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# New Quaternary Ammonium Salts and Metal Complexes of Organylheteroacetic Acids with Diaza-18-crown-6 Ether

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**Abstract**—Quaternary ammonium salts $2(RCH_2COO)^{-}(2H{\cdot}DACE)^{+}$ were synthesized in up to 98% yield by the reaction of biologically active organylheteroacetic acids (OHA) $RCH_2COOH$ with diaza-18-crown-6 ether (DACE).

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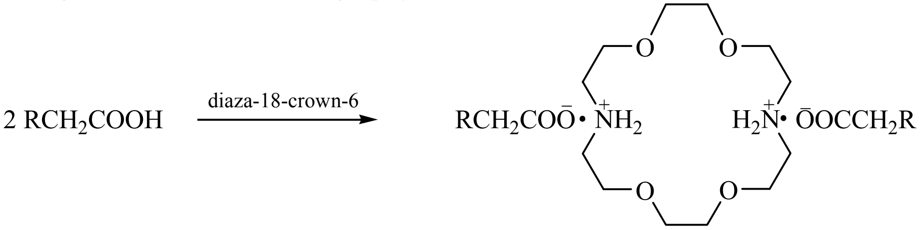
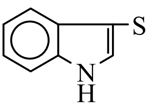
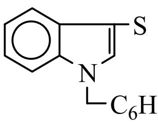
Complexes of crown ethers with protic acids and their metal salts attract the attention of researchers not only due to their specific molecular and stereoelectronic structure but also due to the possibility of their practical use [1, 2]. Complexation with crown ethers increases physiological activity of a number of chemical compounds. Apparently, this is related with the ability of the formed complexes to pass through the cell and hemato-organic barriers. In particular, specific complexing properties of crown ethers allow their use for the design of new drugs. Among them are cardio- and neurotropic drugs possessing cancerostatic, cation transport effect and affecting the vegetative nervous system. On their basis biocides, antimicrobial, antiparasite and other drugs were prepared [1, 2]. Paramagnetic complexes of lanthanides with crown ethers can be used as nanodimensional thermosensors for in vivo nuclear magnetic resonance tomography, cartography of body temperature and diagnostics of diseases [3].

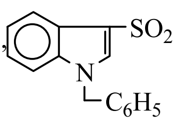
Earlier we have shown that tris(2-hydroxyethyl)ammonium salts of organylheteroacetic acids (OHA), $[RYCH_2COO]^{-}{\cdot}[NH(CH_2CH_2OH)]_3^{+}$ (R = Ar, Het; Y = O, S, $SO_2$), belonging to 2,8,9-trihydroprotatranes [4], is a new class of biologically active compounds, promising for design of adaptogens, immunomodulators, drugs with antitumor and protecting effect from the UHF radiation, stimulators of protein biosynthesis, regulators of microorganisms and plants growth [5–11].

In a search for new immunoactive compounds we have synthesized the earlier unknown quaternary ammonium salts **I–VI** by the reaction of OHA with diaza-18-crown-6 ether (DACE) in the ratio of 2:1 and in the yield up to 98%:



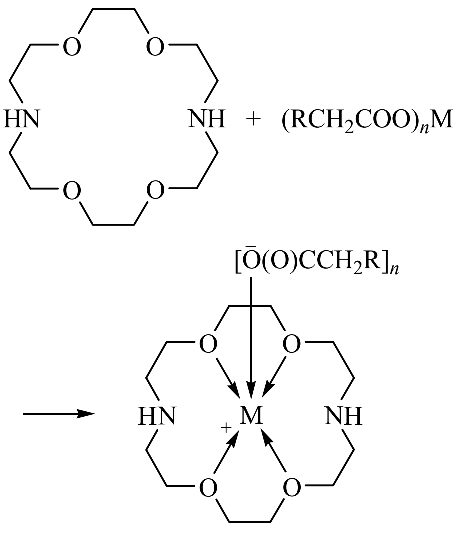
**I**–**V**: R = *o*-$CH_3$–$C_6H_4O$ (**I**), *p*-Cl–$C_6H_4S$ (**II**), *p*-$ClC_6H_4SO_2$ (**III**),


(**IV**),


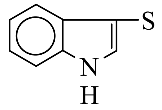
(**V**),


(**VI**).

The biogenic metal (Na, K, Zn) salts of OHA form with DACE complex compounds **VII–XI**:



**VII–XI**

R = *o*-OH–$C_6H_4O$, M = K (**VII**); R = *p*-Cl–$C_6H_4SO_2$, M = Na (**VIII**); R = *p*-Cl–$C_6H_4SO_2$, M = K (**IX**), R = *o*-$CH_3$–$C_6H_4O$, M = Zn (**X**); R =  , M = Na (**XI**), *n* = 1, 2.

The synthesized compounds **I–XI** are fine-crystalline colorless compounds. Compounds **I–VI** have clear melting points, whereas compounds **VII–XI** melt in the interval of 5–10°C that may be indicative of their liquid-crystal structure (similar to [12]).

The composition and structure of compounds **I–XI** is proved by the data of elemental analysis, $^1H$, $^{13}C$ NMR and IR spectroscopy. In the IR spectra of **I–VI** wide absorption bands $\nu(NH_2^+)$ are observed in the range 2800–2200 cm$^{-1}$. The bands of the stretching vibrations of the O–C–O fragments of the starting DACE are shifted to high frequencies from 1120, 1100, and 1067 to 1150–1090 cm$^{-1}$ in **I–VI**. Similar shift of the ν(C–O–C) vibration bands is observed in the spectra of **VII–IX**. The bands of the asymmetric and symmetric stretching vibrations of the carboxylate group $COO^-$ in OHA in the spectra of compounds **I–XI** appear in the range 1580–1350 cm$^{-1}$. The values of the main frequencies in the spectra of **I–XI** slightly differ from those determined by us earlier for the triethanolammonium salts of OHA [4]. The bands of the symmetric and asymmetric vibrations of the $SO_2$ group in **III, VI, VIII**, and **IX** are equal to 1164 and 1323 cm$^{-1}$, respectively. We have examined the IR spectra of **X** in more detail. In molecule **X**, the zinc atom forms coordination bonds with oxygen atoms of DACE. This is reflected in the decrease of the C–O–C stretching vibration bands of DACE in the spectrum of complex **X** to 1108, 1058 and 1040 cm$^{-1}$. A narrow band ν(NH) at 3334 cm$^{-1}$ belonging to free NH groups in the spectrum of DACE remains intact in the spectrum of its complex **X** pointing to the absence of coordination interaction of the metal with nitrogen atoms. Earlier we have shown that vibration frequencies $\nu(COO^-)$ 1633 and 1558 cm$^{-1}$ and their difference Δν 75 cm$^{-1}$ in the IR spectrum of $(o\text{-}CH_3C_6H_4OCH_2COO)_2Zn$ are indicative of the presence of bidentate bonds of the metal with carboxylate anion [13]. Apparently, similar bands are present in complex **X** since the values of $\nu(COO^-)$ are equal to 1636, 1568 cm$^{-1}$ and Δν is 68 cm$^{-1}$. The bands of the O→Zn stretching vibrations in the spectrum of **X** appear at 460, 380, and 285 cm$^{-1}$. Therefore, the data of IR spectroscopy and elemental analysis suggest that the zinc atom in complex **X** is coordinated to four oxygen atoms of DACE, lying in one plane, and to oxygen atoms of the two $COO^-$ groups of the carboxylate anions in the axial position.

Screening of immunoactive properties of compounds **I–IV** was performed by their ability to affect the in vitro spontaneous and mitogen (concanavalin A, Con A, Sigma) induced proliferation of splenocytes of mice (antiproliferative properties). Proliferative activity of cells was judged by their ability to incorporate $H_3$-thymidine into the DNA of the dividing cells.

The experiments were carried out on healthy sexually mature hybrid mice of both sexes (CBA×C57BL/6)F1 (CBF1), 8–10 week age, with a body mass of 18–20 g. The results were treated by the non-parametric Wilcoxon-Mann-Whitney test U. The highest immunosuppressing activity was found for compounds **II** and **IV** in dose of 30–300 μg ml$^{-1}$. By the ability to suppress the in vitro spontaneous (**II**, 72%, **IV**, 54%) and Con A-induced (**II**, 99%, **IV**, 39%) proliferation of cells in dose of 300 μg ml$^{-1}$ these compounds can be considered as immunosuppressants. The results of the present work are indicative of advisability of more detailed examination of immunoactive properties of these and related compounds.

## EXPERIMENTAL

IR spectra were recorded on a Varian 3100 FT-IR 75 spectrophotometer. NMR spectra were registered on a Bruker DPX 400 spectrometer (400 MHz for $^1H$

and 100 MHz for $^{13}C$) in $D_2O$ or $CD_3OD$. OHA and their metal salts were synthesized and purified by procedures [13-15].

**Complex I.** To the solution of *o*-$CH_3C_6H_4O\cdot CH_2COOH$ (3.32 g, 0.02 mol) in 10 ml of MeOH the solution of DACE (2.62 g, 0.01 mol) in 10 ml of MeOH was added dropwise, and the mixture was stirred for 12 h at room temperature. The solvent was removed in a vacuum, the solid residue was thoroughly washed with ether and dried in a vacuum to give colorless powder (5.63 g, 98%) with mp 118°C, readily soluble in water, alcohol. $^1H$ NMR ($D_2O$): 7.11–6.68 m (4H, $C_6H_4$), 4.37 s (4H, $CH_2COO$), 3.63–3.56 m (16H, $OCH_2$), 3.15 t (8H, $NCH_2$), 2.13 s (3H, $CH_3$). $^{13}C$ NMR ($D_2O$): 176.80 (C=O), 156.04 ($C_6H_4O$), 140.87–111.56 ($C_6H_4$), 69.42($OCH_2$), 66.99 ($CH_2COO$), 65.29 ($OCH_2CH_2O$), 47.31 ($NCH_2$), 15.53 ($C_6H_4$-$CH_3$).

**Complexes II–V** were prepared similarly. **Compound II**. Yield 89%, mp 113°C. **Compound III**. Yield 93%, mp 122°C. **Compound IV**. Yield 88%, mp 60°C. **Compound V**. Yield 89%, mp 144°C.

**Complex VI** was prepared similarly from suspension of 0.02 mol of 1-benzylindol-3-ylsulfonylacetic acid [prepared by oxidation of 1-benzylindol-3-ylsulfanylacetic acid with hydrogen peroxide in acetic acid, mp 164–166°C; $^1H$ NMR ($CD_3OD$): 8.00–7.23 m (10H, $C_{14}H_{10}N$), 5.46 s (2H, $NCH_2C_6H_5$), 4.22 s (2H, $CH_2SO_2$). $^{13}C$ NMR ($CD_3OD$): 164.98 (C=O), 135.04–119.85 ($C_{14}H_{10}N$), 110.95 ($CH_2SO_2$), 61.08 ($NCH_2C_6H_5$)] in 20 ml of acetone and 0.01 mol of DACE in 25 ml of acetone at 22°C for 3 h. Yield 89%. mp 165°C, soluble in water, alcohol. $^1H$ NMR ($D_2O$): 7.75–7.15 m (10H, $C_{14}H_{10}N$), 5.34 s (2H, $NCH_2C_6H_5$), 4.09 s (2H, $CH_2SO_2$), 3.60–3.55 m (16H, $OCH_2$), 3.11 t (8H, $NCH_2$). $^{13}C$ NMR ($D_2O$): 176.38 (C=O), 137.56–119.01 ($C_{14}H_{10}N$), 110.09 ($CH_2SO_2$), 69.21 ($OCH_2$), 66.99 ($OCH_2$ $CH_2O$), 62.29 ($NCH_2C_6H_5$), 46.46 ($NCH_2$).

**Metal complex IX.** To suspension of *p*-$ClC_6H_4SO_2\cdot CH_2COOK$ (2.72 g, 0.01 mol) in 10 ml of MeOH the solution of DACE (2.62 g, 0.01 mol) in 10 ml of methanol was added dropwise, the reaction mixture was stirred at reflux for 8 h until it became homogeneous. The solvent was removed in a vacuum, the solid residue was crystallized from hot benzene to obtain colorless crystals (5.07 g, 95%) with mp 88–95°C, soluble in water, alcohol. $^1H$ NMR ($D_2O$): 7.49–7.28 m (4H, $C_6H_4$), 4.03 s (3H, $CH_2COO$), 3.27–3.22 m (16H, $OCH_2$), 2.49 t (8H, $NCH_2$). $^{13}C$ NMR ($D_2O$): 170.80 (C=O), 146.05 ($C_6H_4O$), 130.56–130.50 ($C_6H_4$), 70.43 ($OCH_2$), 69.38 ($OCH_2CH_2O$), 48.27 ($NCH_2$). Found, %: C 44.62; H 5.69; K 7.01. $C_{20}H_{32}O_8N_2ClSK$. Calculated, %: C 44.86; H 5.98; K 7.28.

**Metal complexes VII, VIII, X, XI** were prepared similarly**. Compound VII**. Yield 80%. $T_{\text{decomp}}$ 230–240°C. **Compound VIII**. Yield 82%, mp 170–180°C. **Compound X**. Yield 79%, mp 120–130°C. **Compound XI**. Yield 74%, mp 95–100°C.

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