ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 4, pp. 612–616. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.N. Levov, Le Tuan An', A.T. Soldatenkov, Chyong Khong Khieu, V.N. Khrustalev, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 4, pp. 617–620.

Transformations of Dibenzo(γ-oxopiperidino)aza-14-crowns-4 upon Acylation. Molecular Structure of Dibenzo-16-crown-3

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Received January 21, 2007

Abstract—The result of acylation of dibenzoaza-14-crowns-4 containing a 4-oxopiperidine fragment with acetic anhydride depends on the substituent on the nitrogen atom. The NH-substrates initially undergo acylation at the piperidine nitrogen atom, followed by enolization and O-acylation. The acylation of *N*-methyl derivatives is accompanied by cleavage of the piperidine ring at the C–N bond with formation of acetylamino-substituted dibenzo-16-crowns-3. The structure of the latter was determined by X-ray analysis.

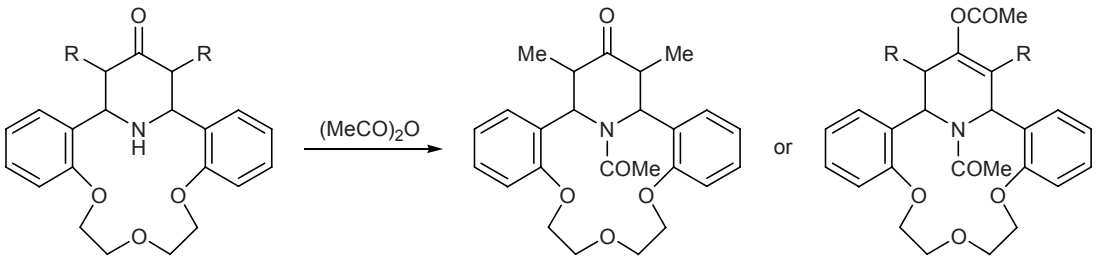
DOI: 10.1134/S1070428008040246

The range of chemical transformations of most known crown and aza crown ethers is fairly narrow and is generally limited to complex formation with metal ions [1]. Incorporation of an oxopiperidine fragment into the macrocyclic crown ether system [2] provides a unique possibility for considerably extending the scope of chemical modifications, while a combination of oxopiperidine and polyether moieties in a single macromolecule makes it possible to study the effect of the polyether bridge on the direction and efficiency of chemical reactions involving the piperidine ring, especially in reactions with ionic reagents. Functionalization of such aza crown ethers should extend their diversity and potential of their biological activity.

The present work was aimed at studying how substituent on the nitrogen atom affects the direction of transformations of dibenzoaza-14-crowns-4 **Ia**, **Ib**, **IVa**, and **IVb** in the acylation with acetic anhydride. When compound **Ia** having no substituent on the nitrogen atom was treated with an equimolar amount of acetic anhydride for a short time, we obtained the corresponding *N*-acetyl derivative **IIa**. Prolonged heating of macrocyclic ketones **Ia** and **Ib** in the presence of a large excess of acetic anhydride was accompanied by their enolization with subsequent O-acylation, which is a fairly rare case for 4-oxopiperidine systems [3] (Scheme 1).

As a result, we isolated from the reaction mixtures N,O-diacylated aza crown ethers **IIIa** and **IIIb** in good yields. The IR spectra of **IIIa** and **IIIb** contained strong absorption bands due to stretching vibrations of both ester (1739–1745 cm^{-1}) and amide carbonyl groups (1638–1651 cm^{-1}). In the mass spectra of these

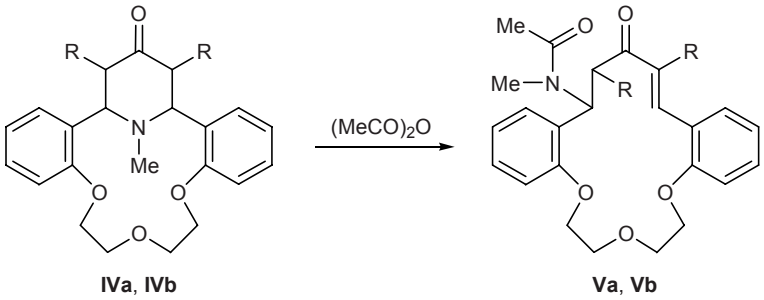
Scheme 1.



Ia, **Ib** **IIa** **IIIa**, **IIIb**

R = Me (**a**), Ph (**b**).

Scheme 2.



IVa, **IVb** **Va**, **Vb**

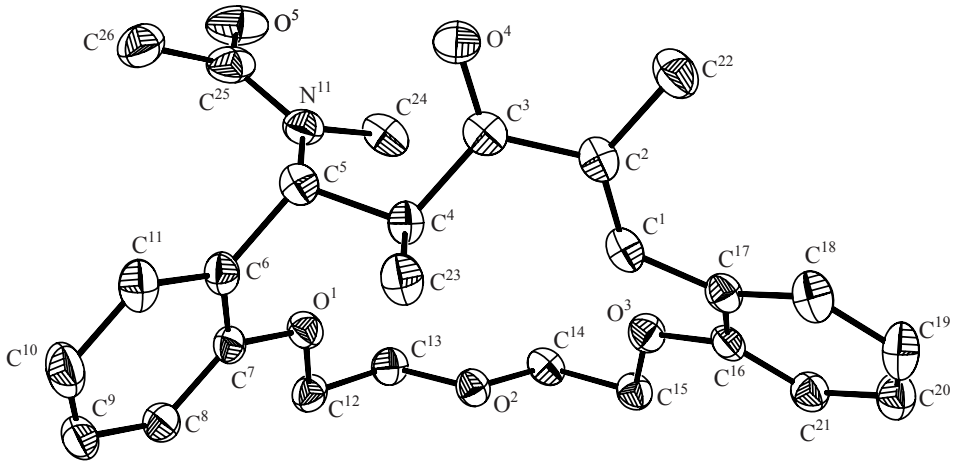
R = Me (**a**), Ph (**b**).

compounds, medium-intensity peaks (I_{rel} 38–39%) of the molecular ions were present. Both aza crown ethers **IIIa** and **IIIb** displayed in the ^{1}H NMR spectra double sets of signals from the NCOMe protons and some other protons in the vicinity of the amide group owing to distortion of symmetry of the tetrahydropyridine fragment.

The acylation of N-methyl-substituted aza crowns **IVa** and **IVb** followed a different path. Regardless of the substituent on C^{22} and C^{24}, the piperidine ring was cleaved at the C–N bond, and the products were dibenzo-16-crowns-3 **Va** and **Vb** having an exocyclic acetylamino group, which were isolated in up to 62% yield (Scheme 2). The structure of compounds **Va** and **Vb** was confirmed by spectral data (for preliminary communication on the synthesis of compound **Va**, see [4]). The ^{1}H NMR spectra of **Va** and **Vb** contained double sets of signals from protons in the amide moiety with an intensity ratio of 1:1.5 for compound **Va** and 1:2 for **Vb**. The formation of a C^{13}=C^{14}HAr fragment follows from the presence in the ^{1}H NMR spectra of double singlets from the 14-H proton in a weak field (δ 8.10–8.14 ppm).

The molecular structure of dibenzo-16-crown-3 **Va**, its conformational parameters, and the size of the internal cavity were determined by X-ray analysis of a single crystal (see figure). The coordinates of atoms, bond lengths, and bond angles in molecule **Va** were deposited to the Cambridge Crystallographic Data Center. According to the X-ray diffraction data, the size of the internal cavity in molecule **Va** (which is a 16-membered crownophane), estimated as the double average distance between the O^1, O^2, O^3, C^1, and C^4 atoms and the centroid of the $C^1C^4O^1O^2O^3$ pentagon, is 4.86 Å. The conformation of the $C^7O^1C^{12}C^{13}O^2C^{14}C^{15}O^3C^{16}$ polyether fragment may be described as t-$g^{(+)}$-t-t-$g^{(-)}$-t (where *t* stands for *trans*, ±180°, and *g* stands for *gauche*, ±60°).

Molecule **Va** possesses two asymmetric centers, C^4 and C^5; so that compound **Va** in crystal is a racemic mixture of a diastereoisomer in which the relative configuration of the above chiral centers is (4*S**,5*R**). The



Structure of the molecule of (10*R**,11*S**)-(13*E*)-10-[acetyl(methyl)amino]-11,13-dimethyl-8,9:15,16-dibenzo-1,4,7-trioxacyclohexadeca-8,13,15-trien-12-one (**Va**) according to the X-ray diffraction data; non-hydrogen atoms are shown as thermal ellipsoids with a probability of 50%.

Principal crystallographic data for (10*R**,11*S**)-(13*E*)-10-[acetyl(methyl)amino]-11,13-dimethyl-8,9:15,16-dibenzo-1,4,7-trioxacyclohexadeca-8,13,15-trien-12-one (**Va**) and refinement parameters

Parameter	Value
Formula	$C_{28}H_{35}NO_6$
Molecular weight	481.57
Temperature, K	120
Crystal system	Triclinic
Space group	*P*-1
a, Å	9.4557(9)
b, Å	14.3143(13)
c, Å	19.7965(18)
α, deg	86.081
β, deg	81.562
γ, deg	72.780
V, Å^3	2530.8
Z	4
d_{calc}, g/cm^3	1.264
F(000)	1032
μ, mm^{-1}	0.088
$2\theta_{max}$, deg	52
Total number of reflections	21089
Number of independent reflections	9864
Number of independent reflections with $I > 2\sigma(I)$	4980
Number of refined parameters	188
R_1 [from reflections with $I > 2\sigma(I)$]	0.0675
wR_2 (from all reflections)	0.1896
Goodness of fit	1.005

two senior substituents at the $C^1=C^2$ are oriented *trans* with respect to each other. A unit cell of **Va** includes two crystallographically independent molecules that are enantiomeric. The only difference between them is the degree of openness of the internal cavity, which is determined by the dihedral angle between the planes of the benzene rings (66.6° in one molecule and 46.4° in the other).

Using PASS Internet program [5], we made an attempt to predict possible biological activity of the obtained compounds. The results showed that aza crown **Ib** and its *N*,*O*-diacetyl derivative **IIIb** may be interesting as inhibitors of topoisomerase I (with a probability of 75 and 69%, respectively), cardioprotectors (69 and 59%), and cell membrane permeability inhibitors (61 and 54%). Enol acetate **IIIb** was also predicted with a high probability (87%) to inhibit aminocarboxymuconatesemialdehyde decarboxylase, as well as to inhibit seborrhea and treat myocardial ischemia with probabilities of 77% and 66%, respectively.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WP-400 spectrometer (400 MHz) using $CDCl_3$ as solvent. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT Incos 50 mass spectrometer with direct sample admission into the ion source. The IR spectra were measured in KBr on a Specord 75IR instrument. Preparative column chromatography was performed on aluminum oxide (100–160 μm). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates. Aza crowns **Ia** and **IVa** were synthesized according to the procedures described in [2, 4].

X-Ray diffraction study of compound (Va). The unit cell parameters and reflection intensities were determined on a Bruker SMART 1000 CCD automatic diffractometer (MoK_α irradiation, graphite monochromator, θ- and ω-scanning). The principal crystallographic data and refinement parameters are given in table. The structure was solved by the direct method and was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were localized objectively by Fourier difference syntheses, and their positions were refined in isotropic approximation. All calculations were performed using SHELXTL PLUS software package [6].

22,24-Diphenyl-8,11,14-trioxa-25-azatetracyclo-[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaen-23-one (**Ib**) and its 25-methyl derivative (**IVb**) were synthesized as described in [2].

Compound Ib. Yield 3.41 g (68%), mp 244–246°C. IR spectrum, ν, cm^{-1}: 3275 (NH), 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.07–4.35 m (10H, OCH_2CH_2O, 22-H, 24-H, NH), 4.68 t (1H, OCH_2-CH_2O, *J* = 12.6 Hz), 4.79 d (2H, 1-H, 21-H, *J* = 10.8 Hz), 6.59 t (2H, 4-H, 18-H, *J* = 7.4 Hz), 6.72 d (2H, 6-H, 16-H, *J* = 8.1 Hz), 6.77 d (2H, 3-H, 19-H, *J* = 7.4 Hz), 7.01–7.15 m (12H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 505 [*M*]$^+$ (32), 477 (16), 387 (13), 386 (12), 297 (35), 296 (60), 208 (21), 178 (38), 165 (54), 152 (25), 131 (38), 118 (100), 91 (54), 90 (84), 89 (43). Found, %: C 78.23; H 6.25; N 2.59. $C_{33}H_{31}NO_4$. Calculated, %: C 78.39; H 6.18; N 2.77.

Compound IVb. Yield 1.04 g (20%), mp 234–236°C. IR spectrum: ν 1698 cm^{-1} (C=O). ^{1}H NMR

spectrum, δ, ppm: 1.71 s (3H, Me), 3.87 d (2H, 1-H, 21-H, J = 14.8 Hz), 3.93–4.13 m (8H, OCH_2CH_2O), 5.34 d (2H, 22-H, 24-H, J = 14.8 Hz), 6.54–7.14 m (18H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 519 $[M]^+$ (100), 491 (8), 401 (5), 400 (4), 178 (10), 165 (19), 135 (28), 119 (17), 118 (34), 91 (23), 90 (23). Found, %: C 78.75; H 6.32; N 2.83. $C_{34}H_{33}NO_4$. Calculated, %: C 78.59; H 6.40; N 2.70.

25-Acetyl-22,24-dimethyl-8,11,14-trioxa-25-aza-tetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),-16,18-hexaen-23-one (IIa). A solution of 0.5 g (1.3 mmol) of aza crown **Ia** and 1.4 g (1.3 mmol) of acetic anhydride in 5 ml of pyridine was heated for 1 h under reflux. The mixture was cooled and diluted with water, and the precipitate was filtered off, dried, and purified by recrystallization from ethanol. Yield 0.41 g (76%), mp 170–172°C. IR spectrum, ν, cm^{-1}: 1699 (C=O, ketone), 1641 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.37 d (3H, Me, J = 6.80 Hz), 1.44 d (3H, Me, J = 6.86 Hz), 2.60 s (3H, COMe), 3.31 m and 3.42 m (1H each, 22-H, 24-H), 3.68–4.20 m (8H, OCH_2CH_2O), 5.45 br.s and 6.32 br.s (1H each, 1-H, 21-H), 6.50 m (4H, 4-H, 6-H, 16-H, 18-H), 6.88 m (4H, 3-H, 5-H, 17-H, 19-H). Mass spectrum, m/z (I_{rel}, %): 423 $[M]^+$ (46), 395 (20), 380 (70), 364 (100), 352 (71), 220 (21), 207 (36), 203 (67), 176 (28), 162 (55), 133 (31), 91 (33). Found, %: C 70.81; H 7.15; N 3.10 $C_{25}H_{29}NO_5$. Calculated, %: C 70.90; H 6.90; N 3.31.

Crown ethers IIIa, IIIb, Va, and Vb (*general procedure*). A solution of 1.3 mmol of aza crown **Ia**, **Ib**, **IVa**, or **IVb** in a mixture of 2.5 ml (25 mmol) of acetic anhydride and 2 ml (25 mmol) of pyridine was heated for 5–10 h under reflux. The solvent was distilled off under reduced pressure, the residue was treated with 20 ml of a saturated solution of sodium carbonate and extracted with chloroform (3×20 ml), the extracts were combined, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure, and the residue was subjected to column chromatography on aluminum oxide using hexane–ethyl acetate (2:1) as eluent. The product was additionally purified by recrystallization from ethanol. Compounds **IIIa**, **IIIb**, **Va**, and **Vb** were isolated as colorless crystalline substances.

25-Acetyl-22,24-dimethyl-8,11,14-trioxa-25-aza-tetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),-16,18,23-heptaen-23-yl acetate (IIIa). Yield 0.64 g (53%), mp 239–241°C. IR spectrum, ν, cm^{-1}: 1739 (C=O, ester), 1638 (C=O, amide). ^{1}H NMR spectrum, δ, ppm (some protons in the vicinity of the amide group gave double signals belonging to the Z and E isomers): 1.18 d and 1.22 d (1.2H and 1.8H, respectively, 22-Me, J = 6.80 Hz), 1.49 s and 1.55 s (1.2H and 1.8H, respectively, 24-Me), 2.29 s (3H, OCOMe), 2.46 s and 2.54 s (1.8H and 1.2H, respectively, NCOMe), 3.12 q.q (1H, 22-H, J = 6.76, 0.8 Hz), 3.30–4.46 m (9H, OCH_2CH_2O, 21-H), 5.13 d and 5.54 d (0.6H and 0.4H, respectively, 1-H, J = 0.8 Hz), 6.09–6.91 m (7H, H_{arom}), 7.64 d and 7.87 d (0.4H and 0.6H, respectively, H_{arom}, J = 7.44 Hz). Mass spectrum, m/z (I_{rel}, %): 465 $[M]^+$ (38), 422 (78), 406 (10), 380 (100), 364 (36), 176 (12), 91 (9). Found, %: C 69.35; H 6.83; N 3.21. $C_{27}H_{31}NO_6$. Calculated, %: C 69.66; H 6.71; N 3.01.

25-Acetyl-22,24-diphenyl-8,11,14-trioxa-25-aza-tetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),-16,18,23-heptaen-23-yl acetate (IIIb). Yield 0.49 g (63%), mp 257–258°C. IR spectrum, ν, cm^{-1}: 1745 (C=O, ester), 1651 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 1.53 s and 2.05 s (2H and 1H, respectively, NCOMe), 1.96 s (3H, OCOMe), 3.44–4.26 m (10H, OCH_2CH_2O, 21-H, 22-H), 4.74 s and 5.33 s (0.67H and 0.33H, respectively, 1-H), 6.05–7.53 m (17H, H_{arom}), 8.54 d (1H, H_{arom}, J = 7.40 Hz). Mass spectrum, m/z (I_{rel}, %): 589 $[M]^+$ (39), 546 (65), 504 (100), 488 (16), 487 (5), 486 (6), 165 (5), 43 (47). Found, %: C 75.13; H 6.05; N 2.25. $C_{37}H_{35}NO_6$. Calculated, %: C 75.36; H 5.98; N 2.38.

(10*R,11*S**)-(13*E*)-10-[Acetyl(methyl)amino]-11,13-dimethyl-8,9:15,16-dibenzo-1,4,7-trioxacyclohexadeca-8,13,15-trien-12-one (Va).** Yield 0.35 g (62%), mp 160–162°C. IR spectrum, ν, cm^{-1}: 1734 (C=O, ketone), 1640 and 1663 (C=O, amide). ^{1}H NMR spectrum, δ, ppm: 0.87 d and 0.90 d (1.8H and 1.2H, respectively, 11-Me, ^3J = 16.6 Hz), 1.86 d and 1.99 d (1.2H and 1.8H, respectively, 13-Me, ^4J = 2.4 Hz), 2.02 s and 2.05 s (1.8H and 1.2H, respectively, COMe), 2.92 s and 2.95 s (1.8H and 1.2H, respectively, NMe), 3.78–4.23 m (8H, OCH_2CH_2O), 4.83–4.93 m (1H, 11-H), 5.07 d and 5.81 d (0.6H and 0.4H, respectively, 10-H, ^3J = 11.0 Hz), 6.77–7.5 m (8H, H_{arom}), 8.1 br.s and 8.14 br.s (0.6H and 0.4H, respectively, 14-H). Mass spectrum, m/z (I_{rel}, %): 437 $[M]^+$ (32), 394 (38), 365 (12), 364 (37), 338 (17), 135 (100), 132 (92), 119 (67). Found, %: C 71.21; H 7.28; N 3.41. $C_{26}H_{31}NO_5$. Calculated, %: C 71.37; H 7.14; N 3.20.

10-[Acetyl(methyl)amino]-11,13-diphenyl-8,9:15,16-dibenzo-1,4,7-trioxacyclohexadeca-8,13,15-trien-12-one (Vb). Yield 0.53 g (73%), mp 122–124°C. IR spectrum, ν, cm^{-1}: 1720 (C=O, ketone), 1638 and 1653 (C=O, amide). ^{1}H NMR spectrum, δ,

ppm: 2.18 s and 2.36 s (1H and 2H, respectively, NCOMe), 3.26 br.s (3H, NMe), 3.95–4.45 (8H, OCH_2-CH_2O), 5.62 d and 6.34 d (0.33H and 0.66H, respectively, 10-H, ^3J = 11.8 Hz), 6.25 d (1H, 11-H, J = 11.8 Hz), 6.55–7.33 m (18H, H_{arom}), 8.56 s and 8.64 s (0.33H and 0.66H, respectively, 14-H). Mass spectrum, m/z (I_{rel}, %): 561 $[M]^+$ (78), 533 (28), 518 (20), 488 (29), 444 (16), 235 (21), 194(92), 165 (20), 135 (71), 91 (36), 77 (14), 56 (61), 43 (100). Found, %: C 77.03; H 6.07; N 2.51. $C_{36}H_{35}NO_5$. Calculated, %: C 76.98; H 6.28; N 2.49.

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