Chemistry of Natural Compounds, Vol. 34, No. 5, 1998

SYNTHESIS OF NEW DERIVATIVES BASED ON BENZO-CROWN ETHERS AND SOME NATURAL AMINES

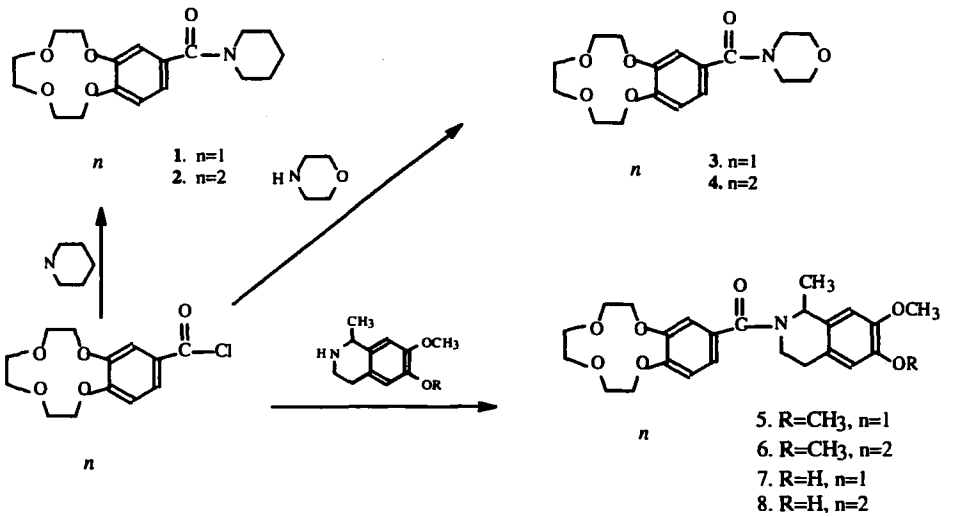
K. M. Valikhanov[a], I. A. Stempnevskaya[a], A. A. Rakhimov[a], M. G. Levkovich[b], and A. K. Tashmukhamedova[a]

UDC 547.944/945.898.639.5.07

The condensation of benzo-crown ether carboxylic acid chlorides with piperidine, morpholine, ethanolamine, N,N-diethylaminoethanolamine, salsolidine, and salsoline has given new derivatives of benzo-12-crown-4 and benzo-15-crown-5. The structures of the compounds synthesized have been shown by their PMR spectra.

The literature contains reports on the synthesis of crown ethers with various groups, including some natural compounds [1]. However, these crown ether derivatives were obtained by the Pedersen cyclization of initial dihydroxy compounds [2]. Such investigations were undertaken with the aim of changing the lipophilicity of the natural compounds and imparting to them selectivity for vitally important cations by virtue of the crown ether fragment.

Our task was to synthesize crown ethers with fragments of physiologically active compounds by condensing these compounds with a ready-formed crown ether molecule. As the fragments of physiologically active compounds we have used piperidine, morpholine, 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline, and 6-hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline. The benzo-crown ether fragment was introduced in the form of the appropriate benzo-crown ether carboxylic acid chloride, which was obtained as we have described in [3]. The following derivatives of benzo-12-crown-4 (B12K4) and benzo-15-crown-5 (B15K5) were obtained by the scheme given below:



a) Tashkent Mirzo Ulugbek State Univerity, fax (3712) 4636 08; b) Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (371) 120 64 75. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 675—678, September-October, 1998. Original article submitted October 13, 1997.

0009-3130/98/3405-0613$20.00

Thus, eight new derivatives of benzo-12-crown-4 and benzo-15-crown-5 containing various functional groups have been obtained. The chlorides of (benzo-12-crown-4)-4′- and (benzo-15-crown-5)-4′-carboxylic acids were equally active in condensation with NH-containing compounds. Condensation with salsoline, which has two reaction centers (NH- and OH-) took place only at the NH- group. Although by TLC we observed the appearance of trace amounts of other products — possibly products of condensation at the OH group —, we succeeded in isolating only the corresponding amides (**7** and **8**).

In the PMR spectra of the piperidides and morpholides (**1—4**) the signals of the protons belonging to the macrocycles were clearly distinguished from the signals of the protons of the substituents. The aromatic protons of the macrocycle were shown by a characteristic splitting of their signals in the form of a doublet, a singlet, and a doublet, corresponding to the protons in positions 5′, 3′, and 6′. The α-protons of the macrocycle were revealed by a multiplet in the 4.0—4.2 ppm region, the β-protons by a multiplet in the 3.75—3.95 region, and the γ-protons (for B12K4) or the γ- and δ-protons (for B15K5) by a singlet at 3.70 ppm. The signals of the protons of the piperidine ring appeared as two singlets at 3.45 ppm (α-CH_2 protons) and 1.6 ppm (β- and γ-CH_2 protons). The protons of the morpholine ring appeared as a solitary singlet at 3.6 ppm.

In the PMR spectra of the salsolidides (**5** and **6**) and the salsolides (**7** and **8**) the aromatic protons of the isoquinoline fragments present in the *ortho*- position to the OCH_3 group were shown by a singlet at 6.5—6.55 ppm and the protons present in the *ortho*- position to the OH group by a singlet at 6.60 ppm; i.e., they were shifted upfield as compared with the aromatic protons of the crown fragment. The most considerable changes in the PMR spectra of these derivatives were observed in the region of appearance of the OCH_2 protons of the macrocycle, since the signals of the OCH_3 groups of the isoquinoline fragments and that of the CH proton in the α- position to the amide group appeared in the same region (3.5—4.0 ppm). A consequence of this was a downfield shift f the signals of the γ- and δ- OCH_2 protons, which led to an unresolved common multiplet of the signals of these protons with the signals of the β-OCH_2 protons. The CH_2 protons of the isoquinoline ring appeared either as an unresolved multiplet in the 1.75—2.75 ppm region or as two triplets at 3.30 and 2.60 ppm. The protons of the CH_3 group were shown by a doublet at 1.43 ppm.

EXPERIMENTAL

(Benzo-12-crown-4)-4′- and (benzo-15-crown-5)-4′-carboxylic acids were obtained as in [3]. The yield of (benzo-12-crown-4)-4′-carboxylic acid was 90%, mp 157—160°C. According to the literature [3]: mp 157—160°C. The yield of (benzo-15-crown-5)-4′-carboxylic acid was 80%, mp 180—182°C. According to the literature [4]: mp 180°C. (Benzo-12-crown-4)-4′-carbonyl chloride was obtained in analogy with [5]; yield 90%. (Benzo-15-crown-5)-4′-carbonyl chloride was obtained similarly, yield 80%. Because of their high reactivities, the acid chlorides were not purified but were used immediately in the condensation reaction.

Condensation Procedure. A solution of 0.002 mole of an active compound with an NH fragment in 10 ml of absolute benzene was treated with 0.001 mole of a crown ether carboxylic acid chloride and potassium carbonate or triethylamine. The reaction mixture was heated at 70°C under reflux for 3—6 h. The course of the reaction was monitored by TLC on Merck Silica Gel 60 plates (Germany) in the chloroform—acetone (3:1) system. After the end of the reaction, the solvent was driven off in a rotary evaporator. The product was isolated by column chromatography followed by crystallization from acetone. This method was used to obtain the following new compounds:

(Benzo-12-crown-4)-4′-carboxylic acid piperidide (1), 60%, mp 68—70°C. PMR spectrum (δ, ppm): 6.98 (1H, d), 6.94 (1H, d), 6.84 (1H, d, ArH), 4.04-4.20 (4H,m, α-OCH_2), 3.74-3.86 (4H, m, β-OCH_2), 3.70 (4H, s, γ-OCH_2), 3.45 (4H, s, -NCH_2), 1.58 (6H, m, β-and γ-CH_2- of piperidine).

(Benzo-15-crown-5)-4′-carboxylic acid piperidide (2), 60%, mp 85—90°C. PMR spectrum (δ, ppm): 6.90 (1H, d), 6.84 (1H, s), 6.76 (1H, d, ArH), 4.0-4.21 (4H, m, α-OCH_2), 3.75-3.92 (4H, m, β-OCH_2), 3.70 (8H, s, γ- and δ-OCH_2), 3.45 (4H, s, -NCH_2), 1.60 (6H, m, β-and γ-CH_2- of piperidine).

(Benzo-12-crown-4)-4′-carboxylic acid morpholide (3), 88%, mp 84—88°C. PMR spectrum (δ, ppm): 7.0 (1H, dd, J=6 Hz, J=2 Hz), 6.95 (1H, d, J=2 Hz), 6.92 (1H, d, J=6 Hz, ArH), 4.0-4.2 (4H, m, α-OCH_2), 3.76-3.90 (4H, m, β-OCH_2), 3.72 (4H, s, γ-OCH_2), 3.60 (8H, s, -CH_2 of morpholine).

(Benzo-15-crown-5)-4′-carboxylic acid morpholide (4), 60%, oil.

PMR spectrum (δ, ppm): 6.91 (1H, d), 6.84 (1H, s), 6.80 (1H, d, ArH), 3.98-4.20 (4H, m, α-OCH_2), 3.75-3.98 (4H, m, β-OCH_2), 3.70 (8H, s, γ- and δ-OCH_2), 3.60 (8H, s, -CH_2 of morpholine).

(Benzo-12-crown-4)-4′-carboxylic acid salsolidide (5), 30%, oil. PMR spectrum (δ, ppm): 6.80-7.10 (3H, m, ArH of the crown ether), 6.54 (2H, s, ArH of salsolidine), 4.05-4.25 (5H, m, α-OCH_2 and NCH), 3.75-3.90 (8H,m, β-and γ-OCH_2), 3.70 (6H, s, OCH_3), 2.30-3.50 (4H, m, CH_2), 1.42 (3H, d, -CH_3 of the salsolidine fragment).

(Benzo-15-crown-5)-4′-carboxylic acid salsolidide (6), 45%, mp 70—73°C. PMR spectrum (δ, ppm): 6.8 (1H,d), 6.9 (1H, s), 6.92 (1H, d, ArH of the crown ether), 6.58 (2H, s, ArH of salsolidine), 4.0-4.20 (4H, m, α-OCH_2), 3.75-3.85 (4H, m, β-OCH_2), 3.80 (8H, s, γ- and δ-OCH_2), 3.65 (7H, s, OCH_3 and NCH), 1.75-2.75 (4H, m, -CH_2), 1.45 (3H, d, CH_3 of the salsolidine fragment).

(Benzo-12-crown-4)-4′-carboxylic acid salsolide (7), 65%, mp 155—160°C. PMR spectrum (δ, ppm): 7.0 (1H,s), 6.98 (1H, d), 6.94 (1H, d, ArH of the crown ether), 6.60 (1H, s, ArH at OH), 6.50 (1H, s, ArH at OCH_3 of salsoline), 5.50 (1H, s, OH), 4.0-4.25 (5H, m, α-OCH_2 and NCH), 3.80-4.0 (8H, m, β- and γ-OCH_2), 3.70 (3H, s, OCH_3), 3.30 (2H, t), 2.62 (2H, t, -CH_2), 1.43 (3H, d, -CH_3 of the salsolidine fragment).

(Benzo-15-crown-5)-4′-carboxylic acid salsolide (8), 40%, mp 146—148°C. PMR spectrum (δ, ppm): 6.62-7.05 (4H, m, ArH of the crown ether and ArH at OCH_3 of salsoline), 6.60 (1H, s, ArH at OH of salsoline),5.55 (1H, s,OH), 3.95-4.20 (5H,m, α-OCH_2 and NCH of salsoline), 3.80-3.95 (4H, m, β-OCH_2), 3.78 (8H, s, γ- and δ-OCH_2), 3.70 (3H, s, -OCH_3), 3.25 (2H, t), 2.60 (2H, t, -CH_2), 1.44 (3H, d, -CH_3 of the salsoline fragment).

REFERENCES

1. U. Elben, H.-B. Fuchs, K. Frensch, and F. Vogtle, Lieb. Ann. Chem., No. 8, 1102 (1979).
2. C. J. Pedersen, J. Am. Chem. Soc., **89**, 7017 (1967).
3. I. A. Stempnevskaya, A. D. Grebenyuk, A. A. Rakhimov, M. G. Levkovich, and A. K. Tashmukhamedova, Uzb. Khim. Zh., No. 4, 53 (1994).
4. M. Bougoin, K. H. Wong, J. Y. Hui, and J. Smid, J. Am. Chem. Soc., **97**, 3462 (1975).
5. Organikum, VEB Deutsche Verlag der Wissenschaften, Berlin [English translation of the 11th German edition, Pergamon Press Ltd, Oxford (1973); Russian translation under the title: General Practical Handbook on Organic Chemistry, Mir, Moscow (1965), p. 410].