Synthesis of a Simple Model of Nactin Antibiotics

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Summary A macrocyclic compound, belonging to the 32-crown-8-tetraester family, a model for the ionophore antibiotics of the nactin series (three-carbon bridges between the oxygen atoms), has been synthesised in excellent yield.

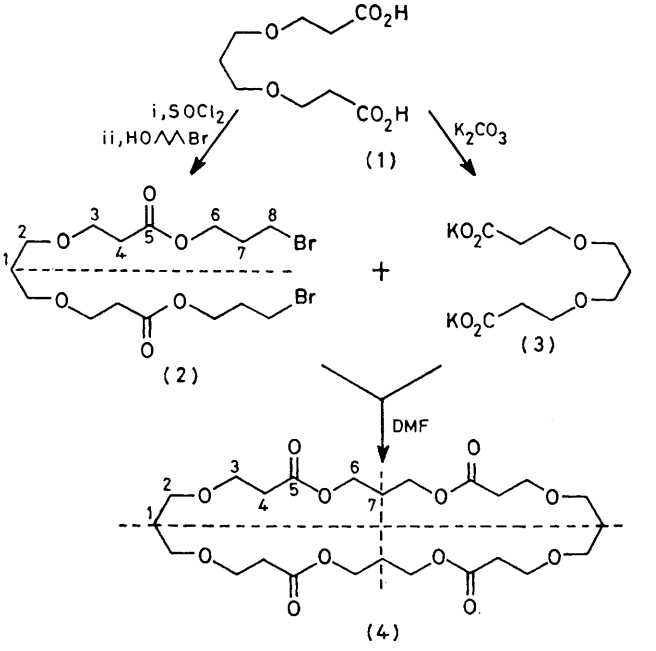
THE natural antibiotics of the nactin series are macrocyclic compounds acting on the permeability of cellular membranes (ionophores);[1] they contain eight oxygen atoms linked by three-carbon bridges, four of the eight cyclic oxygen atoms belong to the ester groups, while the remaining four are ether-type oxygens. The common crown ethers ($-OCH_2CH_2-$ units) have, qualitatively but not quantitatively, the same complexation properties as the ionophore antibiotics, towards alkaline and alkaline-earth cations.

There are few examples of crown ethers in which the oxygen atoms are linked by three-carbon bridges.[2] Recently, a new class of macromolecular polyethers, di- or tetraesters, has been prepared,[3] in which the main ring, formed by the normal $(-OCH_2CH_2-)_n$ sequence, includes one or more diester units (oxalic or malonic derivatives).

We describe here a simple and high yield synthesis of a new macrocyclic compound of the 32-crown-8-tetraester class, the structure of which is closely related to that of nactin antibiotics.

The diacid (**1**) was obtained by adding propane-1,3-diol to two molecules of acrylonitrile[4] followed by acid hydrolysis.[5] The dibromoester (**2**) was obtained in 80% yield by condensing the acid chloride of (**1**) with 3-bromopropan-1-ol in pyridine at -5 °C. Distillation of (**2**) was impossible and the crude product (95% purity) was used for the final stage.

Dibromoester (**2**): formula $C_{15}H_{26}Br_2O_6$ (elemental and m.s. analysis); ^{1}H n.m.r. ($CDCl_3$, Me_4Si): δ 1·80 (2H, quin. 1-H); 2·18 (4H, quin. 7-H); 2·56 (4H, t, 4-H); 3·30—3·80 (12H, m, 2-H + 3-H + 8-H); and 4·22 (4H, t, 6-H). ^{13}C n.m.r. ($CDCl_3$, δ p.p.m. Me_4Si): 29·3 (C-7); 29·9 (C-1); 31·8 (C-8); 35·1 (C-4); 62·2 (C-6); 66·2 (C-2); 67·9 (C-3); and 171·4 (C-5).



The dibromoester (**2**) and the potassium salt of the diacid were stirred for 22 h in dimethylformamide (DMF) at 70—80 °C, which was followed by evaporation of DMF, chloroform extraction, filtration, and solvent evaporation. This gave an oily residue which, after chromatography over silica gel (eluent: acetone) and several extractions with pentane at room temperature, gave the pure macrocycle (**4**)

in 30% overall yield. The homogeneity of the viscous crown ether was controlled by gel permeation chromatography.

Crown ether (**4**): formula $C_{24}H_{40}O_{12}$ (elemental and chemical ionization m.s. analysis); ^{1}H n.m.r. ($CDCl_3$, Me_4Si): δ 1·50—2·20 (8H, m, 1-H + 7-H); 2·58 (8H, t, 4-H); 3·30—3·90 (16H, 2 t, 2-H + 3-H); and 4·20 (8H, t, 6-H); ^{13}C n.m.r. ($CDCl_3$, δ p.p.m. Me_4Si); 28·1 (C-7); 29·9 (C-1); 35·1 (C-4); 61·1 (C-6); 66·2 (C-2); 67·9 (C-3); and 171·4 (C-5).

This relatively easy synthesis gives access to a new class of oxygenated macrocycles, which are models of nactin antibiotics.

(*Received, 25th June* 1979; *Com.* 668.)

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