The Synthesis of Adrenaline Crown Ethers

By **David E. Fenton** * and **Donald Parkin**, Department of Chemistry, The University, Sheffield S3 7HF
Roger F. Newton, Glaxo Group Research Ltd., Ware, Hertfordshire SG12 0DJ

The syntheses of adrenaline-15-crown-5 and adrenaline-18-crown-6 starting from acetovanillone are reported, together with the properties of these compounds. Alkali and alkaline-earth metal complexes of these ligands have been prepared. A method of separating crown ethers based on their preferential complexation of barium is discussed.

THE ability of macrocyclic polyethers such as dibenzo-18-crown-6 to complex with, and to lipophilize, metal cations has been well demonstrated.[1] Such metal complexes have been used as models for alkali-metal carriers in ion-transfer experiments,[2,3] and it has been proposed that complexes between polyethers and organic molecules might simulate the substrate activity of enzymes.[4,5]

We were interested in investigating the properties of molecules containing both a pharmacophoric group and a host matrix capable of cation transport, as the modification of physiologically active molecules might lead to changes in their activity. We report here the synthesis and properties of macrocyclic polyethers incorporating the adrenaline sub-structure.[6]

EXPERIMENTAL

Microanalyses were carried out by the University of Sheffield Microanalytical Service. I.r. spectra were recorded as KBr discs, or thin films, using a Perkin-Elmer 297 i.r. spectrophotometer. Mass spectra were obtained using an MS12 spectrometer. ^{1}H N.m.r. spectra were recorded at 220 MHz using a Perkin-Elmer R34 spectrometer at ambient temperature, and ^{13}C n.m.r. spectra were recorded on a JEOL PFT-100 spectrometer at 25.15 MHz (^{1}H noise-decoupled). Stability-constant measurements were made by obtaining e.m.f. readings in mV from a Radiometer Copenhagen 26 pH meter using a Corning Ag/AgCl reference electrode (476029) and either a Corning N.A.S. 11-18 sodium-ion electrode (476210) or a Corning monovalent cation electrode (476220).

4′-Acetoxy-2,3-benzo-1,4,7,10,13-pentaoxacyclopentadec-2-ene (*4′-Acetoxybenzo-15-crown-5*) (1a).—The method used was that of Kopolow *et al.*[7] *4′-Acetoxybenzo-15-crown-5* was obtained as fluffy, white crystals, m.p. 93—94 °C (Found: C, 61.8; H, 7.3%; $M^{+\bullet}$, 310. $C_{16}H_{22}O_6$ requires C, 61.9; H, 7.2%; M, 310); $\nu_{max.}$ (KBr) 1 660 (C=O) and 1 100 cm^{-1} (C–O); τ ($CDCl_3$) 2.40 (dd, J 2, 8 Hz, 1 H, aromatic), 2.50 (d, J 2 Hz, 1 H, aromatic), 3.15 (d, J 8 Hz, 1 H, aromatic), 5.80—6.20 and 6.30 (2 × m + s, 4 H, 4 H, and 8 H, crown ether ethylenics), and 7.50 (s, 3 H, Me); ^{13}C{^{1}H} n.m.r. ($CDCl_3$) 196.69 (C=O), 153.43, 148.77, 130.62, 123.53, 112.61, and 111.69 (aromatics), 71.17, 70.62, 70.32, 69.35, 69.23, 68.92, and 68.62 (crown ether ring-carbons), and 26.21 (Me) p.p.m.

4′-Bromoacetoxy-2,3-benzo-1,4,7,10,13-pentaoxacyclopentadec-2-ene. (*4′-Bromoacetoxybenzo-15-crown-5*) (2a).—4′-Acetoxy-15-crown-5 (2a) (20 g) was dissolved in chloroform (100 cm^3) and bromine (9.0 g) in chloroform (100 cm^3) was added dropwise with stirring during 2 h. After washing with sodium hydrogencarbonate solution (2 × 100 cm^3) and drying over anhydrous magnesium sulphate, the chloroform was removed under reduced pressure to give an amber coloured oil which slowly solidified. This was stirred in cold diethyl ether to give a yellow solid. Recrystallisation from carbon tetrachloride gave *4′-bromoacetoxybenzo-15-crown-5* as pale yellow crystals (18 g, 74%), m.p. 80—81 °C (Found: C, 49.4; H, 5.5%, $M^{+\bullet}$, 388, 390. $C_{16}H_{21}BrO_6$ requires C, 49.4; H, 5.4%, M, 388); $\nu_{max.}$ (KBr) 1 660 cm^{-1} (C=O); τ ($CDCl_3$), 2.40 (dd, J 2, 8 Hz, 1 H, aromatic), 2.50 (d, J 2 Hz, 1 H, aromatic), 2.16 (d, J 8 Hz, 1 H, aromatic), 5.62 (s, 2 H, CH_2Br), 5.85, 6.10, and 6.27 (2 × m + s, 4 H, 4 H, and 8 H, crown ether ethylenics); ^{13}C{^{1}H} n.m.r. ($CDCl_3$) 189.84 (C=O). 154.10, 149.01, 127.05, 124.07, 113,27, and 111.69 (aromatics), 71.17, 70.26, 69.23, 69.10, 68.98, and 68.62 (crown ether ring-carbons), and 30.58 (CH_2Br) p.p.m.

4′-(N-Methylbenzylaminoacetoxy)benzo-15-crown-5 Hydrochloride (3a).—*N*-Methylbenzylamine (1.26 g) was added to a solution of 4′-bromoacetoxybenzo-15-crown-5 (2a) (2.0 g) in ethyl methyl ketone–ether (2 : 1) (30 cm^3) saturated with nitrogen. Silvery plates were observed after a few minutes, but stirring was continued for 4 h. After filtering, the filtrate was concentrated to give an amber coloured oil. This was extracted with ether several times to give a yellow solid and a pale yellow ether solution. Dry hydrogen chloride gas was passed through the ether solution to give a white hygroscopic precipitate which was filtered off and dried in a vacuum desiccator to give *4′-(N-methylbenzylaminoacetoxy)benzo-15-crown-5 hydrochloride* as a pale yellow solid (1.35 g, 56%) (Found: C, 59.7; H, 6.9; N, 2.7; Cl, 7.0%; $M^{+\bullet}$, 429. $C_{24}H_{32}ClNO_6 \cdot H_2O$ requires C, 59.6; H, 7.1; N, 2.9; Cl, 7.3%; M – HCl, 429); $\nu_{max.}$ (KBr) 1 675 (C=O), and 740, 700 cm^{-1} (benzyl); τ ($CDCl_3$) 2.4—2.6 (m, 7 H, aromatic), 3.18 (d, J 8 Hz, 1 H, aromatic), 5.07 (s, 2 H, NCH_2), 5.26 (s, 2 H, NCH_2), 5.8, 6.0, and 6.20 (2 × m + s, 4 H, 4 H, and 8 H, crown ether ethylenics), and 6.84 (s, 3 H, NMe); ^{13}C{^{1}H} n.m.r. ($CDCl_3$) 189.29 (C=O), 154.77, 148.95, 131.23, 129.96, 129.23, 126.92, 123.40, 112.00, and 111.76 (aromatics), 70.92, 70.14, 70.01, 69.05, 68.86, and 68.50 (crown ether ring-carbons), 56.48 and 58.73 (NCH_2), and 40.95 (NMe) p.p.m.

4′-(N-Isopropylbenzylaminoacetoxy)benzo-15-crown-5 Hydrochloride.—*N*-Isopropylbenzylamine (1.53 g) was added to a solution of 4′-bromoacetoxybenzo-15-crown-5 (2.0 g) in ethyl methyl ketone (30 cm^3) purged with dinitrogen. On stirring for 20 min a silvery precipitate appeared. After 3 h stirring was discontinued, the mixture was filtered, and the filtrate refluxed for a further 2 h. After cooling and filtering, the filtrate was evaporated to leave an orange oil, which on trituration with dry ether gave a yellow solid. This solid was removed and dry hydrogen chloride gas bubbled through the ether solution to give a yellow-brown precipitate. The precipitate was collected wet and dried fully in a vacuum desiccator to give *4′-(N-isopropylbenzyl-*

aminoacetoxy)benzo-15-crown-5 hydrochloride as a pale yellow hygroscopic solid (1.19 g, 48%) (Found: C, 58.8; H, 7.8; N, 2.5; Cl, 6.4%, $M^{+\bullet}$, 445. $C_{26}H_{36}ClNO_6 \cdot 2H_2O$ requires C, 58.9; H, 7.6; N, 2.6; Cl, 6.6%, M − HCl, 445); $\nu_{max.}$ (KBr) 1 670 (C=O), and 760, 705 cm^{-1} (benzyl); τ ($CDCl_3$) 2.3 (m, 2 H, aromatic), 2.6 (s, 5 H, aromatic), 3.2 (d, J 8 Hz, 1 H, aromatic), 5.5—6.3 and 6.32 (m + s, 20 H, crown ether ethylenics and methylenes), 7.4 (septet, 1 H, C*H*Me_2), and 8.3—8.7 (m, 6 H, CHMe_2).

4′-(N-*t-Butylbenzylaminoacetoxy)benzo-15-crown-5 Hydrochloride*.—Sodium iodide (0.77 g) was added to a solution of 4′-bromoacetoxybenzo-15-crown-5 (2a) (2.0 g) in ethyl methyl ketone (30 cm^3) purged with nitrogen, containing *N*-t-butylbenzylamine (1.68 g). The mixture was stirred and refluxed for 20 h and then cooled and filtered to give a yellow solid. The filtrate was evaporated to give an orange oil, which was triturated in dry ether during which time a yellow powder formed. The powder was removed and the ether layer treated with dry hydrogen chloride gas to give a yellow precipitate. This was collected under ether and dried under vacuum to give 4′-(N-*t-butylbenzylamino-acetoxy)benzo-15-crown-5 hydrochloride* (1.0 g, 38%) (Found: C, 58.0; H, 7.3; N, 2.7; Cl, 12.2%; $M^{+\bullet}$, 471. $C_{27}H_{38}ClNO_6 \cdot H_2O$ requires C, 57.7; H, 7.3; N, 2.5; Cl, 12.6%; M − HCl, 471); $\nu_{max.}$ ($CDCl_3$) 1 680 (C=O), and 740, 700 cm^{-1} (benzyl); τ ($CDCl_3$) 2.3—2.6 (m, 7 H, aromatic), 3.2 (d, J 8 Hz, 1 H, aromatic), 5.3 (s, 2 H, NCH_2), 5.5—6.6 and 6.25 (m and s, 18 H, crown ether ethylenes + NCH_2), and 8.7 (m, 9 H, CMe_3).

4′-(*Diethylaminoacetoxy)benzo-15-crown-5 Hydrochloride*.—Diethylamine (0.56 g) was added to a solution of 4′-bromo-acetoxybenzo-15-crown-5 (1.5 g) in ethyl methyl ketone (20 cm^3) purged with nitrogen. White plates were observed after a few minutes, but stirring was continued for 1 h. The mixture was filtered and the yellow filtrate evaporated to give an orange oil. On trituration in dry ether a brown solid was formed, which was removed, and the ether layer treated with dry hydrogen chloride gas to give a white precipitate. This was collected under ether and dried under vacuum to give 4′-(*diethylaminoacetoxy)-benzo-15-crown-5 hydrochloride* (0.96 g, 58%) (Found: C, 55.0; H, 7.6; N, 3.2; Cl, 8.6%, $M^{+\bullet}$, 381. $C_{20}H_{32}ClNO_6 \cdot H_2O$ requires C, 55.1; H, 7.6; N, 3.2; Cl, 8.4; M − HCl 381); $\nu_{max.}$ (KBr) 1 660 cm^{-1} (C=O).

Adrenaline-15-crown-5 Hydrochloride (4a).—4′-(*N*-Methyl-benzylaminoacetoxy)benzo-15-crown-5 hydrochloride (3a) (1.8 g) in ethanol (30 cm^3) was hydrogenated over 10% palladium–carbon (760 mg, 60% H_2O = 300 mg dry) until hydrogen uptake was complete. Fresh catalyst (300 mg dry) was then added to ensure complete hydrogenation. The mixture was filtered and the ethanol removed under reduced pressure to give a colourless oil. Trituration with dry ether gave *adrenaline-15-crown-5 hydrochloride* as a colourless, hygroscopic solid (1.15 g, 79%) (Found: C, 51.6; H, 7.7; N, 3.5; Cl, 9.3%; $M^{+\bullet}$, 341. $C_{17}H_{28}ClNO_6 \cdot H_2O$ requires C, 51.6; H, 7.6; N, 3.5; Cl, 8.9%, M − HCl, 341); $\nu_{max.}$ (KBr) 3 400 cm^{-1} (NH); τ ($CDCl_3$) 1.0 (br s, 1 H, NH or OH), 2.47 and 3.0—3.2 (quin and m, 3 H, aromatic), 5.9, 6.2, and 6.29 (2 × m + s, 4, 4, and 8 H, crown ether ethylenics), 6.9 (d, J 8 Hz, 2 H, NCH_2), and 7.26 (s, 3 H, NMe); τ (D_2O) 2.82 (s, 3 H, aromatic), 4.86 (t, J 8 Hz, 1 H, CH), 5.7, 5.9, and 6.14 (2 × m + s 4 H, 4 H, and 8 H, crown ether ethylenics), 6.57 (d, J 6 Hz 2 H, NCH_2), and 7.10 (s, 3 H, NMe).

Adrenaline-15-crown-5 (5a).—Adrenaline-15-crown-5 hydrochloride (4a) (1.0 g) in distilled water (20 cm^3) was treated with sodium hydroxide (0.15 g) in distilled water (10 cm^3) and then extracted with chloroform (2 × 50 cm^3). The chloroform was separated, dried over anhydrous magnesium sulphate, and evaporated to give *adrenaline-15-crown-5* as a pale yellow solid (0.53 g, 59%), m.p. 104—105 °C * (Found: C, 59.9; H, 7.9; N, 4.1%; $M^{+\bullet}$, 341. $C_{17}H_{27}NO_6$ requires C, 59.8; H, 8.0; N, 4.1%, M, 341); $\nu_{max.}$ (KBr) 3 300 cm^{-1} (NH); τ ($CDCl_3$) 3.10, 3.18 (2 × s, 1 H, 2 H, aromatics), 5.32 (t, J 6 Hz, 1 H, CH), 5.9, 6.1, and 6.28, (2 × m + s, 4 H, 4 H, and 8 H, crown ether ethylenics), 7.33 (d, J 6 Hz, 2 H, NCH_2), and 7.62 (s, 3 H, NMe).

1,14-*Dihydroxy-3,6,9,12-tetraoxatetradecane* (*Pentaethylene Glycol*).—Potassium hydroxide (61.5 g) was dissolved in ethylene glycol (600 cm^3, 668 g), and 1,8-dichloro-3,6-dioxaoctane (86 g) was added. The mixture was heated at 140 °C for 5 days and then cooled and filtered. The filtrate was distilled under water-pump pressure to remove water and ethylene glycol, cooled, and filtered again. The filtrate was then further distilled to give *pentaethylene glycol* as a clear liquid (85.8 g, 80%), b.p. 220—230 °C at water-pump pressure (Found: C, 47.3; H, 9.1%. $C_{16}H_{22}O_6$ requires C, 50.4; H, 9.3%).

1,14-*Ditosyl-3,6,9,12-tetraoxatetradecane*.— Toluene-*p*-sulphonyl chloride (170 g) in 1,4-dioxan (200 cm^3) was added to a solution of pentaethylene glycol (100 g), sodium hydroxide (40 g), and distilled water (200 cm^3) with stirring and cooling. The mixture was shaken for 14 h and then extracted with toluene. The extract was washed with water followed by aqueous sodium carbonate solution, dried over calcium chloride, and filtered. The filtrate was evaporated to give a yellow oil. Chromatography over silica gel and elution with ether afforded 1,14-*ditosyl-3,6,9,12-tetraoxatetradecane* as a yellow oil after evaporation (161.2 g, 70%) (Found: C, 52.3; H, 6.2; S, 11.5%; $M^{+\bullet}$, 546. $C_{22}H_{34}O_{10}S_2$ requires C, 52.7; H, 6.2; S, 11.7%, M, 546); τ ($CDCl_3$) 2.20 and 2.67 (2 × d, J 9 Hz, 8 H, aromatic), 5,8—5.9 and 6.2—6.5 (2 × m, 4 H + 16 H, ether ethylenics), and 7.55 (s, 6 H, 2 × Me).

4′-*Acetoxy-2,3-benzo-1,4,7,10,13,16-hexaoxacyclo-octadec-2-ene* (4′-*Acetoxybenzo-18-crown-6*) (1b).—The method used was a modification of that reported by Kopolow *et al.*[7] and by Pedersen.[1] Sodium hydroxide (0.84 g) in distilled water (2 cm^3) was added to a solution of 3,4-dihydroxyacetophenone (1.59 g) in butanol (20 cm^3) purged with nitrogen. After stirring until a thick yellow-orange precipitate had formed, 1,14-ditosyl-3,6,9,12-tetraoxatetradecane (5.7 g) was added and the mixture refluxed for 3 days. The dark mixture was cooled and filtered, and the silvery solid washed with butanol. The combined filtrates were evaporated to give a dark oil which was extracted with chloroform and filtered. The filtrate was washed with 5% sodium hydroxide solution (4 × 50 cm^3) and dried over anhydrous magnesium sulphate. The chloroform was removed under reduced pressure to give a dark amber oil which was extracted several times with hot n-heptane; on cooling, the extract gave 4′-*acetoxybenzo-18-crown-6* as a white, fluffy crystalline solid (1.94 g, 48%), m.p. 72—74 °C (Found: C, 61.0; H, 7.3%; $M^{+\bullet}$, 354. $C_{18}H_{26}O_7$ requires C, 61.0; H, 7.4%, M, 354); $\nu_{max.}$ 1 660 (C=O) and

* There is a discrepancy between this value and that recorded in the literature (61 °C).[6] The existence of polymorphic forms of cyclic polyethers has been reported, together with the variation in melting points (P. E. Stott, C. W. McCausland, and W. W. Parish, *J. Heterocyclic Chem.*, 1979, **16**, 453). It is possible that such a phenomenon is the cause of the above difference.

1 100 cm^{-1} (C=O); τ ($CDCl_3$) 2.40 (dd, *J* 2, 8 Hz, 1 H, aromatic), 2.52 (d, *J* 2 Hz, 1 H, aromatic), 3.17 (d, *J* 8 Hz, 1 H, aromatic), 5.7, 6.2, 6.28, and 6.34 (2 × m + 2 × s, 4 H, 4 H, 4 H, and 8 H, crown ether ethylenics), and 7.48 (s, 3 H, Me); $^{31}C\{^1H\}$ n.m.r. ($CDCl_3$) 196.57 (C=O); 153.26, 148.58, 130.50, 123.40, 112.6, and 111.81 (aromatics), 70.92, 70.80, 70.68, 69.47, 69.53, 69.10, and 68.92 (crown ether ring-carbons), and 26.21 (Me).

Preparation of Pure 4′-Acetoxybenzo-18-crown-6 via a Barium Perchlorate Complex.—Barium perchlorate (7.3 g) in hot ethanol (50 cm^3) was added to a solution of 4′-acetoxybenzo-18-crown-6 containing 4′-acetoxybenzo-15-crown-5 as impurity (7.7 g) in hot ethanol (50 cm^3), to give a white precipitate. After heating and stirring for 5 min, the mixture was filtered rapidly to give a white solid (10.24 g). This was dissolved in distilled water and shaken with chloroform for 1 h. The chloroform was separated, dried over anhydrous magnesium sulphate, and evaporated to give a pale yellow solid. Recrystallisation from n-heptane gave white fluffy crystals of pure *4′-acetoxybenzo-18-crown-6*, (4.56 g, 87%).

4′-Bromoacetoxy-2,3-benzo-1,4,7,10,13,16-hexaoxacyclooctadec-2-ene (*4′-Bromoacetoxybenzo-18-crown-6*) (2b).—Bromine (1.8 g) in chloroform (50 cm^3) was added dropwise to a solution of 4′-acetoxybenzo-18-crown-6 (1b) (40 g) in chloroform (40 cm^3) with stirring over a period of 2 h. The mixture was then washed with sodium hydrogencarbonate solution (2 × 100 cm^3), dried over anhydrous magnesium sulphate, and evaporated to give a purple-brown oil. This was taken up in hot carbon tetrachloride and treated with charcoal. The charcoal was removed by filtration and the pale yellow solution evaporated to give an amber oil which solidified. Recrystallisation from n-heptane gave pale yellow crystals of *4′-bromoacetoxybenzo-18-crown-6* (3.6 g, 74%), m.p. 99—101 °C (Found: C, 49.7; H, 6.2; Br, 18.5%, $M^{+\bullet}$ 432, 434. $C_{18}H_{25}BrO_7$ requires C, 49.9; H, 5.8; Br, 18.4%, *M*, 432, 434); $\nu_{max.}$ (KBr) 1 670 cm^{-1} (C=O); τ ($CDCl_3$) 2.4—2.52 (m, 2 H, aromatic), 3.17 (d, 1 H, aromatic), 5.61 (s, 2 H, CH_2Br), and 5.8, 6.1, 6.28, and 6.35 (2 × m + 2 × s, 4 H, 4 H, 4 H, and 8 H, crown ether ethylenics).

4′-(N-Methylbenzylaminoacetoxy)benzo-18-crown-6 Hydrochloride (3b).—*N*-Methylbenzylamine (1.68 g) was added to a solution of 4′-bromoacetoxybenzo-18-crown-6 (2b) (3.0 g) in ethyl methyl ketone (50 cm^3) to give a silvery precipitate after a few minutes. Stirring was continued for 4 h and the mixture was then filtered. The filtrate was stirred for a further 8 h, filtered again, and the ethyl methyl ketone removed under reduced pressure to give an orange-amber oil. This was extracted with diethyl ether several times to give a pale yellow solution and a yellow solid. Dry hydrogen chloride gas was passed through the yellow ether solution to give a white, hygroscopic precipitate which was collected wet and dried under vacuum to give *4′-(N-methylbenzylaminoacetoxy)benzo-18-crown-6 hydrochloride* as a pale yellow solid (1.8 g, 55%) (Found: C, 58.5; H, 8.3; N, 2.4; Cl, 7.8%; $M^{+\bullet}$, 473. $C_{26}H_{36}ClNO_7NCl{\cdot}H_2O$ requires C, 59.1; H, 7.3; N, 2.6; Cl, 6.7%; *M* − HCl, 473); $\nu_{max.}$ (KBr) 1 675 (C=O), and 740, 700 cm^{-1} (benzyl); τ ($CDCl_3$) 2.3—2.8 (m, 7 H, aromatic), 3.20 (d, *J* 8 Hz, 1 H, aromatic), 5.08 (s, 2 H, NCH_2), 5.36 (s, 2 H, NCH_2), 5.8—6.36 (m, 20 H, crown ether ethylenics), and 6.94 (s, 3 H, Me).

Adrenaline-18-crown-6 Hydrochloride.—4′-(*N*-Methylbenzylaminoacetoxy)benzo-18-crown-6 hydrochloride (3b) (2.0 g) in ethanol (30 cm^3) was hydrogenated over 10% palladium–carbon (2 × 300 mg dry) until hydrogen uptake was complete. The mixture was filtered and the ethanol removed under reduced pressure to give a colourless oil, which was triturated in dry ether to give *adrenaline-18-crown-6 hydrochloride* as a hygroscopic, colourless solid (1.3 g, 80%) [Found: C, 54.2; H, 8.1; N, 3.5; Cl, 10.7%; $M^{+\bullet}$, 385 (*p* − HCl). $C_{19}H_{32}ClNO_7$ requires C, 54.1; H, 7.6; N, 3.3, Cl, 8.4%; *M* − HCl, 385]; $\nu_{max.}$ ($CDCl_3$) 3 400 cm^{-1} (NH_2); τ (D_2O) 2.84 (s, 3 H, aromatic), 4.88 (t, *J* 6 Hz, 1 H, CH), 5.65, 6.0, 6.18, and 6.22 (2 × m + 2 × s, 4 H, 4 H, 4 H, and 8 H, crown ether ethylenics), 6.59 (d, *J* 6 Hz, 2 H, NCH_2), and 7.11 (s, 3 H, Me).

Adrenaline-18-crown-6 (5b).—Adrenaline-18-crown-6 hydrochloride (2.2 g) was dissolved in distilled water (20 cm^3) and treated with sodium hydroxide (0.21 g) in distilled water (10 cm^3), and then extracted with chloroform (2 × 50 cm^3). The chloroform was separated, dried over magnesium sulphate, and evaporated to give *adrenaline-18-crown-6* as a pale yellow solid (1.2 g, 61%), m.p. 82—83 °C (Found: C, 58.5; H, 7.6; N, 3.5%; $M^{+\bullet}$, 385. $C_{19}H_{31}NO_7$ requires C, 59.2; H, 8.1; N, 3.6%; *M*, 385); $\nu_{max.}$ (KBr) 3 300 cm^{-1} (NH); τ ($CDCl_3$) 3.10 and 3.20 (s and m, 1 H and 2 H, aromatics), 5.00 (t, *J* 6 Hz, 1 H, CH), 5.85, 6.1, and 6.3—6.4 (m, 20 H, crown ether ethylenics), 7.05 (d, *J* 6 Hz, 2 H, NCH_2), and 7.38 (s, 3 H, NMe).

Alkali and Alkaline-earth Metal Complexes.—The following general procedure was used. The metal salt (0.001 mol) in hot ethanol (20 cm^3) was added to the crown ether (0.001 mol) in hot ethanol (20 cm^3) with stirring. The mixture was filtered and left to cool, whereupon the complex precipitated. If no precipitation occurred the ethanol was removed using a rotary evaporator to leave a sticky residue which, on washing with ethyl acetate, gave a solid product. The solids collected were extremely hygroscopic with the exception of the magnesium complexes.

(*Adrenaline-15-crown-5*)·NaNCS·$2H_2O$ (Found: C, 48.2; H, 6.9; N, 6.0; S, 6.9. $C_{18}H_{31}NaN_2O_7S$ requires C, 47.2; H, 6.8; N, 6.1; S, 7.0%).

(*Adrenaline-15-crown-5*)$_2$·$Mg(NCS)_2$·$6H_2O$ (Found: C, 46.3; H, 7.5; N, 5.9; S, 7.9. $C_{36}H_{66}MgN_4O_{18}S_2$ requires C, 46.4; H, 7.1; N, 6.0; S, 6.9%).

(*Adrenaline-15-crown-5*)$_2$·$Mg(ClO_4)_2$ (Found: C, 44.8; H, 6.4; N, 2.9. $C_{34}H_{54}Cl_2MgN_2O_{20}$ requires C, 45.0; H, 6.0; N, 3.0%).

(*Adrenaline-15-crown-5*)$_2$·$Ba(ClO_4)_2$·$2H_2O$ (Found: C, 38.8; H, 5.2; N, 2.5. $C_{34}H_{56}BaCl_2N_2O_{22}$ requires C, 38.7; H, 5.5; N, 2.7%).

(*Adrenaline-18-crown-6*)·NaNCS (Found: C, 51.1; H, 6.3; N, 5.8; S, 7.0. $C_{20}H_{31}N_2NaO_7S$ requires C, 51.5; H, 6.7; N, 6.0; S, 6.8%).

(*Adrenaline-18-crown-6*)·$Mg(ClO_4)_2$·$6H_2O$ (Found: C, 40.7; H, 7.1; N, 2.1. $C_{19}H_{43}Cl_2MgNO_{21}$ requires C, 41.4; H, 6.8; N, 2.5%).

(*Adrenaline-18-crown-6*)$_3$·$[Ba(NCS)_2]_2$·H_2O (Found: C, 43.4; H, 6.5; N, 6.4. $C_{61}H_{95}Ba_2N_7O_{22}S_4$ requires C, 43.6; H, 5.7; N, 5.8%).

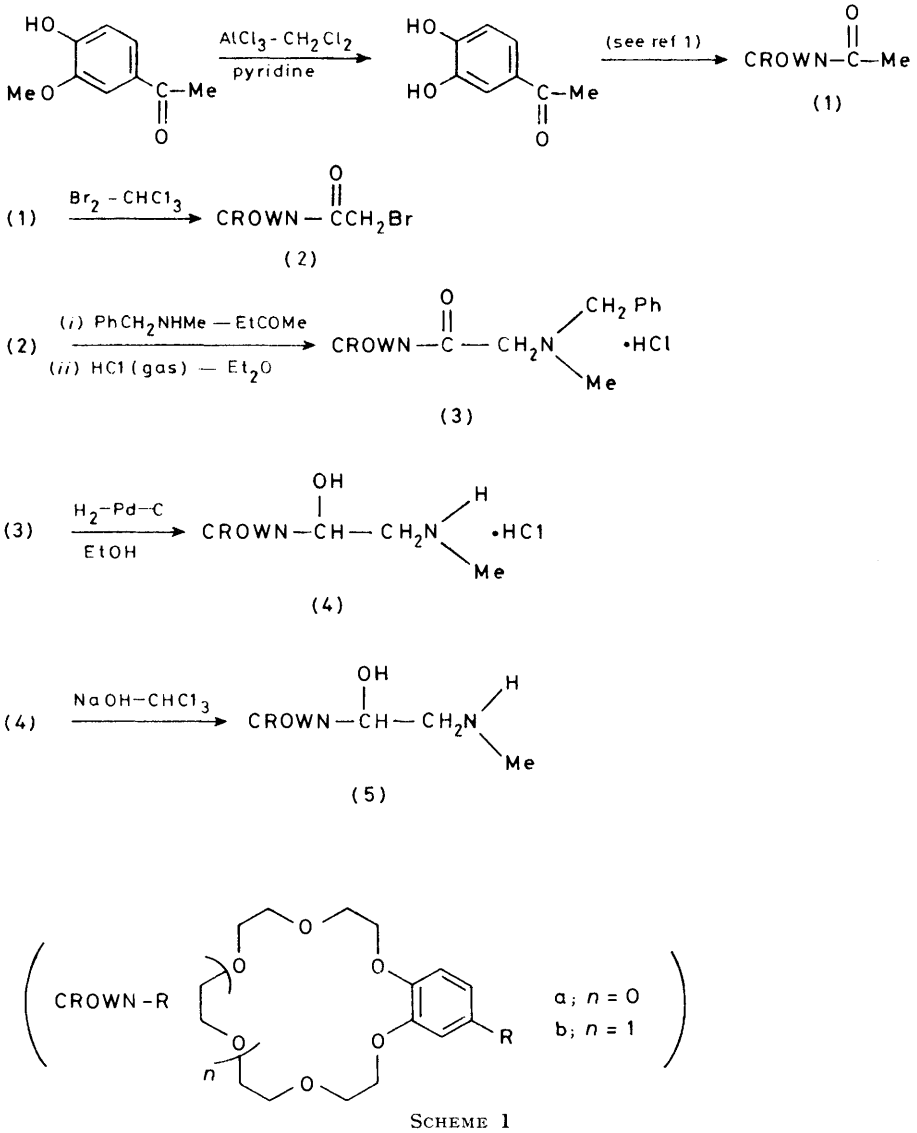
DISCUSSION

The synthetic approach is outlined in Scheme 1. Acetovanillone provided a commercially available starting material, and 3,4-dihydroxyacetophenone was synthesised from it using Lange's method.[8] The acetoxybenzo-crown ethers (1a, b) were then prepared from 3,4-dihydroxyacetophenone by modifications of method V in

Pedersen's classic paper on polyether synthesis.[1,7] The yields averaged 50%, with no evidence for higher macrocycle formation.

Pentaethylene glycol, required as a precursor in the synthesis of (1b), was prepared by the reaction of 1,8-dichloro-3,6-dioxaoctane with KOH in an excess of ethylene glycol. G.c. analysis of the product indicated a 10% presence of tetraethylene glycol and so, as the ditosylate was required for the ether synthesis, the mixture was tosylated in order to facilitate separation using a silica-gel column, and so furnish the pure ditosylate. This procedure was quite time-consuming and so a technique was developed which utilised the separation of (1a) and (1b) after their synthesis from the ditosylate mixture.

The addition of a hot ethanolic solution of $Ba(ClO_4)_2$ to a hot ethanolic solution of the mixture of (1a) and (1b) gave a white precipitate of the complex, (1b)·$Ba(ClO_4)_2$. The corresponding (1a) complex remains in solution. Removal of pure (1b) from the complex was effected by dissolving the precipitate in water followed by chloroform extraction of free (1b). The method is dependent upon the different solubilities of the barium complexes and their relative instability in aqueous media. Barium



SCHEME 1

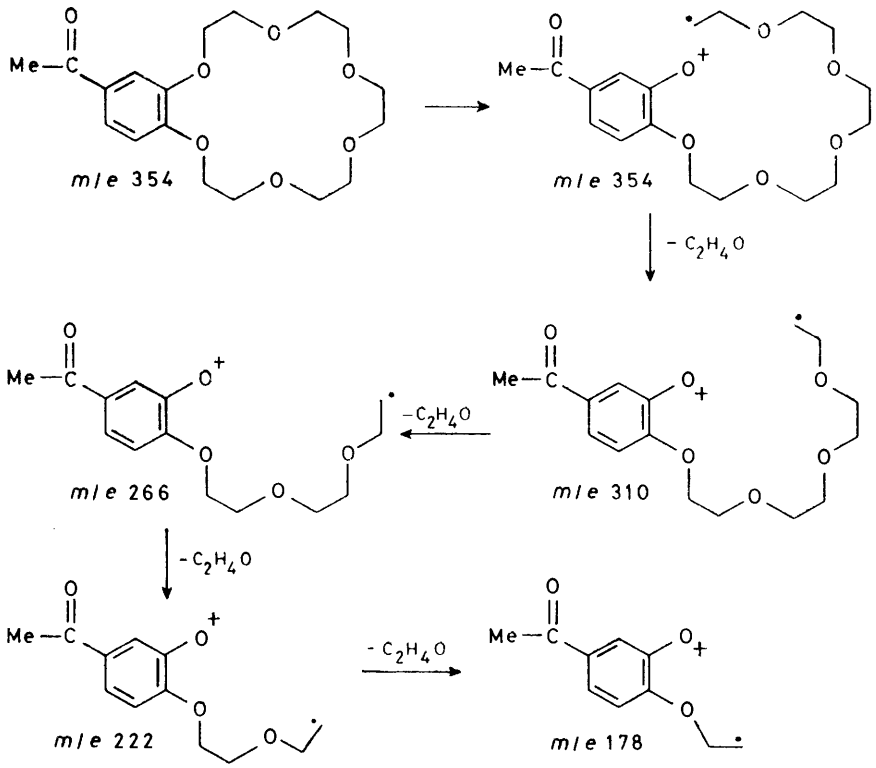
forms 1 : 1 complexes with 18-crown-6 polyethers and 2 : 1 complexes with 15-crown-5 polyethers.[9] In the 2 : 1 complexes the cation is sandwiched between the polyethers and so an organic, lipophilic surface is presented by the complex, aiding solubility in organic solvents. In the 1 : 1 complexes axial sites remain vacant at the metal and are thus available for solvent or anion interaction, and so the lipophilicity is reduced. Complex formation has been used previously in the facile separation of the *cis*-isomers of dicyclohexyl-18-crown-6 [10] and in the purification of 18-crown-6.[11] The former depends on the relative solubilities of $H_3O^+ClO_4^-$ and $Pb(ClO_4)_2$ com-

plexes of the crown ether, and the latter on acetonitrile complex formation. We have experienced no problems of detonation with the $Ba(ClO_4)_2$ complexes; it must be emphasised that perchlorate complexes must be handled with due care.

Controlled bromination of (1) leads to the isolation of (2). If an excess of bromine is used the corresponding dibromoacetoxy-crown ethers are obtained. The use of mild conditions also avoids bromination of the benzene ring of polyether–bromine complex formation as has been observed when benzo-crown ethers receive prolonged exposure to bromine.[12] An attempt was made to reduce the number of steps in the synthesis by synthesising chloroacetoxybenzo-crown ethers from commercially available 4-chloroacetoxycatechol using Pedersen's method.[1] The principal product recovered, however, was (1a).

The remaining steps in Scheme 1 were straightforward and required standard techniques. The hydrochloride salts were found to be extremely hygroscopic and so care must be taken in the work-up procedures. The general nature of the reaction of (2) with secondary amines was illustrated by extending the range of amines used to include diethylamine, *N*-isopropylbenzylamine, and *N*-t-butylbenzylamine.

The compounds prepared were identified by i.r., m.s., and ^1H and ^{13}C n.m.r. (see Experimental section). The ^1H n.m.r. of the adrenaline-crown ethers was compared with the literature values for adrenaline and related compounds and showed close agreement for the adrenaline unit.[13] The m.s. of the compounds confirm the absence of higher homologues and the break-down pattern of the acetoxybenzo-crown ethers is similar to that of benzo-crown ethers [14] (Scheme 2), showing successive loss of 44 mass units (C_2H_4O units). For the bromoacetoxy-crown ethers a second pathway is detected concerned with the loss of CH_2Br from the side-chain prior to successive loss of ethyleneoxy-bridges. The mass spectra of the adrenaline-crown ethers show



SCHEME 2 Mass spectral breakdown pathway for 4′-acetoxybenzo-15-crown-5

successive losses of 44 mass units down to *m/e* 165; one of these losses is probably to removal of $MeNHCH_2$ from the side-chain.

The adrenaline-crown ethers were found to be unusually soluble in a variety of organic solvents, and especially so in water. This is in direct contrast with adrenaline. Alkali and alkaline-earth metal complexes were prepared from (5a) and (5b). When it was possible to isolate solid complexes they were found to be exceptionally hygroscopic, with the exception of the magnesium complexes, and so few analytical results have been obtained. The stoicheiometries observed in those complexes for which analyses are available parallel the stoicheiometries noted for benzo-crown ether complexes.[9] For example, sodium forms 1 : 1 complexes with (5a) and (5b) whereas barium forms 2 : 1 complexes with (5a), and a 3 : 2 complex has been found with (5b). It is not, however, possible to confirm whether this is a genuine ' club sandwich ' as predicted by Pedersen,[1] or

Stability constants for crown ethers with K^+ and Na^+ at 25 °C in MeOH

Crown Ether	Na^+ (1 : 1) log K_1	K^+ (1 : 1) log K_1'	K^+ (2 : 1) log K_3'
Benzo-15-crown-5	2.87	2.20 *	4.80 *
Adrenaline-15-crown-5	2.94	2.63	6.04
		log K_1	
Benzo-18-crown-6	4.35	5.05	
Adrenaline-18-crown-6	4.17	5.15	

* Taken from R. M. Izatt, R. E. Terry, D. P. Nelson, Y. Chan, D. J. Eatough, J. S. Bradshaw, L. D. Hansen, and J. J. Christensen, *J. Amer. Chem. Soc.*, 1976, **98**, 7626; methanol–water (80 : 20). The stability constants are defined by the equilibrium constants K_1' (l mol^{-1}) and K_3' (l^2 mol^{-2}) for complex formation according to the equations $M^+ + L = [ML]^+$ and $M^+ + 2L = [ML_2]^+$.

whether it is a 1 : 1 complex with an additional molecule of uncomplexed ether present as was found for the complex (dibenzo-18-crown-6)$_3$·(RbNCS)$_2$.[1,15] It is proposed that in all the alkali and alkaline-earth metal complexes the polyether matrix interacts with the cation and that the adrenaline chain is not involved with metal bonding.

Magnesium gave complexes with (5a) and (5b) of the types (5a)$_2$·MgX_2·nH_2O (n = 0, 6) and (5b)·MgX_2·$6H_2O$. The retention of the hydration sphere by magnesium has been previously detected[16] in the complex $[Mg(H_2O)_6]^{2+}$·[12-crown-4]·$2Cl^-$ and this suggests that in the above hydrated species the hexa-aquated magnesium cation is present. Both 1 : 1 [17,18] and 2 : 1 [18] complexes of magnesium with benzo-15-crown-5 have been reported. There is crystallographic confirmation of the 1 : 1 complexation in (benzo-15-crown-5)·$Mg(NCS)_2$,[19] but not for (benzo-15-crown-5)$_2$·Mg(picrate)$_2$·$2H_2O$. It is again possible that a free molecule of crown ether is present in such stoicheiometries.

The stability constants of the Na^+ and K^+ complexes of (5a) and (5b) have been determined potentiometrically in methanol, as chloride salts, at 25 °C by the method of Frensdorff.[20] 1 : 1 Complexes are formed between Na^+ and (5a) and (5b) and by analogy with benzo-15-crown-5 complexation reactions K^+ forms a 2 : 1 complex with (5a) and a 1 : 1 complex with (5b).[9] The formation of a 2 : 1 complex is borne out by analysis of the stability constant data.[21] The values obtained for log K are very similar to those for benzo-15-crown-5 complexes and no significant enhancement of complex stability is detected in the adrenaline-crown ether complexes (Table).

Physiological experiments with (5a) and (5b) show that they are inactive at adrenergic receptors.

We thank the S.R.C. for a CASE award (to D. P.) and Dr. D. Hartley for useful discussions.

[0/676 *Received*, 8*th May*, 1980]

REFERENCES

[1] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1967, **89**, 7017.
[2] G. Eisenman, G. Szabo, S. Ciani, S. McLaughlen, and S. Krasne, *Progr. Surf. Membrane Sci.*, 1973, **6**, 139.
[3] D. E. Fenton, *Chem. Soc. Revs.*, 1977, **6**, 325.
[4] D. J. Cram and J. M. Cram, *Science*, 1974, **183**, 803.
[5] J. F. Stoddart, *Chem. Soc. Revs.*, 1979, **8**, 85.
[6] During the course of this project F. Vogtle and his co-workers published results concerned with the introduction of crown ethers into papaverine (*Angew. Chem. Internat. Edn.*, 1976, **11**, 685), cinnarizine, procaine, and dibenzosuberonimine ester (*Chem. Ber.*, 1978, **111**, 1434), and a preliminary communication of crown ethers derived from adrenaline, dopamine, and apomorphine (*Tetrahedron Letters*, 1976, 4895). The approach used for the synthesis of adrenaline-crown-5 is the direct reaction of adrenaline with 1,11-dichloro-3,6,9-trioxaundecane and is in contrast with the procedure described herein.
[7] S. Kopolow, T. E. Hogen-Esch, and J. Smid, *Macromol.*, 1973, **6**, 133.
[8] R. G. Lange, *J. Org. Chem.*, 1962, **27**, 2037.
[9] N. S. Poonia and A. V. Bajaj, *Chem. Revs.*, 1979, **79**, 389.
[10] R. M. Izatt, B. L. Haymore, J. S. Bradshaw, and J. H. Christensen, *Inorg. Chem.*, 1975, **14**, 3133.
[11] G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, 1974, **39**, 2445.
[12] E. Shchori and J. Jagur-Grodzinski, *Israel J. Chem.*, 1972, **10**, 935.
[13] J. Reisch, H. Alfes, and H. Möllman, *Z. anal. Chem.*, 1968, **238**, 29.
[14] D. A. Jaeger and R. R. Whitney, *J. Org. Chem.*, 1975, **40**, 92.
[15] D. Bright and M. R. Truter, *J. Chem. Soc.* (*B*), 1970, 1544.
[16] M. A. Neumann, E. C. Steiner, F. P. van Remoortre, and F. P. Boer, *Inorg. Chem.*, 1975, **14**, 734.
[17] D. G. Parsons and J. N. Wingfield, *Inorg. Chim. Acta*, 1976, **18**, 263.
[18] N. S. Poonia, B. P. Yadav, V. W. Bhagwat, V. Nauk, and H. Manohar, *Inorg. Nuclear Chem. Letters*, 1977, **13**, 119.
[19] J. D. Owen, *J.C.S. Dalton*, 1978, 1418.
[20] K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600.
[21] D. Parkin, Ph.D. Thesis, University of Sheffield, 1979.