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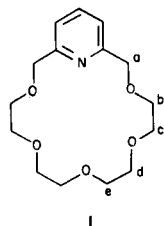
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Received March 21, 1980

Five tetradeuterated analogues (**1a**, **1b**, **1c**, **1d**, and **1e**) of 3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (pyridyl-18-crown-6, **1**) have been prepared corresponding to the five unique protonated carbon atoms of the polyether cycle. Deuterium labeling was  $\geq 99\%$  for four of the compounds and  $\geq 97\%$  for the other (**1a**).

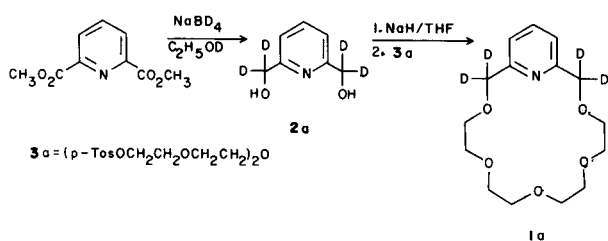
*J. Heterocyclic Chem.*, **17**, 1093 (1980).

Macrocyclic polyethers (crown ethers) have been the subject of numerous reports (2) describing their synthesis and physical and chemical properties. In a study (3) of pyridyl-substituted crown ethers, we required the use of deuterium labeled analogues of 3,6,9,12,15-pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (pyridyl-18-crown-6, **1**) (4). We present here the synthesis of five

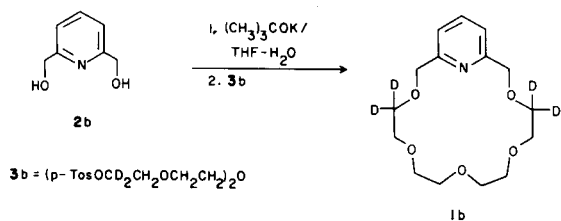


such analogues. The polyether carbons of **1** are designated a, b, c, d, and e, and the corresponding tetradeuterated compounds **1a**, **1b**, **1c**, **1d**, and **1e** were prepared. The synthetic procedures employed here should be useful in labeling other crown ether series.

Scheme I

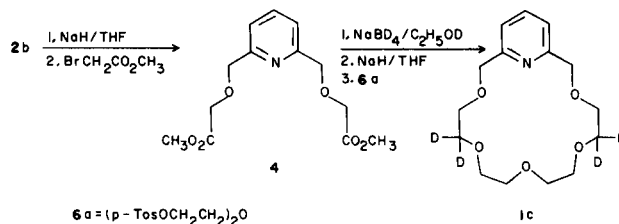


Scheme II



The synthesis of **1a** is outlined in Scheme I. Reduction of dimethyl 2,6-pyridinedicarboxylate with sodium borodeuteride in ethanol-*O-d* yielded 2,6-bis(hydroxymethyl-

Scheme III

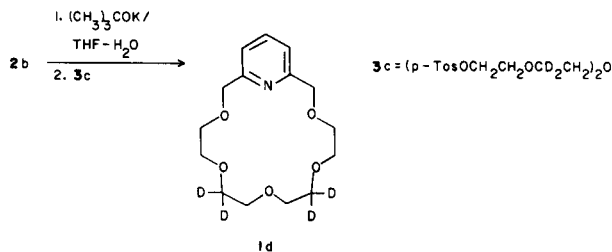


*d*<sub>2</sub>)pyridine (**2a**). This diol was converted to its disodium salt with sodium hydride in tetrahydrofuran (THF), and reaction of the salt with 3,6,9-trioxaundecane-1,11-diol di-*p*-toluenesulfonate (**3a**) yielded **1a**. By mass spectrometry **1a** contained  $\geq 3.88$  atoms of excess deuterium per molecule, which corresponds to  $\geq 97\%$  labeling.

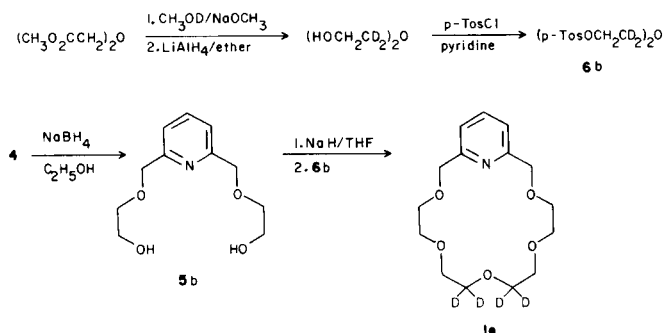
The synthesis of **1b** is outlined in Scheme II. The preparation of 3,6,9-trioxaundecane-1,11-diol-1,1,11,11-*d*<sub>4</sub> di-*p*-toluenesulfonate (**3b**) has been described previously (5), and its reaction with 2,6-bis(hydroxymethyl)pyridine (**2b**) in THF-water containing potassium *t*-butoxide yielded **1b**. By mass spectrometry **1b** contained  $\geq 3.96$  atoms of excess deuterium per molecule, which corresponds to  $\geq 99\%$  labeling.

The preparation of **1c** is outlined in Scheme III. The disodium salt of diol **2b** on reaction with methyl bromoacetate in THF yielded 2,6-bis[(methoxycarbonylmethoxy)methyl]pyridine (**4**), which was reduced with sodium borodeuteride in ethanol-*O-d* to give 2,6-bis[(2-hydroxyethoxy-2,2,2',2'-*d*<sub>4</sub>)methyl]pyridine (**5a**). Reaction of the disodium salt of diol **5a** with 3-oxapentane-1,5-diol di-*p*-toluenesulfonate (**6a**) yielded **1c**, which contained

Scheme IV



Scheme V



$\geq 3.96$  atoms of excess deuterium per molecule.

The synthesis of **1d** is outlined in Scheme IV. The reaction of previously described (5) 3,6,9-trioxaundecane-1,11-diol-4,4,8,8- $d_4$  (**3c**) with **2b** in THF-water containing potassium *t*-butoxide gave **1d**, which by mass spectrometry contained  $\geq 3.96$  atoms of excess deuterium per molecule. The preparation of **1e** is summarized in Scheme V. Exchange of the methylene protons of dimethyl 2,2'-oxydiacetate with methanol-*O-d*-sodium methoxide followed by reduction of the resultant labeled diester with lithium aluminum hydride gave 3-oxapentane-1,5-diol-2,2,4,4- $d_4$ , which was converted to 3-oxapentane-1,5-diol-2,2,4,4- $d_4$  di-*p*-toluenesulfonate (**6b**). Reduction of **4** with sodium borohydride in ethanol yielded 2,6-bis[(2-hydroxyethoxy)methyl]pyridine (**5b**), and treatment of its disodium salt with **6b** gave **1e**, which by mass spectrometry contained  $\geq 3.96$  atoms of excess deuterium per molecule.

## EXPERIMENTAL

The  $^1\text{H}$  nmr spectra were obtained with a Varian HA-100 spectrometer, and deuteriochloroform was used as solvent with tetramethylsilane as internal standard. Mass spectra were recorded with direct sample insertion on a Varian MAT CH-5 mass spectrometer. The ionizing voltage was 70 eV, the filament current 300  $\mu\text{A}$ , and the source temperature 150°. For analytical and preparative gas-liquid chromatography (glc), a 6 ft.  $\times$  1/4 in. aluminum column packed with 1% SE-30 on 60-80 mesh AW-DMCS Chromosorb W was used with helium as carrier gas. For column chromatography, unless specified otherwise, neutral alumina was used with 1% ethanol in dichloromethane as eluent. Tetrahydrofuran (THF) was purified by distillation from lithium aluminum hydride under nitrogen. Microanalyses were performed by Huffman Laboratories, Wheat Ridge, Colorado, and by Galbraith Laboratories, Knoxville, Tennessee. All melting and boiling points are uncorrected.

### 2,6-Bis(hydroxymethyl)pyridine (**2b**).

The preparation of this material followed the procedure of Cram and co-workers (6). From 15.5 g. (9.28 mmoles) of 2,6-pyridinedicarboxylic acid (Aldrich), 16.7 g. (92%) of dimethyl 2,6-pyridinedicarboxylate, m.p. 119-121° [lit. (7) m.p. 121°], was obtained. Then, 14.5 g. (7.44 mmoles) of the diester yielded 10.0 g. (97%) of crude **2b**, which was recrystallized from chloro-

form to give purified material, m.p. 112-114° [lit. (8) m.p. 114.5-115°].

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (pyridyl-18-crown-6, **1**) (**4**).

A solution of 0.347 g. (2.50 mmoles) of **2b** in 15 ml. of THF was added to a stirred solution of 0.600 g. (5.36 mmoles) of potassium *t*-butoxide in 10 ml. of THF under nitrogen. Then a solution of 0.650 g. (1.29 mmoles) of 3,6,9-trioxaundecane-1,11-diol di-*p*-toluenesulfonate (**3a**) (**9**) in 10 ml. of THF was added, and the mixture was refluxed for 30 minutes. After 0.5 ml. of water was added, the reaction mixture was refluxed under nitrogen for 15 hours, cooled to 25°, filtered, and concentrated on a rotary evaporator. The resulting oil was column-chromatographed to give 0.40 g. (54%) of crude **1**, which solidified at 0°. This material was sublimed at 80° (0.05 mm) to give **1**, m.p. 39.0-39.5° [lit. (4) m.p. 40-41°];  $^1\text{H}$  nmr:  $\delta$  3.52 (s, 8H,  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$  nonadjacent to pyridine ring), 3.64 ( $A_2B_2$ , 8H,  $\text{ArCH}_2\text{OCH}_2\text{CH}_2$ ), 4.68 (s, 4H,  $\text{ArCH}_2$ ), 7.16 (d,  $J = 8$  Hz, 2H, 3-ArH), 7.58 (t,  $J = 8$  Hz, 1H, 4-ArH).

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,2,16,16- $d_4$  (**1a**).

With the procedure for **2b**, 0.810 g. (4.16 mmoles) of dimethyl 2,6-pyridinedicarboxylate was converted to 0.230 g. (40%) of 2,6-bis(hydroxymethyl- $d_2$ )pyridine (**2a**) with sodium borodeuteride (99% D) and ethanol-*O-d* (99% D). To a stirred slurry of 0.067 g. (2.8 mmoles) of sodium hydride in 50 ml. of THF under nitrogen was added a solution of 0.200 g. (1.40 mmoles) of **2a** in 50 ml. of THF. After gas evolution ceased, a solution of 0.735 g. (1.46 mmoles) of **3a** (**9**) in 50 ml. of THF was added, and the reaction mixture was refluxed for 16 hours, cooled to 25°, filtered, and concentrated on a rotary evaporator. The residue was column-chromatographed to give 0.090 g. (21%) of **1a**, m.p. 39-39.5° [lit. (4) m.p. 40-41° for **1**];  $^1\text{H}$  nmr:  $\delta$  3.52 (s, 8H,  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$  nonadjacent to pyridine ring), 3.64 ( $A_2B_2$ , 8H,  $\text{ArCD}_2\text{OCH}_2\text{CH}_2$ ), 4.68 (bs,  $< 0.1$  H, residual  $\text{ArCHD}$ ), 7.16 (d,  $J = 8$  Hz, 2H, 3-ArH), 7.58 (t,  $J = 8$  Hz, 1H, 4-ArH). A sample was purified by preparative glc (200°), and by mass spectrometry it contained 3.88 atoms of excess deuterium per molecule.

In a separate purification, ethanol-*O-d* was used along with alumina that had been dried for 48 hours at 400° and treated with deuterium oxide. This modification did not result in **1a** with a higher deuterium content.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-4,4,14,14- $d_4$  (**1b**).

With the procedure used for **1**, 1.31 g. (2.59 mmoles) of 3,6,9-trioxaundecane-1,11-diol-1,1,11,11- $d_4$  di-*p*-toluenesulfonate (**3b**) (**5**) and 0.348 g. (2.49 mmoles) of **2b** gave 0.260 g. (33%) of **1b**, m.p. 39-39.5° [lit. (4) m.p. 40-41° for **1**];  $^1\text{H}$  nmr:  $\delta$  3.52 (s, 8H,  $\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2$ ), 3.64 (s, 4H,  $\text{CH}_2\text{CD}_2$ ), 4.68 (s, 4H,  $\text{ArCH}_2$ ), 7.16 (d,  $J = 8$  Hz, 2H, 3-ArH), 7.58 (d,  $J = 8$  Hz, 1H, 4-ArH). A sample was purified by preparative glc (200°), and by mass spectrometry it contained  $\geq 3.96$  atoms of excess deuterium per molecule.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-5,5,13,13- $d_4$  (**1c**).

A procedure of Cram and Newcomb (10) for **1** with appropriate deuterated reagents gave **1c**. A solution of 5.80 g. (42.0 mmoles) of **2b** in 200 ml. of THF was added to a stirred slurry of 4.90 g. (0.204 mole) of sodium hydride in 200 ml. of THF under nitrogen. After gas evolution ceased, 40.0 g. (0.260 mole) of

methyl bromoacetate was added, and the mixture was refluxed for 8 hours, cooled to 25°, filtered, and concentrated on a rotary evaporator. The residue was dissolved in a mixture of 100 ml. of water and 250 ml. of dichloromethane, and the resulting aqueous layer was acidified to pH 5 with 5% hydrochloric acid. The dichloromethane layer was dried over sodium sulfate, and rotary evaporation left crude product which was column-chromatographed on silica gel with acetone-dichloromethane elution to give 3.86 g. (34%) of 2,6-bis[(methoxycarbonylmethoxy)methyl]pyridine (**4**) (**10**) as an oil; <sup>1</sup>H nmr: δ 3.69 (s, 6H, CH<sub>3</sub>), 4.16 (s, 4H, OCH<sub>2</sub>CO), 4.67 (s, 4H, ArCH<sub>2</sub>), 7.31-7.79 (m, 3H, ArH).

A solution of 1.20 g. (4.24 mmoles) of **4** and 0.540 g. (12.9 mmoles) of sodium borodeuteride (99% D) in 50 ml. of ethanol-*O-d* (99.9% D) was refluxed under nitrogen for 10 hours. The ethanol-*O-d* was removed by distillation, and the residue was dissolved in 30 ml. of water and extracted four times with dichloromethane. The combined extracts were dried over sodium sulfate and rotary evaporated to leave 0.58 g. (58%) of 2,6-bis[(2-hydroxyethoxy-2,2,2',2'-d<sub>4</sub>)methyl]pyridine (**5a**) (**10**) as an oil; <sup>1</sup>H nmr: δ 3.63 (s, 4H, CH<sub>2</sub>CD<sub>2</sub>), 4.51 (bs, 2H, OH), 4.59 (s, 4H, ArCH<sub>2</sub>), 7.12-7.71 (m, 3H, ArH).

A solution of 0.470 g. (2.00 mmoles) of **5a** in 20 ml. of THF was added to a stirred slurry of 0.125 g. (5.23 mmoles) of sodium hydride in 20 ml. of THF under nitrogen. After gas evolution ceased, a solution of 0.828 g. (2.00 mmoles) of 3-oxapentane-1,5-diol di-*p*-toluenesulfonate (**6a**) (**11**) in 20 ml. of THF was added, and the mixture was refluxed for 16 hours, cooled to 25°, filtered, and concentrated on a rotary evaporator. Column-chromatography of the residue gave 0.262 g. (44%) of **1c**, m.p. 39-39.5° [lit. (**4**) m.p. 40-41° for **1**]; <sup>1</sup>H nmr: δ 3.52 (s, 8H, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>), 3.64 (s, 4H, CH<sub>2</sub>CD<sub>2</sub>), 4.69 (s, 4H, ArCH<sub>2</sub>), 7.16 (d, J = 8 Hz, 3H, 3-ArH), 7.58 (t, J = 8 Hz, 1H, 4-ArH). A sample was purified by preparative glc (200°), and by mass spectrometry it contained ≥ 3.96 atoms of excess deuterium per molecule.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-7,7,11,11-d<sub>4</sub> (**1d**).

With the procedure used for **1**, 0.348 g. (2.49 mmoles) of **2b** and 1.31 g. (2.59 mmoles) of 3,6,9-trioxaundecane-1,11-diol-4,4,8,8-d<sub>4</sub> (**3c**) (**5**) gave 0.220 g. (28%) of **1d**, m.p. 39-39.5° [lit. (**4**) m.p. 40-41° for **1**]; <sup>1</sup>H nmr: δ 3.52 (s, 4H, CD<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CD<sub>2</sub>), 3.64 (A<sub>2</sub>B<sub>2</sub>, 8H, CH<sub>2</sub>CH<sub>2</sub>), 4.68 (s, 4H, ArCH<sub>2</sub>), 7.16 (d, J = 8 Hz, 2H, 3-ArH), 7.58 (t, J = 8 Hz, 1H, 4-ArH). A sample was purified by preparative glc (200°), and by mass spectrometry it contained ≥ 3.96 atoms of excess deuterium per molecule.

3,6,9,12,15-Pentaoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene-8,8,10,10-d<sub>4</sub> (**1e**).

In 8.0 g. (0.24 mole) of methanol-*O-d* (99% D) under nitrogen 5 mg. (0.2 mmole) of sodium was dissolved, and then 1.00 g. (8.95 mmoles) of dimethyl 2,2'-oxydiacetate (**5**) was added. The mixture was stirred at 25° for 24 hours, and methanol-*O-d* was removed by vacuum distillation. Without the use of additional

sodium, the above procedure was repeated eight times with fresh 8.0 g. portions of methanol-*O-d*. After the last exchange, 8 drops of 20% deuterium chloride in deuterium oxide (99% D, Aldrich) were added, and methanol-*O-d* was distilled. The resulting diester was reduced with lithium aluminum hydride in ether in standard fashion to give 0.22 g. (33%) of 3-oxapentane-1,5-diol-2,2,4,4-d<sub>4</sub>, which was converted (**9**) to the corresponding di-*p*-toluenesulfonate **6b**. Reduction of diester **4** with sodium borohydride in ethanol with the procedure used for preparation of **5a** gave 2,6-bis[(2-hydroxyethoxy)methyl]pyridine (**5b**). Then with the procedure employed for **1c**, 0.282 g. (1.22 mmoles) of **5b** and 0.440 g. (1.05 mmoles) of **6b** yielded 0.0820 g. (22%) of **1e**, m.p. 39-39.5° [lit. (**4**) m.p. 40-41° for **1**]; <sup>1</sup>H nmr: δ 3.52 (s, 4H, CH<sub>2</sub>CD<sub>2</sub>OCD<sub>2</sub>CH<sub>2</sub>), 3.64 (A<sub>2</sub>B<sub>2</sub>, 8H, CH<sub>2</sub>CH<sub>2</sub>), 4.68 (s, 4H, ArCH<sub>2</sub>), 7.16 (d, J = 8 Hz, 2H, 3-ArH), 7.58 (t, J = 8 Hz, 1H, 4-ArH). A sample was purified by preparative glc (200°), and by mass spectrometry it contained ≥ 3.96 atoms of excess deuterium per molecule.

#### Acknowledgment.

We warmly thank Professors Donald J. Cram and Martin Newcomb for providing crown ether samples and synthetic procedures prior to publication. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Marathon Oil Company for support of this research.

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