Макрогетероциклы
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DOI: 10.6060/mhc131264h

Unexpected Formation of [(Δ³−Piperideino)pyrimidino]−14−crown−4 Ethers in a Petrenko−Kritschenko Type Condensation

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Two novel aza-14-crown-4 ether derivatives bearing fused (Δ³-piperideino)[2,3-e]pyrimidine moieties as subunits were unexpectedly obtained as major products of a modified Petrenko-Kritschenko type cascade condensation of 1-benzyl-4-ethoxycarbonylpiperidin-3-one with 1,5-bis(2-formylphenoxy)-3-oxapentane and ammonium acetate. X-ray structure study was performed to determine the structure of the compounds.

Keywords: Aza-14-crown-4 ether, multicomponent reaction, Petrenko-Kritschenko condensation, X-ray structure.

Неожиданный синтез [(Δ³−пиперидеино)пиримидино]−14−краун−4−эфиров в реакции типа Петренко−Критченко

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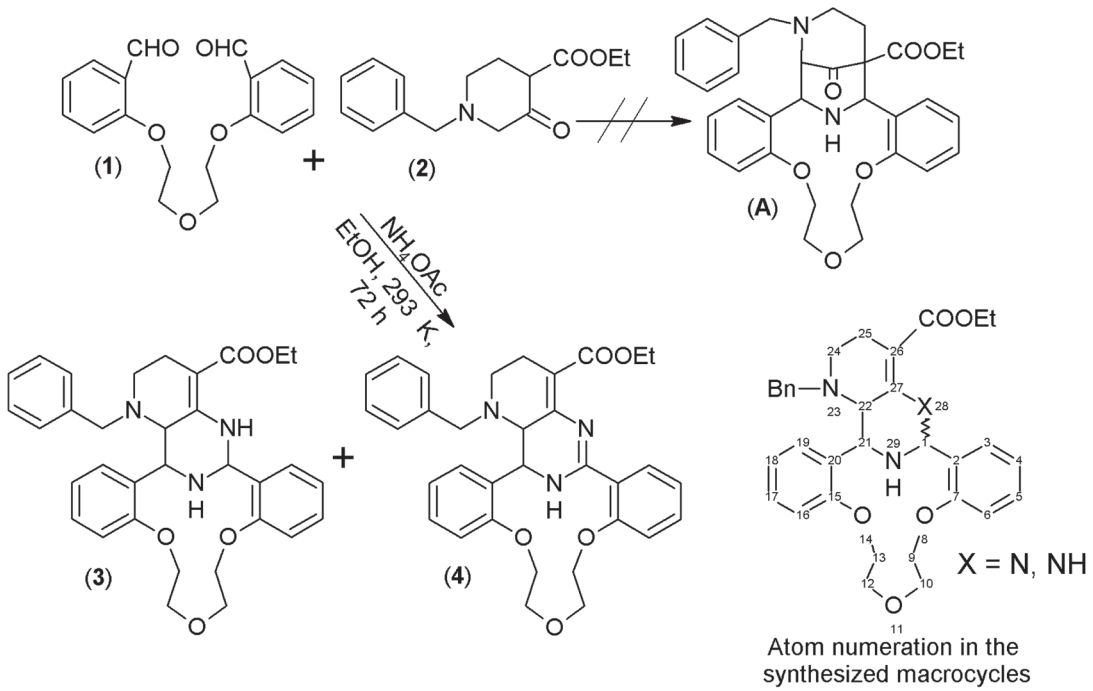
Каскадная конденсация 1-бензил-4-этоксикарбонилпиперидин-3-она с 1,5-бис(2-формилфенокси)-3-оксапентаном и ацетатом аммония в условиях модифицированного метода Петренко-Критченко неожиданно привела к получению двух новых производных аза-14-краун-4-эфира, сочленённого с (Δ³-пиперидеино)[2,3-е] пиримидиновыми фрагментами. Строение полученных соединений было подтверждено методом РСА.

Ключевые слова*:* Аза-14-краун-4-эфир, мультикомпонентная реакция, реакция Петренко-Критченко, РСА.

Introduction of heterocyclic subunits into the structure of macrocyclic crown ethers promises to improve their biological activity.[1,2] A particular interest presents modification of crown macrocycles that involves fusing them with small nitrogenous pharmacophore moieties such as derivatives of pyrrole, pyridine, piperidine, *etc*. Recently we have developed a modified Petrenko-Kritschenko type cascade condensation of 1,5-bis(2-formylphenoxy)-3-oxapentane (**1**) with dialkylketones and ammonium acetate, which afforded high yields of azacrown ethers which include a piperidine subunit.[3-6] When we applied this chemistry to *N*-alkyl substituted piperidin-4-ones as the ketone components, azacrown ethers containing bispidine (3,7-diazabicyclo[3.3.1]nonane) subunit were obtained.[7-9] The initial purpose of the present study was to synthesize a novel azacrown derivative of 2,7-diazabicyclo[3.3.1] nonane (**A**) using *N*-benzyl substituted piperidin-3-one (**2**) as the ketone component in an analogous multicomponent condensation with 1,5-bis(2-formylphenoxy)-3-oxapentane (**1**) and ammonium acetate as the starting materials.



Scheme 1. Reaction of the podand aldehyde with *N*-benzylpiperidone-3.

The reaction[§] (Scheme 1) was carried out under mild conditions and proceeded smoothly at room temperature during 72 hours to give a mixture of two compounds with unexpected molecular weights (MW). Two peaks were observed in LC/MS spectrum of the formed precipitate. Mass spectrum corresponding to the first peak indicated the formation of a product with MW 553, while the other peak corresponded to a product with MW 555. The expected bispidino-crown ether (**A**) has MW 556. Both the detected components were isolated by column chromatography and single crystals were prepared by slow evaporation. An X-ray diffraction study was performed, which unambiguously defined the structure and geometry of compounds **3** and **4** to be correspondingly [octahydro(pyridino)pyrimidino]-

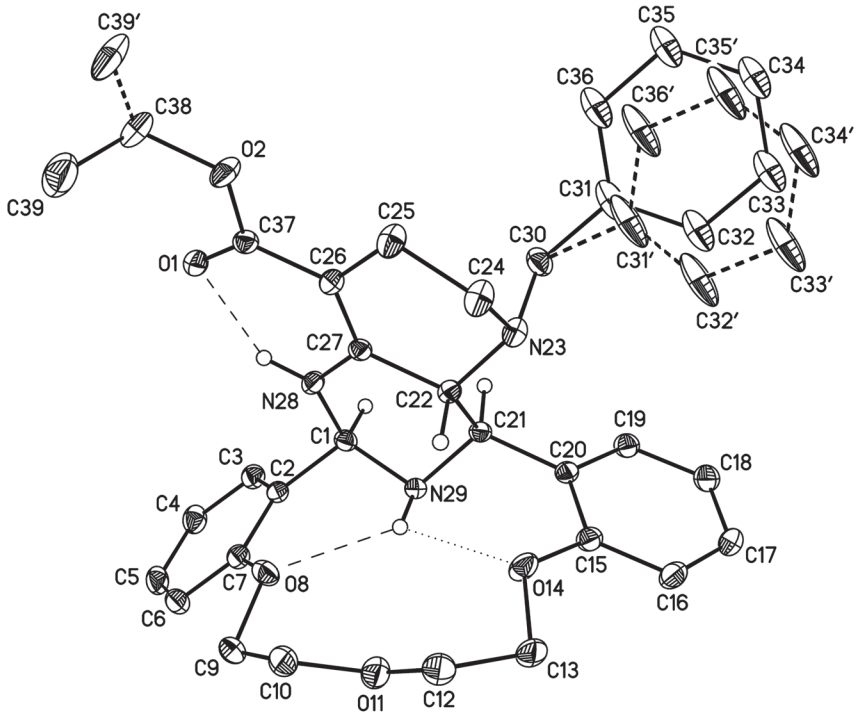


Figure 1. Structure of azacrown ether **3** according to X-ray study data.

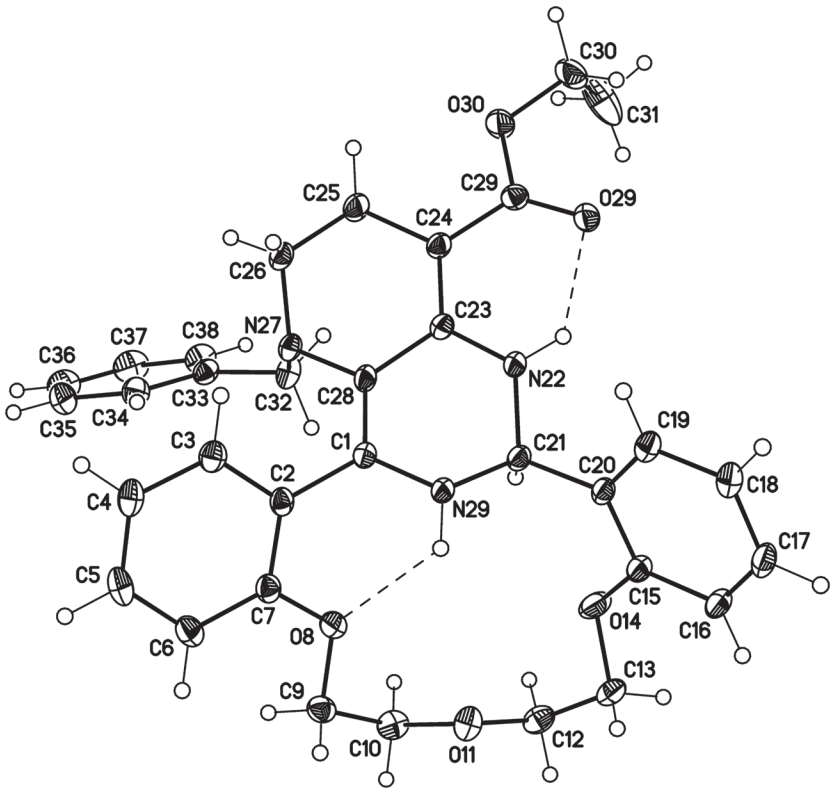
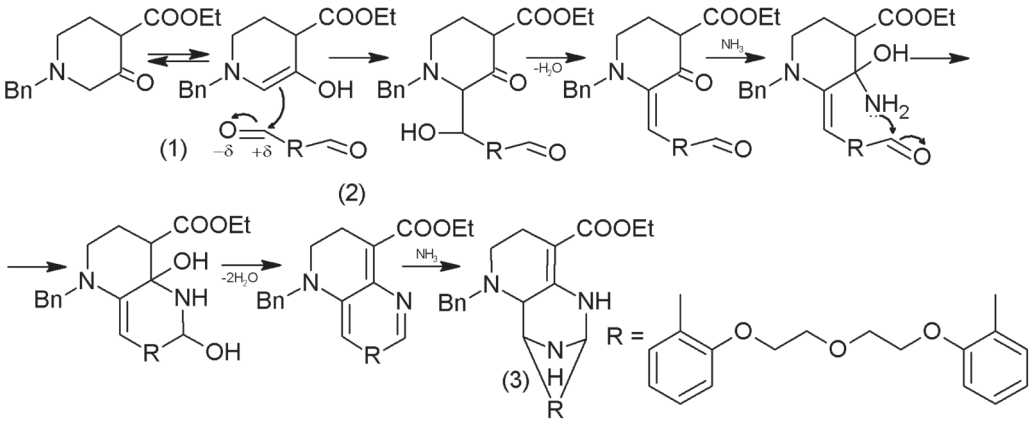


Figure 2. Structure of azacrown ether **4** according to X-ray study data.

azacrown ether and [hexahydro(pyridino)pyrimidino] azacrown ether (Figures 1 and 2). The detailed X-ray data will be published in a separate paper.

The suggested mechanism of formation of compound **3** is presented in Scheme 2. The multicomponent process appears to start with a crotonic-type intermolecular condensation of one aldehyde group of podand **1** with the activated methylene group of 3-piperidone (**2**). The subsequent step is addition of a molecule of ammonia to the ketone group resulting in its conversion into a hydroxy-amino function, which then reacts with the second aldehyde group of the podand residue, thus forming the intermediate aza-16-crown-4-ether moiety, fused with a piperidine ring. As the formed macrocycle contains an 1,4-azadiene moiety, it undergoes double Mannich-type cycloaddition of another molecule of ammonia, followed by dehydration to afford the major product **3**. Determination of the mechanism of formation of a second double bond, leading to the minor product **4**, requires additional research. The driving force of this process is presumably the formation of a conjugated diene further stabilized with nitrogen lone electron pairs.

Acknowledgements. We thank the National Foundation for Science and Technology Development (NAFOSTED), Hanoi, Vietnam (grant No 104.02-2012.44) for the financial support of this work. The authors would like also to thank Chembridge Corp. for the opportunity to use LC/MS analysis.



Scheme 2. Suggested mechanism of the formation of azacrown ether **3**.

Notes

[§]*Ethyl 23-benzyl-8,11,14-trioxa-23,28,29-triazapentacyclo[19.7.1.0^{2,7}.0^{15,20}.0^{22,27}]nonacosa-2,4,6,15(20),16,18,26-heptaene-26-carboxylate* (**3**) *and ethyl 23-benzyl-8,11,14-trioxa-23,28,29-triazapentacyclo[19.7.1.0^{2,7}.0^{15,20}.0^{22,27}]nonacosa-2,4,6,15(20),16,18,21,26-octaene-26-carboxylate* (**4**). A solution of ammonium acetate (5.0 g, 65 mmol), 1,5-bis(2-formylphenoxy)-3-oxapentane (1.57 g, 5.0 mmol) and 1-benzyl-4-ethoxycarbonylpiperidin-3-one (1.48 g, 5.0 mmol) in a mixture of ethanol (30 ml) and acetic acid (2 ml) was magnetically stirred at room temperature for 3 days. The formed precipitate was filtered off, washed with ethanol and chromatographically purified on silica gel (eluating with hexane-ethylacetate, 3:1). Compound **3** was obtained as light-beige crystals (1.67 g, 2.55 mmol, 51.0 %). R_f 0.31. M.p. 179-181 °C. Found: C 71.53; H 6.22; N 7.37. $C_{33}H_{35}N_3O_5$ requires: C 71.33; H 6.71; N 7.56 %. *m/z* (APCI) (%): 555(100) [(M+H)$^+$]. IR (KBr) ν_{max} cm^{-1}: 3299 m, 3270 m, 1645 s, 1580 s. ^{1}H NMR ($CDCl_3$, 300 K) δ_H ppm: 1.24 (3H, t, ^3J=6.8, CH_2CH_3), 2.16 and 2.71 (1H and 3H, correspondingly, both m, -NCH_2CH_2-), 3.49 (1H, d, ^2J=8.7, NCH_2Ar), 3.78, 3.89 and 4.12 (2H, 3H and 8H, correspondingly, all m, -$OCH_2CH_2OCH_2CH_2O$-, CH_2CH_3, NCH_2Ar, H-21 and -22), 4.71 (1H, br. s, NH-29), 6.05 (1H, s, H-1), 6.74 (2H, t, ^3J=7.6, H-4 and H-18), 6.81, 7.13, 7.25 and 7.32 (4H, 2H, 3H and 2H, correspondingly, all m, $H_{arom.}$), 8.92 (1H, s, NH-28). Compound **4** was obtained as dark-yellow crystals (0.83 g, 1.5 mmol, 30.0 %). R_f 0.53. M.p. 101-103 °C. Found: C 71.53; H 6.22; N 7.37. $C_{33}H_{35}N_3O_5$ requires: C 71.59; H 6.37; N 7.59 %. *m/z* (APCI) (%): 553(100) [(M+H)$^+$]. IR (KBr) ν_{max} cm^{-1}: 3453 s, 3374 m, 1644 s, 1599 s. ^{1}H NMR ($CDCl_3$, 300 K) δ_H ppm: 1.29 (3H, t, ^3J = 7.2 and 6.8, CH_2CH_3), 2.26 and 2.78 (1H and 3H, correspondingly, both m, -NCH_2CH_2-), 3.50 and 3.85 (1H each, both d, ^2J=13.2 each, NCH_2Ar), 3.73-4.15 (10H, m, -$OCH_2CH_2OCH_2CH_2O$- and CH_2CH_3), 4.83 (1H, s, NH-29), 6.05 (1H, s, H-1), 6.73 (2H, dd, ^3J=7.7, ^4J=1.6, H-6 and H-16), 6.8 (2H, broad t, ^3J=8.9, H-4 and H-18), 6.97-7.09 (5H, m, H_{arom}), 7.28 (2H, m, H_{arom}), 7.47 (H, dd, ^3J=7.6, ^4J=1.6, H-3), 7.87 (H, dd, ^3J=7.6, ^4J=1.2, H-19), 8.61 (1H, s, NH-28).

The ^{1}H NMR spectra were recorded on a Bruker WP-400 spectrometer. The IR spectra were obtained in KBr pellets on an Infralum FT-801 Fourier spectrophotometer. The elemental analysis was carried out on a Eurovector EA-3000 analyzer. LC/MS analysis was performed using an Agilent 1100 series chromatograph equipped with Agilent 1100 series DAD (wavelength 254±4 nm was used for detection), Sedex 75 ELSD and Agilent LC/MSD VL mass spectrometer (ionization in APCI interface). The X-ray structure study of compounds **3** and **4** was conducted on a Bruker SMART 1000 CCD automated diffractometer, with MoKα-radiation, graphite monochromator, θ- and ω-scan. The crystallographic data can be found in Cambridge Structural Database (CCDC numbers are 931720 and 931721 for compounds **3** and **4**, correspondingly).

The following reagents were used in the course of the present study. *N*-Benzyl-4-ethoxycarbonylpiperidin-3-one (**2**), silica gel and ammonium acetate were purchased from Alfa Aesar. All other reagents were used as received. 1,5-Bis(2-formylphenoxy)-3-oxa-pentane (**1**) was synthesized according to the published procedure.[4]

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Received 03.12.2013
Accepted 18.12.2013