Chemistry of Natural Compounds, Vol. 44, No. 4, 2008

SYNTHESIS OF ISOBORNYLPHENOLS CONTAINING HETEROCYCLIC AND BENZYLIC FRAGMENTS

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UDC 547.563.4'599+547.94

*The alkaloids salsolidine, salsoline and (*R*)-*N*-benzyl-1-phenylethylamine were added to 4-methyl-2-isobornylphenol using an aminomethylation reaction.*

Key words: terpenophenols, aminomethylation, salsolidine, salsoline, diastereomers.

We previously reported the synthesis of various conjugates containing terpenophenol and chlorin fragments in a single molecule [1, 2]. In continuation of research on the construction of molecules based on terpenophenols containing functional groups with physiological activity, we added heterocyclic moieties generated from the isoquinoline alkaloids (*S*)-salsolidine (**2a**) and (*R*)-salsoline (**2b**). The combination in the synthesized molecules of a sterically hindered phenol and natural biomolecule fragments (alkaloids and terpene) suggested that new physiologically active properties with a broad spectrum of action could arise. It is known that preparations containing salsoline and salsolidine reduce arterial blood pressure and exert a general sedative action with little toxicity [3].

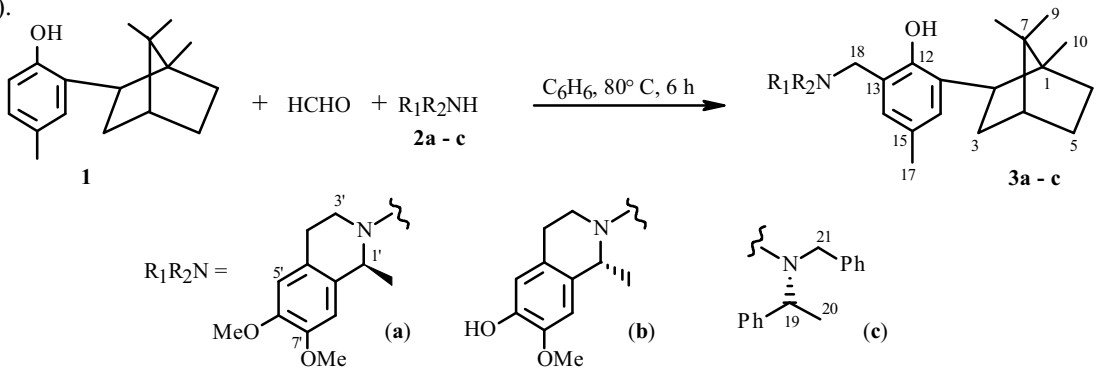
In addition to adding the isoquinoline fragments, the reaction of 4-methyl-2-isobornylphenol with optically active (*R*)-*N*-benzyl-1-phenylethylamine (**2c**) was carried out in order to expand the set of terpenophenol derivatives containing additional benzyl groups in their structure.

The new groups were introduced into the terpenophenol using a three-component one-step aminomethylation reaction, which was successfully used previously to synthesize simple Mannich bases [2] (Scheme 1).

The structure of **3** was confirmed using IR and NMR spectroscopy and mass spectrometry (for **3b**, elemental analysis). According to the NMR spectra, **3** exists as a mixture of two diastereomers (1:1 ratio). This is explained by the fact that the starting terpenophenol **1** is a mixture of enantiomers. The presence of diastereomers was evident as a doubling of the resonances of certain protons of the terpenophenol groups of amines **3** in the PMR spectra (resonances of methyls Me-8, Me-9, and Me-10 for **3a**; Me-9 and Me-10, for **3b**; Me-10, OH, and bridges on C-18, C-19, and C-21, for **3c**).

Neither of the enantiomers of starting terpenophenol **1** was preferentially involved in the studied reactions.

The structure of the terpene fragment did not change during the studied transformations (according to ^{13}C NMR spectroscopy).



Scheme 1

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0009-3130/08/4404-0455

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker Avance II spectrometer (operating frequency 300 MHz). Resonances were assigned using ^{13}C NMR spectra in JMOD mode and two-dimensional NMR spectroscopy. IR spectra in thin layers and KBr disks were recorded on a Shimadzu IR Prestige 21 IR-Fourier spectrometer. MALDI mass spectra were obtained in a Vision-2000 spectrometer. Melting points were determined on a Kofler stage. The course of reactions was monitored by TLC on Sorbil plates. Plates were developed using $KMnO_4$ solution [$KMnO_4$, 15 g; H_2O, 300 mL; H_2SO_4 (conc.), 0.5 mL].

Benzene was dried over $CaCl_2$ and distilled over metallic Na. We used petroleum ether (bp 65-70°C) and silica gel 70/230 μm (packed moist) for column chromatography. We used chemically pure paraform. Compound **1** was synthesized from *p*-cresol and camphene [4]. (*S*)-Salsolidine (**2a**) and (*R*)-salsoline (**2b**) were isolated from their hydrochlorides [5]. The spectral properties of **2a** and **2b** agreed with those published [6]. We used (*R*)-*N*-benzyl-1-phenylethylamine (**2c**, Alfa Aesar) to synthesize amine **3c**.

Synthesis of Amines 3a-c. 4-Methyl-2-isobornylphenol (**1**, 2.0 mmol) and paraform (2.4 mmol) were dissolved in dry benzene (20 mL) at room temperature, treated with amine **2** (2.4 mmol), and refluxed for 6 h. When the reaction was finished the excess of solvent was removed at reduced pressure. The reaction mixture was separated over a column (silica gel 70/230 μm) with elution by petroleum ether:Et_2O with an increasing fraction of the latter.

2-[((*S*)-6,7-Dimethoxy-1-methyl-3,4-dihydro-2(1*H*)-isoquinolinyl)methyl]-4-methyl-6-{(1*RS*)-1,7,7-trimethylbicyclo[2.2.1]heptan-*exo*-2-yl}phenol (3a). Yellow semicrystalline mass, yield 94%. IR spectrum (thin layer, cm^{-1}): 1252 (C–O), 1232 (C–N). Calc. for $C_{30}H_{41}NO_3$, $[M]^+$ 463.309; found 463.312.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.77/0.85 (s, 3H, Me-10); 0.83/0.84 (s, 3H, Me-9); 0.92/0.93 (s, 3H, Me-8); 1.27-1.46 (m, 5H), 2.52-2.67 (m, 1H), 2.81-3.01 (m, 2H) (H-5, CH_2-18, H-1′, CH_2-3′, CH_2-4′); 1.50-1.63 (m, 3H, H-3, CH_2-6); 1.79-1.87 (m, 2H, H-4, H-5); 2.15-2.23 (m, 1H, H-3); 2.25 (s, 3H, Me-17); 3.09-3.21 (m, 1H, H-4); 3.29 (t, 1H, J = 9.0, H-2); 3.84 [d, 3H, J = 3.1, (H-1′)-Me]; 3.87 (s, 6H, 2 × OMe); 6.52 and 7.06 (d, J = 3.0, and br.s, 1H each, H-14, H-16); 6.59 and 6.64 (both s, 1H each, H-5′, H-8′); 11.23 (br.s, 1H, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ): 12.08/12.19 (C-10), 20.34 (C-9), 20.89 (C-8), 21.48 (C-17), 27.54 (C-5), 33.73/33.80 (C-3), 39.59 (C-6), 42.38, 42.84 (C-3′, C-4′), 44.65/44.69 (C-2), 45.74 (C-4), 47.89 (C-7), 49.78/48.80 (C-1), 54.89 [(C-1′)-Me], 55.33 (C-1′), 55.84/55.94 (2 × OMe), 57.04/57.17 (C-18), 110.25/110.42, 127.84/127.90 (C-14, C-16), 111.32, 126.63 (C-5′, C-8′), 120.42/120.50 (C-15), 124.93, 125.16 [C-6, C-7, (C-4′)-C-(C-5′), (C-1′)-C-(C-8′)], 130.40/130.47 (C-11), 147.47/147.65 (C-13), 155.04/155.17 (C-12).

(1*R*)-2-(2-Hydroxy-5-methyl-3-{(1*RS*)-1,7,7-trimethylbicyclo[2.2.1]heptan-*exo*-2-yl)benzyl}-7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-6-ol (3b). Yellow powder, mp 74-76°C, yield 71%. IR spectrum (KBr, cm^{-1}): 3549, 3439 (OH); 1273 (C–O); 1233 (C–N). $C_{22}H_{35}NO$.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79/0.90 (s, 3H, Me-10); 0.85/0.87 (s, 3H, Me-9); 0.94 (s, 3H, Me-8); 1.29-1.46 (m, 5H), 2.52-2.64 (m, 1H), 2.80-2.99 (m, 2H, H-5, CH_2-18, H-1′, CH_2-3′, CH_2-4′); 1.52-1.67 (m, 3H, H-3, CH_2-6); 1.81-1.89 (m, 2H, H-4, H-5); 2.15-2.25 (m, 1H, H-3); 2.27 (s, 3H, Me-17); 3.09-3.25 (m, 1H, H-4); 3.32 (t, 1H, J = 8.9, H-2); 3.85-3.96 [m, 6H, (H-1′)-Me, OMe]; 6.52 and 7.08 (d, J = 3.6 and br.s, 1H each, H-14, H-16); 6.65 and 6.68 (both s, 1H each, H-5′, H-8′); 10.50 (br.s, 1H, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ): 12.09/12.19 (C-10), 20.34 (C-9), 20.90 (C-8), 21.49 (C-17), 27.55 (C-5), 33.73/33.82 (C-3), 39.59 (C-6), 42.33, 42.78 (C-3′, C-4′), 44.66/44.70 (C-2), 45.75 (C-4), 47.90 (C-7), 49.79 (C-1), 54.97 [(C-1′)-Me], 55.34 (C-1′), 55.95 (OMe), 57.01/57.16 (C-18), 109.47/109.66, 127.84/127.89 (C-14, C-16), 114.17, 126.62 (C-5′, C-8′), 120.43/120.52 (C-15), 125.71, 125.94, 126.54 [C-6′, C-7′, (C-4′)-C-(C-5′), (C-1′)-C-(C-8′)], 130.40/130.47 (C-11), 144.15/145.14 (C-13), 155.07/155.20 (C-12).

2-((Benzyl((*R*)-1-phenylethyl)amino)methyl)-4-methyl-6-[(1*RS*)-1,7,7-trimethylbicyclo[2.2.1]heptan-*exo*-2-yl}phenol (3c). Colorless semicrystalline mass, yield 52%. IR spectrum (thin layer, cm^{-1}): 3439 (OH); 1274 (C–O); 1231 (C–N). Calc. for $C_{33}H_{41}NO$, $[MH]^+$ 467.319; found 468.318.

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81/0.82 (s, 3H, Me-10); 0.86 (s, 3H, Me-9); 0.92 (s, 3H, Me-8); 1.29-1.49 (m, 1H), 1.59-1.68 (m, 3H), 1.84-1.92 (m, 2H), 2.11-2.22 (m, 1H, CH_2-3, CH_2-4, H-5, CH_2-6); 1.54 and 1.60 (both d, 3H each, J = 7.0, 7.0, Me-20); 2.26 (s, 3H, Me-17); 3.36 (br.t, 1H, J = 9.0, H-2); 3.19 (d, 1H, J = 13.3), 3.88-3.95 (m, 1H),

3.44/3.68 (d, 1H, J = 13.3), 3.48/3.84 (d, 1H, J = 13.8, CH_2-18, CH_2-21); 4.07/4.16 (q, 1H, J = 7.0, H-19); 6.63/6.65 and 7.03 (d, J = 1.7 and s, 1H each, H-14, H-16); 7.28-7.45 (m, 10H, 2 × Ph); 10.43/10.61 (br.s, 1H, OH).

^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ): 12.11/12.40 (C-10), 14.19/16.19 (C-20), 20.45 (C-9), 20.95 (C-8), 21.52 (C-17), 27.60 (C-5), 33.89/34.05 (C-3), 39.71/39/73 (C-6), 44.65/44.68 (C-2), 45.82 (C-4), 47.95 (C-7), 49.82 (C-1), 52.89, 53.16, 53.67/53.79 (C-18, C-21), 56.37/56.46 (C-19), 120.65/120.73, 130.32, 137.84/137.90 (C-11, C-13, C-15), 126.80/126.89, 127.88/127.95 (C-14, C-16), 138.69, 139.83 [C(Ph)-C-21, C(Ph)-C-19], 154.66 (C-12), 126.70, 127.38, 127.48/127.56, 128.21, 128.28, 128.44, 128.58, 128.77, 129.33/129.38 (2 × Ph).

ACKNOWLEDGMENT

The work was supported by the Russian Foundation for Basic Research (Project No. 07-03-01132), the President of the Russian Federation (Program of Support for Leading Scientific Schools, Grant NSh-4028.2008.3), and a Grant from the Urals Division, Russian Academy of Sciences.

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