MACROHETEROCYCLES.

51.* SYNTHESIS OF MACROCYCLIC POLYAMINES IN A BIPHASIC SYSTEM

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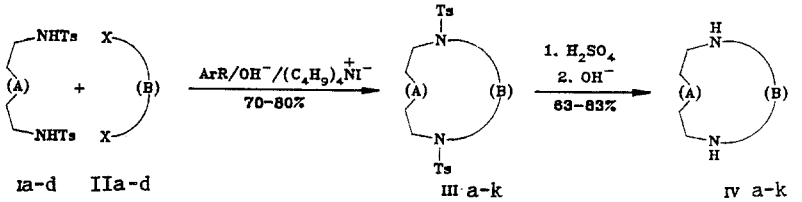
Macrocyclic polyamines are conveniently synthesized by condensation of bissulfonamides with ditosylates or dibromides of glycols in the biphasic system toluene(xylene)—aqueous sodium hydroxide.

Macrocyclic polyamines are an interesting class of organic ligands. They are used for selective extraction and analytical determination of metal ions, control of their redox properties, stabilization of unusual oxidation states, modeling enzyme-catalyzed processes, and as catalysts [2-4].

Macrocyclic amines are commonly synthesized by acylating acyclic polyamines with chloroanhydrides or esters of dicarboxylic acids under high dilution conditions with subsequent reduction of the macrocyclic amides formed [5, 6]. These compounds are more conveniently synthesized by alkylating bissulfonamides with ditosylates or mesylates of glycols in the presence of hydrides or alkali metal alcoholates in DMF [3, 4, 7].

The large quantities of dry solvents and (or) hydrides or alkali metal alcoholates required as well as the relatively small yields of the desired products make these synthesis methods difficult even under laboratory conditions.

In the present work, we describe a convenient synthesis of macrocyclic polyamines based on alkylation of bissulfonamides by dibromides or ditosylates of glycols in the biphasic system toluene (xylene)—aqueous sodium hydroxide. Tetrabutylammonium iodide was used as catalyst.



Ia-d IIa-d III a-k IV a-k

Ia A=NTs, b A=NTs$(CH_2)_2$NTs, c A=CH_2NTsCH_2, d A=$(CH_2NTsCH_2)_2$; II a X=Br, b–d X=OTs; a B=$(CH_2)_3$, b B=$(CH_2)_2$, c B=$(CH_2)_2$NTs$(CH_2)_2$, d B=$=CH_2(CH_2NTsCH_2)_2CH_2$; III, IVa A=NR, b–d A=NR$(CH_2)_2$NR, e–g A=CH_2NRCH_2, h–k A=$(CH_2NRCH_2)_2$; III, IVa,b,e,h B=$(CH_2)_2$, c,j B=$(CH_2)_2$NR$(CH_2)_2$, d,g,k B=$CH_2(CH_2NRCH_2)_2CH_2$, f,i B=$(CH_2)_3$; III R=Ts, IV R=H

The starting bissulfonamides Ia-d were synthesized by reaction of the corresponding polyamines with p-toluenesulfonylchloride in the biphasic system ether—aqueous NaOH [8]. 1,3-Dibromopropane (IIa) and 1,2-di(p-tolylsulfoxy)ethane (IIb) were prepared by reaction of 1,3-propandiol with phosphorus tribromide [9] and ethylene glycol with p-toluenesulfonylchloride [10], respectively. Compounds IIc and IId were prepared by reaction of the corresponding aminoglycols with p-toluenesulfonylchloride in methylene chloride—aqueous NaOH or in dioxane with triethylamine.

*For Communication 50, see [1].

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TABLE 1. Macrocyclic Polyamines

Compound	Empirical formula	mp, °C	PMR spectrum,* δ, ppm	M** found	M** calc.	Yield, %
IIIa	$C_{27}H_{33}N_3O_6S_3$	222...224	2,25 (9H, s, CH_3); 3,30 (12H, s, NCH_2); 7,40 (12H, m, C_6H_4)	436	436	80
IIIb	$C_{36}H_{44}N_4O_8S_4$	290	2,35 (12H, s, CH_3); 3,30 (16H, s, NCH_2); 7,50 (16H, m, C_6H_4)	633	633	86
IIIc	$C_{45}H_{55}N_5O_{10}S_5$	276...280	2,00 (15H, s, CH_3); 2,90 (20H, s, NCH_2); 7,10 (20H, m, C_6H_4)	831	831	85
IIId	$C_{54}H_{66}N_6O_{12}S_6$	289...293	2,00 (18H, s, CH_3); 3,00 (24H, s NCH_2); 2,70 (24H, m, C_6H_4)	1028	1028	85
IIIe	$C_{29}H_{37}N_3O_6S_3$	210...211	1,66 (4H, m, CH_2); 2,16 (9H, s, CH_3); 3,03 (12H, m, NCH_2); 7,20 (12H, m, C_6H_4)	464	464	80
IIIf	$C_{30}H_{39}N_5O_6S_3$	170...171	1,86 (6H, m, CH_2); 2,30 (9H, s, CH_3); 3,13 (12H, m, NCH_2); 7,36 (12H, m, C_6H_4)	478	478	66
IIIg	$C_{47}H_{59}N_5O_{10}S_5$	270	1,70 (4H, m, CH_2); 2,23 (15H, s, CH_3); 3,17 (20H, m, NCH_2); 7,30 (20H, m, C_6H_4)	859	859	90
IIIh	$C_{38}H_{48}N_4O_8S_4$	280...283	1,75 (4H, m, CH_2); 2,26 (12H, s, CH_3); 3,10 (16H, m, NCH_2); 7,40 (16H, m, C_6H_4)	662	662	83
IIIi	$C_{39}H_{50}N_4O_8S_4$	284...285	1,90 (6H, m, CH_2); 2,40 (12H, s, CH_3); 3,16 (16H, m, NCH_2); 7,40 (16H, m, C_6H_4)	676	676	85
IIIj	$C_{47}H_{59}N_5O_{10}S_5$	225...228	1,83 (4H, m, CH_2); 2,36 (15H, s, CH_3); 3,26 (20H, m, NCH_2); 7,40 (20H, m, C_6H_4)	858	858	87
IIIk	$C_{56}H_{70}N_6O_{12}S_6$	295...300	1,50 (4H, m, CH_2); 2,23 (18H, s, CH_3); 3,10 (24H, m, NCH_2); 7,23 (24H, m, C_6H_4)	1056	1056	78
IVa	$C_6H_{15}N_3$	60...62	2,30 (3H, s, NH); 2,75 (12H, s, NCH_2)	129	129	73
IVb	$C_8H_{20}N_4$	117	2,50 (4H, s, NH); 2,80 (16H, s, NCH_2)	172	172	85
IVc	$C_{10}H_{25}N_5$	97	1,90 (5H, s, NH); 2,67 (20H, s, NCH_2)	215	215	70
IVd	$C_{12}H_{30}N_6$	148...150	1,83 (6H, s, NH); 2,70 (24H, s, NCH_2)	258	258	75
IVe	$C_8H_{19}N_3$	Oil	1,65 (4H, m, CH_2); 2,50 (3H, s, NH); 2,76 (12H, m NCH_2)	157	157	75
IVf	$C_9H_{21}N_3$	15...16	1,61 (6H, m, CH_2); 2,30 (3H, s, NH); 2,70 (12H, m, CH_2)	171	171	63
IVg	$C_{12}H_{29}N_5$	66...68	1,43 (4H, m, CH_2); 2,00 (5H, s, NH); 2,63 (20H, m NCH_2)	243	243	83
IVh	$C_{10}H_{24}N_4$	172	1,66 (4H, m, CH_2); 2,30 (4H, s CH_3); 2,73 (16H, m, NCH_2)	200	200	68
IVi	$C_{11}H_{26}N_4$	98...100	1,63 (6H, m, CH_2); 2,21 (4H, s, NH); 2,67 (16H, m, NCH_2)	214	214	70
IVj	$C_{12}H_{29}N_5$	70...71	1,60 (4H, m, CH_2); 1,90 (5H, s, NH); 2,67 (20H, m, NCH_2)	243	243	70
IVk	$C_{14}H_{34}S_6$	73...75	1,33 (4H, m, CH_2); 2,13 (28H, NCH_2, NH)	286	286	78

*Spectra for IIIb-d were taken in CF_3COOH.

**For IIIa-k, values for [M − Ts] are given since M is absent.

The cyclization was carried out at the boiling point of the organic solvent for 8-10 h. The yields of N-tosylated macrocyclic polyamines IIIa, b, and i-k for reaction in xylene were 15-20% higher than in toluene. The optimal concentrations for equimolar amounts of reagents were 0.03-0.04 M.

In contrast to the earlier report [7], we did not find [2+2] condensation products. In our case, [1+1] cyclization products formed regardless of the type of reagents. For example, the yield of IIIb for condensation of bissulfonamide Ia and ditosylate IIc was 78%, whereas it was 86% for reaction of Ib with ditosylate IIb.

The tosyl groups in compounds IIIa-d were removed by heating in conc. H_2SO_4. The sulfates formed were converted to the bases using NaOH with subsequent extraction of the macrocyclic polyamines using chloroform. For IIId and f-k, ion exchange gave a better separation.

EXPERIMENTAL

PMR spectra were taken from a BS-467 Tesla (60 MHz) instrument in $CDCl_3$ or CF_3COOH with HMDS as internal standard. Mass spectra were recorded on a Varian MAT-112 instrument. TLC was performed on 60 F (Merck) aluminum oxide or on Silufol UV-254 (Chemapol) plates. Ion-exchange chromatography was carried out on AGMP-50 (Bio-Rad) resin using an aqueous ammonia gradient.

Properties of compounds III and IV are given in Table 1. Elemental analyses for C, H, and N agreed with those calculated.

N,N',N"-Tritosyl-1,5-diamino-3-azapentane (Ia), N,N',N",N"'-tetratosyl-1,8-diamino-3,6-diazaoctane (Ib), N,N',N"-tritosyl-1,7-diamino-4-azaheptane (Ic), and N,N',N",N"'-tetratosyl-1,10-diamino-4,7-diazadecane (Id) were prepared analogously to [8], 1,3-dibromopropane (IIa) by the method of [9], 1,2-di(p-toluenesulfoxy)ethane (IIb) by the method of [10].

O,O',N-Tritosyldiethanolamine (IIc, $C_{25}H_{29}NO_8S_3$). A. A solution of 57 g (0.3 mole) p-toluenesulfonylchloride in 100 ml anhydrous dioxane was added dropwise with stirring to a solution of 10.5 g (0.1 mole) diethanolamine, 33 g (0.3 mole) anhydrous triethylamine, and 30 ml anhydrous dioxane at 0-5°C. Stirring at 20°C was continued for 3-5 h. The reaction mixture was poured into ice water (500 g) and stirred until the product crystallized. The solid was filtered, washed with water, dried, and recrystallized from ethanol.

B. A solution of 22.9 g (0.12 mole) p-toluenesulfonylchloride in 40 ml methylene chloride was added dropwise at 10-15°C with vigorous stirring to a mixture of 4.2 g (0.04 mole) diethanolamine, 0.4 g triethylbenzylammonium chloride, 30 ml 30% NaOH, and 80 ml methylene chloride. After the p-toluenesulfonylchloride had reacted (4-6 h, monitored by TLC), the mixture was poured into 200 ml water. The organic layer was separated, washed with water, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was recrystallized from ethanol. Yield 80%, mp 98-100°C. PMR spectrum (in $CHCl_3$): 2.35 (9H, s, CH_3); 3.25 (4H, t, NCH_2); 4.01 (4H, t, OCH_2); 7.17-7.80 ppm (12H, m, arom.).

O,O',N,N'-Tetratosyl-N,N'-bis(2-oxyethyl)ethylenediamine (IId, $C_{34}H_{40}N_2O_{10}S_4$) was prepared analogously to IIc by method B. Yield 72%, mp 147-149°C. PMR spectrum (in $CHCl_3$): 2.33 (12H, s, CH_3); 3.20 (8H, m, NCH_2); 3.20 (8H, m, CH); 4.00 (4H, t, OCH_2); 7.10-7.70 ppm (16H, m, arom.).

N-Tosylated Macrocyclic Polyamines (IIIa-k) (general method). A mixture of 25 mole tetrabutylammonium iodide, 200 ml toluene (xylene), and 100 ml 5% NaOH was boiled and 0.02 mole bissulfonamide Ia-d and 0.02 mole alkylating agent IIa-d in 400 ml solvent were added. The mixture was boiled with vigorous stirring for 8-10 h. The precipitate that formed was filtered. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed. The residue was combined with the precipitate and the mixture was boiled with stirring in 200 ml water. The precipitate was filtered off in hot water. The precipitate was then boiled with 500 ml alcohol. The mixture was cooled to 18-20°C. Compounds IIIa-k were filtered off as white powders.

Macrocyclic Polyamines IVa-c and e (general method). A solution of 5 mmole N-tosylated macrocyclic polyamine IIIa-c or e in 20 ml concentrated H_2SO_4 (d = 1.835) was heated at 100-105°C for 30-48 h. After cooling to 0°C, the solution was basicified to pH 10-11 with aqueous NaOH. The salt that precipitated was filtered off. The filtrate was extracted with chloroform (5-8 × 50 ml). The combined extracts were dried over anhydrous Na_2SO_4.

The chloroform was evaporated. The residue was boiled with hexane (3 × 50 ml). The combined hexane extracts were evaporated to yield the macrocyclic polyamines.

Macrocyclic Polyamines IVd and f-k (general method). A solution of 5 mmole N-tosylated macrocyclic polyamine in 30 ml concentrated H_2SO_4 (d = 1.835) was heated at 100-105°C for 50-70 h. After cooling, the solution was poured into 500-700 ml ethanol. The sulfate precipitate that formed was filtered off under nitrogen, washed with ether, dried in vacuum, dissolved in a minimal amount of water, and converted to the base on a column filled with AGMP-1 ion-exchange resin in the OH-form. The residue remaining after removal of solvent from the eluent was dried in vacuum.

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