TERPENE AMINES.

III. SYNTHESIS AND STUDY OF THE STRUCTURE OF N-CYCLOALKYL-1,7,7-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YLAMINES

N. G. Kozlov, T. I. Pekhk, and T. K. Vyalimyae

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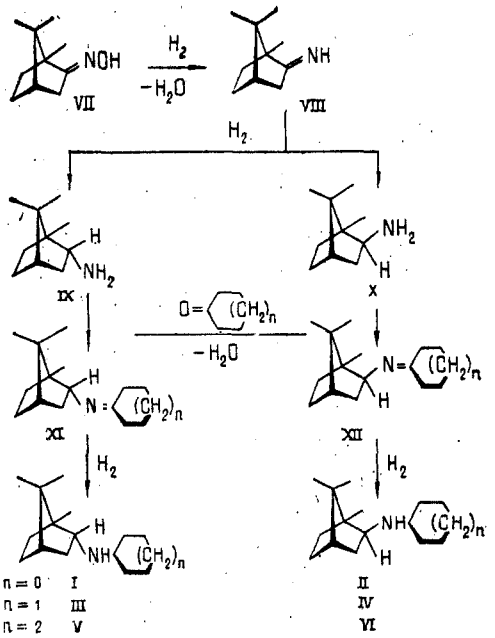
The reductive amination of cycloalkanones by camphor oxime has been studied. A probable scheme has been put forward for the occurrence of the reaction and the stereochemical composition of its products have been determined. It has been established with the aid of the ^{13}C NMR method that the reaction forms a mixture of isomeric optically active N-cycloalkyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines with a ratio of the endo to exo isomers of 4 : 1. The absolute configurations of the amines synthesized have been determined.

The synthesis of nitrogen-containing compounds in the terpene series is of considerable interest because these substances possess a wide range of biological action. An important role is played by the determination of the configurations of these compounds, since it is known that the spatial structure has a decisive influence on the biological activity of organic compounds participating in processes of vital activity. It is known from the literature [1, 2] that amino derivatives of the camphane series possess pronounced antiviral activity in relation to the influenza A_2 (Asia) virus. However, at the present time only amines and their derivatives of the d- and d,l- series have been studied [3-5], and the synthesis and stereochemistry of N-substituted l-amino derivatives of the camphane series have not been described in the literature.

Continuing investigations [6, 7] on the synthesis of terpene amines, we have performed for the first time the one-stage synthesis of N-cycloalkyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines (I-VI) by the reductive amination of alicyclic ketones with l-camphor oxime (VII).



Institute of Physical Organic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk. Institute of Chemical and Biological Physics, Academy of Sciences of the Estonian SSR, Tallin. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 41-46, January-February, 1983. Original article submitted February 16, 1982.

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TABLE 1. Composition and Yields of the Products of the Reductive Amination of Cyclohexanone by Camphor Oxime on Copper Catalysts (T = 250°C; V = 0.2 h^{-1}; molar ratio of oxime to ketone 1.0 : 1.5; pressure of hydrogen 15 atm)

Catalyst	Composition of the catalysate							
	III+IV	XI+XII	dicyclohexylamine	IX+X	camphor	borneols*	cyclohexanol + cyclohexylamine	cyclohexanone
15% Cu/Al_2O_3	Tr.	—	24,77	4,70	17,67	2,16	49,04	1,66
15% Cu/Al_2O_3+2% LiOH	35,73	Tr.	18,33	5,06	7,05	5,34	28,68	Tr.
15% Cu/Al_2O_3+6% LiOH	41,52	Tr.	16,40	5,10	6,25	10,00	25,15	1,05
36% Cu/ZnO	54,50	3,25	7,20	5,15	3,55	4,15	12,80	2,41
36% Cu/MgO	57,76	3,55	4,66	5,20	4,66	2,01	10,42	2,35

*The ratio of endo and exo isomers in the borneol—isoborneol mixture determined by the GLC method was 1.5 : 1.0.

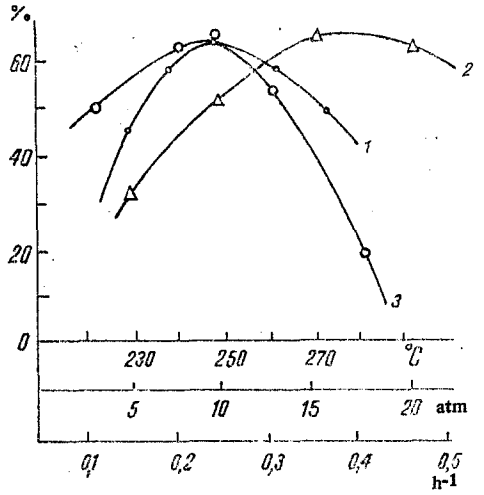


Fig. 1. Dependence of the yield (%) of N-cyclohexyl-1,7,7-trimethylbicyclo[2.2.1]hex-2-ylamine on: 1) the temperature (P = 15 atm, V = 0.2 h^{-1}); 2) the pressure (t = 250°C, V = 0.2 h^{-1}); 3) the space velocity (T = 250°C, P = 15 atm); catalyst 36% Cu/MgO.

The main direction of the reaction is the synthesis of compounds (I-VI), the formation of which takes place as the result of a series of reactions taking place in parallel and successively that involve the hydrogenation of various chemical bonds and condensation on the surface of the heterogeneous catalyst. The first stage of the reaction is the hydrogenation of the hydroxyimino group of (VII), which takes place through a stage of the formation of camphor imine (VIII), with the production of a mixture of bornylamine (IX) and isobornylamine (X) in a ratio of 4 : 1. Literature information [8] confirms the high activity of reduced copper in this reaction. The following stage of the reaction is the condensation of the primary amines (IX) and (X) with the cycloalkanone to form the corresponding ketimines (XI) and (XII), the hydrogenation of which on the surface of the catalyst gives the desired reaction products — the secondary amines (I-VI) containing in each case a mixture of the endo (I, III, V) and the exo (II, IV, VI) isomers in a ratio of 4 : 1.

However, we do not exclude the possibility that the reduction of the oxime to the amine is accompanied simultaneously by a partial reduction of the ketone to the alcohol with their subsequent interaction. It has been established that in the reaction under investigation ketones are actually reduced to the corresponding alcohols which, when they are passed in admixture with the oxime (VII), form the same reaction products (I-VI) as the ketones themselves. Thus, for example, the reductive amination of cyclohexanol with the oxime (VII) has given N-cyclohexyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamine (III + IV) with a yield of 41%.

The study of the reaction mixture showed that the catalysate contained, in addition to the main products of the reaction, (I-VI), intermediate products such as: a mixture of the camphylamines (IX) and (X), a mixture of the ketimines (XI) and (XII), camphor, a mixture of borneols, the cycloalkamine, the cycloalkanol, the dicycloalkylamine, and the unchanged

cyclanone, the presence of which confirms the scheme for the occurrence of the reaction that we have suggested. The formation of a mixture of borneols takes place as the result of the reduction of the camphor, the product of the hydrolysis of the oxime (VII), and of the cycloalkyl derivatives of camphor imine (XI and XII) [9]. The remaining by-products are formed as the result of the amination of camphor imine (VIII) and of the primary amines (IX and X). The ammonia liberated in this process reacts with the cyclanone or the cyclanol, giving the cycloalkylamine which also, on undergoing deamination, forms the cycloalkylamine. The absence from the reaction products of dicycloalkylcamphylamines and dicamphylamines, which can be obtained as the result of this reaction, is explained by the high steric hindrance to their formation. Under our conditions the occurrence of the deamination reaction can be favored by catalysts of acid nature.

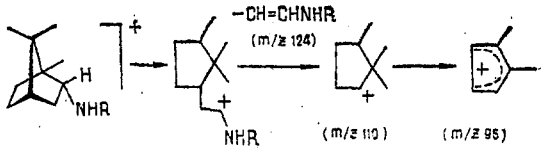
It has been shown [10, 11] that the active centers participating in the deamination of primary amines on alumina are coordination-unsaturated aluminum ions. The influence of a change in the acid characteristics of the catalyst during the reaction has been studied for the case of the reductive amination of cyclohexanone by the oxime (VII) (Table 1). Modification of the catalyst with alkali or the use of supports of a different chemical nature has a substantial influence on the yield of the main products and the byproducts of the reaction. The copper—alumina catalyst which we have studied in this reaction is a typical bifunctional catalyst in which the carrier of the acid functions is the alumina. Modification of the catalyst with lithium hydroxide (2 and 6%) led to an increase in the yield of the desired products (III) and (IV) and to a decrease in the formation of dicyclohexylamine. The use of ZnO and MgO, typical basic oxides [12], as supports confirmed the influence of the acidic-basic characteristics of the supports on the properties of the catalysts. A copper—alumina catalyst modified with 6% of lithium hydroxide approximated in its activity to the copper—zinc and copper—magnesium catalysts. Of the catalysts studied, the greatest activity in this reaction was possessed by a copper—magnesium catalyst containing 36% of copper.

The influence of the main parameters of the process — the temperature, the pressure, and the space velocity — on the yield of secondary amines (III) and (IV) was studied for the case of the reaction of cyclohexanone with the oxime (VII) in the presence of a 36% Cu/MgO catalyst. The results obtained are shown in Fig. 1. The optimum conditions for performing the reaction are a temperature of 240-250°C, a pressure of hydrogen of 15 atm, and a space velocity of passage of the mixture of 0.2 h^{-1}.

From the mixture of products obtained as the result of the reaction we isolated the individual stereoisomeric optically active N-cycloalkyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines, the endo compounds (III) and (V), and the exo compounds (IV) and (VI). It must be mentioned that the reductive amination of cyclanones by the oxime (VII) formed mainly the endo isomers of the amines, which are the most thermodynamically stable, judging from conformational schemes.

The IR spectra of the secondary amines of the camphane series (I-VI) are characterized by the presence of broad, but not intense, absorption with a maximum in the 3350-3300 cm^{-1} region which must be assigned to the stretching vibrations of a > NH group. Absorption bands at 3000-2800, 1455, 1385, 1370, and 1130 cm^{-1} are due to the vibrations of the bonds of structural fragments of the camphane skeleton.

The mass spectra of N-cycloalkylbornylamines contain the peaks of the molecular ions M^+. Subsequent fragmentation under the action of electron impact is probably connected with the cleavage of the C_1-C_2 bond of the camphane skeleton [13] and takes place in accordance with the scheme given below



where R represents cyclohexyl.

Analysis of the ^{13}C NMR spectra of mixtures of the isomeric N-cycloalkyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines and their salts is a convenient method of determining

the structures and relative amounts of the stereoisomers in the mixtures. As the criterion for determining configuration and structure by the ^{13}C NMR method we used a comparison of the experimental chemical shifts with the calculated figures and a comparison of the multiplicities of the ^{13}C resonance lines in the off-resonance spectra. In the assignment of the signals we used the chemical shifts of the ^{13}C nuclei in the isomeric borneols and bornyl chloride [14] and also in bornylamines and N-methyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines [5]. In the determination of the configurations of the individual isomers, the most characteristic feature is the chemical shift of the C_6 atom, which in the endo isomer must unconditionally experience a large ($\sim$ 10 ppm) upfield shift, as in the isomeric borneols and bornyl chlorides. The endo isomers are distinguished from the exo isomers also by a greater difference in the degrees of screening of the C_8 and C_9 atoms. We must mention the incorrect assignment of the ^{13}C chemical shifts of the isomeric N-methylbornylamines given by Kiyooka and Suzuki [5]; in this case, the basis for the assignment for the chemical shifts was not their ^{13}C NMR spectra, but other considerations.

The optical rotatory dispersion curves for the individual stereoisomers of the N-cycloalkyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines have the form of smooth positive curves for the exo isomers and, conversely, smooth negative curves for the endo isomers.

The absolute configurations of the stereoisomeric N-cycloalkyl-1,7,7-trimethylbicyclo-[2.2.1]hept-2-ylamines synthesized were determined on the basis of their optical activities and spatial structures: (−)-(1S : 1R : 4S) for the endo isomers (I, III, and V) and (+)-(1S : 2S : 4S) for the exo isomers (II), (IV) and VI).

EXPERIMENTAL

The reaction products were investigated by methods described previously [6].

Camphor Oxime (VII). This was obtained by the method of Krestinskii and Bardyshev [16]. mp 118°C; $[\alpha]_D^{20}$ + 45.5° (ethanol).

N-Cyclopentyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines (I and II). A mixture of 16.7 g of the oxime (VII) and 12.6 g of cyclopentanone was passed, in an apparatus of the flow-through type, at a space velocity of 0.2 h^{-1}, a temperature of 250°C, and a pressure of hydrogen of 15 atm, through a layer of 36% Cu/MgO catalyst. By vacuum fractionation the catalysate yielded a fraction with bp 195-205°C (15 mm) containing $\sim$ 85% of (I) and (II). The desired product was isolated from it by the PGLC method in a purity of 99%, with a ratio of endo and exo isomers of 4 : 1. bp 195-200°C (15 mm). IR spectrum (cm^{-1}): 1125, 1370, 1385, 1450, 1470, 1640, 2875, 2945, 3360. Mass spectrum, m/z: 221 (M^+), 206, 192, 166, 164, 150, (100%), 138, 124, 112, 110, 95, 87, 71, 69, 55.

The passage of dry hydrogen chloride through an ethereal solution of the amines (I and II) yielded the hydrochloride. mp 260-263°C. ^{13}NMR spectrum (ppm, δ, TMS): C_1 − 50.2; C_2 − 65.7; C_3 − 34.8; C_4 − 45.5; C_5 − 28.6; C_6 − 28.4; C_7 − 49.5; C_8 − 20.1; C_9 − 19.1; C_{10} − 14.1; C_{11} − 61.1; C_{12} − 31.0; C_{13} − 25.1; C_{14} − 24.8; C_{15} − 30.8 for the endo isomer (I); C_2 − 67.4; C_3 − 35.9; C_4 − 46.1; C_5 − 27.4; C_6 − 37.7; C_8 − 21.0; C_9 − 20.7, C_{10} − 12.4; C_{11} − 12.4; C_{12} − 60.9 for the exo isomer (II).

N-Cyclohexyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines (III and IV). A mixture of 16.7 g of the oxime (VII) and 14.4 g of cyclohexanone was passed in an apparatus of the continuous flow-through type under similar conditions. Vacuum fractionation isolated from the catalysate a fraction with bp 210-220°C (15 mm) containing $\sim$ 80% of the product (III, IV). The desired product (III, IV) was isolated from this fraction by the PGLC method with a purity of 99% and a ratio of the endo and exo isomers of 4 : 1. bp 211-216°C (15 mm). IR spectrum, cm^{-1}: 965, 1060, 1375, 1380, 1465, 1580, 2860, 2950, 3445. Mass spectrum m/z: 235 (M^+), 220, 192, 164 (100%), 136, 124, 110, 98, 95, 81, 67, 55.

The passage of dry hydrogen chloride through an ethereal solution of the amines (III, IV) yielded the hydrochloride with mp 250-253°C. ^{13}C NMR spectrum (ppm, δ, TMS); the endo isomer: C_1 − 50.1; C_2 − 63.6; C_3 − 35.5; C_4 − 45.6; C_5 − 28.3; C_6 − 28.5; C_7 − 49.6; C_8 − 20.1; C_9 − 19.1; C_{10} − 14.0; C_{11} − 59.9; C_{12} − 30.8; C_{13} − 25.7; C_{14} − 25.9; C_{15} − 25.7 C_{16} − 30.4. The exo isomer: C_1 − 49.8; C_2 − 65.1; C_3 − 36.7; C_4 − 46.2; C_5 − 27.5; C_6 − 37.6; C_8 − 20.9; C_9 − 20.7; C_{10} − 12.4; C_{11} − 59.7; C_{12} − 30.7; C_{13} − 25.7; C_{14} − 25.9; C_{15} − 25.7; C_{16} − 29.8.

The individual isomers were isolated from the mixture of amines (III) and (IV) by Feltkamp's method [15]: (1S : 2R : 4S), endo, (III). bp 211-213°C (15 mm), $[\alpha]_D^{20}$ − 35.7°

(ethanol), d_4^{20} 0.9406, n_D^{20} 1.4962, MR_D 73.11, calc. 73.09.(1S : 2S : 4S), exo, (IV). bp 215-217°C (15 mm), $[\alpha]_D^{20}$ + 39.8° (ethanol), d_4^{20} 0.9445, n_D^{20} 1.4983, MR_D 73.10, calc. 73.09.

N-Cycloheptyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamines (V, VI). Under similar conditions, 16.7 g of the oxime (VII) and 16.8 g of cycloheptanone were passed in a continuous apparatus of the flow-through type. By vacuum fractionation, the catalysate yielded a fraction with bp 170-185°C (10 mm) containing ~ 85% of a mixture of (V) and (VI). The desired product (V, VI) was isolated by the PGLC method with a purity of 99% and a ratio of endo and exo isomers of 4 : 1; bp 175-185°C (10 mm), d_D^{20} 1.4999. IR spectrum, cm^{-1}: 1375, 1380, 1475, 1575, 2875, 2950, 3460. Mass spectrum, m/z: 249 (M^+), 234, 192, 178 (100%), 152, 136, 110, 95, 82, 70, 55.

The passage of dry hydrogen chloride through an ethereal solution of the amines (V, VI) yielded the hydrochloride. mp 231-233°C.

The individual isomers were isolated by Feltkamp's method [14] from the mixture of amines (V, VI): (1S : 2R : 4S), endo, (V). bp 174-176°C (9 mm), $[\alpha]_D^{20}$ −31.2° (ethanol), d_4^{20} 0.9439, n_D^{20} 1.4998, MR_D 77.69,calc. 77.71.(1S : 2S : 4S), exo, (VI). bp 182-183°C (10 mm), $[\alpha]_D^{20}$ + 34.5° ethanol, d_4^{20} 0.9462, n_D^{20} 1.5008, MR_D 77.63, calc. 77.71.

The elementary analyses of compounds (I-VI) corresponded to the calculated figures.

SUMMARY

A method has been developed for obtaining N-cycloalkyl-1,7,7-trimethyl-bicyclo[2.2.1]-hept-2-ylamines by the reductive amination of cyclohexanones with camphor oxime. It has been shown that the most active and selective catalyst for this reaction is 36% Cu/MgO. It has been established that the reaction forms a mixture of endo and exo isomers of the secondary amines in a ratio of 4 : 1. The absolute configurations of the amines synthesized have been determined. A scheme of the reaction mechanism has been put forward.

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