Russian Journal of General Chemistry, Vol. 72, No. 6, 2002, pp. 974–975. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 6, 2002, pp. 1041–1042.

Synthesis of Polyfunctional Terpenoids from Monoterpenes and *N*-(2-Mercaptopropyonyl)glycine

L. E. Nikitina, V. A. Startseva, I. A. Vakulenko, and V. V. Plemenkov

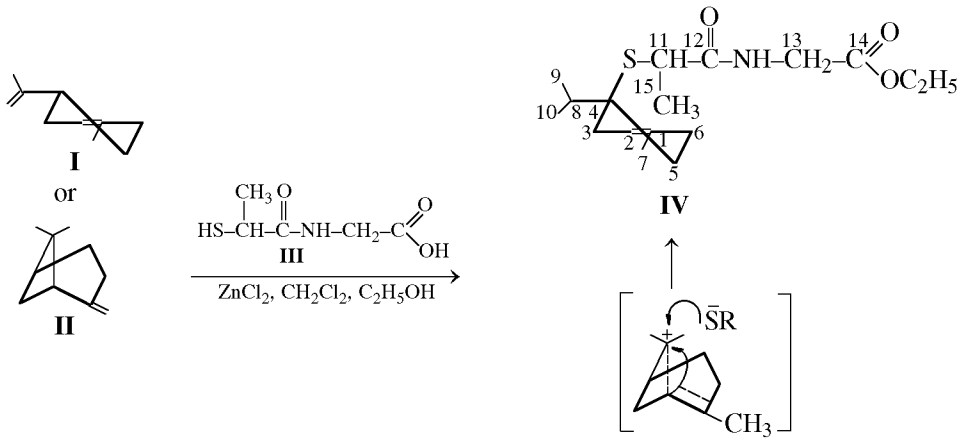
Kurashov Kazan State Medical University, Kazan, Tatarstan, Russia

Received September 27, 2000

Abstract — Addition of *N*-(2-mercaptopropyonyl)glycine to (+)-limonene or (–)-β-pinene in the presence of a Lewis acid involves the mercapto group; simultaneously, the carboxyl function is esterified by ethanol used as solvent. Both reactions give rise to a terpenoid of the menthane structure, which contains, along with a sulfide group, a peptide fragment promising in terms of biologic activity, as well as an ester group.

Many natural monoterpenoids exhibit diverse biologic activity, antitumor inclusive [1, 2]. The biologic activity of these compounds can be much enhanced by chemical modification. In particular, testing our prepared sulfur-containing monoterpenoids for antitumor activity, performed at the National Cancer Institute (USA), showed that some of them act as growth inhibitors (level 40–50%) with respect to *Leukemia*, *Non-Small Cell Lung Cancer*, and *CNS Cancer* and *Melanoma*. In our turn, we found that some monoterpenoids exhibit nematocide and antiparasitic activity (agaist *Psoroptes* tisks) comparable with that of ethanol and combined with low toxicity.

Earlier we studied reactions of limonene with mono- and bifunctional mercaptanes (alkanethiols, mercatoethanol, mercaptoacetic acid) [3]. Searching for synthetic approaches to new polyfunctional terpenoids, we reacted (+)-limonene (**I**) and (–)-βpinene (**II**) with *N*-(2-mercaptopropyonyl)glycine (**III**) containing, along with a mercapto group, a peptide fragment and a carboxyl function, in the presence of catalytic amount of zinc chloride. The reactions gave one and the same compound **IV** isolated, in both cases, by column chromatography on silica gel. The reaction of β-pinene with thiol **III** involves rearrangement into the *p*-menthane system, which is characteristic of this terpene.



Simultaneously with thiol addition to the terpene double bond, there occurs esterification of the carboxy group with ethanol taken as solvent along with methylene chloride. Using this solvent mixture allowed us to obtain a homogeneous reaction mixture, whereas with other solvents the system remained heterogeneous because of the poor solubility of either crystalline thiol **III** or zinc chloride. Under the above conditions the reactions occur almost instantaneously in high yields. With β-pinene, the yield of the reaction product is slightly higher (87% against 76% with limonene). The lower yield of the target product in

1070-3632/02/7206-0974 $27.00 © 2002 MAIK "Nauka/Interperiodica"

the reaction with limonene is explained by the formation of a small amount (4%) of *p*-cymene and tarring products, which is characteristic of limonene reactions with sulfur-containing reagents in the presence of Lewis acids [4].

It should be noted that the reactions of limonene with alkanethiols, we studied earlier provide anti-Markovnikov adducts, whereas its reactions with mercatoacetic acid and thiol **III** occur according to the Markovnikov rule. Presumably, the reactions with alkanethiols involve initial formation of a complex between the thiol and Lewis acid, which then attacks an exocyclic double bond of the terpene to give a tertiary carbocation. Upon elimination of zinc chloride, the bulky thioalkyl group comes to the least sterically congested C^9 atom [3]. The presnce in the thiol of such a strongly acceptor group, such as the carboxy group in mercaptoacetic acid and the peptide fragment in thiol **III**, appears to favor stabilization of anion SR^-, and the reaction begins with proton attach on the terpene double bond.

EXPERIMENTAL

The IR spectrum was obtained on a Specord IR-75 instrument in Vaseline oil. The ^1H and ^{13}C NMR spectra of compound **IV** in $CDCl_3$ were taken on a Varian Unity spectrometer (300 and 75.43 MHz). The mass spectrum of adduct **IV** was measured on an Incos-50B mass spectrometer combined with a Varian-3400 gas chromatograph, SE-30 capillary column, diameter 0.25 mm, ionizing energy 70 eV, injector temperature 250°C, ion source temperature 150°C. The reaction products were isolated on silica gel (100/160 μ).

Ethyl *N*-[2-(S-menth-1-en-8-yl)mercaptopropyonyl]glycine (IV). To 4 mmol of terpene we successively added at room temperature and with stirring 4 mmol of thiol **III** in 10 ml of CH_2Cl_2 and 2 ml of C_2H_5OH and 2 mmol of $ZnCl_2$ in 2 ml of C_2H_5OH. After 30 min, the reaction mixture was treated with 100 ml of water and then with CH_2Cl_2 (4×20 ml). The extract was washed with water (5×50 ml) and dried with $MgSO_4$. The solvent was removed, and the adduct was isolated by column chromatography on silica gel (hexane–ether, 1 : 1). Yield of compound **IV** 87% (in the reaction with β-pinene) and 76% (in the reaction with limonene). Mass spectrum of compound **IV**, *m/z* (I_{rel}, %): 327.3 (3) (M^+), 192.1 (10), 169.1 (37), 159.2 (43), 137.1 (61), 121.1 (6), 104.1 (14), 93.2 (22), 81.2 (100), 69.1 (15), 43.1 (210), 41.2 (18). IR spectrum, ν, cm^{-1}: 3440, 1680 [C(O)NH], 1745 [C(O)O], 1650 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.3 s (1H, HC^2), 4.2 q (2H, $OC\mathit{H}_2CH_3$, 8.5 Hz), 4.01 d.d (2H, $C^{13}H_2$, 7.0, 3.6 Hz), 3.44 q [1H, $C^{11}\mathit{H}(CH_3)$ 8.7 Hz], 3.35 s (1H, NH), 1.64 s (3H, C^7H_3), 1.45 s, 1.47 s (6H, $2CH_3C^8$), 1.25 t (3H, $OCH_2C\mathit{H}_3$, 8.5 Hz), 0.97 d (3H, $C^{17}H_3$, 8.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 175.05 (C^{14}), 171.15 (C^{12}), 138.10 (C^2), 125.40 (C^1), 123.02 (C^{13}), 97.00 (C^{15}), 63.04 (C^{11}), 60.05 (C^8), 47.02, 44.04, 42.05, 40.01, 31.03, 24.06, 22.00, 15.08, 15.03 (C^3–C^7, C^9, C^{10}, C^{16}, C^{17}).

ACKNOWLEDGMENTS

The work was financially supported by the INCO–COPERNICUS Foundation (grant no. IC-15-CT-98-015015).

REFERENCES

1. Wattenberg, L.W., Sparnins, V.L., and Barany, G., *Cancer Res.*, 1989, vol. 49, no. 10, p. 2689.
2. Schaffer, E.M., Liu, J.-J., Green, J., Dangler, C.A., and Milner, J.A., *Cancer Lett.*, 1996, vol. 102, p. 199.
3. Morgunova, V.A., Nikitina, L.E., Plemenkov, V.V., Chugunov, Yu.V., and Fazlyeva, M.G., *Zh. Org. Khim.*, 2000, vol. 36, no. 4, pp. 512–514.
4. Nikitina, L.E., Plemenkov, V.V., Shaikhutdinov, R.A., and Klochkov, V.V., *Zh. Org. Khim.*, 1996, vol. 32, no. 7, p. 1007.