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3,4,4-TRICHLORO-3-BUTENOATES OF CERTAIN TERPENOLS, STEROLS, AND PLANT PHENOLS

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*Esters **1b-15b** were synthesized by reacting terpenols **1a-7a**, sterols **8a-12a**, and plant phenols **13a-15a** with 3,4,4-trichloro-3-butenyl chloride.*

Key words: 3,4,4-trichloro-3-butenoic acid, esters, terpenols, sterols, plant phenols, chemical transformation.

Esterification of hydroxyls in molecules of natural compounds is an important method for increasing their biological activity. Significant success has been achieved in steroid chemistry. For example, such well-known medicinal preparations as testosterone enanthate, 17α-hydroxyprogesterone capronate, cortisone acetate, and deoxycorticosterone trimethylacetate are esters of the corresponding natural steroid hormones [1].

Our goal was to prepare new derivatives of natural compounds as esters of 3,4,4-trichloro-3-butenoic acid. We selected the following natural compounds: terpenols (citronellol **1a**, geraniol **2a**, linalool **3a**, (-)-1*R*,2*R*,5*R*-menthol **4a**, terpineol **5a**, borneol **6a**, and isoborneol **7a**), sterols (cholesterol **8a**, β-sitosterol **9a**, stigmasterol **10a**, ergosterol **11a**, and lanosterol **12a**), and plant phenols (eugenol **13a**, vanillin **14a**, and vanillal **15a**). Most of these compounds are biologically active. On the other hand, it is known that chloro-substituted aliphatic carboxylic acids and their derivatives typically are highly biologically active. Thus, 3,4,4-trichloro-3-butenoic acid acts as a herbicide [2]. Salts of 2,3,4,4-tetrachloro-2-butenoic acid are active bactericides and herbicides [3]. It should be noted that esters of carboxylic acids are usually more biologically active than their acids and salts [4].

Many preparative methods have been proposed for the synthesis of esters. We selected a method that consists of reacting the appropriate alcohols or phenols with 3,4,4-trichloro-3-butenyl chloride in absolute diethylether in the presence of pyridine. The principal advantages of this method are the simplicity of the reaction, the mild conditions, the ease of product isolation, and the good reproducibility. This reaction was used to transform starting alcohols and phenols **1a-15a** into the corresponding esters **1b-15b** in yields of 74-86%.

The structures of the products were found unambiguously using spectral data. In particular, IR spectra of the terpenol and sterol esters **1b-12b** contain at 1730-1745 cm^{-1} bands for ester carbonyl stretchings of the 3,4,4-trichloro-3-butenoates. The IR spectra of phenol esters **13b-15b** have this band at 1750-1770 cm^{-1}. Furthermore, the IR spectra of these compounds have characteristic bands at 1608-1610 cm^{-1} that correspond to stretching of the double bond in 3,4,4-trichloro-3-butenoic acid. The ^{1}H NMR (PMR) spectra of **1b-15b** have signals for the corresponding protons in the starting materials. The position of the signals for protons geminal to the O atoms of the esters is interesting. In particular, the signals for H-3 in PMR spectra of sterol esters **8b-12b** are shifted to weak field by about 1.1 ppm compared with the positions of the analogous protons in the spectra of starting sterols **8a-12a**. This shift is due to acylation of the 3β-hydroxyls in these sterols by 3,4,4-trichloro-3-butenoic acid. The characteristic 2H singlet for CH_2CCl near 3.6 ppm in the PMR spectra is also consistent with the presence of this moiety in **1b-15b**.

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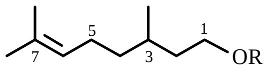
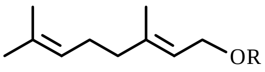
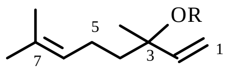


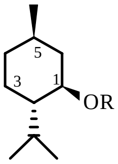
1a-b



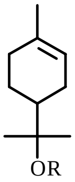
2a-b



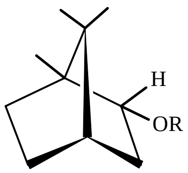
3a-b



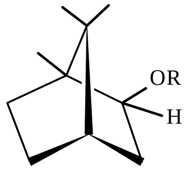
4a-b



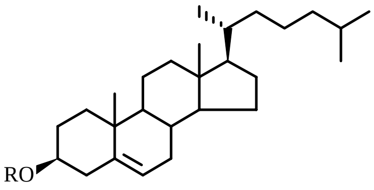
5a-b



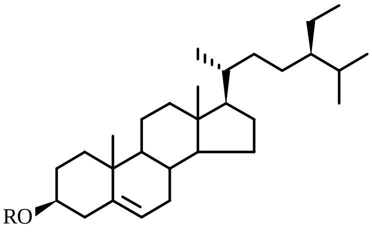
6a-b



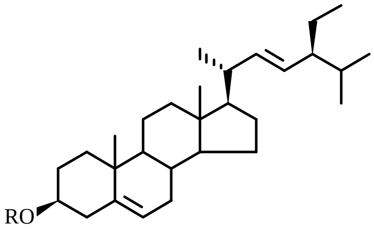
7a-b



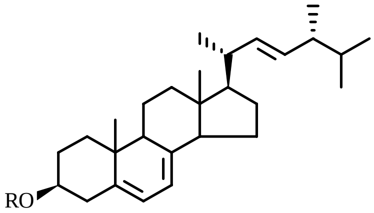
8a-b



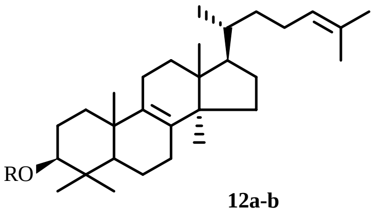
9a-b



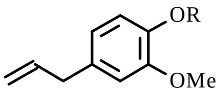
10a-b



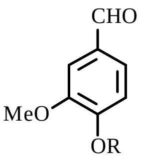
11a-b



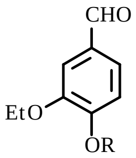
12a-b



13a-b



14a-b



15a-b

a: R = H;
b: R = $COCH_2CCl{=}CCl_2$

It should be noted that most of the starting materials **1a-15a** used by us are applied in practice, in particular, in perfumes and cosmetics [5-8]. Therefore, it can be assumed that there may be compounds with valuable properties among the esters of 3,4,4-trichloro-3-butenoic acid **1b-15b** that we synthesized for the first time. Investigations in this direction are continuing. The results will be published elsewhere.

EXPERIMENTAL

IR spectra were recorded on a Protege-460 Fourier spectrophotometer in KBr disks (**7b-12b**) or as thin layers (**1b-6b**, **13b-14b**); PMR, on a Tesla-567A (100 MHz) spectrometer in $CDCl_3$. Chemical shifts are given on the δ scale with TMS internal stsandard. UV spectra were recorded on a Specord UV-Vis instrument for $1\cdot10^{-4}$ solutions in *n*-butanol. Molecular weights (M) were determined by cryoscopy in benzene. We used neutral aluminum oxide L 40/250 μ with Brockman activity level II for column chromatography.

3,4,4-Trichloro-3-butenoic Acid Esters 1b-15b (General Method). A solution of the appropriate alcohol or phenol (10 mmole) (**1a-15a**) in absolute diethylether (50 mL) was treated at 20-23°C with 3,4,4-trichloro-3-butenyl chloride (10 mmole) using the literature method [9] and then pyridine (10 mmole) in one portion. The reaction mixture was shaken vigorously 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 with water and $NaHCO_3$ solution (5%), and dried over $CaCl_2$. The desiccant was filtered off. The solvent was removed. Compounds **1b-6b** and **13b-14b** were purified by column chromatography over Al_2O_3 with elution by hexane; **7b-12b** and **15b**, by crystallization at low temperature from benzene:hexane.

Using this method, we prepared:

Citronellol 3,4,4-Trichloro-3-butenoate 1b. Yield 80%, d_{20}^{20} 1.0980, n_D^{20} 1.4915. Found (%): C 51.62, H 6.70, Cl 32.15; calc. for $C_{14}H_{21}Cl_3O_2$ (%): C 51.32, H 6.46, Cl 32.46. M: found 311.9; calc. 327.7. IR spectrum (ν, cm^{-1}): 3050 (=C–H); 2964, 2926, 2873, 2855 (CH_{Alk}); 1744 (C=0); 1670, 1610 (C=C); 1456 (CH_2); 1331, 1263, 1181 (C–O); 974, 922 (C–Cl); 768 (=C–H). UV spectrum (λ_{max}, ε): 209 (11000). PMR spectrum (δ, ppm, J/Hz): 0.86 (CH_3 on C-3, d, ^3J = 5.4), 1.05-2.10 (7H, m, C-2—C-5 protons), 1.56 (s, CH_3 on C-7), 1.64 (d, ^4J = 1.2, CH_3 on C-7), 3.57 (s, CH_2CCl), 4.16 (t, ^3J = 7.5, CH_2-1), 5.06 (tq, ^3J = 6.2, CH-6).

Geraniol 3,4,4-Trichloro-3-butenoate 2b. Yield 81%, d_{20}^{20} 1.1657, n_D^{20} 1.5040. Found (%): C 51.81, H 6.04, Cl 32.22; calc. for $C_{14}H_{19}Cl_3O_2$ (%): C 51.63, H 5.88, Cl 32.66. M: found 312.7; calc. 325.7. IR spectrum (ν, cm^{-1}): 3050, 3030 (=C–H); 2967, 2926, 2856 (CH_{Alk}); 1744 (C=0); 1665, 1610 (C=C); 1448 (CH_2); 1324, 1251, 1180 (C–O); 977, 921 (C–Cl); 770 (=C–H). UV spectrum (λ_{max}, ε): 210 (12000). PMR spectrum (δ, ppm): 1.55 (s, CH_3 on C-3), 1.60 (s, $2CH_3$ on C-7), 1.95-2.15 (m, CH_2-4 and CH_2-5), 3.56 (s, CH_2CCl), 4.64 (2H, d, ^3J = 7.4, 2H-1), 5.05 (t, J = 6.2, H-6), 5.29 (t, ^3J = 7.4, H-2).

Linalool 3,4,4-Trichloro-3-butenoate 3b. Yield 83%, d_{20}^{20} 1.1196, n_D^{20} 1.4995. Found (%): C 51.79, H 6.05, Cl 32.40; calc. for $C_{14}H_{19}Cl_3O_2$ (%): C 51.63, H 5.88, Cl 32.66. M: found 314.5; calc. 325.7. IR spectrum (ν, cm^{-1}): 3090, 3050, 3020 (=C–H); 2972, 2929, 2875, 2855 (CH_{Alk}); 1743 (C=O); 1680, 1645, 1610 (C=C); 1451 (CH_2); 1333, 1268, 1171 (C–O); 975, 921 (C–Cl); 870, 835, 765 (=C–H). UV spectrum (λ_{max}, ε): 210 (12000). PMR spectrum (δ, ppm): 1.55 (s, $2CH_3$ on C-7), 1.64 (s, CH_3 on C-3), 1.60-2.05 (m, CH_2-4 and CH_2-5), 3.52 (s, CH_2CCl), 4.95-6.10 (m, CH_2-1, CH-2, CH-6).

(-)-1*R*,2*S*,5*R*-Menthol 3,4,4-Trichloro-3-butenoate 4b. Yield 74%, d_{20}^{20} 1.1473, n_D^{20} 1.4970, $[\alpha]_D^{20}$ -42°. Found (%): C 51.72, H 6.58, Cl 32.11; calc. for $C_{14}H_{21}Cl_3O_2$ (%): C 51.32, H 6.46, Cl 32.46. M: found 319.1; calc. 327.7. IR spectrum (ν, cm^{-1}): 2955, 2925, 2870 (CH_{Alk}); 1746 (C=O); 1610 (C=C); 1455 (CH_2); 1330, 1260, 1180 (C=O); 980, 921 (C–Cl). UV spectrum (λ_{max}, ε): 209 (8000). PMR spectrum (δ, ppm, J/Hz): 0.82 (d, ^3J = 6.5, CH_3 on C-5), 0.95 [d, ^3J = 6.7, $(CH_3)_2CH$–], 3.65 (s, CH_2CCl), 4.78 (dt, $^3J_{aa}$ = 10.1, $^3J_{ae}$ = 4.7, H-1).

Terpineol 3,4,4-Trichloro-3-butenoate 5b. Yield 79%, d_{20}^{20} 1.2549, n_D^{20} 1.5085. Found (%): C 51.94, H 6.11, Cl 32.27; calc. for $C_{14}H_{19}Cl_3O_2$ (%): C 51.63, H 5.88, Cl 32.66. M: found 316.0; calc. 325.7. IR spectrum (ν, cm^{-1}): 3050 (=C–H); 2980, 2960, 2929, 2840 (CH_{Alk}); 1736 (C=O); 1655, 1610 (C=C); 1455, 1445 (CH_2); 1332, 1272, 1180 (C–O); 975, 920 (C–Cl); 765 (=C–H). UV spectrum (λ_{max}, ε): 207 (11000). PMR spectrum (δ, ppm): 1.43 (s, $2CH_3$), 1.61 (s, CH_3), 3.49 (s, CH_2CCl), 5.33 (br.s, C=CH).

Borneol 3,4,4-Trichloro-3-butenoate 6b. Yield 76%, d_{20}^{20} 1.1030, n_D^{20} 1.5065. Found (%): C 51.68, H 6.01, Cl 32.54; calc. for $C_{14}H_{19}Cl_3O_2$ (%): C 51.63, H 5.88, Cl 32.66. M: found 317.4; calc. 325.7. IR spectrum (ν cm^{-1}): 2956, 2880 (CH_{Alk}); 1743 (C=O); 1610 (C=C); 1480, 1470, 1454 (CH_2); 1335, 1263, 1187 (C–O); 972, 923 (C–Cl). UV spectrum (λ_{max}, ε): 209 (8000). PMR spectrum (δ, ppm): 0.80 (s, CH_3), 0.84 (s, CH_3), 0.86 (s, CH_3), 3.59 (s, CH_2CCl), 4.89 (m, H-2).

Isoborneol 3,4,4-Trichloro-3-butenoate 7b. Yield 80%, mp 35-36°C. Found (%): C 51.70, H 5.94, Cl 32.50; calc. for $C_{14}H_{19}Cl_3O_2$ (%): C 51.63, H 5.88, Cl 32.66. M: found 316.3; calc. 325.7. IR spectrum (ν cm^{-1}): 3009, 2988, 2957, 2940, 2876 (CH_{Alk}); 1735 (C=O); 1610 (C=C); 1474, 1454 (CH_2); 1259, 1184 (C–O); 979, 919 (C–Cl). UV spectrum (λ_{max}, ε): 209 (8000). PMR spectrum (δ, ppm): 0.75 (s, CH_3), 0.78 (s, CH_3), 0.91 (s, CH_3), 3.62 (s, CH_2CCl), 4.88 (m, H-2).

Cholesterol 3,4,4-Trichloro-3-butenoate 8b. Yield 83%, mp 94-95°C. Found (%): C 67.04, H 8.71, Cl 18.77; calc. for $C_{31}H_{47}Cl_3O_2$ (%): C 66.72, H 8.49, Cl 19.06. M: found 531.8; calc. 558.1. IR spectrum (ν cm^{-1}): 3035 (=C–H); 2960, 2939, 2909, 2868, 2852 (CH_{Alk}); 1736 (C=O); 1626, 1610 (C=C); 1439 (CH_2); 1333, 1269, 1190 (C–O); 970, 919 (C–Cl); 762 (=C–H); 1467. UV spectrum (λ_{max}, ε): 209 (11000). PMR spectrum (δ, ppm): 0.62 (s, CH_3-18), 1.07 (s, CH_3-19), 3.54 (s, CH_2CCl), 4.45-4.80 (m, H-3), 5.25-5.45 (m, H-6).

***β*-Sitosterol 3,4,4-Trichloro-3-butenoate 9b.** Yield 79%, mp 76-77°C. Found (%): C 67.93, H 8.98, Cl 17.95; calc. for $C_{33}H_{51}Cl_3O_2$ (%): C 67.62, H 8.77, Cl 18.15. M: found 564.2; calc. 586.1. IR spectrum (ν cm^{-1}): 3030 (=C–H); 2958, 2940, 2869, 2851 (CH_{Alk}); 1741 (C=O); 1640, 1608 (C=C); 1466 (CH_2); 1332, 1263, 1190 (C–O); 974, 920 (C–Cl); 765 (=C–H). UV spectrum (λ_{max}, ε): 209 (11000). PMR spectrum (δ, ppm): 0.62 (s, CH_3-18), 1.12 (s, CH_3-19), 3.56 (s, CH_2CCl), 4.45-4.85 (m, H-3), 5.25-5.45 (m, H-6).

Stigmasterol 3,4,4-Trichloro-3-butenoate 10b. Yield 81%, mp 137-138°C. Found (%): C 68.04, H 8.53, Cl 17.98; calc. for $C_{33}H_{49}Cl_3O_2$ (%): C 67.86, H 8.46, Cl 18.21. M: found 566.3; calc. 584.1. IR spectrum (ν cm^{-1}): 3040 (=C–H); 2960, 2942, 2931, 2905, 2880, 2863, 2850 (CH_{Alk}); 1739 (C=O); 1700, 1670, 1610 (C=C); 1470, 1440 (CH_2); 1262, 1255, 1195 (C–O); 970, 918 (C–Cl); 805, 775, 760 (=C–H). UV spectrum (λ_{max}, ε): 209 (12000). PMR spectrum (δ, ppm): 0.62 (s, CH_3-18), 1.05 (s, CH_3-19), 3.57 (s, CH_2CCl), 4.45-4.85 (m, H-3), 4.95-5.45 (m, H-6, H-22, H-23).

Ergosterol 3,4,4-Trichloro-3-butenoate 11b. Yield 77%, mp 160-161°C. Found (%): C 67.89, H 8.13, Cl 18.51; calc. for $C_{32}H_{45}Cl_3O_2$ (%): C 67.66, H 7.98, Cl 18.72. M: found 544.5; calc. 568.1. IR spectrum (ν cm^{-1}): 3045 (=C–H); 2955, 2910, 2840, 2869, 2849 (CH_{Alk}); 1741 (C=O); 1700, 1655, 1610, 1600 (C=C); 1460 (CH_2); 1331, 1202 (C–O); 970, 919 (C–Cl); 835, 760 (=C–H). UV spectrum (λ_{max}, ε): 205 (11000), 258 (5000), 267 (6000), 279 (6000). PMR spectrum (δ, ppm): 0.62 (s, CH_3-18), 1.04 (s, CH_3-19), 3.57 (s, CH_2CCl), 4.45-4.95 (m, H-3), 5.05-6.65 (m, H-6, H-7, H-22, H-23).

Lanosterol 3,4,4-Trichloro-3-butenoate 12b. Yield 82%, mp 115-116°C. Found (%): C 68.45, H 8.72, Cl 17.53; calc. for $C_{34}H_{51}Cl_3O_2$ (%): C 68.27, H 8.59, Cl 17.78. M: found 579.6; calc. 598.1. IR spectrum (ν cm^{-1}): 2949, 2924, 2910, 2882, 2860, 2831 (CH_{Alk}); 1731 (C=O); 1685, 1665, 1610 (C=C); 1470, 1455, 1430 (CH_2); 1319, 1245, 1180 (C–O); 970, 925 (C–Cl); 755 (=C–H). UV spectrum (λ_{max}, ε): 210 (12000). PMR spectrum (δ, ppm): 0.62 (s, CH_3-18), 1.02 (s, CH_3-19), 3.56 (s, CH_2CCl), 4.35-4.65 (m, H-3), 4.90-5.20 (m, H-24).

Eugenol 3,4,4-Trichloro-3-butenoate 13b. Yield 80%, d_{20}^{20} 1.2954, n_D^{20} 1.5510. Found (%): C 50.44, H 4.11, Cl 31.38; calc. for $C_{14}H_{13}Cl_3O_3$ (%): C 50.10, H 3.90, Cl 31.69. M: found 320.7; calc. 335.6. IR spectrum (ν cm^{-1}): 3075, 3060, 3005 (=C–H and CH_{Ar}); 2976, 2938, 2914, 2845 (CH_{Alk}); 1770 (C=O); 1639, 1610 (C=C); 1605, 1508 (Ar); 1464, 1450 (CH_2); 1335, 1269, 1200, 1152, 1121, 1035 (C–O); 973, 920 (C–Cl); 852, 822, 801, 760, 753 (=C–H and CH_{Ar}). UV spectrum (λ_{max}, ε): 208 (20000), 270 (2000), 282 (2000). PMR spectrum (δ, ppm, J/Hz): 3.52 (d, ^3J = 6.7, CH_2Ar), 3.75 (s, CH_3O), 3.82 (s, CH_2CCl), 4.85-5.20 (m, $C{=}CH_2$), 5.65-6.25 (m, C=CH), 6.55-7.00 (m, 3H-Ar).

Vanillin 3,4,4-Trichloro-3-butenoate 14b. Yield 76%, d_{20}^{20} 1.4391, n_D^{20} 1.5745. Found (%): C 44.81, H 3.10, Cl 32.49; calc. for $C_{12}H_9Cl_3O_4$ (%): C 44.55, H 2.80, Cl 32.87. M: found 312.9; calc. 323.6. IR spectrum (ν cm^{-1}): 3070, 3010 (CH_{Ar}); 2975, 2940, 2840, 2740 (CH_{Alk}); 1770, 1700 (C=O); 1610 (C=C); 1602, 1503, 1470, 1423, 1390 (Ar); 1340, 1275, 1200, 1145, 1110, 1030 (C–O); 970, 920 (C–Cl); 870, 830, 810, 780, 735 (CH_{Ar}). UV spectrum (λ_{max}, ε): 204 (13000), 218 (15000), 254 (6000), 306 (3000). PMR spectrum (δ, ppm): 3.90 (s, CH_3O), 3.92 (s, CH_2CCl), 7.18-7.54 (m, 3H-Ar), 9.94 (s, CHO).

Vanillal 3,4,4-Trichloro-3-butenoate 15b. Yield 86%, mp 62-63°C. Found (%): C 46.67, H 3.45, Cl 31.19; calc. for $C_{13}H_{11}Cl_3O_4$ (%): C 46.25, H 3.28, Cl 31.51. M: found 321.6; calc. 337.6. IR spectrum (ν cm^{-1}): 3070 (CH_{Ar}); 2980, 2960, 2935, 2885, 2870, 2845, 2795, 2745 (CH_{Alk}); 1752, 1701 (C=O); 1610 (C=C); 1603, 1589, 1507, 1470, 1445, 1435, 1410, 1399, 1383 (Ar); 1323, 1355, 1290, 1257, 1183, 1158, 1113, 1103, 1039 (C–O); 976, 924 (C–Cl); 869, 804, 789, 773, 745, 730 (CH_{Ar}). UV spectrum (λ_{max}, ε): 204 (14000), 217 (14000), 254 (6000), 307 (4000). PMR spectrum (δ, ppm, J/Hz): 1.37 (t, ^3J = 7.4, CH_3), 3.87 (s, CH_2CCl), 4.10 (q, $\underline{CH_2}Me$), 7.20-7.45 (m, 3H-Ar), 9.89 (s, CHO).

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