Chemistry of Natural Compounds, Vol. 37, No. 4, 2001

NEW DERIVATIVES OF DIBENZO-18-CROWN-6 WITH SALSOLIDINE AND SALSOLINE FRAGMENTS

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UDC 547.944/945.898.639.5.07

New derivatives of dibenzo-18-crown-6 were prepared by condensing 4′,4″(5″)-dibenzo-18-crown-6-dicarboxylic acid dichloride with salsolidine and salsoline. The structures of these compounds were proved by PMR and IR spectral methods.

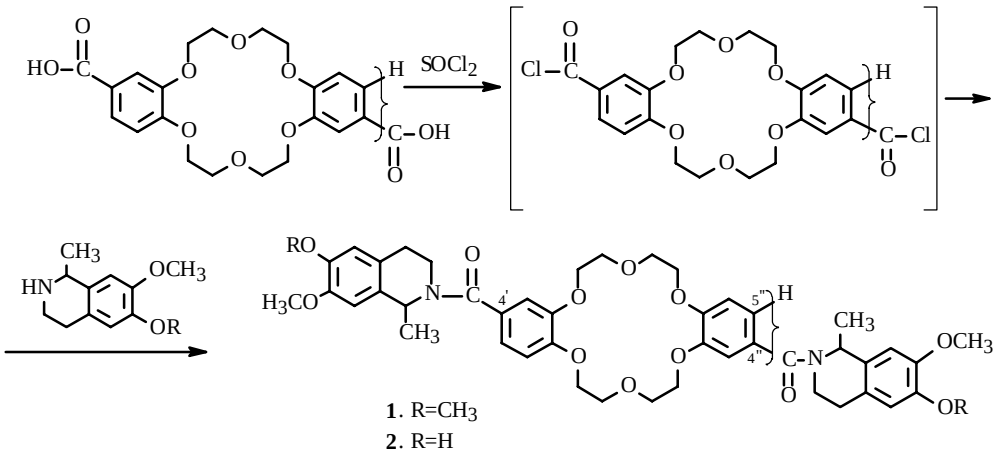
Key words: dibenzo-18-crown-6, salsolidine, salsoline.

Pharmacologists and physicians find preparations based on crown ethers to be attractive. These include existing medicinal preparations to which a crown ether is bonded and crown ethers themselves with various pharmocophoric substituents.

The ability to form lipophilic complexes with metal ions and to effect transport of the ions across artificial and biological membranes makes them models of natural ionophores. Selective ionophores for K, Ca, and Mg and Ca-ion channel-formers and -blockers have been discovered among crown ethers [1-9].

Natural ionophores and their synthetic analogs are also interesting because of their ability to form inclusion complexes with various organic compounds including medicinals. Compounds such as urea, thiourea, acetonitrile, and acetone and charged cations such as alkylammonium, guanidinium, uronium, and imidazolium are incorporated into the macrocyclic cavity as a "guest." This property of crown ethers makes it possible to apply them broadly for intensify the transport and bioavailability of various N-containing medicinal preparations, vitamins, amino acids, nitrogenous bases, and certain hormones (catecholamines etc.).

The present article is a continuation of our work. Preliminary data obtained during a study of the transport properties of bilayer membranes modified by crown-ether derivatives with isoquinoline alkaloids (salsoline and salsolidine) enable the property changes of the substituted derivatives relative to the initial compounds to be followed [10, 11].



1. R=CH_3
2. R=H

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0009-3130/01/3704-0361$25.00

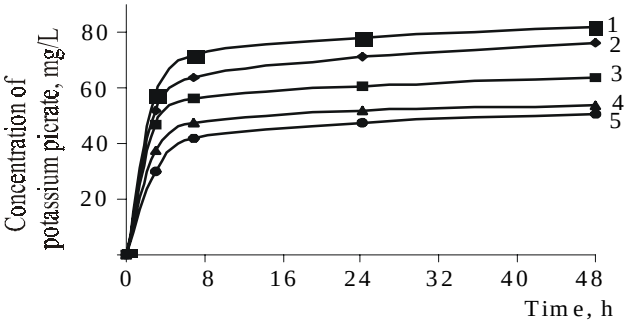

Fig. 1. The effect of potassium picrate transfer depending in time. 1 - DB18C6-disalsolinide; 2 - DB18C6-disalsolidinide; 3 - DB18C6; 4 - salsoline; 5 - salsolidine.

In continuation of the work on preparation of crown ethers with certain natural amines [12], we prepared new derivatives of dibenzo-18-crown-6 (DB18C6) with 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (salsolidine) and 1-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (salsoline). The DB18C6 fragment was introduced into the alkaloid using dibenzo-18-crown-6-dicarboxylic acid dichloride according to the scheme 1.

The obtained products are mixtures of structural isomers (4′,4″- and 4′,5″-).

PMR spectra of the disalsolidinide and disalsolinide of DB18C6 (**1** and **2**) consist of two characteristic sets of signals belonging to the crown ether and the substituents, salsoline or salsolidine. The spectrum of the crown ether has the typical signals: broad multiplets for OCH_2 in the range 3.7-4.2 ppm and a characteristic 3H ABC system for the benzene ring in the aromatic part of the spectrum [12].

Salsolidine and salsoline also have the usual signals for them: a doublet (J = 6.5 Hz) for methyl at 1.45 ppm and a singlet for methoxy at 3.8 ppm, singlets for aromatic protons (two for salsoline at 6.72 and 6.52 ppm and one for salsolidine at 6.53 ppm), and a very complicated unresolved spectrum of methylene protons in the range 2.3-3.5 ppm. The signal for the methine NCH proton is hidden under the very strong signals of the macrocyclic protons, methoxys, and, possibly, the NCH_2 signals of the substituent itself. The position of this signal was approximated from the distortion in the doublet for the methyl geminal to it. The ratio of intensities of the right and left components of the doublet and the magnitude of the splitting of the methyl signal were used to estimate that the position of the methine signal is shifted to weak field by ~1.5 ppm relative to the signal of the methyl itself.

The structures of the obtained amides were confirmed by IR spectra. The IR spectrum of DB18C6—salsolidinide exhibits the following peaks (cm^{-1}): 1626, NCO stretching (ν); 1519, C=C aromatic stretching; 1359, CH_3 symmetric deformations (ν), which are uncharacteristic of CH_2 groups; 1260 and 1138, macrocycle C–O–C stretching (ν); 859, deformations of isolated aromatic CH groups (1,2,4 substitution); and 815, deformations of two adjacent aromatic CH groups (1,2,4 substitution). The IR spectrum of DB18C6—salsolinide exhibits the following peaks (cm^{-1}): 3414, H-bonded OH stretchings (ν); 1607, NCO stretching (ν); 1516, C=C aromatic stretching; 1364, CH_3 symmetric deformations (ν), 1263 and 1137, macrocycle C–O–C stretching (ν); 868, isolated aromatic CH deformations (1,2,4 substitution); and 818, deformations of two adjacent aromatic CH groups (1,2,4 substitution).

The membrane active properties of salsolidine, salsoline, DB18C6, 4′4″(5″)-DB18C6-dicarboxylic acid disalsolidinide and 4′4″(5″)-DB18C6-dicarboxylic acid disalsolinide were studied in conditions of passive ionic transport investigation (thick membrane method) by analogy with [15]. The Fig. 1 shows the measurements of the amount of transferring potassium picrate: the transfer of potassium picrate by alkaloids is almost equalily (50-53 mg/L), by DB18C6 - on 10-14 mg/L more, and by modified products - on 25-30 mg/L more in comparison with starting alkaloids.

Thus, the modification of alkaloids by crown ethers leads to increasing of membrane activity of both initial alkaloids (almost in 1.5 times) and crown ether itself (~ in 1.3 times).

EXPERIMENTAL

4′4″(5″)-Dibenzo-18-crown-6-dicarboxylic acid was prepared according to the literature method [13] in 90% yield,

mp 285-290°C, lit. mp 295-308°C [13]. The dichloride of the dicarboxylic acid was prepared as before [14] in 90% yield. The dichloride was not isolated because of its high reactivity. It was used immediately in the condensation.

NMR spectra were recorded on a Tesla BS 567A spectrometer at working frequency 100 MHz in $CDCl_3$ with HMDS as internal standard. IR spectra were recorded on a Perkin—Elmer System 2000 IR-Fourier spectrometer using pressed KBr pellets.

Condensation of Dibenzo-18-crown-6-dicarboxylic Acid with Salsolidine and Salsoline. Salsoline or salsolidine (0.004 mole) was dissolved in absolute benzene (20 mL), treated with the diacid dichloride (0.001 mole) and potash (or triethylamine), and refluxed at 70°C for 3-6 h. The reaction was monitored using TLC on Merck Silica Gel 60 (Germany) plates with elution by $CHCl_3$:$(CH_3)_2CO$ (3:1). Solvent was removed in a rotary evaporator when the reaction was finished. The product was isolated by column chromatography [Al_2O_3, $CHCl_3$:$(CH_3)_2CO$:C_6H_{14}, 3:1:0.5] and subsequent recrystallization from acetone. The following new compounds were obtained by this method.

4′,4″(5″)-DB18C6-dicarboxylic acid disalsolidinide (1), 58%, mp 115-120°C. PMR spectrum (δ, ppm): 7.58 (2H, d), 7.48 (2H, s), 6.8 (2H, d, ArH of crown ether), 6.88 and 6.83 (2H, s), 6.52 (2H, s, ArH of salsolidine), 4.05-4.20 (8H, m, α-OCH_2), 3.88-4.05 (9H, m, β-OCH_2 and NCH), 3.8 (13H, s, OCH_3 and NCH), 2.35-3.5 (8H, m, CH_2), 1.45 (6H, d, CH_3). IR spectrum (KBr, ν, cm^{-1}): 1626, 1582, 1519, 1359, 1260, 1138, 859, 815.

4′,4″(5″)-DB18C6-dicarboxylic acid disalsolinide (2), 83%, mp 235-240°C. PMR spectrum (δ, ppm): 7.5 (2H, d), 7.4 (2H, s), 6.98 (2H, d, ArH of crown ether), 6.72 (2H, s), 6.52 (2H, s, ArH of salsoline), 4.20-4.45 (2H, m, NCH), 3.96-4.2 (8H, m, α-OCH_2), 3.75-3.96 (8H, m, β-OCH_2), 3.68 (6H, s, OCH_3), 2.9-3.45 (4H, m), 2.6-2.9 (4H, m, CH_2), 1.5 (6H, d, CH_3). IR spectrum (KBr, ν, cm^{-1}): 3414, 1607, 1516, 1364, 1263, 1137, 868, 818.

REFERENCES

1. B. A. Tashmukhamedov, A. I. Gagel′gans, A. B. Shkinev, M. V. Zamaraeva, K. Kh. Usmanov, S. R. Farzalieva, and A. K. Tashmukhamedova, *Bioorg. Khim.*, **5**, No. 3, 429 (1979).
2. U. Z. Mirkhodzhaev, P. B. Usmanov, and A. K. Tashmukhamedova, *Khim. Prir. Soedin.*, 241 (1979).
3. A. V. Shkinev, A. I. Gagel′gans, B. A. Tashmukhamedov, and A. K. Tashmukhamedova, *Khim. Prir. Soedin.*, 242 (1979).
4. A. V. Shkinev, A. I. Gagel′gans, and A. K. Tashmukhamedova, *Khim. Prir. Soedin.*, 243 (1979).
5. B. A. Tashmukhamedov, A. I. Gagel′gans, A. V. Shkinev, M. V. Zamaraeva, U. Z. Mirkhodzhaev, M. I. Asrarov, and A. K. Tashmukhamedova, *Khim. Prir. Soedin.*, 234 (1981).
6. B. A. Tashmukhamedov, A. I. Gagel′gans, U. Z. Mirkhodzhaev, A. V. Shkinev, M. V. Zamaraeva, S. N. Klyuev, A. K. Tashmukhamedova, N. Zh. Saifullina, and I. A. Stempnevskaya, *Biomembrany*, **1**, No. 3, 273 (1984).
7. U. Z. Mirkhodzhaev, V. A. Boldyrev, A. K. Tashmukhamedova, and B. A. Tashmukhamedov, *Dokl. Akad. Nauk Uzb. SSR*, No. 12, 36 (1986).
8. U. Z. Mirkhodzhaev, V. A. Boldyrev, A. K. Tashmukhamedova, V. P. Tatarskii, I. N. Dimant, and B. A. Tashmukhamedov, *Biofizika*, **34**, No. 2, 235 (1989).
9. U. Z. Mirkhodzhaev, M. U. Tuichibaev, A. K. Tashmukhamedova, M. M. Rakhimov, and B. A. Tashmukhamedov, *Dokl. Akad. Nauk Uzb. SSR*, No. 8, 52 (1987).
10. B. T. Sagdullaev, K. M. Valikhanov, A. K. Tashmukhamedova, and U. Z. Mirkhodzhaev, in: Materials of the Third Conference of Biochemists of Uzbekistan, Tashkent (1996), p. 63.
11. B. T. Sagdullaev, K. M. Valikhanov, A. K. Tashmukhamedova, and U. Z. Mirkhodzhaev, in: Materials of the International Conference "Effect of Physicochemical Factors on Metabolic processes." Part 1, Andizhan (1997), p. 112.
12. K. M. Valikhanov, I. A. Stempnevskaya, A. A. Rakhimov, M. G. Levkovich, and A. K. Tashmukhamedova, *Khim. Prir. Soedin.*, 675 (1998).
13. A. K. Tashmukhamedova, N. V. Poleshko, and I. A. Stempnevskaya, *Khim. Prir. Soedin.*, 95 (1983).
14. *Organikum Organisch-chemisches Grundpraktikum*, Veb Deutscher Verlag der Wissenschaften, Berlin 1964.
15. S. Shinkai, I. Nakaji, T. Ogawa, K. Shigematsu, and O. Manabe, *J. Amer. Chem. Soc.*, **103**, 111 (1981).