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LETTERS TO THE EDITOR

New Method of Synthesis of Biologically Active Get(aryl)chalcogenylacetates of Tris(2-hydroxyethyl)ammonium

S. N. Adamovich[a]*, E. N. Oborina[a], I. A. Ushakov[b], and A. N. Mirskova[a]

[a] *A.E. Favorskii Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia*
**e-mail: mir@irioch.irk.ru*

[b] *Irkutsk National Research Technical University, Irkutsk, Russia*

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Abstract—Physiologically and pharmacologically active het(aryl)chalcogenylacetates of tris(2-hydroxyethyl)ammonium of pharmacopeial purity have been synthesized by the reaction of het(aryl)chalcogenylacetic acids with sodium (potassium) hydroxide and triethanolamine hydrochloride by one-pot method in quantitative yield (up to 99.8%).

Keywords: het(aryl)chalcogenylacetates of tris(2-hydroxyethyl)ammonium, triethanolamine hydrochloride, crezacine

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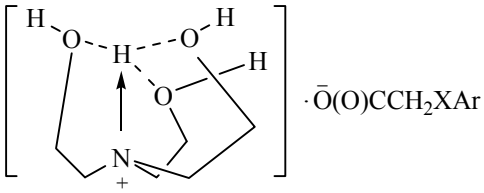
Earlier we obtained a series of aryl(oxy)(sulfanyl)-(sulfonyl)acetates of tris(2-hydroxyethyl)ammonium $ArXCH_2COO^-\cdot HN(CH_2CH_2OH)_3$ (**1**) (X = O, S, SO_2) [1–4]. By the methods of IR and NMR spectroscopy, X-ray and elemental analysis the atrane, more specifically, protatrane structure of these compounds was determined [1].



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It is assumed that the unique structure of compounds **1** is responsible for the high physiological activity. Thus, the ability to accelerate many times the growth and development of microorganisms, plants and animals make them effective biostimulators [2]. Besides, they demonstrate antitrombotic, antisclerotic, immunotropic, anticancer, antometastatic activity [2, 3, 5]. As a consequence, compounds **1** can be used for working out new synthetic biostimulators for agriculture, biotechnology and microbiology, and advanced drugs. For example, 2-methylphenyloxyacetate of tris(2-hydroxyethylammonium is known as a permitted for use stimulator and adaptogen of wide spectrum of action under the name crezacine [2].

It must be noted that all so far obtained compounds of series **1**, including crezacine, were synthesized by the reaction of the corresponding aryloxy or arylsulfanylacetic acids with tris(2-hydroxyethyl)amine. The yields of the products were high (75–90%) but their purity was low [6, 7]. Crezacine of purity sufficient for use in medicine [8] can be obtained only by complex multistep procedure, but the yields decrease to 55–65%. The main reason of low purity of crezacine is a difficult method of purification of triethanolamine (TEA), which is a viscous, hygroscopic, highly boiling liquid. The problem is that even pure triethanolamine prepared by a vacuum fractional distillation contains impurities formed during high-temperature distillation. When storing triethanolamine even in closed vessel in the absence of light the coloration is strengthened [9].

The goal of this work was to work out an efficient method for preparation of crezacine and its analogs of pharmacopeia purity. This goal is achieved by the use of triethanolamine hydrochloride and potassium or sodium salts of get(aryl)chalcogenylacetic acids formed *in situ*. The reaction was performed by one-pot method in boiling methanol and ethanol during 3–4 h. The yield and purity of the target reaction products **2**–**10** reach 99.8% (Scheme 1).

Scheme 1.

$$Ar–X–CH_2COONa(K) + HCl\cdot N(CH_2CH_2OH)_3 \xrightarrow[-NaCl\ (KCl)]{} Ar–X–CH_2C\bar{O}O\cdot\overset{+}{H}N(CH_2CH_2OH)_3$$

Ar = Ph (**2**), 2-ClC_6H_4 (**3**), 4-ClC_6H_4 (**4**), 2-HOC_6H_4 (**5**), 2-$NO_2C_6H_4$ (**6**), 2-MeC_6H_4 (**7**), indol-3-yl (**8**), 1-benzylindol-3-yl (**9**); X = O (**2**, **5**, **6**), S (**3**, **8**), SO_2 (**4**, **9**), Se (**10**).

The novelty of the method is that instead of viscous hygroscopic difficultly purified triethanolamine we use solid, chemically stable easily purified by crystallization triethanolamine hydrochloride, and instead of free acids their Na(K)-salts prepared directly in the process of the synthesis of compounds **2**–**10**. Note that so far no such irreversible reactions of ionic exchange were known for triethanolamine hydrochloride.

General procedure for the synthesis of get(aryl)-chalcogenylacetates of tris(2-hydroxyethyl)ammonium (2–10). A mixture of 0.01 mol of get(aryl)-chalogenylacetic acid and 0.01 mol of NaOH or KOH in 30 ml of methanol or ethanol was stirred at reflux for 1 h, then 0.01 mol of triethanolamine hydrochloride was added. The mixture was stirred for another 2–3 h, then cooled to 5–10°C. The precipitate of NaCl or KCl was filtered off, the solvent was distilled off to obtain a solid product in the yield and purity of 99.7–99.8%.

Phenyloxyacetate of tris(2-hydroxyethyl)ammonium (2). Yield 99.7%, mp 70–71°C, purity 99.7%. IR spectrum, ν, cm^{-1}: 1591 (C=O), 2200–2800 br (N^+H), 3308 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.70–7.10 m (5H, Ph), 3.65 t (6H, OCH_2, J = 5.6 Hz), 3.35 s (2H, OCH_2), 3.19 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 180.27 (C=O), 111.00–125.05 (Ph), 56.37 (OCH_2), 53.11 (OCH_2), 52.92 (NCH_2).

2-Chlorophenylsulfanylacetate of tris(2-hydroxylethyl)amonium (3). Yield 99.7%, mp 90–91°C, purity 99.7%. IR spectrum, ν, cm^{-1}: 1598 (C=O), 2210–2820 br (N^+H), 3310 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.77–7.12 m (4H, C_6H_4), 3.71 t (6H, OCH_2, J = 5.6 Hz), 3.45 s (2H, SCH_2), 3.21 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 179.17 (C=O), 110.10–131.15 (C_6H_4), 57.27 (OCH_2), 53.00 (SCH_2), 52.72 (NCH_2).

4-Chlorophenylsulfonylacetate of tris(2-hydroxylethyl)ammonium (4). Yield 99.8%, mp 121°C, purity 99.8%. IR spectrum, ν, cm^{-1}: 1602 (C=O), 2220–2830 br (N^+H), 3330 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.65–7.20 m (4H, C_6H_4), 3.68 t (6H, OCH_2, J = 5.6 Hz), 3.55 s (2H, SO_2CH_2), 3.18 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 180.15 (C=O), 114.11–132.17 (C_6H_4), 57.18 (OCH_2), 54.23 (SO_2CH_2), 52.99 (NCH_2).

2-Hydroxyphenyloxyacetate of tris(2-hydroxyethyl)-ammonium (5). Yield 99.7%, mp 130°C, purity 99.7%. IR spectrum, ν, cm^{-1}: 1597 (C=O), 2210–2805 br (N^+H), 3315 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.46–7.22 m (4H, C_6H_4), 3.57 t (6H, OCH_2, J = 5.6 Hz), 3.35 s (2H, OCH_2), 3.08 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 179.18 (C=O), 113.13–129.18 (C_6H_4), 56.19 (OCH_2), 53.13 (OCH_2), 52.09 (NCH_2).

2-Nitrophenyloxyacetate of tris(2-hydroxyethyl)-ammonium (6). Yield 99.7%, mp 133°C, purity 99.7%. IR spectrum, ν, cm^{-1}: 1601 (C=O), 2200–2800 br (N^+H), 3310 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.71–7.11 m (4H, C_6H_4), 3.50 t (6H, OCH_2, J = 5.6 Hz), 3.30 s (2H, OCH_2), 3.00 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 181.20 (C=O), 118.13–131.18 (C_6H_4), 55.20 (OCH_2), 53.23 (OCH_2), 53.00 (NCH_2).

2-Methylphenyloxyacetate of tris(2-hydroxyethyl)-ammonium (7). Yield 99.8%, mp 81°C, purity 99.8%. IR spectrum, ν, cm^{-1}: 1598 (C=O), 2215–2809 br (N^+H), 3310 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.77–7.11 m (4H, C_6H_4), 3.57 t (6H, OCH_2, J = 5.6 Hz), 3.33 s (2H, OCH_2), 3.09 t (6H, NCH_2, J = 5.6 Hz), 1.80 s (3H, Me). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 181.17 (C=O), 112.11–122.15 (C_6H_4), 56.07 (OCH_2), 53.11 (OCH_2), 52.92 (NCH_2), 23.20 (Me).

1*H*-Indol-3-ylsulfanylacetate of tris(2-hydroxyethyl)ammonium (8). Yield 99.8%, mp 92–93°C, purity 99.8%. IR spectrum, ν, cm^{-1}: 1591 (C=O), 2200–2800 br (N^+H), 3308 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.70–7.12 m (5H, Ind), 3.77 t (6H, OCH_2, J = 5.6 Hz), 3.37 s (2H, SCH_2), 3.19 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 177.27 (C=O), 138.96–105.88 (Ind), 57.37 (OCH_2), 57.11 (SCH_2), 50.91 (NCH_2). Found, %: C 54.01; H 6.77; N 7.80; S 9.09. $C_{16}H_{24}O_5N_2S$. Calculated, %: C 53.91; H 6.78; N 7.86; S 8.99.

1-Benzindol-3-ylsulfonylacetate of tris(2-hydroxyethyl)ammonium (9). Yield 99.7%, mp 93°C, purity 99.7%. IR spectrum, ν, cm^{-1}: 1607 (C=O), 2200–2800 br (N^+H), 3300 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 7.98–7.23 m (10H, C_8H_5N, C_6H_5), 5.44 br. s (2H, $C\underline{H}_2Ph$), 4.06 br. s (2H, SO_2CH_2), 3.83 t (6H, OCH_2, J = 5.6 Hz), 3.32 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 166.45 (C=O), 135.52–110.15 (C_8H_5N, C_6H_5), 63.16 (SO_2CH_2), 54.80 (OCH_2), 54.73 (NCH_2), 49.43 ($\underline{C}H_2Ph$). Found, %: C 57.90; H 6.11; N 5.95. $C_{23}H_{30}N_2O_5S$. Calculated, %: C 57.67; H 6.26; N 5.85.

Phenylselenylacetate of tris(2-hydroxyethyl)ammonium (10). Yield 99.7%, mp 99°C, purity 99.7%. IR spectrum, ν, cm^{-1}: 1597 (C=O), 2212–2830 br (N^+H), 3309 (OH). ^1H NMR spectrum (D_2O), δ, ppm: 6.77–6.56 m (5H, Ph), 3.66 t (6H, OCH_2, J = 5.6 Hz), 3.33 s (2H, $SeCH_2$), 3.14 t (6H, NCH_2, J = 5.6 Hz). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 179.29 (C=O), 133.06–123.08 (Ph), 56.47 (OCH_2), 56.10 ($SeCH_2$), 54.98 (NCH_2).

NMR spectra (in D_2O or CD_3OD) were registered on a Bruker DPX-400 spectrometer [400.13 (^1H), 101.62 MHz (^{13}C)], internal reference HMDS. IR spectra were recorded on a Bruker IFS-25 spectrometer. The purity of compounds was determined by the method of potentiometric titration (ionometer EA-74).

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CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

REFERENCES

1. Voronkov, M.G., Albanov, A.I., Aksamentova, T.N., Adamovich, S.N., Chipanina, N.N., Mirskov, R.G., Kochina, T.A., Vrazhnov, D.V., and Litvinov, M.Yu., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 11, p. 2339. doi 10.1134/S1070363209110097
2. Mirskova, A.N., Adamovich, S.N., Mirskov, R.G., and Voronkov, M.G., *Russ. Chem. Bull*., 2014, no. 9, p. 1869. doi 10.1007/s11172-014-0679-3
3. Mirskova, A.N., Adamovich, S.N., Mirskov, R.G., Kolesnikova, O.P., and Schilde, U., *Open Chem*., 2015, vol. 13, p. 149. doi 10.1515/chem-2015-0018
4. Ushakov, I.A., Voronov, V.K., Adamovich, S.N., Mirskov, R.G., and Mirskova, A.N., *J. Mol. Struct*., 2016, vol. 1103, p. 125. doi 10.1016/j.molstruc.2015.08.074
5. RF Patent 2623034, 2017; *Byull. Izobret*., 2017, no. 18.
6. D'yakov, V.M., Prokhoda, E.F., Semenova, N.I., Voronkov, M.G., and Stetsenko, E.F., Author's Certificate 515742, 1973; *Byull. Izobret*., 1976, no. 20.
7. RF Patent 2268879, 2006; *Byull. Izobret*., 2006, no. 3.
8. RF Patent 2098088, 1997; *Byull. Izobret*., 1997, no. 5.
9. RF Patent 2393147, 2010; *Byull. Izobret*., 2010, no. 12.