ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 12, pp. 2710–2714. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © Yu.A. Kondratenko, T.A. Kochina, V.S. Fundamensky, Yu.G. Vlasov, 2015, published in Zhurnal Obshchei Khimii, 2015, Vol. 85, No. 12, pp. 1978–1982.

Triethanolammonium Salts of Biologically Active Carboxylic Acids

Yu. A. Kondratenko[a], T. A. Kochina[a,b], V. S. Fundamensky[c], and Yu. G. Vlasov[b]

[a] *Grebenshchikov Institute of Silicate Chemistry, Russian Academy of Sciences, nab. Makarova 2, St. Petersburg, 199034 Russia*
e-mail: kondratencko.iulia@yandex.ru

[b] *St. Petersburg State University, St. Petersburg, Russia*

[c] *St. Petersburg State Institute of Technology (Technical University), St. Petersburg, Russia*

Received May 14, 2015

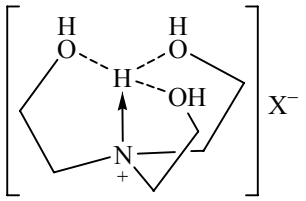
Abstract—Triethanolammonium salts (protatranes) of biologically active carboxylic acids (nicotinic, cinnamic, benzoic, salicylic, oxalic, malonic, succinic, malic, citric) were synthesized in yields exceeding 90%. The structure of the synthesized compounds was studied by IR spectroscopy and X-ray diffraction analysis.

Keywords: triethanolamine, biologically active carboxylic acids, protatranes

DOI: 10.1134/S1070363215120075

Earlier it was found that the conversion of biologically active carboxylic acids into their triethanolammonium salts $NH^+(CH_2CH_2OH)_3X^-$ (X^- = anion of carboxylic acid) strongly increases their biological activity and expands the spectrum of their action [1–10]. Even the first representative of this class of compounds, triethanolammonium salt of 2-methylphenyloxyacetic acid $[2\text{-}CH_3C_6H_4OCH_2COO]^-\cdot[NH(CH_2CH_2OH)_3]^+$ (drug "Trecrezan") showed much higher growth-regulating activity for plants and animals than the original acid [6, 7]. Trecrezan possesses immunomodulating and adaptogenic effect, stimulates the cell and humoral immunity and the system of interferones-α and -γ, sustains the work capacity of the organism and increases the resistance to climate and toxic loads [8–10].

From the X-ray structural analysis data [11–13], triethanolammonium cation has a tricyclic atrane structure closed by three intramolecular hydrogen bonds ("Chinese lantern"), where X is the anion of a protic acid.

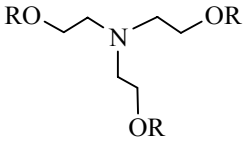


Owing to the structure, and by analogy with silatranes, the triethanolammonium salts of protic acids were named "protatranes" [14]. Apparently, just the atrane structure determines biological activity of protatranes.

In the present work, the earlier unknown triethanolammonium salts of carboxylic acids having a wide spectrum of activity (antibacterial, antimicrobial, antiseptic, antitoxic, antitumor, etc.) were synthesized in order to obtain potentially biologically active compounds.

Protatranes **1–9** (Table 1) were synthesized in high yields by interaction of triethanolamine with the corresponding acids using the known procedure [16, 17] by reflux of the mixture of the corresponding carboxylic acid and triethanolamine in methanol during 1 h. The obtained compounds are water-soluble colorless solids (**1–3, 5–7**) or viscous liquids (**4, 8, 9**) (Scheme 1).

It should be noted that the reaction of carboxylic acids with triethanolamine in the presence of 1,3-dicyclohexylcarbodiimide and catalytic amounts of dimethylaminopyridine leads to the formation of full esters of triethanolamine [15]:

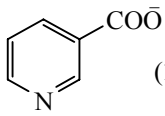
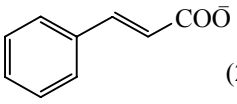
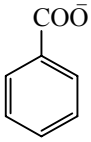
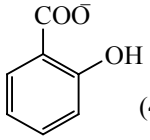


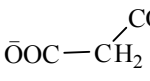
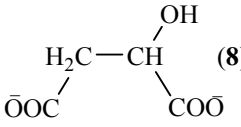
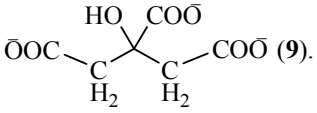
Scheme 1.

$$N(CH_2CH_2OH)_3 + HX\ (H_2X) \rightarrow [NH(CH_2CH_2OH)_3]^+ X^-$$
1–6

$$2N(CH_2CH_2OH)_3 + H_2X \rightarrow [NH(CH_2CH_2OH)_3]_2^+ X^{2-}$$
7, **8**

$$3N(CH_2CH_2OH)_3 + H_3X \rightarrow [NH(CH_2CH_2OH)_3]_3^+ X^{3-}$$
9

X^{n-} =  (**1**),  (**2**),  (**3**),  (**4**),  (**5**),

 (**6**),  (**7**),  (**8**),  (**9**).

In the IR spectra of protatranes **1–9** a wide band of ν(OH) vibrations is observed in the range 3360–3060 cm^{-1} (Table 2) caused by the vibrations of three hydroxy groups of the cation, whose oxygen atoms are involved in the formation of hydrogen bonds with the N^+H hydrogen atom, and the hydrogen atoms at these oxygens, with anion X^-. The relative position of the ν (OH) frequencies allows assessing the strength of the hydrogen bonds of the hydroxy groups with the carboxylate anion. In the IR spectra of protatranes **4** and **6** the ν(OH) bands appear at lower frequencies (3060 and 3140 cm^{-1}), than in the spectra of other protatranes (3240–3360 cm^{-1}). This is indicative of a higher strength of hydrogen bonds formed by the OH groups of the protatrane cation with the carboxylic group of anion X^-. In the spectrum of pure triethanolamine the ν(OH) vibrations appear at 3311 cm^{-1} as a strong wide band ($\Delta\nu_{1/2} \approx 400\ cm^{-1}$) [16]. A wide band of $\nu(N^+H)$ is present in all spectra in the range 2800–3000 cm^{-1}.

It was known that the degree and nature of interaction between the cation and anion in proptatrane is reflected in the frequencies of symmetric and asymmetric vibrations $\nu(COO^-)$ [16, 18]. The difference between these values (Δν) is used as a criterion of the structure of the molecule. Using the methods of IR spectroscopy and X-ray analysis it was shown that the value of $\Delta\nu > 200\ cm^{-1}$ points to a significant asymmetry of the carboxylic group, while the value of $\Delta\nu < 200\ cm^{-1}$ is indicative of its approximate symmetry [18]. The molecule of protatrane **5** is characterized by the vibration bands of the carboxylate anion at 1640 [$\nu_{as}(COO^-)$] and 1410 cm^{-1} [$\nu_s(COO^-)$] (Table 2). The value of Δν equal to 230 cm^{-1} points to a significant asymmetry of the carboxylic group. For

Table 1. Elemental analysis, melting points, and yields of protatranes **1–3** and **5–7**[a]

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
1	91	57–59	52.41	8.10	10.43	$C_{12}H_{20}N_2O_5$	52.93	7.70	10.29
2	95	70–72	60.40	8.27	4.90	$C_{15}H_{23}NO_5$	60.59	7.79	4.71
3	94	92–93	58.71	8.19	5.32	$C_{13}H_{21}NO_5$	57.55	7.80	5.16
5	90	70–73	40.12	6.90	6.19	$C_8H_{17}NO_7$	40.17	7.16	5.86
6	90	87–89	42.68	7.84	5.47	$C_9H_{19}NO_7$	42.68	7.56	5.53
7	95	74–75	46.12	9.18	6.84	$C_{16}H_{36}N_2O_{10}$	46.15	8.71	6.73

[a] Protatranes **4**, **8,** and **9** were obtained with a yield of 99% as a liquids.

Table 2. IR spectra of protatranes **1–9**

Comp. no.	ν(COO⁻), cm⁻¹		Δν, cm⁻¹	ν(OH), cm⁻¹
1	1590	1410	180	3350
2	1560	1410	150	3355
3	1600	1400	200	3350
4	1570	1380	190	3060
5	1640	1410	230	3360
6	1570	1400	170	3140
7	1640	1410	230	3350
8	1570	1380	190	3240
9	1580	1370	210	3240

protatrane **6**, $\Delta\nu = 170$ cm^{-1}, shows, on the contrary, an approximate symmetrical binding of the carboxylate anion. In the spectra of protatranes **5** and **6** also the stretching vibration bands of the carboxylic group ν(COOH) appear at 1720 and 1710 cm^{-1} respectively. In general, the region of 1500–700 cm^{-1} in the spectra of protatranes **1–9** resembles that in the spectrum of triethanolamine and differs by the presence of much more intense bands at 1500–1000 cm^{-1}, in most cases shifted to higher frequencies (bending vibrations of the methylene groups).

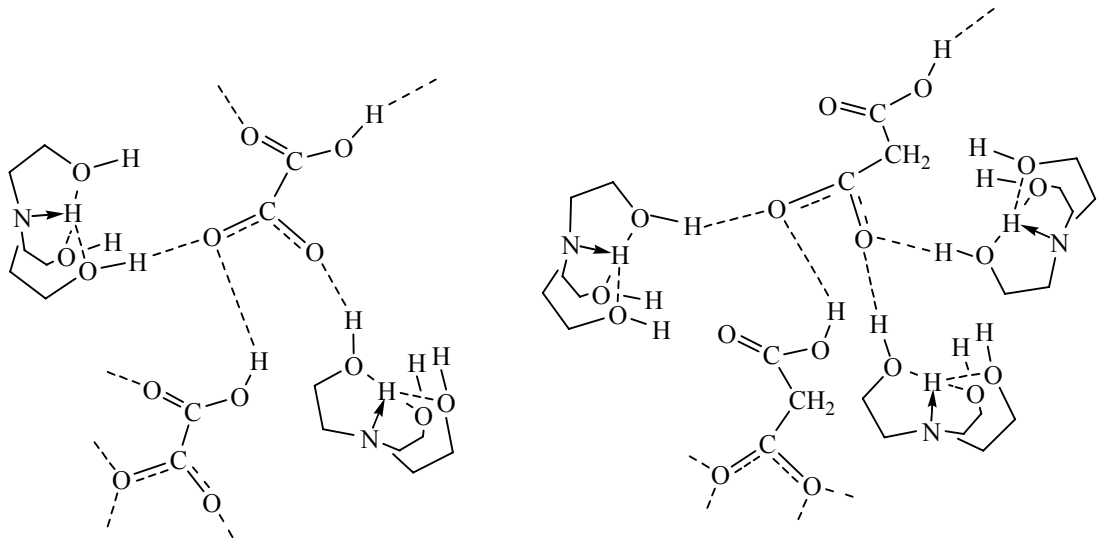
Investigation of protatranes **5** and **6** by the X-ray method confirmed the conclusions made on the basis of the IR spectroscopy data. Thus, in protatrane **5**, one oxygen atom of the oxalate anion forms two hydrogen bonds: with the OH group of the cation and with another molecule of the oxalate anion, whereas the second oxygen atom is linked only with one OH group of the cation (structure **A**). A similar structure with nonequivalent binding of the carboxylate anion can be expected in the case of protatranes **3**, **7**, and **9** with $\Delta\nu > 200$ cm^{-1} (Table 2). In protatrane **6** with $\Delta\nu = 190$ cm^{-1} each oxygen atom of the carboxylic group forms two hydrogen bonds: one with two OH groups of the two cations, and another one with the cation and with malonate anion (structure **B**). It can be assumed that other protatranes **1, 2, 4, 8** with $\Delta\nu < 200$ cm^{-1} have the structure close to that of protatrane **6**, or they have the structure in which each oxygen atom of the carboxylic group forms one hydrogen bond with the cation or another anion (Scheme 2).

Therefore, the structure of triethanolammonium salts of carboxylic acids (protatranes) **1–9** depends on the type and strength of hydrogen bonds between the protatrane cation and carboxylate anion, which affects the frequencies of stretching vibrations of OH- and COO⁻ groups. The results of X-ray analysis prove this conclusion.

EXPERIMENTAL

IR spectra of protatranes in KBr or in microlayer (for liquids) were obtained on an IR Fourier

Scheme 2.



A **B**

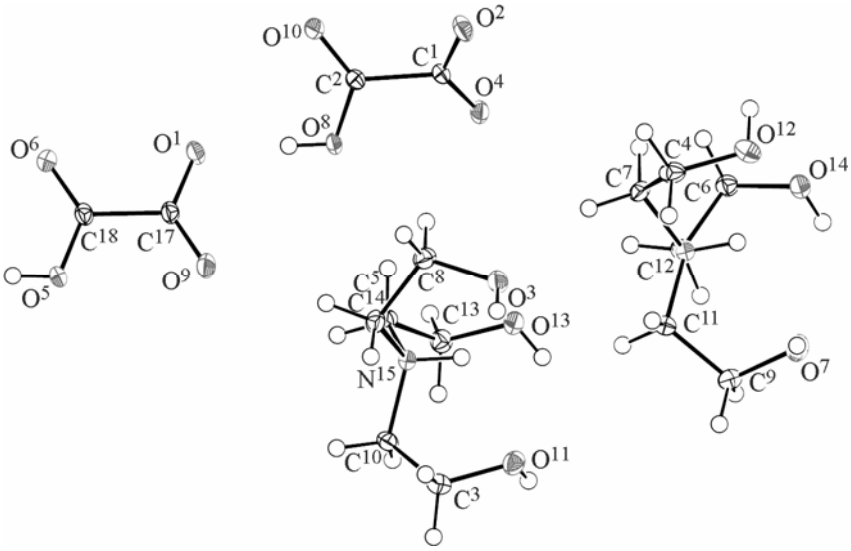


Fig. 1. Crystalline structure of protatrane **5**.

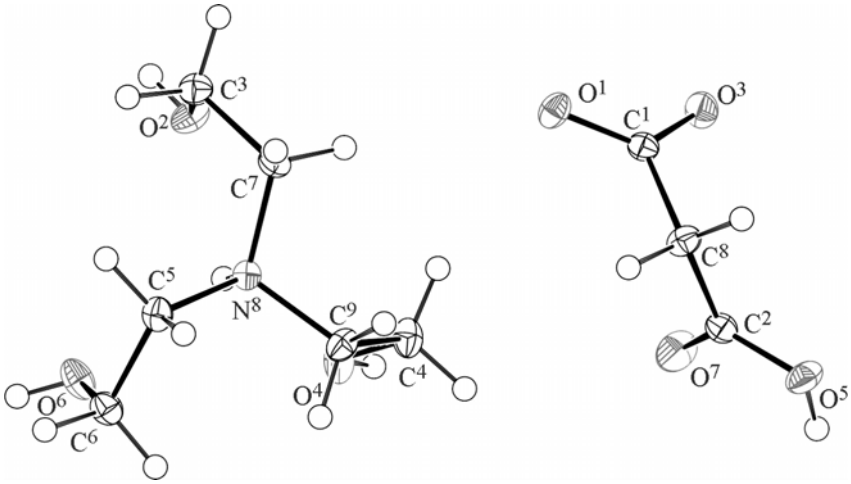


Fig. 2. Crystalline structure of protatrane **6**.

spectrometer Nicolet 8700 (Thermo Scientific). Elemental analysis was performed on a C,H,N-analyzer Euro EA3028-HT. For X-ray analysis colorless monocrystals were chosen of 0.21 × 0.13 × 0.18 and 0.25 × 0.16 × 0.09 mm size. The analysis was performed on a Supernova (Agilent Technologies, Oxford Diffraction) diffractometer with CuK_α-radiation.

ACKNOWLEDGMENTS

This work was performed using the equipment of the Resource Centers of St. Petersburg State University "Optical and laser methods of material research," "X-ray diffraction methods of study," and "Methods of analysis of the composition of matter."

REFERENCES

1. Mirskova, A.N., Levkovskaya, G.G., Kolesnikova, O.P., Perminova, O.M., Rudyakova, E.V., and Adamovich, S.N., *Russ. Chem. Bull*., 2010, vol. 59, no. 12, p. 2236. DOI: 10.1007/s11172-010-0384-9.
2. Mirskova, A.N., Mirskov, R.G., Adamovich, S.N., and Voronkov, M.G., *Chem. Sustainable Develop*., 2011, vol. 19, no. 5, p. 429.
3. Adamovich, S.N., Mirskov, R.G., Mirskova, A.N., and Voronkov, M.G., *Russ. Chem. Bull*., 2012, vol. 61, no. 6, p. 1260. DOI: 10.1007/s11172-012-0172-9.
4. Mirskova, A.N., Adamovich, S.N., and Mirskov, R.G., *Pharm. Chem. J*., 2012, vol. 46, no. 7, p. 392. DOI: 10.1007/s11094-012-0807-z.
5. Kolesnikova, O.P., Kudaeva, O.T., Sukhenko, T.G.,

Limonov, V.L., Kozlov, V.A., Mirskova, A.N., and Voronkov, M.G., *Dokl. Biol. Sci*., 2003, vol. 391, nos. 1–6, p. 306. DOI: 10.1023/A:1025186114079.
6. Voronkov, M.G., Dyban, A.P., D'yakov, V.M., and Simbirtsev, N.L., *Dokl. Biol. Sci*., 1999, vol. 364, nos. 1–6, p. 23.
7. Voronkov, M.G., Dolmaa, G., Tserenpil, Sh., Ugtakhbayar, O., and Chimidtsogzol, A., *Dokl. Biol. Sci*., 2005, vol. 404, nos. 1–6, p. 367. DOI: 10.1007/s10630-005-0138-2.
8. Shabanov, P.D., Zarubina, I.V., Bolekhan, A.V., Ryleeva, A.Yu., Zhumasheva, A.B., and Tsygan, V.N., *Russ. Med. Zh*., 2005, no. 12, p. 33.
9. Voronkov, M.G., Kolesnikova, O.P., Rasulov, M.M., and Mirskova, A.N., *Pharm. Chem. J*., 2007, vol. 41, no. 5, p. 244. DOI: 10.1007/s11094-007-0054-x.
10. Voronkov, M.G. and Rasulov, M.M., *Pharm. Chem. J*., 2007, vol. 41, no. 1, p. 1. DOI: 10.1007/s11094-007-0001-x.
11. Starova, G.S., Fundamensky, V.S., Semenova, N.V., and Voronkov, M.G., *Dokl. Akad. Nauk SSSR*, 1981, vol. 260, no. 4, p. 888.
12. Odabasoglu, M. and Buyukgungor, O., *Acta Cryst. Sect. E,* 2007, vol. 63, no. 1, p. 186. DOI: 10.1107/S160053680605238X.
13. Loginov, S.V., Abramkin, A.M., Rybakov, V.B., Sheludyakov, V.D., and Storozhenko, P.A., *Crystallogr. Rep*., 2012, vol. 57, no. 4, p. 521. DOI: 10.1134/S1063774512040141.
14. Verkade, J.G., *Coord. Chem. Rev*., 1994, vol. 137, p. 233. DOI: 10.1016/0010-8545(94)03007-D.
15. Gruzdev, M.S., Akopova, O.B., and Frolova, T.V., *Russ. J. Gen. Chem*., 2013, vol. 83, no. 4, p. 652. DOI: 10.1134/S1070363213040075.
16. Voronkov, M.G., Kochina, T.A., Vrazhnov, D.V., Litvinov, M.Y., Albanov, A.I., Aksamentova, T.N., Adamovich, S.N., Chipanina, N.N., and Mirskov, R.G., *Russ. J. Gen. Chem*., 2009, vol. 79, no. 11, p. 2339. DOI: 10.1134/S1070363209110097.
17. Naiini, A.A., Pinkas, J., Plass, W., Young, V.G., and Vercade, J.G., *Inorg. Chem*., 1994, vol. 33, p. 2137. DOI: 10.1021/ic00088a014.
18. Deacon, G.B. and Phillips, R.J., *Coord. Chem. Rev*., 1980, vol. 33, p. 227. DOI: 10.1016/S0010-8545(00)80455-5.