ISOCAMPHANONE IN SYNTHESIS OF 3-ALKYL- AND 6-ALKYL-SUBSTITUTED CAMPHOR DERIVATIVES

N. G. Kozlov, L. A. Popova, T. K. Vyalimyaé,
G. V. Nesterov, V. O. Knizhnikov, and Yu. K. Ol'dekop

UDC 547.599.6

On the interaction of isocamphanone with butyllithium, 2-butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-endo-2-ol is formed stereospecifically. As a result of skeletal rearrangements of carbonium ions taking place in the course of the reaction, the Ritter reaction of this tertiary alcohol with acetonitrile and benzonitrile has given endo-3-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylacylamines and endo-6-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylacylamines.

Isocamphanone (5,5,6-trimethylbicyclo[2.2.1]heptan-2-one) is a byproduct of the manufacture of synthetic camphor and has found no high-grade use. In spite of the fact that it is a very close structural analog of camphor, isocamphanone has not been found in natural sources. We have shown previously [1] that as the result of the Ritter reaction of 5,5,6-dimethylbicyclo[2.2.1]heptan-exo-2-ol, obtained on the reduction of isocamphanone (I) with lithium tetrahydroaluminate, it is possible to effect a transition to derivatives of the camphor series and, namely, N-isobornylacylamines. In view of this, it appeared of interest to study the possibility of synthesizing alkyl-substituted derivatives of camphor as the result of the skeletal rearrangement of tertiary alcohols based on isocamphanone that have not previously been described.

In the present paper we consider the interaction of butyllithium with isocamphanone and the behavior of the resulting tertiary alcohol — 2-butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-2-ol — under the conditions of the Ritter reaction.

The action of butyllithium on isocamphanone gave a 75% yield of 2-butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-endo-2-ol (II), the structure of which was established on the basis of the results of ^{13}C NMR spectroscopy. The chemical shift of the C-2 atom was 79.5 ppm. The assignment of the signals of the other carbon-13 atoms (Table 1) was made on the basis of the multiplicities of the lines in the spectrum recorded without suppression of interaction with protons, and also by a comparison with the chemical shifts of the ^{13}C nuclei in the spectra of model compounds such as endo- and exo-2-methylnorborneols, exo-6-methyl-exo-2- and -endo-2-norborneols and 1,2,3,3-tetramethylbicyclo[2.2.1]heptan-endo-2-ol [2, 3]. As can be seen from the figures given, the addition of butyllithium to the carbonyl group of isocamphanone took place stereospecifically with the formation of an individual isomer of the alcohol (II).

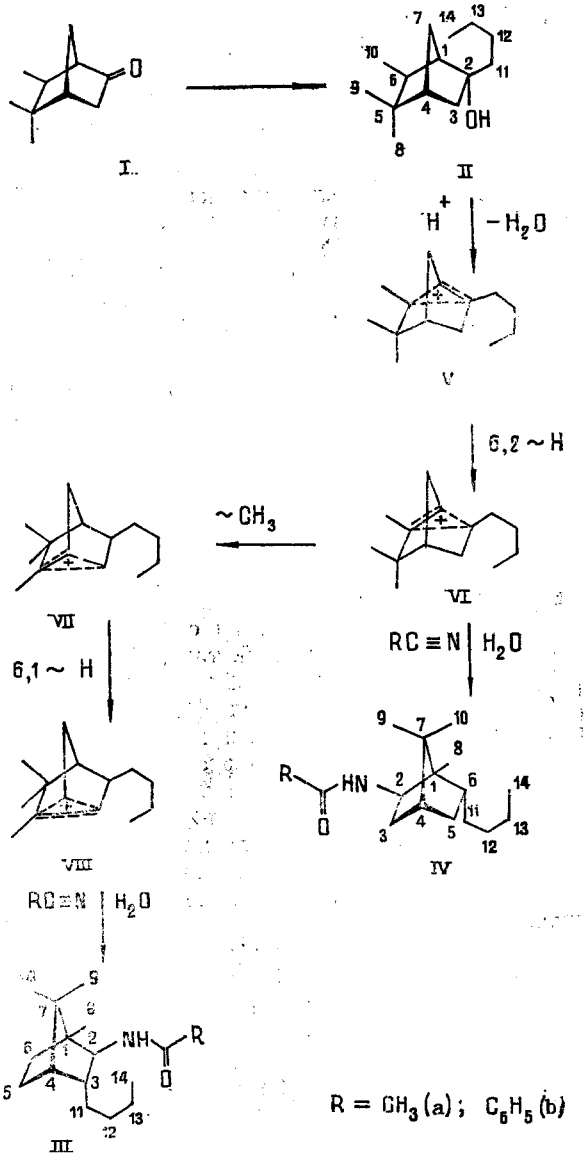
The Ritter reaction of 2-butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-endo-2-ol (II), with acetonitrile and benzonitrile was carried out under standard conditions. It was established that the reaction formed a mixture of the two isomeric amides (III) and (IV) in a ratio of 1:2 according to the results of GLC analysis.

By column chromatography on silica gel, endo-3-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylacetamide (IIIa) was isolated in the individual form (purity according to GLC 97%) from the mixture of amides (IIIa) and (IVa) obtained as the result of the interaction of alcohol (II) with acetonitrile. The structure of the amide (IIIa) was shown by IR, mass, and NM spectroscopy. The IR spectrum of compound (IIIa) contained adsorption bands at 3330, 3080, and 1550 cm^{-1}, corresponding to the vibrations of a N—H bond in substituted amides, and a band at 1650 cm^{-1} characterizing the vibrations of a C=O bond (amide I). In the mass spectrum there was a peak of the molecular ion M^+ with a relative intensity of 23%. The PMR spectrum of the amide (IIIa) contained three singlets of methyl groups at 0.79, 0.87, and

Institute of Physical Organic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk. Translated from Khimiya Prirodynkh Soedinenii, No. 6, pp. 807-812, November-December, 1988. Original article submitted February 10, 1988; revision submitted May 19, 1988.

 0009-3130/88/2406-0686$12.50

0.94 ppm, the values of the chemical shifts of which permitted the assumption of the presence of a 1,7,7-trimethylbicyclo[2.2.1]heptane skeleton in the compound. In addition, the signal at 3.43 ppm of a proton bound to a carbon atom in an amide group was identified in the spectrum in the form of a doublet of doublets.



The spin-spin coupling constant (SSCC) J = 10 Hz indicated the existence of vicinal interaction of this proton with a proton attached to a nitrogen atom (5.28 ppm, doublet), while J = 5 Hz corresponded to the SSCC characteristic for 1,3-endo-exo interaction between protons. The ^{13}C NMR spectrum of the amide (III) showed the signal of the C-2 carbon atom linked with the amide group at 63.8 ppm. The assignment of the other signals in the spectrum (see Table 1) was made on the basis of the multiplicities of the lines in the off-resonance spectrum, and also of a comparison with the calculated values of the chemical shifts obtained on the basis of the principle of structural additivity using values of the chemical shifts of model compounds close in structure such as N-(1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-yl)acylamines [4]. For a reliable assignment of the signals of the carbon atoms, the spatial environment of which changes as the result of 1,4-nonbound interactions on passing from one isomer to another must be taken into account.

Thus, in the determination of the configuration of the amide group at C-2, one must consider the chemical shifts of the C-6 and C-8 atoms. A calculation of the chemical shifts of these atoms showed that they should amount to 36.1 and 12.0 ppm in the exo-2 isomer and 27.5 and 14.0 ppm in the endo-2 isomer, respectively. On the basis of the calculated figures, the isolated compound (IIIa) was assigned to configuration of the isomer with the amide group

TABLE 1. ^{13}C NMR Spectra of Compounds (II)-(IV)

Compound	Chemical shifts of the ^{13}C nuclei, ppm, TMS, carbon atom						
	1	2	3	4	5	6	7
II experiment	57,7d	79,5s	39,8t	51,2d	30,8s	38,3d	36,5t
IIIa calculated	47,3s	63,0d	48,5d	48,3d	19,1t	36,1t	50,2s
experiment	48,1s	63,8d	48,3d	48,1d	20,0t	36,3t	49,7s
IVa calculated	52,0s	58,0d	40,0t	47,0d	35,0t	47,0d	51,0s
experiment	51,3s	57,6d	44,8t	45,8d	36,7t	46,8d	50,6s
IIIb experiment	47,8s	64,2d	48,5d	48,2d	20,0t	36,4t	50,8s
IVb experiment	50,4s	57,3d	44,1t	48,2d	36,3t	47,8d	50,3s

Compound	Chemical shifts of the ^{13}C nuclei, ppm, TMS, carbon atom						
	8	9	10	11	12	13	14
II experiment	26,2q	27,5q	15,8q	43,7t	26,5t	24,5t	14,8q
IIIa calculated	12,0q	20,5q	20,2q	32,7t	29,2t	23,1t	13,9q
experiment	12,6q	29,9q	20,1q	31,5t	30,7t	23,0t	14,3q
IVa calculated	11,9q	22,0q	20,0q	31,0t	30,0t	23,0t	14,0q
experiment	11,8q	22,4q	20,6q	31,1t	30,9t	23,5t	14,4q
III b experiment	12,5q	20,8q	20,2q	31,7t	30,6t	23,1t	14,2q
IVb experiment	12,0q	21,0q	20,5q	31,6t	30,9t	23,0t	14,3q

The chemical shifts of the ^{13}C carbon atoms in substituent R were: 169.0 s (C=O) and 23.7 q ($CO\underline{C}H_3$) in the amide (IIIa); 170.9 s (C=O) and 23.5 q ($CO\underline{C}H_3$) in the amide (IVa); and 166.8 s (C=O), 135.4 s (ipso), 162.9 d (ortho), 128.5 d (meta), and 131.2 d (para) in amides (IIIb) and (IVb).

at the C-2 atom in the exo-position. On the basis of the PMR results given above, in this case, the second substituent, namely the butyl group, must be present at the C-3 atom in the endo-position. The value of the chemical shift of the C-5 atom, 20.0 ppm, in the ^{13}C NMR spectrum of the amide (IIIa) is additional evidence of the endo-arrangement of the butyl group since, according to calculations, if it had the exo-arrangement it should amount to 28.0 ppm. The good agreement of the experimentally obtained values of the chemical shifts for amide (IIIa) with the calculated values (see Table 1) permits the unambiguous assignment to the compound (IIIa) obtained of the structure of endo-3-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylacetamide.

The second component of the mixture of compounds (III) and (IV) obtained was obviously endo-6-butyl-1,7,7-trimethyl[2.2.1]hept-exo-2-ylacetamide (IVa). The structure of amide (IVa) was confirmed by the results of NMR spectroscopy. The PMR spectrum of the compound had three singlets of methyl groups at 0.80, 0.89, and 0.93 ppm, the signal of the proton at a nitrogen atom (5.67 ppm) in the form of a doublet, and the signal of a proton at a carbon atom linked to an amide group (3.83 ppm) appearing in the spectrum in the form of a characteristic doublet of triplets [5], which shows the presence in compound (IVa) of an amide group at the C-2 atom in the exo-position and of a methylene group in position 3. The chemical shift of the C-2 atom in the ^{13}C NMR spectrum amounted to 57.6 ppm. The assignment of the other signals in this spectrum was made on the basis of the multiplicities of the lines in the off-resonance spectrum, and also of a comparison with the calculated values of the chemical shifts obtained on the basis of model compounds of the camphane series [4].

A criterion of the assignment of the structure of amide (IVa) to the isomer with the exo-orientation of the amide group at the C-2 atom and the endo-orientation of the butyl group of the C-6 atom is the value of the chemical shift of the methyl group at the C-1 atom which was 11.8 ppm. According to calculations, in the exo-2-exo-6 isomer the value of the chemical shift of this carbon atom should not exceed 10 ppm. The good agreement of the experimentally obtained and the calculated chemical shifts of amide (IVa) (see Table 1) show the correctness of the proposed structure for it of endo-6-butyl-1,7,7-trimethylbicyclo[2.2.1]-hept-exo-2-ylacetamide. The structures of the endo-3-butyl-1,7,7-trimethylbicyclo[2.2.1]-hept-exo-2-ylbenzamide (IIIb) and the endo-6-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylbenzamide (IVb) obtained as the result of the interaction of alcohol (II) with benzonitrile were shown similarly. The values of the chemical shifts of the ^{13}C nuclei for these compounds are given in Table 1.

On the basis of the results obtained, it may be assumed that the carbonium ion (V) initially formed on the protonation of alcohol (II) was converted as the result of a 6,2-hydride shift into the "nonclassical" cation (VI). The addition of a nucleophile (nitrile) to this cation is, according to stereoelectronic demands [6], possible only from the exo-side of the molecule, as a result of which the 2-exo isomer of the amide (IV) is formed stereospecifically. It must be mentioned that udner these conditions the substituent (butyl group) at the C-6 atom, which is included in a three-center bond of the cation (VI), assumed the endo-orientation. The formation, as the result of the reaction, of endo-3-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylacylamine (III) probably takes place as the result of a 5,6-migration of the exo-CH_3 group taking place in the carbocation (VI). The cation (VII) so obtained is converted as the result of a 6,1-hydride shift in the "nonclassical" cation (VIII), the addition to which of the nucleophile gives the amide (III).

EXPERIMENTAL

The reaction products were analyzed by GLC on a LKhM-7A chromatograph with programming of the temperature from 90 to 200°C using a packed column (0.5 × 2000 mm) containing Apiezon K (12%) on the support Chromosorb W (60-80 mesh) + 10% KOH. ^1H and ^{13}C NMR spectra were taken on a Bruker WM-360 spectrometer with resonance frequencies for ^1H and ^{13}C of 360.13 and 90.52 MHz, respectively. The concentration of the solutions was 1:4 by volume in deuterochloroform or deuteromethanol. The chemical shifts of the ^1H 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.

2-Butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-endo-2-ol (II). In a current of argon, 120 ml of a 1 N solution of butyllithium in absolute diethyl ether was added dropwise to a solution of 15.2 g of 5,5,6-trimethylbicyclo[2.2.1]heptan-2-one (I) in 200 ml of absolute diethyl ether. The reaction mixture was stirred at room temperature (25°C) for 8 h and was treated with water. The ethereal solution was dried with $CaCl_2$. After the solvent had been distilled off, the product was redistilled in vacuum, which gave 15.7 g (75%) of the tertiary alcohol (II). $C_{14}H_{26}O$, bp 124-125°C (5 mm Hg), n_D^{22} 1.4796. Found, %: C 80.05, H 12.53. Calculated, %: C 79.94, H 12.46, O 7.60. λ_{max}^{KBr}, cm^{-1}: 3480 (O–H), 2970, 1470, 1385, 1375, 1280, 1020 (C–H).

Mass spectrum, m/z (%): 210 (M^+; 11), 192, 168, 153, 149, 135, 125, 121, 110 (100), 95, 85, 69, 58.

PMR spectrum, $CDCl_3$, ppm: 0.72 d (3H, exo-CH_3-6, J = 7.9 Hz), 0.77 s (3H, endo-CH_3-5), 0.79 t (3H, CH_3-13), 0.97 s (3H, exo-CH_3-5), 1.22 m (7H), 1.36 m (2H), 1.47 m (2H), 1.62 dt (1H), 1.82 s (1H, O–H), 1.97 q (1H, endo-H-6).

Ritter Reaction of 2-Butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-2-ol (II). A. With vigorous stirring and cooling (0-5°C), 5 ml of concentrated H_2SO_4 was added dropwise to 4.2 g of the alcohol (II) and 2.2 g of acetonitrile. After addition of the acid, stirring was continued at room temperature for 8 h. Then the reaction mixture was neutralized with aqueous ammonia solution and was extracted with diethyl ether. The ethereal extract was dried with $CaCl_2$ and, after the solvent had been distilled off, 3.2 g (64%) of a mixture of amides (IIIa) and (IVa) was obtained in a ratio of 1:2. $C_{16}H_{29}ON$, bp 165-170°C (5 mm Hg). Found, %: C 76.51, H 11.47, N 5.39. Calculated, %: C 76.44, H 11.63, N 5.57. λ_{max}^{KBr}, cm^{-1}: 3330, 3080 (N–H), 2960, 2880 (C–H), 1650 (C=O), 1550 (N–H), 1450, 1385, 1375, 1195 (C–H).

Mass spectrum, m/z (%): 251 (M^+; 23), 236, 208, 192, 177, 165, 151, 135, 121, 109 (100), 95, 86, 70, 55.

By column chromatography on Chemapol silica gel L40/100 (with diethyl ether as eluent) from the mixture of amides (IIIa) and (IVa) the amide (IIIa) was isolated with a purity, according to GLC, of 97%; mp 139-140°C (ethanol).

PMR spectrum, $CDCl_3$, ppm: 0.79 s (3H, CH_3-1), 0.87 s (3H, CH_3-7), 0.89 t (3H, CH_3-13), 0.94 s (3H, CH_3-7), 1.24 m (7H), 1.50 m (3H), 1.64 m (1H), 1.80 m (1H), 1.98 s (3H, $COCH_3$), 3.43 dd (1H, endo-H-2, $^3J_{NH}$ = 10 Hz, $^3J_{exo\text{-}H\text{-}3}$ = 5 Hz), 5.28 d (1H, N–H, $^3J_{endo\text{-}H\text{-}2}$ = 10 Hz).

The eluate collected after the separation of the amide (IIIa) contained endo-6-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylacetamide (IVa) with a purity, according to GLC, of 80%, in admixture with amide (IIIa); bp 169-171°C (5 mm Hg).

PMR spectrum, $CDCl_3$, ppm: 0.80 s (3H, CH_3-1), 0.84 t (3H, CH_3-13), 0.89 s (3H, CH_3-7), 0.93 s (CH_3-7), 1.30 m (6H), 1.45 m (4H), 1.59 m (1H), 1.96 s (3H, $COCH_3$), 2.13 dd (1H, exo-H-6, $^3J_{exo\text{-}H\text{-}5}$ = 9.8 Hz, $^3J_{endo\text{-}H\text{-}5}$ = 5 Hz), 3.83 dt (1H, endo-H-2, $^3J_{exo\text{-}H\text{-}3}$ = 4.8 Hz, $^3J_{endo\text{-}H\text{-}3}$ = 7 Hz, $^3J_{N\text{-}H}$ = 10 Hz), 5.67 d (1H, N–H).

B. From 4.2 g of the alcohol (II) and 3.5 g of benzonitrile was obtained 2.6 g (42%) of a mixture of the amides (IIIb) and (IVb) in a ratio of 1:2; $C_{21}H_{31}ON$, bp 195-198°C (5 mm Hg). Found, %: C 80.37, H 10.05, N 4.35. Calculated, %: C 80.46, H 9.97, N 4.47. λ_{max}^{KBr}, cm^{-1}: 3360 (N–H), 3060, 3030 (C–H arom.), 2990-2880 (C–H), 1650 (C=O), 1540 (N–H), 1470, 1390, 1375, 1280 (C–H), 713, 693 (C–H arom.).

Mass spectrum, m/z (%): 313 (M^+; 19), 298, 284, 270, 257, 242, 214, 192, 188, 177, 148, 135, 121 (100), 105, 95, 77, 51.

The mixture of compounds (IIIb) and (IVb) so obtained was separated by column chromatography into two fractions. The first, enriched with endo-3-butyl-1,7,7-trimethylbicyclo-[2.2.1]hept-exo-2-ylbenzamide (IIIb) contained the amide (IVb) as impurity (about 20%), while the second, enriched with endo-6-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylbenzamide (IVb) contained about 15% of the amide (IIIb) as impurity.

PMR spectrum of the amide (IIIb), $CDCl_3$, ppm: 0.78 s (3H, CH_3-1), 0.89 s (3H, CH_3-7), 0.91 t (3H, CH_3-13), 1.04 s (3H, CH_3-7), 1.20 m (6H), 1.55 m (4H), 1.70 m (1H), 1.86 m (1H), 3.66 dd (1H-endo-H-2, $^3J_{N\text{-}H}$ = 9.8 Hz, $^3J_{exo\text{-}H\text{-}3}$ = 5 Hz), 6.02 d (1H, N–H), 7.42 m (5H, arom.).

PMR spectrum of the amide (IVb), $CDCl_3$, ppm: 0.80 s (3H, CH_3-1), 0.85 t (3H, CH_3-13), 0.92 s (3H, CH_3-7), 1.02 s (3H, CH_3-7), 1.35 m (6H), 1.50 m (4H), 1.65 m (1H), 2.25 dd (1H, exo-H-6, $^3J_{exo\text{-}H\text{-}5}$ = 9.5 Hz, $^3J_{endo\text{-}H\text{-}5}$ = 5 Hz), 4.03 dt (1H, endo-H-2, $^3J_{exo\text{-}H\text{-}3}$ = 5 Hz, $^3J_{endo\text{-}H\text{-}3}$ = 6.5 Hz, $^3J_{N\text{-}H}$ = 10 Hz), 6.11 d (1H, N–H), 7.71 m (5H, arom.).

CONCLUSIONS

The interaction of isocamphanone with butyllithium leads stereospecifically to the formation of 2-butyl-5,5,6-trimethylbicyclo[2.2.1]heptan-endo-2-ol. By the Ritter reaction of this tertiary alcohol with acetonitrile and with benzonitrile, as the result of skeletal rearrangements of carbonium ions taking place during the reaction, endo-3-butyl-1,7,7-trimethylbicyclo[2.2.1]hept-exo-2-ylacylamines and endo-6-butyl-1,7,7-trimethylbicyclo[2.2.1]-hept-exo-2-ylacylamines have been synthesized.

LITERATURE CITED

1. N. G. Kozlov, G. V. Nesterov, and S. A. Makhnach, Zh. Obshch. Khim., 55, No. 9, 2097 (1985).
2. J. M. Coxon and P. L. Steel, Aust. J. Chem., 32, No. 11, 2441 (1979).
3. J. B. Stothers, C. T. Tan, and K. C. Teo, Can. J. Chem., 54, No. 8, 1211 (1976).
4. R. M. Carman and K. L. Greenfield, Aust. J. Chem., 37, No. 9, 1785 (1984).
5. S. Tadashi, E. Shoji, and O. Takeshi, Bull. Chem. Soc. Jpn., 43, No. 4, 1251 (1970).
6. V. A. Barkhash, Nonclassical Carbocations [in Russian], Nauka, Novosibirsk (1984).