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Synthesis and Molecular Structure of Dibenzo [4–(α–Thienyl– and α–Pyrrolyl)pyrido]aza–14–crown–4 Ethers

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An effective synthesis of dibenzo[4-(heteroaryl)pyrido]aza-14-crown-4 ethers was elaborated by one-step domino condensation of 1,4-bis(2-acetylphenoxy)-3-oxapentane, thiophene- and pyrrolcarbaldehyde and ammonia, in acetic acid. Molecular structure of dibenzo[4-(2-thienyl)pyrido]aza-14-crown-4 ether was established by X-ray analysis.

Keywords: Azacrown ethers, dibenzo and pyrido fused crown ethers, 2-formyl substituted thiophene and pyrrole, synthesis, X-ray analysis.

Синтез и молекулярная структура дибензо[4–(α–тиенил– и α–пирролил)пиридо]аза–14–краун–4 эфиров

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Дибензо[4-(гетарил)пиридо]аза-14-краун-4-эфиры были получены с высоким выходом в ходе однореакторной домино-конденсации в среде уксусной кислоты 1,4-бис(2-ацетилфенокси)-3-оксапентана, тиофен- и пирролкарбальдегидов и аммиака. Строение молекулы дибензо[4-(2-тиенил)пиридо]аза-14-краун-4-эфира было подтверждено методом РСА.

Ключевые слова: Азакраун-эфиры, дибензо- и пиридо-аннелированные краун-эфиры, 2-формилтиофен, 2-формилпиррол, синтез, рентгеноструктурный анализ.

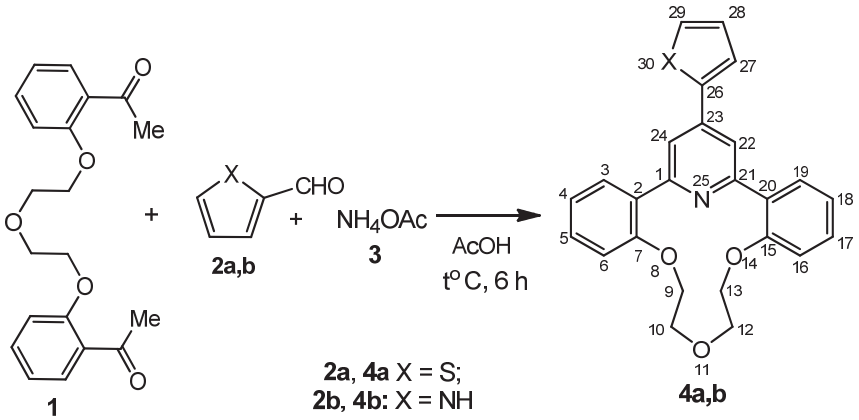
Azacrown ethers have found widespread application in science and technology.[1,2] Recently, the synthesis of aza-crown ethers bearing fused nitrogen-containing heterocyclic rings has drawn the interest of scientists because such combination can enhance the properties of both components, including biological activity.[2-7] By using domino reactions in the synthesis of azacrown ethers, we had earlier obtained dibenzo[(γ-phenyl)pyrido)]aza-14-crown-4 ether from benzaldehyde, 1,4-bis(2-acetylphenoxy)-3-oxapentane (**1**) and ammonium acetate. In addition we had established that such 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).[8] Therefore, we continued our studies with the aim to obtain analogs bearing other aryl groups in γ-position. In this communication we report the synthesis of thienyl (compound **4a**) and pyrrolyl (compound **4b**) azacrown derivatives, as well as the results of X-ray analysis of the molecular structure of dibenzo[4-(α-thienyl)pyrido)aza-14-crown-4 ether (**4a)**.

Condensation of 2-formylthiophene (**2a)** or 2-formylpyrrol **(2b)**, with 1,4-bis(2-acetylphenoxy)-3-oxapentane (**1)** and ammonium acetate (**3**) was conducted under heating (reflux for 6 h in acetic acid in air). The expected aza-14-crown-4 ethers (**4a**,**b**) were prepared and isolated in good yields.

The structures of the products **4a**,**b** were determined by NMR, MS and IR spectrometry and X-ray analysis as well. ^{1}H NMR spectrum of compound **4a** showed multiplets at 3.83 and 4.13 ppm (4H each) for 8 protons of the polyether moiety and a singlet at 7.50 ppm for two β-protons belonging to the pyridine ring (H-22, H-24). Eight protons of the two benzene rings showed four signals at 6.95; 7.01; 7.33 and 7.36 ppm. Three protons of the γ-thienyl group gave three signals (1H each) at 7.13, 7.40 and 7.54 ppm, respectively.

The structural formula of compound **4a** was unequivocally confirmed by X-ray crystallography. The general shape of the molecule **4a** and the packing of its molecules in the crystal are shown below (the atoms are presented with their crystallographic numbering).

In the crystal, one molecule of **4a** forms a complex with one water molecule via two hydrogen bonds (O-H… N25 and O-H…O11). The molecule **4a** possesses γ-thienyl substituted pyridine ring which has one nitrogen atom with sp^2-configuration and a 14-crown-4 ether ring which includes three oxygen atoms. Lengths of valence and hydrogen



Scheme 1.

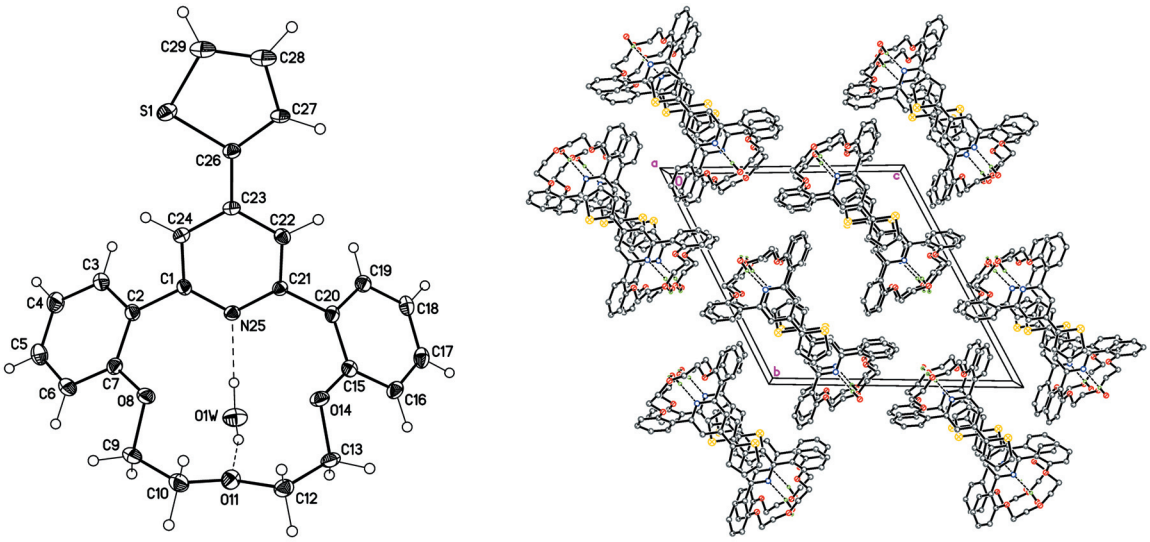


Figure 1. Molecular structure and crystal packing of compound **4a**.

Table 1. Lengths (*l,* Å) of valence and hydrogen bond in the units D-H…A in compound **4a**, distance (*d*, Å) between atoms D and A, angles (*Θ*, deg).

Unit D-H...A	*l*(D-H)	*l*(H...A)	*d*(D...A)	*Θ*<(DHA)
O(1W)-H(1WA)...O(11)^{i}	0.90	1.98	2.857(2)	166
O(1W)-H(1WB)...N(25)^{i}	0.90	2.00	2.868(2)	163
O(2W)-H(2WA)...N(25A)^{ii}	0.90	2.03	2.922(2)	170
O(2W)-H(2WB)...O(11A)^{ii}	0.90	2.13	2.936(2)	149

Relative symmetry operation: (i) x, y+1, z; (ii) x+1, y, z.

bonds, and also angles between them in the fragments of the complex water/compound **4a** (D-H…A, where D – donor atom, A – acceptor atom) are given in Table 1. The basic crystallographic data are presented in Table 2.

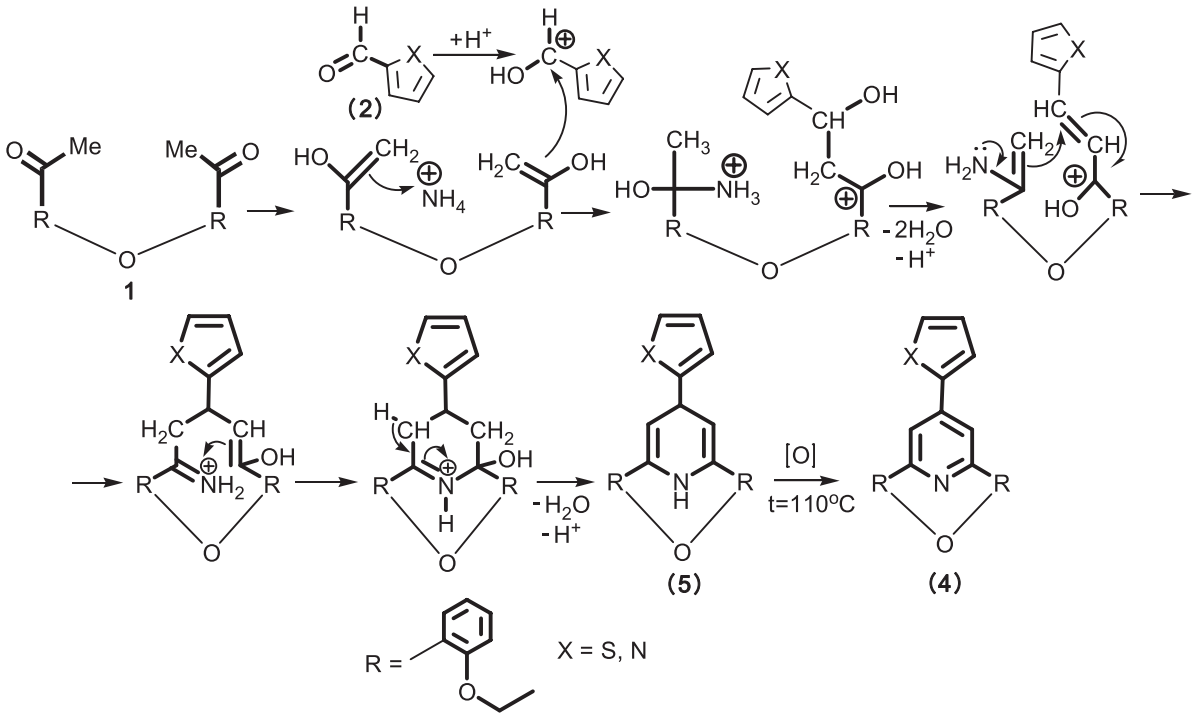
The structure of compound **4a** was unambiguously established by X-ray diffraction analysis. The molecular structure of compound **4a** is shown in Figure 1 along with the atomic numbering scheme. Compound **4a** crystallizes in the triclinic space group *P*-1 with the two crystallographically independent molecules in the unit cell. The geometries of the two crystallographically independent molecules are very similar.

Compound **4a** comprises the aza-14-crown-3 ether skeletal moiety and adopts a bowl conformation (Figure 1). The configuration of the C7–O8–C9–C10–O11–C12–C13–O14–C15 polyether chain is t–g$^{(-)}$–t–t–g$^{(+)}$–t (t = *trans*, 180°; g = *gauche*, ±60°). The dihedral angle between the planes of the benzene rings fused to the aza-14-crown-3 ether moiety is 61.8(2) and 60.3(2)° for the two crystallographically independent molecules, respectively. Due to the presence of conjugation the thienyl substituent lies practically within the pyridine ring plane.

In the crystal, the molecules of compound **4a** form quite steady associates with the solvate water molecules by

Table 2. Basic crystallographic data and parameters for the refinement of compound **4a**.

Compound	**4a**
Empirical formula	$C_{25}H_{23}NO_4S$ $C_{25}H_{21}NO_3S.H_2O$
Molecular mass	433.50
Temperature (K)	120(2)
Crystal system	Triclinic
Space group	P-1
a, Å	6.8631 (3)
b, Å	19.9169 (10)
c, Å	20.0634 (10)
α, deg	61.596 (1)
β, deg	80.624 (1)
γ, deg	80.478 (1)
Volume (V), Å^3	2367.9 (2)
No. of molecules in a unit cell (Z)	4
μ, mm^{-1}	0.166
No. of measured reflexions	31720
No. of independent reflexions	13817



Scheme 2.

the intermolecular hydrogen bonds (Table 1). The H-bonded associates are further linked into doubled columns along the a axis by the π-π stacking interactions between the thiophene and pyridine fragments {the (S1–C26–C27–C28–C29)/(C21A–C22A–C23A–C24A–C1A–N25A) interplane distance is 3.363(2) Å; the (C21–C22–C23–C24–C1–N25)/(S1A–C26A–C27A–C28A–C29A) [1+x, y, z] interplane distance is 3.358(2) Å; the shortest C...C distances are 3.254(2) Å (C22A...C28') and 3.276(2) Å (C22...C28B)} (Figure 2). The columns are arranged at van-der-Waals distances.

The assumed reaction mechanism for the synthesis of compounds **4a**,**b** is presented below. The domino reaction is supposed to proceed via Michael additions, aldol condensation, dehydration and, finally, oxidation-aromatization with the formation of the pyridine ring.

The proposed reaction mechanism is very similar to Hantzsch dihydropyridine synthesis,[9] however, the nature of the final oxidative step requires additional research. We suggest air oxygen to be the oxidative agent, but a Zelinsky type conjugate hydration-dehydration[9] process can also take place.

The PASS software,[10] designed to predict biological activity of novel substances, estimated that compounds **4a,b** could possess valuable bioactivities such as imidazoline receptor agonist (70.7 % probability), membrane permeability inhibitor (67.9 %) and phobic disorders treatment (69.6 %).

X-Ray Structure Determination

Data were collected on a Bruker SMART APEX II CCD diffractometer (λ(MoK$_\alpha$)-radiation, graphite monochromator, ω and φ scan mode) and corrected for absorption using the *SADABS* program.[11] For details, see Table 2. The structure of **4a** was solved by direct methods and refined by the full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The crystal contains two crystallographically independent molecules in the unit cell. The two thienyl substituents of the two independent molecules of 4a are disordered over two sites related by rotation on 180° around the C–C$_{Py}$ bond, with the occupancies of 0.80:0.20 each. The independent part of the unit cell of **4a** contains two water and two chloroform solvate molecules. The chloroform solvate molecules were found to be strongly disordered and could not be modeled satisfactorily. The contribution to the scattering by these molecules was removed by the use of the utility *SQUEEZE* in *PLATON98*.[12] The hydrogen atoms of the solvate water molecules were localized in the difference-Fourier map and included in the refinement with fixed positional (the rider mode) and isotropic displacement parameters. The other hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters (U_{iso}(H) = 1.2U_{eq}(C)). All calculations were carried out using the *SHELXTL* program.[13] Crystallographic data for **4a**·H$_2$O·CHCl$_3$ have been deposited with the Cambridge Crystallographic Data Center. CCDC 979537 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: *deposit@ccdc.cam.ac.uk* or *www.ccdc.cam.ac.uk*).

Experimental

Melting points were determined in open capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on a EuroVector EA-3000 analyzer. The IR spectra were recorded in KBr disks on an Infralum FT-801 spectrometer. The ^{1}H NMR spectra were recorded on a Bruker WP-400 instrument in CDCl$_3$, TMS as internal standard. 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 ESI mode). X-Ray structural analysis of compound **4a** was measured on an APEX2 (Bruker, 2005). All X-ray related analyses and calculations were carried out with SAINT (Bruker, 2001) and SHELXTL (Sheldrick, 2008).

*23-(2-Thienyl)-8,11,14-trioxa-25-azatetracyclo-[19.3.0^{2,7}.0^{15,20}]pentacosa-1(25),2,4,6,15(20),16,18,21,23)nonaene (**4a**).* A mixture of diketone **1** (1.71 g, 5.00 mmol), 2-thienylaldehyde (**2a**) (0.53 g, 5.00 mmol) and ammonium acetate (10 g, 0.13 mol) was refluxed in acetic acid (50 ml) for 6 hours. The reaction mixture was left to cool to room temperature and then neutralized with aqueous sodium carbonate. Afterward, the product was extracted with ethyl acetate (3×50 ml). The solvent was then evaporated under vacuum. The product **4a** was then purified by column chromatography (eluting with CHCl$_3$-hexane 1:1) and recrystallized from ethanol. Single crystals for X-ray studies were grown from ethanol (96 % non-absolute). Yield 0.96 g (46 %), white crystals. M.p. = 198-199 °C. Found: C 72.19; H 5.12; N 3.35. $C_{25}H_{21}NO_3S$ requires: C 72.27; H 5.09; N 3.37. Mass spectrum, (LCMS), *m/z* (I_{rel}, %): 416 [M+1]$^+$ (100). IR (KBr) ν_{max} cm^{-1}: 1596 s, 1250 s. ^{1}H NMR (CDCl$_3$, 300 K) δ_H ppm: 3.83 and 4.13 (4H each, m each, (OCH$_2$CH$_2$)$_2$O); 6.95 (2H, d, *J* = 8.0 Hz, H-6 and H-16); 7.01 (2H, t, *J* = 7.5 Hz, H-4 and H-18); 7.13 (1H, t, *J* = 5.0 and 3.5 Hz, H-4' thienyl); 7.33 (2H, d.d, *J* = 7.9 and 1.5 Hz, H-3 and H-19); 7.36 (2H, t.d, *J* = 8.0 and 1.5 Hz, H-5 and H-17); 7.40 (1H, d.d, *J* = 5 and 1.0 Hz, H-3' thienyl); 7.50 (2H, s, H-22 and H-24); 7.54 (1H, d.d, *J* = 3.5 and 1.0 Hz, H-5' thienyl).

*23-(2-Pyrrolyl)-8,11,14-trioxa-25-azatetracyclo-[19.3.0^{2,7}.0^{15,20}]pentacosa-1(25),2,4,6,15(20),16,18,21,23)nonaene (**4b**).* Prepared in a similar manner from the mixture of diketone **1** (5.00 mmol), 2-pyrrolylaldehyde (**2b**) (5.00 mmol) and ammonium acetate (0.13 mol). White crystals (0.42 g, 44 %). M.p. = 223-224 °C. Found: C 75.30; H 5.61; N 7.05. $C_{25}H_{22}N_2O_3$ requires: C 75.36; H 5.57; N 7.03. Mass spectrum (LCMS), *m/z* (I_{rel}, %): 399 [M+1]$^+$ (100). IR (KBr) ν_{max} cm^{-1}: 1600 m, 1249.26 s. ^{1}H NMR (CDCl$_3$, 300 K) δ_H ppm: 3.80 and 4.04 (4H each, m each, (OCH$_2$CH$_2$)$_2$O); 6.21 (1H, br.m, H-4' pyrrol); 6.57 (1H, br.s, H-3' pyrrol); 6.81 (2H, d, *J* = 8.0 Hz, H-6 and H-16); 6.88 (1H, br.s), signals of H-5', H-4 and H-18 protons are overlapped; 6.89 (2H, d.d, *J* = 8.0 and 7.8 Hz, H-4, and H-18); 7.07 (2H, d, *J* = 7.8 Hz, H-3 and H-19); 7.12 (2H, s, H-22 and H-24); 7.26 (2H, t.d, *J* = 8.0 and 1.6 Hz, H-5 and H-17).

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