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CHEMISTRY

Synthesis of Novel Spirocyclopropylmalonates and Barbiturates

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Abstract—Alkylidenemalonates have been subjected to dichlorocyclopropanation to produce novel spiro-*gem*-dichlorocyclopropylmalonates in quantitative yields. The latter have been reacted with urea in the presence of sodium ethoxide to produce the corresponding barbiturates in 80–95% yields. The cleavage of the spiro-gem-dichlorocyclopropylmalonate carbocycle with ethanol with the aid of aluminum chloride has led to ethyl ethers, while carbocycle expansion with isobutyraldehyde has afforded polysubstituted tetrahydrofurans. The prepared compounds have been structurally characterized in detail by ^{1}H and ^{13}C NMR spectroscopy.

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Substituted malonates and barbiturates (pyrimidine-2,4,6-triones) exhibit high biological and pharmacological activity and are widely used in medicinal chemistry [1–3]. This work describes the methods of synthesis of spiro-*gem*-dichlorocyclopropylmalonates and the corresponding barbiturates on their basis, which are of considerable interest as NADH dehydrogenase complex inhibitors. The presence of *gem*-dichloromethyl group enhances the biological activity and selectivity of these molecules as compared with the known cyclopropane derivatives [1, 4, 5].

In this work, we carried out the condensation of malonic ester **1** (Scheme 1) with aldehydes **2a** and **2b** to form alkylidenemalonates **3a** and **3b**, which were subjected to dichlorocarbonation for the first time to afford spiro-*gem*-dichlorocyclopropylmalonates **4a** and **4b**. In turn, the latter were used as initial compounds for preparing new spirocyclic barbiturates **5a** and **5b**. The yields of products **4a**, **4b**, **5a**, and **5b** were 80–90% as calculated for malonate **1**.

The cleavage of carbocycle in malonates **4a** and **4b** with ethanol led to ethyl ethers **6a** and **6b** (yield 20–30%). Ring expansion in compounds **4a** and **4b** under the action of isobutyraldehyde **6b** allowed the preparation of polysubstituted tetrahydrofurans **7a** and **7b** (yield 15–20%).

The ^{1}H NMR spectra of compounds **3a** and **3b** confirmed the formation of double bond upon the condensation of diethyl malonate **1** with aldehydes **2a** and **2b**. The proton signal of the methyne group in compound **3a** appears at δ_H 6.95 ppm as a triplet with spin–spin coupling constant $J = 79$ Hz. In compound **3b**, it appears at δ_H 6.75 ppm as a doublet with spin–spin coupling constant $J = 10.5$ Hz. The ^{13}C NMR spectra of compounds **3a** and **3b** display resonances of carbon atoms of the CH groups under consideration at δ_C 149.13 and 154.76 ppm, respectively. The carbon atoms of ethoxycarbonyl groups in compounds **3a** and **3b** show characteristic signals: at δ_C 165.60–168.43 ppm for C=O group, at δ_C 61.09–61.44 ppm for CH_2 group, and at δ_C 14.03–14.07 ppm for CH_3 group.

The ^{1}H NMR spectra of compounds **4a** and **4b** exhibit characteristic proton signal of CH group of *gem*-dichlorocyclopropane ring in the region δ_H 2.41 ppm as a multiplet for **4a** and at δ_H 2.25 ppm as a doublet with spin–spin coupling constant $J = 10.8$ Hz for **4b**. The methyl groups of the isopropyl moiety in compound **4b** display resonances as two doublets at δ_H 0.95 and 1.85 ppm with spin–spin coupling constant $J = 6.6$ Hz, while the CH_3 group of compound **4a** shows a signal at δ_H 0.95 ppm as a triplet with spin–spin coupling constant $J = 7.4$ Hz. The proton signals of ethoxycarbonyl groups in compounds **4a** and **4b** have close chemical shits (the protons of CH_2 groups appear at δ_H 4.25–4.30 ppm as a triplet of doublets with spin–spin coupling constant $J = 2.4$ and 7.2 Hz, the protons of CH_3 groups have δ_H 1.25–1.35 ppm as quadruplet with spin–spin coupling constants $J = 4.5$, 4.8, and 7.2 Hz).

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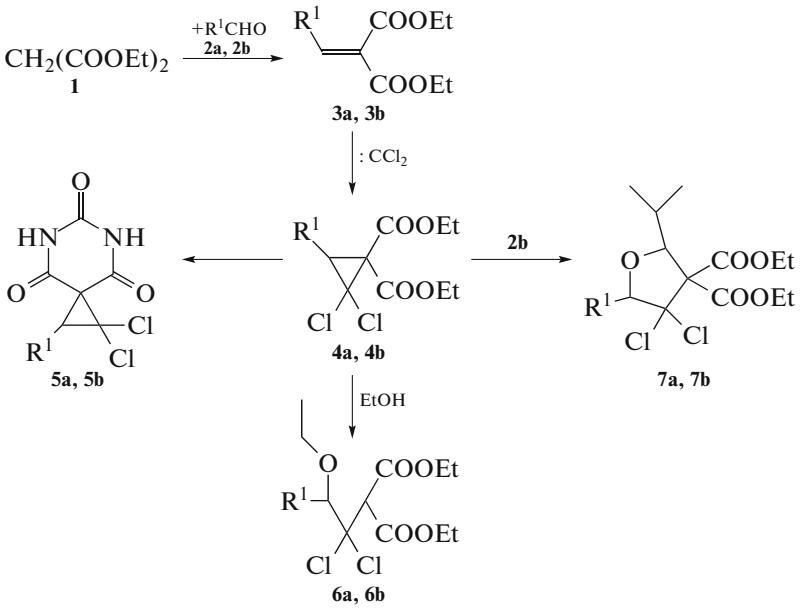


R^1 = Bu (**2a, 3a, 4a, 5a, 6a, 7a**),
R^1 = *i*-Bu (**2b, 3b, 4b, 5b, 6b, 7b**)

Scheme 1.

The ^{13}C NMR spectra of compounds **4a** and **4b** show signals of quaternary carbon atoms (from cyclopropane ring at the CCl_2 group and the carbon atom of the malonic ester moiety) appear in the region δ_C 76.40–76.70 and 52.10–55.60 ppm, respectively. The signal of CH group of this ring displays resonance at δ_C 39.03 for **4a** and at δ_C 46.50 ppm for compound **4b**. The chemical shifts of carbon atoms of ethoxycarbonyl groups for these compounds virtually coincide with the similar signals for compounds **3a** and **3b**.

The data of ^1H and ^{13}C NMR and 2D COSY, HSQC, and HMBC correlation spectra for prepared 5,7-diazaspiro[2.5]octane systems **5a** and **5b** indicate that the *gem*-dichlorocyclopropane ring spiro-fused with the pyrimidine-2,4,6-trione heterocycle persists upon transformations of compounds **4a** and **4b**. This is evidenced by the presence of characteristic signals of the protons and carbon atoms of the *gem*-dichlorocyclopropane ring. The pyrimidine-2,4,6-trione moiety of molecules **5a** and **5b** is confirmed by the presence of two symmetrical C=O groups appeared in ^{13}C NMR spectra as signals at δ_C 167.50 ppm and one C=O group (between two NH groups) at δ_C 148.41 ppm, which is typical for barbiturates **5** [3].

The ^1H NMR spectra of compounds **6a** and **6b** exhibit additional proton signals of the CH_3CH_2O groups (δ_H 1.17 ppm for $\underline{CH_3}CH_2O$ and δ_H 3.60–3.75 ppm for $CH_3\underline{CH_2}O$ protons), which confirms ring cleavage with ethanol in malonates **4a** and **4b**. The signal of the methyne proton at the C(3) atom is observed at 3.05 ppm, while the signal of the proton at the C(1) atom appears as a singlet at 3.73 ppm.

In the ^{13}C NMR spectra of compounds **6a** and **6b**, the signal of the tertiary carbon atom of the CCl_2 group in the cyclopropane ring is shifted downfield (δ_C 88.40 ppm).

The ^1H NMR spectra of compounds **7a** and **7b**, display proton signals typical for isopropyl group. In particular, the proton signal of the methyne group at C(5) of this ring appears in the region δ_H 3.64 and 4.15 ppm for compounds **7a** and **7b**, respectively.

The ^{13}C NMR spectra of compounds **7a** and **7b** exhibit carbon resonances with chemical shifts δ_C 74.29–74.81 ppm for C(1) and δ_C 75.40–76.20 ppm for C(2) of the CCl_2 group, which indicates ring expansion in compounds **4a** and **4b** under the action of isobutyraldehyde **2b**.

Thus, we accomplished the synthesis of previously unknown spiro-*gem*-dichlorocyclopropylmalonates and barbiturates, which are of interest as biologically and pharmacologically active compounds.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300.13 MHz (^1H) and 75.47 MHz (^{13}C) in $CDCl_3$ (D_2O for **5a** and **5b**) using Me_4Si as an internal reference. Mass spectra were obtained on a ThermoFisher

Table 1. ^{1}H and ^{13}C NMR spectra of compounds **3a**, **3b**–**7a**, **7b**

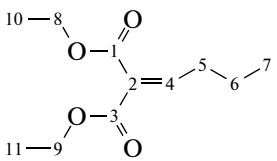
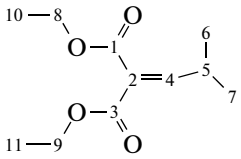
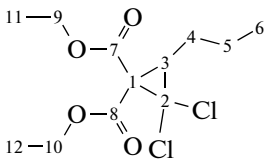
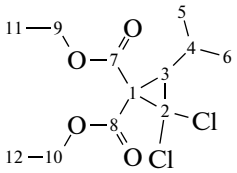
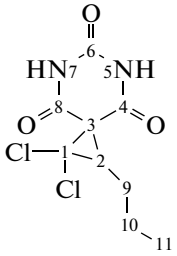
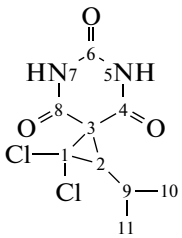
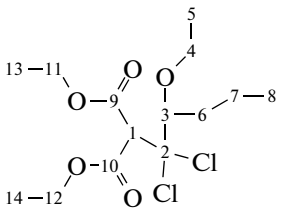
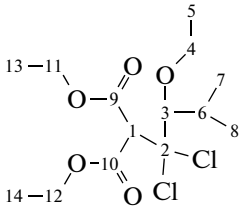
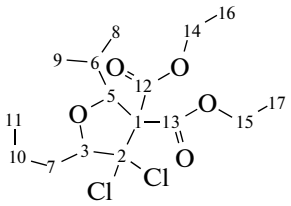
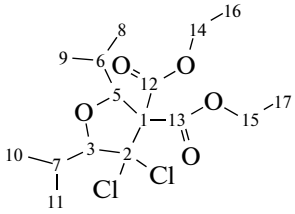
Compound (yield, %)	^{1}H, ppm	^{13}C, ppm	*m/z*, (I_{rel}, %)
3a (95) 	0.90 (t, 3H, C^7H_3, ^3J 7.4), 1.25 (t, 6H, $C^{10}H_3$, $C^{11}H_3$, ^3J 7.1), 1.50 (q, 2H, C^6H_2 ^3J 7.4), 2.25 (q, 2H, C^5H_2 ^3J 7.4; 7.6), 4.15 (q, 4H, C^8H_2, C^9H_2 ^3J 7.1), 6.95 (t, 1H, C^4H_1, ^3J 7.9)	13.03 (C^7), 14.03 (C^8+C^9), 21.56 (C^6), 31.57 (C^5), 61.09 (C^8 + C^9), 128.75 (C^2), 149.13 (C^4), 165.60 (C^1), 168.43 (C^3)	M^+ = 214 (>1), 169 (15), 127 (16), 122 (100), 99 (24), 94 (32), 68 (10), 55 (11), 41(9)
3b (93) 	1.05 (d, 6H, C^6H_3, C^7H_3, ^3J 6.6), 1.25 (t, 6H, $C^{10}H_3$, $C^{11}H_3$, ^3J 7.3), 2.65 (m, 1H, C^5H), 4.15 (q, 4H, C^8H_2, C^9H_2, ^3J 7.1), 6.75 d (1H, C^4H, ^3J 10.5)	14.07 (C^{10}+C^{11}), 21.74 ($C^{6+}C^7$), 29.33 (C^5), 61.44(C^8+C^9), 126.50 (C^2), 154.76 (C^4), 164.60 (C^1), 168.43 (C^3)	M^+ = 214 (>1), 169 (20), 127 (20), 122 (100), 99 (26), 68 (20), 55 (13), 41(9)
4a (90) 	0.95 (t, 3H, C^6H_3, ^3J 7.4), 1.25 (q, 6H, $C^{11}H_3$, $C^{12}H_3$, ^3J 4.5; 4.8; 7.2), 1.50–1.60 (q, 4H, C^4H_2, C^5H_2, ^3J 6.8), 2.41 (m, 1H, C^3H), 4.25 (td, 4H, C^9H_2, $C^{10}H_2$, ^2J 2.4; ^3J 7.2)	13.97 (C^{11} + C^{12}), 21.21 (C^6), 27.96 (C^5), 39.03 (C^4), 40.70 (C^3), 52.10 (C^1), 61.44 (C^9 + C^{10}), 76.40 (C^2), 164.2 (C^{11+12})	M^+ = 285 (absent), 258 (25), 225 (38), 215 (42), 195 (60), 169 (85), 160 (100), 141 (21), 123 (70), 99 (23), 79 (65), 43 (45)
4b (85) 	0.95 (d, 3H, C^5H_3, ^3J 6.6), 1.85 (d, 3H, C^6H_3, ^3J 6.6), 1.35 (q, 6H, $C^{11}H_3$, $C^{12}H_3$, ^3J 4.5; 4.8; 7.2), 2.70 (m, 1H, C^4H), 2.25 (d, 1H, C^3H, ^3J 10.8), 4.30 (td, 4H, C^9H_2, $C^{10}H_2$, ^2J 2.4; ^3J 7.2)	13.90 (C^{11}+C^{12}), 22.21 (C^{5+6}), 26.80 (C^4), 46.50 (C^3), 55.60 (C^1), 61.44 (C^9 + C^{10}), 76.70 (C^2), 164.82 (C^{7+8})	M^+ = 294(absent), 259 (45), 225 (44), 215 (32), 195 (60), 169 (80), 160 (100), 141 (23), 123(73), 99 (24),79 (61), 43(43)
5a (85) 	0.90 (t, 3H, $C^{11}H_3$, ^3J 7.0), 1.30 (dd, 1H, C^9H_a, ^2J 7.3; ^3J 4.8), 1.50 (q, 2H, $C^{10}H_2$, ^3J 7.3), 1.70 (dd, 1H, C^9H_b, ^2J 7.1; ^3J = 4.5), 2.10 (d, 1H, C^2H, ^3J 5.3), 4.60 (br s, NH, H_2O)	13.09 (C^{11}), 21.17 (C^{10}), 28.96 (C^9), 37.36 (C^2), 52.71 (C^3), 84.56 (C^1), 148.41 (C^6), 167.50 (C^{4+8})	–
5b (80) 	1.00 (m, 1H, C^9H), 1.10 (dd, 6H, $C^{10+11}H_3$, ^3J 6.5), 2.20 (d, 1H, C^2H, ^3J 10.8)	21.00 (C^{10+11}), 31.33 (C^9), 53.21 (C^3), 148.41(C^6), 167.50 (C^{4+8})	–
6a (20) 	1.00 (t, 3H, C^8H_3, ^3J 7.0), 1.17 (t, 3H, C^5H_3, ^3J 7.1), 1.30 (t, 6H, $C^{13}H_3$, $C^{14}H_3$, ^3J 7.3), 2.65–2.70 (m, 4H, C^6H_2, C^7H_2), 3.05 (s, 1H, C^3H), 3.60–3.70 (m, 2H, C^4H_2), 3.73 (s, C^1H), 4.15 (q, 4H, $C^{11}H_2$, $C^{12}H_2$, ^3J 7.2)	14.03 (C^8), 14.77 (C^7), 15.00 (C^{13+14}), 21.17(C^6), 33.22 (C^5), 63.61 (C^{11+12}), 64.21 (C^4), 65.33 (C^1), 88.40 (C^2), 102.33 (C^3), 166.21 (C^{9+10})	–

Table 1. (Contd.)

Compound (yield, %)	^{1}H, ppm	^{13}C, ppm	m/z, (I_{rel}, %)
6b (30) 	0.95 (d, 3H, C^7H_3, ^3J 6.6), 0.95 (d, 3H, C^8H_3, ^3J 6.6), 1.30 (t, 6H, $C^{13}H_3$, $C^{14}H_3$, ^3J 7.3), 2.65–2.70 (m, C^6H), 3.05 (s, 1H, C^3H), 3.60–3.71 (m, 2H, C^3H_2), 3.73 (s, C^1H), 4.15 (q, 4H, $C^{11}H_2$, $C^{12}H_2$, ^3J 7.2)	15.00 (C^{13+14}), 22.21 (C^{7+8}), 26.80 (C^6), 33.22 (C^5), 63.61 (C^{11+12}), 64.21 (C^4), 65.33 (C^1), 88.40 (C^2), 102.33 (C^3), 166.21 (C^{9+10})	–
7a (15) 	1.00 (d, 6H, C^8H_3, $C^{11}H_3$, ^3J 8.0), 1.09 (d, 6H, C^9H_3, $C^{10}H_3$, ^3J 8.1), 1.30 (t, 6H, $C^{16}H_3$, $C^{17}H_3$, ^3J 7.0), 1.75 (m, 1H, C^6H), 2.68 (m, 1H, C^7H), 3.64 (d, 1H, C^5H, ^3J 6.4), 4.00 (d, 1H, C^2H, ^3J 6.5), 4.15 (q, 4H, $C^{14}H_2$, $C^{15}H_2$, ^3J 7.1)	14.33 (C^{11}), 15.01 (C^{16+17}), 16.77 (C^{10}), 18.51 (C^{8+9}), 31.21 (C^6), 33.11 (C^7), 65.22 (C^{14+15}), 74.29 (C^1), 75.40 (C^2), 90.33 (C^3), 96.21 (C^5), 167.25 (C^{12+13})	–
7b (20) 	1.00 (d, 6H, C^8H_3, $C^{11}H_3$, ^3J 8.0), 1.09 (d, 6H, C^9H_3, $C^{10}H_3$, ^3J 8.1), 1.30 (t, 6H, $C^{16}H_3$, $C^{17}H_3$, ^3J 7.0), 1.75 (m, 1H, C^6H), 2.68 (m, 1H, C^7H), 4.00 (d, 1H, C^2H, ^3J 6.5), 4.15 (d, 1H, C^5H, ^3J 6.5), 4.15 (q, 4H, $C^{11}H_2$, $C^{12}H_2$, ^3J 7.1)	15.21 (C^{16+17}), 16.77 (C^{8+11}), 18.55 (C^{9+10}), 31.71 (C^{6+7}), 65.77 (C^{14+15}), 74.81 (C^1), 76.20 (C^2), 90.36 (C^3), 96.22 (C^5), 165.35 (C^{12+13})	–

Dash indicates that spectra were not recorded.

Scientific Thermo Finnigan MAT 95 XP high-resolution GC-mass spectrometer system at ionizing voltage 70 eV (ionizing chamber temperature 250°C, direct inlet temperature 50–270°C, heating rate 10 K/min). Gas-liquid chromatography was performed on a Chrom-5 instrument (Laboratory Equipment, Czechoslovakia, column 1.2 m long, 5% SE-30 silicone as a stationary phase) using Chromaton N-AW-DMCS as a sorbent (Ekolan, Russia, 0.16–0.20 mm, working temperature 50–300°C, helium as a carrier gas).

Synthesis of alkylidenemalonates 3a and 3b. A solution of 8 g (0.1 mol) of aldehyde **2a** or **2b**, 16 g (0.1 mol) of diethyl malonate **1**, 0.85 g (0.01 mol) of piperidine, and 1.2 g (0.02 mol) of acetic acid in 40 mL of C_6H_6 was heated at reflux with a Dean–Stark trap for 3 h until water evolution ceased. The resultant mixture was cooled and washed with water until the pH in the solution became neutral, dried with Na_2SO_4, the solvent was removed by rotary evaporation to give 20 g of diethyl butylidenemalonate (**3a**) (yield 95%), bp 101°C (6 mmHg) and 19.7 g of diethyl (2-methylpropylidene)malonate (**3b**) (yield 93%), bp 106°C (6 mmHg).

Dichlorocarbonylation of alkylidenemalonates 3a and 3b were carried out by previously described procedure [6]. Diethyl 2,2-dichloro-3-propylcyclopropane-1,1-dicarboxylate (**4a**), yield 12.6 g (90%), bp 145°C (2 mmHg); diethyl 2,2-dichloro-3-isopropylcyclopropane-1,1-dicarboxylate (**4b**), yield 14 g (85%), bp 154°C (2 mmHg) were obtained.

Synthesis of substituted barbiturates 5a and 5b. Three grams (0.04 mol) of urea was added to a solution of sodium ethoxide prepared by dissolution of 0.5 g (0.024 mol) of sodium in 11 mL of anhydrous ethanol, 2.3 g (0.008 mol) of diethyl 2,2-dichloro-3-propylcyclopropane-1,1-dicarboxylate (**4a**) or 2.3 g of diethyl 2,2-dichloro-3-isopropylcyclopropane-1,1-dicarboxylate (**4b**) was added dropwise with stirring. The mixture was heated under reflux for 4 h until precipitate formed. The mixture was cooled to ambient temperature, the precipitate was separated by filtration, and the filtrate was evaporated. The solid residue was washed with hexane using a Buchner funnel. The resultant powder was dried in air. 1,1-Dichloro-2-propyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (**5a**), yield 1.9 g (85%), mp 149°C; 1,1-dichloro-2-isopropyl-5,7-diazaspiro[2.5]octane-4,6,8-trione (**5b**), yield 1.7 g (80%), mp 151°C.

Cleavage of malonates 4a and 4b with ethyl alcohol. A solution of 1.35 g (0.01 mol) of $AlCl_3$ in 50 mL of methylene chloride was added dropwise with stirring to a mixture of 2.3 g (0.008 mol) of diethyl 2,2-dichloro-3-propylcyclopropane-1,1-dicarboxylate (**4a**) or 2.3 g of diethyl 2,2-dichloro-3-isopropylcyclopropane-1,1-dicarboxylate (**4b**), 0.9 g (0.009 mol) of

ethyl alcohol and 40 mL of methylene chloride and the mixture was stirred at 50°C for 8 h. Next, the reaction mixture was washed with water and extracted with dichloromethane. The organic layers were combined, dried with $MgSO_4$, and the solvent was removed in vacuum. The residue was chromatographed on silica gel (benzene : ethyl acetate = 8 : 2) to give 0.5 g (yield 20%) of diethyl (1,1-dichloro-2-ethoxy-3-methylbutyl)malonate (**6a**), $R_f = 0.44$ and 0.6 g (yield 30%) of diethyl (1,1-dichloro-2-ethoxy-3-methylisobutyl)malonate (**6b**), $R_f = 0.49$.

Cleavage of malonates 4a and 4b with aldehyde 2b. A solution of 1.3 g (0.01 mol) of $AlCl_3$ in 50 mL of methylene chloride was added dropwise to a mixture of 2.3 g (0.008 mol) of diethyl 2,2-dichloro-3-propylcyclopropane-1,1-dicarboxylate (**4a**) or 2.3 g of diethyl 2,2-dichloro-3-isopropylcyclopropane-1,1-dicarboxylate (**4b**), 0.9 g (0.009 mol) of isobutanal **2b**, and 40 mL of methylene chloride and the mixture was stirred at 30°C for 8 h. Next, an aqueous 5% HCl solution was added to pH = 3, and the reaction mixture was extracted with dichloromethane (3 × 8 mL). The organic layers were combined, dried with $MgSO_4$, and the solvent was removed by rotary evaporation. The residue was chromatographed on silica gel (benzene : ethyl acetate = 8 : 2) to give 0.3 g (yield 15%) of diethyl 4,4-dichloro-2,5-diisopropyldihydrofuran-3,3(2*H*)-dicarboxylate (**7a**), $R_f = 0.63$ and 0.5 g (yield 20%) of diethyl 4,4-dichloro-2,5-diisopropyldihydrofuran-3,3(2*H*)-dicarboxylate (**7b**), $R_f = 0.68$.

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