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PREPARATION OF C-ALKYLATED MACROCYCLIC POLYAMINES

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Macrocyclic polyamines have attracted increasing attention because of their unique property to form very stable chelates with various heavy metal ions[1-6]. Unsubstituted macrocyclic tetraamines of different ring size are now readily available by convenient preparations reported recently[7,8]. We also reported that macrocyclic polyamines attached to polystyrene via N-C linkage(from chloromethylated polystyrene and cyclic polyamines) also bound various heavy metal ions very effectively, but, the binding was considerably weakened compared with unsubstituted macrocyclic polyamines. This reduced binding is partly due to the N-alkylation of the polyamines in the polymer, as ascertained by the independent measurements of metal binding rates and equilibria of N-alkylated polyamines which are not attached to polystyrene. These findings reveal that connection of macrocyclic amines via N-alkylation is less appropriate for the preparation of metal binding resins than the alternative, the connection with the polymer via a ring carbon.

In this report, we wish to describe a new synthetic route to 14-membered cyclic tetraamines(7b-e), 1,4,8,11-tetraazacyclotetradecane(7a) skelton bearing substituents on C_6, through an aminolysis of malonates with the polyamine. To be noteworthy is that the cyclized product is obtained predominantly under usual conditions (contentration, solvent, terperature) and is much convenient than the high-dilution technique.

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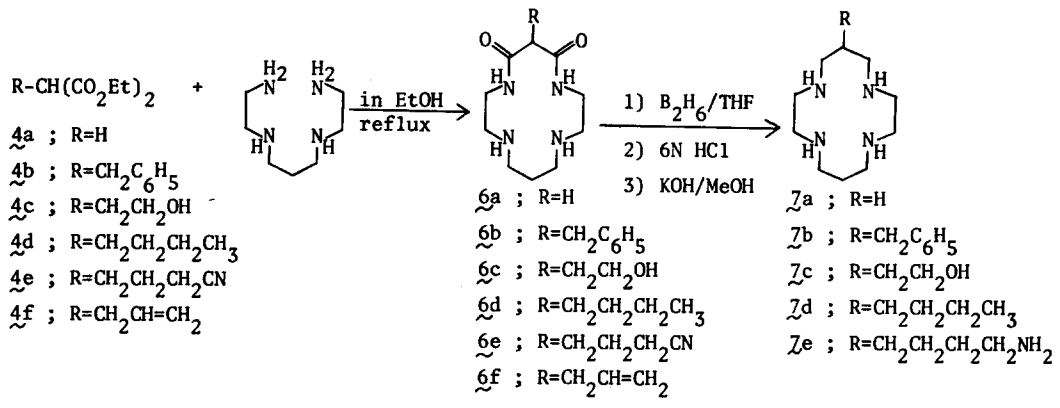

Thus, condensation of 1,3-(2'-aminoethylamino)-propane (5 ; 16.0 g, 0.1 mol) with diethyl malonate(4a ; 16.0 g, 0.1 mol) in ethanol(100 ml) under reflux for 3 days gave 7.0 g (30% isolated yield) of 2,4-dioxo-1,5,8,12-tetraazatetradecane(6a ; 14-N4-diamide), which was isolated through silica gel chromatography eluted with $CHCl_3$-MeOH (5:1); mp 176-177°(recrystallized from EtOH); mass spectrum, m/e 228(M^+), m/e 185(M^+-CONH); NMR(100 MHz, $CDCl_3$) 1.68(multiplet, 2H, C-CH_2-C), 1.82(singlet, 2H, -NH-), 2.70(multiplet, 8H, CH_2-N-CH_2), 3.36(singlet, 2H, CO-CH_2-CO), 3.41(multiplet, 4H, CO-N-CH_2), 7.20(broad, 2H, C-NH-CO); IR(KBr) 3200, 3050, 2950, 2900, 2825, 1480, 1460, 1420, 1160, 1140 and 1100 cm^{-1}.

Cyclic diamide 6a(1.13 g, 5 mmol) thus obtained was smoothly reduced with a large excess of diborane(18 mmol) in refluxing tetrahydrofuran(30 ml) for 24 hr. After treatment with 6N-HCl and KOH/MeOH, the corresponding cyclic tetraamine, 7a was obtained in 80% yield(820 mg); mp 185°(lit[9] 185°, recrystallized from benzene, sublimed at 100°/2mmHg). Yield of 7a was very much reduced when the amide was reduced with lithium aluminum hydride.

The present preparation of cyclic polyamines from malonates has a significant advantage in that any desirable substituent can be introduced on the carbon atom of the macrocyclic polyamine skeleton starting from corresponding substituted malonates. Thus, benzyl, hydroxymethyl, butyl, ω-cyanopropyl and allyl groups were successfully introduced to the 3-position of the cyclic tetraamide skeleton, 6b-f, and the subsequent reduction with diborane afforded the corresponding cyclic amines, 7b-d, except ω-cyano-

propyl derivative, 6e, in which the cyano group was reduced simultaneously to give rise to the ω-aminobutyl derivative, 7e. Physical and spectral properties of the macrocyclic amides(6b–f) and amines(7b–e) thus obtained are summarized in Table I and Table II.

A variety of macrocyclic tetraamines having various functional groups at remote position are also readily available starting from 6c, 6e, 6f or 7c, 7e. Detailed analysis of the metal binding is now in progress.

Table I. Physical and Spectral Properties of the Macrocyclic Amides (6b–e)

amide	reaction time (day)	mp(°C)	yield[a] (%)	elemental analysis calcd.(%) (found.(%)) C	H	N	NMR(100 MHz, $CDCl_3$ or D_2O) δ(ppm)
6b (colorless prisms)	3	225-228	25	64.12 (63.92)	8.23 (8.33)	17.60 (17.53)	7.20(s, 5H); 7.00(broad, 2H); 3.60-3.00(m, 5H); 3.20(s, 2H); 2.80-2.50(m, 8H); 1.70(s, 2H); 1.60(m, 2H)
6c (colorless prisms)	3	200-201	40	52.92 (52.87)	8.88 (8.99)	20.57 (20.44)	3.80(m, 7H); 2.80-2.56(m, 8H); 2.08(m, 2H); 1.70(q, 2H, J=6 Hz)
6d (colorless prisms)	4	215-217	25	59.12 (58.73)	9.92 (9.97)	19.70 (19.64)	3.60(m, 2H); 3.20(m, 3H); 2.70(m, 8H); 1.75(m, 4H); 1.30(m, 4H); 0.85(t, 3H, J=6 Hz)
6e (colorless prisms)	4	178-180	30	56.92 (57.00)	8.53 (8.68)	23.71 (23.70)	7.50(broad, 2H); 3.60-3.05 (m, 5H); 2.70(m, 8H); 2.41(t, 2H, J=6 Hz); 2.41(s, 2H); 2.00(m, 2H); 1.70(m, 4H)
6f (colorless prisms)	4	216-218	25	58.18 (58.05)	9.02 (9.15)	20.88 (20.77)	5.70(m, 2HO; 5.18(d, 2H, J=16 Hz); 3.90-3.30(m, 5H); 3.05(m, 8H); 2.59(t, 2H, J=6 Hz); 1.82(m, 2H)

a) based on 5

Table II. Physical and Spectral Properties of the Macrocyclic Amines (7b-e)

amine	mp(°C)	yield(%)[a]	NMR(100 MHz, $CDCl_3$) δ(ppm)	mass(m/e)
7b (colorless needles)	155-156	65	7.20(m, 5H); 2.20(s, 4H); 2.90-2.40(m, 19H); 1.70(q, 2H, J=6 Hz)	290(M^+) 216($M^+-C_3H_{10}N_2$)
7c (colorless needles)	116-118	55	3.64(t, 2H, J=6 Hz); 2.74(m, 17H); 3.10(s, 5H); 1.72(m, 4H)	244(M^+) 170($M^+-C_3H_{10}N_2$)
7d (colorless needles)	138-140	60	2.90-2.35(m, 17H); 1.72(q, 2H, J=6Hz); 2.24(s, 4H)	256(M^+) 182($M^+-C_3H_{10}N_2$)
7e (colorless needles)	132-133	70	2.90-2.50(m, 5H); 1.72(q, 2H, J=6 Hz); 2.30(s, 6H); 1.36(m, 6H)	271(M^+) 197($M^+-C_3H_{10}N_2$)

a) Based on cyclic amides (6b-e) used.

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