SYNTHESIS OF 4′,4″(5″)-DIBENZO-18-CROWN-6-DISULFONIC ACID DISALSOLIDINIDE, DISALSOLINIDE, AND DIANABASINIDE*

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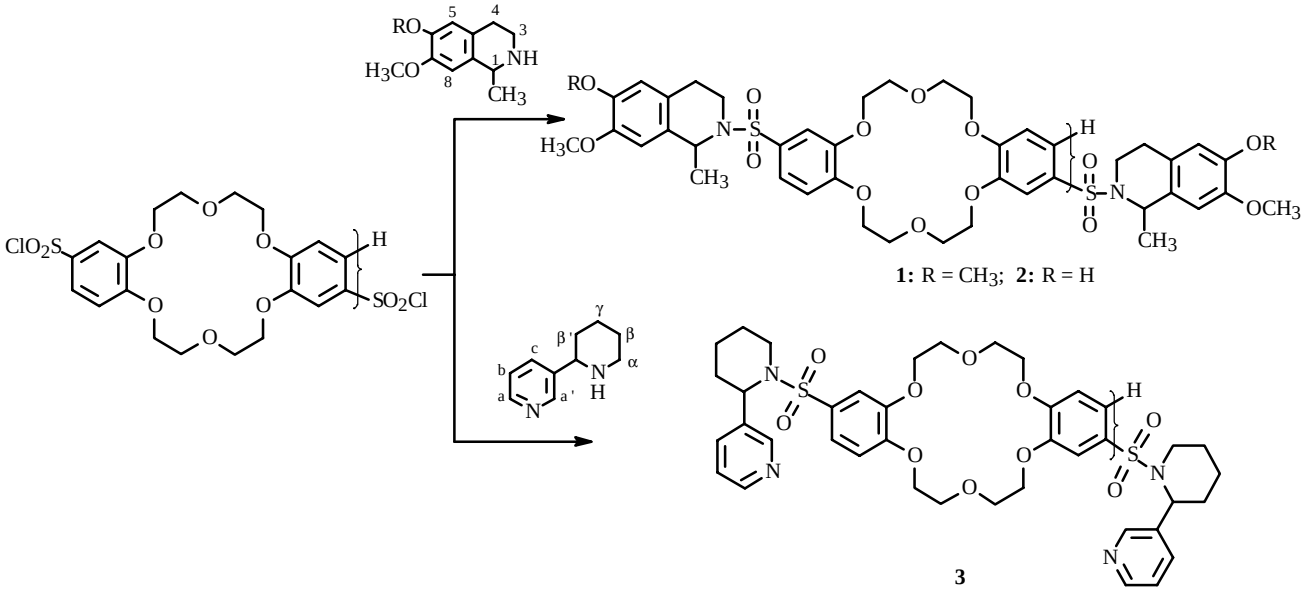
New disulfamides of dibenzo-18-crown-6 with salsolidine, salsoline, and anabasine were prepared by condensation of the corresponding alkaloids with 4′,4″(5″)-dibenzo-18-crown-6-disulfonyl chlorides.

Key words: salsolidine, salsoline, anabasine, 4′,4″(5″)-dibenzo-18-crown-6-disulfonyl chloride, sulfonylation.

Sulfonylation using benzo-crown-ether sulfonic acids is a promising method for modifying alkaloids containing a secondary amino group. Sulfamides of cytisine were previously prepared: 4′,4″(5″)-dibenzo-18-crown-6-disulfonic acid dicytisinide and 4′-*sec*-butyl- and 4′-acetyl-4″(5″)-dibenzo-18-crown-6-sulfonic acid cytisinides [1]. In continuation of the synthesis, we selected three alkaloids as substrates for sulfonylation: salsolidine, salsoline, and anabasine. We used 4′,4″(5″)-dibenzo-18-crown-6-disulfonyl chloride, which was prepared by sulfochlorination of 4′,4″(5″)-dibenzo-18-crown-6 (DB18C6), as the reagent [2].

The first two alkaloids are medicinal preparations with antispasmodic and hypotensive action [3]. Anabasine is also used in medicine [4] and agriculture [5]. The combination in one molecule of a membrane-active fragment and alkaloid with medicinal action is very interesting because it can sharply lower the active dose of the preparation owing to an increase of cell permeability and complexing properties of the macrocycle. The active parts of the molecule can generate new useful properties. It should also be noted that the reaction products contain the sulfamide pharmacophore (Scheme 1).



1: R = CH_3; **2:** R = H

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The first step was reaction of DB18C6 and chlorosulfonic acid in $CHCl_3$ to produce 4′,4″(5″)-DB18C6-disulfonyl chloride [2]. In the second step, the alkaloids in absolute benzene with triethylamine were sulfonated by 4′,4″(5″)-DB18C6-disulfonyl chloride. The structures of the sulfamides were confirmed by PMR spectra. The resulting products were mixtures of the 4′,4″- and 4′,5″-isomers.

The PMR spectrum of 4′,4″(5″)-DB18C6-disulfonic acid disalsolidinide (**1**) exhibits weak field signals for aromatic protons of the benzenes of DB18C6 and the benzene of the salsolidine. The crown-ether benzene protons give a doublet at 7.30 ppm for protons in the 5′,5″(4″) positions; a singlet at 7.00 ppm, for 3′,3″(6″) positions; and a strong 2H signal at 6.74 ppm, for 6′,6″(3″) positions. Two protons of the benzene in the isoquinoline fragment appear as a singlet at 6.50 ppm. The hydrogenated isoquinoline fragment gives a quartet of methine protons (H-1) at 5.0 ppm. A doublet for methyl protons at 1.3 ppm is clearly seen in the spectrum. The macrocycle protons appear as a multiplet at 3.41-4.05 ppm that is overlapped by a strong singlet of four methoxyls.

The PMR spectrum of 4′,4″(5″)-DB18C6-disulfonic acid disalsolinide (**2**) shows two protons in the 5′,5″(4″) positions of the DB18C6 benzene also at 7.30 ppm; two protons in 3′,3″(6″) positions, a singlet at 7.20 ppm; protons in 6′,6″(3″) positions, a doublet at 6.90 ppm. Protons in *p*-positions of the salsoline benzene are nonequivalent, giving two singlets at 6.60 (H-5) and 6.30 (H-8) ppm. The methine proton (H-1) next to the heterocyclic N gives a characteristic quartet at 5 ppm; the macrocyclic protons, a strong multiplet at 3.60-4.40 ppm that is overlapped by signals of two methoxyls. The tetrahydroisoquinoline core appears as a 4H triplet in the 3-position relative to N at 2.75 ppm and in the 4-position relative to N as a second triplet at 1.44 ppm; six methyls, a doublet at 1.25 ppm.

The PMR spectrum of 4′,4″(5″)-DB18C6-disulfonic acid dianabasinide (**3**) contains pyridine protons at the weakest field. A singlet for the two H-a′ protons appears at 8.51 ppm. Next to it are the two H-a protons, which give a doublet at 8.45 ppm. A doublet for H-c protons of the pyridine ring is shifted to weak field compared with pyridine and appears at 7.72 ppm. The two H-b protons of the pyridine give two doublets centered at 7.43 ppm. These are partially overlapped by a doublet of aromatic protons for the benzene of the crown ether in the 5′,5″(4″) position at 7.38 ppm. Next are signals for crown-ether aromatic protons in the classical sequence: a singlet for 3′,3″(6″) protons appears at 7.28 ppm; a doublet for 6′,6″(3″) protons, centered at 7.07 ppm. The two anabasine methine protons at the site of the pyridine and piperidine compounds (H-α') give an unresolved signal at 5.20 ppm. A multiplet for eight protons of α-CH_2O groups of the macrocycle appears at 3.95-4.25 ppm; a multiplet of eight β-CH_2O protons, at 3.75-3.95 ppm. Four protons in the α-position of the piperidine ring give a triplet centered at 2.05 ppm; β-, β'-, and γ-protons of piperidine, a multiplet centered at 1.30 ppm.

EXPERIMENTAL

PMR spectra were obtained on an XL-100 spectrometer (Varian) at working frequency 100 MHz.

Preparation of 4′,4″(5″)-DB18C6-disulfonic Acid Disalsolidinide (1). A mixture of salsolidine (0.15 g, 0.7 mmol) and DB18C6-disulfonyl chloride (0.20 g, 0.36 mmol) was dissolved in absolute benzene (3 mL) and treated by micropipette with triethylamine (0.07 mL, 0.7 mmol). The solution was refluxed. The solid dissolved. Refluxing was continued for 2.5 h. The mixture was left overnight at room temperature and refluxed another 2 h. The solution was neutral. The solid was filtered off and washed with benzene. The benzene layer was washed with water, dried over $MgSO_4$, and passed over a thin layer of Al_2O_3 to remove resinous products. The product did not give a Beilstein test for halogen. After distilling solvent, the product was recrystallized from alcohol. Yield 0.14 g (43.4%), mp 107-111°C. PMR spectrum (δ, ppm): 7.30 [2H, d, ArH 5′,5″(4″)], 7.00 [2H, s, ArH 3′3″(6″)], 6.74 [2H, d, ArH 6′,6″(3″)], 6.50 (4H, s, H-5, 8), 5.00 (2H, q, H-1), 3.41-4.05 (28H, m, α-OCH_2, β-OCH_2, OCH_3), 1.30 (6H, d, CH_3).

Preparation of 4′,4″(5″)-DB18C6-disulfonic Acid Disalsolinide (2). A mixture of DB18C6-disulfonyl chloride (0.60 g, 1.08 mmol) and salsoline (0.51 g, 2.6 mmol) in absolute benzene (21 mL) was treated with triethylamine (1 mL). The resulting mixture was refluxed for 2 h, left overnight at room temperature, and refluxed another 2 h. The solid changed appearance with more boiling. The benzene was decanted. The solid was refluxed three times with fresh portions of benzene and washed with water. The solution was neutral. The light yellow powder was dried in a drying chamber. A Beilstein test for halogen was negative. Yield 0.79 g (84.9%), mp 158-160°C.

PMR spectrum (δ, ppm): 7.30 [2H, d, ArH 5′,5″(4″)], 7.20 [2H, s, ArH 3′,3″(6″)], 6.90 [2H, d, ArH 6′,6″(3″)], 6.60 (2H, s, H-5), 6.30 (2H, s, H-8), 5.00 (2H, q, H-1), 3.60-4.40 (22H, m, α-OCH_2, β-OCH_2, OCH_3), 2.75 (4H, t, H-3), 1.44 (4H, t, H-4), 1.25 (6H, d, CH_3).

Preparation of 4′,4″(5″)-DB18C6-disulfonic Acid Dianabasinide (3). Anabasine hydrochloride (0.19 g, 0.89 mmol) was mixed with $NaHCO_3$ (0.07 g, 0.9 mmol) and absolute benzene (12 mL). The mixture was boiled for 1 h. Carbon dioxide was given off. The solid changed appearance. After 1 h, DB18C6-disulfonyl chloride (0.2 g, 0.36 mmol), triethylamine (0.2 mL), and benzene (20 mL) were added. The mixture was boiled for 5.5 h. An orange color developed. Gas bubbles were given off. The mixture was left overnight at room temperature. The benzene layer was washed with water. The solution was basic. The orange color transferred into water. The benzene layer was washed with dilute HCL and water until the washings were neutral. The aqueous solutions were combined, acidified, evaporated on a water bath to a small volume, and made basic with $NaHCO_3$. The resulting pink solid was filtered off. The product was dissolved in absolute benzene with heating. After removing benzene, the remaining oil was dissolved in isopropanol, from which white crystals precipitated. Yield 0.1 g (33%), mp 82-89°C.

PMR spectrum (δ, ppm): 8.51 (2H, s, $H_{a'}$), 8.45 (2H, d, H_a), 7.72 (2H, d, H_c), 7.43 (2H, dd, H_b), 7.38 [2H, d, ArH 5′,5″(4″)], 7.28 [2H, s, ArH 3′,3″(6″)], 7.07 [2H, d, ArH 6′,6″(3″)], 5.20 (2H, s, $H_{\alpha'}$), 3.95-4.25 (16H, m, α-OCH_2, β-OCH_2), 2.05 (4H, t, H_α), 1.30 (12H, m, $H_{\beta,\beta',\gamma}$).

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