ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 6, pp. 936–939. © Pleiades Publishing, Ltd., 2013.
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SHORT COMMUNICATIONS

Synthesis of 2-(2,5-Dihydrofuran-3-yl)-2-oxoethyl Carboxylates

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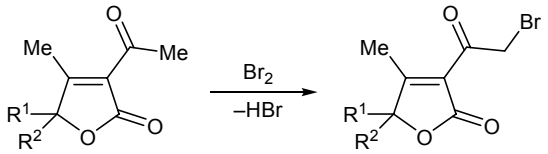
Received July 26, 2012

DOI: 10.1134/S1070428013060262

It is known that compounds containing a γ-lactone ring exhibit a broad spectrum of biological activity [1]. In order to obtain new γ-lactone derivatives containing other pharmacophoric structural fragments we examined the reaction of 3-(2-bromoacetyl)-4,5,5-trialkylfuran-2(5*H*)-ones **IIa** and **IIb** with a number of functionally substituted carboxylic acids. Initial bromoacetylfuranones **IIa** and **IIb** were synthesized by bromination of 3-acetyl derivatives **Ia** and **Ib** [2] with bromine in glacial acetic acid at room temperature (Scheme 1). Molecules **Ia** and **Ib** possess two reaction centers capable of reacting with bromine, acetyl group on C^3 and endocyclic double C=C bond. In the ^{1}H NMR spectra of the products we observed signals at δ 4.52 (**IIa**) and 4.54 ppm (**IIb**) which are typical of $BrCH_2$ protons; this means that the bromination occurred at the acetyl group.

Scheme 1.

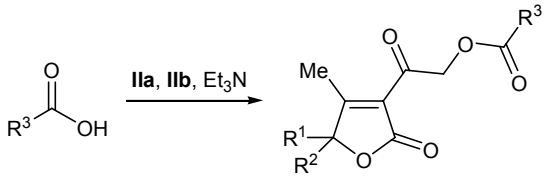


Ia, **Ib** **IIa**, **IIb**

$R^1 = R^2 = Me$ (**a**), $R^1R^2 = (CH_2)_5$ (**b**).

Molecules of some medicines, e.g., nifedipine, furazolidone, and ergocalciferol (vitamin D_2), contain nitrophenyl, furyl, and vinyl fragments [3]. On the other hand, the importance of amino acid derivatives as biologically active substances is beyond doubt. Therefore, as functionally substituted carboxylic acids we used 4-nitrobenzoic, 3-(2-furyl)acrylic, 4-methoxycinnamic, and N-substituted amino acids. The reactions of compounds **IIa** and **IIb** with functionalized carboxylic acids were carried out in boiling acetone in the presence of triethylamine. On the basis of spectral data, the products were assigned the structure of 2-oxo-2-(2-oxo-2,5-dihydrofuran-3-yl)ethyl carboxylates **IIIa**–**IIIr** (Scheme 2).

Scheme 2.



IIIa–**IIIr**

III, $R^3 = 4\text{-}O_2NC_6H_4$, $R^1 = R^2 = Me$ (**a**), $R^1R^2 = (CH_2)_5$ (**b**); $R^3 = 4\text{-}MeOC_6H_4CH{=}CH$, $R^1 = R^2 = Me$ (**c**), $R^1R^2 = (CH_2)_5$ (**d**); R^3 = 2-FuCH=CH, $R^1 = R^2 = Me$ (**e**), $R^1R^2 = (CH_2)_5$ (**f**); $R^3 = 4\text{-}MeOC_6H_4CH{=}C(NHAc)$, $R^1 = R^2 = Me$ (**g**), $R^1R^2 = (CH_2)_5$ (**h**); R^3CO = Phth–Gly–, $R^1 = R^2 = Me$ (**i**), $R^1R^2 = (CH_2)_5$ (**j**); R^3CO = Phth–Ala–, $R^1 = R^2 = Me$ (**k**), $R^1R^2 = (CH_2)_5$ (**l**); R^3CO = Phth–β-Ala–, $R^1 = R^2 = Me$ (**m**), $R^1R^2 = (CH_2)_5$ (**n**); R^3CO = Phth–Val–, $R^1 = R^2 = Me$ (**o**), $R^1R^2 = (CH_2)_5$ (**p**); R^3CO = Phth–Met–, $R^1 = R^2 = Me$ (**q**), $(CH_2)_5$ (**r**); Phth = phthaloyl.

Esters **IIIa**–**IIIr** were tested for antibacterial activity according to the procedure described in [4]. All these compounds displayed a moderate antibacterial activity; however, the activity of **IIIj**, **IIIl**, and **IIIm** approached or even exceeded that of furazolidone used as control.

Thus, our results indicate that 2-oxo-2-(2-oxo-2,5-dihydrofuran-3-yl)ethyl esters derived from functionalized carboxylic acids are promising as potential antibacterial agents.

3-(2-Bromoacetyl)-4,5,5-trialkylfuran-2(5*H*)-ones IIa and IIb (*general procedure*). Compound **Ia** or **Ib**, 0.018 mol, was dissolved in 20 ml of glacial acetic acid containing one drop of 48% hydrobromic

acid, and 0.027 mol of bromine was added dropwise under stirring at such a rate that the temperature did not exceed 20°C. The mixture was then stirred for 30 min, diluted with 30 ml of water, and extracted with chloroform (3×20 ml), and the extract was washed with water (3×20 ml), dried over magnesium sulfate, and evaporated.

3-(2-Bromoacetyl)-4,5,5-trimethylfuran-2(5*H*)-one (IIa). Yield 91%, yellow–green oily substance, R_f 0.77. IR spectrum, ν, cm^{-1}: 1765 (C=O, lactone), 1690 (C=O, ketone), 1610 (C=C). ^1H NMR spectrum, δ, ppm: 1.52 s (6H, 5-CH_3), 2.36 s (3H, 4-CH_3), 4.52 s (2H, CH_2Br). Found, %: C 43.45; H 4.27; Br 32.55. $C_9H_{11}BrO_3$. Calculated, %: C 43.75; H 4.49; Br 32.34.

3-(2-Bromoacetyl)-4-methyl-5,5-pentamethylenefuran-2(5*H*)-one (IIb). Yield 96%, yellow–brown oily substance, R_f 0.81. IR spectrum, ν, cm^{-1}: 1770 (C=O, lactone), 1695 (C=O, ketone), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 1.86–1.28 m (10H, CH_2), 2.38 s (3H, CH_3), 4.54 s (2H, CH_2Br). Found, %: C 50.33; H 5.01; Br 27.91. $C_{12}H_{15}BrO_3$. Calculated, %: C 50.19; H 5.27; Br 27.83.

2-Oxo-2-(2-oxo-2,5-dihydrofuran-3-yl)ethyl carboxylates IIIa–IIIr (*general procedure*). A mixture of 4 mmol of the corresponding carboxylic acid, 4 mmol of compound **IIa** or **IIb**, and 4 mmol of triethylamine in 10 ml of anhydrous acetone was heated for 2–5 h under reflux. The mixture was cooled, diluted with 30 ml of water, and extracted with chloroform (3×20 ml), the extract was washed with a dilute aqueous solution of $NaHCO_3$ and with water, dried over $MgSO_4$, and evaporated, and the residue was reprecipitated from acetone–hexane, 1:4.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 4-nitrobenzoate (IIIa). Yield 88%, mp 176–178°C, R_f 0.81. IR spectrum, ν, cm^{-1}: 1740 (C=O, lactone), 1710 (C=O, ester), 1640 (C=O, ketone), 1610 (C=C), 1540 (NO_2), 1500 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 1.44 s (6H, 5-Me), 2.12 s (3H, 4-Me), 4.50 s (2H, CH_2O), 8.50–8.00 q (4H, H_{arom}). Found, %: C 55.95; H 4.82; N 4.45. $C_{15}H_{15}NO_7$. Calculated, %: C 56.07; H 4.70; N 4.35.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 4-nitrobenzoate (IIIb). Yield 68%, mp 153–155°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 1753 (C=O, lactone), 1720 (C=O, ester), 1655 (C=O, ketone), 1615 (C=C), 1527 (NO_2), 1480 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 1.88–1.26 m (10H, CH_2), 2.40 s (3H, 4-Me), 4.60 s (2H, CH_2O), 8.46–8.00 q (4H, H_{arom}). Found, %: C 66.80; H 5.44; N 3.98. $C_{19}H_{20}NO_5$. Calculated, %: C 66.65; H 5.89; N 4.09.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 3-(4-methoxyphenyl)prop-2-enoate (IIIc). Yield 70%, mp 120–122°C, R_f 0.51. IR spectrum, ν, cm^{-1}: 1760 (C=O, lactone), 1740 (C=O, ester), 1670 (CH=CH), 1615 (C=O, ketone), 1610 (C=C), 1580 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 1.64 s (6H, 5-Me), 2.32 s (3H, 4-Me), 3.70 s (3H, CH_3O), 4.58 s (2H, CH_2O), 7.70–6.65 m (6H, $C_6H_4CH=CH$). Found, %: C 63.93; H 5.74. $C_{17}H_{18}O_5$. Calculated, %: C 64.14; H 5.69.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 3-(4-methoxyphenyl)-prop-2-enoate (IIId). Yield 60%, mp 158–160°C, R_f 0.61. IR spectrum, ν, cm^{-1}: 1757 (C=O, lactone), 1720 (C=O, ester), 1630 (CH=CH), 1618 (C=C), 1602 (C=O, ketone), 1590 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 1.84–1.24 m (10H, CH_2), 2.38 s (3H, 4-Me), 3.80 s (3H, CH_3O), 4.60 s (2H, CH_2O), 7.80–6.82 m (6H, $C_6H_4CH=CH$). Found, %: C 68.99; H 6.05. $C_{22}H_{24}NO_6$. Calculated, %: C 68.74; H 6.29.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 3-(2-furyl)prop-2-enoate (IIIe). Yield 90%, mp 138–140°C, R_f 0.47. IR spectrum, ν, cm^{-1}: 3180–3140 (C–H, furyl), 1745 (C=O, lactone), 1720 (C=O, ester), 1630 (C=O, ketone), 1615 (C=C), 1600 (C=C). ^1H NMR spectrum, δ, ppm: 1.55 s (6H, 5-Me), 2.22 s (3H, 4-Me), 4.40 s (2H, CH_2O), 6.30 d and 6.52 d (1H each, CH=CH), 7.90–7.30 m (3H, Fu). Found, %: C 62.98; H 5.34. $C_{16}H_{16}O_6$. Calculated, %: C 63.15; H 5.29.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 3-(2-furyl)prop-2-enoate (IIIf). Yield 62%, mp 149–151°C, R_f 0.58. IR spectrum, ν, cm^{-1}: 2990–2975 (C–H, furyl), 1755 (C=O, lactone), 1725 (C=O, ester), 1625 (C=O, ketone), 1610 (C=C), 1605 (C=C). ^1H NMR spectrum, δ, ppm: 1.88–1.24 m (10H, CH_2), 2.44 s (3H, 4-Me), 4.52 s (2H, CH_2O), 6.38 d and 6.60 d (1H each, CH=CH), 7.80–7.20 m (3H, Fu). Found, %: C 66.44; H 5.66. $C_{19}H_{20}O_6$. Calculated, %: C 66.27; H 5.85.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 2-acetamido-3-(4-methoxyphenyl)-prop-2-enoate (IIIg). Yield 75%, mp 91–93°C, R_f 0.68. IR spectrum, ν, cm^{-1}: 3370, 3310 (NH), 1670 (C=O, amide), 1755 (C=O, lactone), 1735 (C=O, ester), 1630 (C=O, ketone), 1615 (C=CH), 1610 (C=C), 1520 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 1.62 s (6H, 5-Me), 2.15 s (3H, CH_3CO), 2.35 s (3H,

4-Me), 3.75 s (3H, CH_3O), 4.54 s (2H, CH_2O), 7.33 s (1H, CH=), 7.70–6.75 m (4H, H_{arom}), 9.15 s (1H, **N**H). Found, %: C 62.44; H 5.85; N 3.27. $C_{21}H_{23}NO_7$. Calculated, %: C 62.83; H 5.77; N 3.48.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 2-acetamido-3-(4-methoxyphenyl)prop-2-enoate (IIIh). Yield 72%, mp 123–125°C, R_f 0.56. IR spectrum, ν, cm^{-1}: 3300 (NH), 1690 (C=O, amide), 1753 (C=O, lactone), 1710 (C=O, ester), 1630 (C=O, ketone), 1615 (C=C), 1610 (CH=C), 1510 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.24–1.84 m (10H, (CH_2), 2.06 s (3H, CH_3CO), 2.38 s (3H, 4-Me), 3.82 s (3H, CH_3O), 4.60 s (2H, CH_2O), 7.20 d (1H, CH=), 7.64–6.84 m (4H, H_{arom}), 9.32 s (1H, NH). Found, %: C 65.45; H 5.99; N 3.35. $C_{24}H_{27}NO_7$. Calculated, %: C 65.29; H 6.16; N 3.17.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)acetate (IIIi). Yield 71%, mp 135–136°C, R_f 0.81. IR spectrum, ν, cm^{-1}: 1740 (C=O, lactone), 1710 (C=O, ester), 1650 (C=O, imide), 1640 (C=O, ketone), 1610 (C=C). ^1H NMR spectrum, δ, ppm: 1.62 s (6H, 5-Me), 2.24 s (3H, 4-Me), 4.44 s (2H, CH_2O), 5.17 s (2H, CH_2N), 7.90–7.75 m (4H, H_{arom}). Found, %: C 61.14; H 4.88; N 3.45. $C_{19}H_{17}NO_7$. Calculated, %: C 61.45; H 4.61; N 3.77.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)acetate (IIIj). Yield 82%, mp 157–159°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 1749 (C=O, lactone), 1722 (C=O, ester), 1655 (C=O, imide), 1621 (C=O, ketone), 1608 (C=C). ^1H NMR spectrum, δ, ppm: 1.86–1.24 m (10H, CH_2), 2.38 s (3H, 4-Me), 4.50 s (2H, CH_2O), 5.22 s (2H, CH_2N), 7.96–7.80 m (4H, H_{arom}). Found, %: C 64.38; H 5.07; N 3.52. $C_{22}H_{21}NO_7$. Calculated, %: C 64.23; H 5.15; N 3.40.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propionate (IIIk). Yield 85%, mp 88–89°C, R_f 0.80. IR spectrum, ν, cm^{-1}: 1750 (C=O, lactone), 1715 (C=O, ester), 1655 (C=O, imide), 1650 (C=O, ketone), 1615 (C=C). ^1H NMR spectrum, δ, ppm: 1.18 d (3H, CH_3), 1.58 s (6H, 5-Me), 2.35 s (3H, 4-Me), 4.50 s (2H, CH_2O), 4.95 q (1H, CH), 8.10–7.78 m (4H, H_{arom}). Found, %: C 62.09; H 5.05; N 3.33. $C_{20}H_{19}NO_7$. Calculated, %: C 62.33; H 4.97; N 3.63.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propionate (IIIl). Yield 73%, mp 141–143°C, R_f 0.72. IR spectrum, ν, cm^{-1}: 1753 (C=O, lactone), 1717 (C=O, ester), 1650 (C=O, imide), 1620 (C=O, ketone), 1612 (C=C). ^1H NMR spectrum, δ, ppm: 1.12 d (3H, CH_3), 1.84–1.26 m (10H, (CH_2), 2.44 s (3H, 4-Me), 4.58 s (2H, CH_2O), 5.00 q (1H, CH), 8.00–7.80 m (4H, H_{arom}). Found, %: C 65.10; H 5.22; N 3.38. $C_{23}H_{23}NO_7$. Calculated, %: C 64.93; H 5.45; N 3.29.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propionate (IIIm). Yield 71%, mp 57–58°C, R_f 0.83. IR spectrum, ν, cm^{-1}: 1755 (C=O, lactone), 1735 (C=O, ester), 1650 (C=O, imide), 1630 (C=O, ketone), 1610 (C=C). ^1H NMR spectrum, δ, ppm: 1.57 s (6H, 5-Me), 2.38 s (3H, 4-Me), 3.55 t (2H, CH_2), 3.85 t (2H, CH_2), 4.40 s (2H, CH_2O), 8.15–7.75 m (4H, H_{arom}). Found, %: C 62.15; H 5.14; N 3.48. $C_{20}H_{19}NO_7$. Calculated, %: C 62.33; H 4.97; N 3.63.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 3-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)propionate (IIIn). Yield 70%, mp 151–153°C, R_f 0.68. IR spectrum, ν, cm^{-1}: 1753 (C=O, lactone), 1717 (C=O, ester), 1645 (C=O, imide), 1618 (C=O, ketone), 1610 (C=C). ^1H NMR spectrum, δ, ppm: 1.86–1.24 m (10H, CH_2), 2.42 s (3H, 4-Me), 3.60 t (2H, CH_2), 3.92 t (2H, CH_2), 4.46 q (2H, CH_2O), 8.00–7.70 m (4H, H_{arom}). Found, %: C 65.14; H 5.38; N 3.38. $C_{23}H_{23}NO_7$. Calculated, %: C 64.93; H 5.45; N 3.29.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-methylbutanoate (IIIo). Yield 79%, mp 79–80°C, R_f 0.81. IR spectrum, ν, cm^{-1}: 1745 (C=O, lactone), 1720 (C=O, ester), 1645 (C=O, imide), 1630 (C=O, ketone), 1605 (C=C). ^1H NMR spectrum, δ, ppm: 0.86 d (6H, **Me**$_2$CH), 1.68 s (6H, 5-Me), 1.80 m (1H, Me$_2$C**H**), 2.35 s (3H, 4-Me), 4.44 s (2H, CH_2O), 4.58 d (1H, CHN), 8.20–7.70 q (4H, H_{arom}). Found, %: C 63.66; H 5.88; N 3.21. $C_{22}H_{23}NO_7$. Calculated, %: C 63.91; H 5.61; N 3.39.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-3-methylbutanoate (IIIp). Yield 76%, mp 164–165°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1749 (C=O, lactone), 1720 (C=O, ester), 1660 (C=O, imide), 1614 (C=O, ketone), 1605 (C=C). ^1H NMR spectrum, δ, ppm: 0.80 d (6H, **Me**$_2$CH), 1.84–1.26 m (10H, CH_2), 1.90 m (1H, Me$_2$C**H**), 2.40 s (3H, 4-Me), 4.58 s (2H, CH_2O), 4.60 d (1H, CHN), 8.00–7.70 q (4H$_{arom}$). Found, %: C 66.43; H 5.78; N 3.25. $C_{25}H_{27}NO_7$. Calculated, %: C 66.21; H 6.00; N 3.09.

2-Oxo-2-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-4-(methylsulfanyl)butanoate (IIIq). Yield 83%, mp 66–67°C, R_f 0.80. IR spectrum, ν, cm^{-1}: 1750 (C=O, lactone), 1730 (C=O, ester), 1650 (C=O, imide), 1625 (C=O, ketone), 1610 (C=C), 1450 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.95 q (2H, C**H**$_2$CH), 1.62 s (6H, 5-Me), 2.42 s (3H, 4-Me), 3.52 t (2H, CH_2S), 4.45 s (3H, CH_3S), 4.52 s (2H, CH_2O), 5.12 t (1H, CH), 8.00–7.70 q (4H, H_{arom}). Found, %: C 59.11; H 5.46; N 2.98. $C_{22}H_{23}NO_7S$. Calculated, %: C 59.31; H 5.20; N 3.14.

2-(4-Methyl-2-oxo-5,5-pentamethylene-2,5-dihydrofuran-3-yl)-2-oxoethyl 2-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)-4-(methylsulfanyl)butanoate (IIIr). Yield 84%, mp 139–141°C, R_f 0.67. IR spectrum, ν, cm^{-1}: 1753 (C=O, lactone), 1717 (C=O, ester), 1655 (C=O, imide), 1614 (C=O, ketone), 1605 (C=C), 1460 (C–S). ^{1}H NMR spectrum, δ, ppm: 0.90 q (2H, C**H**$_2$CH), 1.86–1.24 m (10H, CH_2), 2.40 s (3H, 4-Me), 3.58 t (2H, CH_2S), 4.40 s (3H, CH_3S), 4.60 s (2H, CH_2O), 5.08 t (1H, CH), 8.00–7.70 q (4H, H_{arom}). Found, %: C 61.99; H 5.39; N 2.94. $C_{25}H_{27}NO_7S$. Calculated, %: C 61.84; H 5.60; N 2.88.

The IR spectra were recorded on a Nicolet Avatar 330-FT-IR spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were obtained on a Varian Mercury-300 spectrometer at 300 MHz using DMSO-d_6–CCl_4 (1:3) as solvent. TLC analyses were carried out on Silufol UV-254 plates using acetone–chloroform–benzene (1:1:4) and acetone–hexane–ethanol–benzene (1:1:2:4 and 1:1:1:3) as eluents; spots were detected by treatment with iodine vapor.

This study was performed under financial support by the State Science Committee at the Ministry of Education and Science of Armenia (program for support of studies by young scientists 2010, grant no. 11B-1d033).

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