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SYNTHESIS OF BICYCLO-HEPTANE, 6-OXABICYCLO-OCTANE AND 3-AZABICYCLO-NONENE DERIVATIVES IN THE COURSE OF 1,2,4-TRIMETHYL-4-ISOPROPENYLCYCLOHEXENE CYCLIZATION

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Carbocyclic and heterocyclic compounds of the bicyclo[2.2.1]-heptane, 6-oxabicyclo[3.2.1]octane, and 3-azabicyclo[3.3.1]-nonene series were obtained from the reaction between 1,2,4-trimethyl-4-isopropenylcyclohexene (a dimer of 2,3-dimethyl-buta-1,3-diene) and CH_3CN in the presence of H_2SO_4, which was accompanied by intramolecular cyclization.

Electrophilic addition to 1,5-diene hydrocarbons is often synchronous with intramolecular $C^+ - \pi$-cyclization, and as this proceeds, differences in the nucleophilicity of the double bond dictate to a significant extent which course the reaction will take.

In a previous work [1] we showed that when 1,2,4-trimethyl-4-isopropenylcyclohexene (I) reacts with HCOOH at 25°C, over 90% of the resultant product mixture (yield 55%) has the structure of bicyclo[2.2.1]heptane (II 70%, III 12%, IV 1%) and tricyclo-[2.2.1.$0^{2,6}$]heptane (VI 10%). An aromatic hydrocarbon (V 10%), whose proportion of the product mixture increased to 40% when the reaction proceeded at 75°C, was also formed as a by-product, i.e., the primary course of the diene (I) reaction was intramolecular $C^+ - \pi$-cyclization (Scheme 1).

At the same time, no cyclization products were found in the case of acid isomerization of dipentene VII and sylvestrene VIII [2]. The main reaction course for these dienes is the migration of the exocyclic double bond, which is impossible in diene I due to the presence of the CH_3 group at position 4. For diene I, cyclization is probably facilitated by the fact that the isopropenyl group can have an axial arrangement in the transition state (Scheme 2).

It was thought worthwhile to study the behavior of diene I under Ritter reaction conditions using acetonitrile, whose addition to the unsaturated hydrocarbon is catalyzed by sulfuric acid. The reaction between diene I and CH_3CN was carried out at 25°C using various molar ratios of the diene and the acid, and also in the presence of nucleophilic solvents capable of suppressing the rearrangements [3].

When diene I reacted with H_2SO_4 (in the absence of CH_3CN), the more nucleophilic exocyclic double bond was protonated, affording carbocation A, in which closure of the $C_{(1)}-C_{(7)}$ bond occurred. The resultant cation B either underwent a Wagner-Meerwein rearrangement (ion D), yielding subsequently hydrocarbon III, or stabilized by shedding a proton, to give hydrocarbons II, IV, and VI. Together with these reactions, cation A may give rise through CH_3 group displacement to cation B, which forms the aromatic hydrocarbon V via diene E (unstable under the given reaction conditions) and cation F. The latter reactions are typical of six-membered hydrocarbons with two double bonds and have been described previously in the literature [2].

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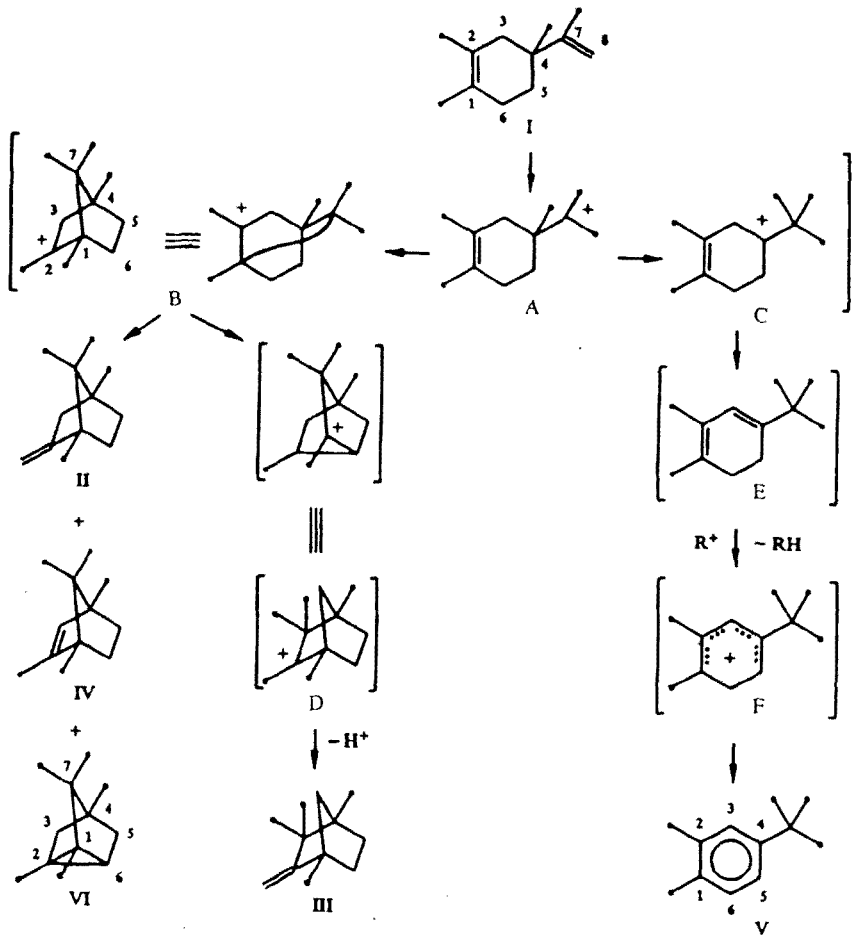
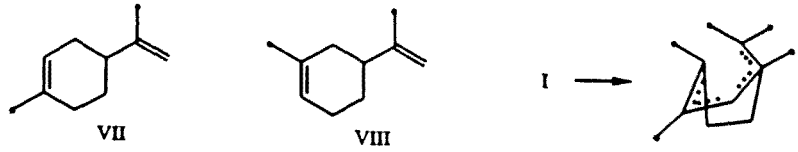
Scheme 1



Scheme 2



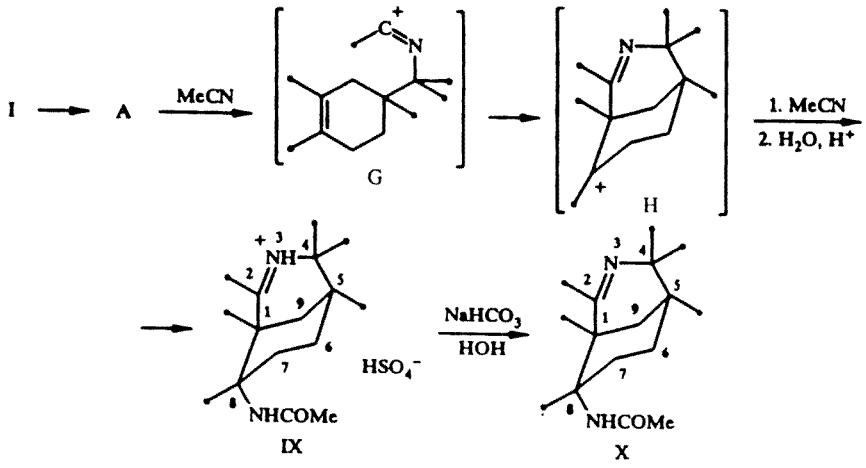
When diene I reacted with H_2SO_4 in the presence of CH_3CN (1:1:90 reagent molar ratio), the sole product was exo-8-acetamidohexamethyl-3-azabicyclo[3.3.1]nonene hydrosulfate (IX) in 84% yield. The likely reaction mechanism is shown in Scheme 3 (see Scheme 3 on following page.)

Addition of CH_3CN to cation A produced nitrile ion G, and the intramolecular closure of the bond in this ion afforded cation H. The latter was stabilized by the capture of a second CH_3CN molecule, resulting in hydrosulfate IX. When this salt was hydrolyzed with aqueous $NaHCO_3$ solution, cyclic azomethine X was formed.

When diene I reacted with H_2SO_4 in the presence of CH_3CN using a higher proportion of the acid (1:5:90 reagent molar ratio), amides of bicyclo[2.2.1]heptane structure constituted the main products. According to GLC and ^{13}C NMR data the number of amides totalled 10. Carbon atom sp^2 signals were not found in the ^{13}C NMR spectrum of this mixture, while the chromatography-mass spectrum exhibited molecular ion peaks (M^+ 223) which were constituted with the addition of one acetonitrile molecule. These data confirmed the fact that the resultant amides were of bicyclic structure. Although separation proved difficult due to their similar R_f values, it was possible to isolate exo-2-acetylamino-1,2,4,7,7-pentamethylbicyclo-[2.2.1]heptane (XI) in 25% yield and exo-2-acetylamino-1-endo-3,4,7,7-pentamethylcyclo[2.2.1]heptane (XII) in 7% yield.

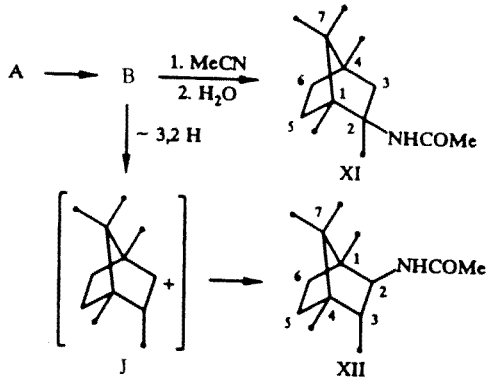
These results demonstrate that $C^+ - \pi$-cyclization of the initial cation A occurred under the given conditions, with the resultant cation B being stabilized by acetonitrile. In addition, carbocation A may undergo a Wagner-Meerwein rearrangement

Scheme 3



and hydrogen atom displacements, resulting in isomeric acetylamines. Specifically, an eno-3,2-hydrogen displacement gave rise to cation J which, when stabilized, yielded amide XII (Scheme 4).

Scheme 4



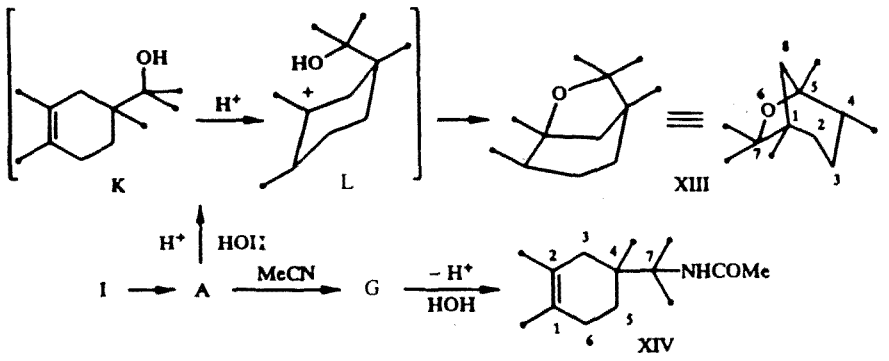
Since we have shown in a previous report that under Ritter reaction conditions nucleophilic solvents (e.g., water) are able to suppress rearrangement [3], an investigation was also undertaken into the behavior of diene I with H_2SO_4 in the presence of CH_3CN (1:5:90:12 reagent molar ratio). In this case a mixture of acetylamines was afforded in 30% yield, in which the proportion of compounds XI and XII reached 80%. That is to say, $C^+ - \pi$-cyclization did occur, but further rearrangements were essentially suppressed.

When an even greater water ratio was used in the reaction mixture (1:5:90:25 reagent ratio), $C^+ - \pi$-cyclization was also suppressed in cation A and the only products were those formed through stabilization by external nucleophiles. Thus when cation A was stabilized by water, the resultant alcohol K was evidently protonated at the double bond and converted, via cation L, into 1-endo-4,5,7,7-pentamethyl-6-oxabicyclo[3.2.1]octane (XIII). However, when cation A added a CH_3CN molecule to give cation G and then added water, acetylamine XIV resulted (Scheme 5) (see Scheme 5 on following page.)

The structure and component ratio of the reaction mixtures were substantiated using mass spectrometry and ^1H and ^{13}C NMR spectroscopy techniques. ^{13}C chemical shift figures for the synthesized compounds were in line with calculated values. The calculations were made using ^{13}C NMR data for 2,7,7-trimethyl-6-oxabicyclo[3.2.1]octane, 1,5-dimethyl-bicyclo[3.2.1]-octane and bicyclo[3.2.1]octane [4, 5], with allowance made for vicinal interactions.

Because of its low concentration in the synthesized mixture it was not possible to detect all the signals for hydrocarbon IV in the C NMR spectrum. Its presence in the mixture was, therefore, deduced from data in communication [6] and from the fact that a doublet was found at 129.4 ppm in the ^{13}C NMR spectrum. The structure of salt X was not at variance with the literature data for azomethine perchlorate X [7].

Scheme 5



In summary, diene I reacted with CH_3CN in the presence of sulfuric acid to produce several different compounds, the product depending on the reaction conditions, the medium acidity and the quantity of solvent used. Variation in the solvation properties of the solvent, which affect the capacity of the developing carbocations to regroup, is probably the significant factor determining the course of the reaction.

In the case of low sulfuric acid concentrations, solvation of the monocyclic ion A inhibited interaction between the carbocation center and the cyclohexene double bond, resulting in the formation of a compound with a bicyclo[3.3.1]nonane structure.

When a large amount of sulfuric acid was present, the reaction proceeded in a different manner, and compounds with the structure of bicyclo[2.2.1]heptane predominated in the product mixture.

With the addition of water to the reaction mixture, the monocyclic carbocation A rearranged into ion B. Further reactions by carbocation B were suppressed and in this case the main reaction products were acetamides of bicyclo-[2.2.1]heptane structure.

When an even higher water proportion was present in the reaction mixture, $C^+ - \pi$-cyclization in carbocation A was almost completely suppressed. In this case the reaction products, namely an amide of cyclohexane structure and a compound with the structure of oxabicyclo[3.2.1]octane, stemmed from stabilization of carbocation A by external nucleophiles alone.

EXPERIMENTAL

GLC analysis of the reagents and products was performed on Tsvet-1, LKhM-8 MD and Khrom-5 instruments with flame ionization detection, using 50000 × 0.25 mm capillary columns and squalane, PEG and OV-101 (on a modified-surface glass column) as the stationary phase, and nitrogen as the carrier gas. NMR spectra were obtained on a Bruker AM-500 spectrometer at frequencies of 500.17 (^1H) and 125.77 (^{13}C) MHz, using $CDCl_3$ as the standard. IR spectra were recorded on a UR-20 instrument in a film or petroleum jelly medium. Chromatography-mass spectroscopy analysis was carried out on a Finnigan MAT 112S in electron collision mode (70 eV ionization energy, 220°C source temperature) using a glass capillary column, with SE-54 as the stationary phase.

All the reactions were performed at 25°C.

1,2,4-Trimethyl-4-isopropenylcyclohexene (I). Synthesis and purification of diene (I) are described in report [1], bp 98-99°C (24 mm Hg). Mass spectrum, *m/z* (I, %): 164[M^+] (44), 149 (21), 135 (32), 121 (87), 109 (33), 108 (21), 107 (74), 106 (20), 93 (19), 91 (23), 82 (92), 67 (100). PMR spectrum: 1.00 (3H, s, 4-CH_3); 1.58 and 1.61 (2 to 3H, 2s, 1-CH_3 and 2-CH_3); 1.73 (3H, s, 7-CH_3); 1.48 and 1.62 (2H, m, 5-H); 1.76 and 2.09 (2H, d, 3-H); 1.91 (2H, m, 6-H); 4.65 and 4.72 ppm (2H, d, 8-H).

^{13}C NMR spectra: 123.56 and 123.78 ($C_{(1)}$ and $C_{(2)}$); 18.41 and 19.01 (1-CH_3, 2-CH_3); 42.89 ($C_{(3)}$); 37.70 ($C_{(4)}$); 32.70 ($C_{(5)}$); 29.59 ($C_{(6)}$); 25.05 (4-CH_3); 18.93 (7-CH_3); 108.78 (CH_2=); 151.06 ppm ($C_{(7)}$).

1,4,7,7-Tetramethyl-2-methylenebicyclo[2.2.1]heptane (II), 1,2,2,4-teramethyl-3-methylbenebicyclo[2.2.1]heptane (III), 1,2,4,7,7-pentamethyltricyclo[2.2.1.$0^{2,6}$]heptane (VI) and 1,2-dimethyl-4-tert-butylbenzene (V) have been described in a previous report [1].

exo-8-Acetylamino-1,2,4,4,5,8-hexamethyl-3-azabicyclo[3.3.1]-non-2-ene Hydrosulfate (IX). When 1.2 g of 96% H_2SO_4 and 58 ml acetonitrile had been added to 2 g (0.012 moles) diene I, the mixture was stirred for 7 h. The resultant

precipitate of compound IX was washed with ether and recrystallized from ethanol, mp 223-225°C (yield 85%). Mass spectrum, *m/z* (I, %): 205 (M^+-HSO_4-CH_3CONH_2) (16), 190 (7), 164 (6), 150 (38), 121 (32), 109 (14), 108 (25), 107 (61), 106 (24), 105 (9), 93 (12), 91 (19), 83 (11), 79 (11), 55 (12), 43 (14), 42 (42), 41 (100). PMR spectrum ($CDCl_3-CD_3OD$): 0.96 (3H, s, 5-CH_3); 1.33 and 1.36 (2 to 3H, 2s, 4,4-$(CH_3)_2$); 1.41 (3H, s, 8-CH_3); 1.53 (3H, s, 1-CH_3); 2.00 (3H, s, CH_3CO); 2.50 (3H, s, 2-CH_3); 1.18 and 2.38 (2H, m, 7-H); 1.58 and 1.78 (2H, m, 6-H); 1.36 and 1.40 (2H, m, 9-H); 5.34 (1H, broad s, NH); 7.52 ppm (1H, s, NH). IR spectrum (KBr): 590, 855, 1040 (HSO_4), 1520, 1550 (NH, CN), 1620 (C=N), 1675 (C=O), 2700, 3000 (=CH), 3320 cm^{-1} (NH). ^{13}C NMR spectrum: 46.43 ($C_{(1)}$); 22.41 (1-CH_3); 191.98 ($C_{(2)}$); 22.97 (2-CH_3); 64.89 ($C_{(4)}$); 18.18 and 25.85 (4,4-$(CH_3)_2$); 31.13 ($C_{(5)}$); 24.11 (5-CH_3); 33.66 ($C_{(6)}$); 31.20 ($C_{(7)}$); 57.69 ($C_{(8)}$); 19.43 (8-CH_3); 35.40 ($C_{(9)}$); 23.13 ($\underline{CH_3}CONH$); 171.46 ppm (C=O). Found, %: C 52.97; H 8.51; N 7.41; S 8.70. $C_{16}H_{30}O_5N_2S$. Calculated, %: C 53.00; H 8.36; N 7.73; S 8.84.

exo-8-Acetylamino-1,2,4,4,5,8-hexamethyl-3-azabicyclo[3.3.1]-non-2-ene (X). A saturated $NaHCO_3$ solution was added to 0.6 g (0.002 moles) of salt IX until an alkaline reaction was obtained. The chloroform extract was washed with water and dried with $MgSO_4$. Yield 94%. Mass spectrum, *m/z* (I, %); 264 (M^+) (34), 249 (9), 205 (16), 190 (15), 178 (13), 164 (25), 152 (26), 151 (39), 150 (67), 148 (17), 136 (20), 129 (45), 127 (18), 126 (15), 110 (22), 109 (32), 108 (19), 84 (13), 83 (30), 70 (22), 68 (18), 58 (27), 57 (21), 55 (27), 43 (60), 42 (100). PMR spectrum ($CDCl_3$, 90 MHz); 0.75 (3H, s, 5-CH_3); 0.98 (3H, s, 1-CH_3); 1.09 and 1.12 (2 to 3H, 2s, 4,4-$(CH_3)_2$); 1.37 (3H, s, 8-CH_3); 1.90 (3H, s, 2-CH_3); 2.00 (3H, s, $\underline{CH_3}CO$); 5.21 (1H, broad s, NH), 1.12 and 2.29 (2H, m, 7-H); 1.13 and 1.57 (2H, m, 6-H); 1.35 and 1.36 ppm (2H, m, 9-H). ^{13}C NMR spectrum: 44.23 ($C_{(1)}$), 27.21 (1-CH_3); 169.35 ($C_{(2)}$); 61.13 ($C_{(4)}$); 19.17 and 21.68 (4,4-$(CH_3)_2$); 33.76 ($C_{(5)}$); 25.95 (5-CH_3); 30.33 ($C_{(7)}$); 32.45 ($C_{(6)}$); 57.28 ($C_{(8)}$); 21.68 (8-CH_3); 37.75 ($C_{(9)}$, 24.10 (CH_3CONH); 169.50 ppm (C=O).

exo-2-Acetylamino-1-endo-3,4,7,7-pentamethylbicyclo[2.2.1]-heptane (XII). When 3 g of 96% H_2SO_4 and 29 ml acetonitrile had been added to 1 g (0.006 moles) diene I, the mixture was stirred for 6 h. After appropriate treatment the residue was fractionated on silica gel (40-100 μ, 5:1 hexane–ethyl acetate elutriator). One of the fractions (7% yield) comprised the individual compound XII. ^{13}C NMR spectrum: 49.4 ($C_{(1)}$); 64.2 ($C_{(2)}$); 47.4 ($C_{(3)}$); 40.7 ($C_{(4)}$); 26.6 ($C_{(5)}$); 35.6 ($C_{(6)}$); 49.9 ($C_{(7)}$); 14.2, 13.5, 12.4, 18.5, 17.5 (1-, 3-, 4-, 7-, 7-CH_3), 23.5 (CH_3CO), 169.6 ppm (C=O).

exo-2-Acetylamino-1,2,4,7,7-pentamethylbicyclo[2.2.1]heptane (XI). A mixture of 3 g 96% H_2SO_4, 29 ml acetonitrile and 1 g (0.006 moles) diene I was stirred for 3.5 h, then poured into water and extracted with chloroform. When the extract had been washed with water and dried with $MgSO_4$, the solvent was distilled off and the residue was sublimated. Yield 35%, purity 85%. Mass spectrum, *m/z* (I, %): 223 (M^+) (2), 165 (18), 150 (12), 136 (14), 121 (18), 109 (100), 58 (19). PMR spectrum ($CDCl_3$): 0.75 (syn) and 0.90 (anti) (2 to 3H, 2s, 7,7-$(CH_3)_2$); 0.83 (3H, s, 4-CH_3); 0.92 (3H, s, 1-CH_3); 1.34 (3H, s, 2-CH_3); 1.16 (endo) and 1.40 (exo) (2H, 2m, 5-H); 1.34 and 1.64 (2H, 2m, 6-H); 1.50 (endo) and 2.29 (exo) (2H, 2m, 3-H); 1.90 ppm (3H, s, $\underline{CH_3}CONH$). ^{13}C NMR spectrum: 52.73 ($C_{(1)}$): 59.74 ($C_{(2)}$); 51.41 ($C_{(3)}$); 46.87 ($C_{(4)}$); 33.46 ($C_{(5)}$); 30.44 ($C_{(6)}$); 49.54 ($C_{(7)}$); 10.96 (1-CH_3); 22.23 (2-CH_3); 15.68 (4-CH_3); 18.61 and 18.30 (7,7-$(CH_3)_2$); 23.94 (CH_3CONH), 167.49 ppm (C=O).

1-endo-4,5,7,7-Pentamethyloxabicyclo[3.2.1]octane (XIII) and 4-(Acetylaminoisopropyl)-1,2,4-trimethylcyclohexene (XIV). A mixture of 1 g (0.006 moles) diene I, 3 g 96% H_2SO_4, 24 ml acetonitrile and 2.7 ml water was stirred for 4 h. After appropriate treatment the residue was fractionated on silica gel (40-100 μ, 1:1 chloroform–ethyl acetate elutriator). The first fraction corresponded to compound XIII (yield 27%). Mass spectrum, *m/z* (I, %): 182 (M^+) (4), 157 (5), 125 (100), 124 (12), 109 (12), 95 (5), 83 (10), 82 (18), 69 (5), 67 (10), 55 (15), 43 (55), 41 (23). ^{13}C NMR spectrum: 43.58 ($C_{(1)}$); 35.59 ($C_{(2)}$); 29.23 ($C_{(3)}$); 39.17 ($C_{(4)}$); 79.41 ($C_{(5)}$); 83.13 ($C_{(7)}$); 50.33 ($C_{(8)}$); 15.33 (4-CH_3); 19.77 (7-endo-CH_3); 20.49 (1-CH_3), 23.96 (5-CH_3); 27.41 ppm (7-exo-CH_3). The second fraction comprised a mixture of amides XIV and XI in 5:1 ratio (yield 15%). ^{13}C NMR spectrum of compound XIV: 123.76 and 123.66 ($C_{(1)}$ and $C_{(2)}$); 38.03 ($C_{(3)}$); 39.04 ($C_{(4)}$); 27.79 ($C_{(5)}$); 28.78 ($C_{(6)}$); 59.44 ($C_{(7)}$); 18.14 and 19.06 (1-CH_3 2-CH_3); 17.69 (4-CH_3); 21.33 and 21.62 (7,7-$(CH_3)_2$); 24.18 and 169.42 ppm (CH_3CO).

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