Chemistry of Natural Compounds, Vol. 48, No. 1, March, 2012 [Russian original No. 1, January-February, 2012]

REACTION OF ISOCEMBROL AND ALCOHOLS ON CLAY

O. I. Yarovaya,* D. V. Korchagina,
N. F. Salakhutdinov, and G. A. Tolstikov

UDC 547.992

The reactions of isocembrol with allyl and methyl alcohols on K-10 clay were studied.

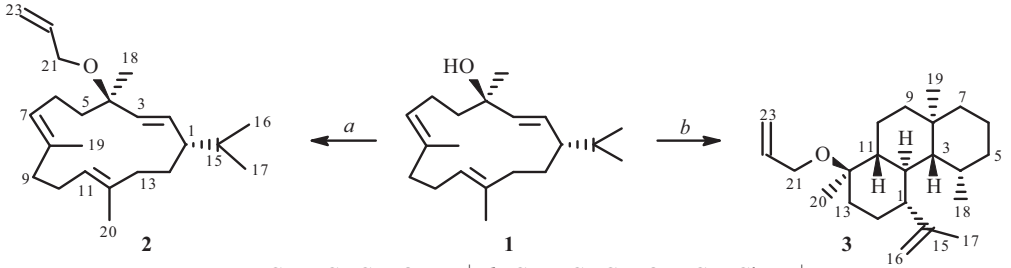
Keywords: isocembrol, K-10 clay.

Isocembrol (**1**) is a diterpene component of *Pinus sibirica* gum and a representative of a broad group of cembranoids. It incorporates a 14-membered ring, a tertiary alcohol, and three *trans*-double bonds in the ring. The principal sources of cembranoids are coniferous plants, tobacco, and marine invertebrates, especially corals. Cyclic alcohol **1** was first isolated from the neutral part of *P. sibirica* Mayr gum [1] and was described under the name thunbergol as the principal component of the neutral part of *Pseudotsuga menziessi* Mirb. Franco gum [2]. Compound **1** was also detected in marine corals [3], tobacco leaves [4], and propolis [5].

We improved the method for isolating **1** from *P. sibirica* gum. The previously reported method [1] was used as a prototype. According to that method, gum is saponified by NaOH solution (1%). Neutral unsaponified substances are extracted by Et_2O and fractionated by vacuum distillation. The residual after distillation is chromatographed twice successively over basic Al_2O_3 (1:15 and 1:50 ratios). Compound **1** is isolated in 1.9% yield of the neutral fraction and 0.5% of the total gum mass. We proposed isolating **1** from the neutral part of the gum by extraction with nonpolar solvents (hexane, petroleum ether) and successive purification of the target product by column chromatography. This method has several advantages over the known methods. The solvents and gum extraction method are selected such that the resulting mixture containing **1** is fluid and easily subjected to either chromatography or vacuum distillation. The yield of target product using the proposed method was 2.9–3.8% of the total gum mass and 18–22% of the hexane-extract mass. This was significantly greater than the yield of known methods. The spectral characteristics of isolated **1** agreed with those published [6].

The properties of **1** are insufficiently studied despite its relative availability. Isomerization of **1** in formic acid that leads to the formation of bi- and tricyclic compounds [7], epoxidation by per-acids [8], and hydroxylation [9] were studied. Epoxidation of **1** by *t*-BuOOH in the presence of $VO(acac)_2$ was performed efficiently [10]. Further transformations of the resulting epoxy derivative were studied. Oxidation of **1** by pyridinium chlorochromate produced conjugated enones [11].

Herein results of a study of the reactions of **1** with allyl and methyl alcohols on K-10 clay are reported. Adding **1** to an allyl alcohol–clay system gave an intermolecular product, the allyl ether of isocembrol **2**, as the principal product. The reaction was conducted without solvent. Adding CH_2Cl_2 to the system increased significantly the amount of isomerization products. Thus, adding **1** to a CH_2Cl_2–allyl alcohol–clay system gave **3** as the principal product (Scheme 1). Compound **3** was formed as a result of intramolecular cyclization and subsequent reaction with allyl alcohol. Furthermore, a mixture of cembrenes was formed.



2 **1** **3**

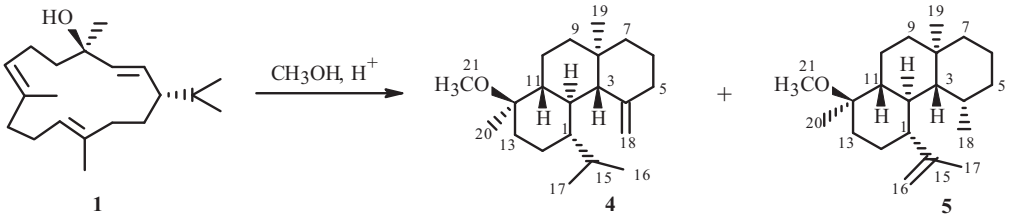
a. CH_2=$CHCH_2OH$, H^+; *b*. CH_2=$CHCH_2OH$, CH_2Cl_2, H^+

Scheme 1

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, 630090, Novosibirsk, Prosp. Akad. Lavrent′eva, 9, e-mail: ooo@nioch.nsc.ru. Translated from *Khimiya Prirodnykh Soedinenii*, No. 1, January–February, 2012, pp. 54–57. Original article submitted May 11, 2011.

 0009-3130/12/4801-0056

The reaction of **1** with methyl alcohol with clay catalysis formed products **4** and **5** in a 1:1 ratio (Scheme 2). These products resulted from intramolecular cyclization of starting **1** with further trapping of cations by the alcohol molecules. Compounds with analogous types of frameworks were obtained previously from the isomerization of **1** in formic acid [7].



1 **4** **5**

Scheme 2

Attempts to carry out the reaction of **1** with other alcohols such as ethyl, isobutyl, and benzyl did not give the intermolecular products. Dissolution of **1** in CH_2Cl_2 on clay gave a complicated mixture of isomerization products.

We noticed that the chemical shifts of resonances for the C^{12} methyls in **3**–**5** were very similar to each other in PMR and ^{13}C NMR spectra. This indicated that they had the same orientation in all three instances. A comparison of the ^{13}C NMR spectra of **3**–**5** with published spectra of pairs of hydroxyl compounds **4** and **5** that were epimers at C^{12} [7] allowed these methyls to be assigned the axial orientation because their chemical shifts were observed to be similar namely in this position. The chemical shifts of the $C^{20}H_3$ groups in the axial position for the hydroxy derivatives of **4** and **5** were ~22.4 ppm whereas they would be ~29.2 ppm if they were in the equatorial position. The steric placements of the other substituents in **3**–**5** were assigned in analogy with those of related structures that were described before [7].

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-500 spectrometer (operating frequencies 500.13 MHz for ^1H and 125.76 MHz for ^{13}C). The internal standards were the $CD(H)Cl_3$ resonances (δ_H 7.24 ppm; δ_C 76.90 ppm). The structures of the compounds were established using ^1H—^1H double resonance spectra and ^1H–^1H two-dimensional homonuclear correlation spectra (^1H–^1H COSY) in addition to ^{13}C–^1H two-dimensional heteronuclear correlation spectroscopy for direct (^{13}C–^1H COSY, $^1J_{C,H}$ = 160 Hz) and through-space spin–spin coupling constants (COLOC, $^{2,3}J_{C,H}$ = 10 Hz). The multiplicities of resonances in ^{13}C NMR spectra were determined from spectra recorded with J-modulation or off-resonance irradiation of protons.

The purity of starting materials was monitored and reaction products were analyzed using GC on a Biokhrom-1 chromatograph with various columns: a) glass capillary column (53,000 × 0.26 mm, XE-60 stationary phase); b) quartz capillary column (13,000 × 0.22 mm, SE-54 phase). We used a flame-ionization detector and He carrier gas. Mass spectra (ionizing electron energy 70 eV) were measured in a DFS Thermo Scientific high-resolution mass spectrometer. The reaction was carried out on K-10 clay (calcined at 110°C for 3 h). Column chromatography used Merck silica gel (60–200 μm). The atomic numbering in the compounds is given for assignment of resonances in NMR spectra and does not always agree with the atomic numbering according to the nomenclature. Specific rotation is expressed in $(deg \cdot mL)(g \cdot dm)^{-1}$; solution concentration, $(g) \cdot (100\ mL)^{-1}$.

Isolation of 1 from Gum. The acidic and neutral parts were separated by dissolving gum (107 g) in hexane (250 mL), washing with NaOH solution (200 mL, 5%), and adding saturated NaCl solution (150 mL). A three-layered mixture formed. The hexane extract contained the neutral part of the gum; the aqueous, a mixture of salts of resinous acids. Furthermore, a plasticine-like mass formed and converted into a gummy resin upon drying. The mass of the hexane extract was 21.6 g; of the dry resin, 78 g. GC–MS analysis of the hexane extract showed that the principal components of the neutral part were α-pinene (41.5%), 3-carene (12.2%), β-pinene (6.8%), β-phellandrene (3.6%), and isocembrol (21.6%). Column chromatography was used to isolate **1** from the neutral part of the gum. Thus, the mixture (4 g) was placed onto a column with silica gel (40 g, 100–160 μm, compound:adsorbent ratio ~1:10) and eluted by hexane with an EtOAc gradient from 2 to 15% to afford **1** (0.82 g) with an impurity (5%) of epi-isocembrol, an isomer at the 4-position (the ratio according to NMR). The course of the chromatography was monitored using TLC plates with a solvent system of EtOAc (20%) in hexane and by analyzing fractions on the GC. The yield was 20.5% of the neutral part and 4.1% of the total gum mass. Isomers were

separated over silica gel impregnated with $AgNO_3$ (5%) (compound:adsorbent ratio 1:20) to afford **1** {0.75 g, $[\alpha]_D^{25}$ 65° (*c* 1.2, $CHCl_3$), 18.7% yield of the neutral part and 3.8% of the total gum mass}.

Reaction of 1 with Allyl Alcohol on K-10 Clay. Clay (0.35 g) in allyl alcohol (2 mL) was stirred, treated with **1** (0.35 g), held at room temperature for 2 h, and filtered off. The clay was washed with Et_2O. The mass of the resulting mixture was 0.34 g. Column chromatography over SiO_2 (eluent hexane with an EtOAc gradient from 0 to 10%) isolated **2** (0.28 g) and starting **1** (0.05 g).

(1*E*,5*E*,9*R*,10*E*,12*S*)-9-(Allyloxy)-12-isopropyl-1,5,9-trimethylcyclotetradeca-1,5,10-triene (2). Yield 80%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.81 and 0.84 (3H each, d, J = 6.8, CH_3-16, CH_3-17), 1.24 (3H, s, CH_3-18), 1.29 (1H, dddd, ^2J = 13.8, $J_{14,13}$ = 10.5, $J_{14,1}$ = 5.1, $J_{14,13'}$ = 3.8, H-14), 1.39–1.46 (1H, m, H-5), 1.50 (3H, br.s, CH_3-20), 1.57 (3H, br.s, CH_3-19), 1.48–1.61 (2H m, H-15, H-14′), 1.66–1.73 (1H, m, H-1), 1.93 (1H, ddd, ^2J = 14.0, $J_{13',14'}$ = 12.0, $J_{13'14}$ = 3.8, H-13′), 1.96–2.13 (6H, m, H-5′, H-6, 2H-9, H-10, H-13), 2.15–2.25 (1H, m, H-10′), 2.44–2.53 (1H, m, H-6′), 3.79 (1H, dddd, ^2J = 12.8, $J_{21,22}$ = 5.5, $J_{21,23cis}$ = 1.5, $J_{21,23trans}$ = 1.5, H-21), 3.84 (1H, dddd, ^2J = 12.8, $J_{21',22}$ = 5.0, $J_{21',23cis}$ = 1.5, $J_{21',23trans}$ = 1.5, H-21′), 4.90–5.03 (1H, m, H-11), 5.06 (1H, dddd, $J_{23cis,22}$ = 10.3, ^2J = 2.0, $J_{23cis,21}$ = 1.5, $J_{23cis,21'}$ = 1.5, H-23_{cis}), 5.17 (1H, dd, $J_{2,3}$ = 15.8, $J_{2,1}$ = 9.3, H-2), 5.17–5.21 (1H, m, H-7), 5.25 (1H, dddd, $J_{23trans,22}$ = 17.2, ^2J = 2.0, $J_{23trans,21}$ = 1.5, $J_{23trans,21'}$ = 1.5, H-23_{trans}), 5.45 (1H, d, $J_{3,2}$ = 15.8, H-3), 5.88 (1H, dddd, $J_{22,23trans}$ = 17.2, $J_{22,23cis}$ = 10.3, $J_{22,21}$ = 5.5, $J_{22,21'}$ = 5.0, H-22).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.73 (q, C-20), 15.02 (q, C-19), 19.12 (q, C-16), 20.49 (q, C-17), 21.73 (t, C-6), 23.35 (q, C-18), 23.53 (t, C-10), 27.72 (t, C-14), 33.13 (d, C-15), 36.58 (t, C-13), 38.86 (t, C-9), 42.88 (t, C-5), 46.00 (d, C-1), 63.32 (t, C-21), 77.16 (s, C-4), 115.05 (t, C-23), 124.79 (d, C-11), 128.71 (d, C-7), 131.88 (s, C-8), 132.04 (s, C-12), 132.24 (d, C-2), 135.19 (d, C-3), 136.36 (d, C-22).

Found: *m*/*z* 330.2910 $[M]^+$, $C_{23}H_{38}O$; calcd: 330.2917, $[\alpha]_D^{25}$ 6.3° (*c* 0.7, $CHCl_3$).

Storing **1** (0.35 g) with a mixture of clay (0.4 g), allyl alcohol (2 mL), and CH_2Cl_2 (2 mL) for 12 h afforded after analogous work up and column chromatography compound **3** (0.13 g) and a mixture of cembrenes (0.12 g).

(1*R*,4*R*,4a*R*,4b*R*,5*S*,8a*R*,10a*R*)-1-(Allyloxy)-1,5,8a-trimethyl-4-(prop-1-en-2-yl)tetradecahydrophenanthrene (3). Yield 37%.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.73 (3H, d, $J_{18,4}$ = 7, CH_3-18), 0.88 (3H, s, CH_3-19), 1.05 (1H, dd, $J_{3a,2a}$ = 10.1, $J_{3a,4e}$ = 3.8, H-3a), 1.14 (3H, s, CH_3-20), 1.57 (1H, ddd, $J_{2a,1a}$ = $J_{2a,3a}$ = $J_{2a,11a}$ = 10.1, H-2a), 1.75 (3H, br.s, CH_3-17), 2.05–2.12 (1H, m, H-4e), 3.82–3.91 (2H, m, H-21), 4.68 (1H, br.s, H-16), 4.70 (1H, m, all J < 2, H-16′), 5.06 (1H, ddt, $J_{23cis,22}$ = 10.3, ^2J = 2.0, $J_{23trans,21}$ = 1.5, H-23_{cis}), 5.24 (1H, ddt, $J_{23trans,22}$ = 17.2, ^2J = 2.0, $J_{23trans,21}$ = 1.5, H-23_{trans}), 5.89 (1H, ddt, $J_{22,23trans}$ = 17.2, $J_{22,23cis}$ = 10.3, $J_{22,21}$ = 5.0, H-22), 1.00–1.81 (m, other protons).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 16.81 (q, C-18), 17.15 (t, C-6), 19.23 (q, C-20), 20.78 (t, C-10), 21.32 (q, C-19), 22.40 (q, C-17), 28.13 (d, C-4), 30.68 (t, C-14), 34.26 (t, C-5), 34.48 (t, C-13), 34.76 (s, C-8), 38.24 (d, C-2), 43.16 and 45.58 (both t, C-7 and C-9), 49.53 (d, C-1), 50.59 (d, C-11), 56.32 (d, C-3), 61.33 (t, C-21), 76.60 (s, C-12), 110.17 (t, C-16), 115.04 (t, C-23), 136.43 (d, C-22), 150.05 (s, C-15).

Found: *m*/*z* 330.2919 $[M]^+$, $C_{23}H_{38}O$; calcd: 330.2917, $[\alpha]_D^{25}$ –7.6° (*c* 0.6, $CHCl_3$).

Reaction of 1 with Methyl Alcohol on K-10 Clay. Clay (0.4 g) in anhydrous MeOH (2 mL) was stirred, treated with **1** (0.35 g), held at room temperature for 5 h, and filtered off. The clay was washed with Et_2O. The mass of the resulting mixture was 0.34 g. Column chromatography over SiO_2 (eluent hexane with an EtOAc gradient from 0 to 10%) afforded a mixture of **4** and **5** (0.23 g) in a 1:1 ratio and a mixture of cembrenes (0.06 g). Isomers **4** and **5** were separated over silica gel impregnated with $AgNO_3$ (5%, eluent hexane with an EtOAc gradient from 0 to 5%) to afford **4** (0.08 g) and **5** (0.085 g) that both crystallized on standing.

(1*R*,4*S*,4a*R*,4b*S*,8a*R*,10a*R*)-1,8a-Dimethyl-4-isopropyl-1-methoxy-5-methylenetetradecahydrophenanthrene (4). Yield 23%, mp 77–78°C.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.56 and 0.81 (3H, d, CH_3-16 and 3H, d, J = 6.5, CH_3-17), 0.70 (3H, s, CH_3-19), 0.87 (1H, dddd, $J_{1,14a}$ = 12.0, $J_{1,2}$ = 10.1, $J_{1,14e}$ = 2.5, $J_{1,15}$ = 1.2, H-1), 1.07 (1H, dddd, ^2J = 13.5, $J_{14a,13a}$ = 13.5, $J_{14a,1}$ = 12.0, $J_{14a,13e}$ = 3.8, H-14a), 1.11 (3H, s, CH_3-20), 1.09–1.36 (5H, m, 2H-7, H-9, H-10, H-11), 1.42 (1H, ddd, $J_{2,1}$ = $J_{2,3}$ = $J_{2,11}$ = 10.1, H-2), 1.55 (1H, d, $J_{3,2}$ = 10.1, H-3), 1.76 (1H, ddd, ^2J = 12.0, $J_{13e,14a}$ = 3.8, $J_{13e,14e}$ = 3.3, H-13e), 1.99 (1H, dddd, ^2J = 11.8, $J_{5a,6a}$ = 11.8, $J_{5a,6e}$ = 7.5, $J_{5a,18}$ = 1.2, H-5a), 2.03 (1H, sept d, $J_{15,16(17)}$ = 6.5, $J_{15,1}$ = 1.2, H-15), 2.25 (1H, dddd, ^2J = 11.8, $J_{5e,6a}$ = 4.0, $J_{5e,6e}$ = 3.3, $J_{5e,18}$ = 1.2, H-5e), 3.16 (3H, s, OCH_3), 4.43 and 4.73 (2H, both br.s, H-18). Resonances of other protons were observed as overlapping multiplets in the range 1.45–1.71 ppm.

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 17.05 (q, C-16), 18.18 (q, C-20), 18.96 (t, C-10), 20.23 (q, C-19), 22.89 (t, C-14), 23.37 (q, C-17), 25.51 (t, C-6), 26.26 (d, C-15), 36.26 (t, C-13), 37.16 (d, C-2), 37.54 (s, C-8), 39.15 (t, C-5), 41.56 (t, C-9), 42.40 (t, C-7), 47.80 (q, C-21), 52.16 (d, C-11), 54.72 (d, C-1), 55.85 (d, C-3), 76.93 (s, C-12), 105.36 (t, C-18), 149.85 (s, C-4).

Found: *m*/*z* 304.2767 $[M]^+$, $C_{21}H_{36}O$; calcd: 304.2761, $[\alpha]_D^{25}$ –5.6° (*c* 0.8, $CHCl_3$).

(1*R*,4*R*,4a*R*,4b*R*,5*S*,8a*R*,10a*R*)-1-Methoxy-1,5,8a-trimethyl-4-(prop-1-en-2-yl)tetradecahydrophenanthrene (5). Yield 24%, mp 48–50°C.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.73 (3H, d, $J_{18,4}$ = 7.0, CH_3-18), 0.88 (3H, s, CH_3-19), 1.05 (1H, dd, $J_{3a,2a}$ = 10.1, $J_{3a,4e}$ = 3.8, H-3a), 1.11 (3H, s, CH_3-20), 1.58 (1H, ddd, $J_{2a,1a} = J_{2a,3a} = J_{2a,11a}$ = 10.1, H-2a), 1.75 (3H, br.s, CH_3-17), 2.05–2.12 (1H, m, H-4e), 3.14 (3H, s, OCH_3), 4.68 and 4.71 (2H, br.s, and m, all J < 2, H-16), resonances of other protons were observed as overlapping multiplets in the ranges 1.00–1.16, 1.17–1.38, and 1.42–1.80 ppm.

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 16.82 (q, C-18), 17.18 (t, C-6), 18.83 (q, C-20), 20.78 (t, C-10), 21.35 (q, C-19), 22.45 (q, C-17), 28.18 (d, C-4), 30.56 (t, C-14), 33.45 (t, C-13), 34.31 (t, C-5), 34.82 (s, C-8), 38.24 (d, C-2), 43.18 and 45.63 (both t, C-7 and C-9), 48.88 (q, C-21), 49.55 (d, C-1), 50.26 (d, C-11), 56.41 (d, C-3), 76.19 (s, C-12), 110.18 (t, C-16), 150.10 (s, C-15).

Found: *m*/*z* 304.2759 $[M]^+$, $C_{21}H_{36}O$; calcd: 304.2761, $[\alpha]_D^{25}$ –2.3° (*c* 0.55, $CHCl_3$).

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