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Synthesis of Novel phenoxy - isobutyric acid derivatives of choline and some of its salt

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Abstract: In connection with some work on the bactericidal properties of lecithins the author had occasion to prepare some of the salts of choline. In looking through the literature it was found that the choline used in recent investigations was prepared and isolated by methods which it was thought might be simplified nowadays it's for acting physiologically acceptable excipients. In a second aspect, the present invention relates to novel salt of substituted alpha-phenoxy – isobutyric acids and derivatives that are photostable when compared to other salts of substituted alpha-phenoxy – isobutyric acid derivatives. We summarized the synthetic methodology yield, structural characteristic (NMR, Mass spectrum and C, H, N analysis) in their properties.
Key words: Choline salt preparation; alpha-phenoxy – isobutyric acid derivatives and its choline salt.

Introduction

In connection with some work on the bactericidal properties of lecithins the author had occasion to prepare some of the salts of choline[1]. In looking through the literature it was found that the choline used in recent investigations was prepared and isolated by methods which it was thought might be simplified[2]. In a second aspect, the present invention relates to novel salt of substituted alpha-phenoxy – isobutyric acids and derivatives preparation[3] that are exhibit photo stability when compared to other salts of substituted alpha-phenoxy – isobutyric acid derivatives. These salts are useful for pharmaceutical formulations in a form of molecular dispersions that contain at least one of these novel salts. These novel salts can be used to treat hyperlipidemia or coronary heart diseases[4]. Their unique properties have sparked considerable interest from theoretical chemicals and biological stand points. The preparation of α-phenoxy isobutyric acid derivatives of choline salt, α-phenoxy isobutyric acid derivatives and choline hydroxide solution or choline chloride were added. The product crystallized out of solution and the slurry was mixed at 65°C for half an hour. Then reaction mixture stirred at room temperature for several hours. The solution was filtered and the rinsed with 5mL of isopropanol. The solid was dried in vacuum oven at 40-50°C for several hours.

Experimental

Liquid substances were distilled prior to use. Melting points were uncorrected. 1HNMR spectra were measured on a Bruker Avance 400 (400MHz) spectrometer using TMS as the internal standard. Elemental analysis were measured on a (HERAEUS CHNO, Rapid) analyzer. Sonication were performed in Shanghi Branson- CQX ultrasonic cleaner (with a frequency of 25KHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40KHz, 59 KHz and nominal power 250 W Shanghai Kudos ultrasonic

Instrument Co., Ltd.,) The reaction flask were located in the cleaner where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

Preparation-1:

The preparation of α-phenoxy isobutyric acid derivatives (scheme-1) of choline salt, α-phenoxy isobutyric acid derivatives 3.75mmol isopropanol 10mLwere mixed in a 50mL round bottomed flask at 65°C for 30-60 minutes. The reaction mixture to get clear solution. A solution of choline hydroxide in methanol (4.13mmol, 45 Wt%) was diluted with 5mL isopropanol and approximately two thirds of the solution was added to the α-phenoxy isobutyric acid derivatives suspension. The reaction mixture was stirred at 30 minutes at 65°C. The remaining one third of the choline hydroxide solution was added followed by a 4.5 mL rinse of the addition funnel with isopropanol. After 30 minutes solid is thrown out. The product crystallized out of solution and the slurry was mixed at 65°C for half an hour. The reaction mixture cooled to 20-25°C over 5 hours. Then reaction mixture stirred at 20-25°C for overnight. The product was filtered off and rinsed with 5mL isopropanol. The solid was dried in a vacuum oven at 35-40°C for 24 hours. The dry weight of solid was 1.25gm or 90% yield.

Preparation -2: Alternate method for making choline salt (using choline chloride):

The preparation of α-phenoxy isobutyric acid derivatives of choline salt, α-phenoxy isobutyric acid derivatives 3.75 mmol and sodium bicarbonate 3.75mmol were suspended in methanol 10mL were mixed in a 50mL round bottomed flask at 55°C to dissolved the solids. A solution of choline chloride 4.13 mmol in 5ml of methanol was added. The solution was filtered to remove the precipitated sodium chloride and the filter rinsed with 5 ml of methanol. The filtrate was diluted with 10ml of isopropanol and concentrated to a volume of approximately 30ml. The solution was filtered and the rinsed with 5ml of isopropanol. The filtrate was concentrated to solid residue weighing 2.4g. The residue was suspended in 10ml of isopropanol and heated to 65°C for 30-60 minutes cooled to 20-25°C over 5 hours, and mixed at 20-25°C for 24 hours. The product was filtered off and rinsed with 5ml of isopropanol. The solid was dried in vaccum oven at 50°C for 24 hours. The dry weight of solid was 1.1gm or 79.3% yield.

(**1**). (2-Hydroxyethyl)trimethylammonium 2-[2-(phenoxy)-2-methylpropionate] 2-methyl propionate; Melting point 225-227°C. ^{1}H NMR (400MHz, D_2O), §7.2-7.00 (d, 11.2Hz, 2H), 6.9-6.7 (t, 12Hz, 2H) 6.5 (t, 9.2Hz, 1H), 4.03(m, 2H), 3.49(m, 2H) 3.17(s, 9H), 1.59(s, 12H); m/z : 369, 265, 250, 235, 220, 179, 134, 115, 104, 93, 86, 65, 49, 45, 30, 28, 18, 15; Anal. Calcd for $C_{19}H_{31}NO_6$: C 61.79, H 8.4, N 3.76; found C 61.71, H 8.3, N 3.79;

(2). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-propanoylphenoxy)-2-methylpropionate] 2-methyl propionate; Melting point 232-235°C. ^{1}H NMR (400MHz, D_2O), § 7.4-7.3(d, 9.5Hz, 2H), 7.2-7.1(d, 10.1Hz, 2H), 4.1(m, 2H), 3.3(m, 2H) 3.17(s, 9H), 2.7 (s, 12H), 2.3(q, 2H), 1.8(t, 3H); m/z : 425, 321, 292, 276, 264, 235, 219, 191, 190, 172, 149, 131, 130, 104, 102, 87, 73, 60, 57, 49, 45, 29, 17; Anal. Calcd for $C_{22}H_{35}NO_7$: C 62.09, H 8.23, N 3.27; found C 62.06, H 8.31, N 3.25;

(**3**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-benzoylphenoxy)-2-methylpropionate] 2-methylpropionate; Melting point 251-254°C. ^{1}H NMR (400MHz, D_2O), §7.5-7.3 (d, 10.2Hz, 4H), 7.2(d, 9.5Hz, 2H), 7.1-7.00(t, 12.00Hz, 2H), 6.9(t, 1H), 4.4(m, 2H), 3.5(m, 2H) 3.2(s, 9H), 2.6(s, 12H); m/z: 473, 369, 324, 292, 283, 264, 238, 197, 173, 153, 131, 105, 104, 93, 86, 77, 73, 66, 49, 45, 17; Anal. Calcd for $C_{26}H_{35}NO_7$: C 65.94, H 7.34, N 2.96; found C 65.92, H 7.32, N 2.94;

(4). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-hexanoylphenoxy)-2-methylpropionate] 2-methylpropionate; Melting point 243-246°C. ^{1}H NMR (400MHz, D_2O), § 7.5-7.3(d, 9.3Hz, 2H), 7.3-7.1(d, 10.5Hz, 2H), 4.0(m, 2H), 3.2(m, 2H) 3.0(s, 9H), 2.7(s, 12H), 2.4(t, 2H), 2.3(m, 2H), 2.1-2.00(s, 4H), 1.8(t, 3H); m/z: 467, 363, 348, 318, 292, 277, 264, 233, 232, 191, 172, 131, 130, 104, 99, 93, 86, 79, 73, 71, 66, 49, 45, 17, 15; Anal. Calcd for $C_{25}H_{41}NO_7$: C 64.22, H 8.78 N 2.3; found C 64.21, H 8.76, N 2.98;

(**5**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-octanoylphenoxy)-2-methylpropionate] 2-methylpropionate; Melting point 305-307°C. ^{1}H NMR (400MHz, D_2O), § 7.5-7.3(d, 10.2Hz, 2H), 7.2-7.00(d, 9.2Hz, 2H), 4.6(m, 2H), 3.4(m, 2H) 3.1(s, 9H), 2.7(s, 12H), 2.4(t, 2H), 2.3(m, 2H), 1.9(broad, s, 8H), 1.7(t, 3H); m/z: 495, 391,

376, 346, 305, 292, 288, 261, 260, 219, 172, 127, 131, 130, 104, 99, 93, 86, 73, 66, 49, 45, 17, 15; Anal. Calcd for $C_{27}H_{45}NO_7$: C 65.43, H 9.09, N 2.83; found C 65.41, H 9.07, N 2.82;

(**6**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-acetophenoxy)-2-methylpropionate] 2-methylpropionate; Melting point 235-237°C. ^{1}H NMR (400MHz, D_2O), § 7.4-7.3 (d, 9.5Hz, 2H), 7.2-7.1(d, 10.1Hz, 2H), 4.1(m, 2H), 3.2(m, 2H) 3.1(s, 9H), 2.7(s, 12H), 2.3(s, 3H); m/z: 411, 307, 292, 264, 262, 221, 177, 176, 172, 135, 131, 130, 104, 93, 86, 73, 66, 49, 45, 43, 17, 15; Anal. Calcd for $C_{21}H_{33}NO_7$: C 61.29, H 8.03, N 3.40; found C 61.28, H 8.04, N 3.41;

(**7**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-butanoylphenoxy)-2-methylpropionate] 2-methylpropionate; Melting point 258-259°C. ^{1}H NMR (400MHz, D_2O), § 7.5-7.2 (d, 9.3Hz, 2H), 7.2-7.00(d, 9.8Hz, 2H), 4.7(m, 2H), 3.7(m, 2H) 3.4(s, 9H), 2.7(s, 12H), 2.3(t, 2H), 1.9(m, 2H), 1.7(t, 3H); m/z: 439, 335, 292, 290, 264, 249, 205, 204, 172, 163, 131, 130, 104, 93, 86, 73, 71, 66, 49, 45, 43, 17; Anal. Calcd for $C_{23}H_{37}NO_7$: C 62.84, H 8.42, N 3.19; found C 62.83, H 8.40, N 3.17;

(**8**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-penatanoylphenoxy)-2-methylpropionate] 2-methyl propionate; Melting point 264-265°C. ^{1}H NMR (400MHz, D_2O), § 7.5-7.3 (d, 9.3Hz, 2H), 7.3-7.1(d, 10.5Hz, 2H), 4.0(m, 2H), 3.2(m, 2H) 3.1(s, 9H), 2.7(s, 12H), 2.4(t, 2H), 1.9(m, 2H), 1.8-1.6(m, 2H), 1.4(t, 3H); m/z: 453, 349, 334, 304, 292, 264, 263, 219, 218, 177, 172, 131, 130, 104, 93, 86, 85, 73, 66, 57, 49, 45, 17, 15; Anal. Calcd for $C_{24}H_{39}NO_7$: C 65.56, H 8.61, N 3.09; found C 65.53, H 8.60, N 3.07;

(**9**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-(3,4-dichlorobenzoyl)phenoxy)-2-methyl-propionate] 2-methylpropionate; Melting point 302-303°C. ^{1}H NMR (400MHz, D_2O), § 7.9(s, 1H), 7.7-7.5(d, 1H), 7.4(d, 1H), 7.3-7.20(d, 2H), 7.00-6.9(d, 2H), 3.9(m, 2H), 3.5(m, 2H) 3.2(s, 9H), 2.7(s, 12H); m/z: 542, 438, 402, 393, 352, 308, 307, 292, 266, 264, 174, 172, 142, 131, 130, 104, 93, 86, 73, 66, 49, 45, 36, 17, 15: Anal. Calcd for $C_{26}H_{33}NO_7Cl_2$: C 57.55, H 6.09, N 2.58; found C 57.54, H 6.08, N 2.57;

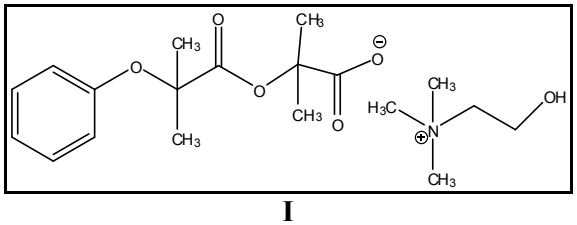
(**10**). (2-Hydroxyethyl)trimethylammonium 2-[2-(2,6-dichlorobenzoyl)phenoxy)-2-methylpropionate] 2-methyl propionate; Melting point 307-308°C ^{1}H NMR (400MHz, D_2O), § 7.9-7.8(d, 2H), 7.7-7.6(t, 1H), 7.5-7.3(d, 2H), 7.2-7.00(d, 2H) 4.2(m, 2H), 3.3(m, 2H) 3.0(s, 9H), 2.6(s, 12H); m/z: 542, 438, 402, 393, 352, 308, 307, 292, 266, 264, 174, 172, 142, 131, 130, 104, 93, 86, 73, 66, 49, 45, 36, 17, 15: Anal. Calcd for $C_{26}H_{33}NO_7Cl_2$: C 57.58, H 6.09, N 2.58; found C 57.56, H 6.07, N 2.57;

(**11**). (2-Hydroxyethyl)trimethylammonium 2-[2-(4-cyclohexanoylphenoxy)-2-methylpropionate] 2-methyl propionate; Melting point 279-281°C. ^{1}H NMR (400MHz, D_2O), § 7.5-7.4(d, 2H), 7.2-7.0(d, 2H), 4.2(m, 2H), 3.5(m, 2H) 3.3(s, 9H), 3.1(m, 1H), 2.6(s, 12H), 2.5-2.3(q, 4H) 2.00-1.8(br, s, 6H); m/z: 479, 375, 330, 292, 289, 264, 245, 244, 203, 172, 131, 130, 111, 104, 93, 86, 83, 73, 66, 49, 45, 17: Anal. Calcd for $C_{26}H_{41}NO_7$: C 65.11, H 8.56, N 2.92; found C 65.10, H 8.54, N 2.91;

Result and discussions:

In the present study synthesis of α-phenoxy – isobutyric acid derivatives of choline salt was our initial objective. With the ultimate goal of producing pure α-phenoxy – isobutyric acid and its choline salts producing in the reaction. The present invention will be described in two different aspects. Each of these two aspects of the present invention are treated separately under different headings for the convenience under and should not be construed as limiting the present invention in any way[5]. These headings are pharmaceutical formulation of α-phenoxy – isobutyric acid derivatives of its choline salt, physiologically acceptable salts or derivatives thereof and novel salts of α-phenoxy – isobutyric acid derivatives.

As used herein the term of α-phenoxy – isobutyric acid derivatives of choline salt refers to having the following formula-**I**.



I

The preparation of α-phenoxy isobutyric acid derivatives of choline salt, α-phenoxy isobutyric acid derivatives and choline hydroxide solution or choline chloride were added. The product crystallized out of solution and the slurry was mixed at 65°C for half an hour. Then reaction mixture stirred at room temperature for several hours. The solution was filtered and the rinsed with 5mL of isopropanol. The solid was dried in vacuum oven at 40-50°C for several hours.

The physiologically acceptable salts of the present invention are preferably base addition salts. The basic addition salts include salts with inorganic bases[6] including (but not limited to metal hydroxides carbonates of alkali metal, alkaline earth metals or transistion metals, or with organic bases, including but not limited to ammonia basic ammonia acids such as arginie and lysine, amines)

The physiologically acceptable derivatives of the present invention are preferably carboxylic acid derivatives that are reconvert able in vivo to the free carboxylic acid[7]. Thus the preferred physicologically acceptable derivatives of α-phenoxy – isobutyric acid are prodrug of α-phenoxy – isobutyric acid derivatives. The conversion of acid prodrugs in vivo may occur under the physiological condition[8], that the prodrug experiences during its passage or may involve cleavage by enzymes, especially esterase, acceptable the prodrug as substrate.

The term "molecular dispersion" as used herein and as known to one skilled in the art, describes systems in which substance, in the present case at least part and particularly the predominant part of the α-phenoxy – isobutyric acid content is homogeneously dispersed in the binder component[9]. In a molecular dispersion, the dispersed substance is free of interfaces. In this case, the binder usually forms a matrix which, according to the present invention is formed by the binder component or at least by a predominant part of the binder component advantageously, the enteric binder[10].

According to this embodiment, the content of active substance crystals in a formulation of the present invention is preferably below about 15% and most preferably, below about 10% statements about crystals contents relate to the total amount of the active substances[11], particularly, the α-phenoxy – isobutyric acid content.

It is also possible to add excipients such as, but not limited to, masking flavors and odor-masking agents, particularly, sweeteners and odorants[12].

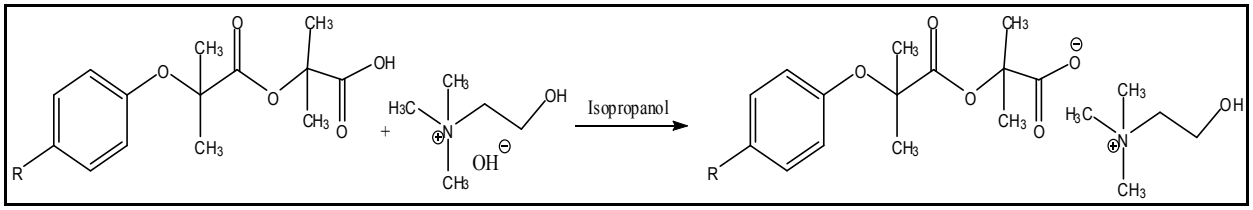
Further particular embodiments involving excipients are known to those skilled in the art as described, for example in Fiedler, H.B., Lexikon der Eilfsstoffefir Fharmazie, Kosmetik and angrenzende Gebiete, 4th edition, Aulendorf: ECV-Editio-cantor-Verlag (1996).

The only requirement for the suitability of the excipients is usually the compatibility with the active substances and excipients used. The excipients ought not to impair the formation of molecular dispersions. The formulations and dosage forms of the present invention are mainly used in pharmacy, for example in the pharmaceutical sector as lipid regulating agents and novel salts of α-phenoxy – isobutyric acid derivatives.

In another aspect, the present invention relates to novel salts of α-phenoxy – isobutyric acid derivatives. In one embodiment, these novel salts are selected from the group consisting of choline the structure of each of these salts is provided in example Table (1). The novel salts of the present invention are base addition salts that can be prepared by combining α-phenoxy – isobutyric acid derivatives and a base in a suitable solvent system and then mixing at an appropriate temperature. The determination of a suitable solvent system and approptiate temperature for preparing such salts can be readily determined by one of ordinary skill in the art[13]. By way of example and not of limitation examples of solvents that can be used to make the novel salts[14] of the presents invention like isopropanol, methanol, ethylacetate, ethanol, n-butanol…..etc.,

As described in detail in the examples, certain characterization and performance data, were examined for each of the above described novel salts of the present invention. This analytical data is summarized.

Scheme-1:



Scheme-2:

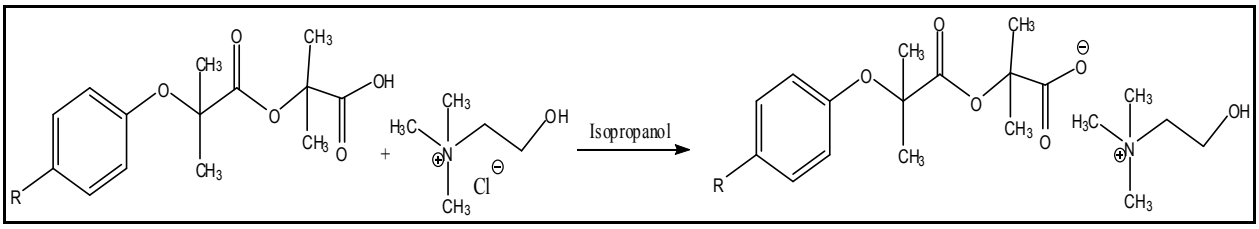


Table-1:

Compound	R	Yield
1	H	90%
2	CH_3CH_2CO	65%
3	C_6H_5CO	75%
4	$CH_3(CH_2)_4CO$	82%
5	$CH_3(CH_2)_6CO$	68%
6	CH_3CO	73%
7	$CH_3(CH_2)_2CO$	86%
8	$CH_3(CH_2)_3CO$	92%
9	3,4 Cl_2-C_6H_3CO	59%
10	2,6 Cl_2-C_6H_3CO	63%
11	Cyclohexyl-CO	79%

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