ADVANCES IN THE FIELD OF THE SYNTHESIS OF AMINO DERIVATIVES OF TERPENOIDS

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Information on the synthesis of amino derivatives of monoterpenes by the reduction of oximes by the Leuckart reaction, and by the reductive amination of ketones by amines and nitriles is generalized. The stereochemistry of the amines formed as the result of the above-mentioned reactions is discussed.

Amines form one of the least studied classes of terpene derivatives. In spite of this, some of them are used in the national economy, and, in particular, as antioxidants for fuel oils, and in the preparation of effective drugs and pesticides.

Amino derivatives of terpenoids are obtained by the amination of alcohols, halogen-containing compounds, and carbonyl compounds, by the reduction of nitro compounds and oximes, and by the Hofmann, Curtius, and other reactions. The synthesis of amines of monoterpenes, namely bornylamines, by the reaction of camphor with formamide was first performed by Leuckart [1] in 1887, and by the reduction of camphor oxime by Forster [2] in 1898. Since then a large number of publications devoted to the study of particular aspects of the reactions mentioned have appeared and also a number of reviews [3-6]. The results of investigations performed up to 1955 have been generalized most completely (those by the Leuckart reaction in a paper by B. M. Bogoslovskii [3]).

In the present paper we have attempted, without repeating previous work, to give a review of the literature on the preparation of amines of terpenoids by the reduction of oximes, by the Leuckart reaction, and by the reductive amination of carbonyl-containing terpene compounds, to reflect the advances in the field of the study of these compounds, and to consider the stereochemistry of some known terpene amines.

Synthesis of Amines by the Reduction of Oximes

The reduction of the oxime group in a compound leads to a new asymmetric center, and therefore the reaction usually forms a mixture of stereoisomeric amines. Thus, for example, in the reduction of menthone oxime (1), menthylamines with three asymmetric centers are obtained that exist as eight stereoisomeric optically active forms [7-10].

The reduction of oximes can be carried out both with sodium in ethanol and by catalytic hydrogenation. The influence of the reduction conditions on the composition of the mixture of stereoisomeric amines is shown in the following way: in the reduction of the oxime (I) with sodium in ethanol, only menthylamine (II) and isomenthylamine (III) are formed [4, 11-13]. If the reaction is performed in the presence of platinum black in glacial acetic acid, the main product is neomenthylamine (IV), while on hydrogenation in the presence of Raney nickel in methanol it is predominantly neoisomenthylamine (V) that is produced. The total yield of amines here amounts to 40-60% [14].

A similar influence of the reaction conditions have been detected in the reduction of carvomenthone oxime (VI). The reaction forms the stereoisomeric optically active carvomenthylamine (VII), isocarvomenthylamine (VIII), neocarvomenthylamine (IX), and neoisocarvomenthylamine (X) [15-19].

Thus, on the reduction of oximes by sodium in ethanol the main products are the amines (II) and (VII) which are the most stable, having the triequatorial arrangement of the substituents, as can be seen from the conformational schemes. Catalytic hydrogenation gives the less thermodynamically stable amines in which one (IV, IX, and X) or two (V) substituents in the cyclohexane ring are present in the axial position [16, 20].

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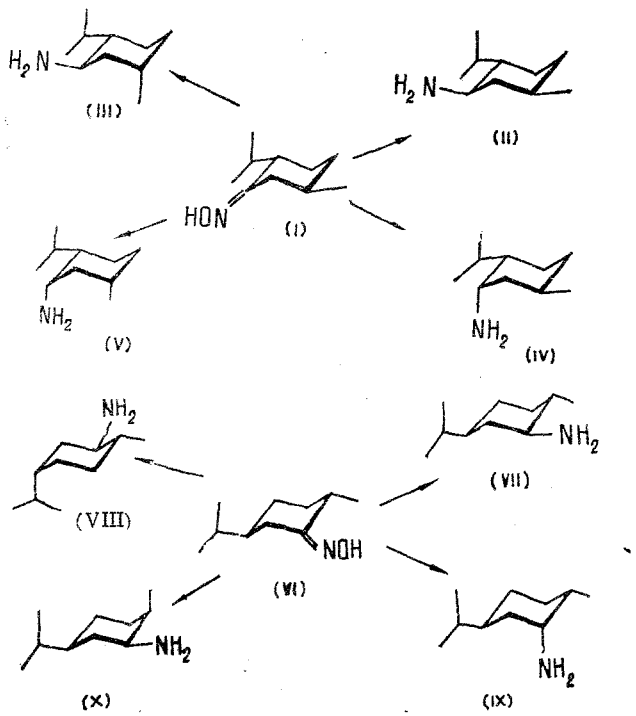
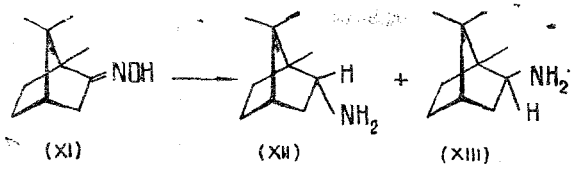


It is interesting to trace the influence of the conditions of performing the reaction on the reduction of certain oximes containing endo- and exocyclic double bonds. The reduction of carvone oxime with zinc dust in glacial acetic acid [21] forms a mixture of cis- and trans-carvylamines while when it is reduced with lithium tetrahydroaluminate in tetrahydrofuran the cis-carvylamines are the sole product [22]. In both cases the double carbon-carbon bonds are unaffected. If, however, the reaction is carried out under more severe conditions as, for example, by sodium in ethanol, partial hydrogenation of the double bonds take place. The dihydrocarvylamine so formed contains only an exocyclic double bond. When pulegone oxide is reduced under similar conditions, the exocyclic double bond is again retained. From this it may be concluded that under the action of sodium in ethanol only the most reactive, endocyclic, double bonds of unsaturated oximes are reduced. Unfortunately there is no information in the literature on the synthesis of completely hydrogenated amines from carvone and pulegone oximes.

The reduction of the oximes of camphor (XI) and its analogs is of great interest for the study of the stereochemistry of the reaction, since the amines formed in this process exist in two stereosiomeric forms: endo- and exo-. The first is analogous to the axial, and the second to the equatorial, position in the cyclohexane ring. The endo- and exo-forms of the bornylamines and their analogs are stable three-dimensional isomers, since the rigidity of the bicyclo[2,2,1]heptane skeleton ensures the strict fixation of the position of the amino group.

The reduction of camphor oxime under various conditions forms the endo- and exo-bornylamines (bornylamine and isobornylamine, XII and XIII, respectively) in the ratios given below.

Reducing agent	endo-Bornylamine %	exo-Bornylamine %	Literature
Na/EtOH	70—80	20—30	23, 24
$LiAlH_4$	10 (30)	90 (70)	25, 26, 27
Raney Ni	—	100	27, 29
PtO_2/MeOH	15	85	30
Hg cathode	1	99	26

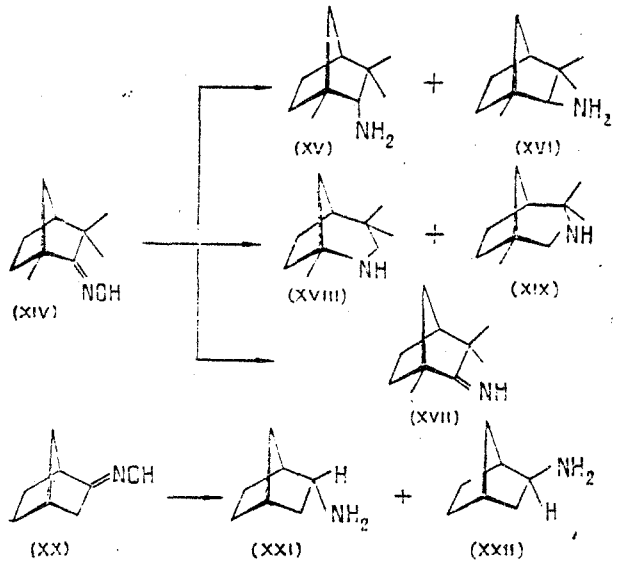


It must be mentioned that on reduction by sodium in ethanol the thermodynamically most stable endo-bornylamine is formed predominantly. Catalytic reduction with a higher selectivity has the other stereochemical direction. In this case, the main product of the reaction is the less stable exo-bornylamine [5, 6].

There is contradictory information on the reduction of fenchone oxime (XIV), fenchone being a very close analog of camphor. Thus, Huckel and Meinhardt [25] state that the reduction of (XIV) with lithium tetrahydroaluminate or with sodium in ethanol forms a mixture of endo- and exo-fenchylamines (XV and XVI, respectively), the ratios of the isomers being as follows:

Reducing agent	endo-Fenchylamine %	exo-Fenchylamine %	Literature
Na/EtOH	83	17	25, 32
$LiAlH_4$	65—70	34—35	25, 31
Raney Ni	70—75	25—30	31
PtO_2/MeOH	75	25	31

According to Huckel and Sheel [31], the hydrogenation of (IV) in the presence of Raney nickel in ethanol gave a mixture of fenchylamines containing mainly endo- form (XV), the total yield of amines being 80-95%.

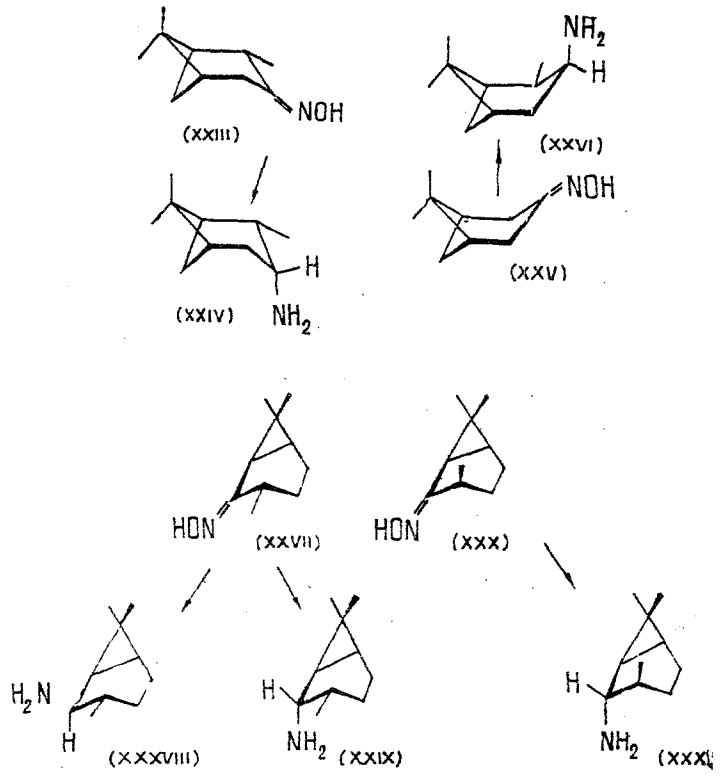


However, it was later established [27] that under the conditions described (Raney Ni/ethanol), the reduction of fenchone oximes forms only fenchimine (CVII) (99%), while the action of lithium tetrahydroaluminate forms a complex mixture of nitrogen-containing compounds (with a yield of 90%), including 53% of endo-fenchylamine (XV), 5% of 1,4,4-trimethyl-2-azabicyclo[3.2.1]octane (XVIII), 37% of 1,4,4-trimethyl-3-azabicyclo[3.2.1]octane (XIX), and 5% of fenchimine (XVII).

The reduction of norcamphor oxime (XX) gives a mixture of endo- and exo-norbornylamines (XXI and XXII, respectively), and in this case, on the basis of conformational schemes, the more thermodynamically stable is exo-norbornylamine, which is also formed predominantly on reduction by sodium in ethanol:

Reducing agent	endo-Norbornylamine, %	exo-Norbornylamine, %	Literature
Na/EtOH	25	75	26
$LiAlH_4$	100	—	26
PtO_2/MeOH	90	10	5
Hg cathode	100	—	26

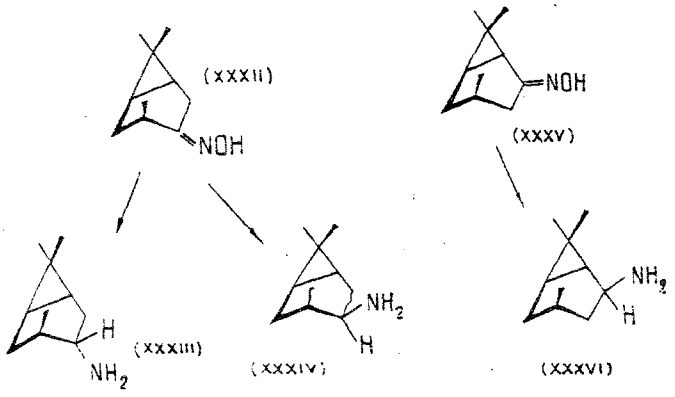
The literature contains a description of the stereochemistry of the reduction of ketone oximes of the pinane and carane series. The reduction of the oxime of 2βH-pinan-3-one (XXIII) in the presence of platinum black in glacial acetic acid led to the synthesis of 2βH-pinyl-3β-amine (XXIV). Under analogous conditions the oxime of 2αH-pinan-3-one (XXV) formed 2αH-pinyl-3β-amine (XXVI) [33].



The reduction of the oxime of (+)(1R:3S:6S)-trans-caran-2-one (XXVII) by sodium in ethanol led to the formation of (+)(1R:2R:3S:6S)-trans-caran-cis-2-ylamine (XXVIII), while its reduction with lithium tetrahydroaluminate gave (+)(1R:2S:3S:6S)-trans-caran-trans-2-ylamine (XXIX) [34, 35].

Similar results were obtained in the reduction of the oxime of (-)-trans-caran-2-one [36]. The reduction of the oxime of (-)-cis-caran-2-one (XXX) with sodium in ethanol forms (-)-cis-caran-trans-2-ylamine (XXXI).

The reduction with sodium in ethanol of the oxime of (-)-cis-caran-4-one (XXXII) gives (-)-cis-caran-trans-4-ylamine (XXXIII), while its reduction in the presence of a platinum catalyst forms mainly (+)-cis-caran-cis-4-ylamine (XXXIV) [36, 37]. The reduction of oxime of (+)-cis-caran-5-one (XXXV) with sodium in ethanol leads to the formation of (-)-cis-caran-cis-5-ylamine (XXXVI) [37].



Thus, on the reduction of the oximes of ketones of the pinane and carane series the same laws are observed as in the reduction of the oximes of menthone, carvomenthone, camphor, etc. The action on an oxime of sodium in ethanol forms the most thermodynamically stable isomer of the amine, while catalytic reduction usually gives the less stable isomer.

The reaction described above is widely used for the synthesis of various primary amines. However, there is no information on the literature on the one-stage synthesis of secondary

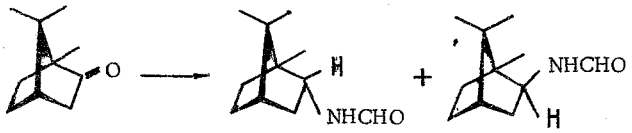
amines from oximes of terpene ketones. N-Substituted amines are usually obtained by the alkylation of primary amines with alkyl halides. A number of N-alkyl- and N-methyaryl derivatives of d- and dl-bornylamines, for example, have been synthesized by this method [38, 39].

The essence of the method is as follows. The bornylamines are heated with an alkyl halide in a sealed tube for 8-12 h. The mixture of secondary and tertiary amines formed as the result of the reaction is separated via the nitroso compound [40]. As we shall see, the synthesis is lengthy and laborious, and the yield of N-substituted bornylamines does not exceed 30%.

Synthesis of Amines by the Leuckart Reaction

In the Leuckart reaction, the reductive amination of aldehydes and ketones is performed by the action of formamide and formic acid on them [3].

Leuckart was the first to study the reaction of camphor (XXXVII) with ammonium formate [1]. The reaction was performed in a sealed tube at 220-240°C for 4-5 h. This gave a mixture of formyl-endo- and -exo-bornylamines (XXXVIII and XXXIX, respectively), while a very small amount of dibornylamine was detected as a by-product.



(XXXVII) (XXXVIII) (XXXIX)

A modification on the method under consideration is the use of a mixture of formamide and ammonium formate or ammonium carbonate with 85-90% formic acid as the formylating agent [41]. The reaction takes place particularly completely with the use of stable water-insoluble ketones having boiling points above 120°C. The addition of catalytic amounts of water-abstracting substances, such as anhydrous gypsum and cobalt chloride, and also acetic acid, ammonium sulfate, and magnesium, zinc, or iron chloride, to the reaction mixture accelerates the formation of the formyl derivatives of the amines [42-47]. However, the mechanism of the catalytic action of these substances, like the mechanism of the Leuckart reaction itself, has not been definitively elucidated. The existence of a formamido compound formed as an intermediate has been shown on the basis of a study of the absorption curves of the reaction mixture in the ultraviolet region of the spectrum. The water liberated in the second stage hydrolyses the formamide which leads to the formation of ammonium formate, serving as a reducing agent. The following stage of the reaction is the addition of the formate ion to the positive center of the formamido compound, and the last stage, in the opinion of the authors under consideration, is the transfer of a proton from the ammonium ion formed by the intermediate compound, which leads to the production of the formyl derivative of the amine.

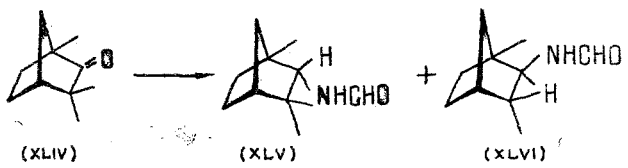
In spite of the fact that the mechanism of the Leuckart reaction has not been accurately established, the stereochemistry of the reaction for certain ketones of the terpene series has been determined fairly reliably.

Thus, for example, it has been shown that the action of ammonium formate on (-)-menthone (XL) forms a mixture of formyl derivatives of menthylamines the main component of which is (+)-formylneomenthylamine (XLI) [48, 49]. Under the same conditions carvomenthone (XLII) gives predominantly formylneocarvomenthylamine (XLIII) [15].

(XL) (XLI)

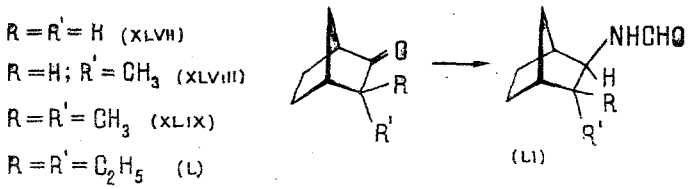
(XLII) (XLIII)

Camphor, when subjected to the Leuckart reaction by the method of Ingersoll et al. [41], gave a mixture of formyl derivatives of endo- and exo-fenchylamines (XLV and XLVI, respectively) containing about 80% of the endo isomer. When a mixture of ammonium formate with formamide and 90% formic acid was used [51], the composition of the mixture of formyl derivatives of fenchylamines did not change appreciably. From norcamphor (XLVII), 3-methylnorcamphor (XLVIII), camphenilone (XLIX), and 3,3-diethylnorcamphor (L) by the Leuckart reaction a number of isomeric formyl derivatives of endo- and exo-3,3-R,R'-bicyclo[2,2,1]hept-2-ylamines (LI) have been synthesized [52], in which the amount of the exo- isomer considerably predominated.



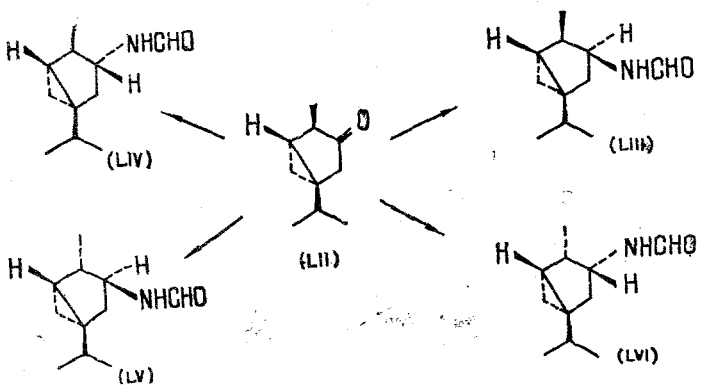
(XLIV) (XLV) (XLVI)

By Leuckart reaction, from (-)-thujone (LII) has been obtained a mixture of four stereoisomeric formyl derivatives: derivatives of (-)-thujylamine (LIII), (-)-neothujylamine (LIV), (+)-isothujylamine (LV), and (+)-neoisothujylamine (LVI) [53-55].



(LI)

On the basis of the facts given it may be concluded that in all cases the Leuckart reaction forms a mixture of stereoisomeric formyl derivatives of amines the composition of which is determined only by the spatial structure of the initial ketones and does not depend appreciably on the conditions of performing the reaction.



The literature contains descriptions of synthesis of secondary and tertiary amines by the Leuckart reaction. For this purpose N-alkyl- or N,N-dialkylformamides are used in place of formamide [56-58]. Similar results have been obtained on the use as formylating agent of a mixture of a primary or secondary amine and formic acid [57, 58].

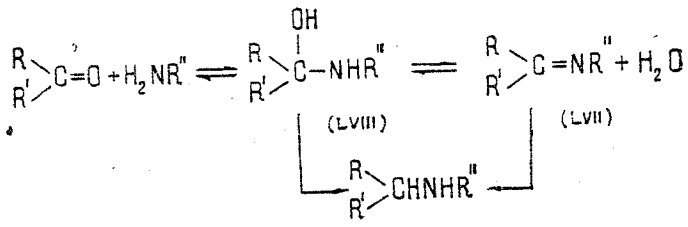
N-Methyl-substituted amines can be obtained by the reduction of the formyl derivatives [59-61]. For example, N-methyl-exo-bornylamine has been synthesized by the reduction of formyl-exo-bornylamine with lithium tetrahydroaluminate [62-64].

We may note that at the present time the Leuckart reaction is probably the main method of synthesizing amines from terpene aldehydes and ketones. However, the procedure for performing the reaction has serious disadvantages which limit the range of its application. These disadvantages include its two-stage nature and the prolonged heating of the reaction mixture at a comparatively high temperature. Unsaturated terpene aldehydes and ketones undergo isomerization and the formation of resins during this process, which does not permit their use in this reaction.

Synthesis of Amines by the Reductive Amination of Terpene Ketones

The capacity of primary amines for forming azomethines (Schiff's bases) (LVII) with aldehydes and ketones and the comparative ease with which the latter undergo reduction to amines permits secondary amines to be synthesized by the direct amination of carbonyl-containing compounds.

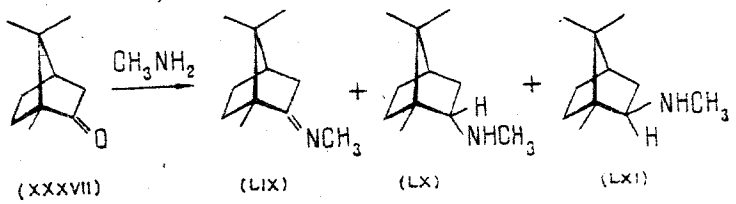
The range of application of this reaction is extremely broad. The reductive amination of aldehydes and ketones by amines takes place through a stage of the formation of the product (LVIII) of the addition of the amine to the carbonyl-containing compound which either hydrogenates to the amine or splits out water forming a Schiff's base (LVII) which is reduced to the amine [65].



As a rule, the hydroamination of aldehydes and ketones is carried out under a pressure of hydrogen in an autoclave in the presence of heterogeneous catalysts. Platinum, palladium, and nickel may be used as catalysts for the reaction.

For example, in the reaction of d-camphor (XXXVII) with methylamine [66] under these conditions, a mixture of N-bornylidenemethylamine (LIX), N-methyl-endo-bornylamine (LX), and N-methyl-exo-bornylamine (LXI) was obtained:

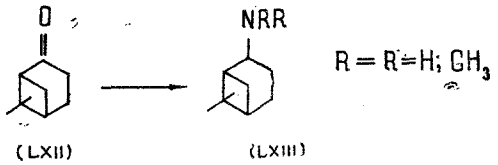
Catalyst	Composition of the reaction products, %			Total yield of amines, %
	N-Bornylidene-methylamine	N-Methyl-endo-bornylamine	N-Methyl-exo-bornylamine	
Raney Ni	82.8	1,3	15.9	65
5% Pd/C	30,4	3,9	65.7	61
PtO_2	3,7	4,6	91,7	70
Without a catalyst	100.0	—	—	100



(XXXVII) (LIX) (LX) (LXI)

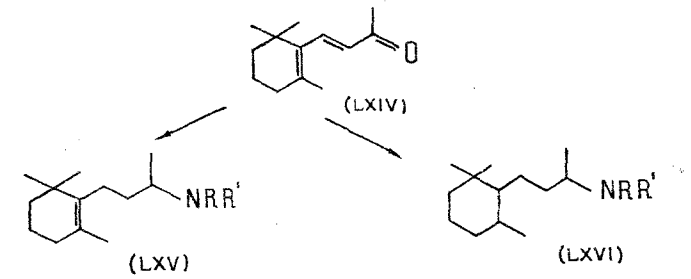
It can be seen from the facts given that with respect to their efficacy and selectivity the catalyst used can be arranged in the sequence Pt > Pd > Raney Ni. It must be mentioned that in this case the thermodynamically less stable exo isomer predominated in the mixture of N-methyl-endo- and -exo-bornylamines.

The nopinylamines (LXIII) have been synthesized by the catalytic hydrogenation of nopinone (LXII) in the presence of ammonia or diemthylamine [67].



(LXII) (LXIII)

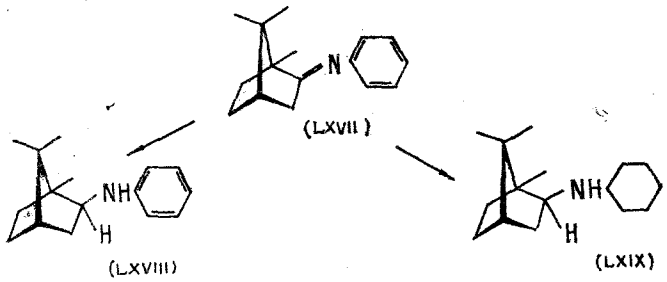
N-Alkyldihydroionylamines (LXV) and N-alkyltetrahydroionylamines (LXVI) have been obtained from α-ionone, β-ionone (LXIV), or ψ-ionone and various amines in the presence of platinum or nickel catalysts [68-70]. It was established that in the process of exhaustive hydrogenation the double bond in the side chain is first reduced and then the ketimine grouping, and lastly the double bond in the ring.



R = H; H ; H; ; H ; H ; H ; CH_3; CH_3.

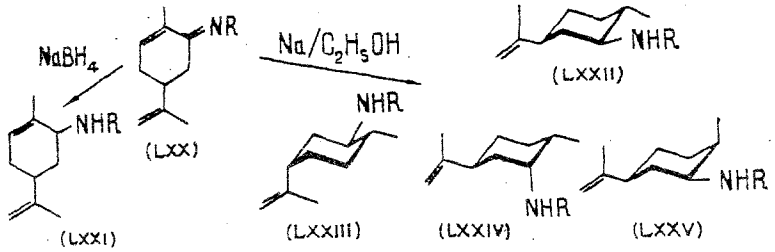
R' = CH_3; C_2H_5; C_3H_7; C_4H_9; C_6H_{11}; $CH_2C_6H_5$; CH_3; $CH_2C_6H_5$.

A two-stage method of synthesizing N-substituted terpene amines is more widely used at the present time. In the first stage a ketone is condensed with an amine in the presence of water-abstracting compounds, as a result of which a Schiff's base is formed [71]. Then the latter is reduced in the presence of various catalysts to the corresponding amine [72]. It must be mentioned that the stereochemical composition of the reaction products is determined just by the second stage of the reaction, and therefore it is interesting to consider the influence of the conditions of reducing certain Schiff's bases on the structure of the amines formed in this process. For example, the reduction of N-bornylideneaniline (LXVII) in the presence of skeletal nickel at 100-150°C forms N-phenyl-exo-bornylamine (LXVIII), while at 150-200°C it forms N-cyclohexyl-exo-bornylamine (LXIX) [73].



The reduction of Schiff's bases is usually carried out in milder conditions; for example, by alkali metal hydrides or with other reducing agents [74-77]. The reduction of N-menthylidenalkylamines with potassium tetrahydroborate gave the corresponding N-alkylmenthylamines with a yield of about 50% [78].

The action of sodium tetrahydroborate on a carvylidenealkylamine (LXX) has yielded a N-alkylcarvylamine (LXXI). When it was reduced under more severe conditions (by sodium in isopropanol), a mixture of N-alkyldihydrocarvylamines containing dihydrocarvylamine (LXXII), dihydroisocarvylamine (LXXIII), dihydroneocarvylamine (LXXIV), and dihydroneoisocarvylamine (LXXV) in a ratio of 2:6:1:1 was formed [79].



A new one-stage method of synthesizing secondary amines was developed in the laboratory of organic catalysis of the Institute of Physical Organic Chemistry of the Academy of Sciences of the Belorussian SSR in 1975 [80]. The essence of this method is that aldehydes or ketones are subjected to catalytic hydroamination by nitriles [81-84].

N-Substituted bornylamines have been synthesized by this method from camphors and aliphatic or aromatic nitriles [85]. The reaction was performed in the following way: a solution of camphor in the appropriate nitrile was passed in a current of hydrogen through a bed

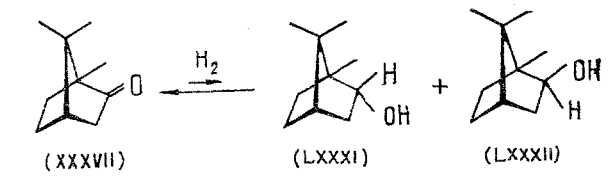
TABLE 1. Yields and Compositions of the Products of the Hydroamination of Camphor by Nitriles (pressure of hydrogen 15 atm, space velocity 0.3 h^{-1}, temperature 240°C)

Initial compounds	Total yield of amines, %	Composition of the reaction products, %				Composition of the mixture of N-alkylbornylamines, %	
		N-bornylidenealkylamine	camphor	mixture of borneols	isocamphane	-endo-	-exo-
Camphor Acetonitrile	66,3	6,7	14,0	8,0	5,0	80,4	19,6
Camphor Acrylonitrile	62,2	5,8	18,0	8,0	6,0	80,6	19,4

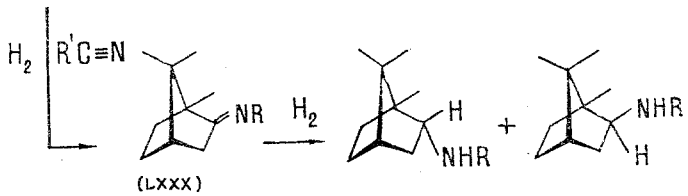
of copper-alumina catalyst modified with lithium hydroxide in an apparatus of the flow-through type. The results of the catalytic hydroamination of l-camphor by aliphatic nitriles are given in Table 1.

The main products of the reaction are N-alkylbornylamines, which consist of a mixture of endo and exo isomers in a ratio of 4:1 [86]. N-Ethyl-endo-bornylamine (LXXVI), N-propyl-endo-bornylamine (LXXVII), N-ethyl-exo-bornylamine (LXXVIII), and N-propyl-exo-bornylamine (LXXIX) have been synthesized by the method described above.

In addition to the main reaction product, the catalysate was found to contain the corresponding Schiff's base (LXXX). It was established by GLC that during the reaction the camphor (XXXVII) is partially reduced with the formation of a mixture of endo- ane exo-borneols (LXXXI and LXXXII) in a ratio of 1.5:1.0. The hydroamination reaction of l-camphor is composed of the following stages: the reduction of the nitrile to the primary amine, the condensation of the amine with the camphor to form an azomethine, and the hydrogenation of the latter.



(XXXVII) (LXXXI) (LXXXII)



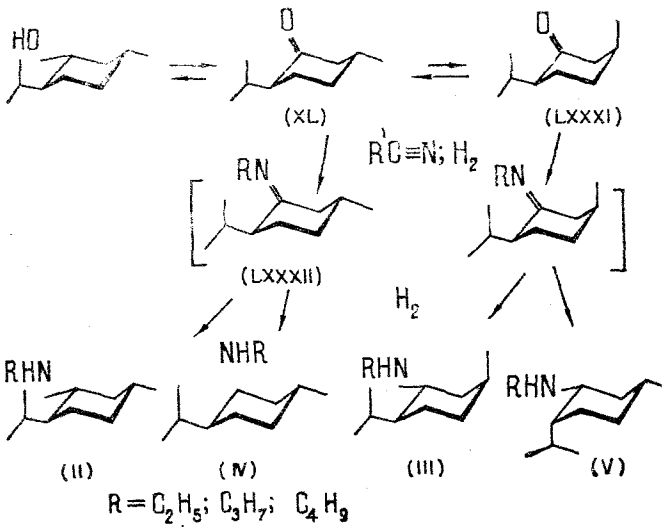
(LXXX) (LXXVI) (LXXVIII)
(LXXVII) (LXXIX)

$R = C_2H_5$
$R = C_3H_7$

The reductive amination of l-menthol by aliphatic nitriles under conditions similar to those given above has also been studied [87]. A scheme of occurrence of the reaction has been proposed and the stereochemical composition of its products has been determined.

The reaction forms a mixture of isomeric optically active N-alkylmenthylamines (II), -neomenthylamines (IV), -isomenthylamines (III), and -neoisomenthylamines (V) in a ratio of 54:24:17:5.

The main components of the mixture of amines (II-V) are the products (II and IV) of the reductive amination of menthone (XL) (about 80%), which is sterically more favorable than isomenthone (LXXXI) and predominates in the (XL)-(LXXXI) equilibrium. Of the amines (II-V), the most stable on the basis of the usual conformational ideas, is the N-alkylmenthylamine (II) with the triequatorial arrangement of the substituents in the cyclohexane ring, its amount in the mixture of amines being about 60%. The least stable is the neoisomenthylamine (V), the amount of which in the mixture is ~5%. The predominant formation of N-alkylmenthylamine is explained by both energy and steric factors. Compounds with the equatorial arrangement of the substituents are more stable because of the smaller steric stresses than in compounds with the axial arrangement of the substituents. This is confirmed by thermodynamic calculations [88]. The spatial influence of an isopropyl group adjacent to the reaction cen-



ter of the Schiff's base (LXXXII) consists in the fact that the hydrogenation of a >C=N bond in the axial direction is sterically more favorable [89], because of which N-alkylmenthylamines with the equatorial arrangement of the amino group are formed.

Individual N-alkylmenthylamines (II) and N-alkylneomenthylamines (IV) have been isolated by preparative GLC from the mixture of secondary amines (II-V) obtained as the result of the reaction.

Two methods of synthesizing N-substituted 2-methyl-5-(1-methylethyl)cyclohexylamines by the hydroamination of (+)-S-carvone with aliphatic nitriles [90] and of the hydroamination of some aldehydes and ketones by (+)-S-carvone oxime [91] have been proposed. The optimum conditions for performing these processes have been determined.

As a result of these reactions, a mixture of N-substituted carvomenthylamines (VII), isocarvomenthylamines (VIII), neocarvomenthylamine (IX), and neoisocarvomenthylamines (X) in a ratio of 65:20:10:5 is formed.

The hydroamination of (+)-S-carvone (LXXXIII) by aliphatic nitriles takes place through a stage of the reduction of the nitriles to the primary amines followed by their condensation with the ketone to form Schiff's bases and the hydrogenation of the latter to the corresponding secondary amines (method A). In the course of the reaction the double carbon-carbon bonds of the carvone are completely reduced, and therefore each of the amines formed, having three asymmetric centers (C_1, C_2, and C_5) can exist as four stereoisomeric optically active forms — N-substituted carvo-, isocarvo-, neocarvo-, and neoisocarvomenthylamines.

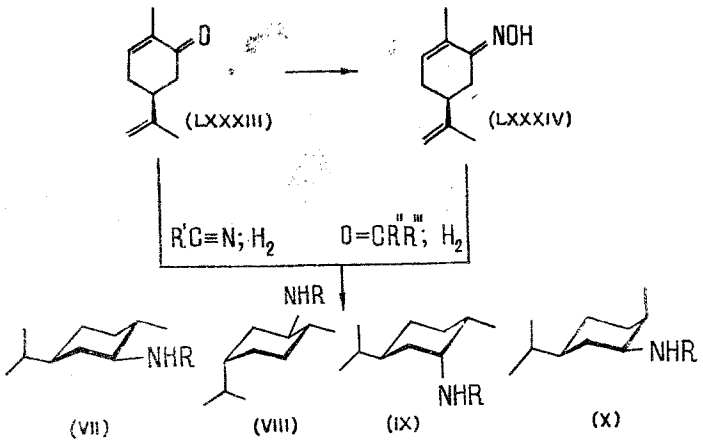
N-Ethyl, N-propyl-, and N-but-2-ylmethyl-5-(1-methylethyl)cyclohexylamines have been synthesized by the procedure described.

Experimental results on the reduction of oximes to primary amines under conditions close to those of the hydroamination reaction [92] have permitted (+)-S-carvone oxime (LXXXIV) to be used for the first time as the direct aminating agent of some aldehydes and ketones.

The reaction of the oxime with a carbonyl-containing compound takes place by a complex mechanism of concerted hydrogenation and condensation reactions taking place in parallel and successively on the surface of the catalysts [93, 94]. The main reaction products are N-substituted 2-methyl-5-(1-methylethyl)cyclohexylamines.

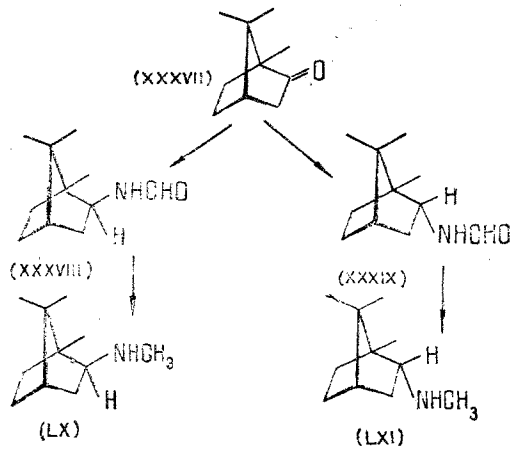
This method (B) of the synthesis of N-substituted 2-methyl-5-(1-methylethyl)cyclohexylamines considerably broadens the possibilities of using secondary amines of this series, since the wide variety of aldehydes and ketones in the domestic industry permits the synthesis of amines of very diverse structures. N-(1-methylpropyl), N-(1-ethylpropyl)-, N-(1-methylbutyl)-, N-(1-methylpentyl)-, N-(1-ethylpentyl)-, N-cyclopentyl-, N-cyclohexyl-, and N-benzyl-2-methyl-5-(1-methylethyl)cyclohexylamines have been synthesized by this method.

A study of the reactions considered above at various pressures of hydrogen, space velocities, and temperatures, has permitted the optimum conditions for their performance to be determined. The maximum yield of secondary amines is obtained at temperatures of 230-240°C,



a hydrogen pressure of 15 atm. and a space velocity of feed of the initial mixture of 0.3 h^{-1}.

Since, as already mentioned, the Leuckart reaction — the hydroamination of aldehydes and ketones — is one of the main methods of obtaining terpene amines, the reductive amination of camphor (XXXVII) by formamide in an apparatus of the flow-through type in a current of hydrogen in the presence of a copper-alumina catalyst has been studied [95]. In addition to the formyl derivatives of amines (XXXVIII and XXXIX), the reaction products contained N-methylcamphylamines (LX and LXI), formed as the result of the reduction of the formyl group.



Thus, it has been shown for the first time that under the conditions of the hydroamination reaction by the action of formamide on a ketone it is possible to obtain N-methyl-substituted amines in one stage.

* *
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In recent years, the greatest advances in the field of the synthesis of monoterpene amines has been achieved just in the field of the catalytic amination of carbonyl compounds. Thus, on the basis of the developments of recent years a large number of valuable drugs and pesticidal preparations have been obtained by the reductive amination of various carbonyl compounds of the terpene series [96-98].

And although the overwhelming number of amines is today obtained by traditional methods (from halogen-containing compounds, by the reduction of nitro compounds, or by the Leuckart reaction), in the very near future the reductive amination of carbonyl compounds of the terpene series will obviously become one of the main methods of obtaining monoterpene amines, and this primarily because of the accessibility of the terpene ketones.

The most important problem is becoming the choice of highly effective and selective catalysts for the reductive amination of the carbonyl compounds, since only on the basis of

such catalysts is it possible to create a modern waste-free manufacture. In this connection, work on the use of readily available copper-containing catalysts must be considered extremely promising.

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