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MODIFICATION OF SALSOLINE, SALSOLIDINE, AND ANABASINE WITH DIBENZO-24-CROWN-8-DICARBOXYLIC ACID DICHLORIDE

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New derivatives of dibenzo-24-crown-8-dicarboxylic acid diamide with salsoline, salsolidine, and anabasine moieties were prepared by condensation of the alkaloids with 4′,4″(5″)-dibenzo-24-crown-8-dicarboxylic acid dichloride.

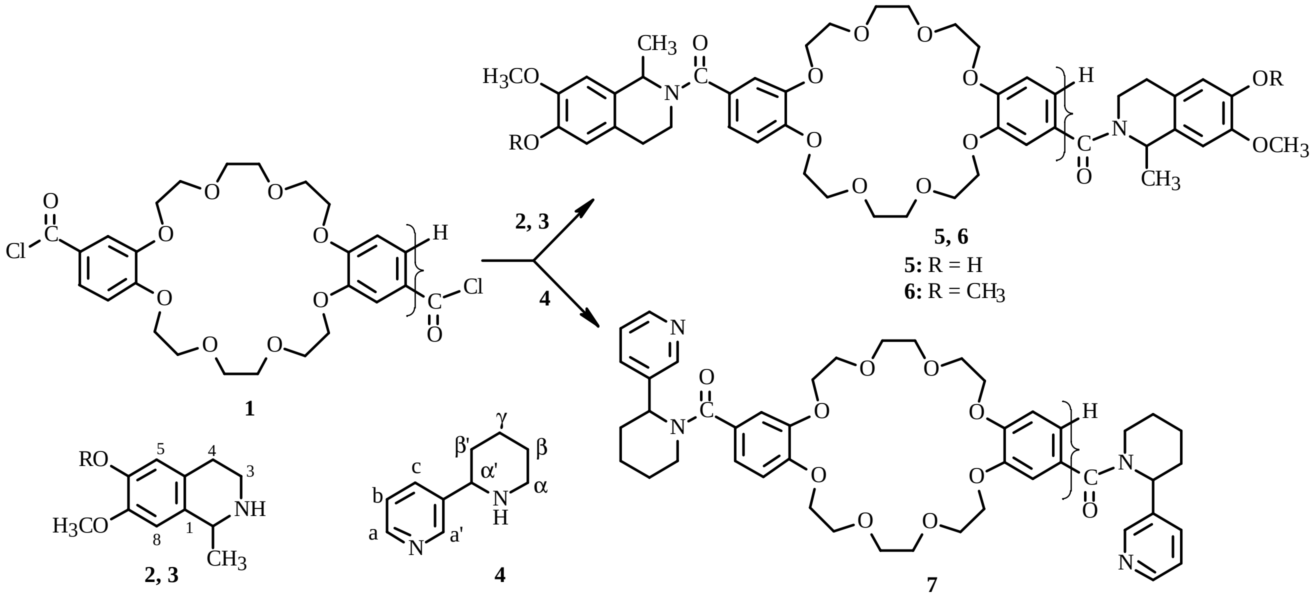
Key words: salsoline, salsolidine, anabasine, dibenzo-24-crown-8, *N*-acylation.

In continuation of the synthesis of derivatives of benzocrown ethers with alkaloid moieties containing a secondary amine, we employed carboxylic and sulfonic [1-5] acid chlorides, in particular, 4′,4″(5″)-dibenzo-24-crown-8-dicarboxylic acid dichloride (**1**). The reaction of this acid chloride with cytisine has been previously described [3]. In the present work, three alkaloids, salsoline (**2**), salsolidine (**3**), and anabasine (**4**), were acylated.

The resulting derivatives are interesting because they contain an alkaloid with distinct physiological activity and a crown-ether moiety that can coordinate to metal cations.

We used the previously demonstrated method [2, 3] consisting of boiling a suspension of the reagents and anhydrous potash in absolute benzene. The course of the reaction was monitored by TLC on Al_2O_3 and Silufol using $CHCl_3$:alcohol in various ratios. The products were the disalsolinide (**5**), disalsolidinide (**6**), and dianabasinide (**7**) of 4′,4″(5″)-DB24C8-dicarboxylic acid.

The syntheses were carried out according to the scheme below.



1

2, 3

4

5, 6
5: R = H
6: R = CH_3

7

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The structures of the products were proved using PMR spectra.

The PMR spectrum of **5** contained at weak field signals for the aromatic protons of the benzene ring of DB24C8 and the benzene ring of salsoline. The benzene protons of the crown ether gave doublets for the 5′- and 5″(4″)-protons at 7.20 ppm and singlets characteristic of the 3′- and 3″(6″)-protons at 6.97 ppm in addition to a doublet for the two 6′- and 6″(3″)-protons at 6.78 ppm. The two protons of the benzene ring of the isoquinoline appeared as a singlet at 6.50 ppm (for the 5-proton). The nonequivalent proton in the 8-position appeared as a singlet at 6.32 ppm. The methine proton next to the heterocyclic N atom gave a multiplet at 5.14 ppm. The four methylene protons in the 3-positions next to the N atom appeared as a triplet at 3.12 ppm; in the 4-position, as a second triplet at 1.92 ppm. The six methyl protons gave a doublet at 1.20 ppm. The macrocyclic protons appeared as a strong multiplet at 3.97-3.62 ppm, on which the signals of the two methyls were superimposed.

The PMR spectrum of **6** showed a doublet for the two protons in the 5′- and 5″(4″)-positions of the DB24C8 benzene rings at 7.17 ppm. The two protons in the 3′- and 3″(6″)-positions gave a singlet at 6.80 ppm. There was a strong doublet at 6.67 ppm for the two protons in the 6′- and 6″(3″)-positions. The two protons of the isoquinoline benzene ring in the 5- and 8-positions appeared as a singlet at 6.37 ppm. The hydrogenated part of the isoquinoline gave a multiplet for the two methine protons at 5.17 ppm. The isoquinoline methylene protons appeared as two triplets at 3.07 ppm (protons in the 3-positions) and 2.40 ppm (protons in the 4-position). A doublet for six methyl protons at 1.40 ppm was well resolved in the spectrum. The macrocycle protons gave a multiplet at 4.02-3.45 ppm, on which the signals of four methoxyls were superimposed.

The PMR spectrum of **7** had resonances for the pyridine protons at the weakest field. A singlet for the two H-a′ protons was well resolved at 8.42 ppm. Next to it the two H-a protons gave a doublet at 8.32 ppm. The H-c protons of the pyridine gave a doublet at 7.45 ppm; the two H-b protons, a doublet of doublets centered at 7.12 ppm. Next the aromatic protons of the benzocrown ether in the 5′- and 5″(4″)-positions appeared at 7.03 ppm, a singlet for the 3′- and 3″(6″)-protons at 6.85 ppm, and a doublet for the 6′- and 6″(3″)-protons centered at 6.70 ppm. The two methine protons of anabasine at the site of pyridine and piperidine attachment (H-α') gave a triplet centered at 5.57 ppm. The 24 macrocycle protons appeared as a multiplet at 4.10-3.50 ppm. The four α-protons of the piperidine ring gave a triplet centered at 2.75 ppm. The piperidine β-, β'-, and γ-protons appeared as a multiplet centered at 1.50 ppm.

EXPERIMENTAL

4′,4″(5″)-DB24C8-Dicarboxylic acid was prepared [3] in 96% yield, mp 240-247°C, lit. [3] mp 235-240°C. The diacid dichloride of 4′,4″(5″)-DB24C8 dicarboxylic acid was isolated by a method analogous to the published one [3]. PMR spectra were recorded on a XL-100 (Varian) spectrometer at working frequency 100 MHz in CCl_4 + ($C_6D_6 \approx 0.1\%$) solutions with HMDS internal standard. Analytical TLC was performed on prefabricated Silufol plates (Silpearl UV 254).

General Method of *N*-acylation. Compound **1** was prepared from the acid and thionylchloride taken in a 1:4 mole ratio in absolute benzene and was used without further purification after distillation of benzene in a rotary evaporator. The solid was again treated with absolute benzene (20-25 mL), a two-fold molar excess of alkaloid, and the same excess of anhydrous potash. The reaction began even at room temperature. The solution was refluxed and isolated from air until the spot of the alkaloid disappeared on TLC [Al_2O_3, $CHCl_3$ (16 mL):alcohol (6 drops)] after 7 h (salsoline), 3.5 h (salsolidine), or 5 h (anabasine). The benzene solution was washed with water, HCl (1:1), $NaHCO_3$ solution, and water (until neutral). The solvent was partially removed.

4′,4″(5″)-DB24C8-Dicarboxylic acid disalsolinide (5) was separated in two parts, one soluble in benzene with mp 99-101°C (one spot on TLC) and a solid that was poorly soluble in benzene that dissolved in hot alcohol. TLC showed that the main product was contaminated by a substance that remained at the origin and could be removed by passing the product over a thin layer of Al_2O_3 using $CHCl_3$:alcohol (2:1). Fractions 1-4 contained a single compound. Yield of disalsolinide [0.4 g from 0.49 g (0.82 mmol) of **1**] (51%), mp 96-99°C.

PMR spectrum (δ, ppm, J/Hz): 7.20 [2H, d, ArH 5′,5″(4″), J = 2.5], 6.97 [2H, s, ArH 3′,3″(6″)], 6.78 [2H, d, ArH 6′,6″(3″), J = 12.5], 6.50 (2H, s, H-5), 6.32 (2H, s, H-8), 5.14 (2H, m, H-1), 3.97-3.62 (30H, m, α-OCH_2, β-OCH_2, γ-OCH_2, OCH_3), 3.12 (4H, t, H-3), 1.92 (4H, t, H-4), 1.20 (6H, d, CH_3).

4′,4″(5″)-DB24C8-Dicarboxylic acid disalsolidinide (6) was dissolved in absolute benzene and chromatographed over a small column of Al_2O_3 using $CHCl_3$ (16 mL):alcohol (16 drops). The first three fractions contained the pure disalsolidinide.

Subsequent fractions contained the disalsolinide and starting materials (as impurities). TLC of the starting alkaloid confirmed that it had an impurity of salsoline. Yield of disalsolidinide [0.64 g from 0.48 g (0.82 mmol) of **1**] (78%), mp 80-82°C. Subsequent fractions had an impurity of the disalsolinide and starting material.

PMR spectrum (δ, ppm, J/Hz): 7.17 [2H, d, ArH 5′,5″(4″), J = 3.7], 6.80 [2H, s, ArH 3′,3″(6″)], 6.67 [2H, d, ArH 6′,6″(3″), J = 12.5], 6.37 (2H, s, H-5,8), 5.17 (2H, m, H-1), 4.02-3.45 (36H, m, α-OCH_2, β-OCH_2, γ-OCH_2, OCH_3), 3.07 (4H, t, H-3), 2.40 (4H, t, H-4), 1.40 (6H, d, CH_3).

4′,4″(5″)-DB24C8-Dicarboxylic Acid Dianabaside (7). In contrast with the previous experiments, we used anabasine hydrochloride. Crystals with mp 75-80°C formed in a concentrated benzene solution. During removal of benzene, a solid that was poorly soluble in benzene appeared on the walls of the flask. This was washed with HCl (1:1), $NaHCO_3$ solution, and water and dissolved in alcohol with heating. The solution was refluxed. After distillation of a part of the alcohol, the crystals with mp 73-77°C that formed in the solution began to dissolve in benzene and $CHCl_3$. TLC [$CHCl_3$ (16 mL):alcohol (8 mL)] of the crystals from benzene and alcohol gave the same R_f value. Yield of dianabasinide [0.42 g from 0.74 g (1.38 mmol) of **1**] (37%), mp 73-77°C.

PMR spectrum (δ, ppm, J/Hz): 8.42 (2H, s, H-a′), 8.32 (2H, d, H-a, J = 5.0), 7.45 (2H, d, H-c, J = 2.5), 7.12 (2H, dd, H-b, J_1 = 7.5, J_2 = 32), 7.03 [2H, d, ArH 5′,5″(4″)], J = 5.0), 6.85 [2H, s, ArH 3′,3″(6″)], 6.70 [2H, d, ArH 6′,6″(3″), J = 10.0], 5.57 (2H, t, H-α'), 4.10-3.50 (24H, m, α-OCH_2, β-OCH_2, γ-OCH_2), 2.75 (4H, t, H-α), 1.50 (12H, m, H-β,β',γ).

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