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1 **Synthesis of the symmetrical methylene diesters from carboxylic ionic liquids.**

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Draft

1 **ABSTRACT**

2 The reaction between carboxylic ionic liquids and dichloromethane, which provokes the
3 formation of symmetrical methylene diesters, was carried out. The synthesis of these ionic liquid
4 compounds was carried out in a microwave reactor and the characterization by spectroscopic
5 techniques of methylene diesters (methylene di-2-furoate, methylene di-2-picolinate, methylene
6 dianthranilate, and methylene dioleate) is described and the crystal structures discussed. The
7 crystal packing of methylene dianthranilate is characterized by trimer formation due to hydrogen
8 bonding *via* interactions between the hydrogen atom of the primary amine group and the oxygen
9 of the carboxylic group.

10 **Keywords:** Ionic liquids, methylene diesters, dichloromethane, crystal structure, hydrogen
11 bonding

12

1. Introduction

Nowadays, ionic liquids (ILs) are almost ubiquitous in many industrial processes such as BASIL¹, which produces coxyphenylphosphines; BASF², for the separation of azeotropic mixtures and alcohol chlorination; DIFASOL³, patented by the French Institute of Petroleum and used for the dimerization of alkenes; and DEGUSSA⁴, where the ILs are used as paint additives and as electrolytes in lithium batteries; in addition, there are processes such as EASTMANN⁵, for obtaining acetic acid, and NOVARTIS⁶.

The previously mentioned applications have to do with well-acknowledged features that ILs possess such as extremely strong polarization and solvation properties, nevertheless, the studies on their chemical and thermal stabilities, among other characteristics, are still a current topic. The present work deals with the study of the reaction between the ILs and a carboxylate-type anion, using dichloromethane as a common solvent for the easy synthesis of methylene diesters (MDEs) with high yield rates.

The potential application of MDEs in the medicine branch has been described in the literature. Heffernan et al. have described the MDE application of a 4H-furo[3,2-b]pyrrole-5-carboxylic acid as an oxidation inhibitor of D-amino acids, which allows the use of these compounds in Alzheimer treatments and as anticonvulsants⁷, where MDEs derived from valproic acid⁸ have also been reported regarding this purpose.

Researchers at the University of Toulouse synthesized symmetric and asymmetric MDEs, including the structure of an antimicrobial drug, levofloxacin, in the molecule, and evaluated them in-vitro as growth inhibitors of carcinogenic tumours⁹.

At Oxford and Cambridge Universities, researchers reported on the application of a MDE as an analogue compound of cyclic ADP-ribose^{10,11} whereas in Israel, the same structure was identified as part of a psychotropic agent and as a prodrug with anticarcinogenic effects¹²⁻¹⁶. In addition, methylene-dipropionate features anti-fungal properties and can be used for preserving organic materials¹⁷.

There are several patents on the application of MDEs, derived either from acrylic or methacrylic acids, in the preparation of polymers for different purposes such as hydrophobic coatings in contact lenses^{18,19}, preparation of magnetic spheres²⁰, enhanced oil recovery (EOR)²¹, dental resins²² and agents for the formation of images^{23,24}. MDEs derived from fatty acids (stearic and tricosanoic) have been reported as paint compounds for thermal transfer²⁵.

According to the aforesaid, the search for new synthesis pathways for obtaining compounds suitable for being the precursors of pharmaceutical drugs, among other purposes, is a current task in the scientific field. In the present work, four MDEs were synthesized from trialkylammonium carboxylates by means of a reaction with dichloromethane under mild conditions in microwave (MW) reactor: methylene di-2-furoate, methylene di-2-picolinate, methylene dianthranilate and methylene dioleate with a yield rate above 80 %.

2. Materials and methods

All the chemical compounds used for the syntheses and tests (except otherwise stated) had >98 % purity and were purchased from Sigma-Aldrich. All the synthesized compounds were characterized by ¹H and ¹³C NMR, and infrared (IR) spectroscopy. IR spectra were recorded on a Thermoscientific Nicolet 8700 Spectrometer. ¹H (300 MHz) and ¹³C NMR (75.4 MHz) spectra were recorded on a JEOL Eclipse-300 equipment in CDCl₃, and chemical shifts are expressed in ppm relative to tetramethylsilane as the internal standard. Three ILs (methyltriethylammonium 2-furoate, methyltriethylammonium anthranilate and methyltriethylammonium picolinate) were synthesized starting from methyltriethylammonium methylcarbonate as feedstock, while the (2-hydroxyethyl)trimethylammonium oleate was synthesized starting from (2-hydroxyethyl)trimethylammonium bicarbonate.

Methyltriethylammonium methyl carbonate (1): 20.00 g of triethylamine (198 mmol) reacted with 35.61 g (396 mmol) of dimethyl carbonate in 30 mL of methanol. The synthesis was performed using a Parr reactor model 4848, designed for synthesis; the reactor was equipped

1 with a stirrer as well as temperature controls, and the reaction mixture was kept at 150 °C under
2 stirring for 6 h. Once the reaction was finished, the mixture was filtered, and the solution
3 evaporated with vacuum to remove both the residual dimethyl carbonate (b. p. 90.3 °C) and
4 methanol (b. p. 64.7 °C). The crude compound was washed thrice with ethyl acetate (3 x 50 mL).
5 Finally, the solvents were removed with vacuum. The 33.34 g of yellow viscous liquid were
6 obtained with a yield of 89 %. *FTIR*: 2987, 2619, 1462, 1643, 2987, 1462, 1369, 1196, 976, 837
7 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 1.37 (t, $J=7.14$ Hz, 9H), 3.13 (s, 3H), 3.35 (s, 3H), 3.45–3-
8 53 (m, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 7.9, 52.2, 55.7, 58.7, 158.3 ppm.

9 *Methyltriethylammonium 2-furoate (2a)*: 2.93 g of 2-furoic acid (26 mmol) were
10 dissolved in 25 mL of methanol, and 25 mL of methanol solution containing 5.00 g (26 mmol) of
11 methyltriethylammonium methyl carbonate (1) were added to the mixture. The reaction occurred
12 with the release of gas. The reaction was kept under constant stirring for 30 min at 40 °C. After
13 reaction completion, the solvents were removed by vacuum evaporation and the product was
14 washed thrice with ethyl acetate (3 x 50 mL). Finally, the synthesized ILs were dried under
15 vacuum. The 5.50 g of the brown-yellow liquid were obtained with a yield of 93 %.

16 *FTIR*: 2979, 1639, 1588, 1482, 1396, 1360, 1005, 922, 805, 725 cm^{-1} . ^1H NMR (300 MHz,
17 CD_3OD): δ 1.22 (t, $J=2.04$ Hz, 9H), 2.85 (s, 3H), 3.22–3.27 (m, 6H), 6.39–6.40 (m, 1H), 6.84 (m,
18 1H), 7.46 (m, 1H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ 8.1, 57.1, 60.3, 112.3, 114.5, 144.9,
19 152.7, 166.6 ppm.

20 *Methyltriethylammonium anthranilate (2b)*: It was prepared by following the same
21 procedure as the one described for methyltriethylammonium 2-furoate, but using 3.57 g (26
22 mmol) of anthranilic acid instead of 2-furoic acid, obtaining 5.90 g of IL as a brown-yellow-
23 waxy liquid with a yield of 90 %. *FTIR*: 3356, 3250, 2981, 1610, 1530, 1363, 1310, 761, 658 cm^{-1} .
24 ^1H NMR (300 MHz, CD_3OD): δ 1.12 (t, $J=2.00$ Hz, 9H), 2.78 (s, 3H), 3.10–3.15 (m, 6H), 6.50
25 (t, $J=6.84$, 1H), 6.59 (d, $J=7.98$, 1H), 7.00 (t, $J=6.87$, 1H), 7.71 (dd, $J_1=7.71$, $J_2=1.65$, 1H) ppm.

1 ^{13}C NMR (75 MHz, CD_3OD): δ 8.1, 57.1, 60.3, 117.0, 117.7, 121.5, 132.3, 132.9, 151.0, 176.0
2 ppm.

3 *Methyltriethylammonium 2-picolinate (2c)*: It was prepared by following the same
4 procedure as the one described for methyltriethylammonium 2-furoate, but using 3.20 g (26
5 mmol) of 2-picolinic acid instead of 2-furoic acid, obtaining 5.45 g of IL as a brown semisolid
6 with a yield of 88 %. FTIR: 3045, 2998, 1610, 1563, 1394, 1047, 839, 744, 708 cm^{-1} . ^1H NMR
7 (300 MHz, CD_3OD): δ 1.15 (t, $J=1.98$ Hz, 9H), 2.80 (s, 3H), 3.15-3.24 (m, 6H), 7.29-7.28 (m,
8 1H), 7.72 (t, $J=6.80$, 1H), 7.86 (d, $J=7.68$ 1H), 8.44 (d, $J=4.11$, 1H) ppm. ^{13}C NMR (75 MHz,
9 CD_3OD): δ 8.1, 57.0, 60.2, 124.9, 126.0, 138.2, 149.6, 156.9, 172.8 ppm.

10 *(2-Hydroxyethyl)trimethylammonium oleate (3)*: 2.90 g of oleic acid (10.27 mmol) were
11 mixed with 2.29 g of choline bicarbonate (13.86 mmol) in 25 mL of ethanol. The reaction
12 occurred at room temperature under constant stirring for 4 h. The solvent was removed by
13 vacuum evaporation and the product was washed thrice with ethyl acetate (3 x 50 mL). Finally, a
14 drying process took place under vacuum at 90 °C for 6 h. A yellowish liquid was obtained with a
15 yield of 95 % (3.63 g). FTIR(cm^{-1}): 3255, 3020, 2921, 2850, 1566, 1466, 1421, 1097, 949, 871,
16 723. ^1H NMR (301 MHz, $\text{acetone-}d_6$) δ 4.67 (m, 2H), 3.40 (m, 2H), 3.10 (s, 9H), 2.85 (m, 6H),
17 2.66 (s, 1H), 1.41 (m, 20H), 0.60 (d, 2H), 0.45 (t, 3H), 0.20 (t, 3H). ^{13}C NMR (76 MHz, Acetone-
18 d_6) δ (ppm): 180.71, 130.67, 130.39, 68.66, 57.63, 56.62, 54.66, 38.98, 32.53, 27.86, 27.70,
19 27.41, 23.25, 18.61, 14.35.

20 *Methylene di-2-furoate (4a)*: methyltriethylammonium 2-furoate (2a) (0.455 g, 2 mmol)
21 was dissolved in dichloromethane (5 mL). The solution was poured into a tube of the Microwave
22 300 Synthesis Reactor from Anton Paar, designed for synthesis and equipped with a stirrer as
23 well as temperature controls. The reaction mixture was kept at 130 °C under stirring at 600 rpm,
24 pressure of 12.1 bar, power of 15 W for 10 min. Once the reaction was finished,
25 dichloromethane was removed under vacuum. The product was dissolved in 20 mL of hot
26 ethanol and filtered over charcoal. The resulting solution was then placed in a freezer (263 K) for

24 h; after this time, crystals of the compound were harvested. White crystals were obtained with a yield of 87 % (0.20 g). *M.p.* 119-121 °C. *FTIR*: 3143, 2999, 2347, 1724, 1472, 1285, 1171, 1057, 968, 785 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 6.16 (s, 2H), 6.53-6.55 (m, 2H), 7.29-7.30 (m, 2H), 7.63-7.64 (m, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 79.3, 112.2, 119.8, 143.4, 147.4, 157.0 ppm.

Methylene dianthranilate (4b): methyltriethylammonium anthranilate (2b) (0.51 g, 2 mmol) was dissolved in dichloromethane (5 mL). The solution was poured into a tube of a Microwave 300 Synthesis reactor from Anton Paar. The reaction mixture was kept at 130 °C under stirring at 600 rpm, pressure of 12.1 bar, and power of 15 W for 10 min; then dichloromethane was removed under vacuum. The product was dissolved in 20 mL of hot ethanol and filtered over charcoal. The resulting solution was then placed in a freezer (263 K) for 24 h; after this time, yellow crystals of the compound were harvested with a yield of 83 % (0.24 g). *M.p.* 103-105 °C. *FTIR*: 3489, 3375, 2977, 2377, 1717, 1613, 1596, 1490, 1297, 1235, 1156, 1037, 995, 743 cm^{-1} . ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 6.12 (s, 2H), 6.53 (t, $J=7.14$, 2H), 6.69 (s, 4H), 6.80 (d, $J=8.25$, 2H), 7.25 (t, $J=7.17$, 2H), 7.74 (d, $J=8.25$, 2H) ppm. ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 79.3, 107.5, 115.0, 116.7, 130.7, 134.8, 152.0, 166.0 ppm.

Methylene di-2-picolinate (4c): methyltriethylammonium 2-picolinate (2c) (0.48 g, 2 mmol) was dissolved in 5 mL of dichloromethane. The reaction mixture was kept at 130 °C in Microwave Synthesis reactor under stirring at 600 rpm, pressure of 12.1 bar, and power of 15 W for 10 min; then dichloromethane was removed under vacuum. The product was dissolved in 20 mL of hot ethanol and filtered over charcoal. The resulting solution was then placed in a freezer (263 K) for 24 h; obtaining a yellow solid with a yield of 81 % (0.21 g). *M.p.* 74-76 °C. *FTIR*: 3437, 3111, 3081, 2923, 2854, 2152, 1737, 1613, 1453, 1282, 1161, 1067, 986, 746, 699, 682 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 6.40 (s, 2H), 7.51-7.53 (m, 2H), 7.85-7.90 (m, 2H), 8.20 (d, $J=7.98$, 2H), 8.80 (d, $J=4.11$, 2H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 81.4, 125.8, 127.5, 137.2, 146.8, 150.1, 163.6 ppm.

1 *Methylene dioleate (4d)*: (2-hydroxyethyl)trimethylammonium oleate (3) (0.52 g, 1.4
2 mmol) was dissolved in dichloromethane (6 mL). The reaction mixture was kept at 130 °C in
3 MW reactor under stirring 600 rpm, pressure of 12.1 bar, and power of 15 W for 20 min; then
4 dichloromethane was removed under vacuum. The product was dissolved in 20 mL of hexane and
5 then placed in a freezer (263 K) for 24 h. The precipitate was filtered and discarded, while the
6 hexane solution was evaporated, obtaining a yellow waxy compound with a yield of 80 % (0.32
7 g). *FTIR*(cm^{-1}): 2921, 2850, 1660, 1566, 1466, 1421. ^1H NMR (300 MHz, CDCl_3): δ 5.74 (d,
8 $J=12.8$ Hz, 2H), 5.33 (m, 4H), 2.19 (t, 4H), 2.0 (d, $J=5.6$ Hz, 8H), 1.56 (m, 4H), 1.28 (d, $J=10.3$
9 Hz, 44H), 0.88 (t, $J=6.6$ Hz, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 172.4, 129.7, 78.9, 31.9,
10 29.3, 27.2, 22.7, 14.1 ppm.

11

12 3. Results and discussion

13 The synthesis methods of the symmetric MDEs can be divided into three groups: 1) the
14 most widely employed is by using methylene chloride derivatives obtained from the
15 corresponding carboxylic acids with thionyl chloride^{26,7,27}; also methylene iodides²⁸ or methylene
16 fluorides²⁹ can be used instead of carboxylic acid methylene chlorides.; 2) by the oxidation
17 method and, finally, 3) by using carboxylic acid salts and methane dihalides with phase transfer
18 catalysts.

19 Formaldehyde or paraformaldehyde can be used in the synthesis of MDEs to form a
20 methylene bridge between the two fragments of carboxylic acids; in this sense, even anhydrides
21 of carboxylic acids^{17,30} can be used instead of carboxylic acid methylene halides; the
22 disadvantages of this method are that the reaction times are above 18 h at 100 °C and the use of a
23 Grignard reagent is needed.

1 An original synthesis method of MDEs through the oxidation of alcohols or amines
2 with benzyltriethylammonium permanganate³¹, however, the formed reaction product is a
3 mixture of MDEs (62 %), chloromethane of the corresponding alcohol (11 %) and non-reacted
4 raw material (18 %), which implies low final MDE yields.

5 Another MDE synthesis method is based on the use of methane dihalides and on sodium,
6 potassium or cesium salts from the corresponding carboxylic acids³². Despite the implementation
7 of available and economic raw materials, this method features the disadvantage of performing
8 the reaction under phase transfer catalytic conditions, which implies the use of catalysts such as
9 polyethylene glycol 600³³, 18-crown-6-ether³⁴, ionic exchange resins of the Amberlite IRA-400³⁵
10 type, and hexamethylphosphoramide³⁶.

11 The preparation method of a symmetrical MDE by mixing benzoic acid, a quaternary
12 amine salt (tetrabutylammonium sulfate) as catalyst and sodium hydroxide under reflux
13 conditions in dichloromethane for 4 days³⁷ lacks of good yields and the reaction times are too
14 long. Notwithstanding, each one of these methods has serious disadvantages such as the use of
15 expensive catalysts, low product yields or long reaction times³⁸. In our previous work, we
16 reported the synthesis of symmetrical methylene dibenzoic esters with a yield of 80 % using
17 trioctylammonium benzoate, obtained from Aliquat 336TM, and silver benzoate³⁹.

18 In this work, we present a new synthesis pathway of symmetrical MDEs from carboxylic ILs
19 obtained from the corresponding methyl carbonate or carbonate ILs using MW energy. The
20 carboxylic ILs were obtained in two stages: the synthesis of methyltriethylammonium methyl
21 carbonate using dimethyl carbonate (DMC) with triethylamine⁴⁰; in the case of
22 methyltriethylammonium 2-furoate (2a), methyltriethylammonium anthranilate (2b) and
23 methyltriethylammonium 2-picolinate (2c) were interchanged by a carboxylic acid as show in
24 Figure 1; in the case of (2-hydroxyethyl)trimethylammonium oleate (3), we started from choline

bicarbonate and oleic acid as show in Figure 2. It is noteworthy that the carbonate anion was derived from a soft acid, which enabled the easy exchange by any desired anion.

Figure 1. Synthesis scheme of methyltriethylammonium ILs (2a-c).

Figure 2. Synthesis scheme of (2-hydroxyethyl)trimethylammonium oleate (3).

The esterification reactions have been extensively explored with the use of MWs⁴¹. The carboxylic ILs interacted as anions with dichloromethane forming MDEs (Figure 3), where the MWs greatly accelerated the course of this reaction by generating charged leaving groups, reducing the reaction time drastically and the use of catalysts was avoided, forming the corresponding MDEs with good yield rates (Table1). In most cases, the reaction times were decreased up to 10 minutes, which shows not only the occurrence of purely thermal effects of the MWs, but also the probable effect of MWs on the position of the transition state along the reaction coordinate axis.

This pathway allows the synthesis of MDEs derived from substituted aromatic carboxylic acids, heterocyclic and alkylic acids, which stems from its versatile features and short reaction times, which even enable the researcher to obtain MDEs with bulky groups.

Figure 3. Synthesis scheme of symmetrical MDEs.

Table 1. Synthesized compounds.

By analyzing the spectra of the obtained MDEs, it can be said that the corresponding preparation method, using ILs as precursors, enables the synthesis of these compounds not only with good yield rates, but also with the right purity. As it can be observed in the NMR spectra of the MDEs, three 1.1-3.5 ppm signals disappeared for proton and 8.1-60.2 ppm for ¹³C from the cationic branch of the ILs and a ¹³C signal at 157-176 ppm corresponding to the carboxylic group. On the

other hand, new signals at 6.12-6.40 ppm for proton and at 79.3 and 81.4 ppm for ^{13}C , which belong to the methylene bridge, can be seen, and another ^{13}C signal at 157-166 ppm corresponds to the ester carbonyl. The same trend prevails in the FTIR spectra, where new characteristic bands of aromatic esters appear at 1717-1737 cm^{-1} and 1235-1285 cm^{-1} , and the bands of the carboxylic acid groups at 1610 cm^{-1} disappeared.

The structures of the MDEs were confirmed by X-ray analysis (Figures 4-7), however, MD-oleate and MD-2-picolinate did not form the crystalline compounds, so it was impossible to confirm their structure by this technique. Crystal data, data collection and structure refinement details, where carbon atoms were treated as riding: $\text{C}-\text{C} = 0.0019 \text{ \AA}$ for methylene di-2-furoate and $\text{C}-\text{C} = 0.0115 \text{ \AA}$ for methylene dianthranilate are summarized in Table 2.

Figure 4. Molecular structure of MDF with atom labels.

Figure 5. Molecular structure of MDA with atom labels.

Figure 6. Crystal packing of MDF.

Figure 7. Crystal packing of MDA.

Table 2. Experimental X-ray details.

The X-ray data indicate that these compounds have symmetrical crystal structures, where MDF crystallized in the monoclinic form, while MDA occurred in the trigonal form (Tables S1-S4). The 5- and 6-member rings remain planar, and carboxyl groups are located in the plane of the corresponding ring, while the methylene group is slightly rotated with respect to the furanoic or anthranilic rings. Selected geometric parameters are summarized in Tables S5-S6.

It is pertinent to note that the geometry of the cycles did not change during the formation of the MDEs, so the $\text{C}_2-\text{C}_1-\text{C}_6$ angle is 119.7° , just like the $\text{N}_1-\text{C}_2-\text{C}_1$ (122.5°) and $\text{N}_1-\text{C}_2-\text{C}_3$ angles (119.7°) are equal to the corresponding angles of the anthranilic acid, while the angles corresponding to $\text{C}_1-\text{C}_7-\text{O}_2$, $\text{C}_1-\text{C}_7-\text{O}_1$, and $\text{C}_8-\text{C}_{14}-\text{O}_3$ and distances between C and O atoms (C_7-

O₁, C₇-O₂, C₁₄-O₃, C₁₄-O₄) slightly increased in comparison with the acid, making the ester group occupy more space than the carboxylic group of the acid⁴³. The same trend exists for MDF, where the angles and distances in the ring are very similar to those of furan; so, in our case, the C(3)-C(4) distance is 1.427 Å and the C(10)-O(6)-C(7) angle is 106.19°; 1.430 and 106.6°, respectively, have been reported in the literature^{44,45}.

The distances of the C-O bonds in the methylene group are 1.43 Å for both cases and are in good agreement with those reported for methylene dibenzoate³⁹. The angles formed by the carbon atom of the methylene group and the vicinal oxygen are equal to 116 Å for MDF, which coincides with methylene dibenzoate. However, for MDA, this distance is 115.2 Å; this slight reduction of the angle can be explained by the hydrogen bond formed between compounds due to interactions between the amine group N—H...O—C and oxygen of the carboxylic group of MDA (Tables S7 and S8). In the crystal, the molecules are linked by the aforesaid interactions, forming the crystal packing, where there are no other significant intermolecular interactions.

4. Conclusions

New symmetrical methylene diesters were obtained with good yields from the reaction between methylene chloride and the corresponding IL with a carboxylic anion under MW reaction, and their structures were confirmed by spectroscopic techniques and X-ray crystallography.

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References

- (1) Maase, M.; Massonne, K. In *Ionic liquids IIIB: Fundamentals, Progress, Challenges, and*

- 1 *Opportunities*; Oxford University Press, 2005; Vol. 902, pp 126–132. doi:10.1021/bk-
2 2005-0902.ch010.
- 3 (2) Maase, M.; Massonne, K.; Halbritter, K.; Noe, R.; Bartsch, M.; Siegel, W.; Stegmann, V.;
4 Flores, M.; Huttenloch, O.; Becker, M. Method for the Separation of Acids From
5 Chemical reaction Mixtures by Means of Ionic Fluids. WO/2003/062171, 2003.
- 6 (3) Olivier-Bourbigou, H.; Favre, F.; Forestière, A.; Hugues, F. In *Green Catalysis*; 2010.
7 doi:10.1002/9783527628698.hgc005.
- 8 (4) Endter, F. *Chemie Ing. Technik* **2004**, 30 (5), 305. doi:10.1002/cite.330300506.
- 9 (5) Phillips, G. W.; Falling, S. N.; Godleski, S. A.; Monnier, J. R. Continuous process for the
10 manufacture of 2,5-dihydrofurans from γ,δ -epoxybutenes. United States patent 5,315,019,
11 1994.
- 12 (6) Koch, P.; Küsters, E. Ionic liquids as solvents in headspace gas chromatography. United
13 States Patent 7,569,149 B2, 2009.
- 14 (7) Heffernan, M. L. .; Dennis, R.; Dorsey, J. M.; Foglesong, R. J.; Jones, M. L.; Ogbu, C. O.;
15 Soukri, M.; Spear, K. L.; Orsini, M. A. Preparation of prodrugs of fused heterocyclic
16 inhibitors of D-amino acid. WO2011017634A2, 2011.
- 17 (8) Paolo, C.; Vittorino, S.; Villani, F. Preparation, testing and formulation of valproic and
18 valproenoic acid esters as anticonvulsants. EP 250997, 1988.
- 19 (9) Korolyov, A.; Dorbes, S.; Azéma, J.; Guidetti, B.; Danel, M.; Lamoral-Theys, D.; Gras,
20 T.; Dubois, J.; Kiss, R.; Martino, R.; Malet-Martino, M. *Bioorganic Med. Chem.* **2010**, 18
21 (24), 8537. doi:10.1016/j.bmc.2010.10.039.
- 22 (10) Rosen, D.; Bloor-Young, D.; Squires, J.; Parkesh, R.; Waters, G.; Vasudevan, S. R.;
23 Lewis, A. M.; Churchill, G. C. *Biochem. Biophys. Res. Commun.* **2012**, 418 (2), 353.

- doi:10.1016/j.bbrc.2012.01.025.
- (11) Conway, S. J.; Thuring, J. W.; Andreu, S.; Kvinlaug, B. T.; Roderick, L. H.; Bootman, M. D.; Holmes, A. B. *Aust. J. Chem.* **2006**, 59 (12), 887. doi.org/10.1071/CH06357
- (12) Nudelman, A.; Rephaeli, A.; Gil-Ad, I.; Abraham, W. Conjugated psychotropic drugs and uses thereof. US Patent 7,939,525 B2, 2011.
- (13) Rephaeli, A.; Waks-Yona, S.; Nudelman, A.; Tarasenko, I.; Tarasenko, N.; Phillips, D. R.; Cutts, S. M.; Kessler-Icekson, G. *Br. J. Cancer* **2007**, 96 (11), 1667. doi:10.1038/sj.bjc.6603781.
- (14) Rephaeli, A.; Entin-Meer, M.; Angel, D.; Tarasenko, N.; Gruss-Fischer, T.; Bruachman, I.; Phillips, D. R.; Cutts, S. M.; Haas-Kogan, D.; Nudelman, A. *Invest. New Drugs* **2006**, 24 (5), 383. doi:10.1007/s10637-006-6213-1.
- (15) Entin-Meer, M.; Rephaeli, A.; Yang, X.; Nudelman, A.; VandenBerg, S. R.; Haas-Kogan, D. A. *Mol. Cancer Ther.* **2005**, 4 (12), 1952. doi:10.1158/1535-7163.
- (16) Nudelman, A.; Levovich, I.; Cutts, S. M.; Phillips, D. R.; Rephaeli, A. *J. Med. Chem.* **2005**, 48 (4), 1042. doi:10.1021/jm049428p.
- (17) Kensler, D. L.; Kohn, G. K.; Walgenbach, D. D. Compositions for preserving crops and animal feedstuffs. US4123552 A, 1978.
- (18) Wu, D.; Qian, X.; Dallas-Pruitt, J. Silicone hydrogel lens with a grafted hydrophilic coating. US 8409599 B2, 2013.
- (19) Linhardt, J. G.; Salamone, J. C.; Ammon, D. M.; Hook, D. J. Polymerizable surfactants use as comonomers in forming ophthalmic devices. US 2006/0134169 A1, 2006.
- (20) Wang, L.; Deng, Y.; Adeerhamite, O.; Shoukuan, F. Preparation of nano-scale microspheres of magnetic acrylic-based-polymers. CN 1328065 A, 2011.

- 1 (21) Kurian, P. V.; Joyce, W. H.; Kin-Tai, C. Block copolymers for recovering hydrocarbon
2 fluids from a subterranean reservoir. US7989401 B2, 2011.
- 3 (22) Seher, J.; Viohl, J. *Dtsch. Zahnarztl. Z.* **1992**, 47, 634.
- 4 (23) Holmes, M. J.; Klaveness, J.; Rongved, P.; Strande, P. Preparation of acylals and analogs
5 for preparation of biolabile crosslinked ultrasound imaging agents. WO 9217213 A1,
6 1992.
- 7 (24) Goff, D. L.; Yuan, E. L.; Proskow, S. Photopolymerizable polyamide ester resin
8 compositions containing an oxygen scavenger. US4414312 A, 1983.
- 9 (25) Okura, H. Thermal-transfer media containing heat-fusible ink. JP 01026494 A, 1989.
- 10 (26) Binderup, E.; Hansen, E. T. *Synth. Commun.* **1984**, 14 (9), 857.
11 doi:10.1080/00397918408075729.
- 12 (27) Horribin, D. F.; Manku, M.; McMordie, A.; Knowles, P.; Redden, P.; Pitt, A. Fatty acid
13 esters as bioactive compounds. WO 1996034855A1, 2001.
- 14 (28) Mal, D.; Jana, A.; Ray, S.; Bhattacharya, S.; Patra, A.; De, S. R. *Synth. Communications*
15 **2008**, 38 (22), 3937. doi:10.1080/00397910802238809.
- 16 (29) Schlosser, M.; Limat, D. *Tetrahedron* **1995**, 51 (20), 5807. doi:10.1016/0040-
17 4020(95)00251-3.
- 18 (30) Sydnese, L. K.; Sandberg, M. *Tetrahedron* **1997**, 53 (37), 12679. doi:10.1016/S0040-
19 4020(97)00789-8.
- 20 (31) Schmidt, J.; Schäfer, H. J. *Angew. Chemie* **1981**, 20 (1), 104. doi:10.1002/anie.198101041
- 21 (32) Benitez, P.; Delgado, A.; Farrera, J.-A.; Ribó, J. M. *Synth. Commun.* **1997**, 27 (10), 1697.
22 doi:10.1080/00397919708004080.

- 1 (33) Kavitate, B. P.; Salunkhe, M.; Wadgaonkar, P. *Synth. Commun.* **1997**, 27 (10), 1703.
2 doi:10.1080/00397919708004081.
- 3 (34) Sukhanov, N. N.; Chetverikov, V. N. *Armyanskii Khimicheskii Zhurnal* **1987**, 40, 323.
- 4 (35) Salunkhe, D. G.; Jagdale, M. H.; Salunkhe, M. M.; Wadgaonkar, P. P. *Bull. des Sociétés*
5 *Chim. Belges* **1987**, 96 (3), 247. doi:10.1002/bscb.19870960311.
- 6 (36) Shaw, J. E.; Kunerth, D. C. *J. Org. Chem.* **1974**, 39 (13), 1968. doi:10.1021/jo00927a048.
- 7 (37) Holmberg, K.; Hansen, B. *Tetrahedron Lett.* **1975**, 16 (27), 2303.
- 8 (38) Klaveness, J.; Strande, P.; Wiggen, U. N. Polymers containing diester units. US5534250
9 A, 1996.
- 10 (39) Likhanova, N.; Lijanov, I.; Morelos-Alvarado, L.; Martínez-García, M.; Hernández-
11 Ortega, S.; Olivares-Xometl, O. *Curr. Org. Chem.* **2013**, 17 (1), 79.
- 12 (40) Yagi, O.; Shimizu, S. *Chem. Lett.* **1993**, 22 (12), 2041.
- 13 (41) R. Martínez-Palou, *Química en Microondas*. 2006, CEM-Publishing, Matthews,
14 N.C., ISBN. 0-9722-2292-1.
- 15 (42) Macrae, C. F.; Bruno, I. J.; Chisholm, J. A.; Edgington, P. R.; McCabe, P.; Pidcock, E.;
16 Rodriguez-Monge, L.; Taylor, R.; Van de Streek, J.; Wood, P. . *J. Appl. Crystallogr.*
17 **2008**, 41, 466. doi:10.1107/S0021889807067908.
- 18 (43) Takazawa, H.; Ohba, S.; Saito, Y. *Acta Crystallogr. Sect. C. Struct. Chem.* **1986**, 42,
19 1880. doi:10.1107/S0108270186090182.
- 20 (44) Bradley, M. K.; Robinson, J.; Woodruff, D. P. *Surf. Sci.* **2010**, 604 (11–12), 920.
21 doi:10.1016/j.susc.2010.02.021.
- 22 (45) Ansari, M. F.; Siddiqui, S. M.; Ahmad, K.; Avecilla, F.; Dharavath, S.; Gourinath, S.;
23 Azam, A. *Eur. J. Med. Chem.* **2016**, 124, 393. doi:10.1016/j.ejmech.2016.08.053.

Figure 1. Synthesis scheme of methyltriethylammonium ILs (2a-c).

Figure 2. Synthesis scheme of (2-hydroxyethyl)trimethylammonium oleate (3).

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Figure 3. Synthesis scheme of symmetrical MDEs.

Figure 4. Molecular structure of MDF with atom labels.

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Figure 5. Molecular structure of MDA with atom labels.

Figure 6. Crystal packing of MDF.

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Figure 7. Crystal packing of MDA.

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Table 1. Synthesized compounds.

IL	IL Structure	MDE Structure	MDE Name
Methyltriethyl ammonium 2-furoate (2a)			Methylene di-2-furoate (4a)
Methyltriethyl ammonium anthranilate (2b)			Methylene dianthranilate (4b)
Methyltriethyl ammonium 2-picolinate (2c)			Methylene di-2-picolinate (4c)
(2-Hydroxyethyl) trimethylammonium oleate (3)			Methylene dioleate (4d)

Structures in the Table 1:

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Table 2. Experimental X-ray details.

Crystal data	Methylene di-2-furoate	Methylene dianthranilate
Chemical formula	C ₁₁ H ₈ O ₆	C ₁₅ H ₁₄ N ₂ O ₄
MW	236.17	286.28
Crystal system, space group	Monoclinic, P 2 ₁ /c	Trigonal, P 3 ₂
Temperature (k)	150	298
Cell angles(°)	$\alpha=90, \beta=90.335, \gamma=90$	$\alpha=90, \beta=90, \gamma=120$
Unit cell dimensions: a, b, c (Å)	9.8738(3), 14.7366(5), 6.9632(2)	17.8996(11), 17.8996(11), 4.1331(3)
V (Å ³)	1013.17(5)	1146.81(16)
D _x , g/cm ³	1.548	1.244
Z	4	3
Radiation type	MoK α	CuK α
Absorption coefficient, μ (mm ⁻¹)	0.129	0.764
Crystal size (mm)/shape	0.279×0.189×0.157/ prism	0.406×0.036×0.027/needle

T _{min} , T _{max}	0.965, 0.980	0.693, 0.754
Index ranges	$-13 \leq h \leq 13, -20 \leq k \leq 20, -9 \leq l \leq 9$	$-2 \leq h \leq 22, -22 \leq k \leq 21, -4 \leq l \leq 4$
Reflections collected	17796	29130
Independent reflections	2709 [$R(\text{int}) = 0.0319$]	3002 [$R(\text{int}) = 0.0720$]
Measurement device	Bruker Smart Apex CCD diffractometer 01-670-01	Bruker D8 Venture geometry diffractometer 208039-01
Max. and min. transmission	0.9803 and 0.9653	0.7542 and 0.6926
Refinement method	Full-matrix least-squares on F^2	
Data/ restraints/ parameters	2709 / 0 / 154	3002 / 7 / 202
Goodness-of-fit on F^2	1.048	1.186
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0392, wR2 = 0.0940$	$R1 = 0.0667, wR2 = 0.1567$

<i>R</i> indices (all data)	<i>R</i> 1 = 0.0494, <i>wR</i> 2 = 0.1023	<i>R</i> 1 = 0.1082, <i>wR</i> 2 = 0.1771
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Computer programs: Data collection: *APEX2* v2012.10.0; cell refinement: *APEX2* v 2012.10.0; data reduction: 8 *SAINT V8.27B*; program(s) used to solve structure: *SHELXS2012*; program(s) used to refine 9 structures: *SHELXL2014/7*. For the analysis and visualization of the structures, we used the program *Mercury 3.8*⁴².

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