TERPENE AMINES.

IV. SYNTHESIS AND STUDY OF THE STRUCTURE OF AMINES FROM d-FENCHONE

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The reductive amination of d-fenchone by aliphatic nitriles has been studied. A probable reaction pathway is suggested, and the stereochemical composition of the products has been determined. It has been established with the aid of ^{13}C NMR that the reaction forms a mixture of isomeric optically active N-alkyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-ylamines with a 3:1 ratio of endo and exo isomers. The absolute configurations of the amines synthesized have been determined.

In spite of the fact that fenchone is an extremely close analog of camphor, its derivatives have been studied to a comparatively small degree. This can be explained by the relatively low reactivity of the carbonyl group in the fenchone molecule due to the steric effect of the neighboring alkyl groups.

Fenchylamine and its derivatives are intermediates in the synthesis of some biologically active compounds [1]. However, the stereochemistry and properties of N-alkyl-substituted amines of the 1,3,3-trimethylbicyclo[2.2.1]heptane series have not been discussed in the literature. In view of this, the study of the known methods for their preparation and the development of new ones is of undoubted importance. We have shown previously [2] that catalytic hydroamination is a convenient method for the synthesis of many difficultly accessible secondary amines. Expanding our initial investigations, we have included d-fenchone (1,3,3-trimethylbicyclo[2.2.1]heptan-2-one) among the oxygen-containing compounds participating in the hydroamination reaction.

The present paper gives the results of the synthesis of N-alkyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-ylamines by the reductive amination of fenchone with aliphatic nitriles. We set ourselves two tasks: in the first place, to determine the optimum conditions for this reaction, and, in the second place, to establish the stereochemistry of the reaction products.

The reaction was performed in the vapor phase at 220-260°C under a hydrogen pressure of 10-15 atm in the presence of a copper—aluminum oxide catalysts modified with lithium hydroxide. Under these conditions, the reaction of d-fenchone (I) with aliphatic nitriles (acetonitrile, acrylonitrile, or butyronitrile) forms a mixture of isomeric endo-N-alkyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-ylamines (II) and the corresponding exo compounds (III) in a ratio of 3:1 and with a yield of 50-60%. α-Fenchol (V) and β-fenchol (VI) were identified in the catalysate together with the main reaction product, N-fenchylidenalkylamines (IV) (Table 1).

In the reductive amination of the ketone (I) by aliphatic nitriles, the main direction is the formation of secondary amines (II, III) taking place in accordance with the scheme given below. (Top, following page.)

In the course of the reaction, the initial nitrile is reduced to a primary amine on the metallic centers of the catalyst. Simultaneously with this the partial hydrogenation of the ketone (I) to a mixture of α- and β-fenchols takes place. The formation of the secondary amines (II, III) takes place in the course of two competing reactions: the intermolecular dehydration of the alcohols (V, VI) with the primary amine on the surface of the heterogeneous catalyst, and the formation of a N-fenchylidenalkylamine (IV) with its subsequent reduction. We consider that the proportion of the second process is considerably predominating. This is

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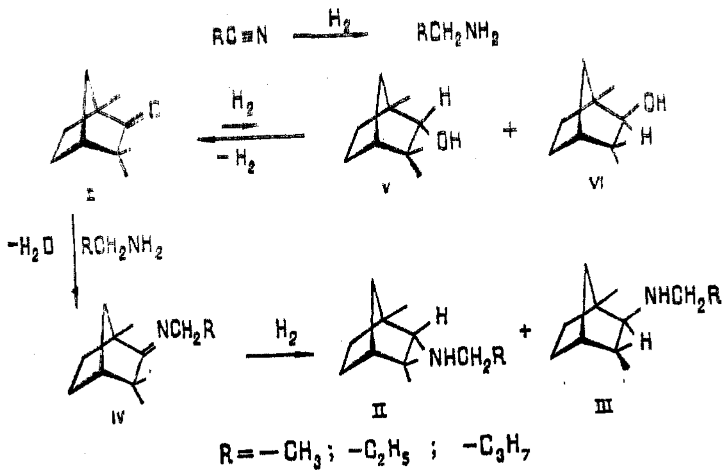


also confirmed by preceding investigations of the hydroamination of camphor [3]. Consequently, the ratio of endo and exo isomers in the mixture of amines (II, III) is determined by the stage of the hydrogenation of the $>C{=}N$ bond of compound (IV). As a result of the cis addition of hydrogen from the exo or the endo side of the molecule of (IV), the endo- or the exo-N-alkylfenchylamine, respectively, is formed. As can be seen from Table 1, in the products of all the reactions the N-alkyl-endo-fenchylamines predominate, as in the case of the hydroamination of camphor where the N-alkylbornylamines predominate in the reaction products, which indicates the preferential exo-addition of hydrogen. The absence of difenchylamine, which can be obtained as the result of a deamination reaction, from the reaction products must be noted. This is explained by the steric hindrance for its formation connected with the presence of methyl groups in the α-position to the reaction center. Also with this is connected the slight fall in the yield of desired product as compared with that in the reaction with camphor.

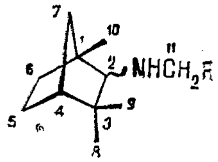
In determining the optimum conditions for the performance of the reaction under investigation, we established that the maximum yield of N-alkylfenchylamines is achieved when using a catalyst containing 10-15% of copper and 4-6% of lithium hydroxide deposited on γ-alumina, a pressure of hydrogen of 15 atm, a temperature of 250°C, and a space velocity of passage of the mixture of 0.25 h^{-1}. On departing from the optimum conditions established, the yield of desired product falls and the amount of byproducts in the catalysate rises considerably.

The mixtures of products obtained as the result of the reactions were separated by preparative GLC. The compounds obtained were identified by IR, mass, and ^{13}C NMR spectroscopy, and also by spectropolarimetry. The IR spectra of the amines produced contained absorption bands in the 3330 cm^{-1} region due to the stretching vibrations of a secondary amino group. Bands at 3000-2800, 1465, 1375, 1365, and 1135 cm^{-1} correspond to the vibrations of structural fragments of the hydrocarbon skeletons of compounds (II) and (III). The mass spectra of the amines contained the peaks of the molecular ions M^+ (intensity as a proportion of the maximum peak in the spectrum ~15%). The subsequent fragmentation of the compounds investigated under the action of electron impact is due to the cleavage of $>C_2{-}NH{-}$ and $-NH{-}C_{11}<$ bonds and takes place with the formation of the $(M - NHCH_2R)$ and $(M - CH_2R)$ ions, respectively. The structures and configurations of the isomeric N-alkylfenchylamines were established from their ^{13}C NMR spectra by comparing the chemical shifts obtained previously with the previously known ^{13}C chemical shifts of α- and β-fenchols [4] and also of the N-alkylbornylamines [13]. The assignment of the isomers was easily carried out on the basis of the characteristic chemical shifts of the C_2, C_6, C_8, C_9, and C_{10} carbon nuclei. The carbon-13 chemical shifts assigned in this way are given in Table 2. The ratios of the endo and exo isomers of the N-alkylfenchylamines in the mixtures were determined from the ratios of the intensities of the four lowest-field signals of the carbon atoms in the spectra. The optical rotatory dispersion curves of the mixtures of amines (II, III) obtained formed smooth negative curves. On the basis of the structures and optical activities of the mixtures of amines, their absolute configurations were determined as (−)-(1S:2S:4R) for the endo isomers (II) and (−)-(1S:2R:4R) for the exo isomers (III).

TABLE 1. Composition and Yields of the Products of the Reductive Amination of d-Fenchone

Initial compounds	Total yield of amines, %	Composition of the catalysate, %			Composition of the mixture of N-alkylfenchylamines, %	
		N-fenchylidenalkylamine	fenchone	mixture of α- and β-fenchols	endo isomer	exo isomer
Fenchone and acetonitrile	64,0	3.5	17.5	15,0	71,0	29,0
Fenchone and acrylonitrile	59 0	5,5	19,0	16,5	69 0	31,0
Fenchone and butyronitrile	67,0	3,0	16,5	13,5	69,0	31,0

TABLE 2. Chemical Shifts of the ^{13}C Nuclei (δ, tetramethylsilane) of Some N-Alkylfenchylamines



R	Configuration	Chemical shifts, ppm													
		C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}	C_{13}	C_{14}
C_2H_5	1S : 2S : 4R-endo	49.1	73,9	39,3	49.1	26.4	26,6	43.0	32,6	20,9	20.5	52,8	24,0	11,9	
C_2H_5	1S : 2R : 4R-exo	49,1	75,5	43,6	49,1	25,7	36,9	42,1	28,1	24,0	18.4	53,3	23,9	11,9	
C_3H_7	1S : 2S : 4R-endo	49,3	74,2	39,4	49.3	26,5	26,7	43.1	32.7	20,9	20.5	50.6	33,3	20,6	14,0
C_3H_7	1S : 2R : 4R-exo	49,2	75,9	43,7	49,3	25,7	37,1	42,3	28.1	24.1	18,3	51,1	33,2	20,6	14,0

EXPERIMENTAL

The analysis of the reaction products was carried out as previously [3]. The d-fenchone used had bp 67-68°C (10 mm Hg), d_4^{20} 0.9453, n^{20} 1.4620, $[\alpha]_D^{20}$ + 64.68°, and had been isolated by fractionation from fennel oil.

N-Ethyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-ylamines (II and III), R= CH_3. A mixture of 15.3 g of d-fenchone and 6.2 g of acetonitrile was passed in an apparatus of the flow-through type with a space velocity of 0.25 h^{-1} at a temperature of 250°C and a hydrogen pressure of 15 atm through a layer of catalyst consisting of 15% copper and 6% of lithium hydroxide deposited on γ-alumina. Vacuum fractionation of the catalysate gave a fraction containing 80% of the desired product, bp 105-115°C (15 mm). By preparative GLC, this fraction yielded the desired product with a purity of 98% and a ratio of endo and exo isomers of 3:1. bp 110-112°C (15 mm), d_4^{20} 0.8285, n_D^2 1.4732. MR_D found 61.44, calculated 61.41; $[\alpha]_D^{20}$ −34.3° (ethanol). IR spectrum (cm^{-1}); 1135, 1365, 1465, 2880, 2960, 3320.

N-Propyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-ylamine (II and III), R = C_2H_5. A mixturere of 15.3 g of fenchone and 7.9 g of acrylonitrile was passed in an apparatus of the flow-through type for continuous reactions under conditions similar to those given above. Vacuum fractionation of the catalysate yielded a fraction with bp 120-130°C (15 mm) containing 85% of the desired product. The desired product (II, III, R = C_3H_7) was isolated from this fraction by PGLC with a purity of 99%, the ratio of endo and exo isomers being 3:1. bp 125-127°C (15 mm), d_4^{20} 0.7732, n_D^{20} 1.4712, MR_D found 70.68, calculated 70.67, $[\alpha]_D^{20}$ −31.1° (ethanol). IR spectrum (cm^{-1}): 1135, 1365, 1375, 1465, 2880, 2960, 3320. Mass spectrum (m/z): 195 (M^+), 178, 166, 152, 136, 126, 121, 112, 72 (100%), 70.55.

N-Butyl-1,3,3-trimethylbicyclo[2.2.1]hept-2-ylamine (II and III), R = C_3H_7. A mixture of 15.3 g of fenchone and 10.4 g of butyronitrile was passed under conditions similar to those of the preceding experiments in an apparatus of the flow-through type. Vacuum fractionation of the catalysate yielded a fraction with bp 135-140°C (15 mm) containing 85% of a mixture of (II) and (III), R= C_3H_7. The desired product was isolated from this by the PGLC method with a purity of 99% and a ratio of the endo and exo isomers of 3:1. bp 138-139°C (15 mm), d_4^{20} 0.7305, n_D^{20} 1.4700, MR_D found 79.97, calculated 79.91, $[\alpha]_D^{20}$ −29.8 (ethanol). IR spectrum (cm^{-1}): 1130, 1370, 1385, 1455, 2880, 2960, 3300.

The results of the elementary analysis of all the compounds obtained corresponded to the calculated figures.

SUMMARY

The catalytic hydroamination of d-fenchone by aliphatic nitriles in an apparatus of the flow-through type has been studied. The optimum conditions for the performance of the reaction have been determined. The scheme is suggested for the mechanism of the formation of secondary amines. The absolute configurations of the compounds obtained have been established.

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NMR STUDY OF ALKALOIDS.

V. ^{13}C NMR SPECTRA AND RECONSIDERATION OF THE STRUCTURES OF 11- AND 10-HYDROXYPLEIOCARPAMINES AND THE STRUCTURES OF NEW ALKALOIDS FROM *Vinca erecta*

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The structures of phenolic alkaloids isolated previously from *Vinca erecta* Rgl. et Schmalh. have been reconsidered on the basis of the results of a study of their ^{13}C NMR spectra, and it has been shown that a base with mp 228-229° has the structure of 11-hydroxystrictamine and an amorphous base of the same composition isomeric with it is 10-hydroxystrictamine. The structures of two new indolenine alkaloids — ercinamine and ercinaminine — have been determined from an analysis of ^{13}C NMR spectra, and also on the basis of PMR and IR spectra and chemical transformations.

Previously, on the basis of an analysis of the UV, IR, PMR, and mass spectra, a phenolic base with mp 228-229°C isolated from the plant *Vinca erecta* Rgl. et Schmalh. [1] was ascribed the structure of 11-hydroxypleiocarpamine (I). The pleiocarpamine skeleton in (I) was proposed on the basis of the composition and the absence from its IR and PMR spectra of the signals of N—H and N—CH_3 groups, and also the closeness of its mass-spectrometric fragmentation and that of pleiocarpamine [1]. Then an amorphous base (II) with the same composition as (I) was isolated from the same plant. On the assumption that base (II) also had a pleiocarpamine skeleton and analyzing the chemical shifts of the aromatic protons in the PMR spectra of (I), (II), and other hydroxy- and methoxy-substituted indole alkaloids, we came to the conclusion that (I) was 10-hydroxypleiocarpamine and (II) was 11-hydroxypleiocarpamine [2]. In order to elucidate the skeletons and structures of alkaloids (I) and (II), we have now studied the ^{13}C spectrum of (I) (Fig. 1).

The assignment of the signals of the carbon atoms was made on the basis of the results of an experiment with incomplete decoupling of C—H interactions, i.e., from the multiplicities of the signals in the off-resonance spectrum, and also by comparing the ^{13}C CSs with the ^{13}C CSs given in the literature for alkaloids of similar structure taking the α-, β-, and γ-contributions into account [3, 4]. As can be seen from Fig. 1, in the 100-192 ppm region of the

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