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SYNTHESIS OF 1,4,7,7-TETRAMETHYLBICYCLO[2.2.1]HEPT-exo-2-YLACYLAMINES

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A procedure has been developed for the selective preparation of 2-methylisoborneol by the action of methyllithium on camphane. It has been shown that the interaction of 2-methylisoborneol with aceto- and benzonitriles in the presence of sulfuric acid gives, as the result of a rearrangement of the carbon skeleton, high yields of the corresponding 1,4,7,7-tetramethylbicyclo[2.2.1]hept-exo-2-ylacylamines, which possess an anticataleptic action.

Tertiary bicyclic alcohols of the camphane series are some of the least studied monoterpenoid derivatives, since they are not found in nature and their synthesis from camphane by the action of organomagnesium compounds takes place with low yields [1, 2]. Therefore, 2-methylcamphanol, in particular, has hitherto remained a poorly accessible compound for the study of its reactivity and spatial structure. At the same time, it is known [3] that the use of organolithium compounds enables tertiary alcohols to be obtained from ketones selectively and with high yields.

In the present paper we consider the interaction of camphor with methyllithium. It has been established that this gives a 52% yield of the individual 1,2,7,7-tetramethylbicyclo[2.2.1]heptan-*exo*-2-ol (**2**) the structure of which was determined on the basis of the results of ^{13}C NMR spectroscopy from the chemical shifts of the ^{13}C nuclei, having values characteristic for a camphane carbon skeleton, and the multiplicities of the signals in the spectra recorded without the suppression of coupling with protons. The chemical shift of the C^2 carbon atom was 79.3 ppm. The *exo*-configuration of the hydroxy group at the C^2 atom was established on the basis of a comparison with the spectra of model compounds — borneol, isoborneol, and *exo*-2- and *endo*-2-methylnorborneols [4]. A criterion for the determination of the *exo*-configuration of the hydroxy group was the chemical shift of the carbon atom of the methyl at the C^2 atom, which was 26.9 ppm. This value agrees well with literature figures for *endo*-2-methylnorborneol, for which the chemical shift of the analogous methyl group is 25.8 ppm. while for *exo*-2-methylnorborneol it is 30.4 ppm [4].

Also in favor of the structure of the alcohol (**2**) with the *endo*-position of the methyl group of the C^2 atom is the chemical shift of the C^6 carbon atom of 31.2 ppm coinciding with the shift of the analogous carbon atom in 1,7,7-trimethyl-2-phenylbicyclo[2.2.1]heptan-*exo*-2-ol [5]. As can be seen from the facts given, the addition of methyllithium to the carbonyl group of camphor takes place selectively from the less spatially hindered *endo*-side of the molecule with the formation of the individual *exo*-isomer of the alcohol (**2**).

It must be mentioned that, in our opinion, of derivatives of the camphane series the greatest interest in connection with the synthesis of biologically active compounds is presented by nitrogen-containing compounds, which possess a broad spectrum of biological activity [6]; they include 1,4,7,7-tetramethylbicyclo[2.2.1]hept-*exo*-2-ylacylamines, which exhibit anticataleptic activity [7].

As we have shown previously [8], 1,7,7-trimethyl-2-phenylbicyclo[2.2.1]heptan-*exo*-2-ol interacts with various nitriles under the conditions of acid catalysis by sulfuric acid with the formation of 1,7,7-trimethyl-4-phenylbicyclo[2.2.1]hept-*exo*-2-ylacylamines as a consequence of a rearrangement of an intermediate carbocation formed in the course of the reaction. We assumed that on the nucleophilic addition of nitriles to 2-methylisoborneol in the presence of sulfuric acid it might be possible

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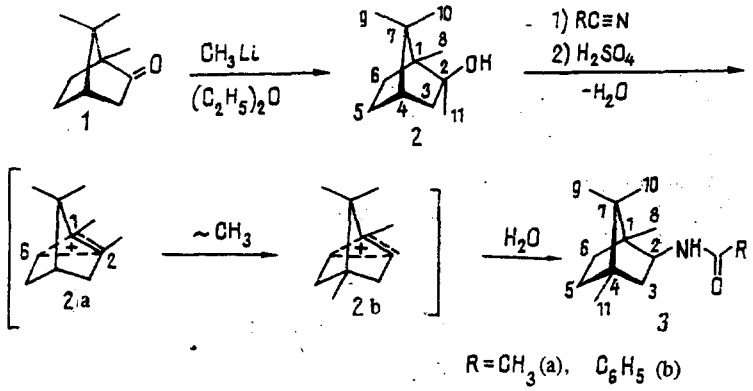
to obtain the corresponding 1,4,7,7-tetramethylbicyclo[2.2.1]hept-*exo*-2-ylacylamines. In a study of this reaction we have shown that the action of acetonitrile or benzonitrile on 2-methylisoborneol in the presence of sulfuric acid leads to the selective formation of the corresponding 1,4,7,7-tetramethylbicyclo[2.2.1]hept-*exo*-2-ylacetamide (**3a**) and -benzamide (**3b**) in high yields.

The structures of the compounds obtained were shown by ^{13}C and ^{1}H NMR spectroscopies in combination with IR spectroscopy and mass spectrometry. Thus, the IR spectra of compounds (**3a**) and (**3b**) had bands at ~3350, 3050, and 1530 cm^{-1}, corresponding to the vibrations of N—H bonds in substituted amides, and a band at ~1640 cm^{-1} that is characteristic for the vibrations of a C=O bond (amide band I). In the mass spectra of compound (**3a**) and (**3b**) there were the peaks of the molecular ions M^+ with intensities of ~10% of that of the maximum peaks in the spectrum.

The signals of four methyl groups in the form of singlets in a strong field (0.68-0.93 ppm) in the PMR spectra permitted the assumption of the presence of a 1,4,7,7-tetramethylbicyclo[2.2.1]heptane carbon skeleton in the amides synthesized (**3a**) and (**3b**). The singlet of a methyl group at 0.68 ppm in the spectrum of compound (3a) and one at 0.72 pm in the spectrum of compound (**3b**), were assigned to the methyl group at the C^4 atom. A signal in the form of a doublet of triplets at 3.89 ppm in the spectrum of compounds (**3a**) and one at 4.09 ppm in the spectrum of compound (**3b**) were characteristic for a proton in the *endo*-position at the C^2 atom linked with the amide group [8].

The ^{13}C NMR spectra of compounds (**3a**) and (**3b**) (see the Experimental part) corresponded to the proposed structure with methyl groups in the 1,4,7,7-positions of a bicyclic heptane carbon skeleton with an amide substituent at the C^2 atom, while the chemical shifts of 36.5 and 35.5 ppm for compounds (**3a**) and (**3b**), respectively, for the C^6 carbon atom, connected with the C^2 atom by spatial interaction, confirmed the *exo*-configuration of the amide group, since for the *endo*-configuration the chemical shift of this atom should be 27.5 ppm [4].

On the basis of the results obtained, a scheme for the transformation of 2-methylisoborneol (**2**) can be represented in the following way.



As a consequence of a 3,2-shift of a methyl group, the nonclassical carbocation (**2a**) formed initially on protonation is transformed into the nonclassical cation (**2b**), the stabilization of which by a nucleophile (nitrile) is possible only from the *exo*-side of the molecule, as a result of which the *exo*-isomer of amide (**3**) is formed stereoselectively. It must be mentioned that the methyl group introduced into the camphane skeleton by the action of methyllithium entered at the bridgehead atom C^4 as a result of a rearrangement taking place in the course of the Ritter reaction.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were taken on a Bruker M-360 spectrometer with resonance frequencies of 360.134 MHz for ^{1}H and 90.56 MHz for ^{13}C. The concentration of the solutions was ~10% in deuterochloroform. The chemical shifts of the ^{1}H and ^{13}C nuclei were determined relative to the internal standard tetramethylsilane. IR spectra were taken on a UR-20 spectrometer, and mass spectra on a MKh-1320 instrument.

The initial compound used for the syntheses was racemic camphor with mp 177-178°C.

1,2,7,7-Tetramethylbicyclo[2.2.1]heptan-*exo*-2-ol (2). In a current of argon, 120 ml of a 1 N solution of methyllithium in absolute diethyl ether was added dropwise to a solution of 15.2 g (0.1 mole) of camphor in 200 ml of dilute

diethyl ether. The reaction mixture was stirred at room temperature for 4 h and was then treated with water. The ethereal layer was dried with calcined magnesium sulfate. After the solvent had been distilled off, recrystallization from hexane yielded 8.7 g (52%) of 2-methylisoborneol (**2**). mp 168—170°C. According to the literature [1]: mp 153-155°C. IR spectrum (KBr, λ_{max}, cm^{-1}: 3450 (O−H), 2960 s, 2930 s, 2880 m, 1455 m, 1390 m, 1100 w. Mass spectrum (m/z): 168 (32%, M^+), 153, 150, 135, 121, 108 (100%), 95, 81, 69. PMR spectrum: (δ, ppm): 0.93 (s, 3H, C^7-CH_3- syn), 0.97 (s, 3H, C^7-CH_3-anti) 1.10 (s, 3H, C^1-CH_3), 1.25 (s, 3H, C^2-CH_3-endo), ^{13}C NMR spectrum (δ, ppm): 48.9 (s, C^1), 79.3 (s, C^2), 47.2 (t, C^3), 45.3 (d, C^4), 26.8 (t, C^5), 31.2 (t, C^6), 46.7 (s, C^7), 9.1 (q, C^8), 26.9 (q, C^9), 21.3 (q, C^{10}), 21.0 (q, C^{11}).

1,4,7,7-Tetramethylbicyclo[2.2.1]hept-*exo*-2-ylacetamide (3a). With vigorous stirring and cooling to +5°C, 5 ml of concentrated sulfuric acid was added dropwise to a solution of 5.6 g (0.033 mole) of 2-methylisoborneol (**2**) and 4.1 g (0.1 mole) of acetonitrile. The reaction mixture was stirred for 2 h and was then neutralized by the addition of a 25% aqueous solution of ammonia. The product was extracted with diethyl ether, and the extract was washed with water and dried with calcined magnesium sulfate. After the solvent had been distilled off, 6.5 g (93.4%) of 1,4,7,7-tetramethylbicyclo[2.2.1]hept-*exo*-2-ylacetamide (**3a**) was obtained. mp 162° (ethanol). IR spectrum (KBr, λ_{max}, cm^{-1}): 3320 w, 3070 w, (N−H), 2980 m, 2950 s, 2880 s, 1640 (C=O), 1540 s, (N−H), 1450 m, 1390 m, 1360 m, 1290 m, 695 w. Mass spectrum, m/z: 209 (12%, M^+), 194, 166, 150, 135, 123, 109 (100%), 107, 95, 84. PMR spectrum (δ, ppm): 0.68 (s, 3H, C^4-CH_3), 0.76 (s, 3H, C^7-CH_3- syn), 0.86 (s, 3H, C^7-CH_3-anti), 0.89 (s, 3H, C^1-CH_3), 1.20-1.30 (m, 3H) 1.40 (t.t., 1H, C^3-H-exo, $J_{H^3\text{-exo},H^3\text{-endo}}$ = 12.7 Hz, $J_{H^3\text{-exo-}H^2\text{-endo}}$ = 4.9 Hz), 1.49 (q.d, 1H), 1.88 (d.d, 1H, C^3-H-endo, $J_{H^3\text{-endo-}h^3\text{-endo}}$ = 12.7 Hz, $J_{H^3\text{-endo-}H^2\text{-endo}}$ = 9.3 Hz), 1.95 (s, 3H, $COCH_3$), 3.89 (d.t, 1H, C^2-H-endo, $J_{H^2\text{-endo-}H^2\text{-exo}}$ = 9.3 Hz, $J_{H^2\text{-endo,N-H}}$ = 8.8 Hz, $J_{H^2\text{-endo, }H^2\text{-exo}}$ = 4.9 Hz), 5.35 (1H, N−H), $J_{N-H,H^2\text{-endo}}$ = 8.8 Hz). ^{13}C NMR (δ, ppm), 47.6 (s, C^1), 57.3 (d, C^2), 45.5 (t, C^3), 48.6 (s, C^4), 35.5 (t, C^5), 36.5 (t, C^6), 52.1 (s, C^7), 12.9 (q, C^8), 16.4 (q, C^9), 18.2 (q, C^{10}), 18.7 (q, C^{11}), 172.7 (s, C^{12}), 22.7 (q, C^{13}).

1,4,7,7-Tetramethylbicyclo[2.2.1]hept-*exo*-2-ylbenzamide (3b). By the method described above, 5.6 g (0.03 mole) of alcohol (**2**), 10.2 g (0.1 mole) of benzonitrile, and 5 ml of concentrated sulfuric acid gave 3.7 g (21.3%) of the amide (**3b**). mp 92°C (hexane).

IR spectrum (KBr, λ_{max}, cm^{-1}): 3360 s (N−H), 3050 w, 3030 w (C−$H_{arom.}$), 2950 s, 2870 m, 1645 s (C=O), 1580 m (C−$H_{arom.}$), 1530 s (N−H), 1470 s, 1380 m, 1370 m, 1310 w, 1270 m, 710 s, 690 m (C−$H_{arom.}$) Mass spectrum, m/z: 259 (10%, M^+), 245, 194, 166, 150, 135, 123 (100%), 110, 95, 84, 77. PMR spectrum (δ, ppm): 0.72 (s, 3H, C^4-CH_3), 0.86 (s, 3H, C^7-CH_3-syn), 0.91 (s, 3H, C^7-CH_3-anti), 0.93 (s, 3H, C^1-CH_3), 1.20-1.35 (m, 3H), 1.45 (t.t, 1H, C^3-H-exo, $J_{H^3\text{-exo},H^3\text{-endo}}$ = 12.7 Hz, $J_{H^3\text{-exo},H^2\text{-endo}}$ = 4.9 Hz), 1.57 (q.d, 1H), 1.97 (d.d, 1H, C^3-H-endo, $J_{H^3\text{-endo, }H^3\text{-exo}}$ = 12.7 Hz, $J_{H^3\text{-endo, }H^2\text{-endo}}$ = 9.3 Hz), 4.09 (d.t, 1H, C^2-H-endo, $J_{H^2\text{-endo, }H^3\text{-endo}}$ = 9.3 Hz, $J_{H^2\text{-endo, N-H}}$ = 8.8 Hz, $J_{H^2\text{-endo, }H^3\text{-exo}}$ = 4.9 Hz), 6.05 (d, 1H, N−H, $J_{N-H,H^2\text{-endo}}$ = 8.8 Hz), 7.44 (m, 5$H_{arom.}$). ^{13}C NMR (δ, ppm): 47.0 (s, C^1), 56.8 (d, C^2), 45.6 (t, C^3), 48.0 (s, C^4), 34.4 (t, C^5), 35.6 (t, C^6), 51.0 (s, C^7), 12.8 (q, C^8), 15.9 (q, C^9), 18.1 (q, C^{10}), 18.2 (q, C^{11}), 167.6 (s, C^{12}), 126.8, 128.6, 131.2 (d, C_{arom}).

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