SELECTIVE CONVERSION OF THE OXIMES OF PINOCAMPHONE AND ISOPINOCAMPHONE INTO BICYCLIC LACTAMS

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A method is proposed for the selective conversion of oximes of terpene ketones of the pinane (2,6,6-trimethylbicyclo[3.1.1]heptane) series into the corresponding bicyclic lactams which consists in the action on these oximes of sulfuric acid in a weak nucleophile — a nitrile. The fact that the interaction takes place through the stage of formation of N-acylamidines — products of the nucleophilic stabilization of the intermediate carbocations — permits the rearrangement of the latter and the formation of monocyclic products to be avoided, which makes it possible to obtain in good yields bicyclic lactams, the synthesis of which by other methods is problematical.

The interest of researchers in the Beckmann rearrangement of oximes of bicyclic terpene ketones is due to the fact that the azalactams formed in this process are used as intermediates for obtaining pharmacologically active compounds [1]. However, attempts to perform the Beckmann rearrangement of the above-mentioned oximes by classical procedures using mineral acids leads predominantly to the formation of unsaturated monocyclic nitriles [1-3], which is connected with the high degree of strain of the carbon skeleton of bicyclo[3.1.1]heptane derivatives, leading to the cleavage of a carbon—carbon bond in the bicyclic cation formed initially. The use of weak Lewis acids, such as benzene- and p-toluenesulfonyl chlorides, as catalysts likewise does not lead to the desired results, since, as a rule, the required azalactams are formed in insignificant amounts [4-6]. In view of this, the search for methods for the selective transformation of oximes of bicyclic ketones into the corresponding lactams is continuing to represent an urgent problem.

We have shown previously [7] that under the conditions of the Ritter reaction — i.e., under the action of sulfuric acid in acetonitrile — the (E- isomer of the oxime of cis-verbanone (the oxime of cis-4,6,6-trimethylbicyclo[3.1.1]heptan-2-one) (I) is selectively rearranged into a bicyclic lactam — cis-5,7,7-trimethyl-2-azabicyclo[4.1.1]octan-3-one (II). In the course of the present investigation we have studied the transformations under the conditions of this reaction of structural analogues of the oxime (I) — the E- isomers of the oxime of pinocamphone (oxime of trans-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one) (III) and of the oxime of isopinocamphone (oxime of cis-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one) (IV). It has been established that, under the conditions of the Ritter reaction, compounds (III) and (IV) undergo transformations analogous to those described for oxime (I), which lead to the selective formation of bicyclic lactams — trans-2,7,7-trimethyl-3-azabicyclo[4.1.1]octan-4-one (V) and cis-2,7,7-trimethyl-3-azabicyclo[4.1.1]octan-4-one (VI), respectively.


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The structures of lactams (V) and (VI) were shown by IR, mass, \(^1\)H NMR, and \(^{13}\)C NMR spectroscopies. Thus, the IR spectrum of lactam (V) contained bands at 3270 and 3190 cm\(^{-1}\) corresponding to the vibrations of an NH group, and a band at 1640 cm\(^{-1}\), corresponding to the vibrations of carbonyl groups in lactams. The mass spectrum of this compound had the peak of the molecular ion, \(M^+\) 167, with an integral intensity of 36% of the maximum in the spectrum. The IR and mass spectra of the isomeric lactam (VI) had a similar form (see the Experimental part). The assignment of the signals in the PMR spectra was made by comparison with the spectrum of a model compound — the lactam (II) — and also by analysis of the magnitudes of the spin—spin coupling constants (SSCCs) of the protons. Thus, in the spectrum of the lactam (V) the signal of the \(C^2-H\) proton present in the \(\alpha\)-position to the nitrogen atom appeared at \(\delta\) 3.72 ppm in the form of a multiplet. The signals of the protons at the \(C^5\) atom, which are adjacent to the carbonyl group, appeared in the form of doublets of doublets at \(\delta\) 2.74 and 2.70; a SSCC of 18.0 Hz corresponded to a geminal interaction of these protons with one another, while constants of 2.0 Hz corresponded to vicinal interaction with the \(C^6-H\) proton (\(\delta\) 1.93, multiplet). The signal of the proton at \(C^1\) had the form of a doublet of triplets; a constant of 7.2 Hz corresponded to interaction with the pseudoequatorial proton at the \(C^8\) atom (\(C^8-H_e\)), and constants of 2.0 Hz to interaction with the \(C^2-H\) and \(C^8-H_a\). The signal of the lactam (VI) had a similar form while the chemical shifts of the protons at the \(C^1\), \(C^2\), \(C^5\), and \(C^6\) atoms of the isomeric compounds (V) and (VI) had extremely close values.

The assignment of the signals of the carbon atoms on the basis of their multiplicities in the \(^{13}\)C NMR spectra recorded without suppression of interaction with protons caused no difficulties. Thus, signals in the form of doublets with chemical shifts of 49.9, 47.7, and 37.8 ppm in the spectrum of lactam (V) were assigned to the carbon atoms \(C^2\), \(C^1\), and \(C^6\), respectively, triplets at \(\delta\) 37.4 and 22.7 ppm to the \(C^5\) and \(C^8\) atoms, and a singlet with a chemical shift of 38.6 ppm to the \(C^7\) atom. Quartets of methyl groups appeared at \(\delta\) (ppm) 1.16 (d, \(3J = 6.6\) Hz, \(C^2-CH_3\)), 0.97 (s, \(C^7-CH_3\)-syn), and 1.27 (s, \(C^7-CH_3\)-anti). The PMR spectrum of lactam (VI) had a similar form while the chemical shifts of the protons at the \(C^1\), \(C^2\), \(C^5\), and \(C^6\) atoms of the isomeric compounds (V) and (VI) had extremely close values.

The selectivity of the transformation of the oximes of bicyclic terpene ketones of the pinane series into the corresponding lactams under the conditions of the Ritter reaction and the practically complete absence of monocyclic compounds in the reaction mixture, in spite of the presence of such a "severe" agent as sulfuric acid is obviously due to the intermediate formation, in the course of the transformation, of bicyclic addition products — N-acetylamidines (VII) and (VIII) — which are hydrolyzed under the reaction conditions with the splitting out of a molecule of acetamide to give the corresponding lactams. We have shown the participation in the transformations under consideration of bicyclic N-acetylamidines that are the products of a nucleophilic stabilization of the intermediate bicyclic carbocations in the case of oximes of terpene ketones of the bicyclo[2.2.1]heptane series — camphor and isofenchone.

The performance of the reaction in other nitriles led to the same results, but with a decrease in the nucleophilicity there was some increase in the amount of unsaturated monocyclic nitriles in the reaction mixture, which is obviously connected with a fall in the rate of formation of products (VII) and (VIII).

EXPERIMENTAL

\(^1\)H and \(^{13}\)C NMR spectra were taken on a Bruker WM-360 spectrometer with a resonance frequency of 360.134 MHz for \(^1\)H and 90.56 MHz for \(^{13}\)C. The concentration of the solutions was \(\sim 10\%\) in deuterochloroform. Chemical shifts were determined relative to an internal standard — HMDS. IR spectra were recorded on a UR-20 spectrometer, and mass spectra on a MKh-1320 instrument.