Synthesis of Macrocyclic Oxo-crown Ethers from αω-Bis-diazo-ketones and Polyethylene Glycols

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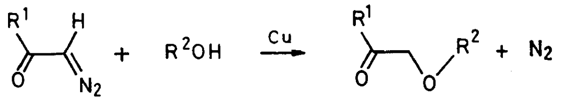
Summary Derivatives of macrocyclic crown ethers in which two ethereal oxygen atoms have been replaced by carbonyl groups have been synthesised by the bis-(acetylacetonato)copper-catalysed cyclisation of αω-bis-diazo-ketones with polyethylene glycols; three such oxo-crown ethers complex with potassium ion in chloroform.

The ester group has been incorporated into synthetic crown ethers as a potential binding site to mimic the naturally occurring antibiotics of the valinomycin group, some of whose members, *e.g.* nonactin and valinomycin itself, depend on intra-annular ester carbonyl groups for their ability to bind alkali metal cations.[1,2] The idea that specificity of metal-ion binding to crown ethers can be modified by replacing one or more ethereal oxygen atom by another heteroatom or group capable of electron donation has been an important feature of developments with synthetic ionophores.[1,2] One disadvantage of using the ester carbonyl group for this purpose is its lability. Cram[3] and Stoddart[4] have discussed advantages and consequences of using the ketonic carbonyl group as a potential binding site, but their preliminary approaches to oxo-crown ethers require several-step syntheses. We describe a much more direct approach to the problem of inserting ketonic carbonyl groups into macrocyclic crown ethers.



(1)

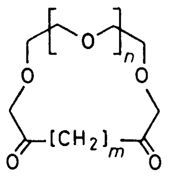
The synthesis utilises the fact that α-diazo-ketones undergo copper-catalysed αα-addition of alcohols giving α-alkoxy-ketones[5] (equation 1). This reaction was used to construct a cyclic bis-alkoxy-ketone of type (A) through the combination of a symmetrical αω-bis-diazo-ketone (**1**), and a symmetrical polyethylene glycol (**2**). If the chain

$N_2CHCO[CH_2]_mCOCHN_2$ (**1**)

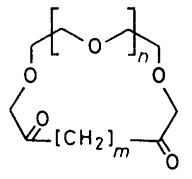
$HOCH_2[CH_2OCH_2]_nCH_2OH$ (**2**)

lengths *m* and *n* in the acyclic components are sufficiently short both carbonyl groups in the cyclic product will be restricted to extra-annular orientations as shown in (A), but as *m* and/or *n* increase so will the conformational mobility of the ring, offering conformations in which one or both carbonyl groups become intra-annular, as in (B) and (C), and thereby available as potential binding sites in conjunction with the ethereal oxygen atoms.

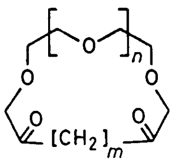
The dioxo-26-crown-5 (**3**) was prepared by slowly adding a solution of 1,9-bis(diazoacetyl)nonane (**1**; *m* = 9) (1·8 g) and tetraethylene glycol (**2**; *n* = 3) (1·9 g) in benzene (250 cm³) to a stirred solution of Cu(acac)₂ (0·1 g) (Hacac = acetylacetone) in benzene (75 cm³) at 60 °C. After 24 h the solvent was removed and the residue purified by silica gel chromatography, giving (**3**) as a viscous oil (0·6 g, 21%); ¹H n.m.r. δ 4·0 (4H, s, OCH_2CO), 3·6—3·65 (16H, m, OCH_2CH_2O), 2·3—2·7 (4H, t, CH_2CO), and 1·0—2·0 (14H, m, $[CH_2]_7$); ν_{max} 1700 cm⁻¹; *m/e* 402 (M^+). In a similar manner tetraethylene glycol combined with 1,8-bis(diazoacetyl)octane (**1**; *m* = 8) and 1,6-bis(diazoacetyl)-hexane (**1**; *m* = 6) to produce the 25- and 23-membered dioxo-crown (**4**) and (**5**), respectively. Oxo-crowns based on triethylene glycol (**2**; *n* = 2) could also be obtained, 1,8-bis(diazoacetyl)octane (**1**; *m* = 8) producing the dioxo-22-crown-4 (**6**) (7%) and 1,6-bis(diazoacetyl)hexane (**1**; *m* = 6) the dioxo-20-crown-4 (**7**) (26%). Preliminary complexation studies using the Zeise's salt extraction method[6] revealed that dioxo-crowns (**3**), (**4**), and (**5**) complex with potassium ion in chloroform solution to the extent of 86, 60, and 53%, respectively.



(A)

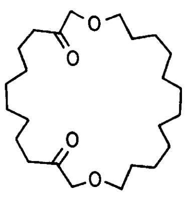


(B)

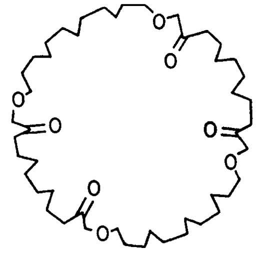


(C)

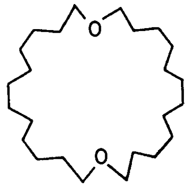
(3); *m* = 9, *n* = 3
(4); *m* = 8, *n* = 3
(5); *m* = 6, *n* = 3
(6); *m* = 8, *n* = 2
(7); *m* = 6, *n* = 2



(8)



(9)



(10)

Chromatographic and mass spectrometric analyses of the crude products of all these cyclisation reactions showed the presence of higher oligomers, particularly those derived from combination of two molecules of each reactant, and in one other case a tetrameric cyclic product was isolated as the major product. Treatment of 1,8-bis(diazoacetyl)-octane (**1**; $m = 8$) with dodecane-1,12-diol in benzene containing Cu(acac)$_2$ gave a separable mixture of the dimeric 26-membered compound (**8**) (*ca.* 10%) and the tetrameric 52-membered compound (**9**) (*ca.* 40%), m.p. 80—81 °C, distinguishable by mass spectrometry and molecular weight measurements. Wolff–Kishner reduction of (**1**) gave 1,14-dioxacylohexacosane (**10**).

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[1] The binding properties of members of the valinomycin group and related compounds have been reviewed: W. Simon, W. E. Morf, and P. Ch. Meier, *Struct. Bonding* (*Berlin*), 1973, **16**, 113.

[2] For comprehensive surveys of synthetic crown ethers and related macrocycles see 'Synthetic Multidentate Macrocyclic Compounds,' eds. R. M. Izatt and J. J. Christensen, Academic Press, New York, 1978; J. S. Bradshaw and P. E. Stott, *Tetrahedron*, 1980, **36**, 461; 'Progress in Macrocyclic Chemistry,' Vol. 1, eds. R. M. Izatt and J. J. Christensen, Wiley, New York, 1979.

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