SYNTHESIS OF TERTIARY AMIDOMETHYL DERIVATIVES OF 2-ISOBORNYL-4-METHYLPHENOL

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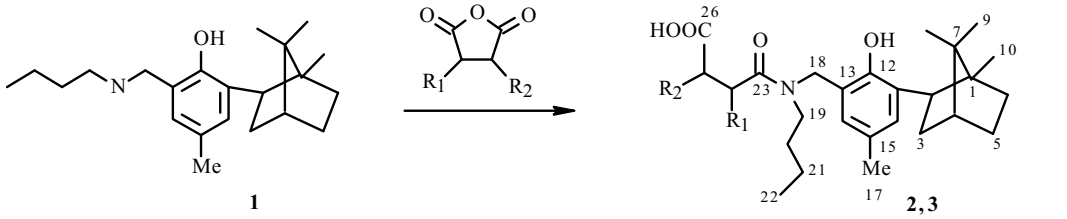
*Derivatives containing tertiary amidomethyl groups were prepared by reaction of a secondary aminomethyl derivative of 2-isobornyl-4-methylphenol with succinic and phthalic anhydrides and (*1S*)-camphanic acid chloride.*

Keywords: terpenophenols, tertiary amides, anhydrides, (*1S*)-camphanic acid chloride, diastereomers.

Terpenophenols are known to have a broad spectrum of physiological activity [1]. It was shown recently that phenols with an isobornyl substituent exhibit antithrombogenic and antithrombocytic activities [2] and are used as local infection agents [3].

Amides are natural compounds with varied and exceedingly effective biological activity [4]. The amide group often acts as a linker for binding various structural fragments in order to create new biological molecules [5].

In continuation of research on the preparation of terpenophenol derivatives, we synthesized new tertiary amides via nucleophilic substitution at a carbonyl C atom. Reaction of the previously synthesized secondary aminomethyl derivative of 2-isobornyl-4-methylphenol (**1**) [6] with equimolar amounts of succinic and phthalic anhydrides produced in quantitative yields the corresponding amides **2** and **3**.

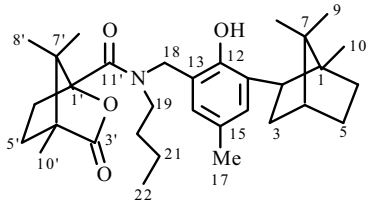


1 **2, 3**

2: $R_1 = R_2 = H$; **3:** R_1-R_2 =

IR spectra of the synthesized derivatives **2** and **3** contained in the range 1610–1620 cm^{-1} an absorption band characteristic of tertiary amides. The ^{13}C NMR spectra of these same compounds had resonances at weak field that were characteristic for C atoms of two C=O groups (170–180 ppm).

Reaction of **1** with optically active (1*S*)-camphanic acid chloride in the presence of triethylamine produced in 90% yield amide **4**, which was a mixture of diastereomers **4′** and **4″** in a 1:1 ratio (according to PMR spectroscopy). The different chromatographic mobility as determined by TLC enabled a partial separation of this mixture by column chromatography and the isolation from it of one of the diasteromers with >95% diastereomeric purity.



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A peculiarity of the diastereomers of **4** was the inequivalence of resonances for certain protons in the PMR spectra. Thus, this inequivalence for the methylene protons of CH_2-18, which links the terpenophenol and amide groups, consisted of a substantial difference of the chemical shifts (4.24 and 4.70 ppm for one diastereomer; 4.40 and 4.58, for the second).

Thus, new tertiary amidomethyl derivatives of terpenophenol were prepared. The isobornylphenol derivative was partially separated into diastereomers.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance II spectrometer (operating frequency 300 MHz and 75 MHz, respectively). IR spectra were recorded in thin layers on an IR-Fourier IR Prestige 21 spectrometer (Shimadzu). Melting points were determined on a Kofler block. The course of reactions was monitored by TLC on Sorbfil plates. Benzene was dried over $CaCl_2$ and distilled over metallic sodium. We used petroleum ether (bp 65–70°C). Diethylether was freshly distilled. Column chromatography used silica gel (Alfa Aesar, 70/230 μm, packed wet). Succinic (Alfa Aesar) and phthalic anhydride (chemically pure) were used without further purification. The synthesis of **4** used (1*S*)-camphanic acid chloride (Alfa Aesar) and triethylamine (Sigma-Aldrich).

4-(Butyl(2-hydroxy-5-methyl-3-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)benzyl)amino)-4-oxobutanoic Acid (2). Amine **1** (99 mg, 0.3 mmol) was dissolved in benzene, treated with succinic anhydride (30 mg, 0.3 mmol), and stirred at room temperature for 30 min. The course of the reaction was monitored by TLC (Sorbfil, petroleum ether:Et_2O, 1:5). When the reaction was finished solvent was evaporated at reduced pressure to afford **2** (129 mg, 100%), colorless semi-crystalline mass, $C_{26}H_{39}NO_4$. IR spectrum (thin layer, ν, cm^{-1}): 3119 (COO–H), 1713 (C=O in COOH), 1614 (C=O, amide-I).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.75 (3H, s, Me-10), 0.84 (3H, s, Me-9), 0.89 (3H, s, Me-8), 1.01 (3H, t, J = 7.3, Me-26), 1.31-1.47 (3H, m), 1.53-1.72 (5H, m), 1.77–1.92 (2H, m, CH_2-25, H-3, CH_2-6, H-4, CH_2-5, CH_2-24), 2.11–2.21 (1H, m, H-3), 2.28 (3H, s, Me-17), 2.56–2.88 (4H, m, CH_2-20, CH_2-23), 3.31–3.39 (3H, m, H-2, CH_2-21), 4.31 and 4.57 (1H each, both d, J = 14.6 and J = 14.6, CH_2-18), 6.74 and 7.10 (1H each, both d, J = 1.5 and J = 1.5, H-14, H-16), 9.17 (1H, br.s, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 12.06 (C-10), 13.78 (C-26), 20.11 (C-20), 20.38 (C-9), 20.82 (C-8), 21.49 (C-17), 27.57 (C-5), 29.26 and 30.04 (C-24, C-25), 34.00 (C-3), 39.48 (C-6), 45.13 (C-2), 45.79 (C-4), 46.89 (C-18), 46.90 (C-21), 47.31 (C-7), 47.97 (C-23), 49.84 (C-1), 121.17, 126.84 and 132.03 (C-11, C-13, C-15), 128.82 and 129.31 (C-14, C-16), 153.01 (C-12), 172.91 (C-19), 178.02 (C-22).

2-(Butyl(2-hydroxy-5-methyl-(1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl)benzyl)carbamoyl)benzoic Acid (3). Amide **3** was prepared by the method described for **2** using phthalic anhydride. Yield 99.5%, colorless oil, $C_{30}H_{39}NO_4$. IR spectrum (thin layer, ν, cm^{-1}): 3125 (COO–H), 1710 (C=O in COOH), 1619 (C=O, amide-I).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.73 (3H, t, J = 7.5, Me-22), 0.81 (3H, s, Me-10), 0.83 (3H, s, Me-9), 0.90 (3H, s, Me-8), 1.07–1.14 (2H, m), 1.31–1.38 (2H, m), 1.49–1.82 (7H, m), 3.08–3.13 (2H, m, CH_2-3, H-4, CH_2-5, CH_2-6, CH_2-19, CH_2-20, CH_2-21), 2.29 (3H, s, Me-17), 3.43 (1H, t, J = 9.0, H-2), 3.93–5.82 (2H, m, CH_2-18), 6.78 (1H, s), 7.14 (1H, s), 7.37 (2H, s), 7.45-7.60 (1H, m), 8.09-8.12 (1H, m, H-14, H-16, H-27, H-28, H-29, H-30), 9.21 (1H, br.s, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 12.16 (C-10), 13.46 (C-22), 20.38 (C-9), 20.87 (C-8), 21.52 (C-17), 27.55 (C-5), 29.50 and 29.70 (C-20, C-21), 33.94 (C-3), 39.40 (C-6), 45.14 (C-2), 45.55 (C-4), 45.97 (C-18), 48.00 (C-7), 48.62 (C-19), 49.91 (C-1), 120.92, 126.86, 127.52, 132.89, 137.56 (C-11, C-13, C-15, C-24, C-25), 127.16, 128.33, 129.08, 129.23, 131.34, 132.89 (C-14, C-16 and C-27, C-28, C-29, C-30), 153.26 (C-12), 169.24 (C-23), 173.23 (C-26).

(1*S*,4*R*)-*N*-Butyl-*N*-(2-hydroxy-5-methyl-3-{(1*RS*)-1,7,7-trimethylbicyclo[2.2.1]hept-*exo*-2-yl}benzyl)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-carboxamide (4). Amine **1** (198 mg, 0.6 mmol) was dissolved in benzene, treated with (1*S*)-(–)-camphanic acid chloride (195 mg, 0.9 mmol) and triethylamine (0.13 mL, 0.9 mmol), stirred at room temperature for 30 min, and left overnight. The course of the reaction was followed by TLC (Sorbfil, petroleum ether:Et_2O, 5:1). The mixture was cooled and filtered to remove the insoluble ammonium salt. Solvent was evaporated at reduced pressure. The solid was separated over a column (silica gel 70/230 μm, petroleum ether:Et_2O with increasing fraction of Et_2O) to afford two fractions of total mass 275 mg (total yield 90%). The first fraction contained diastereomerically enriched amide **4′** (41 mg, >95% *de* according to PMR spectroscopy). The second fraction contained a mixture of diastereomers **4′** and **4″** (234 mg). Resonances of **4″** were identified by comparison with the spectrum of pure **4′**.

Compound **4′**, colorless oil, $[\alpha]_D^{22}$ +5.1° (*c* 0.3, $CHCl_3$), $C_{32}H_{47}NO_4$. IR spectrum (thin layer, ν, cm^{-1}): 3557, 3142 (OH), 1794 (C=O, camphanic acid), 1599 (C=O, amide-I).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.72 (3H, s), 0.81 (3H, s), 0.86 (3H, s), 0.89 (3H, s), 1.09 (3H, s), 1.15 (3H, s) (Me-8, Me-9, Me-10, Me-8′, Me-9′, Me-10′), 1.00 (3H, t, J = 7.3, Me-22), 1.27–1.47 (4H, m), 1.52–1.61 (3H, m), 1.65–1.90 (4H, m), 1.92–2.05 (2H, m), 2.12–2.24 (1H, m), 2.47–2.57 (1H, m), 3.41–3.63 (2H, m, CH_2-3, H-4, CH_2-5, CH_2-6, CH_2-5′, CH_2-6′, CH_2-19, CH_2-20, CH_2-21), 2.27 (3H, s, Me-17), 3.35 (1H, t, J = 9.2, H-2), 4.39 and 4.52 (1H each, both d, J = 14.4, J = 14.4, CH_2-18), 6.74 and 7.10 (1H each, both br.d, H-14, H-16), 9.31 (1H, s, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 9.59, 16.75, 17.80, 21.48 (C-8, C-9, C-8′, C-9′), 12.20 (C-10), 13.80 (C-22), 20.21 (C-9), 20.80 (C-17), 19.93, 27.51, 29.17, 30.64, 32.13, 33.74, 39.35, 47.30 (C-3, C-5, C-5′, C-6, C-6′, C-19, C-20, C-21), 45.09 (C-2), 45.75 (C-4), 46.75 (C-18), 47.94 (C-7), 49.88 (C-1), 53.99, 55.57 (C-4′, C-7′), 92.82 (C-1′), 120.61, 126.88, 131.69 (C-11, C-13, C-15), 129.45, 129.49 (C-14, C-16), 153.10 (C-12), 168.89 (C-11′), 178.04 (C-3′).

Compound **4″** was isolated as a mixture with diastereomer **4′** in a 1.7:1 ratio, colorless semi-crystalline mass, $C_{32}H_{47}NO_4$. IR spectrum (thin layer, ν, cm^{-1}): 3555, 3145 (OH), 1798 (C=O, camphanic acid), 1601 (C=O, amide-I).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.71 (3H, s), 0.82 (3H, s), 0.86 (3H, s), 0.95 (3H, s), 1.09 (3H, s), 1.19 (3H, s, Me-8, Me-9, Me-10, Me-8′, Me-9′, Me-10′), 0.99 (3H, t, J = 7.3, Me-22), 1.32–1.46 (4H, m), 1.53–1.62 (3H, m), 1.65–1.90 (4H, m), 1.93–2.01 (2H, m), 2.09–2.17 (1H, m), 2.46–2.55 (1H, m), 3.40–3.64 (2H, m, CH_2-3, H-4, CH_2-5, CH_2-6, CH_2-5′, CH_2-6′, CH_2-19, CH_2-20, CH_2-21), 2.26 (3H, s, Me-17), 3.32 (1H, t, J = 8.9, H-2), 4.23 and 4.70 (1H each, both d, J = 14.4, J = 14.4, CH_2-18), 6.73 and 7.09 (1H each, both br.d, H-14, H-16), 9.15 (1H, s, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 9.59, 16.72, 17.95, 21.43 (C-8, C-9, C-8′, C-9′), 12.07 (C-10), 13.80 (C-22), 20.40 (C-9), 20.80 (C-17), 19.93, 27.52, 29.30, 30.69, 31.84, 33.87, 39.60, 47.09 (C-3, C-5, C-6, C-19, C-20, C-21, C-5′, C-6′), 45.22 (C-2), 45.77 (C-4), 46.59 (C-18), 47.99 (C-7), 49.74 (C-1), 53.87, 55.57 (C-4′, C-7′), 92.55 (C-1′), 120.74, 126.83, 131.88 (C-11, C-13, C-15), 129.28, 129.32 (C-14, C-16), 152.89 (C-12), 168.99 (C-11′), 178.07 (C-3′).

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