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TERPENE AMINES.

V. SYNTHESIS AND STUDY OF THE STRUCTURE OF N-SUBSTITUTED TETRAHYDROIONYLAMINES

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The catalytic hydroamination of a mixture of α- and β-ionones by aliphatic nitriles and amines has been studied. A scheme of the occurrence of the reaction has been put forward. It has been established that the reaction forms in each case a mixture of secondary amines containing two pairs of diastereomers. The optimum conditions for the performance of the process have been determined.

It is known that substituted ionylamines and their derivatives are effective plant growth regulators [1]. However, there is little information in the literature [2, 3] on the synthesis and stereochemistry of amino derivatives of α- and β-ionones. In view of this, the study of known methods for their preparation, the development of new ones, and the synthesis from them of amines of this series that have not previously been described are of great importance. We have shown previously [4] that catalytic hydroamination is an extremely convenient method for synthesizing difficultly accessible amines from unsubstituted monocyclic terpene ketones. On expanding our initial investigations, we have included among the oxygen-containing terpene compounds participating in the hydroamination reaction ionone (cyclocitrylideneacetone), which contains a mixture of two isomers α (I) and β (II) in a ratio of 40:60.

In the present paper we consider the synthesis of N-substituted 1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamines (tetrahydroionylamines) by the reductive amination of ionol with nitriles or amines. During the work we pursued two aims: in the first place, to determine the optimum conditions for the performance of this reaction; and, in the second place, to synthesize secondary amines of the tetrahydroionone series not previously described and to study their properties and structures.

The reaction was performed in the vapor phase in the temperature interval of 210-270°C under a pressure of hydrogen of 10-20 atm. in the presence of a copper-aluminum oxide catalyst modified with lithium hydroxide. An investigation of the reductive amination of ionone by aliphatic nitriles or amines at various temperatures, pressure of hydrogen, and space velocities of the passage of the reaction mixture enabled us to determine the optimum conditions for its performance. The maximum yields of the desired reaction products — the secondary amines (III-VI) — were achieved at a temperature of 250°C, a hydrogen pressure of 15 atm, and a space velocity of 0.2 h^{-1}. The catalyst used contained 15% of copper and 6% of lithium hydroxide deposited on industrial γ-alumina. A further rise in the temperature of the reaction was accompanied by an increased formation of by-products. An increase in the pressure had a favorable influence on the yield of desired products but somewhat lowered the selectivity

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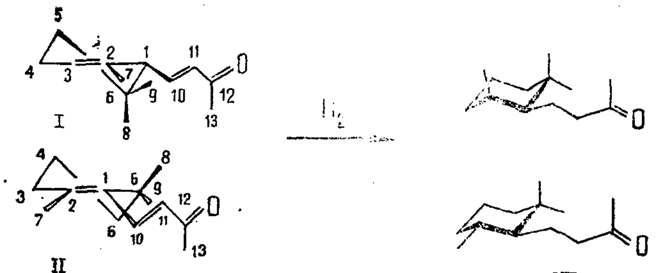
TABLE 1. Yield and Compositions of the Products of the Reductive Amination of Ionone by Aliphatic Nitriles and Amines (hydrogen pressure 15 atm, temperature 250°C, space velocity 0.2 h^{-1}, catalyst 15% copper/Al_2O_3 + 6% lithium hydroxide)

R_1	Composition of the reaction products, %				
	secondary amines, (III-VI)	primary amines (IX)	tertiary amines (X)	the tetrahydroionol (VIII)	the tetrahydroionol (VII)
CH_3	72	10	8	5	5
C_2H_5	68	12	10	5	5
C_3H_7	65	15	10	5	5
$CH(CH_3)_2$	65	20	—	10	5
C_6H_{11}	50	25	—	15	10

of the process. When the reaction was performed under the optimum conditions the mixture of products the composition of which is given in Table 1 was formed.

As can be seen from Table 1, in the reductive amination of ionone the main direction is the formation of secondary amines. On the basis of the results obtained, we consider that in the course of the reaction the reduction of the initial nitrile to the primary amine takes place on the metallic centers of the catalyst, the dialkylamine being formed as a by-product as the result of the deamination reaction. Simultaneously with this, the hydrogenation of the ionone (I, II) takes place with the formation of a mixture of saturated ketones (VII) and alcohols (VIII). The formation of the secondary amines (III-VI) obviously takes place through a stage of the formation of a Schiff's base with its subsequent reduction. The absence from the catalysate of the Schiff's base presumably formed is probably due both to the ease with which these compounds are reduced to amines under the conditions and to the fact that, obviously, its formation is the limiting stage of the reaction. The primary amines (IX) are formed under the action on the oxygen-containing compound (I, II, VII, and VIII) of the ammonia that is liberated in the deamination of the primary amine. The formation of the tertiary amines (X) probably takes place as the result of the interaction of the dialkylamines with the alcohol (VIII).



I

II

VII

$$R_1C{\equiv}N \xrightarrow{H_2} R_1CH_2NH_2$$

$$R_1CH_2NH_2 \xrightarrow[-NH_3]{} (R_1CH_2)_2NH$$

III,V. R_2= H; R_3= $NHCH_2R_1$

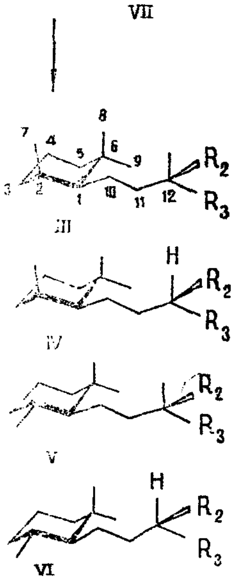
IV,VI. R_2= CH_3; R_3= $NHCH_2R_1$

where R_1= CH_3; C_2H_5; C_3H_7; $CH(CH_3)_2$; C_6H_{11}

VIII. R_2=H; R_3=OH

IX. R_2=H; R_3=NH_2

X. R_2 = R_3=$NHCH_2R_1$



III

IV

V

VI

It must be mentioned that since, during the reaction, the complete hydrogenation of the double carbon—carbon bonds of the initial compound takes place, the amines (III-VI) formed as the result of the reaction, which have three asymmetric centers at C_1, C_2, and C_{12} can exist in eight stereoisomeric forms. It is known [5] that 1,2-disubstituted* cyclohexane derivatives exist in the form of two isomers, cis [(1S:2S:12R) — (III); and (1S:2S:12S) — (IV)] and trans [(1S:2R:12R) — (V); and (1S:2R:12S) — (VI)], each of which can exist in two configurations (1S:2S:12R) and (1R:2R:12R); (1S:2S:12R) and (1R:2R:12R); (1S:2R:12R) and (1R:2S:12R); and (1S:2R:12S) and (1R:2S:12S) which are connected with one another by a conversion transition. In these pairs of isomeric disubstituted cyclohexanes, the trans isomers (V and VI) are the more stable because in them the two substituents are orientated equatorially while is the cis isomers (III, IV) one substituent has the axial orientation. The diaxial conformation of the stereoisomers (1R:2R) is, of course, less suitable. Since, as is already established [6], the most thermodynamically stable isomers of the secondary amines are formed as the result of the hydroamination reaction, on the basis of the possible configurations the N-substituted 1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamines obtained have been assigned the most stable conformations with the equatorial arrangement of the substituent at C_1.

The individual secondary amines (III-VI) were isolated by vacuum fractionation from the catalysates obtained as the result of the reaction. Because the isomers present in the compounds obtained have close physicochemical properties and are not separated into individual substances by the usual methods, it was impossible to isolate the individual isomers in the pure form and to characterize them.

The structures of the N-substituted-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamines synthesized were shown by IR, mass, and ^{13}C NMR spectroscopy. The IR spectra of the secondary amines investigated each had a characteristic absorption band in the 3300-3400 cm^{-1} region due to the splitting vibrations of the secondary amino group. A band at 1230-1210 cm^{-1} was due to the stretching vibrations of the C—N bond that are characteristic for the IR spectra of secondary amines. Bands at 2970, 2930, 2870, and 2850 cm^{-1} characterize the symmetrical and antisymmetrical stretching vibrations of the C—H bonds in methyl and methylene groups. Bands at 1385 and 1370 cm^{-1} (characteristic doublet) and also at 1170 and 1140 cm^{-1} correspond to the deformation vibrations of the C—H bonds in a gem-dimethyl group. Bands at 1460 and 740-720 cm^{-1} are due to the antisymmetrical deformation vibrations of C—H bonds in the methylene groups of a cyclohexane ring.

The mass spectra of all the secondary amines obtained included peaks corresponding to the molecular ions M^+. The main direction of the further fragmentation of the compounds investigated under the action of electron impact was the cleavage of the $-NH-C_{12}<$ bond with the formation of the ion $(M - CH_2R_1)$.

The ^{13}C NMR spectra of all the secondary amines obtained were recorded. This permitted us to establish that, judging from the number of lines in the spectrum and their intensities, the N-substituted 1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamines each contained mixture of all four possible stereoisomers in approximately equal amounts. In view of this, the assignment of the lines in the ^{13}C NMR spectra proved to be impossible.

The presence of all four stereoisomers in each of the amines obtained was also confirmed by GLC analysis.

EXPERIMENTAL

The purity of the compounds obtained was determined by the GLC method on a DuPont 8800 chromatograph at 23°C using a column filled with Zorbax ODS. Spectrophotometer at 254 nm. The working solution used was CH_3OH (100%).

IR spectra were recorded on a UR-20 spectrometer in the frequency range of 400-3800 cm^{-1} with slit program 4 at a rate of scanning of 60 cm^{-1}/min. The compounds were recorded in the form of liquid films between KBr plates.

Mass spectra were taken on a Varian MAT-311 instrument with a cathodic emission current of 1000 mA and an energy of the ionizing electrons of 10 eV. The samples were evaporated at room temperature, and the temperature of the ion source was 200°C.

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*The gem-dimethyl group in position 6 is not taken into account in this case.

^{13}C NMR spectra were taken on WH-90 instrument (Bruker) with a resonance frequency for ^{13}C of 22.62 MHz in the regime of complete decoupling from protons. Deuterochloroform was used for stabilization. All the spectra were recorded in the regime of integrating detection using a memory with a volume of 8K for the real part of the spectrum.

As the initial compound for synthesis we used a mixture of α- and β-ionones in a ratio of 40:60. n_D^{22} 1.5049. IR (cm^{-1}): 990, 1140, 1180, 1255, 1365, 1380, 1440, 1455, 1625, 1630, 1675, 1690, 1720, 2875, 2930, 2965. ^{13}C NMR spectrum (ppm), α-ionone: C_1 — 132.3, C_2 — 135.9, C_3 — 33.5, C_4 — 18.9, C_5 — 39.7, C_6 — 34.0, C_7 — 21.7, C_8 — 28.8, C_9 — 28.7, C_{10} — 143.0, C_{11} — 131.8, C_{12} — 198.4, C_{13} — 27.1. β-ionone: C_1 — 54.2, C_2 — 131.6, C_3 — 122.6, C_4 — 23.0, C_5 — 31.2, C_6 — 32.5, C_7 — 22.8, C_8 — 26.8, C_9 — 27.8, C_{10} — 148.9, C_{11} — 132.3, C_{12} — 198.2, C_{13} — 26.9.

N-Ethyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine. A mixture of 19.2 g of ionone and 6.2 g of acetonitrile was passed into an apparatus of the flow-through type at a space velocity of 0.2 h^{-1} at 250°C and a pressure of hydrogen of 15 atm through a layer of catalyst consisting of 15% of copper and 6% of lithium hydroxide deposited on γ-Al_2O_3. By vacuum fractionation of the catalysate, the desired product was obtained with a purity of 97%; bp 129-130°C (10 mm), n_D^{20} 4749. IR spectrum (cm^{-1}): 720, 810, 980, 1135, 1175, 1210, 1375, 1385, 1460, 2730, 2860, 2875, 2935, 2970, 3300. Mass spectrum (m/z): 225 (M^+), 211, 209, 197, 181, 175, 171, 164, 159, 156, 152, 138, 135, 124, 122, 110, 108, 101, 99, 96, 94, 92. $C_{15}H_{31}N$. Calculated: M 225.421.

N-Propyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine. A mixture of 19.2 g of ionone and 7.9 g of acrylonitrile was passed into an apparatus of the flow-through type under conditions similar to those for the preceding experiment. Vacuum fractionation of the catalysate yielded the desired product with a purity of 98%. bp 145-147°C (10 mm), n_D^{27} 1.4740. IR spectrum (cm^{-1}): 890, 1080, 1100, 1130, 1220, 1240, 1340, 1365, 1375, 1465, 2875, 2935, 2965, 3300. Mass spectrum (m/z): 239 (M^+), 223, 211, 209, 181, 164, 153, 137, 129, 124, 121, 113, 110, 109, 100, 99, 95, 87. $C_{16}H_{33}N$. Calculated: M 239.448

N-Butyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine. A mixture of 19.2 g of ionone and 10.4 g of butyronitrile was passed under conditions similar to those of the preceding experiments into an apparatus of the flow-through type. Vacuum fractionation of the catalysate yielded the desired product with a purity of 95%, bp 152-154°C (10 mm), n_D^{24} 1.4690. IR spectrum (cm^{-1}): 770, 790, 960, 980, 1100, 1135, 1175, 1220, 1255, 1290, 1340, 1365, 1375, 1465, 2740, 2875, 2935, 2970, 3300. Mass spectrum (m/z): 253 (M^+), 239, 237, 211, 209, 197, 181, 164, 157, 137, 127, 124, 114, 110, 108, 100, 95, 87, $C_{17}H_{35}N$. Calculated: M 253.475.

N-Isobutyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine. A mixture of 19.2 g of ionone and 11.0 g of isobutylamine was passed under conditions similar to those of the preceding experiments into an apparatus of the flow-through type. Vacuum fraction of the catalysate yielded the desired product with a purity of 99%. bp 149-151°C (10 mm), n_D^{22} 1.4719. IR spectrum (cm^{-1}): 730, 960, 980, 1080, 1100, 1130, 1175, 1220, 1250, 1365, 1375, 1385, 1465, 1470, 2875, 2935, 2960, 3330. Mass spectrum (m/z): 253 (M^+), 239, 237, 211, 209, 181, 175, 164, 159, 153, 127, 124, 110, 108, 101, 96, 94, 87, 82, 70. $C_{17}H_{35}N$. Calculated: M 253.475.

N-Cyclohexyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine. A mixture of 19.2 g of ionone and 14.9 g of cyclohexylamine was passed into an apparatus of the flow-through type under conditions similar to those of the preceding experiments. Vacuum fractionation of the catalysate yielded the desired product with a purity of 97%, bp 189-190°C (10 mm), n_D^{23} 1.4871. IR spectrum (cm^{-1}): 720, 790, 850, 890, 960, 980, 1030, 1120, 1145, 1220, 1260, 1345, 1365, 1375, 1385, 1450, 1475, 2860, 2930, 2960, 3300. Mass spectrum (m/z): 279 (M^+), 265, 263, 251, 237, 235, 225, 223, 221, 209, 207, 197, 195, 181, 164, 152, 139, 127, 112, 100, 96, 87, 82. $C_{19}H_{37}N$. Calculated: M 279.513.

In addition to the substances mentioned above, the following by-products of the reaction were also isolated from the catalysates: 1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine with bp 118-119°C (10 mm), n_D^{24} 1.4765. IR spectrum (cm^{-1}): 770, 790, 815, 980, 1080, 1100, 1120, 1215, 1345, 1365, 1370, 1375, 1465, 1475, 2875, 2940, 2965, 3300.

The following were isolated in the form of enriched mixtures containing impurities of other compounds: N,N-diethyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine [found (mass spectrometrically) M^+ 253, $C_{17}H_{35}N$. Calculated M 253.475]; N,N-dipropyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine [found (mass spectrometrically) M^+ 281, $C_{19}H_{39}N$. Calculated M 281.529]; and N,N-dibutyl-1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamine [found (mass-spectrometrically) M^+ 309, $C_{21}H_{43}N$. Calculated M 309.583].

The presence of the alcohols (VIII) and ketones (VII) in the catalysates was shown by t the method of adding authentic samples of these compounds, obtained by the hydrogenation of ionone, to the reaction mixture.

SUMMARY

The catalytic hydroamination of a mixture of α- and β-ionones by aliphatic nitriles and amines has been studied. The optimum parameters for the occurrence of the process have been determined. It has been established that the reaction forms a mixture of stereoisomeric N-substituted 1-methyl-3-(2,6,6-trimethylcyclohexyl)propylamines. A scheme of the course of the reaction is proposed.

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SYNTHESIS OF DERIVATIVES OF PENTOPYRANIC ACID

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N^4-Benzoylcytosine 1-(methyl 2,3,4-tri-O-acetyl-β-D-glucopyranosiduronate) has been obtained with a yield of 70% by the glycosylation of the trimethylsilyl derivative of N^4-benzoylcytosine with methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate in the presence of three equivalents of $SnCl_4$ as condensing agent. Cytosine 1-(β-D-glucopyranosiduronamide) (IV) — the amide of pentopyranic acid — has been synthesized in practically quantitative yield by the ammonolysis of the nucleoside (I).

In a study of the biosynthesis of the antibiotic blasticidin S Seto et al. [1] isolated from the culture liquid of a strain of *Streptomyces griseochromogenes* a whole series of intermediate products, among which pentopyranic acid (I), which is a cytosine nucleoside of D-glucopyranuronic acid, was detected.

In 1976, Fox et al. [2] synthesized this compound by the glycosylation of N^4-acetylcytosine with methyl 1,2,3,4-tetra-O-acetyl-β-D-glucopyranuronate (II), but the yield of the protected nucleoside was only 20%.

We have found that the glycosylation of the silyl derivative of N^4-benzoylcytosine with compound (II) in the presence of three equivalents of $SnCl_4$ as condensing agent leads to the formation of N^4-benzoylcytosine 1-(methyl 2,3,4-tri-O-acetyl-β-D-glucopyranosiduronate) (III) with a yield of 70%.

The PMR spectrum ($J_{1',2'}$ = 8.5 Hz) and the positive Cotton effect of the B_{2U} band in the CD spectrum of compound (III) show its β-anomeric configuration.

The ammonolysis of compounds (III) gave cytosine 1-(β-D-glucopyranosiduronamide) (IV) — the amide of pentopyranic acid (I) — in practically quantitative yield. (See scheme on page 581).

The spectral characteristics (UV, CD, PMR) of the compounds obtained are in complete correspondence to the structures ascribed to them.

Peat Institute, Academy of Sciences of the Belorussian SSR, Minsk. Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 617-619, September-October, 1983. Original article submitted August 11, 1982.

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