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Synthesis of Tetrakisbenzo–31(34)–crown–7(8) Ethers

Truong Hong Hieu,[a,c] Nguyen T. T. Phuong,[d] Anatoly T. Soldatenkov,[e]
Vasily E. Kotsuba,[e] Elena I. Polyakova,[e] Nguyen Van Tuyen,[a,b] Tran T. Thanh Van,[d]
Dang T. Tuyet Anh,[a,b] and Le Tuan Anh[d@]

[a]*Institute of Chemistry, Vietnam Academy of Science and Technology, Hanoi, Vietnam*
[b]*Graduate University of Science and Technology, Vietnam Academy of Science and Technology, Hanoi, Vietnam*
[c]*Department of Biotechnology, Vietnam-Russia Tropical Centre, Hanoi, Vietnam*
[d]*Faculty of Chemistry, University of Science, Vietnam National University, Hanoi, Vietnam*
[e]*RUDN University, 117198 Moscow, Russia*
[@]*Corresponding author E-mail: anhlt.vnu@gmail.com*

*Condensations of 1,5-bis(2-formylphenoxy)-3-oxapentane (**1a**) or 1,8-bis(2-formylphenoxy)-3,6-dioxanoctane (**1b**) podands and 1,8-bis(2-acetylphenoxy)-3,6-dioxanoctane (**2**) gave two novel crown ethers: tetrakis-(benzo)-31-crown-7 ether (**5**) and tetrakis(benzo)-34-crown-8 ether (**6**). Their molecular structures were established by IR, NMR and MS methods.*

Keywords: Tetrakis(benzo)-31-crown-7 ether, tetrakis(benzo)-34-crown-8 ether, Petrenko-Kritchenko reaction, diketon, dialdehyde.

Синтез тетрабензо–31(34)–краун–7(8) эфиров

Т. Х. Хиеу,[a,c] Н. Т. Т. Фьонг,[d] А. Т. Солдатенков,[e] В. Е. Коцюба,[e] Е. И. Полякова,[e]
Н. В. Туен,[a,b] Т. Т. Т. Ван,[d] Д. Т. Т. Ань,[a,b] Л. Т. Ань[d@]

[a]*Институт химии, Вьетнамская академия науки и технологии, Ханой, Вьетнам*
[b]*Высший университет науки и техники, Вьетнамская академия наук и технологии, Ханой, Вьетнам*
[c]*Факультет биотехнологии, Российско-Вьетнамский Тропический центр, Ханой, Вьетнам*
[d]*Факультет химии, Университет науки, Вьетнамский национальный университет, Ханой, Вьетнам*
[e]*Российский университет дружбы народов, 117198 Москва, Россия*
[@]*E-mail: anhlt.vnu@gmail.com*

*Конденсация подандов, 1,5-бис(2-формилфенокси)-3-оксапентана (**1a**) или 1,8-бис-(2-формилфенокси)-3,6-диоксаноктана (**1b**), с 1,8-бис(2-ацетилфенокси)-3,6-диоксаноктаном (**2**) привела к образованию двух новых краун-эфиров – тетракис(бензо)-31-краун-7 эфира (**5**) и тетракис(бензо)-34-краун-8 эфира (**6**). Их молекулярная структура была подтверждена методами ИК, ЯМР спектроскопии и масс-спектрометрии.*

Ключевые слова: Тетракис(бензо)-31-краун-7 эфир, тетракис(бензо)-34-краун-8 эфир, реакция Петренко-Криченко, дикетон, диальдегид.

In the previous publications,[1,2,3] we have reported on the preparations of dibenzo[γ-(aryl)pyrido]aza-14-crown-4 ethers from arylaldehyde, 1,5-bis(2-acetylphenoxy)-3-oxapentane and ammonium acetate by Petrenko-Kritchenko reaction. These new compounds containing γ-phenylpyridine ring exhibited cytotoxicity to several cancer cell lines: Hepatocellular carcinoma (Hep-G2); Rhabdosarcoma (RD), Human Uterine (FL); Human Breast adenocarcinoma (MCF7).[1,3] In addition, using the similar domino reaction for synthesis of new azacrown ether, we have obtained a macroheterocyclic system containing two azacrown ether fragments.[4]

With the aim of preparing ditopic systems (**3a**,**b**), we have studied condensation of bis(2-formylphenoxy)-3,6-dioxaoctane (**1a**) or bis(2-formylphenoxy)-3-oxapentane (**1b**) with bis(2-acetylphenoxy)-3-oxapentane and ammonium acetate. However, instead of the expected azacrown systems (**3a**,**b**) the tetrakis(benzo)crown ethers (**4a**,**b**) were isolated by column chromatography with the low yield (20–28 %).[5,6]

The structure of (**4a**,**b**) were determined by IR, NMR, MS and X-ray analysis. The volume of internal cavity of macrocycle **(4b)** is equal to 125 Å^3. The dihedral angles between the benzene planes of C1, C43-C47/C5-C10, C5-C10/C18-C23, C18-C23/C27-C32 and C27-C32/C1,C43-C47 are 64.91(8), 65.14(8), 61.64(8) and 56.67(9)°, respectively.[5,6]

To optimize the reaction and continue developing of novel tetrakis(benzo)crown ethers, the similar condensations of two dialdehydes (**1a**,**b**) with diketones (**2**) without ammonium acetate were studied. The reaction was stirred in system $K_2CO_3/H_2O/C_2H_5OH$ for 3 h at 50 °C. The formed yellow wax-like precipitate was separated and recrystallized from ethanol. Macroheterocycles 31-crown-7 ethers (**5**) and 34-crown-8 ether (**6**) were obtained in good yields (up to 88 %).

The structure of compounds (**5**, **6**) was determined by NMR, IR spectrometry and MS spectrometry. Thus, in the ^{1}H NMR spectra of macroheterocycle tetrakis(benzo)31-crown-7 ether (**5**) the signals of sixteen aromatic proton appeared in the region δ 6.85–7.54 ppm and four vinylketone protons (CH=CH–C=O) were observed in the weak field at δ 7.60 ppm and δ 7.78 ppm as two doublets (2H of each: H–2, H–3 and H–28, H–29). Spin-spin coupling constant ^3J of ethylene protons is equal to 16.5 Hz in both cases, which indicated the *trans-position* of –Ph and –(C=O)–Ph substituents. Signals from the polyether groups (–CH_2O–) appeared as four multiplets in the region δ 3.54-4.17 ppm. The ^{13}C NMR spectra show many pairs of symmetric carbon atoms. All methylene carbon appear in the region of δ 68.65, 68.73, 69.27, 70.01, 70.70 ppm, and $C_{carbonyl}$ (C4, C27) is observed at 194.46 ppm. Its IR spectrum displays absorption bands at 1643 cm^{-1} which is characteristic for C=O bonds. HPLC-MS (ESI) gave a clear [M+Na]$^+$ peak at 687.25671 which agrees with the overall molecular formula of 31-crown-7 ether (**5**). Compound (**6**) is a 34-membered crownophane with the vinylketone protons resonate in the weak field at δ 7.36 and 7.88 ppm with the spin-spin coupling constant ^3J = 16.0 Hz in both cases. All the signals of aromatic proton appear in the region δ 6.80–7.56 ppm and the signals of twenty four methylene protons (–CH_2O–) overlap each other and give rise to six multiplets in the region of δ 3.26–4.13 ppm. The

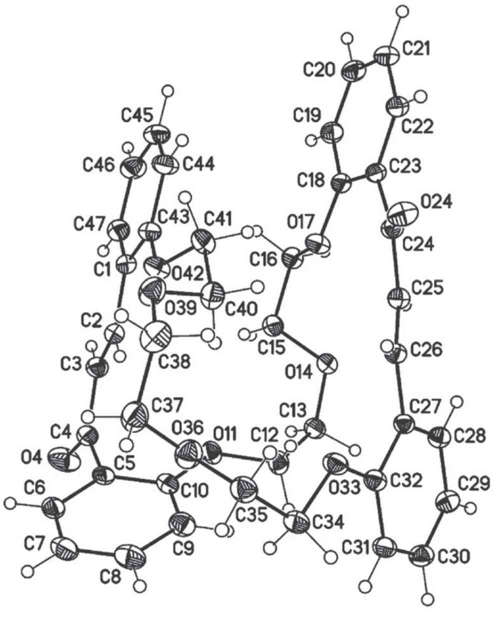
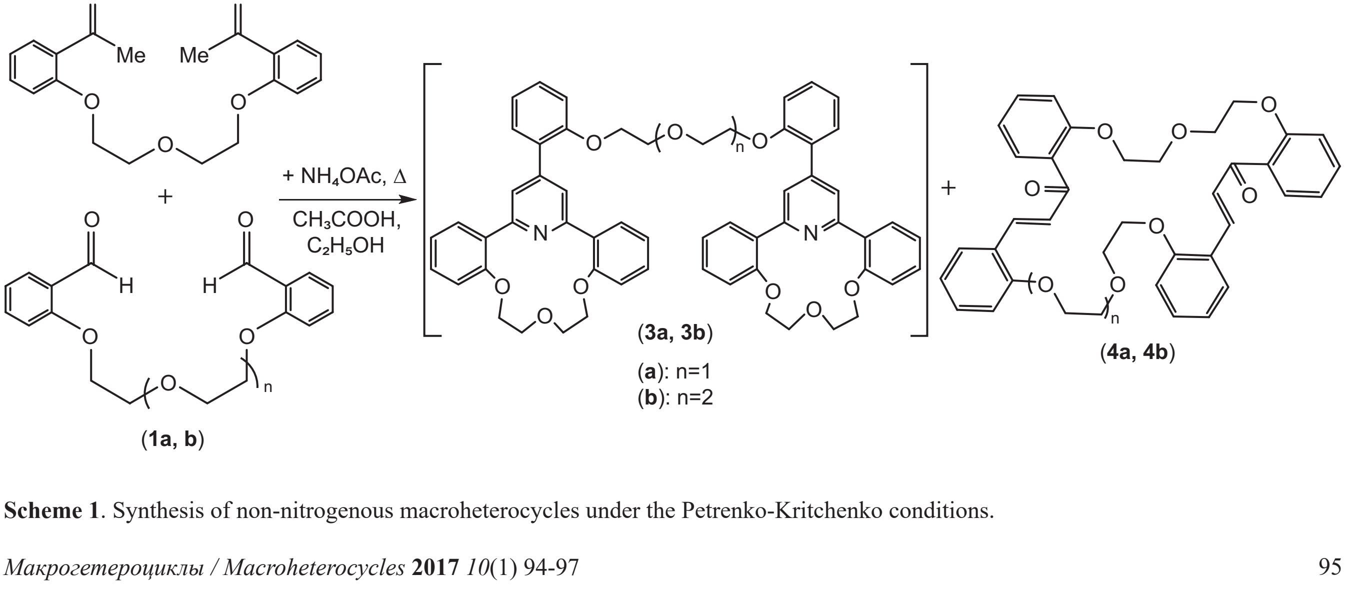
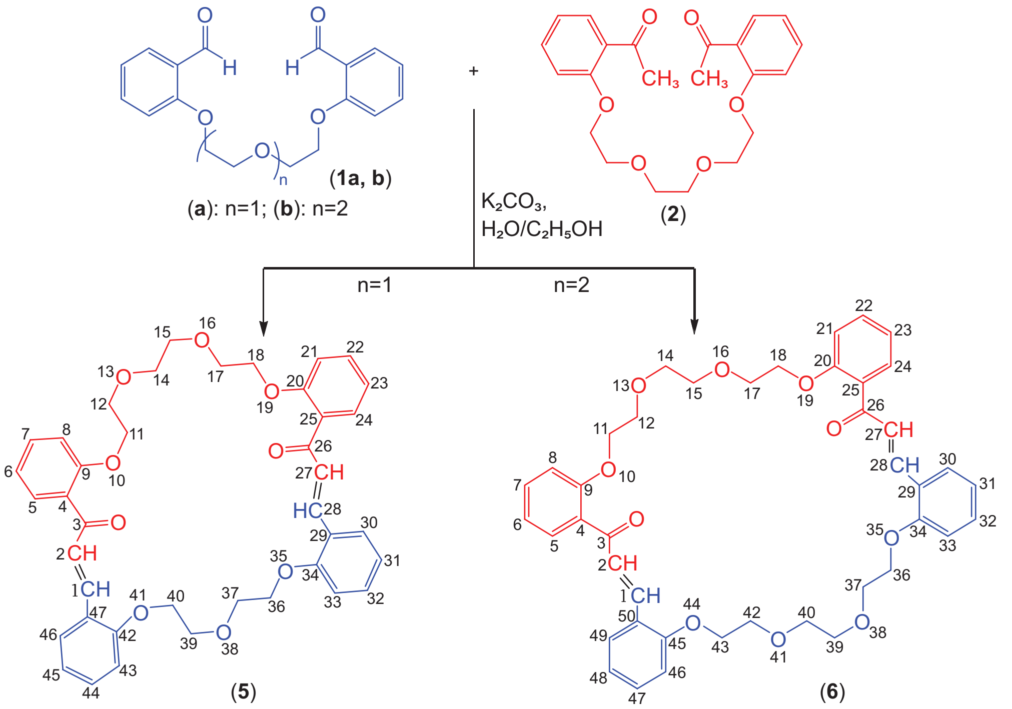


Figure 1. General view and crystallographic numeration of compound (**4b**) according to X-ray study data.



Scheme 1. Synthesis of non-nitrogenous macroheterocycles under the Petrenko-Kritchenko conditions.



Scheme 2. Synthesis of tetrakis(benzo)-31-crown-7 ether and tetrakis(benzo)-34-crown-8 ether.

IR absorption band near 1654 cm^{-1} confirmed the presence of C=O functional groups. The structure of compound (**6**) was further supported by its LC-MS spectra (ESI), indicating the clear $[M+H]^+$ ion peak at *m/z* 709.2.

All of non-nitrogenous macroheterocycles (**4a**,**b**, **5**, **6**) are interesting as effective complexing ligands in the coordination chemistry.

Experimental

Melting points were determined using a Raga melting point apparatus. IR spectra were recorded on Shimadzu FT IR PC (S) 8201spectrometer by using KBr pellets and the absorption frequencies are expressed in reciprocal centimeters (cm^{-1}). NMR spectra was taken on BRUKER 500 MHz spectrometer using TMS as an internal reference. The chemical shifts were expressed in parts per million (ppm). ESI-MS were recorded in LTQ orbitrap XL mass spectrometer, Thermo Scientific Company

(2E,28E)-11,14,17,20,36,39,42-Heptaoxapentacyclo-[41.4.0.0^{5,10}.0^{21,26}.0^{30,35}]-heptatetraconta-1(43),2,5(10),6,8, 21,23,25,28,30,32,34,44,46-tetradecaen-2,28-dione (5). A solution of 1,5-bis(2-formylphenoxy)-3-oxapentane (**1a**) (0.41 g, 1.30 mmol) in ethanol (10 ml) and a solution of 1,8-bis(2-acetylphenoxy)-3,6-dioxanoctane (**2**) (0.50 g, 1.30 mmol) in ethanol (10 ml) were added simultaneously to a suspension of K_2CO_3(5.0 g, 36 mmol) in 30 ml water/ethanol (1:1). The reaction mixture was magnetically stirred at 50 °C for 3 days. The formed precipitate was filtered off, washed with ethanol and chromatographically purified on silica gel (eluating with hexane-ethylacetate, 2:1). Compound (**5**) was obtained as 0.74 g light-yellow crystals (85.0 %). R_f=0.64 (*n*-hexane/EtOAc, 1:1). M.p. 126–128 °C. IR (KBr) ν cm^{-1}: 2920, 2870, 1643, 1599, 1485. ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K) δ_H ppm: 3.54, 3.88, 4.00 and 4.17 (all m, 6H, 5H, 5H and 4H, respectively, $-CH_2CH_2O-$); 6.85-7.54 (16H, m, $H_{arom.}$), 7.60 and 7.78 (both d, 2H each, O=C–CH_{trans}=CH, *J*=16.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, 300 K) δ_C ppm: 68.65 (C38, C40), 68.73 (C13, 18), 69.27 (C15, C16), 70.01 (C12, C19), 70.70 (C37, C41),112.75 (C34, C44), 112.79 (C9, C22), 120.93 (C7, C24), 121.10 (C46, C32), 124.44 (C3, C28), 128.63 (C6, C25), 129.44 (C1, C30), 130.01 (C33, C45), 130.17 (C5, C26), 131.43 (C31, C47), 132.27 (C8, C23), 139.30 (C2, C29), 157.10 (C35, C43), 157.97 (C10, C21), 194.46 (C4, C27). HRMS calcd. for $C_{40}H_{40}NaO_9$ $[M+Na]^+$: 687.25700, found: 687.25671.

(2E,28E)-11,14,17,20,36,39,42,45-Octaoxapentacyclo-[41.4.0.0^{5,10}.0^{21,26}.0^{30,35}]-pentaconta-1(46),2,5(10),6,8,21,23, 25,28,30,32,34,47,49-tetradecaen-2,28-dione (6). A solution of 1,8-bis(2-formylphenoxy)-3,6-dioxanoctane (**1b**) (0.41 g, 1.30 mmol) in ethanol (10 ml) and a solution of 1,8-bis(2-acetylphenoxy)-3,6-dioxanoctane (**2**) (0.46 g, 1.30 mmol) in ethanol (10 ml) were added simultaneously to a suspension of K_2CO_3 (5.0 g, 36 mmol) in 30 ml water/ethanol (1:1). The reaction mixture was magnetically stirred at 50 °C for 3 days. The formed precipitate was filtered off, washed with ethanol and chromatographically purified on silica gel (eluating with hexane-ethylacetate, 2:1). Compound (**6**) was obtained as light-yellow crystals (0.74 g, 1.11 mmol, 88.0 %). R_f=0.51 (*n*-hexane/EtOAc, 1:1). M.p. 174–176 °C. IR (KBr) ν cm^{-1}: 2932, 2872, 1655, 1599, 1485. ^{1}H NMR ($CDCl_3$, 500 MHz, 300 K) δ_H ppm: 3.26, 3.57, 3.64, 3.87, 4.03 and 4.13 (all m, 4H each, respectively, $-CH_2CH_2O-$); 6.80–7.56 (16H, $H_{arom.}$), 7.36 and 7.89 (both d, 2H each, O=C–CH_{trans}=CH, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz, 300 K) δ_C ppm: 68.33, 68.51, 69.34, 69.73, 70.67, 71.11, 112.46, 112.79, 120.87, 120.92, 124.26, 127.95, 128.73, 130.13, 130.17, 131.45, 132.47, 138.61, 157.17, 157.94, 193.87. MS (*m/z*): 709.2 $[M+H]^+$. Found (%): C 71.29; H 6.17. $C_{42}H_{44}O_{10}$ requires (%): C 71.17; H 6.26.

In conclusion, two novel crown ethers, tetrakis(benzo)-31-crown-7 ether (**5**) and tetrakis(benzo)-34-crown-8 ether (**6**), were successfully synthesized by condensation reaction of podands 1,5-bis(2-formylphenoxy)-3-oxapentane (**1a**), 1,8-bis(2-formylphenoxy)-3,6-dioxanoctane (**1b**) and 1,8-bis(2-acetylphenoxy)-3,6-dioxanoctane (**2**). The molecular structures of non-nitrogenous macroheterocycles were established by IR, NMR, and MS. Both of them are interesting as effective complexing ligands in the coordination chemistry.

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