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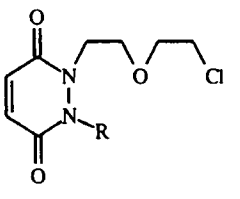
CHEMISTRY OF CROWN ETHERS. SYNTHESIS OF NEW CROWN ETHERS CONTAINING A PYRIDAZINE RING

T. R. Akopyan and E. G. Paronikyan

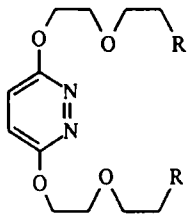
A method for preparation of crown ethers containing a pyridazine ring based on 1,2-dihydro-3,6-dioxopyridazine was developed.

In expanding our studies [1], new crown ethers of the pyridazine series were synthesized. 1,2-Dihydro-3,6-dioxopyridazine [4, 5] and di-, tri-, and tetraethylene glycol dichlorides were used as the starting compounds. Crown ethers containing benzene, cyclohexane [2], benzimidazole [3] and other rings are synthetic complexones. They can form complexes with alkali metal ions and some organic compounds and transport them through different biological membranes.

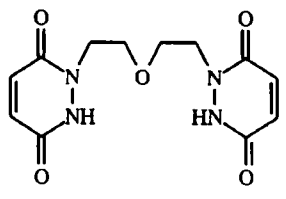
1,2-Dihydro-3,6-dioxo-N-(3-oxa-5-chloropentyl)pyridazine (I) and 1,2-dihydro-3,6-dioxo-N,N-bis(3-oxa-5-chloropentyl)-pyridazine (II) were obtained by the reaction of 1,2-dihydro-3,6-dioxopyridazine potassium salt with 3-oxa-1,5-dichloropentane. 3,6-bis(1,4-Dioxa-6-hydroxyhexyl)pyridazine (III) was synthesized from 3,6-dichloropyridazine [6]; when treated with thionyl chloride, it was transformed into 3,6-bis(1,4-dioxa-6-chlorohexyl)pyridazine (IV). 1,5-bis(1,2-Dihydro-3,6-dioxopyridazyl-1)-3-oxapentane (V) was obtained as a result of the reaction of compound I and 1,2-dihydro-3,6-dioxopyridazine or two moles of 1,2-dihydro-3,6-dioxopyridazine with 1 mole of 3-oxa-1,5-dichloropentane in the presence of potassium hydroxide. Crown ethers (VI-XII) were synthesized from equimolar quantities of 1,2-dihydro-3,6-dioxopyridazine and the corresponding dichloride, and compounds VIII and XII were separated as complexes with KCl (1:1 and 1:3, respectively).



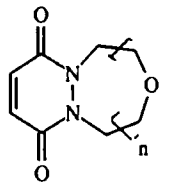
I R = H
II R = $(CH_2)_2O(CH_2)_2Cl$



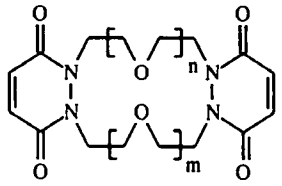
III R = OH
IV R = Cl



V



VI n = 1; VII n = 2
VIII n = 3



IX n = 1, m = 1; X n = 1, m = 2
XI n = 2, m = 2; XII n = 3, m = 1

The structures of the synthesized compounds were confirmed by the results of elemental analysis and by the PMR, IR, and mass spectral data. The purity of the compounds was evaluated by TLC.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Republic of Armenia, Erevan 375014. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1693-1695, December, 1997. Original article submitted April 17, 1997.

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TABLE 1. Characteristics of the Synthesized Crown Ethers

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f	Yield, %
		C	H	N			
VII	$C_{10}H_{14}N_2O_4$	53,13 / 52,90	7,22 / 7,09	12,53 / 12,33	Oil	0,72	45,0
VIII·KCl	$C_{12}H_{18}N_2O_5 \cdot KCl$	41,64 / 41,80	5,14 / 5,26	8,25 / 8,12	255...256	0,76	26,1
IX	$C_{16}H_{20}N_4O_6$	52,66 / 52,73	5,41 / 5,51	15,52 / 15,37	30...32	0,79	20,9
XI	$C_{20}H_{28}N_4O_8$	52,96 / 53,09	5,97 / 6,23	12,61 / 12,38	Oil	0,75	44,2
XII·3KCl	$C_{20}H_{28}N_4O_8 \cdot 3KCl$	44,16 / 44,05	5,39 / 5,19	10,57 / 10,31	260...262	0,74	33,5

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in liquid petrolatum. The mass spectra were made on an MX-1303 with direct sample introduction in the ionization region and ionizing electron energy of 30 eV and admission temperature 40-50°C below the melting point of the substance. The PMR spectra were made on a Varian T-60. TMS was the internal standard. The melting points were determined on a Boetius RNMK-05 stage. Thin-layer chromatography was performed on UF-254 plates in pyridine water systems, 20:1 (I, II); 15:1 (IV); 30:1 (III, V-XII), development with iodine vapors.

1,2-Dihydro-3,6-dioxo-N-(3-oxa-5-chloropentyl)pyridazine (I). A solution of 5.6 g (0.1 mole) of potassium hydroxide in 100 ml of 75% ethanol was added to a suspension of 11.3 g (0.1 mole) of 1,2-dihydro-3,6-dioxopyridazine in 100 ml of ethanol, heated to boiling. The mixture was boiled for 1 h, then 14.3 g (0.1 mole) of 3-oxa-1,5-dichloropentane was added and boiling was continued for 40-42 h. The residue was filtered off and the filtrate was evaporated. Then 50 ml of water was added to the sediment. The precipitated crystals of product I were filtered off, washed with water, and dried. Yield of 4.7 g (21.5%). Mp = 180-181°C (from water). IR spectrum: 3200 (NH), 1680 (C=O), 1600 (C=C), 1140 (C−O−C) cm^{-1}. Found, %: C 43.87; H 5.11; Cl 16.01; N 12.93. $C_8H_{11}ClN_2O_3$. Calculated, %: C 43.95; H 5.07; Cl 16.22; N 12.81. R_f = 0.73.

1,2-Dihydro-3,6-dioxo-N,N'-bis(3-oxa-5-chloropentyl)pyridazine (II). The reaction mixture prepared, as described above, from 0.1 mole of 1,2-dihydro-3,6-dioxopyridazine in 100 ml of ethanol, 0.2 mole of potassium hydroxide in 100 ml of 75% ethanol, and 0.2 mole of 3-oxa-1,5-dichloropentane, was boiled for 30 h. The residue was filtered off and the solvent was evaporated. Then 50 ml of water was added to the sediment and it was extracted with ether. The extract was evaporated to a small volume, and the precipitated crystals of product II were filtered off, washed with a small amount of ether, and dried. Yield of 1.5 g (4.6%). Mp = 122-123°C (from water). IR spectrum: 1680 (C=O), 1600 (C=C), 1150 (C−O−C) cm^{-1}. PMR spectrum (pyridine-D_5): 3.6-4.0 (12H, m, $6CH_2$); 4.34-4.51 (4H, m, $2CH_2Cl$); 6.79 ppm (2H, s, CH ≡ CH). Mass spectrum, *m/e* (%): 324/326 (M^+) (100/45), 261 (65), 245 (59), 218 (32). Found, %: C 44.51; H 5.53; Cl 21.23; N 8.89. $C_{12}H_{18}Cl_2N_2O_4$. Calculated, %: C 44.31; H 5.56; Cl 21.49; N 8.61. R_f = 0.79.

3,6-bis(1,4-Dioxa-6-hydroxyhexyl)pyridazine (III). A solution of 14.9 g (0.1 mole) of 3,6-dichloropyridazine in 150 ml of diethylene glycol was added by drops to a solution of 25.6 g (0.2 mole) of diethylene glycol monosodium salt in 100 ml of diethylene glycol at 120-140°C. The reaction mixture was held at the same temperature for 10 h. The residue was filtered off and the solvent was distilled off. Product III was separated by vacuum distillation of the sediment. Yield of 19 g (65.5%). Bp = 230-232°C/2 mm Hg. Mp = 54-55°C (from benzene). IR spectrum: 3200-3300 (OH), 1610 (C=C, C=N), 1150 (C−O−C) cm^{-1}. PMR spectrum (acetone-D_6): 3.55-4.0 (12H, m, $6CH_2$); 4.41-4.72 (4H, m, $2CH_2$); 7.05 ppm (2H, s, CH=CH). Found, %: C 50.24; H 7.05; N 9.82. $C_{12}H_{20}N_2O_6$. Calculated, %: C 49.98; H 6.97; N 9.71. R_f = 0.75.

3,6-bis(1,4-Dioxa-6-chlorohexyl)pyridazine (IV). A solution of 15 g (0.125) mole of thionyl chloride in 50 ml of dry benzene was added by drops to 14.4 g (0.05 mole) of compound III in 150 ml of boiling dry benzene. Boiling was continued for 8-10 h until separation of hydrogen chloride stopped. After cooling, the benzene layer was washed with water to neutral reaction, dried over anhydrous magnesium sulfate, the benzene was distilled off, and the residue crystallized on standing. Yield of 10.0 g (62.2%). Mp = 41-42°C (from water). PMR spectrum (CCl_4): 3.6-4.0 (12H, m, $6CH_2$); 4.41-4.68 (4H, m, $2CH_2Cl$); 6.9 ppm (2H, s, CH=CH). Found, %: C 44.21; H 5.84; Cl 21.52; N 8.31. $C_{12}H_{18}Cl_2N_2O_4$. Calculated, %: C 44.31; H 5.56; Cl 21.80; N 8.61. R_f = 0.74.

1,5-bis(1,2-Dihydro-3,6-dioxopyridazyl-1)-3-oxapentane (V). Product V was obtained similar to compound I from 11.3 g (0.1 mole) of 1,2-dihydro-3,6-dioxopyridazine, 5.6 g (0.1 mole) of potassium hydroxide, and 7.16 g (0.05 mole) of 3-oxa-1,5-dichloropentane. After boiling the reaction mixture for 40-42 h, the residue was filtered and the solvent was distilled off. Then 20 ml of ice water was added to the sediment, and the precipitated crystals of product V were filtered off, washed with water and ether, and dried. Yield of 2.0 g (13.6%). Mp = 163-164°C (from water–acetone mixture, 1:15). IR spectrum: 3200 (NH), 1680 (C=O), 1590 (C=C), 1140 (C–O–C) cm^{-1}. Found, %: C 48.84; H 4.65; N 19.11. $C_{12}H_{14}N_4O_5$. Calculated, %: C 48.99; H 4.79; N 19.04. R_f = 0.74.

1,4-Dioxo-1,4,5,6,7,9,10,11-octahydro[1,2-*d*]-1,4,5-oxadiazepine (VI). Product VI was prepared similar to compound I from 0.1 mole of 1,2-dihydro-3,6-dioxopyridazine, 0.2 mole of potassium hydroxide, and 0.1 mole of 3-oxa-1,5-dichloropentane. After distillation of the solvent, the residue was dissolved in 50 ml of water and extracted with ether. The aqueous layer was neutralized with hydrochloric acid, the precipitated crystals of unreacted 1,2-dihydro-3,6-dioxopyridazine were filtered, and the water was evaporated until dry. The crystalline residue was washed several times on the filter with absolute ethanol. The filtrate was evaporated, and the residue — product VI — was dried in a vacuum desiccator. Yield of 8 g (44.5%). Mp = 70-71°C. IR spectrum: 1680 (C=O), 1600 (C=C), 1140 (C–O–C) cm^{-1}. PMR spectrum (DMSO-D_6): 4.05-4.37 (8H, m, $4CH_2$); 6.63 ppm (2H, s, CH=CH). Mass spectrum, *m/e* (%): 182 (M^+) (100), 154 (20), 139 (35), 125 (48), 124 (60). Found, %: C 52.42; H 5.32; N 15.22. $C_8H_{10}N_2O_3$. Calculated, %: C 52.68; H 5.48; N 15.38. R_f = 0.75.

1,4-Dioxo-1,4,5,6,7,9,10,12,13,14-decahydro[1,2-*g*]-1,4,5,6-dioxadiazepine (VII) and 1,4-dioxo-1,4,5,6,7,9,10,12,13,15,16,17-dodecahydro[1,2-*j*]-1,4,7,10,11-trioxadiazacyclotridecine (VIII) was obtained analogously from 1,2-dihydro-3,6-dioxopyridazine and the corresponding dichlorides (see Table 1).

1,4,12,15-Tetraoxo-1,4,5,6,7,9,10,11,12,15,16,17,18,20,21,23,24,25-octadecahydro-bis-pyridazino[1,2-*g*;1,2-*n*]-1,4,11,7,8,14,15-trioxatetracyclopentadecine (X). A solution of 11.2 g (0.2 mole) of potassium hydroxide in 100 ml of 75% ethanol was added to a suspension of 22.6 g (0.2 mole) of 1,2-dihydro-3,6-dioxopyridazine in 200 ml of ethanol, heated to boiling. The mixture was boiled for 1 h and then 14.3 g (0.1 mole) of 3-oxa-1,5-dichloropentane was slowly added by drops. Boiling was continued for 10 h, then a solution of 11.2 g (0.2 mole) of potassium hydroxide in 100 ml of 75% ethanol was added by drops, boiled for 1 h, and 18.7 g (0.1 mole) of 3,6-dioxa-1,8-dichlorooctane was added by drops. The reaction mixture was boiled for 30 h, the residue was filtered off, the filtrate was evaporated, and the sediment was dissolved in 100 ml of water and extracted with ether. The aqueous layer was neutralized with hydrochloric acid, filtered, and the filtrate was evaporated dry. Product X was separated from the sediment with hot chloroform and crystallized on standing after distillation of the chloroform. Yield of 12.5 g (30.6%). Mp = 150-151°C (water–acetone, 1:20). IR spectrum: 1690 (C=O), 1600 (C=C), 1150 (C–O–C) cm^{-1}. Mass spectrum, *m/e* (%): 408 (M^+) (100), 354 (71), 284 (64), 236 (29). Found, %: C 52.83; H 5.77; N 13.55. $C_{18}H_{24}N_4O_7$. Calculated, %: C 52.95; H 5.92; N 13.72. R_f = 0.80.

Similarly **1,4,12,15-tetraoxo-1,4,5,6,7,9,10,11,12,15,16,17,18,20,21,22-hexadecahydro-bis-pyridazino-[1,2-*d*;1,2-*k*]-1.8,4.5,11,12-dioxatetrazacyclotetradecine (IX), 1,4,15,18-tetraoxo-1,4,5,6,7,9,10,12,13,14,15,18,19,20,21,23,24,26,27,28-eucosahydro-bis-pyridazino[1,2-*g*; 1,2-*q*]-1,4,11,14,7,8,17,18-tetraoxatetrazacycloeucosine (XI)**, and **1,4,12,15-tetraoxo-1,4,5,6,7,9,10,11,12,15,16,17,18,20,21,23,24,26,27,28-eucosahydro-bis-pyridazino[1,2-*d*; 1,2-*k*]-1,4,7,14,10,11,17,18-tetraoxatetrazacycloeucosine (XII)** were prepared from 1,2-dihydro-3,6-dioxopyridazine and the corresponding dichlorides (see Table 1).

REFERENCES

1. S. A. Vartanyan, T. R. Akopyan, and E. G. Paronikyan, Arm. Khim. Zh., **31**, 349 (1978).
2. C. J. Pedersen and H. K. Frensdorf, Angew. Chem., **84**, 16 (1972).
3. M. M. Htay and O. Meth-Cohn, Tetrahedron Lett., No. 6, 469 (1976).
4. R. H. Mizzoni and P. E. Sporri, J. Am. Chem. Soc., **73**, 1873 (1951).
5. P. R. Wood, Anal. Chem., **25**, 1879 (1953).
6. E. A. Steck, R. P. Brundage, and L. T. Fletcher, J. Am. Chem. Soc., **76**, 3225 (1954).