Transformations of (γ–Piperidono)dibenzoaza–14–crown–4 Ethers

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The transformations of dibenzo[γ-piperidono]aza-14-crown-4 ethers were implemented with Li-organic compounds and sodium borohydride under reduction condition. The structures of new compounds were confirmed by $^1$H NMR, IR, MS analysis. X-Ray single-crystal structure study has exactly determined the structure of the representative compound $2g$. According to the PASS program, these obtained new azacrown ethers containing γ-piperidol fragment are interested to develop new biologically active agents such as a CYP2H substrate (60–95 %), membrane permeability inhibitor (60–74 %) and spasmolytic agent (60–92 %).

Keywords: Azacrown ether, Li-organic compound, γ-piperidol, single-crystal X-ray structure.

Превращения (γ–пиперидон)дibenзоaza–14–краун–4–эфиров

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При взаимодействии dibenzo[γ-piperidono]aza-14-crown-4-эфиров с Li-органическими соединениями и борогидридом натрия были получены соответствующие продукты их восстановления, структура которых была подтверждена данными $^1$H ЯМР, ИК спектроскопии и масс-спектрометрии. С помощью рентгеноструктурного анализа была установлена структура соединения $2g$. В соответствии с программой PASS, полученные впервые азакраун-эфиры, содержащие фрагмент γ-пиперидола, представляют интерес для разработки новых биологически активных агентов, таких как CYP2H субстрат (60–95 %), ингибитор проницаемости мембраны (60–74 %) и спазмолитических веществ (60–92 %).

Ключевые слова: Азакраун-эфир, Li-органическое соединение, γ-пиперидол, рентгеноструктураанлиз.
Transformations of (γ-Piperidono)dibenzoazacrown Ethers

Introduction

A large number of heterocyclic compounds containing a γ-piperidol fragment or its ester derivatives have shown different and high biological activities. Besides, major interest of crown ether concerns the studying their complexing ability with metal ions. A presence of nitrogen atom imparts many interesting properties to crown ethers, namely, increasing ability with metal ions and as phase-transfer catalysts. Macrocyclic compounds containing crown ether and γ-piperidol group have attracted activity agents. Imparts many interesting properties to crown ethers, namely, increased ability with metal-ion complexation and as phase-transfer catalysts. Macrocyclic compounds containing crown ether and γ-piperidol fragment continue to develop intensively and we obtained a series of new aza-14-crown-4 ethers containing crown ether and γ-piperidol fragment.

For the synthesis of the target compounds, the method of reduction of azacrown ether (I) with sodium borohydride in ethyl alcohol and the interaction of the γ-piperidone fragment with α-furyllithium, α-thienyllithium, and α-pyridylmethyllithium were studied. From the reaction mixtures, target compounds were isolated by chromatography or recrystallization and according to spectral analyzes the γ-piperidolocrown ethers (2a–d, 2f–h) were described.

Experimental

Reagents were purchased from commercial sources (Sigma-Aldrich) and were used without any additional purifications. Melting points were determined in open capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on Euro Vector EA-3000 analyzer. IR spectra were recorded in KBr disks on an Infralum FT-801 spectrometer. 1H NMR and 13C NMR spectra were recorded in CDCl3 solution at 25 °C, using a Bruker 500 MHz NMR spectrometer; chemical shifts are given in parts per million (δ) and referenced to the appropriate solvent residual peak. Mass spectra were obtained on instruments Finnigan MAT 95 XL (EI, ionizing energy 70 eV). X-ray diffraction data were obtained on an automatic three-circle Bruker APEX-II CCD diffractometer. Column chromatography was performed on silica gel 40–60 mesh.

Dimethyl-23-oxo-8,11,14-trioxa-25-azatetracyclo[19.3.1.02,7.015,20]pentacosa-2,4,6,15(20),16,18-hexaen-22-carboxylate (1a).

Formation of a mixture of 1.0 g (2.1 mmol) of azacrown ether (1a) in 20 ml of ethanol was added over 10 minutes to 0.08 g (2.1 mmol) of NaNH with stirring. The mixture was stirred for 1 hour at 20 °C and then for 30 minutes at 78 °C. The precipitate was filtered off, washed with water and recrystallized from ethyl acetate. White crystals (2a) were obtained with yield of 80 % (0.79 g). M.p. 205–207 °C (from ethyl acetate). Rf = 0.55 (ethylacetae).

To 1.0 g (2.4 mmol) of piperidone (Ib), dissolved in 20 ml of ethanol, 0.09 g (2.4 mmol) of NaNH was added. The reaction mixture was stirred for 1 hour at the boiling point of the solvent, 30 ml of water were added, the crystals were filtered and dried. After recrystallization from alcohol, 0.83 g (83 %) of the product was obtained, white crystals with M.p. 237–239 °C, Rf = 0.67 (ethy lacetate). Found, %: C 70.92, H 6.97, N 6.43. Calculated, %: C 71.07, H 7.16, N 6.63. m/z (Irel, %): 422 [M]+ (3), 430 (2), 439 (5), 435 (5), 437 (9), 438 (11), 439 (10), 440 (11), 441 (12), 442 (13), 443 (13), 444 (14), 445 (14), 446 (15). IR (KBr) νmax cm–1: 3320 (NH), 3439 (OH), 3390 (N=O). H NMR (500 MHz, CDCl3, Me4Si) δ ppm: 3.62 (6H, CH3), 3.86 (2H, H-1, H-22), 4.10 and 4.35 (both 4H each, OH, H), 4.26 (2H, H-23, H-24, H2O). LCMS, m/z rel., %: 422 [M]+ (3), 430 (2), 439 (5), 435 (5), 437 (9), 438 (11), 439 (10), 440 (11), 441 (12), 442 (13), 443 (13), 444 (14), 445 (14), 446 (15). IR (KBr) νmax cm–1: 3320 (NH), 3439 (OH), 3390 (N=O).

Dimethyl-23-oxo-8,11,14-trioxa-25-azatetracyclo[19.3.1.02,7.015,20]pentacosa-2,4,6,15(20),16,18-hexaen-22,24-di-carboxylate (2a).

To a mixture of 1.0 g (2.4 mmol) of piperidone (Ib), dissolved in 20 ml of ethanol, 0.09 g (2.4 mmol) of NaNH was added. The reaction mixture was stirred for 1 hour at the boiling point of the solvent, 30 ml of water were added, the crystals were filtered and dried. After recrystallization from alcohol, 0.83 g (83 %) of the product was obtained, white crystals with M.p. 237–239 °C, Rf = 0.67 (ethylacetae). Found, %: C 70.92, H 6.97, N 6.43. Calculated, %: C 71.07, H 7.16, N 6.63. m/z (Irel, %): 422 [M]+ (3), 430 (2), 439 (5), 435 (5), 437 (9), 438 (11), 439 (10), 440 (11), 441 (12), 442 (13), 443 (13), 444 (14), 445 (14), 446 (15). IR (KBr) νmax cm–1: 3320 (NH), 3439 (OH), 3390 (N=O). H NMR (500 MHz, CDCl3, Me4Si) δ ppm: 3.62 (6H, CH3), 3.86 (2H, H-1, H-22), 4.10 and 4.35 (both 4H each, OH, H), 4.26 (2H, H-23, H-24, H2O). LCMS, m/z rel., %: 422 [M]+ (3), 430 (2), 439 (5), 435 (5), 437 (9), 438 (11), 439 (10), 440 (11), 441 (12), 442 (13), 443 (13), 444 (14), 445 (14), 446 (15). IR (KBr) νmax cm–1: 3320 (NH), 3439 (OH), 3390 (N=O).

Dimethyl-23-oxo-8,11,14-trioxa-25-azatetracyclo[19.3.1.02,7.015,20]pentacosa-2,4,6,15(20),16,18-hexaen-22,24-di-carboxylate (2a).

To a mixture of 1.0 g (2.4 mmol) of piperidone (Ib), dissolved in 20 ml of ethanol, 0.09 g (2.4 mmol) of NaNH was added. The reaction mixture was stirred for 1 hour at the boiling point of the solvent, 30 ml of water were added, the crystals were filtered and dried. After recrystallization from alcohol, 0.83 g (83 %) of the product was obtained, white crystals with M.p. 237–239 °C, Rf = 0.67 (ethy lacetate). Found, %: C 70.92, H 6.97, N 6.43. Calculated, %: C 71.07, H 7.16, N 6.63. m/z (Irel, %): 422 [M]+ (3), 430 (2), 439 (5), 435 (5), 437 (9), 438 (11), 439 (10), 440 (11), 441 (12), 442 (13), 443 (13), 444 (14), 445 (14), 446 (15). IR (KBr) νmax cm–1: 3320 (NH), 3439 (OH), 3390 (N=O). H NMR (500 MHz, CDCl3, Me4Si) δ ppm: 3.62 (6H, CH3), 3.86 (2H, H-1, H-22), 4.10 and 4.35 (both 4H each, OH, H), 4.26 (2H, H-23, H-24, H2O). LCMS, m/z rel., %: 422 [M]+ (3), 430 (2), 439 (5), 435 (5), 437 (9), 438 (11), 439 (10), 440 (11), 441 (12), 442 (13), 443 (13), 444 (14), 445 (14), 446 (15). IR (KBr) νmax cm–1: 3320 (NH), 3439 (OH), 3390 (N=O).
Ethyl 2-[4-ethoxyxycarbonyl]methyl-2-hydroxy-8,11,14-trioxo-25-azatetracyclo[19.3.1.0^3,9,15,17]19-hexaen-23-yl] acetate (2d) and ethyl 2-[4-oxo-8,11,14,25-tetrao-29-azatetracyclo[19.6.1.0^3,9,15,22]24,26,15(20),16,18-hexaen-27-yl] acetate (2e). To 2 g (3.8 mmol) of piperidone (1e), dissolved in 30 ml of ethanol, 0.07 g (1.9 mmol) of NaBH4 was added. The reaction mixture was stirred for 30 minutes at the boiling point of the solvent. Control of reaction was led by TLC. The alcohol was evaporated under vacuum. 50 ml of water and 1 ml of acetic acid were added to the residue, the reaction products were extracted with chloroform (3×30 ml). The combined extracts were dried with anhydrous MgSO4 and evaporated in vacuo. The residue was separated by column chromatography on silica gel, eluting with ethyl acetate:hexane, 1:1 and affording:

A) 0.1 g (6 %) lactone (2e), white crystals with M.p. 196–198 °C, Rf = 0.41 (ethylacetate). Found, %: C 67.22, H 6.44, N 2.86. C16H18NO4. Calculated, %: C 67.35, H 6.49, N 2.91. m/z (λrel. %): 481 [M]+ (8), 393 (3), 297 (9), 148 (12), 134 (19), 119 (11), 91 (15), 77 (10), 43 (100). IR (KBr) ν cm⁻¹: 1725 (C=O), 1775 (O=C). (C=O lacton).

B) 0.5 g (25 %) alcohol (2d), white crystals with M.p. 210–212 °C, Rf = 0.24 (silufol, ethyl acetate). Found, %: C 65.96, H 6.98, N 2.54. C16H18NO4. Calculated, %: C 66.02, H 7.07, N 2.62. m/z (λrel. %): 527 [M]+ (9), 482 (7), 398 (10), 282 (20), 232 (10), 220 (10), 192 (10), 178 (10), 159 (21), 148 (42), 134 (89), 121 (100), 119 (76), 111 (71), 105 (45), 91 (84), 77 (69), 55 (52), 45 (58), IR (KBr) ν cm⁻¹: 1725 and 1712 (shoulder) (C=O), (COOH). νmax cm⁻¹: 1725 and 1712 (shoulder) (C=O). (C=O lacton).

1H NMR (500 MHz, CDCl3, MeSi) δ ppm: 1.11 (t, J = 7.0 Hz, CH3), 1.25 and 2.35 (both dd, 2H, each), 1.60 and J = 6.9 Hz, 2H, CH2), 1.84 ppm: 1.11 (t, J = 7.0 Hz, CH3), 1.25 and 2.35 (both dd, 2H, each), 1.60 and J = 6.9 Hz, 2H, CH2), 2.45 (br.s, 1H, NH), 8.15 (br.s, 1H, NH), 4.51 (br.s, 1H, CH2), 4.51 (br.s, 1H, CH2), 4.51 ppm: 1.11 (t, J = 7.0 Hz, CH3), 1.25 and 2.35 (both dd, 2H, each), 1.60 and J = 6.9 Hz, 2H, CH2), 2.45 (br.s, 1H, NH), 8.15 (br.s, 1H, NH), 4.51 (br.s, 1H, CH2), 4.51 ppm: 1.11 (t, J = 7.0 Hz, CH3), 1.25 and 2.35 (both dd, 2H, each), 1.60 and J = 6.9 Hz, 2H, CH2), 2.45 (br.s, 1H, NH), 8.15 (br.s, 1H, NH), 4.51 (br.s, 1H, CH2), 4.51 ppm: 1.11 (t, J = 7.0 Hz, CH3), 1.25 and 2.35 (both dd, 2H, each), 1.60 and J = 6.9 Hz, 2H, CH2).

In the previous publication,15 a new substance that was isolated in the yield of 35 %. In its high-symmetry 1H NMR spectrum, the protons of two methyl groups give one singlet signal (at 3.53 ppm) of six proton units. Signals from the H-1, H-21 appeared as a multiplet at the region of 3.81 ppm, and other signal of piperidine protons (H-22, H-24) were observed as a doublet at 4.10 ppm. The proton at the nitrogen atom was identified as a broad multiplet signal due to resonance with two protons H-1 and H-21.
Then, we developed new γ-piperidol crown ether by using the reduction method of compounds (1a-d) with sodium borohydride in ethyl alcohol (Scheme 1). From the reaction mixtures, crown ethers containing γ-piperidol (2a-d) were isolated by column chromatography. Their structures were determined by 1H NMR, IR, MS spectrometry. Azacrown ether (2c), which was isolated by a high yield of 75%, apparently indicates the template effect of the crown ether part coordinating the sodium cation, releasing the BH₄⁻ anion for a more effective attack on the carbonyl group. In the case of β,β-disubstituted azacrown (2a), the alcohol yield turned out to be low (only 15%) due to steric hindrances and electronic repulsion for the BH₄⁻ anion approach created by two methoxycarbonyl substituents in the α,α’-positions to the carbonyl group. In the IR spectrum of cyclic amino alcohol (2c), the absorption bands at 3517, 3397 cm⁻¹ (OH) and 3316 cm⁻¹ (NH) confirmed that the carboxyl group has been reduced to alcohol. In 1H NMR spectrum of (2c), a mixture of diastereomers was identified by broadening and superposition of signals of aliphatic and piperidine protons. These HPLC-MS record the presence of two diastereomers with M⁺ 427 each.

In case of reducing compound (1d), two compounds were isolated: the expected piperidol (2d) and compound (2e) containing lactone structure which was confirmed by spectral data. In 1H NMR spectrum of compound (2e), the signal of methyl group was observed in high field at δ = 1.13 ppm as a triple with 3H, which confirmed there was lactonization. In 1H NMR spectrum of compound (2d) signals of six methyl and four methylene protons from ethoxycarbonyl groups were observed. The LC-MS analysis of (2d, 2e) gave their clear [M⁺] peaks with m/z = 481 and 527, respectively.

It is known, [6] that during the reduction of cycloaliphatic and heterocyclic ketones with sodium borohydride, mixtures of alcohols with the R- and S-configuration of the stereogenic center were always formed. In case of cyclic alcohols, the equatorially located OH groups participated in the acylation or trans-esterification reaction much easier than the axial ones. In our case, apparently, the reaction generated diastereomeric alcohols in which the alcohol with the equatorial hydroxyl group underwent an intramolecular trans-esterification reaction with the formation of lactone 2e, and its antipode 2e remains unchanged.

In the second part of this work, interaction of the γ-piperidone fragment of azacrownophane (1e,f) with α-furyllithium, α-thienyllithium, and α-pyridylmethyllithium was studied. The reaction was carried out in absolute tetrahydrofuran with a threefold excess of organolithium compound (Scheme 2). Azacrown ethers (2f-h) were isolated by chromatography on Al₂O₃ with not very high yields (29–46%), probably due to the steric hindrance of the two methyl groups in the α-position of carbonyl group.

The IR spectra of compounds (2f-h) contained the absorption bands due to stretching vibration of the hydroxyl group (OH) (3557–3606 cm⁻¹) and the amine group (NH) (in the region of 3290–3347 cm⁻¹). There is no band of stretching vibrations of carbonyl group (C=O) in the region of 1650–1750 cm⁻¹. The molecular structure of compound 2g, its conformational parameters were unambiguously confirmed by X-ray analysis of a single crystal (Figure 1). The bond lengths and valence angles are given in Tables S1 and S2 (see SI). The size of the internal cavity of crown ether 2g, estimated as doubled average distance between the donor atoms and their centroid (the centroid is the center of the quadrilateral N25-O8-O11-O14), is 4.05 Å. The conformation of the polyether moiety of the molecule

Scheme 1. Synthesis of azacrown ethers (1a-d) by Petrenko-Kritchenko reaction and their reduction with NaBH₄ in ethyl alcohol.
C7-O8-C9-C10-O11-C12-C13-O14-C15 – t-g–t-g–t (t = trans, ± 180°; g = gauche, ± 60°) (Table S3).

Molecule 2g has idealized C₁ (m) symmetry, which, however, does not occur in the crystal due to the presence of ethanol and ethyl acetate solvate molecules. The presence in the structure of two intermolecular O23–H...O(s) and N25...H-O(s) hydrogen bonds with the solvate ethanol molecule leads to a slight distortion of the molecule, which is reflected, in particular, as in the difference in the parameters of the two intramolecular hydrogen bonds N25-H25...O8 [N...O 3.056(17), H...O 2.537(19) Å, angle N-H...O 119.9(15)°] and N25-H25...O14 [N...O 2.9299(17), 2.330(19) Å, angle N-H...O 127.2(16)°] (Table S7), and in the asymmetric arrangement of the thiophene cycle (the angles between the planes of the thiophene and benzene cycles are 63.4 and 49.6°). Due to the presence of these intramolecular hydrogen bonds, the donor atoms of the crown cycle N25, O8, O11, and O14 do not lie in the same plane (the root-mean-square deviation of these atoms from this plane is 0.118 Å). The thiophene substituent at the C23 carbon atom occupies the sterically more favorable equatorial position. The angle between the planes of the benzene cycles of the molecule is 78.5°. The piperidine fragment has the conformation of an almost perfect chair [the value of the modules of its torsion angles is 51.24(15)–57.21(16)°]. This compound is a diastereomer with four asymmetric centers – C1, C21, C22, and C24. The molecules in the crystal represent the racemate with the relative configuration of these stereogenic centers – \textit{rac}-(1R*, 21S*, 22R*, 24S*).

NH-Piperidolouazacrown ether (2e) contained two centers for the electrophilic attack in the acylation. They are both surrounded by bulky substituents, which makes it difficult to predict the accuracy of the acylation sequence. In case of using of acetic anhydride in equimolar amount, a high melting product of mono-acylation 3 at the nitrogen atom was isolated by a yield of 26 %. In IR spectra of compound 3, the absorption bands of the amide group (N–C=O) are observed at 1646 and 1625 cm⁻¹, the band of the ester group (O–C=O) was absent at 1710 cm⁻¹, the absorption band of the unreacted OH group at 3435 cm⁻¹. The structure of azacrown ether 3 was also confirmed by MS spectra ([M+1]⁺, m/z = 470) and ¹H NMR spectra.

**Figure 1.** Molecular structure of azacrown ether 2g in the representation of atoms by anisotropic displacement ellipsoids (40 % probability); intramolecular hydrogen bonds are shown by dashed and dotted lines.

**Scheme 2.** Reaction of organolithium compounds with azacrown ether (1e,f).
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According to the PASS\(^\text{[7]}\) program (Prediction of Activity Spectra for Substances), compounds 2a-d and 3 containing γ-piperidol fragment have the high potential acting as a CYP2H substrate (60–95 %), exhibit membrane permeability inhibitor (60–74 %). In the other side, compounds 2f-h containing 4-aryl-γ-piperidol fragment may show high spasmolytic activity (60–92 %).

Conclusions

In summary, several novel macroheterocycles containing NH-γ-piperidol fragment were obtained by the transformations of dibenzo[(γ-piperidono]aza-14-crown-4 ethers. The NH-γ-piperidol derivatives were characterized by IR, \(^1\)H NMR, LCMS and X-ray diffraction. These azacrown compounds with the polyfunctional group can be useful building blocks for further synthetic manipulations and drug development.

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Scheme 3. Acylation of azacrown ether (2c).