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SYNTHESIS OF NEW CYTISINE DERIVATIVES WITH BENZOCROWN-ETHER FRAGMENTS*

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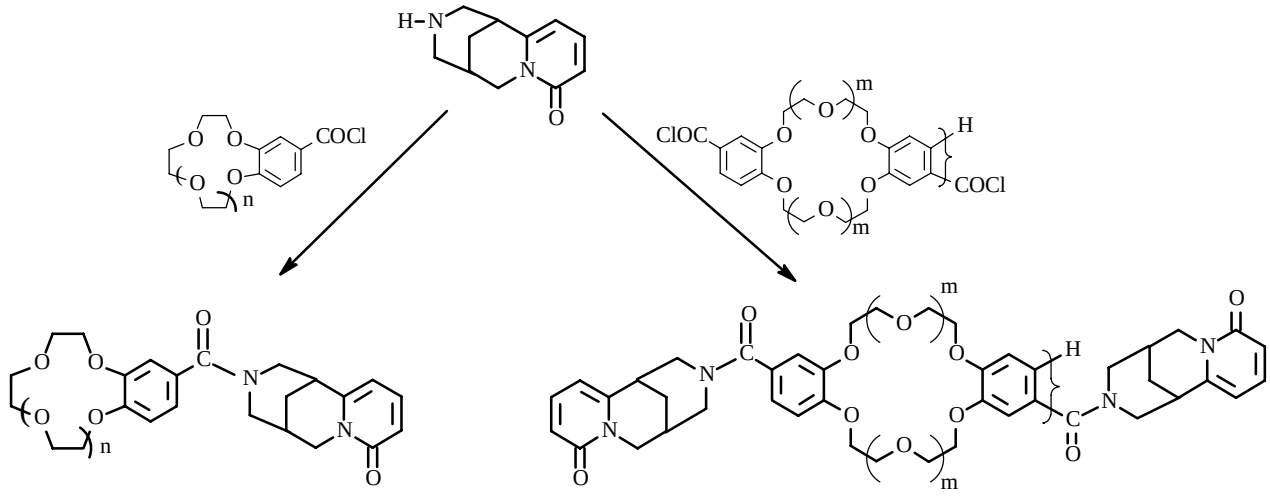
Acylation of cytisine with benzocrown-ethercarboxylic acid chlorides produced a series of new cytisine derivatives containing B12C4, B15C5, DB18C6, and DB24C8 fragments.

Key words: cytisine, benzocrown ethers, acylation.

We developed several methods for introducing the benzocrown-ether fragment into naturally occurring amines [1, 2]. One of these methods consists of acylation of amines by benzocrown-ether carboxylic acid chlorides. Thus, new derivatives of salsolin and salsolidine were synthesized. It was demonstrated that the modified alkaloids have increased membrane activity [1, 3].

We used this method to modify cytisine. Acetyl derivatives of benzo-12-crown-4 (B12C4), benzo-15-crown-5 (B15C5), dibenzo-18-crown-6 (DB18C6), and dibenzo-24-crown-8 (DB24C8) were prepared and oxidized to the corresponding carboxylic acids. The acid chlorides of the benzocrown-ether carboxylic acids were synthesized by the literature method [1, 4] and reacted with cytisine without isolation using the scheme:



1: n = 1; **2:** n = 2 **3:** m =1; **4:** m = 2

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The structures of the prepared compounds (**1-4**) containing B12C4, B15C5, DB18C6, and DB24C8 fragments were established using PMR spectra. The PMR spectra of the new cytisine derivatives with benzocrown-ether fragments typically have sets of signals for the benzocrown ether and cytisine. The spectrum of the benzocrown-ether fragments has the typical signals for the α-protons of the macrocycle as a broad multiplet at 4.0-4.2 ppm; the β-protons, at 3.70-3.95 ppm; the γ-protons, a singlet at 3.70 ppm; and the aromatic protons of the macrocycle, a characteristic 3H ABC-system of benzene signals at 6.8-7.4 ppm [1]. Signals of protons in the α-pyridone ring of cytisine and those on C-8, -9, -7, -11, and -13 (see Experimental) were identified unambiguously in the PMR spectra of **1-4**.

EXPERIMENTAL

PMR spectra were obtained on a Bruker DRX 500 spectrometer at 500 MHz working frequency.

4′-Benzo-12-crown-4- (yield 75-80%, mp 158-160°C, lit. [5] mp 157-160°C), 4′-benzo-15-crown-5- (80%, mp 180-181°C, lit. [7] mp 180°C), 4′,4″(5″)-dibenzo-18-crown-6- (90%, mp 285-300°C, lit. [6] mp 295-308°C), and 4′,4″(5″)-dibenzo-24-crown-8-carboxylic (80%, mp 235-240°C [8]) acids were synthesized as before [5, 6].

The acid chlorides were prepared analogously to the literature [9] and were reacted without isolation.

4′-Benzo-12-crown-4-carboxylic Acid Cytisinide (1). A solution of cytisine (0.54 g, 3.4 mmole) in absolute benzene (10 mL) was treated with the acid chloride of 4′-B12C4-carboxylic acid (0.8 g, 2.8 mmole) in absolute benzene (30 mL) with added K_2CO_3, (0.38 g, 2.8 mmole). The mixture was stirred at room temperature for 2-3 h and left overnight. The course of the reaction was monitored using TLC on Silufol ($CHCl_3$:EtOH, 1:1). The benzene solution was decanted. The solvent was distillated off. The solid containing mainly the crude product was dissolved in $CHCl_3$, washed three times with KOH (5%) and water, extracted three times with HCl (5%), and washed again three times with water. The solvents were distillated off to isol ate the product as an oil that crystallized after repeated grinding with small portions of dry hexane. Yield 0.9 g (73%), mp 168-170°C

PMR spectrum (δ, ppm, J/Hz): 7.30 (1H, d, J = 9, 6.8, H-4), 6.5 (1H, d, J = 1.4, 6.8, H-3), 6.05 (1H, d, J = 9, 1.4, H-5), 7.3 (1H, s, ArH-3′), 6.92 (1H, d, ArH-5′), 6.28 (1H, d, ArH-6′), 3.95-4.10 (4H, m, α-OCH_2), 3.70-3.75 (4H, m, β-OCH_2), 3.65 (4H, s, γ-OCH_2), 4.1 (2H, d, H-10), 3.05-3.30 (5H, m, H-7,11,13), 2.5 (1H, m, H-9), 1.96 (2H, H-8).

4′-Benzo-15-crown-5-carboxylic Acid Cytisinide (2). It was prepared analogously from the acid chloride of 4′-BI5C5-carboxylic acid (0.5 g, 1.5 mmole), cytisine (0.35 g, 1.8 mmole), and K_2CO_3 (0.2 g, 1.5 mole). Yield 0.57 g (78%), mp 70-72°C.

PMR spectrum (δ, ppm, J/Hz): 7.32 (1H, d, J = 9, 6.8, H-4), 6.45 (1H, d, J = 6.8, 1.4, H-3), 6.00 (1H, d, J = 9, 1.4, H-5), 7.28 (1H, s, ArH-3′), 6.85 (1H, d, ArH-5′), 6.30 (1H, d, ArH-6′), 3.90-4.05 (4H, m, α-OCH_2), 3.75-3.85 (4H, m, β-OCH_2), 3.65 (8H, s, δ,γ-OCH_2), 4.05 (2H, d, H-10), 3.05-3.20 (5H, m, H-7,11,13), 2.5 (1H, m, H-9), 2.00 (2H, H-8).

4′,4″(5″)-Dibenzo-18-crown-6-carboxylic Acid Dicytisinide (3). It was prepared analogously from the acid chloride of 4′,4″(5″)-DBI8C6-dicarboxylic acid(0.8 g, 1.6 mmole), cytisine (0.67 g, 3.5 mmole), and K_2CO_3 (0.22 g, 1.6 mmole). Yield 1.06 g (81.5%), mp 206-210°C.

PMR spectrum (δ, ppm, J/Hz): 7.3 (2H, d, J = 9, 6.8, H-4), 6.52 (2H, d, J = 6.8, 1.4, H-3), 6.05 (2H, d, J = 9, 1.4, H-5), 7.4 (2H, d, ArH-5′,5″), 6.75 (2H, d, ArH-3′,3″), 6.65 (2H, d, ArH-6′,6″), 4.20-4.45 (8H, m, α-OCH_2), 4.08-4.20 (8H, m, β-OCH_2), 4.10 (4H, d, H-10), 3.05-3.30 (10H, m, H-7,11,13), 2.45 (2H, m, H-9), 1.98 (4H, H-8).

4′,4″(5″)-Dibenzo-24-crown-8-carboxylic Acid Dicytisinide (4). It was synthesized analogously from the acid chloride of 4′,4″(5″)-DB24C8-dicarboxylic acid (0.4 g, 0.7 mmole), cytisine (0.29 g, 1.5 mmole), and K_2CO_3 (0.1 g, 0.7 mmole). Yield 0.4 g (64.5%), mp 140-144°C.

PMR spectrum (δ, ppm, J/Hz): 7.3 (2H, d, J = 9, 6.8, H-4), 6.48 (2H, d, J = 6.8, 1.4, H-3), 6.10 (2H, d, J = 9, 1.4, H-5), 7.34 (2H, d, ArH-5′,5″), 6.85 (2H, d, ArH-3′,3″), 6.25 (2H, d, ArH-6′,6″), 3.95-4.05 (8H, m, α-OCH_2), 4.75-3.85 (8H, m, β-OCH_2), 3.70 (8H, s, γ-OCH_2), 4.10 (4H, d, H-10), 3.05-3.30 (10H, m, H-7,11,13), 2.5 (2H, m, H-9), 1.98 (4H, H-8).

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