Chemistry of Natural Compounds, Vol. 39, No. 3, 2003

1-ADAMANTANECARBOXYLIC ACID ESTERS OF CERTAIN TERPENOLS, STEROLS, AND PLANT PHENOLS

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

UDC 547.82+547.92+547.362

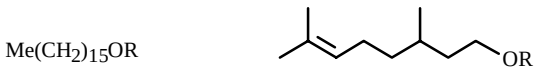
*Esters **1b-15b** were prepared from cetyl alcohol **1a**, terpenols **2a-6a**, sterols **7a-10a**, plant phenols **11a-13a**, and alcohols **14a-15a** by reaction with 1-adamantanecarboxylic acid chloride in the presence of pyridine.*

Key words: terpenols, sterols, phenols, alcohols, 1-adamantanecarboxylic acid, esters.

Adamantane derivatives exhibit a wide spectrum of biological activity. They include compounds with antiviral, curare-like, myorelaxant, anticholinesterase, psychostimulating, neurotropic, and local anesthetic activities [1]. Effective medicinal preparations based on adamantane such as midantanum, memantine, gludantanum, remantadinum, and adaprominum have been produced [2]. New physiologically active compounds are created using the widely applied method of synthesizing analogs of known active compounds, which are obtained by substituting one group in the starting compound by other fragments, in particular, adamantane derivatives [3].

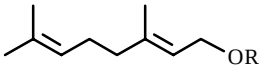
One promising approach to synthesizing new adamantane-containing biologically active compounds is the use of esters, which enables the construction of compounds that contain simultaneously the adamantane pharmacophore [1, 4] and structural elements of terpenols, sterols, and plant alcohols and phenols [5-10].

Our goal was to prepare several new derivatives of natural compounds as esters of 1-adamantanecarboxylic acid. We selected the following natural compounds for the synthesis: cetyl alcohol **1a**, terpenols [citronellol **2a**, geraniol **3a**, (-)-1*R*,2*S*,5*R*-menthol **4a**, borneol **5a**, and isoborneol **6a**], sterols (cholesterol **7a**, β-sitosterol **8a**, lanosterol **9a**, and ergosterol **10a**), plant phenols (eugenol **11a**, vanillin **12a**, and vanillal **13a**), and tetrahydrofurfuryl **14a** and furfuryl **15a** alcohols. The corresponding esters of 1-adamantanecarboxylic acid **1b-15b** were prepared by reacting 1-adamantanecarboxylic acid chloride with alcohols and phenols **1a-15a** in boiling absolute benzene in the presence of pyridine. The yields of the desired products were 77-91%.

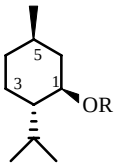


1a-b

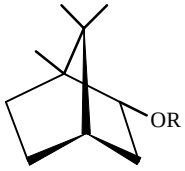
2a-b



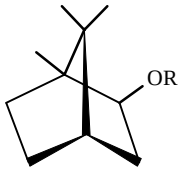
3a-b



4a-b

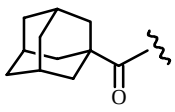


5a-b



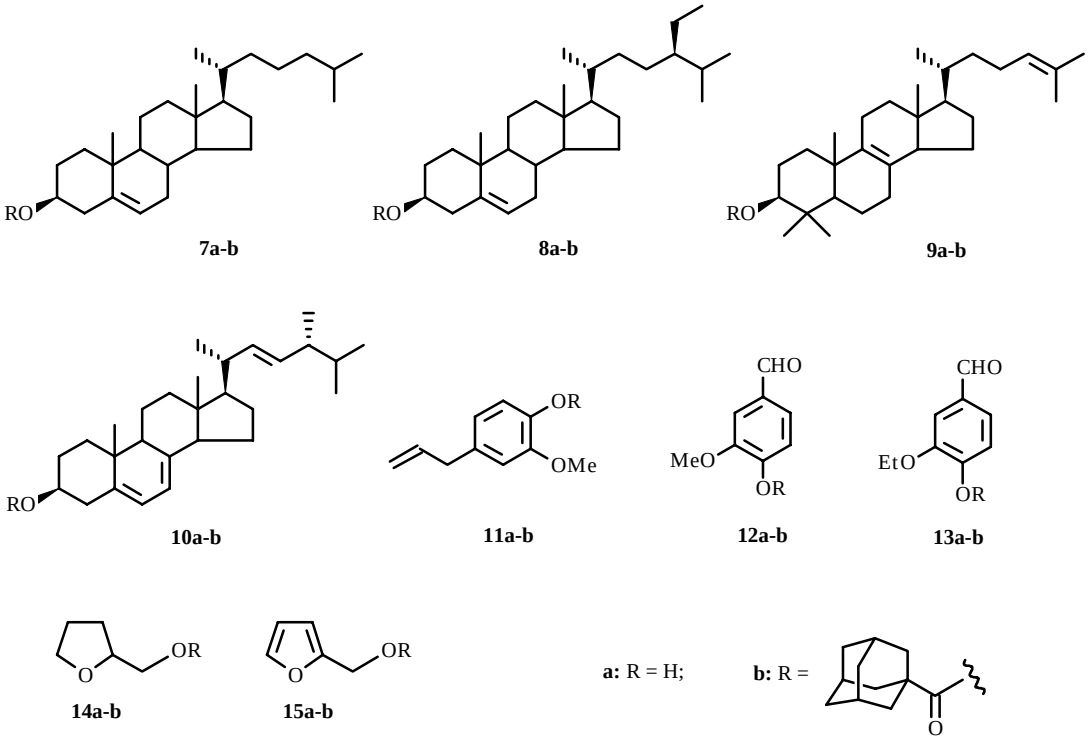
6a-b

a: R = H; **b:** R =



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. 3, pp. 215-218, May-June, 2003. Original article submitted May 13, 2003.

 0009-3130/03/3903-0276$25.00



The structures of **1b**-**15b** were confirmed by elemental analyses, determination of molecular weights, and IR, UV, and PMR spectra. The purity of the products was 98 ± 1%.

EXPERIMENTAL

IR spectra were recorded on a Protege-460 Fourier spectrophotometer in KBr disks (**1b**, **5b**-**13b**) or as thin layers (**2b**-**4b**, **14b**, **15b**). PMR spectra were recorded on a Tesla 587A spectrometer (100 MHz) in $CDCl_3$ solution. Chemical shifts are given in the δ scale with TMS internal standard. UV spectra were recorded on a Specord UV-Vis instrument for solutions ($1 \cdot 10^{-3}$ M) in *n*-butanol. Molecular weights (M) were determined cryoscopically in benzene. Column chromatography used neutral Al_2O_3 L 40/250 μm (Brockman, activity level II).

1-Adamantanecarboxylic acid chloride was prepared by reacting 1-adamantanecarboxylic acid with thionylchloride in benzene by the literature method [4].

1-Adamantanecarboxylic Acid Esters 1b-15b (General Method). A solution of the appropriate alcohol or phenol (**1a-15a**, 10 mmol) in absolute benzene (100 mL) was treated with 1-adamantanecarboxylic acid chloride (10 mmol) and one portion of pyridine (10 mmol). The reaction mixture was refluxed for 10-12 h and cooled to room temperature. The resulting precipitate (pyridinium chloride) was filtered off. The filtrate was washed successively with water and sodium bicarbonate solution (5%) and dried over $CaCl_2$. The desiccant was filtered off. The solvent was removed. Compounds **1b** and **5b-13b** were purified by low-temperature crystallization from ethanol; **2b**-**4b**, **14b**, and **15b**, by column chromatography over Al_2O_3 with elution by hexane.

This method was used to prepare:

1-Hexadecanyl 1-Adamantylmethanoate (1b). Yield 93%, mp 25-26°C. Found (%): C 80.43, H 12.09. Cald. for $C_{27}H_{48}O_2$ (%): C 80.14, H 11.96. M: found 381.5, cald. 404.7. IR spectrum (ν, cm^{-1}): 2925, 2855 (CH_{Alk}); 1730 (C=O); 1470, 1455 (CH_2); 1270, 1235 (C–O). UV spectrum (λ_{max}, ε): 207 (150), 218 (200). PMR spectrum (δ, ppm, J/Hz): 0.89 (t, CH_3), 4.03 (t, ^3J = 6.2, CH_2O).

Citronellyl 1-Adamantylmethanoate (2b). Yield 90%, d_{20}^{20} 1.0216, n_D^{20} 1.4960. Found (%): C 79.34, H 10.93. Cald. for $C_{21}H_{34}O_2$ (%): C 79.19, H 10.76. M: found 306.4, cald. 318.5. IR spectrum (ν, cm^{-1}): 3030 (=CH); 2955, 2907, 2852 (CH_{Alk}); 1727 (C=O); 1618 (C=C); 1453 (CH_2); 1233, 1078 (C–O). UV spectrum (λ_{max}, ε): 204 (4000). PMR spectrum (δ, ppm, J/Hz): 0.94 (d, ^3J = 5.6, CH_3 on C-3), 1.60 and 1.70 (2s, $2CH_3$ on C-7), 4.09 (t, ^3J = 6.4, 2H-1), 4.95-5.25 (m, H-6).

Geraniyl 1-Adamantylmethanoate (3b). Yield 80%, d_{20}^{20} 1.0158, n_D^{20} 1.5025. Found (%): C 80.06, H 10.24. Cald. for $C_{21}H_{32}O_2$ (%): C 79.70, H 10.19. M: found 307.9, cald. 316.5. IR spectrum (ν, cm^{-1}): 3050, 3020 (=CH); 2960, 2907, 2852 (CH_{Alk}); 1727 (C=O); 1676, 1625 (C=C); 1453 (CH_2); 1230, 1074 (C–O). UV spectrum (λ_{max}, ε): 206 (8000). PMR spectrum (δ, ppm, J/Hz): 1.60 (s, CH_3 on C-3), 1.70 (s, $2CH_3$ on C-7), 4.55 (d, ^3J = 6.7, 2H-1), 4.95-5.45 (m, H-2, H-6).

(-)-1*R*,2*S*,5*R*-Menthyl 1-Adamantylmethanoate (4b). Yield 78%, d_{20}^{20} 1.0237, n_D^{20} 1.4990. Found (%): C 79.50, H 10.93. Cald. for $C_{21}H_{34}O_2$ (%): C 79.19, H 10.76. M: found 306.7, cald. 318.5. IR spectrum (ν, cm^{-1}): 2955, 2930, 2907, 2852 (CH_{Alk}); 1726 (C=O); 1453, 1433 (CH_2); 1236, 1079 (C–O). UV spectrum (λ_{max}, ε): 206 (150), 218 (200). PMR spectrum (δ, ppm, J/Hz): 0.74 (d, ^3J = 6.7, CH_3 on C-5), 0.94 (d, ^3J = 6.7, $2CH_3$ on C-8), 4.50-4.80 (m, H-1).

Borneyl 1-Adamantylmethanoate (5b). Yield 82%, mp 176-177°C. Found (%): C 80.03, H 10.25. Cald. for $C_{21}H_{32}O_2$ (%): C 79.70, H 10.19. M: found 303.2, cald. 316.5. IR spectrum (ν, cm^{-1}): 2980, 2955, 2935, 2905, 2850 (CH_{Alk}); 1725 (C=O); 1475, 1453 (CH_2); 1240, 1076 (C–O). UV spectrum (λ_{max}, ε): 206 (150), 218 (200). PMR spectrum (δ, ppm): 0.80 (s, CH_3), 0.86 (s, CH_3), 0.89 (s, CH_3), 4.75-4.93 (m, H-2).

Isoborneyl 1-Adamantylmethanoate (6b). Yield 84%, mp 145-146°C. Found (%): C 80.01, H 10.32. Cald. for $C_{21}H_{32}O_2$ (%): C 79.70, H 10.19. M: found 308.6, cald. 316.5. IR spectrum (ν, cm^{-1}): 3005, 2985, 2955, 2932, 2905, 2850 (CH_{Alk}); 1722 (C=O); 1475, 1453 (CH_2); 1238, 1075 (C–O). UV spectrum (λ_{max}, ε): 206 (150), 218 (200). PMR spectrum (δ, ppm): 0.82 (s, $2CH_3$), 0.97 (s, CH_3), 4.55-4.70 (m, H-2).

Cholesteryl 1-Adamantylmethanoate (7b). Yield 80%, mp 233-234°C. Found (%): C 83.28, H 11.16. Cald. for $C_{38}H_{60}O_2$ (%): C 83.15, H 11.02. M: found 527.1, cald. 548.9. IR spectrum (ν, cm^{-1}): 3035 (=CH); 2935, 2906, 2860, 2850 (CH_{Alk}); 1680 (C=C); 1724 (C=O); 1466, 1452, 1445 (CH_2); 1235, 1078 (C–O). UV spectrum (λ_{max}, ε): 204 (4000). PMR spectrum (δ, ppm): 0.69 (s, CH_3-18), 0.80-1.02 (m, CH_3-21, CH_3-26, CH_3-27), 1.03 (s, CH_3-19), 5.25-5.45 (m, H-6).

***β*-Sitosteryl 1-Adamantylmethanoate (8b).** Yield 90%, mp 205-206°C. Found (%): C 83.44, H 11.31. Cald. for $C_{40}H_{64}O_2$ (%): C 83.27, H 11.18. M: found 558.3, cald. 576.9. IR spectrum (ν, cm^{-1}): 3030 (=CH); 2955, 2933, 2907, 2860, 2851 (CH_{Alk}); 1726 (C=O); 1681 (C=C); 1465, 1452 (CH_2); 1237, 1078 (C–O). UV spectrum (λ_{max}, ε): 204 (5000). PMR spectrum (δ, ppm): 0.69 (s, CH_3-18), 1.03 (s, CH_3-19), 4.35-4.85 (m, H-3); 5.27-5.50 (m, H-6).

Lanosteryl 1-Adamantylmethanoate (9b). Yield 86%, mp 196-197°C. Found (%): C 83.76, H 11.04. Cald. for $C_{41}H_{64}O_2$ (%): C 83.61, H 10.95. M: found 571.4, cald. 589.0. IR spectrum (ν, cm^{-1}): 3030 (=CH); 2980, 2955, 2940, 2911, 2852 (CH_{Alk}); 1714 (C=O); 1679 (C=C); 1465, 1453 (CH_2); 1249, 1082 (C–O). UV spectrum (λ_{max}, ε): 203 (9000), 211 (7000). PMR spectrum (δ, ppm): 0.70 (s, CH_3), 0.85-0.95 (m, $4CH_3$), 1.02 (s, CH_3), 1.55 and 1.63 (s, CH_3-26, CH_3-27), 4.30-4.60 (m, H-3), 4.95-5.25 (m, H-24).

Ergosteryl 1-Adamantylmethanoate (10b). Yield 91%, mp 191-192°C. Found (%): C 84.04, H 10.51. Cald. for $C_{39}H_{58}O_2$ (%): C 83.81, H 10.46. M: found 538.7, cald. 558.9. IR spectrum (ν, cm^{-1}): 3040 (=CH), 2953, 2934, 2906, 2868, 2852 (CH_{Alk}); 1726 (C=O); 1682, 1651 (C=C); 1454 (CH_2); 1239, 1077 (C–O). UV spectrum (λ_{max}, ε): 205 (17000), 260 (7000), 270 (9000), 282 (9000), 294 (6000). PMR spectrum (δ, ppm): 0.64 (s, CH_3), 0.80-1.05 (m, $4CH_3$), 1.09 (s, CH_3), 4.40-4.90 (m, H-3), 5.10-5.75 (m, H-6, H-7, H-22, H-23).

Eugenyl 1-Adamantylmethanoate (11b). Yield 79%, mp 86-87°C. Found (%): C 77.52, H 8.18. Cald. for $C_{21}H_{26}O_3$ (%): C 77.27, H 8.03. M: found 318.3, cald. 326.4. IR spectrum (ν, cm^{-1}): 3070 (=CH); 3055, 3000 (CH_{Ar}); 2970, 2955, 2932, 2905, 2852 (CH_{Alk}); 1742 (C=O); 1640 (C=C); 1605, 1509, 1460, 1450, 1422 (Ar); 1286, 1261, 1219, 1197, 1186, 1149, 1054, 1036 (C–O); 909, 842 (CH_{Ar}). UV spectrum (λ_{max}, ε): 207 (14000), 218 (8000), 272 (3000), 281 (3000). PMR spectrum (δ, ppm, J/Hz): 3.35 (d, ^3J = 6.7, CH_2), 3.79 (s, CH_3O), 4.90-5.25 (m, $=CH_2$), 5.70-6.25 (m, =CH), 6.60-7.00 (m, $3H_{Ar}$).

Vanillinyl 1-Adamantylmethanoate (12b). Yield 79%, mp 118-119°C. Found (%): C 72.71, H 7.11. Cald. for $C_{19}H_{22}O_4$ (%): C 72.59, H 7.05. M: found 303.1, cald. 314.4. IR spectrum (ν, cm^{-1}): 3080, 3005 (CH_{Ar}); 2970, 2934, 2905, 2895, 2855, 2825 (CH_{Alk}); 1743, 1696 (C=O); 1601, 1593, 1508, 1469, 1454, 1425, 1379 (Ar); 1325, 1289, 1262, 1215, 1200, 1175, 1155, 1109, 1045 (C–O); 865, 850, 784, 760, 730, 675 (CH_{Ar}). UV spectrum (λ_{max}, ε): 205 (9000), 223 (14000), 260 (8000), 308 (3000). PMR spectrum (δ, ppm): 3.89 (s, CH_3O), 7.10-7.55 (m, $3H_{Ar}$), 9.94 (s, CHO).

Vanillalyl 1-Adamantylmethanoate (13b). Yield 81%, mp 106-107°C. Found (%): C 73.29, H 7.43. Cald. for $C_{10}H_{24}O_4$ (%): C 73.15, H 7.37. M: found 321.5, cald. 328.4. IR spectrum (ν, cm^{-1}): 3070, 3050, 2995 (CH_{Ar}); 2980, 2909, 2852, 2825 (CH_{Alk}); 1752, 1702 (C=O); 1601, 1585, 1506, 1475, 1455, 1430, 1395, 1380 (Ar); 1325, 1290, 1263, 1210, 1198, 1180, 1157, 1115, 1100, 1038 (C–O); 860, 850, 790, 780, 760, 740, 675 (CH_{Ar}). UV spectrum (λ_{max}, ε): 205 (9000), 224 (13000), 260 (8000), 309 (3000). PMR spectrum (δ, ppm, J/Hz): 1.41 (t, ^3J = 7.3, CH_3), 4.12 (q, ^3J = 7.3, CH_2), 7.10-7.55 (m, $3H_{Ar}$), 9.93 (s, CHO).

Tetrahydrofurfuryl 1-Adamantylmethanoate (14b). Yield 79%, d_{20}^{20} 1.0171, n_D^{20} 1.5085. Found (%): C 73.02, H 9.26. Cald. for $C_{16}H_{24}O_3$ (%): C 72.69, H 9.15. M: found 248.8, cald. 264.4. IR spectrum (ν, cm^{-1}): 2955, 2940, 2906, 2852 (CH_{Alk}); 1728 (C=O); 1453 (CH_2); 1268, 1234, 1184, 1104, 1074, 1021 (C–O). UV spectrum (λ_{max}, ε): 215 (100). PMR spectrum (δ, ppm): 1.50-2.25 [19H, m, $(CH_2)_2$ and $C_{10}H_{15}$], 3.60-4.40 (m, –CHO– and $2CH_2O$).

Furfuryl 1-Adamantylmethanoate (15b). Yield 77%, d_{20}^{20} 1.0510, n_D^{20} 1.5240. Found (%): C 74.09, H 7.93. Cald. for $C_{16}H_{20}O_3$ (%): C 73.82, H 7.74. M: found 251.1, cald. 260.3. IR spectrum (ν, cm^{-1}): 3150, 3120 (CH_{Ar}); 2940, 2907, 2852 (CH_{Alk}); 1727 (C=O); 1678, 1656 (C=C); 1503, 1453 (Ar); 1323, 1268, 1230, 1184, 1152, 1103, 1069, 1016, 980, 955, 921 (C–O); 815, 741, 675, 600 (CH_{Ar}). UV spectrum (λ_{max}, ε): 218 (7000). PMR spectrum (δ, ppm): 1.55-2.15 (15H, m, $C_{10}H_{15}$), 5.02 (2H, s, CH_2O), 6.25-6.40 [m, 2(–CH=)], 7.35-7.45 (m, =CHO–).

ACKNOWLEDGMENT

We thank the Belorussian Republic Foundation for Basic Research (Grant X 03-079), INTAS (Grant 99-00806), and INTERBIOSCREEN (Moscow) for supporting the work.

REFERENCES

1. I. S. Morozov, V. I. Petrov, and S. A. Sergeeva, *Pharmacology of Adamantanes* [in Russian], Volgograd Medical Academy, Volgograd (2001).
2. M. D. Mashkovskii, *Medicinal Preparations* [in Russian], Novaya Volna, Moscow (2001), Vols. 1 and 2.
3. O. N. Zefirova, E. V. Selyunina, N. V. Averina, N. V. Zyk, and N. S. Zefirov, *Zh. Org. Khim.*, **38**, No. 8, 1176 (2002).
4. E. I. Bagrii, *Adamathanes: Preparation, Properties, Applications* [in Russian], Nauka, Moscow (1989).
5. V. A. Pentegova, Zh. V. Dubovenko, V. A. Raldugin, and E. N. Shmidt, *Terpenoids of Coniferous Plants* [in Russian], Nauka, Novosibirsk (1987).
6. V. M. Nikitin, *Chemistry of Terpenes and Resinous Acids* [in Russian], Goslesbumizdat, Moscow and Leningrad (1952).
7. L. M. Shulov and L. A. Kheifits, *Fragrances and Intermediates of the Perfume—Cosmetic Industry, Handbook* [in Russian], Agropromizdat, Moscow (1990).
8. Y. Shaikh, *Specialty Aroma Chemicals in Flavors and Fragrances*, Allured Publishing Corp., Carlo Stream, Illinois (2002).
9. L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publ. Corp., New York (1959).
10. F. J. Zeelen, *Medicinal Chemistry of Steroids*, Elsevier Science Publ., Amsterdam et al. (1990).