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SYNTHESIS OF SOME TERPENE-ALCOHOL, STEROL, AND PLANT PHENOL ESTERS OF 4,5-DICHLOROISOTHIAZOL-3-CARBOXYLIC ACID

E. A. Dikusar,[1] N. I. Nechai,[1] V. I. Potkin,[1] R. V. Kaberdin,[1] N. G. Kozlov,[1] and N. V. Kovganko[2]

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*Previously unknown esters **1b-14b** were prepared by reaction of cetyl alcohol **1a**, terpene alcohols **2a-6a**, sterols **7a-11a**, and plant phenols **12a-14a** with 4,5-dichloroisothiazol-3-carboxylic acid chloride.*

Key words: synthesis, 4,5-dichloroisothiazol-3-carboxylic acid, sterols, natural alcohols, plant phenols.

Chemical modification of natural compounds by various reagents is an important method for preparing new biologically active compounds. Esterification of 3,4,4-trichloro-3-butenoic acid chloride by sterols, terpene alcohols, and natural phenols was used previously to synthesize the corresponding esters [1]. Our goal was to prepare a series of new derivatives of natural compounds, esters of 4,5-dichloroisothiazol-3-carboxylic acid. We selected this acid for modification because isothiazole derivatives have high biological activity. The expansion of the chemistry of isothiazoles, the vigorous development of synthesis methods, and the study of chemical conversions of their derivatives are driven by the wide range of useful properties found for this class of compounds [2], for example, antimicrobial [3, 4], anti-inflammatory, antithrombic, and anticonvulsive activity [5, 6]. Preparations for treating Alzheimer's disease [7], inhibitors of serine protease [8, 9], and physiologically active compounds that react with glutamine receptors [10] are based on them.

We selected the following natural alcohols for the synthesis: cetyl alcohol (**1a**); terpene alcohols citronellol (**2a**), geraniol (**3a**), (-)-1*R*,2*S*,5*R*-menthol (**4a**), borneol (**5a**), and isoborneol (**6a**); sterols cholesterol (**7a**), β-sitosterol (**8a**), stigmasterol (**9a**), ergosterol (**10a**), and lanosterol (**11a**); and plant phenols eugenol (**12a**), vanillin (**13a**), and vanillal (**14a**). Most of these compounds have some biological activity [11-14]. It should be noted that the biological activity of the carboxylate esters is usually greater than that of the acids themselves and their salts [15]. It can be assumed that the esters prepared from natural alcohols **1a-14a**, which contain known pharmacophoric fragments, and 4,5-dichloroisothiazol-3-carboxylic acid, will have high biological activities. In particular, a synergistic effect should be expected for these compounds owing to the mutual influence of the pharmacophores in the target esters **1b-14b**.

We used a method consisting of the reaction of the appropriate alcohols and phenols **1a-14a** with 4,5-dichloroisothiazol-3-carboxylic acid chloride in absolute diethylether in the presence of pyridine. The advantages of this method are the simplicity of the reaction, the mild conditions, the easy separation of desired products, and the good reproducibility. Starting **1a-14a** were converted to the corresponding esters **1b-14b** in yields of 80-94%.

The structures of **1b-14b** were confirmed by elemental analysis, cryoscopic determination of the molecular weight, and PMR, IR, and UV spectra. The compounds were 98 ± 1% pure according to PMR spectroscopy.

1) Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, 220072, Minsk, ul. Surganova, 13, e-mail: evgen 58@mail.ru; 2) Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, 220141, Minsk, ul. Akad. Kuprevicha, 5/2, e-mail: kovganko@iboch.bas-net.by. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 140-143, March-April, 2003. Original article submitted March 28, 2003.

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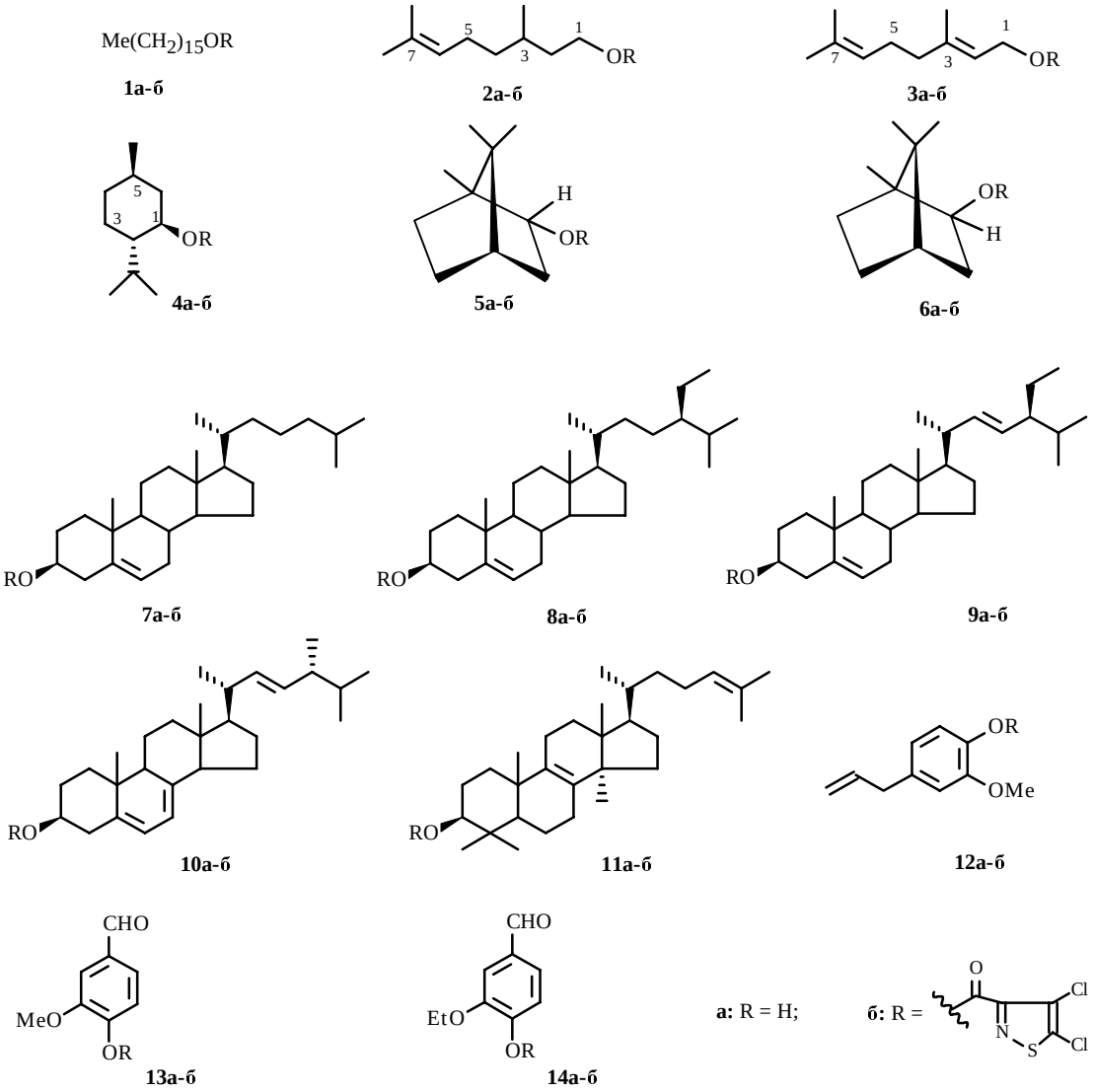

EXPERIMENTAL

IR spectra were recorded on a Protege-460 Fourier-spectrometer in KBr disks (esters **1b** and **4b-14b**) and as thin layers (**2b** and **3b**); PMR spectra, on a Tesla-587A (80 MHz) spectrometer in $CDCl_3$. Chemical shifts were measured relative to TMS. UV spectra were recorded on a Specord UV—Vis instrument using solutions ($1 \cdot 10^{-4}$ M) in *n*-butanol. Molecular weights (M) were determined cryscopically in benzene. Silica gel L 100/160 μm was used for column chromatography with hexane eluent.

4,5-Dichloroisothiazol-3-carboxylic acid [16] and its acid chloride [17] were prepared by the literature methods.

Esters of 4,5-Dichloroisothiazol-3-carboxylic Acid 1b-14b (General Method). A solution of the appropriate alcohol or phenol (**1a-14a**, 10 mmol) in absolute diethylether (50 mL) was treated at 20-23°C with 4,5-dichloroisothiazol-3-carboxylic acid chloride (10 mmol). Pyridine (10 mmol) was added in one portion. The reaction mixture was vigorously shaken and left for 24-36 h at 20-23°C. The precipitate of pyridinium hydrochloride was filtered off. The filtrate was diluted with ether, washed successively with water and sodium bicarbonate solution (5%), and dried over $CaCl_2$. The desiccant was filtered off. The solvent was evaporated. Compounds **1b**, **4b**, and **14b** were purified by low-temperature crystallization from ethanol (96%); esters **2b** and **3b**, by column chromatography over silica gel with elution by hexane.

According to this method we prepared:

1-Hexadecyl Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (1b). Yield 80%, mp 37-38°C. Found (%): C 57.10, H 8.03, Cl 16.50, N 3.18, S 7.34. Cald. for $C_{20}H_{33}C_2NO_2S$ (%): C 56.86, H 7.87, Cl 16.78,N 3.32, S 7.59. M: found 409.7, cald. 422.5. IR spectrum (ν, cm^{-1}): 2955, 2918, 2852 (CH_{Alk}); 1735 (C=O); 1690 (C=C); 1475, 1410, 1356 (CNS); 1223, 1087 (C–O), 981, 940, 860, 840, 742, 718 (CCl). UV spectrum (λ_{max}, ε): 207 (10000), 238 (4000), 271 (5000).

PMR spectrum (δ, ppm, J/Hz): 0.87 (t, ^3J = 5.8, CH_3), 1.15-1.95 [28H, m, $(CH_2)_{14}$], 4.40 (t, ^3J = 7.3, CH_2O).

Citronellol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (2b). Yield 83%, d_{20}^{20} 1.1547, n_{20}^{20} 1.5120. Found (%): C 50.22, H 5.78, Cl 20.86, N 3.95, S 9.44. Cald. for $C_{14}H_{19}Cl_2NO_2S$ (%): C 50.00, H 5.69, Cl 21.09, N 4.17, S 9.54. M: found 328.8, cald. 336.3. IR spectrum (ν, cm^{-1}): 3050 (=CH); 2963, 2925, 2870, 2855 (CH_{Alk}); 1736 (C=O); 1680 (C=C); 1460, 1412, 1377, 1354 (CNS); 1219, 1084 (C–O); 972, 933, 831, 739 (CCl). UV spectrum (λ_{max} ε): 207 (13000), 238 (4000), 270 (5000).

PMR spectrum (δ, ppm, J/Hz): 0.94 (d, ^3J = 5.5, CH_3 on C-3), 1.57 and 1.73 (s, $2CH_3$ on C-7), 4.46 (t, ^3J = 7.6, CH_2-1), 5.08 (dt, ^3J = 6.3, ^4J = 1.1, H-6).

Geraniol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (3b). Yield 88%, d_{20}^{20} 1.1899, n_{20}^{20} 1.5270. Found (%): C 50.42, H 5.24, Cl 20.91, N 4.07, S 9.38. Cald. for $C_{14}H_{17}Cl_2NO_2S$ (%): C 50.31, H 5.13, Cl 21.21, N 4.19, S 9.59. M: found 322.0, cald. 334.3. IR spectrum (ν cm^{-1}): 3055, 3020 (=CH); 2966, 2924, 2856 (CH_{Alk}); 1734 (C=O); 1670 (C=C); 1448, 1409, 1377, 1354 (CNS); 1215, 1082 (C–O); 968, 915, 833, 782, 738 (CCl). UV spectrum (λ_{max}, ε): 206 (19000), 237 (4000), 271 (5000).

PMR spectrum (δ, ppm, J/Hz): 1.57 (s, CH_3 on C-3), 1.65 and 1.73 (s, $2CH_3$ on C-7), 4.91 (d, ^3J = 7.5, CH_2-1), 5.02 (dt, H-6), 5.52 (t, ^3J = 7.5, H-2).

(-)-1*R*,2*S*,5*R*-Menthol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (4b). Yield 84%, mp 47-48°C. Found (%): C 50.13, H 5.86, Cl 20.89, N 3.97, S 9.33. Cald. for $C_{14}H_{19}Cl_2NO_2S$ (%): C 50.00, H 5.69, Cl 21.09, N 4.17, S 9.54. M: found 324.8, cald. 336.3. IR spectrum (ν cm^{-1}): 2960, 2949, 2940, 2919, 2890, 2864, 2847 (CH_{Alk}); 1721 (C=O); 1675 (C=C); 1456, 1405, 1380, 1365, 1352 (CNS); 1219, 1083 (C–O); 976, 954, 912, 851, 737 (CCl). UV spectrum (λ_{max}, ε): 207 (11000), 238 (4000), 270 (5000). PMR spectrum (δ, ppm, J/Hz): 0.83 (d, ^3J = 7.0, CH_3 on C-3), 0.96 [d, ^3J = 7.0, $(CH_3)_2CH$–], 5.05 (dt, $^3J_{aa}$ = 10.2, $^3J_{ae}$ = 4.7, H-1).

Borneol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (5b). Yield 89%, mp 76-77°C. Found (%): C 50.54, H 5.16, Cl 20.92, N 4.02, S 9.44. Cald. for $C_{14}H_{17}Cl_2NO_2S$ (%): C 50.31, H 5.13, Cl 21.21, N 4.19, S 9.59. M: found 325.3, cald. 334.3. IR spectrum (ν, cm^{-1}): 2983, 2955, 2934, 2884, 2870 (CH_{Alk}); 1734, 1718 (C=O); 1485, 1452, 1416, 1389, 1361, 1350 (CNS); 1242, 1018 (C–O); 995, 964, 888, 866, 783, 748, 727 (CCl). UV spectrum (λ_{max}, ε): 207 (10000), 238 (4000), 270 (5000).

PMR spectrum (δ, ppm, J/Hz): 0.93 (s, CH_3), 0.94 (s, CH_3), 0.97 (s, CH_3), 5.18 (ddd, H-2).

Isoborneol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (6b). Yield 86%, mp 56-57°C. Found (%): C 50.57, H 5.18, Cl 20.97, N 4.08, S 9.47. Cald. for $C_{14}H_{17}Cl_2NO_2S$ (%): C 50.31, H 5.13, Cl 21.21, N 4.19, S 9.59. M: found 323.1, cald. 334.3. IR spectrum (ν cm^{-1}): 2981, 2951, 2934, 2877 (CH_{Alk}); 1725 (C=O); 1484, 1455, 1408, 1391, 1357, 1348 (CNS); 1244, 1226, 1049 (C–O); 984, 962, 885, 854, 784, 746 (CCl). UV spectrum (λ_{max}, ε): 207 (10000), 238 (4000), 270 (5000).

PMR spectrum (δ, ppm, J/Hz): 0.90 (s, CH_3), 0.97 (s, CH_3), 1.08 (s, CH_3), 5.00 (t, H-2).

Cholesterol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (7b). Yield 93%, mp 156-157°C. Found (%): C 65.93, H 8.12, Cl 12.34, N 2.29, S 5.51. Cald. for $C_{31}H_{45}Cl_2NO_2S$ (%): C 65.71, H 8.00, Cl 12.51, N 2.47, S 5.66. M: found 543.8, cald. 566.7. IR spectrum (ν cm^{-1}): 3040 (=CH); 2951, 2908, 2868, 2851 (CH_{Alk}); 1731 (C=O); 1670, 1640 (C=C); 1486, 1439, 1406, 1381, 1356 (CNS); 1226, 1082 (C–O); 997, 982, 968, 946, 860, 830, 748 (CCl). UV spectrum (λ_{max}, ε): 208 (13000), 238 (4000), 270 (5000).

PMR spectrum (δ, ppm): 0.64 (s, CH_3-18), 0.80-0.96 (CH_3-21, CH_3-26, CH_3-27), 1.08 (s, CH_3-19), 4.70-5.10 (m, H-3), 5.45 (d, H-6).

***β*-Sitosterol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (8b).** Yield 94%, mp 103-104°C. Found (%): C 66.97, H 8.51, Cl 11.73, N 2.20, S 5.22. Cald. for $C_{33}H_{49}Cl_2NO_2S$ (%): C 66.65, H 8.30, Cl 11.92, N 2.36, S 5.39. M: found 576.4, cald. 594.7. IR spectrum (ν cm^{-1}): 3035 (=CH); 2957, 2940, 2905, 2867 (CH_{Alk}); 1730 (C=); 1670, 1636 (C=); 1466, 1406, 1379, 1356 (CNS); 1227, 1083 (C–O); 998, 983, 860, 835, 743 (CCl). UV spectrum (λ_{max}, ε): 207 (13000), 237 (4000), 270 (5000).

PMR spectrum (δ, ppm): 0.67 (s, CH_3-18), 1.12 (s, CH_3-19), 4.70-5.20 (m, H-3), 5.41 (t, H-6).

Stigmasterol Eter of 4,5-Dchloroisothiazol-3-carboxylic Aid (9b). Yield 92%, mp 170-171°C. Found (%): C 67.12, H 8.13, Cl 11.74, N 2.23, S 5.26. Cald. for $C_{33}H_{47}Cl_2NO_2S$ (%): C 66.87, H 7.99, Cl 11.96, N 2.36, S 5.41. M: found 574.9, cald. 592.7. IR spectrum (ν cm^{-1}): 3040 (=CH); 2954, 2934, 2900, 2867, 2851, 2820 (CH_{Alk}); 1730 (C=O); 1640 (C=O); 1459, 1442, 1408, 1380, 1357 (CNS); 1230, 1084 (C–O); 995, 971, 963, 832, 740 (CCl). UV spectrum (λ_{max}, ε): 206 (20000), 237 (4000), 271 (5000).

PMR spectrum (δ, ppm): 0.72 (s, CH_3-18), 0.74-0.95 (m, $4CH_3$), 1.07 (s, CH_3-19), 4.73-5.20 (m, H-3), 5.05-5.52 (m, H-6, H-22, H-23).

Ergosterol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (10b). Yield 89%, mp 152-153°C. Found (%): C 66.83, H 7.65, Cl 12.13, N 2.18, S 5.31. Cald. for $C_{32}H_{43}Cl_2NO_2S$ (%): C 66.65, H 7.52, Cl 12.30, N 2.43, S 5.56. M: found 559.8, cald. 576.7. IR spectrum (ν cm^{-1}): 3040 (=CH); 2956, 2871 (CH_{Alk}); 1731 (C=O); 1670, 1655, 1637, 1620 (C=C); 1459, 1407, 1382, 1356 (CNS); 1226, 1083 (C–O); 995, 983, 969, 938, 830, 741 (CCl). UV spectrum (λ_{max}, ε): 205 (19000), 263 (11000), 270 (14000), 280 (14000).

PMR spectrum (δ, ppm): 0.63 (s, CH_3-18), 0.75-1.05 (m, $4CH_3$), 1.08 (s, CH_3-19), 4.75-5.20 (m, H-3), 5.10-5.80 (H-6, H-7, H-22, H-23).

Lanosterol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (11b). Yield 88%, mp 104-105°C. Found (%): C 67.62, H 8.32, Cl 11.48, N 2.19, S 5.11. Cald. for $C_{34}H_{49}Cl_2NO_2S$ (%): C 67.31, H 8.14, Cl 11.69, N 2.31, S 5.29. M: found 588.2, cald. 606.7. IR spectrum (ν cm^{-1}): 3050 (=CH); 2950, 2876, 2840 (CH_{Alk}); 1737 (C=O); 1653 (C=C); 1466, 1454, 1394, 1372, 1342 (CNS); 1242, 1084 (C–O); 978, 960, 926, 870, 857, 732 (CCl). UV spectrum (λ_{max}, ε): 205 (20000), 237 (4000), 271 (5000).

PMR spectrum (δ, ppm): 0.71 (s, CH_3), 0.80-1.04 (m, $4CH_3$), 1.06 (s, CH_3), 1.61 and 1.69 (s, CH_3-26, CH_3-27), 4.40-4.70 (m, H-3), 4.70-5.25 (m, H-24).

Eugenol Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (12b). Yield 86%, mp 44-45°C. Found (%): C 49.03, H 3.38, Cl 20.26, N 3.87, S 9.17. Cald. for $C_{14}H_{11}Cl_2NO_3S$ (%): C 48.85, H 3.22, Cl 20.60, N 4.07, S 9.32. M: found 327.8, cald. 344.2. IR spectrum (ν cm^{-1}): 3080, 3070, 3004 (=CH and CH_{Ar}); 2975, 2937, 2920, 2890, 2839 (CH_{Alk}); 1741 (C=O); 1637 (C=C); 1604, 1509 (Ar); 1468, 1451, 1421, 1415, 1401, 1356 (C_3NS); 1324, 1289, 1270, 1202, 1185, 1149, 1120, 1072, 1036 (C–O); 995, 963, 947, 909, 903, 876, 836, 808, 777, 741, 706 (CCl and CH_{Ar}). UV spectrum (λ_{max}, ε): 207 (20000), 222 (10000), 238 (4000), 270 (6000).

PMR spectrum (δ, ppm, J/Hz): 3.41 (d, ^3J = 7.0, CH_2), 3.82 (s, CH_3O), 4.85-5.30 (m, CH_2-), 5.70-6.27 (m, =CH–), 6.65-7.27 (m, 3H-Ar).

Vanillin Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (13b). Yield 83%, mp 163-164°C. Found (%): C 43.62, H 2.25, Cl 21.14, N 3.99, S 9.43. Cald. for $C_{12}H_7Cl_2NO_4S$ (%): C 43.39, H 2.12, Cl 21.37, N 4.22, S 9.65. M: found 316.5, cald. 332.2. IR spectrum (ν cm^{-1}): 3120, 3084, 3055 (CH_{Ar}); 2996, 2973, 2942, 2915, 2869, 2837, 2787, 2742 (CH_{Alk}); 1749, 1685 (C=O); 1665 (C=C); 1601, 1590, 1508, 1468, 1449, 1425, 1397, 1380, 1355, 1318 (CNS and Ar); 1285, 1270, 1185, 1156, 1111, 1087, 1025 (C–O); 963, 854, 864, 839, 819, 781, 741, 707 (CCl and CH_{Ar}). UV spectrum (λ_{max}, ε): 205 (21000), 223 (20000), 259 (13000), 308 (4000).

PMR spectrum (δ, ppm): 3.92 (s, CH_3O), 7.15-7.60 (m, 3H-Ar), 9.94 (s, CHO).

Vanillal Ester of 4,5-Dichloroisothiazol-3-carboxylic Acid (14b). Yield 81%, mp 161-162°C. Found (%): C 45.38, H 2.74, Cl 20.17, N 3.91, S 8.98. Cald. for $C_{13}H_9Cl_2NO_4S$ (%): C 45.10, H 2.62, Cl 20.48, N 4.05, S 9.26. M: found 324.6, cald. 346.2. IR spectrum (ν cm^{-1}): 3115, 3080, 3055 (CH_{Ar}); 2991, 2960, 2939, 2905, 2890, 2870, 2845, 2795, 2755, 2737 (CH_{Alk}); 1750, 1694 (C=O); 1670 (C=C); 1602, 1589, 1508, 1480, 1435, 1398, 1383, 1353, 1316 (CNS and Ar); 1288, 1269, 1185, 1159, 1112, 1072, 1039 (C–O); 975, 966, 954, 867, 839, 819, 786, 742, 709 (CCl and CH_{Ar}). UV spectrum (λ_{max}, ε): 205 (20000), 222 (20000), 258 (12000), 308 (4000). PMR spectrum (δ, ppm, J/Hz): 1.36 (t, ^3J = 7.4, CH_3), 4.18 (q, ^3J = 7.4, CH_2), 7.20-7.65 (m, 3H-Ar), 9.97 (s, CHO).

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