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Biologically active ionic liquids. New analogs of acetylcholine

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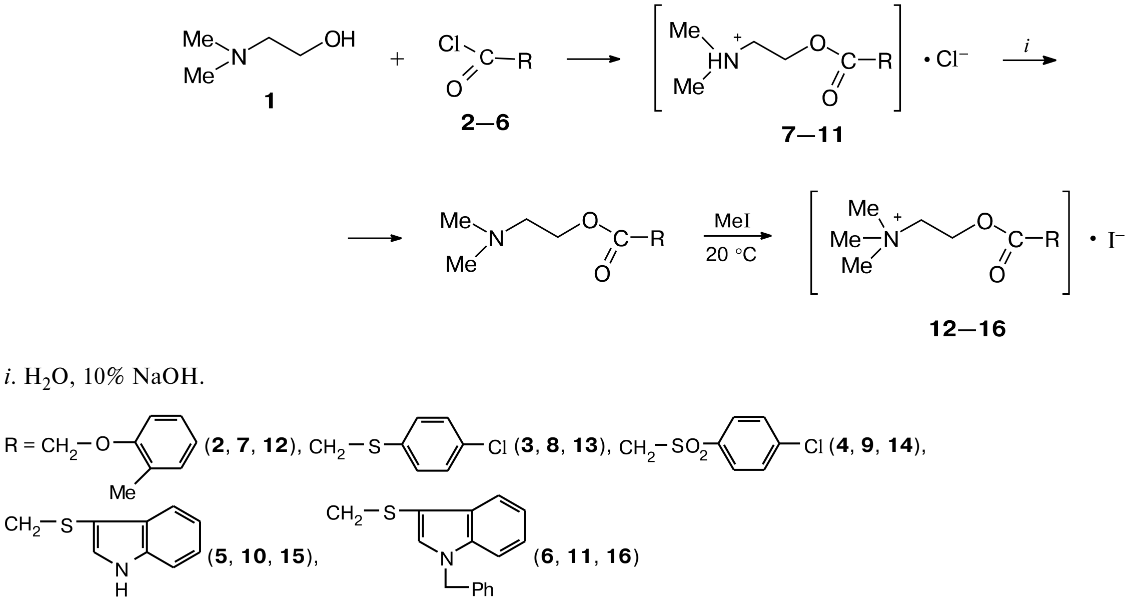
Acetylcholine, an endogenous neurotransmitter, performs one of the most vital functions in a living organism by promoting neuromuscular transmission from its brain and central nervous system to effector organs. This compound has ionic liquid structure and is commonly used as the chloride $(MeCOOCH_2CH_2N^+Me_3)\cdot Cl^-$, which is the first representative of so-called cholinomimetics. The drugs of this group include succinic (succinylcholine, Quelicin) and carbamic acid esters (carbacholine).[1] Another group of drugs that block cholinergic transmission is constituted by cholinolytics containing aryl substituents in the ester group. They include [2-(2-hydroxy-2,2-diphenylacetoxy)ethyl]trimethylammonium iodide $[Ph_2C(OH)COOCH_2CH_2N^+Me_3]\cdot I^-$ (metacin), spasmolytin, arpenal, and thiphen.[1]

In the present work, starting from (2-hydroxyethyl)dimethylamine (**1**) and various acyl chlorides RC(O)Cl (R = 2-methylphenoxymethyl (**2**), 4-chlorophenylsulfanylmethyl (**3**), 4-chlorophenylsulfonylmethyl (**4**), indol-3-ylsulfanylmethyl (**5**), and 1-benzylindol-3-ylsulfanylmethyl (**6**)[2—4]), we synthesized new analogs of acetylcholine with potential biological activity. The products obtained contain either protonated cations and the Cl^- anion (ionic liquids **7**—**11**, m.p. 75—100 °C) or alkylated cations and the I^- anion (salts **12**—**16**, m.p. 160—193 °C) (Scheme 1).

The structures of compounds **2**—**16** were confirmed using ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and elemental analysis. IR spectra were recorded on a Varian 3100 FT-IR75 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a DPX 400 spectrometer (400.13 (^1H) and 101.62 MHz (^{13}C)) in $CDCl_3$ with HMDS as the internal standard. The starting arylheteroacetic acids were prepared as described earlier.[2—4]

2-Methylphenoxyacetyl chloride (2). Thionyl chloride (1.31 g, 0.011 mol) was added to a stirred solution of 2-methylphenoxyacetic acid (1.66 g, 0.01 mol) in benzene (15 mL). The reaction mixture was heated at 80 °C for 3 h until SO_2 ceased to evolve. The solvent was removed and the residue was dried *in vacuo*. Yield 2.51 g (79%), a colorless powder soluble in diethyl ether and benzene, m.p. 135 °C. ^1H NMR, δ: 7.09—6.71 (m, 4 H, C_6H_4); 4.63 (s, 2 H, OCH_2); 2.20 (s, 3 H, Me). ^{13}C NMR,

Scheme 1



i. H_2O, 10% NaOH.

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δ: 170.90 (C=O); 154.38—111.86 (C_6H_4); 64.55 (OCH_2); 14.52 (Me). IR, ν/cm^{-1}: 1760 (C=O). Found (%): C, 58.64; H, 4.70; Cl, 19.49. $C_9H_9ClO_2$. Calculated (%): C, 58.55; H, 4.91; Cl, 19.20.

Acid chlorides **3—6** were obtained from appropriate acids as described for compound **2**.

4-Chlorophenylsulfanylacetyl chloride (3). Yield 71%, colorless liquid, b.p. 113—115 °C (1 mmHg). ^{1}H NMR, δ: 7.19—6.67 (m, 4 H, C_6H_4); 3.70 (s, 2 H, SCH_2). ^{13}C NMR, δ: 175.12 (C=O); 156.07—111.75 (C_6H_4); 49.50 (SCH_2). IR, ν/cm^{-1}: 1780 (C=O). Found (%): S, 14.25; Cl, 32.20. $C_8H_6Cl_2OS$. Calculated (%): S, 14.50; Cl, 32.06.

4-Chlorophenylsulfonylacetyl chloride (4). Yield 90%, powder, m.p. 75—76 °C. ^{1}H NMR, δ: 7.21—6.66 (m, 4 H, C_6H_4); 4.44 (s, 2 H, SO_2CH_2). ^{13}C NMR, δ: 177.00 (C=O); 160.07—111.11 (C_6H_4); 64.00 (SO_2CH_2). IR, ν/cm^{-1}: 1135 ($\nu_s(SO_2)$); 1362 ($\nu_{as}(SO_2)$); 1777 (C=O). Found (%): S, 12.70; Cl, 28.25. $C_8H_6Cl_2O_3S$. Calculated (%): S, 12.66; Cl, 28.01.

Indol-3-ylsulfanylacetyl chloride (5). Yield 76%, pink powder, m.p. 69—70 °C. ^{1}H NMR, δ: 7.77—7.10 (m, 5 H, Ind); 3.45 (s, 2 H, SCH_2). ^{13}C NMR, δ: 176.11 (C=O); 137.18—104.35 (Ind); 44.79 (SCH_2). IR, ν/cm^{-1}: 1778 (C=O).

1-Benzylindol-3-ylsulfanylacetyl chloride (6). Yield 85%, powder, m.p. 72 °C. ^{1}H NMR, δ: 7.75—6.91 (m, 10 H, Ph, Ind); 5.22 (s, 2 H, $PhC\underline{H}_2$); 3.41 (s, 2 H, SCH_2). ^{13}C NMR, δ: 177.01 (C=O); 138.08—105.55 (Ph, Ind); 46.90 (SCH_2). IR, ν/cm^{-1}: 1780 (C=O).

Dimethyl[2-(2-methylphenoxyacetoxy)ethyl]ammonium chloride (7). Solutions of compounds **2** (1.84 g, 0.01 mol) and **1** (0.89 g, 0.01 mol) in diethyl ether were mixed and stirred at 35 °C for 3 h. The precipitate that formed was filtered off, washed with diethyl ether, and dried *in vacuo*. Yield 1.99 g (72 %), a colorless powder soluble in water and EtOH, m.p. 100—104 °C. ^{1}H NMR, δ: 7.19—6.74 (m, 4 H, C_6H_4); 4.45 (s, 2 H, OCH_2COO); 3.82 (t, 2 H, OCH_2); 3.21 (t, 2 H, NCH_2); 2.85 (s, 6 H, N^+Me_2); 2.19 (s, 6 H, Me). ^{13}C NMR, δ: 177.90 (C=O); 150.30—111.10 (C_6H_4); 66.37 ($O\underline{C}H_2COO$); 58.16 (OCH_2); 54.58 (NCH_2); 42.15 (N^+Me_2); 14.52 ($\underline{C}H_3C_6H_4$). IR, ν/cm^{-1}: 1757 (C=O); 2475—2690 (N^+H). Found (%): C, 57.30; H, 7.08; Cl, 13.19. $C_{13}H_{20}ClNO_3$. Calculated (%): C, 57.03; H, 7.36; Cl, 12.95.

Chlorides **8—11** were obtained from alcohol **1** and appropriate acid chlorides **3—6** as described for compound **7**.

[2-(4-Chlorophenylsulfanylacetoxy)ethyl]dimethylammonium chloride (8). Yield 64%, colorless powder, m.p. 98 °C. IR, ν/cm^{-1}: 1760 (C=O); 2500—2710 (N^+H). Found (%): Cl, 22.56; N, 4.38; S, 10.19. $C_{12}H_{17}Cl_2NO_2S$. Calculated (%): Cl, 22.85; N, 4.51; S, 10.33.

[2-(4-Chlorophenylsulfonylacetoxy)ethyl]dimethylammonium chloride (9). Yield 51%, m.p. 80—82 °C. IR, ν/cm^{-1}: 1180 ($\nu_s(SO_2)$); 1330 ($\nu_{as}(SO_2)$); 1740 (C=O); 2450—2680 (N^+H). Found (%): Cl, 22.56; N, 4.38; S, 10.19. $C_{12}H_{17}Cl_2NO_2S$. Calculated (%): Cl, 22.85; N, 4.51; S, 10.33.

[2-(Indol-3-ylsulfanylacetoxy)ethyl]dimethylammonium chloride (10). Yield 52%, a pink hygroscopic powder with no definite melting point. ^{1}H NMR, δ: 7.70—7.12 (m, 5 H, Ind); 3.70 (t, 2 H, OCH_2); 3.39 (s, 2 H, SCH_2); 3.49 (t, 2 H, NCH_2); 2.88 (s, 6 H, N^+Me_2). ^{13}C NMR, δ: 178.19 (C=O); 137.07—105.05 (Ind); 57.46 (OCH_2); 55.55 (NCH_2); 43.09 (SCH_2); 41.19 (N^+Me_2). IR, ν/cm^{-1}: 1749 (C=O); 2505—2800 (N^+H).

[2-(1-Benzylindol-3-ylsulfanylacetoxy)ethyl]dimethylammonium chloride (11). Yield 51%, reddish powder, m.p. 75—79 °C. ^{1}H NMR, δ: 7.76—6.08 (m, 10 H, Ph, Ind); 5.20 (s, 2 H, $PhC\underline{H}_2$); 3.77 (t, 2 H, OCH_2); 3.45 (s, 2 H, SCH_2); 3.27 (t, 2 H, NCH_2); 2.88 (s, 6 H, N^+Me_2). ^{13}C NMR, δ: 177.79 (C=O); 138.00—104.95 (Ph, Ind); 58.16 (OCH_2); 54.58 (NCH_2); 44.00 (SCH_2); 42.15 (N^+Me_2). IR, ν/cm^{-1}: 1756 (C=O); 2510—2785 (N^+H).

Trimethyl[2-(2-methylphenoxyacetoxy)ethyl]ammonium iodide (12). A suspension of compound **7** in water was alkalified with 10% NaOH to pH 9 (NaCl remained dissolved). The precipitate that formed was filtered off, repeatedly washed with water, dissolved in acetone, and dried with Na_2SO_4. Then MeI (1.55 g, 0.011 mol) was added and the reaction mixture was stirred at 20 °C for 18 h. The precipitate that formed was filtered off, washed with acetone, and dried *in vacuo*. Yield 78%, a powder soluble in EtOH and water, m.p. 180—181 °C. ^{1}H NMR, δ: 7.12—6.77 (m, 4 H, C_6H_4); 4.43 (s, 2 H, OCH_2COO); 3.90 (t, 2 H, OCH_2); 3.39 (t, 2 H, NCH_2); 2.89 (s, 9 H, N^+Me_3); 2.20 (s, 3 H, Me). ^{13}C NMR, δ: 175.91 (C=O); 149.30—111.11 (C_6H_4); 65.31 ($O\underline{C}H_2COO$); 58.20 (OCH_2); 55.58 (NCH_2); 53.15 (N^+Me_3); 14.39 ($\underline{C}H_3C_6H_4$). IR, ν/cm^{-1}: 1760 (C=O). Found (%): C, 44.63; H, 5.58; N, 3.59. $C_{14}H_{22}INO_3$. Calculated (%): C, 44.34; H, 5.84; N, 3.69.

Iodides **13—16** were obtained from MeI and appropriate chlorides **8—11** as described for compound **12**.

[2-(4-Chlorophenylsulfanylacetoxy)ethyl]trimethylammonium iodide (13). Yield 77%, powder, m.p. 160—163 °C. ^{1}H NMR, δ: 7.42—6.70 (m, 4 H, C_6H_4); 3.18 (s, 2 H, SCH_2); 3.78 (t, 2 H, OCH_2); 3.29 (t, 2 H, NCH_2); 2.87 (s, 9 H, N^+Me_3). IR, ν/cm^{-1}: 1760 (C=O).

[2-(4-Chlorophenylsulfonylacetoxy)ethyl]trimethylammonium iodide (14). Yield 75%, m.p. 172—174 °C. ^{1}H NMR, δ: 7.42—6.70 (m, 4 H, C_6H_4); 4.55 (s, 2 H, SO_2CH_2); 3.80 (t, 2 H, OCH_2); 3.32 (t, 2 H, NCH_2); 2.87 (s, 9 H, N^+Me_3). IR, ν/cm^{-1}: 1185 ($\nu_s(SO_2)$); 1333 ($\nu_{as}(SO_2)$); 1755 (C=O).

[2-(Indol-3-ylsulfanylacetoxy)ethyl]trimethylammonium iodide (15). Yield 70%, pink powder, m.p. 190—193 °C. ^{1}H NMR, δ: 7.80—7.15 (m, 5 H, Ind); 3.73 (t, 2 H, OCH_2); 3.40 (s, 2 H, SCH_2); 3.25 (t, 2 H, NCH_2); 2.88 (s, 9 H, N^+Me_3). IR, ν/cm^{-1}: 1749 (C=O).

[2-(1-Benzylindol-3-ylsulfanylacetoxy)ethyl]trimethylammonium iodide (16). Yield 71%, red powder, m.p. 178—179 °C. ^{1}H NMR, δ: 7.70—7.01 (m, 10 H, Ph, Ind); 3.80 (t, 2 H, OCH_2); 3.44 (s, 2 H, SCH_2); 3.35 (t, 2 H, NCH_2); 2.88 (s, 9 H, N^+Me_3). IR, ν/cm^{-1}: 1741 (C=O).

References

1. M. D. Mashkovskii, *Lekarstvennye veshchestva* [*Drugs*], Novaya Volna, Moscow, 2000, 14th ed., Vols **1**, **2** (in Russian).
2. A. N. Mirskova, G. G. Levkovskaya, O. P. Kolesnikova, O. M. Perminova, E. V. Rudyakova, S. N. Adamovich, *Russ. Chem. Bull.* (*Int. Ed.*), 2010, **59**, 2236 [*Izv. Akad. Nauk, Ser. Khim.*, 2010, 2181].
3. O. P. Kolesnikova, A. N. Mirskova, S. N. Adamovich, O. T. Kudaeva, R. G. Mirskov, M. G. Voronkov, *Byull. Sib. Otd. Russ. Akad. Med. Nauk* [*Bulletin of the Siberian Branch of the Russian Academy of Medical Sciences*], 2010, 12 (in Russian).
4. A. N. Mirskova, R. G. Mirskov, S. N. Adamovich, M. G. Voronkov, *Khim. v Interesakh Ustoich. Razvit.*, 2011, 467 [*Chem. Sustain. Dev.*, 2011, **19** (*Engl. Transl.*)].

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