0.531 mol of 18-crown-6 (yield 42.5%, calculated on

starting tetraethylene glycol), potassium chloride and at least eight other compounds among which

1,4,7,10,13,16,19,22,25,28,31,34-dodecaoxacyclohexatriacontane, hexaethyleneglycol and unreacted tetraethylene glycol.

5 This crude 18-crown-6 was used as described hereinafter.

EXAMPLE I - Isolation of 18-crown-6 in nitromethane at -20°C

Crude 18-crown-6 (3.021 g), prepared as described above, was dissolved in nitromethane (4 ml). The solution formed was cooled to -20°C and the 18-crown-6-nitromethane complex precipitated was filtered off (1.248 g). The complex was kept
10 for 30 minutes at 70°C and a pressure of 13 Pa, leaving 18-crown-6 in a yield of 37% calculated on starting tetraethylene glycol, or 87% calculated on 18-crown-6 in the crude 18-crown-6. The purity of the 18-crown-6 was higher than
15 99.5%.

Comparative Experiment A - Isolation of 18-crown-6 in acetonitrile at -20°C

Crude 18-crown-6 (3.021 g), prepared as described above, was dissolved in acetonitrile (4 ml). The solution formed
20 was cooled to -20°C and the 18-crown-6-acetonitrile complex was filtered off. The complex was kept for 30 minutes at 70°C and a pressure of 13 Pa, leaving 18-crown-6 in a yield of 27% calculated on starting tetraethylene glycol, or 63% calculated on 18-crown-6 in the crude 18-crown-6. Comparison with
25 Example I shows that complexation with nitromethane allows the 18-crown-6 in a much higher yield.

Comparative Experiment B - Isolation of 18-crown-6 in acetonitrile at -45°C

This experiment is according to the process described in
30 "Synthesis" 1976, 515-516.

Crude 18-crown-6 (39.6 g), prepared as described above, was distilled at a pressure of 20 Pa to give a distillate (21.3 g) boiling at 140-210°C. This distillate was mixed with acetonitrile (53 ml) at 20°C and the mixture formed was cooled

to -45°C . The resultant 18-crown-6-acetonitrile complex was filtered off and subjected to distillation at a pressure of 2 Pa to give a distillate of 18-crown-6 in a yield of 25% calculated on starting tetraethylene glycol, or 59% calculated on 18-crown-6 in the crude 18-crown-6. Comparison with Example I shows that complexation with nitromethane at -20°C allows the 18-crown-6 in a much higher yield than complexation with acetonitrile at -45°C followed by distillation of 18-crown-6.

10 EXAMPLE II - Isolation of 18-crown-6 in nitromethane at $+20^{\circ}\text{C}$

Crude 18-crown-6 (3.04 g), prepared as described above, was mixed with nitromethane (5ml) at 20°C . After 16 hours the precipitate formed was filtered off and kept for 30 minutes at 70°C and a pressure of 13 Pa, leaving 18-crown-6 in a yield of 28% calculated on starting tetraethylene glycol, or 66% calculated on 18-crown-6 in the crude 18-crown-6. Comparison of this yield with the higher yield obtained in Example I shows the favourable influence of the temperature of -20°C when nitromethane is used as the solvent.

20 EXAMPLE III - Isolation of 18-crown-6 in diethyl ether at $+20^{\circ}\text{C}$

Crude 18-crown-6 (3.5 g), prepared as described above, was extracted with four 20-ml portions of diethyl ether. The residue of potassium chloride thus obtained was filtered off, the four filtrates were combined, and the solvent was evaporated. Then, a mixture of nitromethane (0.7 ml) and 5.1 ml of diethyl ether was added at 20°C , which caused an immediate precipitation of the 18-crown-6-nitromethane complex. The complex precipitated was filtered off and kept for 30 minutes at 70°C and a pressure of 13 Pa, leaving 18-crown-6 in a yield of 37% calculated on starting tetraethylene glycol, or 87% calculated on 18-crown-6 in the crude 18-crown-6. Comparison of this yield with the lower yield of Example II shows the favourable influence of the diethyl ether.

30 EXAMPLE IV - Isolation of 18-crown-6 in methanol at $+20^{\circ}\text{C}$

35 Crude 18-crown-6 (3.16 g), prepared as described above, was

mixed with nitromethane (0.6 ml) and methanol (4.4 ml) at 20°C. After 16 hours the precipitate formed was filtered off and kept for 30 minutes at 70°C and a pressure of 13 Pa, leaving 18-crown-6 in a yield of 13%, calculated on starting tetraethylene glycol, or 31%, calculated on 18-crown-6 in the crude 18-crown-6. Comparison of this yield with the higher yields obtained in the Examples II and III shows that in this case diethyl ether and nitromethane are more attractive solvents than methanol.

10 EXAMPLE V - Separation of 18-crown-6 from macrocyclic
polyether No. 3 in diethyl ether

Nitromethane (0.6 ml) was added at 20°C to a solution of 18-crown-6 (1.13 mmol) and macrocyclic polyether No. 3 of the formula page (1.15 mmol) in diethyl ether (6 ml). The precipitate
15 formed was filtered off, washed at 20°C with 1 ml of a diethyl ether/nitromethane (10/1 v/v) mixture and dried with dry air at 20°C. The dried precipitate was the 18-crown-6-nitromethane complex. The complex contained 92% of the starting amount of 18-crown-6 and the molar ratio of 18-crown-6 to macrocyclic
20 polyether No. 3 in the dried precipitate was 97:3. The complex was kept for 30 minutes at 70°C and a pressure of 13 Pa leaving 18-crown-6 containing 3% macrocyclic polyether No. 3.

EXAMPLES VI to XI - Precipitation of the 18-crown-6-nitro-
methane complex in various solvents

25 Nitromethane (1.48 mmol) was added to a solution of 18-crown-6 (0.19 mmol) and macrocyclic polyether No. 3 of the formula page (0.19 mmol) in a solvent (1 ml) at 25°C. The 18-crown-6-nitromethane complex precipitated was filtered off. The filtered material was kept for 30 minutes at 70°C and a
30 pressure of 13 Pa, which caused dissociation into nitromethane, which was sucked off, and 18-crown-6. Then, the 18-crown-6 was weighed and the yield of it on the starting amount of 18-crown-6 was calculated. Six solvents were tested in this manner. Table I presents the results. The purity of the
35 18-crown-6 was 99% in each of the Examples.

Table I

Example	Solvent	Yield of 18-crown- 6, %	The complex crystallized out	
			immediately	over a period of 1 to 4 h
VI	diethyl ether	92	yes	-
VII	tetrahydrofuran	52	-	yes
VIII	1,4-dioxane	23	-	yes
IX	methanol	79	yes	-
X	benzene	45	-	yes
XI	water	35	yes	-

Comparative Experiment C-Precipitation of the 18-crown-6-acetonitrile complex in diethyl ether

Acetonitrile (1.48 mmol) was added to a solution of 18-crown-6 (0.19 mmol) and macrocyclic polyether No. 3 of the formula page (0.19 mmol) in diethyl ether (1 ml) at 25°C. The 18-crown-6-acetonitrile complex crystallized out immediately and was filtered off. It contained 40% of the starting amount of 18-crown-6. Comparison with Example VI shows that nitromethane had complexed a much larger part of the 18-crown-6 than acetonitrile. The purity of the 18-crown-6 was more than 99%.

Comparative Experiments D to H-Attempted precipitation of the 18-crown-6-acetonitrile complex in five solvents

The experiments of Examples VII to XI were carried out with acetonitrile (1.71 mmol) instead of nitromethane (1.15 mmol). In none of the five experiments was a precipitate formed.

Comparative Experiments I to P -Attempted preparation of complexes of nitromethane with macrocyclic polyethers other than 18-crown-6

These eight comparative experiments were carried out with the macrocyclic polyethers listed in Table II. Their structural formulae are shown on the formula page. Each macrocyclic polyether has been given a number which is mentioned in Table II and on the formula page.

Table II

Comparative Experiment	number	Macrocyclic polyether name
I	1	2,3,11,12-dibenzo- 14,7,10,13, 16-hexaoxacyclooctadeca-2,11- diene
J	2	2,3-benzo-1,4,7,10,13,16- hexaoxacyclooctadeca-2-ene
K	3	1,4,7,10,13-pentaoxacyclo- pentadecane
L	4	2,3-benzo-1,4,7,10,13,16,19- heptaoxacycloheneicosa-2-ene
M	5	2,5,8,15,18,21-hexaoxatri- cyclo/20.4.0.0 ^{9,14} /hexacosane
N	6	3,5-benzo-1,7,10,13,16-penta- oxacyclooctadeca-3-ene
O	7	3,4-benzo-1,6,9,12,15-penta- oxacycloheptadeca-3-ene
P	8	1,10-diaza-4,7,13,16,21,24- hexaoxabicyclo/8,8,8/hexa- cosane

In Comparative Experiment No. I nitromethane (1.15 mmol) was added to a saturated solution of macrocyclic polyether No. 1 in diethyl ether (1 ml) at 25°C. In Comparative Experiments J to P nitromethane was added to a solution of 100 mg of the macrocyclic polyether in diethyl ether at 25°C. In none of the eight experiments was a precipitate formed.

Comparative Experiment Q-Attempted preparation of a macrocyclic polyether 1-nitromethane complex

Nitromethane (1.15 mmol) was added at 25°C to a saturated solution of macrocyclic polyether 1 (see Table II and formula page) in methanol (1 ml). No precipitate was formed.

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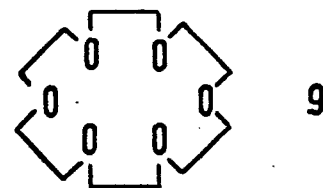
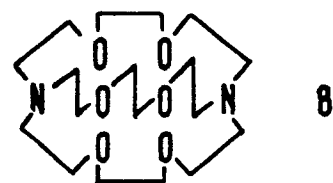
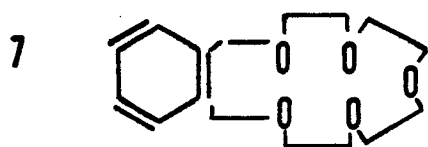
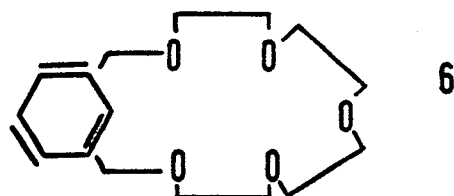
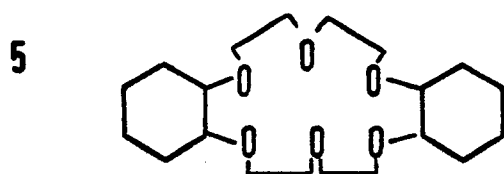
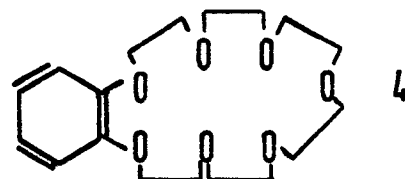
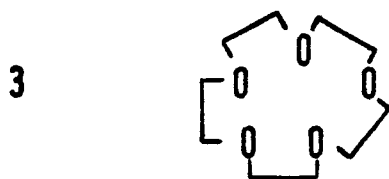
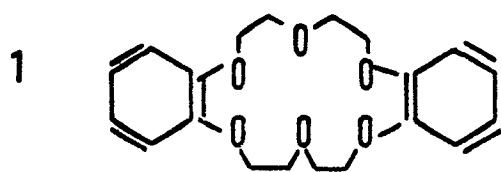
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C L A I M S

1. Process for the isolation of 1,4,7,10,13,16-hexaoxacyclo-octadecane from a mixture also containing one or more other macrocyclic polyethers, characterized by reacting the 1,4,7,10,13,16-hexaoxacyclooctadecane with nitromethane in the
5 presence of a solvent for the said macrocyclic polyethers, to precipitate a complex of 1,4,7,10,13,16-hexaoxacyclooctadecane and nitromethane, separating precipitated complex from the mixture containing the complex, dissociating separated complex and separating the components from each other.
- 10 2. Process as claimed in claim 1, characterized in that the solvent substantially consists of nitromethane.
3. Process as claimed in claim 1, characterized in that the solvent substantially consists of an ether.
4. Process as claimed in claim 3, characterized in that the
15 ether is a dialkyl ether.
5. Process as claimed in claim 4, characterized in that the dialkyl ether is diethyl ether.
6. Process as claimed in claim 3, characterized in that the ether is a cyclic ether.
- 20 7. Process as claimed in claim 6, characterized in that the cyclic ether is 1,4-dioxane.
8. Process as claimed in claim 6, characterized in that the cyclic ether is tetrahydrofuran.
9. Process as claimed in claim 1, characterized in that the
25 solvent substantially consists of an alkanol.

10. Process as claimed in claim 9, characterized in that the alkanol is methanol.
11. Process as claimed in claim 1, characterized in that the solvent substantially consist of a hydrocarbon or a mixture
5 of hydrocarbons.
12. Process as claimed in claim 11, characterized in that the hydrocarbon is benzene.
13. Process as claimed in claim 1, characterized in that the solvent substantially consists of water.
- 10 14. Process as claimed in any one of the preceding claims characterized in that the reaction between 1,4,7,10,13,16-hexaoxacyclooctadecane and nitromethane is carried out at a temperature in the range of from -25°C to $+35^{\circ}\text{C}$.
- 15 15. Process as claimed in claim 2, characterized in that the reaction between 1,4,7,10,13,16-hexaoxacyclooctadecane and nitromethane is carried out at a temperature in the range of from 0°C to -25°C .
- 20 16. Process as claimed in any one of claims 3 to 13, characterized in that the reaction between 1,4,7,10,13,16-hexaoxacyclooctadecane and nitromethane is carried out at a temperature in the range of from 0°C to $+35^{\circ}\text{C}$.
- 25 17. Process as claimed in any one of the preceding claims, characterized in that the 1,4,7,10,13,16-hexaoxacyclooctadecane in the starting mixture has been obtained by reacting tetraethylene glycol with a bis(2-haloethyl)ether in the presence of an alkali metal hydroxide.





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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CHEMICAL ABSTRACTS, vol. 86 (1977) 88.648b, page 446. Columbus Ohio, & Z.Naturforsch. B. Anorg. Chemie, Org. Chem. (1976), 31B (9), 1192-200 (ger.) by El Basyony, A & al. (Inst. Anorg. Angew. Chem. Univ. Hamburg). * Page 446, column 2, 88.648b * -----	1,2	C 07 D 323/00
			TECHNICAL FIELDS SEARCHED (Int. Cl.)
			C 07 D 323/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application C: citation for other reasons
			& members of the same patent family.
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
The Hague	26-02-1978	FRANCOIS	

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