Synthesis of dibenzopiperidinoaza-14-crown-4 ethers and their one-step conversion into dibenzo-16-crown-3

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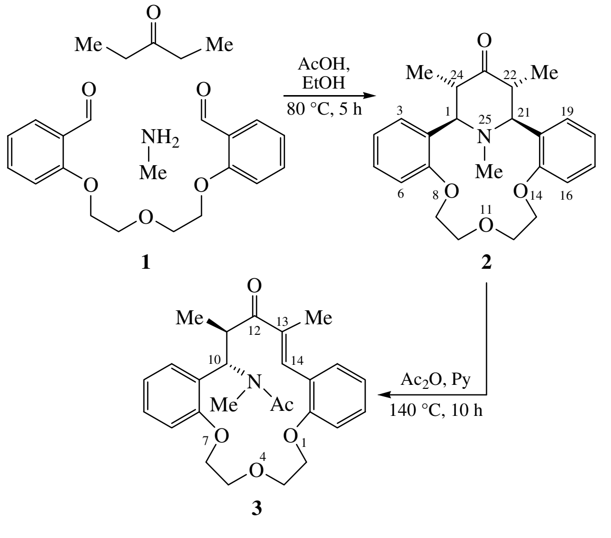
New dibenzoaza-14-crowns-4 containing a fragment of γ-piperidone, in which 2,6-diaryl substituents are connected with polyethylene oxide bridges, were obtained by the Petrenko–Kritchenko reaction and then transformed by acylation into dibenzo-16-crowns-3.

New crown and aza-crown compounds are interesting macrocyclic objects for the study of their space structures, self assembling, chemical and coordination properties and biological activity.[1–7] As a continuation of our studies in piperidone chemistry and biological activity,[8–11] we synthesised a series of γ-piperidones with their 2,6-diaryl substituents mutually bridged by polyethylene oxide chains (spacers). To obtain compounds **2**, we used the Petrenko–Kritchenko reaction[12] of dialkyl ketones with salicylic aldehydes and methylamine with the subsequent etherification of 2,6-diaryl-γ-piperidones by the Pedersen protocol.[13] But this way was found absolutely ineffective in our hands. We used another approach to the Petrenko–Kritchenko reaction, namely, we tried to condensate diethyl ketones with 2-{2-[2-(2-formylphenoxy)ethoxy]ethoxy}benzaldehyde **1** in the presence of methylammonium acetate. The reaction proceeded smoothly at 80 °C in a mixture of ethanol and acetic acid and gave (after 5 h) 22r,24c,25-trimethyl-8,11,14-trioxa-25-azatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2(7),3,5,15(20),16,18-hexaen-23-one (aza-crown **2**) separated in 33% yield.† The simple NMR spectrum of this compound suggests its symmetry. In this spectrum, two protons of the N–CH–Ar group give a doublet signal with ^3J 10.8 Hz, which indicates the *trans* positions of Me and Ar substituents in a piperidine moiety. The high value of this spin–spin coupling constant shows that both pairs of the substituents have simultaneously *trans* diequatorial configurations. Analogously, other **2**-like substances can be synthesised with different dialkyl ketones and salicylaldehydes. We attempted to acylate aza-crown **2** by acetic anhydride to see the possibility of opening a piperidone moiety at the C–N bond.[10,11] The aim was successfully achieved giving rise to the transformation of aza-14-crown-4 **2** into 16-crown-3 ether **3** in 62% yield.†



The structures of compounds **2** and **3** were confirmed by mass spectrometry, ^{1}H NMR spectroscopy† and, in the case of **3**, X-ray analysis.‡

The X-ray analysis of the product derived from aza-crown **2** showed (Figure 1) it to be 11(*S**),13-dimethyl-10(*R**)-(*N*-methyl-*N*-acetyl)amino-12-oxodibenzo[*h*,*o*][1,4,7]trioxacyclohexadec-8,13(*E*),15-triene **3**.‡ In the crystal of compound **3**, two crystallographically independent molecules are enantiomers (racemate).

In the ^{1}H NMR spectrum of **3**, double sets of signals of protons for each methyl and methyne group are observed (with

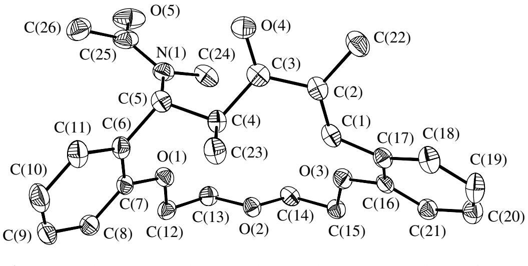


Figure 1 General view and crystallographic numeration of atoms for compound **3** (X-ray diffraction data for one of the enantiomers).

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† ^{1}H NMR spectra were recorded on a Bruker WP-400 spectrometer at 400 MHz, standard TMS, CDCl$_3$. Mass spectra were measured on a Varian MAT 112 spectrometer. Compounds **2** and **3** gave satisfactory elemental analyses.

For **2**: a mixture of **1** (5 g, 16 mmol), diethyl ketone (1.37 g, 16 mmol) and methylammonium acetate (1.64 g, 18 mmol) in ethanol (30 ml) and acetic acid (3 ml) solution was stirred for 5 h at 80 °C. The reaction solution was then concentrated; the residue mixture was treated with a saturated solution of sodium carbonate (50 ml) and extracted with chloroform. The extract was dried with MgSO$_4$; the solvent was distilled off, and the solution was chromatographed on SiO$_2$. A hexane–ethyl acetate (1:1) eluent was used to separate 2.1 g (33%) of **2** as snow-white crystals, mp 212–214 °C (from ethanol). ^{1}H NMR, δ: 0.72 (d, 6H, CMe, ^3J 6.6 Hz), 1.69 (s, 3H, NMe), 2.82 (d, 2H, N–CH–Ar, ^3J 10.8 Hz), 3.76–4.16 [m, 10H, O(CH$_2$CH$_2$O)$_2$, 22-H and 24-H], 6.74–7.26 (m, 8H, Ar–H). MS, *m*/*z* (%): 395 (100) [M$^+$], 380 (19) [M – Me]$^+$, 367 (27) [M – CO]$^+$, 352 (22) [M – Me – CO]$^+$, 338 (48), 135 (52), 119 (54). IR (KBr, ν/cm^{-1}): 1702 (C=O).

For **3**: a solution of aza-crown **2** (0.5 g, 1.3 mmol) in a mixture of acetic anhydride (2.5 ml, 25 mmol) with pyridine (2 ml, 25 mmol) was refluxed for 10 h. After evaporation of the solvents, the residue was quenched with a saturated solution of sodium carbonate (20 ml) and extracted with chloroform. The extract was dried with MgSO$_4$. The residue obtained after evaporation of the solvent was separated by column chromatography (silica gel, hexane–ethyl acetate, 2:1). Thus, 0.35 g (62%) of **3** was prepared as white crystals with mp 160–162 °C (from ethyl acetate–hexane, 1:3). ^{1}H NMR, δ: 0.87 and 0.90 (2d, 1.8H and 1.2H resp., 11-Me, ^3J 16.6 Hz), 1.86 and 1.99 (2d, 1.2H and 1.8H resp., 13-Me, ^4J 2.4 Hz), 2.02 and 2.05 (2s, 1.8H and 1.2H resp., COMe), 2.92 and 2.95 (2s, 1.8H and 1.2H resp., N-Me), 3.78–4.23 [m, 8H, O(CH$_2$CH$_2$O)$_2$], 4.83–4.93 (m, 1H, 11-H), 5.07 and 5.81 (2d, 0.6H and 0.4H resp., 10-H, ^3J 11.0 Hz), 6.77–7.50 (m, 8H, Ar–H), 8.10 and 8.14 (2br. s, 0.6H and 0.4H resp., 14-H). MS, *m*/*z* (%): 437 (32) [M$^+$], 394 (38) [M – COMe]$^+$, 365 (12) [M – MeNCOMe]$^+$, 364 (37), 338 (17), 135 (100), 132 (92), 119 (67). IR (KBr, ν/cm^{-1}): 1640 and 1663 (NC=O), 1734 (CC=O).

a 1:1.5 mole ratio). This fact witnesses for the presence of the amide group isomerism.

Thus, this approach can be promising for the preparation of both aza-crowns and crown compounds **2** and **3**.

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[‡] The crystal of **3** ($C_{28}H_{35}NO_6$, $M = 481.57$) is triclinic, space group $P\bar{1}$, at $T = 120$ K: $a = 9.4557(9)$, $b = 14.3143(13)$ and $c = 19.7965(18)$ Å, $\alpha = 86.081(2)^\circ$, $\beta = 81.562(2)^\circ$, $\gamma = 72.780(2)^\circ$, $V = 2530.8(4)$ Å^3, $Z = 4$, $d_{\text{calc}} = 1.264$ g cm^{-3}, $F(000) = 1032$, $\mu = 0.088$ mm^{-1}.

21089 reflections were measured on a SMART 1000 CCD diffractometer [λ(MoKα) radiation, graphite monochromator, $\omega/2\theta$ scan mode, $\theta_{\max} = 26^\circ$] and corrected for Lorentz and polarization effects. The structure was determined by direct methods and full-matrix least squares refinement with anisotropic thermal parameters for non-hydrogen atoms. The crystal contains a solvate ethyl acetate molecule, which is disordered over two sites with the occupancies 0.7:0.3. The hydrogen atoms were placed in calculated positions and refined in the riding model with fixed thermal parameters. The final divergence factors were $R_1 = 0.0675$ for 4980 independent reflections with $I > 2\sigma(I)$ and $wR_2 = 0.1896$ for all 9864 independent reflections. All calculations were carried out using the SHELXTL PLUS (PC Version 5.10) program.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 275168. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.