The Synthesis of Macrocyclic Polyether-Diesters Incorporating 1,10-Phenanthrolino and 1,8-Naphthyridino Subunits

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The preparation of a series of macrocycles, formed by reaction of HO-(-CH_2-CH_2-O-)$_n$H with 1,10-phenanthroline-2,9-dicarbonyl chloride (n = 2,3,4) and 1,8-naphthyridine-2,7-dicarbonyl chloride (n = 3,4), is described. An improved synthetic route to 2,7-dimethyl-1,8-naphthyridine **9** is also reported.

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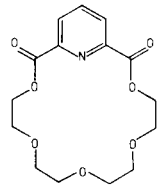
Since the discovery of cyclic polyethers and their cation complexing ability (1), there has been much interest in the synthesis of modified structures with cation selective properties. This is a feature of certain natural macrocyclic antibiotics. In particular, a number of these antibiotics contain carbonyl functions in the macrocycle (2) and it has been noted that modification of a synthetic crown ether structure to a polyether-diester results in a change in cation selectivity (3).

The incorporation of a heterocyclic subunit into the macrocycle has also been much studied (4) and the first combination of pyridine, ester, and polyether (**1**) has been synthesized only recently (5) (6). The presence of the pyridine nitrogen again modifies the complexing properties (7) and **1** is particularly interesting because of its affinity for K^+ over Ba^{2+}, a feature which distinguishes the behaviour of some natural macrocycles (3).



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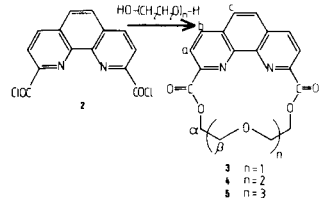
We wished to extend this class of compounds to diaza heterocycles which are good complexing agents in their own right, and report here the synthesis of the first polyether-diester macrocycles incorporating 1,10-phenanthrolino and 1,8-naphthyridino subunits. The first macrocycles containing the 1,8-naphthyridino entity, which contain the polyether chain but not the carbonyl function, have recently been reported (8).

1,10-Phenanthroline.

The starting point for these syntheses was 1,10-phenanthroline-2, 9-dicarboxylic acid (9) which was converted to the acid chloride **2** with thionyl chloride. This compound was not obtained in an analytically pure state. Reaction with the appropriate anhydrous glycol in hot toluene in moderate conditions readily afforded the macrocycles **3-5** in reasonable yield. Compound **4** was obtained as a monohydrate. The structures were assigned on the basis of microanalytical and spectral data. In particular, the mass spectra contained peaks for the appropriate molecular ions which excluded the possibility that the macrocycles were dimeric species.

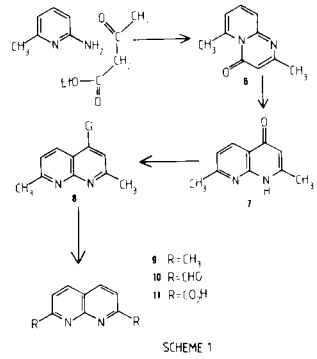


2 3 n=1 4 n=2 5 n=3

The nmr spectra were simple, due to the symmetry in the molecules. The ^1H nmr pattern for the aromatic protons comprised an AB system for Ha,b and a singlet for Hc while the bridging chain gave rise to a series of multiplets for Hα,β, etc., in this order from lowest to highest field (6). Proton decoupled ^{13}C nmr spectra were also obtained and assignments of the aromatic carbon signals were made as previously (9). The methylene carbon resonances were assigned from selective frequency on-resonance decoupling experiments; the ^{13}C signals were monitored while irradiating at a series of frequencies covering the various protons signals. It was of interest to find that the order of methylene carbon resonances was opposite to that for the analogous protons, *i.e.*, the C-α signal was at highest field.

1,8-Napthyridine.

For an analogous synthetic sequence, it was necessary to obtain a substantial amount of 2,7-dimethyl-1,8-naphthyridine. This compound had been prepared previously by a Skraup reaction on 6-methyl-2-pyridinamine (10) but the



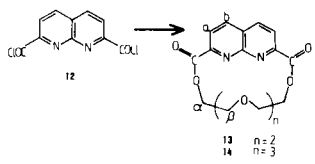
9 R=CH_3 10 R=CHO 11 R=CO_2H

SCHEME 1

reaction gives a low yield and isolation of the product is difficult. We therefore devised a better preparation, utilising some known reactions (Scheme 1).

In the condensation reaction between 6-methyl-2-pyridinamine and ethyl acetoacetate with polyphosphoric acid, ring formation occurs onto the ring nitrogen of the pyridine to give **6** (11). This kinetically favored product was then thermally isomerized at 350° to the desired ring system **7** (12). Reaction of **7** with phosphorus oxychloride gave the chloronaphthyridine **8**, which in turn was hydrogenolyzed over palladium on calcium carbonate to the dimethylnaphthyridine **9**. Though this is a multistep procedure, the overall yield (35%) is somewhat better than from the Skraup reaction, and there is the decided advantage that all steps are experimentally straightforward and can be run on any desired scale.

Oxidation of **9** to the dialdehyde **10** with selenium dioxide in dioxan was achieved in 59% yield. This oxidation had previously been carried out in aqueous dioxan (13) and omission of the water improves the ease of preparation and the yield. Further oxidation to the diacid **11** was carried out with nitric acid and the acid chloride **12** was prepared as for the phenanthroline analog.



12 **13** n = 2, **14** n = 3

Reaction with the appropriate glycol, as before, gave the macrocycles **13** and **14**. Through replacement of the phenanthroline by the naphthyridine subunit reduces the ring size by only one atom, the more elongated arrangment of relevant atoms in the latter requires a longer chain length to bridge the 2,7-positions. Consequently, it was not possible to obtain the desired product (*i.e.*, structure **13** where n = 1) from the reaction with diethylene glycol and only polymeric material resulted. It is interesting that reaction to form **13** was so readily achieved as a CPK molecular model reveals that the alkyl chain is positioned very close to the ring nitrogens.

Structural assignments for these two compounds were based on the same analytical and spectral data as for the phenanthroline analogs. The ^{1}H nmr spectra were as expected with the same trend in chemical shift for the various methylene protons though, for **14**, the β, λ, and δ signals were not clearly separated. In the ^{13}C nmr spectra, the aromatic carbons were assigned by reference to published figures for 1,8-naphthyridine (14), and the methylene carbons by the decoupling technique used for the phenanthroline compounds. For **14**, this resulted in the most downfield signal being assigned to C-β rather than C-δ. There is considerable doubt about this since, for **14** where the proton signals were not separated, it is not certain that the protons were irradiated in sequence δ, λ, β as the decoupling frequency was moved through this group from high to low field.

In this work we have established the minimium size of the macrocyclic polyether-diesters that can be made from these two heterocyclic subunits. The upper limit on ring size has not been investigated and we also intend to study the metal complexing abilities of these compounds.

EXPERIMENTAL

Mass spectra were obtained at 75 eV and infrared spectra as potassium bromide discs. Samples of the macrocycles for microanalysis were dried at 100°/1 mm. Melting points are uncorrected.

1,10-Phenanthroline-2,9-dicarbonyl Chloride (**2**).

1,10-Phenanthroline-2,9-dicarboxylic acid (**9**) (2.2 g) in redistilled thionyl chloride (50 ml) was heated under reflux for 2 hours. The solution was then filtered while hot and the solvent was evaporated *in vacuo* to give **2** (1.9 g, 76%) as a yellow solid, mp 227-228° dec (toluene); ir: 1760 cm^{-1}; ms: m/e (%) 309 (2), 307 (13), 305 (20), 178 (100); ^{1}H nmr (DMSO-d$_6$): δ 8.2 (s, H-5,6, 2H), 8.43 (d, H-3,8, 2H, $J_{3,4}$ = 9 Hz), 8.77 (d, H-4,7, 2H); ^{13}C nmr (DMSO-d$_6$): δ 123.4 (C-3), 128.3 (C-5), 130.5 (C-4a), 138.4 (C-4), 144.2 (C-10b), 147.9 (C-2), 165.8 (C=O).

2,6-Dimethylpyrido[1,2-*a*]pyrimidin-4-one (**6**).

Polyphosphoric acid (65 g) was added to 6-methyl-2-pyridinamine (10.8 g) and ethyl acetoacetate (14.5 g) and the mixture was heated, with stirring, at 100° for 1.25 hours. The viscous mixture was cooled and neutralized with 4*M* sodium hydroxide solution. The solid which separated was filtered and the filtrate was extracted twice with dichloromethane. The original solid product was dissolved in the combined dichloromethane extracts and the solution was dried (magnesium sulfate) and concentrated to give the crude product (9.5 g, 60%), sufficiently pure for the next step. A sample, when recrystallized from light petroleum, had mp 105° [lit (11) mp 105°].

2,7-Dimethyl-1,8-naphthyridin-4(1*H*)-one (**7**).

Liquid paraffin (200 ml) in a 500 ml round-bottom flask was heated to 350° on a heating mantle. The solid **6** (10 g) was added in small portions and the oil was maintained at 350° for 0.5 hour after the addition was complete. To the cooled mixture was added light petroleum (bp 40-70°) (200 ml) and the brown solid was filtered and washed with benzene to give the product (7.5 g, 75%), mp 320° [lit (12) mp 320°].

4-Chloro-2,7-dimethyl-1,8-naphthyridine (**8**).

A mixture of **7** (8.0 g) in phosphorus oxychloride (25 ml) was heated over the range 90-130° during 30 minutes. The solution was then cooled, cautiously poured onto ice, made slightly basic with 30% sodium hydroxide solution (if salts separated at this point they were filtered and washed with chloroform) and extracted three times with chloroform. The dried (magnesium sulfate) extracts were concentrated and the brown residue was suction filtered through silica gel (40 g) using 1:1 dichloromethane/ethyl acetate (500 ml) as eluent. Evaporation of the solvent gave **8** (7.5 g, 85%), mp 83° (light petroleum); ^{1}H nmr (deuteriochloroform): δ 2.75 (s, CH$_3$, 3H), 2.79 (s, CH$_3$, 3H), 7.30 (d, H-6, 1H, $J_{5,6}$ = 8 Hz), 7.32 (s, H-3, 1H), 8.30 (d, H-5, 1H); ^{13}C nmr (deuteriochloroform): δ 24.86 (CH$_3$), 24.9 (CH$_3$), 116.9 (C-4a), 121.9 (C-6), 123.2 (C-3), 132.7 (C-5), 141.1 (C-4), 155.3 (C-8a), 162.2 (C-7), 163.2 (C-2).

Anal. Calcd. for $C_{10}H_9ClN_2$: C, 62.3; H, 4.7; N, 14.5. Found: C, 62.1; H, 4.9; N, 14.4.

2,7-Dimethyl-1,8-naphthyridine (**9**).

A solution of **7** (3.5 g) in 2.5% methanolic potassium hydroxide (100 ml) was hydrogenated at atmospheric pressure, over 5% palladium on calcium carbonate (0.7 g). The catalyst was filtered off and the filtrate

was evaporated. The residue was taken up in dichloromethane (50 ml) and this was washed with water, dried, and concentrated to give the product (2.6 g, 92%), mp 193-194° (cyclohexane) [lit (13) mp 194-195°].

1,8-Naphthyridine-2,7-dicarboxaldehyde (**10**).

Compound **9** (4 g) was added in one portion to a refluxing mixture of selenium dioxide (9 g) and 1,4-dioxan (300 ml). The heating was continued for 3 hours, the mixture was filtered while hot, and the filtrate was concentrated *in vacuo* to *ca.* 200 ml. Dichloromethane (200 ml) was added and the solution was extracted with water (2 × 150 ml). The aqueous extracts were further extracted with dichloromethane (2 × 150 ml). The combined organic fractions were dried and the solvent evaporated to give the dialdehyde (2.8 g, 59%) as a light brown solid, mp 224-225° (ethyl acetate) [lit (14) mp 225-227°]; ir: 1720 cm^{-1}; ^1H nmr (DMSO): δ 8.21 (d, H-3,6, 2H, $J_{3,4}$ = 8 Hz), 8.85 (d, H-4,5, 2H), 10.21 (s, CHO, 2H).

1,8-Naphthyridine-2,7-dicarboxylic Acid (**11**).

A solution of the dialdehyde (**10**) (2 g) in 80% nitric acid (50 ml) was heated under reflux for 3 hours. The resulting pale yellow solution was cooled and poured onto ice. The diacid (1.5 g, 65%) was obtained as a yellow solid, mp 242° dec (methanol); ir: 3250-2800, 1710 cm^{-1}; ms: m/e (%) 218 (2), 216 (28), 199 (100); ^1H nmr (DMSO-d_6): δ 8.28 (d, H-3,6, 2H, $J_{3,4}$ = 9 Hz), 8.76 (d, H-4,5, 2H); ^{13}C nmr (DMSO-d_6): 122.8 (C-3), 124.9 (C-4a), 139.3 (C-4), 152.5 (C-2), 153.6 (C-8a), 165.8 (C=O).

Anal. Calcd. for $C_{10}H_6N_2O_4$: C, 55.1; H, 2.8; N, 12.8. Found: C, 55.1; H, 2.9; N, 12.8.

1,8-Naphthyridine-2,7-dicarbonyl Chloride (**12**).

This compound was prepared as for **2**, in 57% yield and had mp 196-198° dec (benzene); ir: 1760 cm^{-1}; ms: m/e (%) 258 (1), 256 (6), 254 (10), 191 (100); ^1H nmr (DMSO-d_6): δ 8.25 (d, H-3,6, 2H, $J_{3,4}$ = 9 Hz), 8.75 (d, H-4,5 2H); ^{13}C nmr (DMSO-d_6): δ 122.9 (C-3), 125.0 (C-4a), 139.4 (C-4), 152.4 (C-2), 153.6 (C-8a), 165.7 (C=O).

Anal. Calcd. for $C_{10}H_4Cl_2N_2O_2$: C, 47.1; H, 1.6; N, 11.0. Found: C, 47.2; H, 1.7; N, 11.3.

Macrocycle Formation.

To a refluxing solution of the appropriate acid chloride in dry toluene (350 ml/mmole) was added, dropwise during 0.5 hour, a solution of the redistilled glycol (equimolar) in dry toluene (40 ml/mmole). Heating was continued for a further 4 hours (7 hours for **13**). The solution was then allowed to cool and was filtered. The filtrate was concentrated *in vacuo* and the residue was recrystallized to give the macrocycle. The following were prepared in this manner:

3,6,9-Trioxa-20,23-diazatetracyclo[9.8.4.$0^{14,22}$.$0^{17,21}$]tricosa-11,13,15,-17,19(1),20,22-heptaene-2,10-dione (**3**).

This compound was obtained in a yield of 43%, mp 230-231° (toluene); ms: m/e (%), 338 (6), 337 (8), 336 (14), 177 (100); ^1H nmr (DMSO-d_6): δ 3.95 (m, CH_2-β, 4H), 4.55 (m, CH_2-α, 4H), 8.10 (s, Hc, 2H), 8.2 (d, Ha, 2H, $J_{a,b}$ = 9 Hz), 8.6 (d, Hb, 2H); ^{13}C nmr (DMSO-d_6): δ 64.9 (C-α), 69.7 (C-β), 121.8 (Phen-C3), 127.9 (Phen-C5), 129.1 (Phen-C4a), 137.0 (Phen-C4), 143.9 (Phen-C10b), 147.0 (Phen-C2), 164.6 (C=O).

Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.9; H, 4.1; N, 8.3. Found: C, 63.6; H, 4.4; N, 8.1.

3,6,9,12-Tetraoxa-23,26-diazatetracyclo[12.8.4.$0^{17,25}$.$0^{20,24}$]hexacosa-14,16,18,20,22(1),23,25-heptaene-2,13-dione (**4**).

This compound was obtained in a yield of 56% as a monohydrate, mp 200-201° (ethanol-light petroleum); ms: m/e (%) 382 (6), 381 (25), 179 (100); ^1H nmr (DMSO-d_6): δ 3.45 (s, H_2O, 2H), 3.75 (s, CH_2-γ, 4H), 3.85 (m, CH_2-β, 4H), 4.40 (m, CH_2-α, 4H), 8.2 (s, Hc, 2H), 8.45 (d, Ha, 2H, $J_{a,b}$ = 9 Hz), 8.75 (d, Hb, 2H); ^{13}C nmr (DMSO-d_6): 65.7 (C-α), 67.8 (C-β), 69.6 (C-γ), 123.7 (Phen-C3), 128.7 (Phen-C5), 130.6 (Phen-C4a), 138.0 (Phen-C4), 144.8 (Phen-C10b), 147.5 (Phen-C2), 165.8 (C=O).

Anal. Calcd. for $C_{20}H_{20}N_2O_7$: C, 60.0; H, 5.0; N, 7.0. Found: C, 59.8; H, 5.0; N, 6.9.

3,6,9,12,15-Pentaoxa-26,29-diazatetracyclo[15.8.4.$0^{20,28}$.$0^{23,27}$]nonacosa-17,19,21,23,25(1),26,28-heptaene-2,16-dione (**5**).

This compound was obtained in a yield of 52%, mp 189-190° (methanol); ms: m/e (%) 426 (63), 178 (100); ^1H nmr (DMSO-d_6): δ 3.55 (m, CH_2-δ,γ, 8H), 3.75 (m, CH_2-β, 4H), 4.44 (m, CH_2-α, 4H), 8.0 (s, Hc, 2H), 8.21 (d, Ha, 2H, $J_{a,b}$ = 9 Hz), 8.54 (d, Hb, 2H); ^{13}C nmr (DMSO-d_6): 65.6 (C-α), 68.6 (C-β), 70.4 (C-γ), 70.4 (C-δ), 123.7 (Phen-C3), 128.5 (Phen-C5), 130.6 (Phen-C4a), 137.9 (Phen-C4), 144.8 (Phen-C10b), 147.9 (Phen-C2), 165.9 (C=O).

Anal. Calcd. for $C_{22}H_{22}N_2O_7$: C, 62.0; H, 5.2; N, 6.6. Found: C, 61.6; H, 5.2; N, 6.5.

3,6,9,12-Tetraoxa-20,22-diazatricyclo[12.5.3.$0^{17,21}$]docosa-14,16,18,1(20),-21-pentaene-2,13-dione (**13**).

This compound was obtained in a yield of 35%, mp 204-205° (toluene); ms: m/e (%) 333 (24), 332 (100), 130 (92), 129 (68), 128 (96); ^1H nmr (DMSO-d_6): δ 3.95 (s, CH_2-γ, 4H), 4.00 (m, CH_2-β, 4H), 4.45 (m, CH_2-α, 4H), 8.15 (d, Ha, 2H, $J_{a,b}$ = 9 Hz), 8.75 (d, Hb, 2H); ^{13}C nmr (DMSO-d_6): 67.6 (C-α), 68.9 (C-β), 70.1 (C-γ), 122.9 (Naph-C3), 124.8 (Naph-C4a), 139.3 (Naph-C4), 151.3 (Naph-C2), 152.0 (Naph-C8a), 165.2 (C=O).

Anal. Calcd. for $C_{16}H_{16}N_2O_6$: C, 57.8; H, 4.9; N, 8.4. Found: C, 57.7; H, 5.0; N, 8.2.

3,6,9,12,15-Pentaoxa-23,25-diazatricyclo[15.5.3.$0^{20,24}$]pentacosa-17,19,-21,1(23),24-pentaene-2,16-dione (**14**).

This compound was obtained in a yield of 69%, mp 176-177° (ethanol); ms: m/e (%) 377 (23), 376 (100), 128 (71); ^1H nmr (DMSO-d_6): δ 3.6-4.0 (m, CH_2-δ,γ,β, 12H), 4.50 (m, CH_2-α, 4H), 8.26 (d, Ha, 2H, $J_{a,b}$ = 9 Hz), 8.74 (d, Hb, 2H); ^{13}C nmr (DMSO-d_6): δ 66.0 (C-α), 68.4 (C-γ), 69.5 (C-δ), 70.8 (C-β), 122.4 (Naph-C3), 125.3 (Naph-C4a), 139.3 (Naph-C4), 151.2 (Naph-C2), 153.2 (Naph-C8a), 164.7 (C=O).

Anal. Calcd. for $C_{18}H_{20}N_2O_7$: C, 57.4; H, 5.4; N, 7.4. Found: C, 57.4; H, 5.5; N, 7.3.

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