

Synthesis of Dibenzo Derivatives of (4-Oxotetrahydropyrano)-oxa-14-crown-4 and 1,4,7-Trioxacyclohexadeca-8,10,13,15-tetraen-12-one. Transformation of the Latter into (4-Oxopiperidino)aza-14-crown-4

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Abstract—The reaction of diethyl ketone with 2-{2-[2-(2-formylphenoxy)ethoxy]ethoxy}benzaldehyde in acid medium at room temperature gave 43% of dibenzo(4-oxotetrahydropyrano)oxa-14-crown-4. The condensation of the same compounds in boiling ethanol in the presence of alkali involved cascade transformations leading to the formation of thermodynamically more stable dibenzocrownophane which was assigned the structure of 8,9:15,16-dibenzo-1,4,7-trioxacyclohexadec-8,10,13,15-tetraen-12-one (yield 29%). Treatment of an alcoholic solution of the latter with gaseous ammonia or methylamine at 20°C afforded 73–74% of dibenzoaza-14-crowns-4 containing a 4-oxopiperidine fragment.

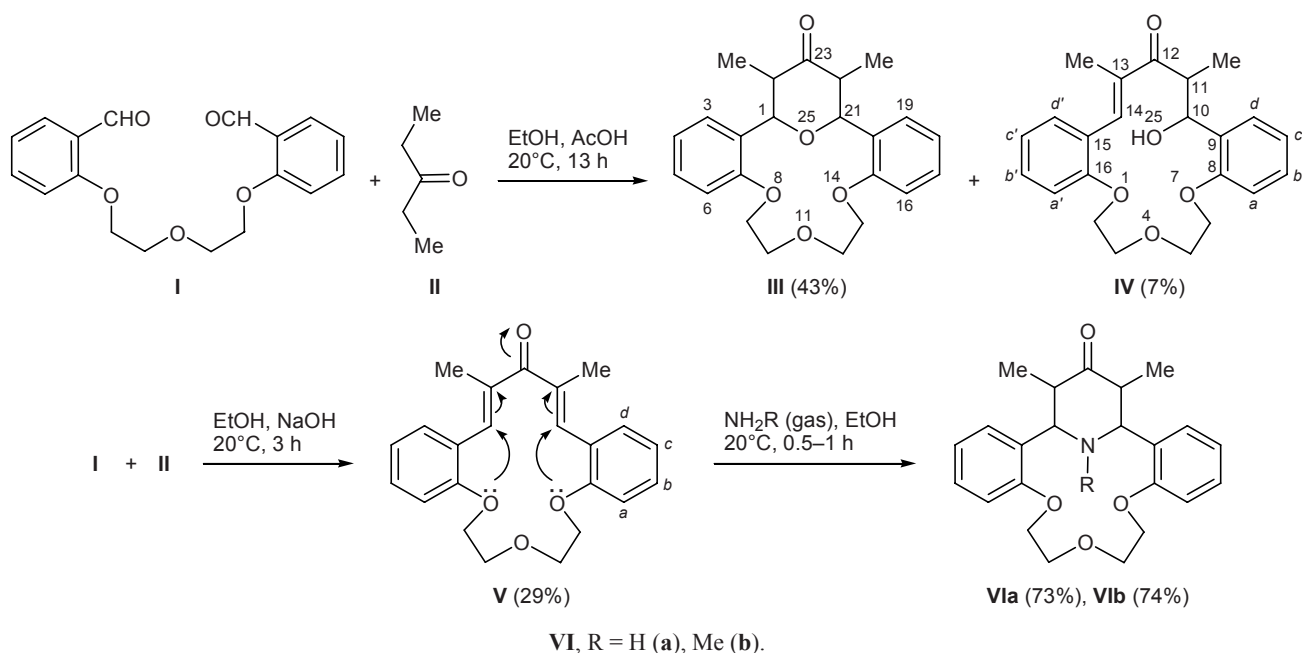
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We reported in [1] on the synthesis of first representatives of a new group of aza crown ethers containing a 4-oxopiperidine fragment whose subsequent functionalization could enhance the potential of biological activity of aza crown compounds. These macroheterocyclic compounds were obtained by three-component condensation of polyether **I** possessing two terminal benzaldehyde fragment, diethyl ketone (**II**), and ammonium or methylammonium acetate. Obviously, the condensation involving formation of a 4-oxopiperidine moiety could take different paths including processes like aldolization (crotonization), Michael addition, and Mannich reaction [2].

Taking into account that intermediate products in the above cascade transformation may have the structure of previously unknown nitrogen-free crown ethers which attract interest from both theoretical and practical viewpoints, in the present work we examined two-component condensation of dialdehyde **I** with diethyl ketone (**II**) in the absence of nitrogen-containing base. The reaction performed at 20°C in ethanol containing a catalytic amount of acetic acid led to the formation of two isomeric nitrogen-free macrocyclic compounds **III** and **IV** (Scheme 1). The major product (yield 43%) was assigned the structure of dibenzo(4-

oxotetrahydropyrano)oxa-14-crown-4 (**III**), while the minor one (yield 7%) was identified as trioxacyclohexadecatriene **IV**. Compounds **III** and **IV** were likely to be formed via tandem aldolization, followed by cyclodehydration (**III**) or partial crotonization (**IV**). Their structure was confirmed by the IR spectra which contained a strong carbonyl absorption band at 1645 cm⁻¹ and by the mass spectra where peaks from the molecular ions (*m/z* 382) with different intensities were present. The fragmentation patterns were also appreciably different. However, only analysis of their ¹H NMR spectra allowed us to reliably determine the structure of **III** and **IV**. Isomer **III** displayed a symmetric ¹H NMR spectrum, providing an indirect support to its symmetric structure. Protons in the methyl groups resonated as a doublet at δ 0.9 ppm with a coupling constant ³*J* of 7.2 Hz. The 22-H and 34-H protons in the tetrahydropyran ring gave a symmetric octet at δ 3.54 ppm with an intensity corresponding to two protons. The two other protons in the six-membered heteroring, 1-H and 21-H, gave rise to a broadened two-proton singlet. Signals from the polyether CH₂O groups appeared as four multiplets (2H each) at δ 3.75–4.35 ppm, and four signals (2H each) in the region δ 6.80–7.47 ppm (*ABCD* spin system) were assigned to aromatic protons.

Scheme 1.



The ^1H NMR spectrum of asymmetric isomer **IV** was also asymmetric. One methyl group (11- CH_3) gave a three-proton doublet at δ 1.00 ppm, and the other (13- CH_3), a singlet at δ 2.03 ppm (3H). Protons in the HOC^{10}H fragment resonated as two broadened singlets (1H each) at 4.79 and 5.56 ppm, and the downfield singlet at δ 7.95 ppm was assigned to the vinylic 14-H proton.

When a mixture of compounds **I** and **II** was heated in alkaline medium, cascade transformations occurred to produce thermodynamically stable dibenzocrownophane **V** (1,4,7-trioxacyclohexadeca-8,10,13,15-tetraen-12-one) as a result of complete crotonization. Compound **V** was isolated in 29% yield by crystallization. Its highly symmetric ^1H NMR spectrum in combination with the IR and mass spectral data reliably confirmed the assumed structure. The ^1H NMR spectrum of **V** contained a singlet at δ 2.06 ppm (6H, CH_3), two multiplets at δ 3.86 and 4.17 ppm (4H each, $\text{OCH}_2\text{CH}_2\text{O}$), and a two-proton downfield signal from 10-H and 14-H.

Analogous 1,5-diaryl-1,4-pentadien-3-one having no polyether linker between the benzene rings was synthesized by us previously [3] and brought into condensation with methylamine. We thus demonstrated that such dienones can be formed as intermediate products in three-component condensations of dialkyl ketones with benzaldehyde and amine and that their subsequent Michael reaction leads to 2,6-diarylpiperi-

din-4-ones. However, the yield of the target piperidinones did not exceed 34% even after keeping in alcohol at 20°C.

Therefore, we made an attempt to examine analogous reaction of macrocyclic ketone **V** with amines under similar conditions to estimate the effect of the aza crown ether linker on the yield of the expected products. We have found that the condensation of **V** with both ammonia and methylamine provides an alternative synthetic route to aza crown ethers **VIa** and **VIb** and that their yields (even after keeping the reaction mixture for 1 h) are twice as large as those in the reactions leading to 2,6-diarylpiperidin-4-ones having no polyether moiety. These findings indicate that the presence of a polyether bridge in molecule **V** is important for spatial preorganization of the 1,4-diene system, favoring Michael addition of amines due to both electronic factors and restricted rotation about formally single $\text{C}^{11}\text{C}^{12}\text{C}^{13}$ ordinary bonds in the diene fragment.

EXPERIMENTAL

The ^1H NMR spectra were recorded from solutions in CDCl_3 on a Bruker WP-400 spectrometer operating at 400 MHz. 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 spectrophotometer.

22,24-Dimethyl-8,11,14,25-tetraoxatetracyclo[19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexaen-23-one (III) and 8,9:15,16-dibenzo-14-hydroxy-11,13-dimethyl-1,4,7-trioxacyclohexadeca-8,10,15-trien-12-one (IV). A solution of 3.14 g (10 mmol) of dialdehyde **I** and 0.86 g (10 mmol) of diethyl ketone (**II**) in a mixture of 30 ml of ethanol and 2 ml of acetic acid was stirred for 13 h at 20°C. The mixture was poured into 100 ml of a saturated solution of sodium carbonate, and the precipitate was filtered off, dried, and subjected to column chromatography on alumogel using ethyl acetate–hexane (1:1) as eluent. Yield of **III** 1.64 g (43%), colorless substance, mp 190–192°C. IR spectrum, ν , cm^{-1} : 1645 (C=O). ¹H NMR spectrum, δ , ppm: 0.90 d (6H, Me, ³J = 7.2 Hz), 3.54 m (2H, 22-H, 24-H), 3.78 m (2H, CH₂O), 4.01 m (2H, CH₂O), 4.11 m (2H, CH₂O), 4.29 m (2H, CH₂O), 5.36 br.s (2H, 1-H, 21-H), 6.80 d.d (2H, H_a, J = 8.2, 1.0 Hz), 7.00 t.t (2H, H_c, J = 7.6, 1.0 Hz), 7.24 t.t (2H, H_b, J = 8.2, 1.2 Hz). Mass spectrum, m/z (I_{rel} , %): 382 (16) [M]⁺, 364 (18), 353 (25), 325 (18), 207 (9), 189 (8), 173 (100), 161 (22), 149 (43), 131 (18), 121 (73), 93 (11), 77 (12), 57 (17). Found, %: C 73.20; H 5.78. C₂₃H₂₂O₅. Calculated, %: C 73.00; H 5.86.

Yield of **IV** 0.27 g (7%), pale yellow crystals, mp 135°C. IR spectrum, ν , cm^{-1} : 3454 (OH), 1670 (C=O). ¹H NMR spectrum, δ , ppm: 1.00 d (3H, Me, J = 7.2 Hz), 2.03 s (3H, Me), 3.80–3.92 m (3H, 11-H, CH₂O), 3.95–4.12 m (3H, CH₂O), 4.14–4.30 m (2H, CH₂O), 4.36 m (1H, CH₂O), 4.79 br.s (1H, 10-H), 5.56 br.s (1H, OH), 6.84 d (1H, H_a, J = 8.1 Hz), 6.93 d (1H, H_a, J = 8.0 Hz), 7.03 m (2H, H_c, H_c'), 7.24 t (1H, H_b, J = 8.1, 7.5 Hz), 7.34 t (1H, H_b', J = 8.0, 7.5 Hz), 7.39 (1H, H_d, J = 7.5 Hz), 7.65 d (1H, H_d', J = 7.5 Hz), 7.95 s (1H, 14-H). Mass spectrum, m/z (I_{rel} , %): 382 (58) [M]⁺, 364 (28), 354 (9), 325 (21), 315 (12), 282 (9), 188 (24), 173 (52), 161 (21), 149 (38), 131 (60), 121 (100), 115 (33), 105 (28), 91 (37), 77 (48), 65 (20). Found, %: C 72.84; H 6.03. C₂₃H₂₂O₅. Calculated, %: C 73.00; H 5.86.

8,9:15,16-Dibenzo-11,13-dimethyl-1,4,7-trioxacyclohexadeca-8,10,12,15-tetraen-12-one (V). A solution of 3.14 g (10 mmol) of dialdehyde **I**, 0.86 g (10 mmol) of pentan-3-one (**II**), and 2 g of sodium

hydroxide in a mixture of 10 ml of ethanol and 20 ml of water was heated for 3 h under reflux with stirring. The mixture was kept for 12 h at 5°C, and the precipitate was filtered off, washed with 50 ml of water, and recrystallized from ethanol. Yield 1.05 g (29%), pale yellow crystals, mp 180–182°C. IR spectrum, ν , cm^{-1} : 1684 (C=O), 1589 (C=C). ¹H NMR spectrum, δ , ppm: 2.06 s (6H, Me); 3.86 m (4H, CH₂O); 4.17 m (4H, CH₂O); 6.85, 6.96, 7.27, and 7.30 (2H each, ABCD system, H_{arom}), 7.45 s (2H, 10-H, 14-H). Mass spectrum, m/z (I_{rel} , %): 364 (100) [M]⁺, 349 (5), 281 (11), 207 (31), 133 (15), 131 (27), 121 (20), 119 (16), 115 (16), 91 (19), 77 (11). Found, %: C 76.32; H 5.83. C₂₃H₂₀O₄. Calculated, %: C 76.65; H 5.59.

22,24-Dimethyl- and 22,24,25-trimethyl-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-ones VIa and VIb (general procedure). Crown ether **V**, 1 g (2.75 mmol), was dissolved in 20 ml of ethanol, and a stream of gaseous ammonia (1 l, 0.71 g, 41.6 mmol) or methylamine (1.29 g, 41.6 mmol), was passed through the solution over a period of 0.5 or 1 h, respectively, under stirring at 20°C. The precipitate was filtered off, washed with diethyl ether (2×30 ml), and recrystallized from ethanol. Compounds **VIa** and **VIb** were isolated as colorless crystals. Yield of **VIa** 0.76 g (73%), mp 238–240°C; yield of **VIb** 0.81 g (74%), mp 165–167°C. The melting points, and the ¹H NMR and mass spectra of **VIa** and **VIb** were consistent with those reported in [1].

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