

S. Auricchio, A. Ricca and O. Vajna de Pava

Istituto di Chimica del Politecnico di Milano, Italy

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A series of macrocyclic-acyclic ether-ester compounds containing the isoxazole ring has been prepared by treating various dihydroxy compounds with 3,5-isoxazoledicarbonyl chloride.

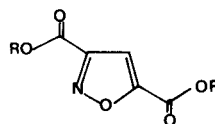
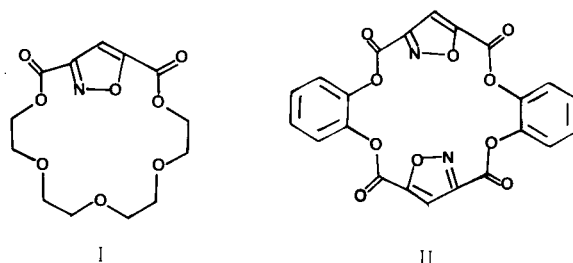
J. Heterocyclic Chem., **18**, 1471 (1981).

Recently many new and interesting cyclic di- and tetra-ester compounds have been prepared to compare the metal complexation properties of synthetic macrocyclic multidentate compounds with those of naturally occurring macrocyclic antibiotics (1-2). In this paper we report the attempts to synthesize a new series of macrocyclic ligands containing one or two isoxazole subcyclic units (I and II).

Compounds I and II were prepared from the 3,5-isoxazoledicarbonyl chloride: compound I is formed by the reaction of dicarbonyl chloride and tetraethylene glycol, ratio 1:1, in benzene solution with appropriate dilution, yield 16%; compound II is formed when isoxazoledicarbonyl chloride reacts with catechol, yield 5%. Compound II might be a mixture of positional isomers depending on cyclisation. On the other hand, the properties of cyclic crown ethers are approximated by acyclic ligands, which often have greater versatility than their cyclic counterparts (3). With this aim in mind, we synthesized two acyclic diesters containing one isoxazole ring (III and IV). Compound III was obtained by the reaction of 3,5-isoxazoledicarbonyl chloride and tetraethylene glycol, ratio 1:2, in a concentrated benzene solution, yield 70%. When 3,5-isoxazoledicarbonyl chloride reacts with 1,12-dodecanediol in dilute solution, only compound IV is obtained and we were unable to evidence the presence of macrocyclic structures.

The proposed structures are consistent with data derived from ir, nmr, mass spectra and combustion analysis. The ir spectra of compounds exhibit carbonyl bands at 1740-1770 cm^{-1} as expected for esters. The nmr spectra of all compounds exhibit peak at 7.4 ± 0.1 for isoxazole hydrogen. Compounds I and III show typical polyether diester peaks at 4.50 ± 0.13 (COOCH_2), 3.87 ± 0.04 ($\text{COOCH}_2\text{CH}_2\text{O}$) and 3.70 ± 0.2 (ether OCH_2). The mass spectra of all compounds show the molecular ion. Work is now in progress to determine the complexation properties of these compounds.

We wish to remember that the incorporation of β -diketone units into multi-heteromacrocycles has been object of a previous research (4) and the isoxazole ring can be considered as a masked β -diketone (5). One of our objectives is to prepare a series of multidentate compounds containing β -diketone units.

III R = $\text{CH}_2(\text{CH}_2\text{OCH}_2)_3\text{CH}_2\text{OH}$ IV R = $\text{CH}_2(\text{CH}_2)_{10}\text{CH}_2\text{OH}$

EXPERIMENTAL

All ir spectra were obtained on a Perkin-Elmer model 137 spectrometer. All nmr spectra were obtained on a Varian EM-390 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Melting points are uncorrected. Mass spectra were taken on a Hitachi-Perkin-Elmer RMU 6D single focusing spectrometer.

3,5-Isoxazoledicarbonylic Acid.

Glyoxylic acid, chloro, ethyl ester oxime (17 g 0.11 mole) and triethylamine (17 g 0.12 mole) each dissolved in 100 ml of dry ethyl ether, were simultaneously and slowly added under stirring to propionic acid (8 g, 0.01 mole). After one day at room temperature, water was added and ether extraction was performed. The extract was dried over sodium sulfate and the solvent was evaporated. The crude solid obtained was refluxed with diluted hydrochloric acid for one day. After evaporation of the solution under vacuum a solid was obtained. Crystallization from ethanol/water gave a crystalline product mp 213° (6).

3,5-Isoxazoledicarbonyl Chloride.

A mixture of 3,5-isoxazoledicarbonylic acid (1.5 g, 0.01 mole), thionyl chloride (16 g, 0.1 mole) and *N,N*-dimethylformamide (0.5 g) was heated at 60° for five hours. The excess of thionyl chloride was removed under reduced pressure and the crude diacid chloride obtained was not purified prior to use (6).

3,6,9,12,15,19-Hexaoxa-18-azabicyclo[15.2.1]eicosa-1(20),17-diene-2,16-dione (I).

3,5-Isoxazoledicarbonyl chloride (3.8 g, 0.02 mole) and tetraethylene glycol (3.88 g, 0.02 mole) each dissolved in 100 ml of dry benzene were simultaneously dripped into 500 ml of rapidly stirring benzene at reflux. After the reaction was complete, solvent was removed under reduced

pressure. The crude product was extracted with boiling hexane and a crystalline product was obtained (1 g, 16%). Recrystallization from ethanol gave white crystals, mp 132°; ir (Nujol): 1740 cm^{-1} ; nmr: δ ppm 7.50 (s, 1H); 4.47 (m, 4H); 3.87 (m, 4H); 3.73 (m, 8H); ms: m/e 316 (M^+ , 1), 272 (12), 288 (32), 184 (24), 111 (100).

Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}_8$: C, 49.52; H, 5.44; N, 4.44. Found: C, 49.60; H, 5.37; N, 4.43 (7).

3,10,13,17,24,28-Hexaoxa-14,27-diazapentacyclo[26.2.1.1^{12,15}.0^{4,9}.0^{18,23}]-triaconta-1(29),4,6,8,12(30),14,18,20,22,26-decaene-2,11,16,25-tetraone (II).

3,5-Isoxazoledicarbonyl chloride (1.9 g, 0.01 mole) was dissolved into 150 ml of anhydrous benzene. Pyrocatechol (0.8 g, 0.01 mole) and pyridine (1.2 g, 0.02 mole) were dissolved in 200 ml of dry benzene. Solutions of diacid and catechol/pyridine were dripped simultaneously into 500 ml of boiling benzene. After the reaction was complete, solid pyridine hydrochloride was removed and benzene was distilled under reduced pressure. The crude product obtained (0.1 g, 5%) was crystallized from methanol, mp 230°, yield 5%; ir (Nujol): 1770 cm^{-1} ; ms: m/e 462 (M^+ , 52), 203 (28), 201 (25), 187 (16), 80 (100).

Anal. Calcd. for $\text{C}_{22}\text{H}_{10}\text{N}_2\text{O}_{10}$: C, 57.15; H, 2.18; N, 6.05. Found: C, 57.25; H, 2.15; N, 6.08.

Di-(13-hydroxy-3,6,8,11-tetraoxatridec-1-yl)3,5-isoxazoledicarboxylate (III).

3,5-Isoxazoledicarbonyl chloride (0.6 g, 0.03 mole) dissolved in 50 ml of dry benzene was dripped into 0.006 mole of tetraethylene glycol in benzene. After chromatographic purification on silica gel with chloroform, compound III was obtained as an oil, yield 70%; ir: 1740 cm^{-1} ; nmr: δ ppm 7.37 (s, 1H), 4.53 (m, 4H), 3.83 (m, 4H), 3.71 (m, 24H); ms: m/e 509 (M^+ , 1H), 378 (3), 272 (5), 155 (80), 140 (100).

Anal. Calcd. for $\text{C}_{21}\text{H}_{35}\text{O}_{13}\text{N}$: C, 49.50; H, 6.92; N, 2.75. Found: C, 49.40; H, 6.89; N, 2.73.

Di(12-hydroxydodecyl)3,5-isoxazoledicarboxylate (IV).

3,5-Isoxazoledicarbonyl chloride (0.01 mole) dissolved into 100 ml of dry benzene and 1,12-dodecanediol (0.01 mole) dissolved into 200 ml of tetrahydrofuran were simultaneously added to 500 ml of boiling benzene. After the reaction was complete, solvent was removed under vacuum. The crude solid was purified by chromatography on silica gel with chloroform and crystallized from ethanol mp 83°, yield 10%; ir (Nujol): 1730 cm^{-1} ; nmr: 7.30 (s, 1H), 4.40 (m, 4H), 3.6] (m, 4H), 1.33 (m, 40H); ms: m/e 525 (M^+ , 1), 324 (5), 296 (9), 266 (14); 55 (100).

Anal. Calcd. for $\text{C}_{22}\text{H}_{51}\text{NO}_7$: C, 66.25; H, 9.78; N, 2.66. Found: C, 66.15; H, 9.69; N, 2.62.

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- (6) Very low yields were obtained using the methods reported for the synthesis of 3,5-isoxazoledicarboxylic acid and 3,5-isoxazoledicarbonyl chloride, C. Musante, *Gazz. Chim. Ital.*, **72**, 134 (1942).
- (7) Molecular weight determined by osmometry is in good agreement with the assigned structure for compound I.