Preparation of New Macrocyclic Polyamines Containing 4-(Phenylethynyl)pyridine Subunit

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Two new tetraazacycloalkane-*N*-acetic acids containing 4-(phenylethynyl)pyridine subunit as a part of macrocycle have been prepared. Two methods for the cyclisation reaction were investigated.

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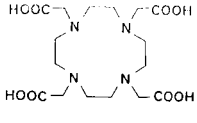
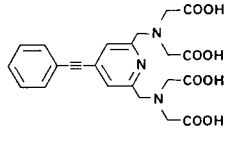
It is known that cyclic 1,4,7,10-tetraazacyclododecane-*N,N'N''N'''*-tetraacetic acid (**I**) and its analogues form quite strong complexes with metal ions [1-6]. The synthesis of the compounds also containing a pyridine subunit as a part of the macrocycle has been reported [4]. Our recent reports describe the preparation of 4-(phenylethynyl)-2,6-bis[*N,N*-bis(carboxymethyl)aminomethyl]pyridine (**II**) and its analogues [7,8].



I



II

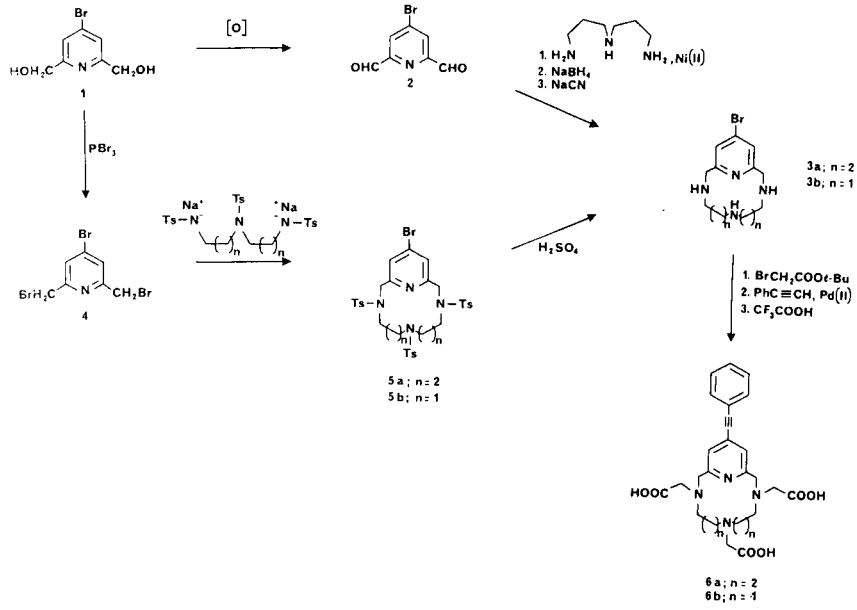
Owing to our interest in the properties of metal complexes of conjugated pyridine structures and because of the good complexing properties of cyclic polyaminocarboxylates, we investigated the synthesis of 15-(phenylethynyl)-3,7,11-tris(carboxymethyl)-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene and 13-(phenylethynyl)-3,6,9-tris(carboxymethyl)-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**6a** and **6b** in Scheme 1).

Results and Discussion.

Two possibilities for the synthesis of the key intermediates **3a** and **3b** were investigated. Firstly, the hydroxy groups of compound **1** [7] were oxidized to the corresponding dialdehyde **2** by dimethyl sulfoxide-oxalyl chloride [9] in high yields. Also selenium dioxide [10] in dioxane was used but the yield was much smaller (5-35% *vs* 79%) with additional isolation problems.

The condensation of 2,6-diformyl- and diacetylpyridine with a suitable polyamine in the presence of a metal cation (template condensation) produces the cyclic diimine complex [10-15]. The Schiff base of nickel(II) and copper(II) complex has been reduced with catalytic hydrogenation [11] or with sodium borohydride [10,15] to the corresponding saturated complex. The free ligand is liberated by treatment with excess sodium cyanide [10,11] or sodium monosulfide [15]. Moore and coworkers [10] have develop-

Scheme 1



ed a method in which these three steps can be made in one pot with good results. Unfortunately when this procedure was used with **2** and bis(3-aminopropyl)amine, the product without a bromogroup dominated over **3a**. The product proportion was 3:1 according to the nmr spectra. The unwanted reaction must be due to the activation ability of nickel(II) cation in the sodium borohydride reduction step because under normal conditions, this reagent does not reduce aromatic bromo groups. For example, **1** is made from the corresponding diester using sodium borohydride [7]. An analogous activation was noticed when we used 4-(phenylethynyl)-2,6-pyridinedicarbaldehyde (**7**) instead of **2**. In that case, the triple bond was reduced to a saturated one. Compound **7** was made from **2** and phenylacetylene in the presence of a small amount of a palladium catalyst and copper(I) iodide [7,8,16-20].

The synthesis *via* the alternative route also starts from **1** which reacted with phosphorus tribromide to produce **4** [7]. This compound reacted with the disodium salt of tosylated bis(3-aminopropyl)amine [21] to yield macrocycle **5a** by using the Richman and Atkins cyclisation procedure [4,22]. This tritosylated cyclic amine was hydrolysed with concentrated sulfuric acid. The free amine **3a** reacted with *t*-butyl bromoacetate in the presence of anhydrous potassium carbonate in acetonitrile to yield the *N*-alkylated product. The bromo group of this compound reacted with phenylacetylene in the presence of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide [7,8,16-20] and finally acid hydrolysis of the resulting ester generated the wanted product **6a**.

It has been reported that the template formation of macrocyclic complexes is not possible with bis(2-aminoethyl)amine [13]. For this reason the smaller macrocycle **3b** was made from **4** and the disodium salt of tosylated bis(2-aminoethyl)amine using the Richman and Atkins cyclisation method and detosylation of **5b** with concentrated sulfuric acid. In further reactions, we did not succeed in the purification of the intermediates. Several attempts to fractionate the products by chromatography on silica gel with various solvent combinations were unsuccessful. For some reason the compounds adsorbed on silica gel and did not move when changing the polarity of the eluent. The size of the cavity may play an important role in that unexpected behaviour. However, we used the same reaction conditions for **3b** as with **3a** without any purification of the intermediate and used crystallization as the purification method of product **6b**.

EXPERIMENTAL

The ir spectra were obtained on neat samples with a Perkin-Elmer 180 spectrometer. The nmr spectra were recorded with a Jeol JNM-GX400 spectrometer in parts per million (δ) downfield from tetramethylsilane. Elemental analysis were performed by Analytical Laboratories, Germany.

Unless specified otherwise, reagent grade reactants and solvents were obtained from chemical suppliers and used as received. Triethylamine and tetrahydrofuran were dried by distillation above sodium and acetonitrile over calcium hydride. 4-Bromo-2,6-pyridinedimethanol (**1**) [7], 4-bromo-2,6-bis(bromomethyl)pyridine (**4**) [7], *N,N',N''*-tritosyl-4-aza-1,7-heptanediamine [21], *N,N'N''*-tritosyl-3-aza-1,5-pentanediamine [23] and their sodium salts [23] were prepared by literature methods.

4-Bromo-2,6-diformylpyridine (**2**).

A solution of dimethyl sulfoxide (3.75 g, 48 mmoles) in dichloromethane (10 ml) was added to a cold (-60°) solution of oxalyl chloride (2.79 g, 22 mmoles) in dichloromethane (10 ml) during 5 minutes. After stirring for 10 minutes at -60°, **1** (2.18 g, 10 mmoles) in dimethyl sulfoxide (5 ml) was added during 5 minutes. After stirring for 20 minutes, triethylamine (28 ml) was added, the reaction mixture was stirred for 5 minutes and then allowed to warm to room temperature. After addition of water (75 ml), the aqueous layer was reextracted with dichloromethane (2 x 100 ml). The combined organic layers were dried with sodium sulfate. Evaporation *in vacuo* left a crude material which was purified by chromatographing on silica gel using dichloromethane as the eluent. The product was crystallized from a mixture of dichloromethane and diethyl ether. The yield was 1.5-1.7 g (69-79%), mp 171.5-172.5°; ir (neat): 2850 cm^{-1} (C-H), 1703 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 8.30 (s, 2H), 10.13 (s, 2H).

Anal. Calcd. for $C_7H_4BrNO_2$: C, 39.29; H, 1.88; N, 6.55; Br, 37.34. Found: C, 39.16; H, 1.79; N, 6.50; Br, 37.24.

4-(Phenylethynyl)-2,6-diformylpyridine (**7**).

A mixture of **2** (1.07 g, 5 mmoles), bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.1 mmole) and copper(I) iodide (38 mg, 0.2 mmole) in dry triethylamine (10 ml) and tetrahydrofuran (30 ml) was deaerated with nitrogen. Phenylacetylene (0.51 g, 5 mmoles) was added to the reaction mixture. After stirring for 4 hours at 65°, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in chloroform (100 ml), washed with water (2 x 20 ml) and dried with sodium sulfate. Evaporation left a crude material which was purified by chromatographing on silica gel using dichloromethane as the eluent. The product was crystallized from a mixture of dichloromethane and diethyl ether. The yield was 0.55-0.67 g (46-64%), mp 116.5-117.5°; ir (neat): 2835 cm^{-1} (C-H), 2220 cm^{-1} (C≡C), 1705 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 7.41-7.60 (m, 5H), 8.21 (s, 2H), 10.17 (s, 2H).

Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.60; H, 3.85; N, 5.96. Found: C, 76.48; H, 3.75; N, 5.88.

15-Bromo-3,7,11-tritosyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**5a**).

The disodium salt of *N,N',N''*-tritosyl-4-aza-1,7-heptanediamine (2.55 g, 4.0 mmoles) was dissolved in *N,N*-dimethylformamide (35 ml) and a solution of **4** (1.37 g, 4.0 mmoles) in *N,N*-dimethylformamide (25 ml) was added at 75° during 1.5 hours. After stirring for 2 hours at 75°, the cooled mixture was poured into ice water (100 ml) with vigorous stirring. The precipitate was filtered and washed with water. After crystallization from ethanol, the yield of product was 1.79-2.66 g (58-86%), mp 187-189°; ir (neat): 1340, 1155 cm^{-1} (SO_2-N); ^1H nmr (deuteriochloroform): δ 1.62 (quin, 4H), 2.42 (s, 3H), 2.45 (s, 6H), 2.83 (t, 4H), 3.24 (t, 4H), 4.24 (s, 4H), 7.29 (d, 2H), 7.35 (d, 4H), 7.59 (d, 2H), 7.71 (s, 2H), 7.72 (d, 4H).

Anal. Calcd. for $C_{34}H_{39}BrN_4O_6S_3$: C, 52.64; H, 5.07; N, 7.22. Found: C, 52.72; H, 5.02; N, 7.18.

13-Bromo-3,6,9-tritosyl-3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),-11,13-triene (**5b**).

Compound **5b** was prepared from the disodium salt of *N,N'N''*-tritosyl-3-aza-1,5-pentanediamine (1.22 g, 2.0 mmoles) and **4** (0.69 g, 2.0 mmoles) in the same manner as **5a** above. After crystallization from ethanol the yield was 1.15-1.21 g (77-81%), mp 255-256°; ir (neat): 1338, 1155 cm^{-1} (SO_2-N); ^1H nmr (deuteriochloroform): δ 2.24 (s, 3H), 2.45 (s, 6H), 2.90 (t, 4H), 3.32 (t, 4H), 4.25 (s, 4H), 7.29 (d, 2H), 7.34 (d, 4H), 7.53 (s, 2H), 7.68 (d, 2H), 7.70 (d, 4H).

Anal. Calcd. for $C_{32}H_{35}BrN_4O_6S_3$: C, 51.40; H, 4.72; N, 7.49. Found: C, 51.64; H, 4.73; N, 7.43.

Detosylation of Compounds **5a** and **5b**.

3,7,11,17-Tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**3a**).

Compound **5a** (2.65 g, 3.4 mmoles) was dissolved in concentrated sulfuric acid (18 ml) and stirred for 8 hours at 105-110°. To a cooled solution ice cold 15% sodium hydroxide solution (200 ml) was added. The mixture was extracted with chloroform (8 x 60 ml). The combined organic phase was dried with sodium sulfate and evaporated *in vacuo*. The residue was a yellowish oil which partly crystallized and was used in the next step without further purification. The yield of crude product was 0.45-0.65 g (48-69%); ^{1}H nmr (deuteriochloroform): δ 1.79 (quin, 4H), 2.66 (t, 4H), 2.81 (t, 4H), 3.26 (broad s, 3H, NH), 3.86 (s, 4H), 7.33 (s, 2H).

Anal. Calcd. for $C_{13}H_{21}BrN_4$: C, 49.85; H, 6.75; N, 17.89. Found: C, 49.68; H, 6.70; N, 17.76.

3,6,9,15-Tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene (**3b**).

The compound **3b** was prepared from **5b** in the same manner as **3a** above. The yield of unpurified product was 0.62-0.85 g (64-88%); ^{1}H nmr (deuteriochloroform): δ 2.41 (t, 4H), 2.79 (t, 4H), 2.85 (broad s, 3H, NH), 3.95 (s, 4H), 7.20 (s, 2H).

Anal. Calcd. for $C_{11}H_{17}BrN_4$: C, 46.33; H, 6.00; N, 19.65. Found: C, 46.31; H, 6.05; N, 19.84.

An Attempt of the Preparation of **3a** from **2**.

Nickel chloride hexahydrate (1.19 g, 5.0 mmoles) was dissolved in ethanol-water (1:1, 30 ml) with bis(3-aminopropyl)amine (0.66 g, 5.0 mmoles). Compound **2** (1.07 g, 5.0 mmoles) was added followed by acetic acid (0.4 ml). After stirring for 2 hours at room temperature and 6 hours at 80° the reaction mixture was cooled (about 0°) in ice. Sodium borohydride (0.76 g, 20.0 mmoles) was added over 30 minutes. The reaction mixture was stirred at room temperature until effervescence ceased and then at 80° for 2 hours. After removing the ethanol *in vacuo* sodium cyanide (2.0 g, 40.8 mmoles) was added and the mixture was stirred for 1 hour at 80°. The cooled solution was extracted with dichloromethane (4 x 25 ml) and dried with sodium sulfate. Evaporation left an oil from which the nmr spectra showed that the product without a bromo group dominated over **3a** (proportion 3:1).

15-(Phenylethynyl)-3,7,11-tris(carboxymethyl)-3,7,11,17-tetraazabicyclo-[11.3.1]heptadeca-1(17),13,15-triene (**6a**).

A solution of **3a** (0.31 g, 1.0 mmole), *t*-butyl bromoacetate (0.59 g, 3.0 mmoles) and potassium carbonate (1.38 g, 10 mmoles) in dry acetonitrile (25 ml) was stirred under a nitrogen atmosphere for 24 hours at room temperature. The mixture was filtered and the filtrate was evaporated *in vacuo*. The oily residue was taken into chloroform (30 ml), washed with water (2 x 10 ml) and dried with sodium sulfate. Evaporation *in vacuo* left a yellow oil which was purified by chromatographing on silica gel using petroleum ether (bp 50-70°)/ethyl acetate (1:1) as the eluent. The yield was 0.26 g (39%); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.26 (quin, 4H), 1.35 (s, 9H), 1.45 (s, 18H), 2.31 (t, 4H), 2.53 (t, 4H), 2.90 (s, 2H), 3.35 (s, 4H), 3.74 (s, 4H), 7.53 (s, 2H). A mixture of this yellowish oil (0.26 g, 0.40 mmole), bis(triphenylphosphine)palladium(II) chloride (7 mg, 0.01 mmole) and copper(I) iodide (4 mg, 0.02 mmole) in dry triethylamine (2.5 ml) and tetrahydrofuran (2.5 ml) was deaerated with nitrogen. Then phenylacetylene (49 mg, 0.48 mmole) was added. After stirring for 24 hours at 45°, the mixture was evaporated *in vacuo*. The residue was dissolved in chloroform (20 ml), washed with water (3 x 5 ml) and dried with sodium sulfate. Evaporation *in vacuo* left a dark oil which was purified by chromatographing on silica gel using petroleum ether (bp 50-70°)/ethyl acetate (5:3) as the eluent. The yield was 0.17 g (63%); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.26 (quin, 4H), 1.34 (s, 9H), 1.46 (s, 18H), 2.32 (t, 4H), 2.54 (t, 4H), 2.90 (s, 2H), 3.37 (s, 4H), 3.77 (s, 4H), 7.40 (s, 2H), 7.47-7.62 (m, 5H). The resulting yellowish oil (0.16 g, 0.24 mmole) was dissolved in trifluoroacetic acid (5 ml) and kept at room temperature for 1.5 hours. Trifluoroacetic acid was evaporated *in vacuo* without heating. The residue was triturated with diethyl ether (15 ml), filtered and finally recrystallized from 2-propanol. The yield was 0.12 g (100%), mp dec >125°; ir (neat): 2215 cm^{-1} (C≡C), 1730, 1680, 1635, 1395, 1200 cm^{-1} (C=O and C-O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.77 (quin, 4H), 2.84 (t, 4H), 3.23 (t, 4H), 3.45 (s, 4H), 3.92 (s, 4H), 4.00 (s, 2H), 7.45-7.62 (m, 7H).

Anal. Calcd. for $C_{27}H_{32}N_4O_6 \cdot xCF_3COOH$: C, 55.95; H, 5.32; N, 9.00. Found: C, 55.56; H, 5.39; N, 8.66.

13-(Phenylethynyl)-3,6,9-tris(carboxymethyl)-3,6,9,15-tetraazabicyclo-[9.3.1]pentadeca-1(15),11,13-triene (**6b**).

The compound **6b** was prepared from **3b** in the same manner as **6a** above. Contrary to **6a**, after the first step the purification by chromatographing on silica gel was not successful and the product was used as such. The final product **6b** was recrystallized twice from 2-propanol. The yield was 74% , mp dec >135°; ir (neat): 2210 cm^{-1} (C≡C), 1725, 1670, 1630, 1395, 1200 cm^{-1} (C=O and C-O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.61 (t, 4H), 3.04 (t, 4H), 3.48 (s, 4H), 4.04 (s, 4H), 4.10 (s, 2H), 7.20-7.78 (m, 7H).

Anal. Calcd. for $C_{25}H_{28}N_4O_6 \cdot xCF_3COOH$: C, 54.55; H, 4.91; N, 9.42. Found: C, 54.17; H, 4.90; N, 9.11.

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