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REACTION OF CYTISINE WITH 4′-SUBSTITUTED DIBENZO-18-CROWN-6 SULFONYLCHLORIDES*

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Sulfamides were synthesized via the reaction of cytisine with 4′,4″(5″)-dibenzo-18-crown-6-disulfonyl-, 4′-sec-butyl-4′(5″)-dibenzo-18-crown-6-sulfonyl-, and 4′-acetyl-4′(5″)-dibenzo-18-crown-6-sulfonylchlorides. The structures of the prepared compounds were confirmed by PMR.

Key words: cytisine, sulfonylation, dibenzo-18-crown-6-sulfonyl cytisinides.

The quinolizidine alkaloid cytisine is used medicinally as a respiratory stimulant. As a rule, it is modified by reactions at the secondary amino group. Numerous substitution reactions of the amino hydrogen by simple and functional groups have been described [1]. Alkylation and acylation reactions dominate. Two sulfamides, N-*p*-toluenesulfonylcytisine and N-naphthosulfonylcytisine, have been described among the hundreds of derivatives. We were interested in substituting the amine hydrogen of cytisine by sulfonic acids derived from dibenzo-18-crown-6 (DB18C6). The resulting sulfamides contain the physiologically active alkaloid, the pharmacologic sulfamide [2], and the crown ether, which is membrane-active and complex-forming. By increasing the lipophilicity the crown imparts to the molecule the ability to bind and transfer through biological membranes cations of calcium, sodium, and other vital metals.

We used active DB18C6 derivatives such as 4′-*sec*-butyl-, 4′-acetyl-, and 4′-sulfo-4″(5″)-DB18C6 sulfonylchlorides. We synthesized 4′,4″(5″)-DB18C6 disulfonylchloride (**1**) by sulfonation of DB18C6 with potassium sulfate in polyphosphoric acid (PPA) [3] and transformation of the resulting 4′,4″(5″)-DB18C6 disulfonic acid into the dichloride using thionylchloride and by sulfochlorination of DB18C6 by chlorosulfonic acid in $CHCl_3$ by the literature method [4]. Sulfonylchlorides of 4′-*sec*-butyl- and 4′-acetyl-DB18C6 were prepared by sulfochlorination of the corresponding monosubstituted DB18C6 as before [4].

The reaction of cytisine with the sulfonylchlorides followed Scheme 1.

4′,4″(5″)-DB18C6 disulfonyl dicytisinide (**2c**) was prepared as two isomers with a single R_f on TLC in C_2H_5OH:C_6H_6:CH_3COOH (2 mL:7 mL:9 drops). Fractional crystallization from alcohol gave the lower melting isomer A with mp 163-165°C. Isomer B has mp 172-176°C and is poorly soluble in hot alcohol. It was recrystallized from $CHCl_3$:C_2H_5OH. The PMR spectra of the isomers are almost identical. They contain signals at weak field that correspond to benzene protons of the crown ether (7.05-7.32 ppm) and to those of the α-pyridone (6.10-6.24 and 7.17 ppm).

The PMR spectra of the cytisinides (**2a** and **b**) with different substituents on the two benzene rings are more complicated owing to the electronic effect of the substituents in the two benzene rings of the DB18C6. The difference in the electronic effect of the *sec*-butyl (+I effect) and sulfamide (-I, -M-effect) in 4′-*sec*-butyl-4″(5″)-DB18C6 sulfocytisinide (**2b**) is reflected in the PMR spectrum by the appearance of singlets for the 3′ and 3″(6″) protons. The singlet of the 3″(6″)-proton is shifted to weak field by the electron-accepting SO_2-cytisine. Its chemical shift coincides exactly with that of the corresponding singlet in the dicytisinide **2c**. The 3′-proton of the benzene substituted by *sec*-butyl resonates at stronger field at 6.85 ppm. The signals for the 5′,5″(4″) and 6′,6″(3″) protons are not resolved.

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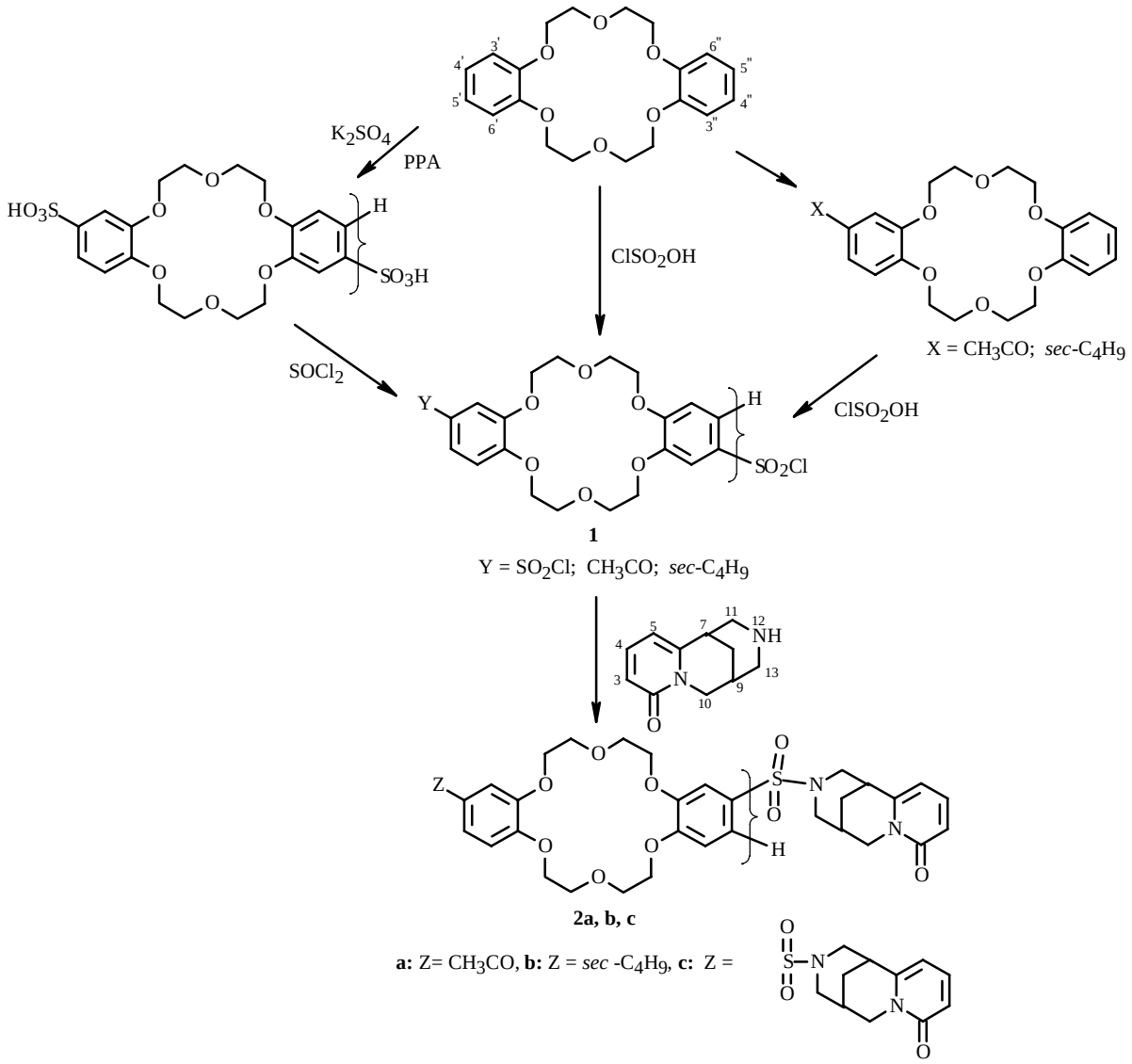

Scheme 1

The second asymmetric 4′-acetyl-DB18C6-4′(5″)-sulfonic acid cytisinide (**2a**) gave a distinct pattern of chemical shifts for the protons of the two different benzene rings owing to the strong electron-accepting properties of the acetyl group. The classical sequence of doublet-singlet-doublet signals for the benzene ring with the acetyl [5] is shifted to weak field compared with the signals for the ring with the sulfamide. The trend in the chemical shifts of protons in the ring with the sulfocytisinide substituent was followed in the three prepared cytisinides.

Signals for the OCH_2– protons of the macrocycle appear at 3.8-4.2 ppm as two multiplets that are identical for the three prepared compounds.

Signals in the PMR spectra of **2a**, **b**, and **c** were assigned to the corresponding atoms of cytisine (see Experimental) by consulting the literature [6].

The structure of 4′-acetyl-4″(5″)-DB18C6-sulfonic acid was confirmed by the distinct singlet of the three acetyl protons at 2.50-2.55 ppm.

The spectrum of 4′-*sec*-butyl-4″(5″)-DB18C6-sulfocytisinide contains four groups of signals at 0.75-1.80 ppm for the *sec*-butyl radical.

EXPERIMENTAL

^{1}H NMR spectra of 4′-*sec*-butyl-DB18C6 were obtained on a XL-100 (Varian) spectrometer at working frequency 100 MHz; of the cytisinides, on a UNITY 400+ spectrometer at working frequency 400 MHz.

Preparation of 4′-Acetyl-DB18C6. DB18C6 (0.73 g, 2 mmole) was added to PPA (7.25 g) with vigorous stirring. The mixture was heated until the solid completely dissolved at 75°C. Glacial acetic acid (0.14 mL, 2.4 mmole) was added by pipette. The course of the reaction was monitored by TLC on aluminum oxide using hexane—acetone (2:1). After 30 min the mixture was cooled and decomposed with water. The solid was washed until the washings were neutral. According to TLC it contained mono- and diacetyl-DB18C6. The mixture was separated over a column packed with aluminum oxide (75 times as much as the solid) using acetone—hexane (1:2). Four fractions were isolated. The second fraction consisted mainly of 4′-acetyl-DB18C6 was separated again to give 4′-acetyl-DB18C6 (0.40 g, 32%), mp 158-163°C, lit. [7] mp 169-171°C.

Preparation of 4′-*sec*-Butyl-DB18C6. DB18C6 (1.08 g, 3 mmole) was dissolved at 60°C in PPA (10.8 g), treated with *sec*-butanol (0.6 mL, 3.5 mmole), held at this temperature for 5 h, decomposed with water, and extracted with $CHCl_3$. The extract was washed with NaOH (20%) and water until the washings were neutral. The $CHCl_3$ was distilled off. The solid was separated by column chromatography using $CHCl_3$—C_6H_{14}—$(CH_3)_2CO$ (15:27:5) to give 4′-*sec*-butyl-DB18C6 (0.27 g, 13%), mp 93-95°C.

PMR spectrum (δ, ppm, J/Hz): 6.72 (4H, s, ArH), 6.46-6.82 (3H, m, ArH), 3.80-4.20 (16H, m, OCH_2), 2.44 (1H, m, CH), 1.46 (2H, m, CH_2), 1.14 (3H, d, J = 7, α-CH_3), 0.80 (3H, t, J = 7, β-CH_3).

Sulfochlorination of 4′-Acetyl-DB18C6. A solution of 4′-cetyl-DB18C6 (0.25 g, 0.62 mmole) in $CHCl_3$ (5 mL) was treated with sulfonylchloride (0.7 g, 0.39 mL, 6 mmole) with cooling by ice-salt at -15°C, stirred for 1 h with cooling. The solution became dark green and layered. Stirring was continued without cooling for 6 h. The mixture was left for 12 h with a $CaCl_2$ trap. The completion of the reaction was determined by TLC. The mixture was decomposed with ice and stirring. The emulsion was exhaustively extracted with $CHCl_3$. The solution was dried over $CaCO_3$. The solvent was removed. The solid was crystallized from alcohol to give 4′-acetyl-4″(5″)-DB18C6 sulfonylchloride (0.07 g, 26%), mp 130-135°C.

Sulfochlorination of 4′-*sec*-Butyl-DB18C6. A solution of 4′-*sec*-butyl-DB18C6 (0.5 g, 1.2 mmole) in $CHCl_3$ (5 mL) was cooled with ice-salt to -15°C, treated dropwise with sulfonylchloride (1.4 g, 0.79 mL, 12 mmole), stirred with cooling for 0.5 h, without cooling for another 3.5 h, and left overnight. A sample for TLC was taken and mixed with water and $CHCl_3$. The solvent system for TLC over aluminum oxide was hexane—acetone (2:1). The reaction mixture was decomposed with ice and extracted three times with $CHCl_3$. The extract was washed with water and dried over $CaCO_3$ for two days. The solvent was removed. The glassy solid was ground with hexane and converted to a powder that contained according to TLC traces of the starting crown ether. It was washed with boiling hexane to give 4′-*sec*-butyl-4″(5″)-DB18C6 sulfonylchloride (0.46 g, 75.4%), mp 102-103°C.

Sulfochlorination of DB18C6. DB18C6 (0.36 g, 1 mmole) was dissolved in $CHCl_3$ (5 mL), cooled to -15°C with ice-salt, and treated dropwise over 10 min with sulfonylchloride (2.33 g, 1.32 mL, 20 mmole). Then, the dropping funnel was washed with $CHCl_3$ (5 mL). The solution became green. Stirring was continued at room temperature for 5.5 h. The mixture was left overnight. The completion of the reaction was determined by TLC over aluminum oxide using hexane—acetone (2:1). The mixture was decomposed by adding ice. The aqueous layer was extracted five times with $CHCl_3$. The extract was neutralized by dry chalk. The solvent was removed. The product was precipitated with hexane as a thick oil that solidified upon grinding with hexane to give an off-white powder (0.97 g) that was washed twice with boiling hexane to remove traces of DB18C6. The disulfonylchloride was recrystallized from benzene to give a compound (0.32 g, 54%) with mp 159-165°C, lit. [4] mp 158-162°C.

Preparation of 4′,4″(5″)-DB18C6 Disulfonylchloride from 4′,4″(5″)-DB18C6 disulfonic Acid. 4′,4″(5″)-DB18C6 disulfonic acid (1 g, 1.9 mmole) was dissolved in DMF (5 mL), treated after 30 min in portions with thionylchloride (2 mL, 2.7 mmole) with cooling, left overnight, and decomposed with icewater. The precipitate was washed with water and dried in air to give the sulfonylchloride (0.4 g, 37%). The product was recrystallized from acetonitrile to give a solid with mp 155-160°C, lit. [4] mp 158-162°C.

Preparation of 4′-*sec*-Butyl-4″(5″)-DB18C6 sulfonic Acid Cytisinide (2c). A solution of cytisine (0.11 g, 0.58 mmole) in absolute benzene (1.5 mL) was treated dropwise with 4′-*sec*-butyl-4″(5″)-DB18C6-sulfonylchloride (0.3 g, 0.58 mmole) in benzene (2 mL) that was previously poured into a flask with triethylamine (0.085 mL, 0.58 mmole). A white precipitate formed immediately upon stirring. After 7 min the mixture was heated on a water bath with a condenser, stirrer,

and $CaCl_2$ trap, refluxed for 2 h, left at room temperature for 12 h, and treated with water. A white precipitate formed and was drawn off and washed with water. The aqueous layer was extracted 3-4 times with benzene. The extract was washed with HCl (1:1) and distilled without drying to give a small amount of solid (0.29 g) that did not give a Beilstein test. The crystals were washed with HCl (1:1) and water until the washings were neutral and dried in air to give the sulfamide (0.26 g, 68%), mp 160-163°C.

PMR spectrum (δ, ppm): 7.35 [2H, m, ArH-5′,5″(4″)], 7.17 (1H, dd, H-4), 7.10 [2H, d, ArH-6′,6″(3″)], 7.05 [1H, s, ArH-3″(6″)], 6.85 (1H, s, ArH-3′), 6.25 (1H, dd, H-3), 6.10 (1H, dd, H-5), 4.10-4.20 (8H, m, α-OCH_2), 3.85-3.95 (8H, m, β-OCH_2), 4.10 (2H, H-10), 3.55-3.70 (5H), 2.60 (1H, m, H-9), 1.80 (2H, t, H-8), 1.80 (1H, m, CH), 1.50 (2H, m, CH_2), 1.10 (3H, d, ArCHC$\underline{H}_3$), 0.75 (3H, t, $CH_2C\underline{H}_3$).

Preparation of 4′-Acetyl-4″(5″)-DB18C6 sulfonic Acid Cytisinide (2a). A solution of cytisine (0.057 g, 0.3 mmole) in benzene (2 mL) was treated with triethylamine (0.043 mL, 0.3 mmole) and a suspension of 4′-acetyl-4″(5″)-DB18C6 sulfonylchloride (0.15 g, 0.3 mmole) in benzene (4 mL). The mixture was refluxed with a $CaCl_2$ trap on a water bath for 4 h, left at room temperature overnight, boiled for another 2 h, and decomposed with water to give two layers. The benzene layer did not contain the cytisinide. The alkaline aqueous layer was combined with the washings from the benzene layer and evaporated on a water bath. The precipitate was drawn off, washed with dilute HCl and water, and dried in air to give sulfamide (0.7 g, 21%), mp 93-98°C, that did not give a Beilstein test and formed one spot on TLC [Silufol, alcohol(2 mL):benzene (7 mL):acetic acid (9 drops)].

PMR spectrum (δ, ppm): 7.58 (1H, d, ArH-5′), 7.32 [1H, dd, ArH-5″(4″)], 7.42 (1H, s, ArH-3′), 7.05 [1H, s, ArH-3″(6″)], 7.10 (1H, d, ArH-6′), 7.03 [1H, d, ArH-6″(3″)], 7.17 (1H, dd, H-4), 6.23 (1H, dd, H-3), 6.10 (1H, dd, H-5), 4.15-4.20 (8H, m, α-OCH_2), 3.85-3.95 (8H, m, β-OCH_2), 4.10-4.20 (2H, H-10), 3.50-3.75 (5H, m), 2.60 (1H, m, H-9), 1.86 (2H, t, H-8), 2.50-2.55 (3H, s, CH_3CO).

Preparation of 4′,4″(5″)-DB18C6 disulfonic Acid Dicytisinide (2c). A solution of cytisine (0.41 g, 2 mmole) in benzene (2.5 mL) was treated with triethylamine (0.3 mL, 2 mmole) and DB18C6 disulfonylchloride (0.6 g, 1.1 mmole) in absolute benzene (8 mL), boiled for 3 h with a $CaCl_2$ trap, left at room temperature overnight, and again boiled for 4 h. The precipitate was drawn off. The benzene solution was washed with HCl (1:4) and water until the washings were neutral, dried over $MgSO_4$, and evaporated. The small amount of solid gave a Beilstein test. The bulk of the precipitate was washed with water and dried in air. The Beilstein test was negative. Washing with HCl (1:1) and water and drying gave the disulfamide (1.05 g). Recrystallization from alcohol gave two isomers: one soluble in hot alcohol (0.49 g, 49.3%), mp 163-165°C (isomer A), and one insoluble in hot alcohol (0.1 g, 10%) that had mp 172-178°C after recrystallization from $CHCl_3$:alcohol (isomer B). The R_f values on TLC were identical.

PMR spectrum (δ, ppm): 7.32 [2H, d, ArH-5′,5″(4″)], 7.17 (2H, dd, H-4), 7.07 [2H, d, ArH-6′,6″(3″)], 7.05 [2H, s, ArH-3′,3″(6″)], 6.24 (2H, d, H-3), 6.10 (2H, d, H-5), 4.15-4.25 (8H, m, α-OCH_2), 3.80-3.95 (8H, m, β-OCH_2), 3.75 (4H, H-10), 3.55-3.80 (10H, H_7+H_{11}+H_{13}), 2.50 (2H, dd, H-9), 1.90 (4H, dd, H-8).

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