ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 2, pp. 340–342. © Pleiades Publishing, Ltd., 2014.
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LETTERS TO THE EDITOR

Aroxyprotatranes: Aroxy Derivatives of Tris-(2-hydroxyethyl)ammonium

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Received August 26, 2013

DOI: 10.1134/S1070363214020340

Protatranes are salts of triethanolamine and protic acids (HX) $[(HOCH_2CH_2)_3NH]^+ \cdot {}^-X$, in which the proton is located at the onium nitrogen atom (N^+–H) (bond length ~0.88–1.01 Å) and forms trifurcate hydrogen bonds with three OH groups resulting in the formation of the tricyclic protatrane cation. Protatranes are compounds of both theoretical and considerable practical interest [1]. Earlier we have shown, that the conversion of biologically active carboxylic (acetylsalicylic, arylhetero-acetic) and other acids to protatranes $[(HOCH_2CH_2)_3NH]^+ \cdot {}^-O(O)CR$, where R = $C_6H_4O(O)CMe$, CH_2YAr (Y = O, S, SO_2), drastically changes their physicochemical properties. Thus, unlike the starting acids, the protatranes of this type are water soluble ionic liquids or low-melting powders [2]. Therewith their pharma-cological activity becomes higher and more diverse [3–6].

Many important biologically active compounds, like hormones (serotonin, thyroxine, adrenaline, dophamine, oxytocin, testosterone, etc.) are phenols, that is, they have the OH group in the aromatic ring responsible for their acidic properties. The reaction of triethanolamine with phenols is poorly studied. We can mention only one recent work on an X-ray analysis of the complex of diethanolamine with 2-bromophenol $[(HOCH_2CH_2)_2(H)NH]^+ \cdot [{}^-OC_6H_4$-Br-2], (the N^+–H bond length is 0.96 Å) [7].

In this work we report on the synthesis of simplest aroxyprotatranes with the goal to obtain new potentially biologically active compounds. Triethanolamine readily reacts with phenol and 2-, 2,4-di-, 2,4,6-trinitrophenols:

$$(HOCH_2CH_2)_3N + HO–C_6H_{5-n}(NO_2)_n \rightarrow [(HOCH_2CH_2)_3NH]^+ \cdot {}^-OC_6H_{5-n}(NO_2)_n,$$

I–IV

n = 0 (**I**), 1 (**II**), 2 (**III**), 3 (**IV**).

Aroxyprotatranes **II–IV** obtained by this reaction in 91–95% yield are solids, compound **I** is an oily liquid. Unlike the starting phenols, compounds **I–IV** are readily soluble in water. Their composition and structure are proved by elemental analysis and the methods of ^1H, ^{13}C, ^{15}N NMR and IR spectroscopy.

Quantum chemical calculations proved the formation of two types of complexes in the reaction of triethanolamine with acids HX $[(HOCH_2CH_2)_3NH]^+ \cdot {}^-X$ [8]: the hydrogen-bonded, in which the interatomic distance N···H is about 1.5 Å, and complexes of proton transfer, in which the length of the covalent N^+–H bond is equal to ~1.0 Å.

Protonation of nitrogen atom in amines is followed by a downfield shift of the ^{15}N NMR signal ($\Delta\delta_N$ = 10–16 ppm) [9]. The ^{15}N NMR signals of protatranes are also shifted relative to triethanolamine (δ_N = –355.0 ppm) by $\Delta\delta_N$ = 15–20 ppm, which is indicative of the positively charged NH^+ moiety and the formation of complexes with proton transfer [8]. In the IR spectra of protatranes a broad band at 2500–3000 cm^{-1} is observed (N^+–H) [1, 8].

Nitrophenols, as rather strong acids, form with triethanolamine complexes with proton transfer **II–IV** and contain the onium nitrogen atom (N^+–H). This is witnessed by significant downfield shift of the ^{15}N NMR signals (NCH_2) relative to triethanolamine ($\Delta\delta_N$ = 16–17 ppm) and the presence of a band at

2800–3075 cm^{-1} (N^+–H) in the IR spectra. Phenol itself, as a more weak acid, gives with triethanolamine a hydrogen-bonded complex $(HOCH_2CH_2)_3NH^{\cdots}OC_6H_5$ (**I**), as witnessed by a small downfield shift of the ^{15}N NMR signal ($\Delta\delta_N$ = 4.6 ppm) and the absence of the $\nu(N^+–H)$ band in the IR spectrum.

It is known that the replacement of the triethanolammonium cation in protatranes $[(HOCH_2CH_2)_3NH]^+ \cdot {}^-O(O)CR$ by the di- or monoethanolammonium cation $[(HOCH_2CH_2)_n(RR')NH]^+$, where n = 1, 2; R = R' = H, Alk may increase the physiological, e.g. cancerostatic, activity [3]. With this in mind, we have synthesized the analogs of aroxyprotatranes $[(Et_3NH]^+ \cdot {}^-OC_6H_2(NO_2)_3$ (**V**), $[(HOCH_2CH_2)_2(Me)NH]^+ \cdot {}^-OC_6H_4(NO_2)$ (**VI**), $[(HOCH_2CH_2)_2(Me)NH]^+ \cdot {}^-OC_6H_2(NO_2)_3$ (**VII**), $[HOCH_2CH_2(Me)_2NH]^+ \cdot {}^-OC_6H_2(NO_2)_3$ (**VIII**) by the reaction of triethylamine (NEt_3), *N*-methyldiethanolamine, and *N,N*-dimethylethanolamine with the corresponding nitrophenols.

One of specific features of salts (ionic liquids), among which protatranes and aroxyprotatranes can be placed, is ionic conductivity [2]. Electroconductivity of 0.1 N aqueous solutions of **I, II, III, IV, VII** varies in the order (σ, mSm/cm): 1.70 (**I**) < 3.25 (**II**) < 3.36 (**III**) < 3.96 (**IV**) < 4.26 (**VII**), that is, increases with the acidity of the starting phenol $HOC_6H_{5-n}(NO_2)_n$, which follows the order (pK_a): 9.98 (n = 0) < 7.23 (n = 1) < 4.01 (n = 2) < 0.42 (n = 3) as well as the basicity of amines increasing in the following order ($pK_{a\,вн^+}$): 7.72 (triethanolamine) < 8.56 (methyldiethanolamine) < 9.22 (dimethylethanolamine) < 10.87 (NEt_3).

Therefore, by the reaction of phenol, 2-, 2,4-di-, and 2,4,6-trinitrophenol with triethanolamine, methyldiethanolamine, dimethylethanolamine and triethylamine a series of new water soluble liquid and solid aroxyprotatranes and their analogues **I–VIII** were synthesized.

IR spectra were recorded in KBr on a Varian 3100FT–IR75 spectrophotometer. NMR spectra were registered in D_2O on a DPX 400 spectrometer with working frequencies 400.13 (^1H), 101.62 (^{13}C) and 40.53 MHz (^{15}N). Electroconductivity was measured for 0.1 N solutions in distilled H_2O at 20°C on a Radelkis OK–102/1 conductometer. Amines were purified by triple distillation. Phenols (99.8%) were purchased from Aldrich. All reactions were carried out in dry argon.

Tris(2-hydroxyethyl)ammonium phenolate (I). To 1.49 g (0.01 mol) of tris(2-hydroxyethyl)amine in 15 mL of methanol 0.94 g (0.01 mol) of phenol in 10 mL of methanol was added dropwise at stirring, the mixture was kept at 30–50°C for 6 h, the solvent was removed, the residue was washed with ether and dried in a vacuum. Yield 2.30 g (95%). Transparent oil. ^1H NMR spectrum, δ, ppm: 8.09 s (5H, C_6H_5), 3.98 t (6H, OCH_2), 3.44 t (6H, NCH_2). ^{13}C NMR spectrum, δ_C, ppm: 158.9 (Ph), 56.0 (OCH_2), 55.9 (NCH_2). ^{15}N NMR spectrum, δ_N, ppm: –350.4. IR spectrum, ν, cm^{-1}: 1310 (ν_s, NO_2), 1510 (ν_{as}, NO_2), 3326 (OH). Found, %: C 59. 52; H 8.99; N 5.88. $C_{12}H_{21}NO_4$. Calculated, %: C 59.23; H 8.69; N 5.75. Compounds **II–VIII** were synthesized in a similar way.

Tris(2-hydroxyethyl)ammonium 2-nitrophenolate (II). Yield 91%, mp 55°C. ^1H NMR spectrum, δ, ppm: 8.44–6.14 m (4H, C_6H_4), 3.80 t (6H, OCH_2), 3.31 t (6H, NCH_2). ^{13}C NMR spectrum, δ_C , ppm: 158.2–121.0 (C_6H_4), 56.7 (OCH_2), 55.8 (NCH_2). IR spectrum, ν, cm^{-1}: 1320 (ν_s, NO_2), 1516 (ν_{as}, NO_2), 2809–3100 (N^+H), 3345 (OH). Found, %: C 50.28; H 7.28; N 9.69. $C_{12}H_{20}N_2O_6$. Calculated, %: C 49.99; H 6.99; N 9.71.

Tris(2-hydroxyethyl)ammonium 2,4-dinitrophenolate (III). Yield 94%, mp 119°C. ^1H NMR spectrum, δ, ppm: 8.50, 7.76, 6.44 m (3H, C_6H_3), 3.82 t (6 H, OCH_2), 3.34 t (6 H, NCH_2). ^{13}C NMR spectrum, δ_C, ppm: 160.1, 141.0, 124.9, 122.8 (C_6H_3), 56.6 (OCH_2), 55.9 (NCH_2). ^{15}N NMR spectrum, δ_N, ppm: –339.5. IR spectrum, ν, cm^{-1}: 1335 (ν_s, NO_2), 1526 (ν_{as}, NO_2), 2857–3121 (N^+H), 3355 (OH). Found, %: C 43.53; H 5.46; N 12.51. $C_{12}H_{19}N_3O_8$. Calculated, %: C 43.24; H 5.74; N 12.60.

Tris(2-hydroxyethyl)ammonium 2,4,6-trinitrophenolate (IV). Yield 3.59 g (95%), mp 129°C. ^1H NMR spectrum, δ, ppm: 8.84 s (2H, C_6H_2), 4.01 t (6H, OCH_2), 3.55 t (6H, NCH_2). ^{13}C NMR spectrum, δ_C, ppm: 162.0, 142.1, 127.0, 125.2 (C_6H_2), 55.5 (OCH_2), 55.1 (NCH_2). ^{15}N NMR spectrum, δ_N, ppm: –337.9. IR spectrum, ν, cm^{-1}: 1325 (ν_s, NO_2), 1549 (ν_{as}, NO_2), 2870–3074 (N^+H), 3354 (OH). Found, %: C 38.40; H 4.52; N 14.99. $C_{12}H_{18}N_4O_{10}$. Calculated, %: C 38.10; H 4.79; N 14.81.

Triethylammonium 2,4,6-trinitrophenolate (V). Yield 95%. Yellow powder, mp 174°C. ^1H NMR spectrum, δ, ppm: 8.79 s (2H, C_6H_2), 3.09 s (6H, CH_2), 1.15 t (9H, NCH_2). IR spectrum, ν, cm^{-1}: 1349 (ν_s, NO_2), 1563 (ν_{as}, NO_2), 2750–3036 (N^+H).

***N*-Methyl-bis(2-hydroxyethyl)ammonium 2-nitrophenolate (VI).** Yield 93%. Viscous oily liquid. ^1H

NMR spectrum, δ, ppm: 8.40–6.44 m (4H, C_6H_4), 3.87 t (4H, OCH_2), 3.35 t (4H, NCH_2), 2.88 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 159.1–119.2 (C_6H_4), 56.5 (OCH_2), 56.0 (NCH_2), 42.5 (NMe). IR spectrum, ν, cm^{-1}: 1327 (ν_s, NO_2), 1554 (ν_{as}, NO_2), 2802–3105 (N^+H), 3383 (OH). Found, %: C 51.41; H 7.30; N 11.12. $C_{11}H_{18}N_2O_5$. Calculated, %: C 51.15; H 7.02; N 10.84.

N-Methyl-bis(2-hydroxyethyl)ammonium 2,4,6-trinitrophenolate (VII). Yield 90%, mp 88°C. ^1H NMR spectrum, δ, ppm: 8.64 m (2H, C_6H_2), 3.88 t (4H, OCH_2), 3.25 t (4H, NCH_2), 2.91 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 160.2–118.1 (C_6H_2), 57.0 (OCH_2), 56.7 (NCH_2), 42.8 (NMe). IR spectrum, ν, cm^{-1}: 1320 (ν_s, NO_2), 1546 (ν_{as}, NO_2), 2870–3074 (N^+H), 3354 (OH). Found, %: C 38.21; H 4.90; N 15.90. $C_{11}H_{16}N_4O_9$. Calculated, %: C 37.93; H 4.63; N 16.08.

N,N-Dimethyl(2-hydroxyethyl)ammonium 2,4,6-trinitrophenolate (VIII). Yield 91%, mp 82°C. ^1H NMR spectrum, δ, ppm: 8.48 m (2H, C_6H_2), 3.87 t (2H, OCH_2), 3.27 t (2H, NCH_2), 2.90 s (6H, Me). ^{13}C NMR spectrum, δ_C, ppm: 159.1–120.8 (C_6H_2), 56.6 (OCH_2), 56.1 (NCH_2), 41.8 (NMe). IR spectrum, ν, cm^{-1}: 1317 (ν_s, NO_2), 1548 (ν_{as}, NO_2), 2852–3051 (N^+H), 3413 (OH). Found, %: C 38.02; H 4.13; N 17.41. $C_{10}H_{14}N_4O_8$. Calculated, %: C 37.74; H 4.43; N 17.60.

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