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ON THE SYNTHESIS OF THE FIRST REPRESENTATIVES OF BIS(BENZO)-BISPIDINOAZA-14-CROWN-4 ETHERS

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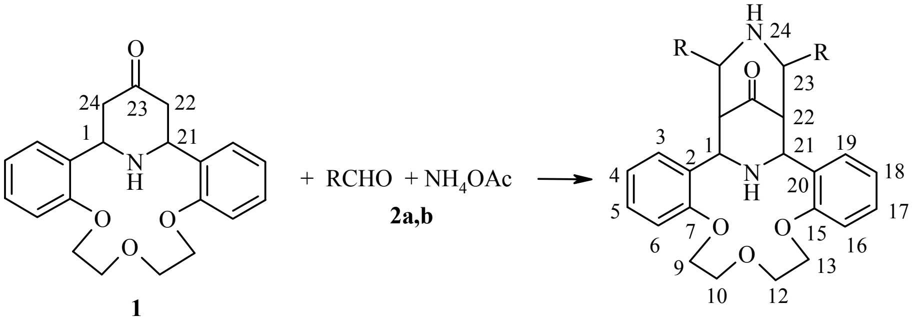
In previous work [1-3], we reported the first syntheses of dibenzoazacrown ethers containing a constituent γ-piperidone fragment in the macrocycle. This success led us to consider the possibility of using these compounds for the construction of a new, more complicated heterocyclic system containing a bispidine fragment in the crown ether part of the macrocycle. Hence, we studied the condensation of azacrownophane **1** [3] with aromatic aldehydes **2a**,**b** and ammonium acetate. Maintenance of this mixture in a solution of ethanol and acetic acid for seven days at 20°C followed by crystallization gave compounds **3a** in 15% yield and **3b** in 11% yield. These azacrown ethers belong to a new group of lariat ethers [4], in which the constituent 3,7-diazabicyclo[3.3.1]nonane fragment has additional sites for coordination with metal cations. These sites are auxiliary upon cooperation with the crown ether part of the molecule. Furthermore, the functionality of this fragment may lead to derivatives of this new heterocyclic system with enhanced potential for biological activity since, as predicted by the PASS Internet program [5], **3a**,**b** may display cardioprotective (69-76%) and antineoplastic activity (62-68%).



1

3a,b

2, 3 a R = 4-FC_6H_4, **b** R = $(MeO)_2C_6H_3$

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The ^{1}H NMR spectra were taken on a Bruker WP-400 spectrometer at 400 MHz in DMSO-d$_6$ with the residual protons of the deuterated solvent serving as the internal standard. The electron impact mass spectra were taken on a Finnigan MAT Incos 50 mass spectrometer at 70 eV. The IR spectra were taken on an IR-75 spectrometer for KBr pellets.

Azacrownophanes 3a,b. A solution of azacrownophane **1** (2.0 g, 5.7 mmol), aldehyde **2a** or **2b** (11.4 mmol), and ammonium acetate (0.87 g, 11.4 mmol) in a mixture of ethanol (30 ml) and acetic acid (2 ml) was maintained for seven days at 20°C. The crystalline precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to give **3a** or **3b**.

23,25-Bis(4-fluorophenyl)-8,11,14-trioxa-24,27-diazapentacyclo[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaen-28-one (3a) was obtained in 15% yield (0.48 g); mp 251-252°C, R_f 0.55 (Silufol, ethanol). IR spectrum, ν, cm^{-1}: 3259 and 3312 (NH), 1719 (C=O), 1060 (C–F). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.63 (2H, H-22, H-26); 2.82 (2H, br. s, NH); 3.41-3.93 (8H, m, $OCH_2CH_2OCH_2CH_2O$); 3.98-4.32 (4H, m, H-1, H-21, H-23, H-25); 6.22, 6.44, 6.75, and 7.01 (2H each, ABCD system, $^3J = 7.47$, $^3J = 7.50$, $^3J = 8.12$, $^4J = 0.82$, H-6,16, H-5,17, H-3,19, H-4,18, respectively); 7.11 and 7.63 (2H each, AA'BB' system, $^3J = 8.49$); C_6H_4F-4). Mass spectrum, *m/z* (I_{rel}, %): 582 $[M]^+$ (20), 566 (7), 459(15), 352 (40), 297 (30), 230 (13), 183 (14), 162 (14), 149 (50), 121 (100), 107 (51), 91 (78), 77 (59). Found, %: C 72.03; H 5.67; N 4.70. $C_{35}H_{32}FN_2O_4$. Calculated, %: C 72.15; H 5.54; N 4.81.

23,25-Bis(3,4-dimethoxyphenyl)-8,11,14-trioxa-24,27-diazapentacyclo[19.5.1.1^{22,26}.0^{2,7}.0^{15,20}]octacosa-2,4,6,15(20),16,18-hexaen-28-one (3b) was obtained in 11% yield (0.41 g); mp 230-232°C. R_f 0.36 (Silufol, ethyl acetate). IR spectrum, ν, cm^{-1}: 3314 and 3304 (NH), 1719 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.87 (2H, m, H-22, H-26); 3.10 (2H, br. s, NH); 3.69 and 3.73 (6H each, both s, OCH_3); 3.63-3.91 (8H, m, $OCH_2CH_2OCH_2CH_2O$); 3.98-4.34 (4H, m, H-1, H-21, H-23, H-25); 6.23, 6.43, 6.73, and 6.99 (2H each, ABCD system, $^3J = 7.25$, $^3J = 7.36$, $^3J = 8.10$, and $^4J = 0.73$ (H-6,16, H-5,17, H-3,19, H-4,18, respectively); 6.89 and 7.11 (2H each, 2d, $^3J = 8.20$, $C_6H_3O_2$); 7.09 (2H, s, $C_6H_3O_2$). Mass spectrum, *m/z* (I_{rel}, %): 666 $[M]^+$ (1), 665 (1), 650 (1), 501 (20), 310 (42), 394 (12), 352 (100), 315 (57), 297 (33), 191 (40), 164 (61), 151 (31), 131 (44), 121 (27), 105 (28), 91 (48), 77 (48). Found, %: C 70.31; H 6.49; N 4.03. $C_{39}H_{42}N_2O_8$. Calculated, %: C 70.25; H 6.35; N 4.20.

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