REDUCTIVE AMINATION IN THE SYNTHESIS OF AZAHETEROCYCLES (REVIEW)

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Methods for obtaining saturated five- and six-membered azaheterocycles based on the use of catalytic intra- and intermolecular hydroamination of dicarbonyl compounds and ketones and amines of the furan series, hydride amination of aldehydes and ketones, and the Leuckart reaction are examined.

Heterocycles of the pyrrolidine and piperidine series and their condensed analogs are the structural foundation of natural alkaloids and synthetic biologically active substances that have a broad spectrum of physiological activity [1-3]. These compounds have found application in the manufacture of herbicides, light-resistant polymers, plasticizers, accelerators of the vulcanization of rubber, special solvents, catalysts of condensation reactions, etc.

The reductive amination of dicarbonyl compounds, which makes it possible to combine amination and reduction, occupies a special place in the arsenal of methods for obtaining azaheterocycles. Catalytically activated hydrogen (catalytic hydroamination in liquid and vapor phases), formic acid and its derivatives (the Leuckart reaction), and complex metal hydrides (hydride amination) are used as the reducing agents.

Reductive amination has been thoroughly studied as applied to the synthesis of amines of the aliphatic, alicyclic, and aliphatic-aromatic series that are formed on the basis of the corresponding monoketones; this has been reflected in a number of reviews [4-9]. Data on the use of reductive amination to obtain saturated nitrogen-containing heterocyclic compounds were not examined in these reviews or in [10], which was devoted to the catalytic synthesis of azaheterocycles.

In the present review we attempted to thoroughly analyze these reactions as a function of the structures of the starting substances, the character of the reducing agent, and the conditions of the processes and to correlate the literature data published in recent years.

1. Catalytic Hydroamination of Carbonyl Compounds

The direct conversion of a carbonyl group to an amino group under heterogeneous catalysis conditions was first developed for aliphatic aldehydes and ketones [11]. The mechanism, kinetics [12-14], and a large number of catalysts of this process [15] have been studied. The first information on heterocyclization in the case of hydrogenation of 1,4-diketones on Raney nickel in the presence of ammonia was published in 1929 [16, 17]. However, this reaction did not receive wide application, evidently because of the relative inaccessibility of 1,4-dicarbonyl compounds.

The largest number of studies devoted to the synthesis of five-membered nitrogen-containing heterocycles in hydroamination processes is based on the use of accessible derivatives of furan, the ring of which serves as a latent supplier of carbonyl groups.

Recent research has established the ability of 1,5-diketones and the products of their intramolecular aldol condensation, viz., β-cycloketols, to undergo conversion to saturated six-membered azaheterocycles through hydroamination [18, 19].

1.1. Hydroamination of 1,4-Diketones and γ-Keto Carboxylic Acids. The catalytic hydroamination of 1,4-diketones has been studied in the case of acetonylacetone. Depending on the conditions, the reaction products are pyrrolidines [16, 17] or mixtures of the latter with pyrroles [20].

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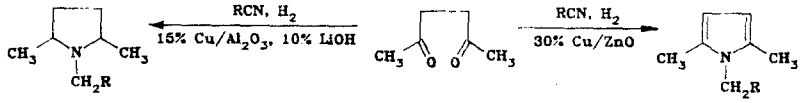
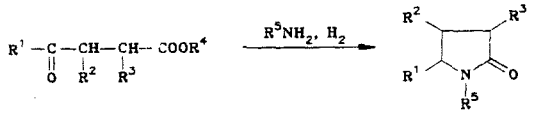
Aliphatic and aliphatic-aromatic nitriles are used as aminating agents in the gas-phase hydroamination of acetonylacetone [21]. The process can be directed to favor the primary formation of pyrrolidines or pyrroles by varying the temperature, the hydrogen pressure, and, chiefly, the nature of the catalyst, viz., copper, which is applied to oxides of the basic, acidic, and semiconductor type [22]:



$R=C_2H_5$, C_3H_7, $CH_2C_6H_5$

The optimum conditions for obtaining saturated bases (in up to 46% yields) are as follows: a temperature of 220°C, a pressure of 0.7 MPa, and the use of 15% Cu/Al_2O_3 promoted with 10% LiOH (to suppress the acidity). A decrease in the temperature and pressure and the use of 30% Cu/ZnO decrease the yields of pyrrolidines to 7-11%. It has been assumed [23] that complexes of different types that are capable of undergoing conversion to pyrroles or pyrrolidines are formed on the surface of the catalyst, depending on its chemical nature.

In contrast to 1,4-diketones, the hydroamination of the more accessible γ-keto carboxylic acids and their esters containing reaction centers with different activities has been thoroughly studied. This reaction is interesting in that it leads to the formation of 2-pyrrolidones, which are cyclic analogs of γ-aminobutyric acid and display diverse biological activities.



R^1=H, Alk, Ar; R^2, R^3, R^4=H, Alk; R^5=H, Alk, Ar, $CH_2COOC_2H_5$, $(CH_2)_nNH_2$, $(CH_2)_nOH$, n=2—6

High yields of lactams were obtained in the reductive methylamination in the gas phase (150-250°C) of levulinic acid and its ethyl ester in the presence of copper chromite promoted with barium or 55% nickel on kieselguhr [24, 25].

5-Alkyl(aryl)-2-pyrrolidones containing $C_{(1)}$—$C_{(13)}$ n-alkyl substituents, radicals with iso structures, and functional groups in the substituent attached to the nitrogen atom were obtained as a result of the hydroamination in the liquid phase of the ethyl esters of a number of γ-keto carboxylic acids [26-36].

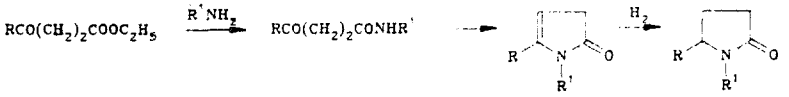
The selectivity of the process is highest when a twofold excess of the aminating agent with respect to the substrate is used. The addition of acids (pH 6) that catalyze the nucleophilic reaction of the amine with the keto group is required in the case of weakly basic aromatic amines, N-(3-aminopropyl)morpholine, and glycine ethyl ester [36, 37]; a slightly acidic medium also hinders self-condensation of glycine ethyl ester [38].

An increase in the number and volume of the substituents attached to the nitrogen atom, for example, the use of 2-amino-(2-hydroxymethyl)propanediol and tert-butylamine, leads to hydrogenation of the starting substances; the only reaction products were the corresponding lactones, which constitutes evidence for the high sensitivity of amination to steric factors.

Platinum [39, 40] and catalysts based on ruthenium proved to be effective catalysts for the hydroamination of esters of keto carboxylic acids. The use of Raney nickel promoted with ruthenium makes it possible to obtain lactams in 70% yields at 100-120°C and a hydrogen pressure of 8-10 MPa. The process occurs at a lower temperature (60°C) on 5% Ru/C. An advantage of ruthenium dioxide is the possibility of its repeated use at room temperature [34].

Since the use of a given method is determined by the accessibility of the starting substances, it should be pointed out that esters of γ-keto carboxylic acids are obtained on the basis of furfural — a product of fundamental organic synthesis [41, 42]. In this connection, a report [29] regarding the fundamental possiblity of passing from β-furylacrylates to γ-lactams without isolation of esters of γ-keto carboxylic acids is of great interest.

Very little is known about the intermediates of the heterogeneous-catalytic transformations of 1,4-dicarbonyl compounds. A possible pathway of the formation of 2-pyrrolidones from esters of γ-keto carboxylic acids (100°C, Ni/Al) through the corresponding amides and pyrrolinones is discussed in [29]:



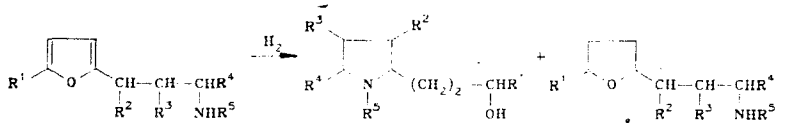
An alternative scheme suggests attack by the nitrogen-containing reagent at the carbon atom of the keto group of the substrate [43].

1.2. Intramolecular Reductive Amination in the Hydrogenation of Amines and Ketones of the Furan Series. The catalytic hydroamination of aldehydes and ketones of the furan series is a known method for the synthesis of furylalkylamines [44-48] and in some cases is an integral part of technological processes [49].

The transformations of furylalkyl(cycloalkyl)amines to five-membered azaheterocycles involve cleavage of the furan ring under hydrolysis or hydrogenolysis conditions. Reactions of this type are characteristic for amines that contain a functional group in the side chain in the 3 position relative to the furan ring. Azacyclization is considered to be the result of intramolecular hydroamination of the intermediately formed amino carbonyl compounds, which contain favorably oriented functional groups.

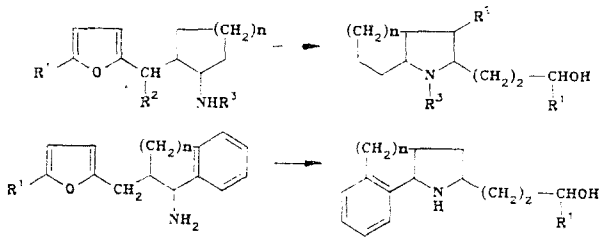
Piperidine is formed in low yield (9%) in the hydrogenation of furfurylamine on Raney nickel under severe conditions (215°C) [50].

Systematic studies of the intramolecular hydroamination of furan compounds in the liquid phase were made by A. S. Ponomarev and co-workers. They developed a method for obtaining diverse alcohols of the pyrrolidine series that are difficult to obtain by other methods by hydrogenation of primary and secondary amines and diamines [51-58] in aqueous acidic solutions (pH 4) at elevated temperatures (80-100°C) and hydrogen pressures (5-10 MPa) in the presence of heterogeneous catalysts based on group VIII metals:



R^1=H, CH_3; R^2, R^3=H, Alk; R^4=H, Alk, Ar; R^5=H, Alk, Ar, $(CH_2)_3NH_2$, $(CH_2)_2OH$

The reaction has extensive preparative possibilities in that it enables one to obtain alkyl-, aryl-, and hydroxy(amino)-alkyl-substituted and N-unsubstituted pyrrolidinylalkanols. Polycyclic alcohols, viz., derivatives of 2,3-trimethylene-pyrrolidine, octahydroindole, benzo[c]octahydroindole, and indanopyrrolidine, are formed when furfuryl-substituted alicyclic amines are used [48, 56, 59]:



R^1,R^2,R^3=H, Alk; n=1,2

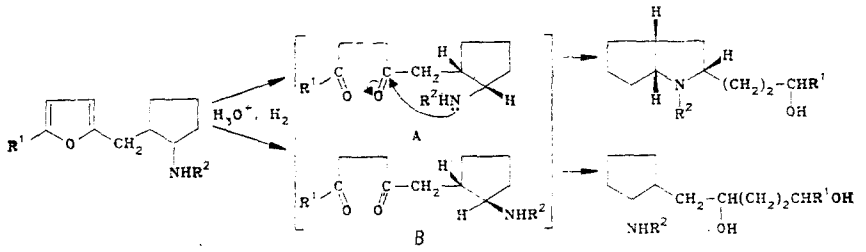
There is evidence to assume that the mechanism of the formation of hydroxyalkylpyrrolidines is the same as in reductive amination and includes the intramolecular reaction of the amino and keto groups in the amino carbonyl compound — the product of acidic hydrolysis of the furan ring [60]. In addition to pyrrolidinylalkanols, tetrahydrofurfurylalkyl(cycloalkyl)-amines are formed as a result of the simultaneous reduction of the double bonds of the furan ring. The relative yields of the reaction products depend to a significant extent on the structure of the starting amines, the reaction conditions, and the nature of the catalyst used. In particular, the presence of alkyl radicals in the side chain of the starting amines promotes an increase in the yields of hydroxyalkylpyrrolidines and hydroxycycloalkylpyrrolidines; this effect decreases with withdrawal of the radical from the ring. This fact can be explained by the electron-donor effect of the alkyl groups, which facilitates acidic hydrolysis of the furan ring and, as a result, the formation of an azaheterocycle [59, 61]. A decrease in the hydrogen pressure from 10 MPa to 5 MPa and the use of catalysts that are ineffective in the hydro-

genation of the multiple bonds of the furan ring under the selected conditions are factors that favor the development of pyrrolidinylalkanols.

The use of Raney cobalt [56], "pickled" Raney Ni and Co treated with 2% acetic acid [62], Pd/C [56], nickel boride [63], industrial nickel on kieselguhr [64], and Ni/Ru [65] has made it possible to obtain alcohols of the pyrrolidine series in up to 80% yields. Raney nickel has proved to be a selective catalyst with respect to amines that include a tetrahydrofuran ring in their molecules [53].

The conversion of N-arylfurylalkylamines to N-arylpyrrolidinylalkanols with retention of the aromatic ring can be realized with the highest yields by the use of Ni/Ru or nickel boride [66]. In the presence of Ni/K in acetic acid the reaction is accompanied by hydrogenolysis of the starting amines at the C—N bond, as evidenced by isolation of acetanilide. The benzene ring is reduced on Raney nickel.

In addition to tetrahydrofurfurylcyclopentylamines and cyclopentano[b]pyrrolidinylalkanols, the corresponding amino diols were isolated in the hydrogenation of 2-furfurylcyclopentylamines [67]:



$R^1, R^2 = H, CH_3$

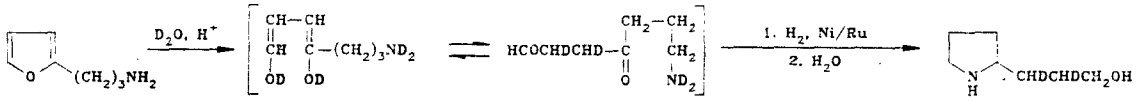
Obtaining these compounds confirms the assumption that the reaction proceeds with opening of the furan ring and the formation of amino dicarbonyl intermediates. The latter are not stable under the reaction conditions and are reduced or cyclized. This reaction pathway is evidently associated with the possibility of a cis or trans orientation of the substituting groups of 1,2-disubstituted cyclopentanes. According to this, of the two possible geometrical isomers of the intermediate amino diketone, only cis-isomer A is capable of undergoing azacyclization because of the close orientation of the functional groups. The trans form (B) undergoes hydrogenation with the formation of an amino diol.

The cis fusion of the carbo- and heterocycles and the cis,cis orientation of the hydrogen atoms at the chiral centers of the pyrrolidine ring were established by structural investigations of the isolated individual isomers of the cyclopenta[b]pyrrolidine alcohols [68].

Amino diols are not formed in the hydrogenation of furfurylcyclohexylamines; this is in conformity with the concept of a chair conformation of the cyclohexane ring with drawn-together substituents in the 1 and 2 positions in the cis and trans forms [69].

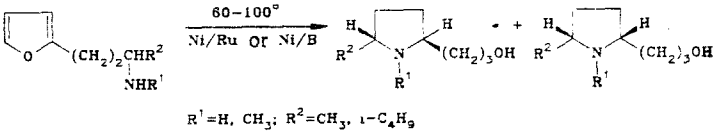
Under the reaction conditions, tertiary furfurylcycloalkylamines are converted to tetrahydrofurfurylalkylamines and cycloaliphatic amino diols, since azacyclization of the intermediate is impossible because of the absence of an active hydrogen atom attached to the nitrogen atom [67].

Experimental data on the hydrogenation of 3-(2-furyl)propylamine in D_2O [60, 70] serve as an argument in favor of the scheme of the formation of pyrrolidinylalkanols proposed above. In a comparative study of the IR spectra of the products of hydrogenation in water and D_2O it was observed that, despite retention of the general pattern of the spectrum, in the latter case one observes the appearance of new bands of stretching and deformation vibrations of CHD groups which are shifted bathochromically in conformity with the isotope effect. A quantitative estimate of the deuterium atoms that were incorporated in the 3-pyrrolidinylpropanol molecule was made on the basis of the ratio of the integral intensities of the stretching vibrations of the CH_2 and CHD groups and data on the isotope exchange of hydrogen [71, 72], and a conclusion regarding the character of the participation of heavy water in the reaction was drawn:



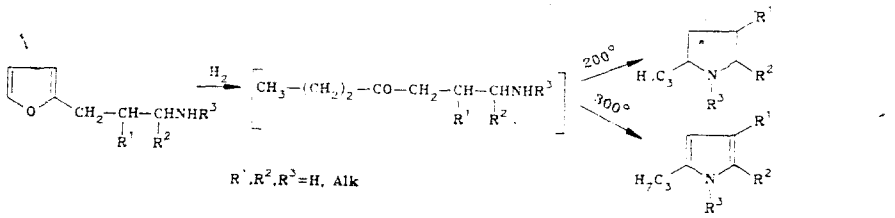
The chief reaction pathway was determined in this way; however, the possibility of the formation of heterocyclic amino alcohols by transformation of the corresponding dihydrofuran derivatives was not excluded [60]. It was established by ^{1}H and ^{13}C NMR spectroscopy and x-ray diffraction analysis that, regardless of the type of catalyst used, the reaction examined above proceeds in a direction that favors the primary formation of hydroxyalkylpyrrolidines with a cis configuration [62, 68, 73].

The temperature has a determining effect on the ratios of the cis,trans-isomeric hydroxyalkylpyrrolidines. The reaction is carried out at 60°C for the preparative synthesis of the cis isomers. Reversible catalytic isomerization, as a result of which a constant ratio of the cis and trans isomers with preponderance of the latter is established, commences at 100°C [74]:



R^1=H, CH_3; R^2=CH_3, i-C_4H_9

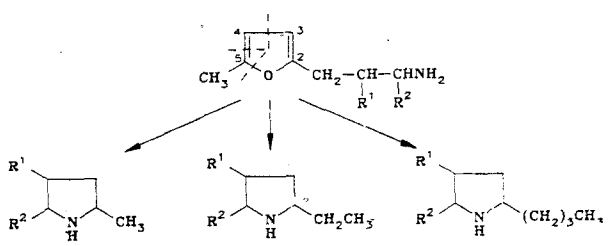
The transformations of furyl-3-aminoalkanes in the gas phase were studied by Shuikin and Bel'skii and co-workers [75-79]. They established that hydrogenolysis of the furan ring at the $C_{(5)}$—O bond and the formation, depending on the temperature, of homologs of pyrrole or pyrrolidine in high yields occur in the presence of platinum catalysts:



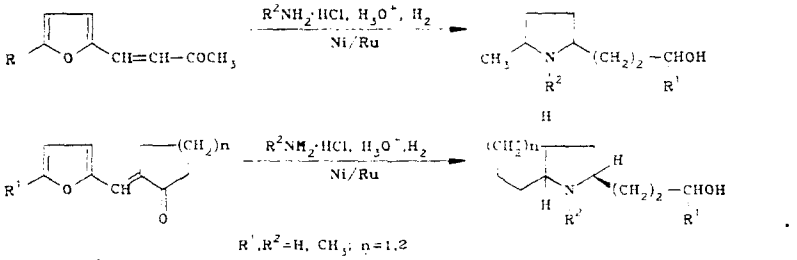
R^1,R^2,R^3=H, Alk

Since pyrroles are hydrogenated at 200°C, whereas the reverse reaction occurs at 300°C, the temperature boundaries of the conversion of γ-furylalkylamines to pyrroles and pyrrolidine are evidently determined by these conditions. The intermediately formed amino ketones could not be isolated because of their rapid cyclization. However, the corresponding N-acetyl-γ-amino ketones were obtained in the hydrogenation of furylalkylamines that were acetylated at the amino group [80].

Selective hydrogenolysis of the furan ring at the C—O bond that is not adjacent to the aminoalkyl substituent was observed in the case of 5-methyl-2-aminoalkylfurans; this may be due to the joint action of the shielding effect and the stronger electron-donor effect of the aminoalkyl group. Under the conditions of vapor-phase hydrogenation on a Raney nickel—aluminum catalyst, hydrogenolysis of the furan ring proceeds in three directions at the $C_{(5)}$—O, $C_{(5)}$—O and $C_{(4)}$—$C_{(5)}$, and $C_{(5)}$—O and $C_{(3)}$—$C_{(4)}$ bonds (conjugate hydrogenolysis) [80]:



Investigations of the direct conversion of α,β-unsaturated ketones and aldehydes of the furan series to five-membered azaheterocycles are of considerable interest, since oxo compounds of the indicated type are among the primary products of the processing of furfural and, correspondingly, fundamental intermediates of organic synthesis on the basis of pentosan-containing raw material. In this connection, a pathway for the stereospecific formation of hydroxyalkyl derivatives of pyrrolidine, cyclopenta[b]pyrrolidine, and octahydroindole holds promise; this pathway consists in the hydroamination, in the presence of Ni/Ru, of furfuralacetone and furfuralcyclopenta(hexa)nones in an acidic aqueous alcohol medium at 60-80°C and a hydrogen pressure of 6-7 MPa [81, 82]. The selected conditions made it possible to combine into one step amination and cleavage of the furan ring in the starting α,β-enones:

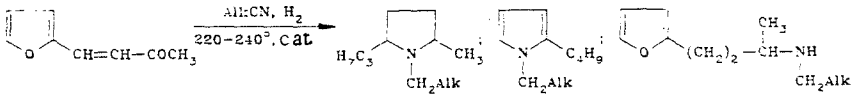


The indicated reaction differs favorably from the previously described reaction [53, 83], since it excludes a step involving obtaining furylalkyl(cycloalkyl)amines from the synthetic scheme. When methylamine hydrochloride is used as the nitrogen-containing reagent, the yields of hydroamination products reach 50-80%. Hydrogenation of the starting substances prevails when methylamine is replaced by a weaker nucleophile, viz., ammonia (in the form of the chloride or as ammonium acetate).

The reactivities of α,β-enones in the indicated reaction decrease on passing from furfurylideneacetone to furfurylidenecyclohexanones and then to furfurylidenecyclopentanones; this is due to the rigidity of the structures of the latter [84]. Deformation of the bond angles, which requires great energy expenditures in the case of cyclopentane derivatives, is inevitable in the formation of the azaheterocycle.

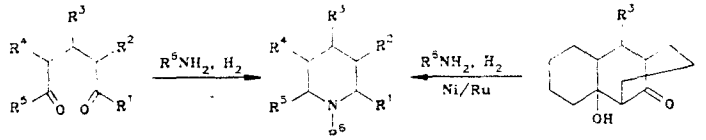
The peculiarities of azacyclization presented above basically resemble the principles of the intramolecular reductive amination of amines of the furan series [53].

The direction of the vapor-phase hydroamination of furfurylideneacetone with aliphatic nitriles in the presence of copper applied to Al, Mg, and Zn oxides is determined by the nature and structure of the support, the state of the metal, and its interaction with the support [85-87]. The use of Cu/Al_2O_3 leads to hydrogenolysis of the furan ring and cyclodehydration of the intermediate γ-amino ketones with the formation of N-alkyl-2-methyl-5-propylpyrrolidines (in 37-46% yields). Secondary furylalkylamines are the principal products in the presence of Cu/MgO. Both of the indicated pathways occur on a Cu/ZnO catalyst. In all cases, in the catalyzates one detects 17-22% pyrrole derivatives, which, in the opinion of the authors in [86], are formed via the scheme of the Yur'ev reaction with simultaneous reduction of the carbonyl group and the vinylene side chain:



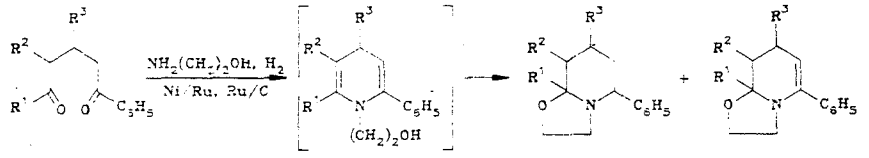
1.3. Hydroamination of 1,5-Diketones and β-Cycloketols. 1,5-Diketones, the position of the carbonyl groups in which determines their exceptionally facile cyclization, including heterocyclization, constitute a unique class of dicarbonyl compounds. The possibility of the use of accessible aldehydes and ketones as a vast raw-material basis, as well as convenient preparative methods of synthesis, makes 1,5-diketones valuable synthones for six-membered heterocyclic compounds [88].

Diketones of various types and products of their intramolecular aldol condensation are capable of undergoing hydroamination under heterogeneous-catalysis conditions (catalysts: 5% Ru/C, Ni/Ru, RuO_2, Raney Ni) with the formation of substituted piperidines, octadecahydroquinolines, biscyclanopiperidines, and their analogs [18, 89-91]:



R^1, $R^5 = C_6H_5$; R^2, $R^4 = H$; $R^1—R^2$, $R^4—R^5$ = cycloalkylene, benzocycloalkylene; $R^3 = H$, CH_3, C_2H_5, Ar, 2-furyl; $R^6 = H$, CH_3, $(CH_2)_2OH$, C_6H_5

A number of principles in the transformations of dioxo compounds as a function of the structure of the substrate (noncyclic, semicyclic, and bicyclic diketones), the nucleophilic reagent (ammonia, methylamine, aniline, ethanolamine), and the nature of the catalyst have been ascertained. The hydroethanolamination of methylenebiscyclanones proceeds most smoothly and unambiguously. It was found that Ni/Ru was an effective catalyst at 100°C [92]; reduced RuO_2 made it possible to lower the temperature of the process to 25°C with retention of the high yields of the products and the activity of the catalyst [93]. Under these conditions, 2,3,5,6-biscyclano-N-β-hydroxyethylpiperidines were obtained in preparative yields of 74-85% in one of the possible stereoisomeric forms [19]. Transition via this pathway to C(9)-substituted N-β-hydroxyethylperhydroacridines is possible on the basis of tricyclic β-ketols [94], since the corresponding arylidene(alkylidene)-1,5-dicyclohexanones have thus far remained difficult to obtain because of their facile intramolecular aldolization. The formation of 9-substituted perhydroacridines attests to retroaldol cleavage of the β-cycloketols under the reaction conditions to give the corresponding 1,5-diketones, which then undergo hydroethanolamination. Ethanolamine reacts as a binucelophile with oxocyclohexylpropanones and 1,5-diphenylpentane-1,5-dione: The principal pathway of the process is the formation of two rings to give derivatives of hydrogenated oxazolopyridines [19]:



$R' = C_2H_5$; $R^2 = H$; $R^3 = H$, Ar; $R'—R^2 = -(CH_2)_4-$

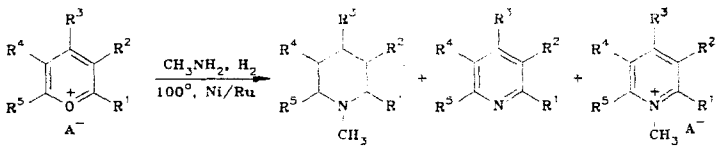
The hydromethylamination of δ-diketones is a method for the synthesis of saturated azaheterocycles of the piperidine series and related condensed systems [18].

Hydroarylamination occurs only for methylenedicyclohexanone, from the threo form of which N-phenylperhydroacridine is formed in 50% yield [95]. When even one six-membered ring in the diketone is replaced by a five-membered ring, amination is completely overwhelmed by reduction of the carbonyl groups.

Different character of the transformations of δ-diketones is observed under the influence of hydrogen and ammonia [18, 90]. Pyridines or mixtures of the latter with piperidines are formed in this case; this is probably associated with the possibility of competitive stabilization of the initially formed dihydropyridines due to aromatization or reduction.

The hydroamination of 1,5-dialdehydes proceeds ambiguously, and little study has been devoted to it. Thus a complex mixture of bases, including 2-aminomethylpiperidine, pyridine, and alkylpyridines, was isolated in the high-temperature hydrogenation of 2-hydroxyhexane-1,5-dial on Raney nickel in an alcohol or aqueous solution of ammonia [96].

The ability of pyrylium salts — products of O-cyclization of 1,5-diketones — to undergo hydroamination was recently observed [97]:

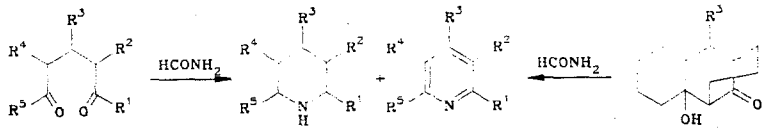


R^1, $R^5 = C_6H_5$; R^2, $R^4 = H$; $R^3 = H$, Alk; $R^1—R^2$, $R^4—R^5$ = cycloalkylene, benzocycloalkylene

This reaction is noteworthy as a method for the synthesis of phenyl-substituted piperidines, since a peculiarity of 1,5-diketones that contain aryl groups attached to the carbonyl carbon atom is their facile transformation to the corresponding diols under similar conditions [97].

2. Carbonyl Compounds in the Leuckart Reaction

The Leuckart reaction is an important synthetic method for obtaining saturated nitrogen-containing heterocycles. The early literature on it is correlated in [8]. 1,5-Diketones and products of intramolecular condensation of methylenedicyclohexanones are converted under the reaction conditions to mixtures of pyridine and piperidine bases. The process is usually realized by heating (130-170°C) a solution of the substrate in formamide or with an excess amount of a mixture of ammonium formate and formamide. One may also start from a equimolar mixture of ammonia or an amine and formic acid. The reaction has been applied to an extensive number of dicarbonyl compounds [98-105]. The yields of pyridine and piperidine bases differ, but the primary formation of the latter is always noted.



$R^1=C_6H_5$; $R^2=H$; $R^3=H$, Alk, Ar; R^1-R^2, $R^4-R^5=-(CH_2)_4-$

The development of NMR spectroscopic methods has made it possible to establish the stereochemical result of the Leuckart reaction. The Leuckart reaction is not stereospecific in most cases. Thus decahydroquinolines are produced in the form of mixtures of cis and trans isomers [106], perhydroacridine is produced in two stereoisomeric forms, viz., trans-syn-trans (α) and trans-anti-cis (β) [107, 108], and 9-methylperhydroacridine is produced in the form of three stereoisomers, viz., α, β, and γ (cis-syn-trans) in a ratio of 5:2:3 [109]. N-Substituted perhydroacridines were also obtained in the form of mixtures: four isomers of N-methylperhydroacridine [α, β, γ, and δ (cis,cis)] [110] and three stereoisomers of N-phenylperhydroacridine (α, β, γ) [111].

The question of the mechanism of the reaction of 1,5-diketones with formamide still remains open. Some researchers [112-114] propose the initial formation of dihydropyridine intermediates, which then undergo disproportionation to pyridine and piperidine bases as a result of hydride transfer from a molecule of the dihydro compound, which acts as a donor, to its protonated form, which acts as a hydride-ion acceptor. Taking into account the fact that the chief products of the reaction are saturated bases, it is assumed that reduction of the intermediate for formic acid proceeds in addition to disproportionation [115]. The development of cyclic amines, which can be isolated in pure form and then hydrolyzed to obtain the free bases, in the reaction of N-formyl derivatives has also been noted [98, 104, 105].

The Leuckart reaction makes it possible to synthesize saturated azaheterocycles in 45-100% yields. However, the severe conditions, the necessity in most cases for separation of the saturated and unsaturated heterocyclic compounds, and the lack of stereospecificity substantially limit the range of application of this reaction.

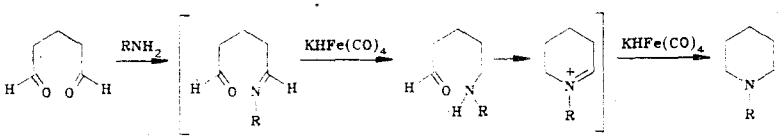
3. Hydride Amination of Dicarbonyl Compounds

Reductive amination with the use of complex metal hydrides generally is advantageous as compared with the traditional Leuckart method, since mild conditions and high stereospecificity are features of this variant of hydroamination. The amination of methylenedicyclohexanones in the presence of KBH_4 in alcohol has been studied in the 1,5-diketone series [116, 117]. Only one isomer of the nitrogen base was isolated in all of the examined cases. β-Perhydroacridine is formed in 80% yield when the threo form of methylenedicyclohexanone is used. It has been noted [118] that asymmetric centers are not involved in this method of amination, since a mixture of α- and β-perhydroacridines was obtained in the same overall yield when the mixture of threo and erythro forms that is usually isolated in the synthesis of methylenedicyclohexanone was subjected to the reaction. This conclusion was also confirmed in the case of the specific synthesis of isomers of N-(β-hydroxyethyl)- and N-(β-aminoethyl)perhydroacridines.

X=CH_2, O; R^1=H, CH_3; R^2=H, $CH_2N(CH_3)_2$; R^3=H, CH_3, $(CH_2)_2OH$, $(CH_2)_2NH_2$

Reduction of the starting oxo compound to the corresponding diols, the yields of which are almost quantitative when dimethylamine is used, proceeds in addition to hydroamination. It is assumed [119] that, in contrast to the Leuckart reaction, dihydropyridines are not formed in borohydride amination, since they are not reduced by complex metal hydrides even under severe conditions. Imino ketones are possibly intermediates of this reaction [120].

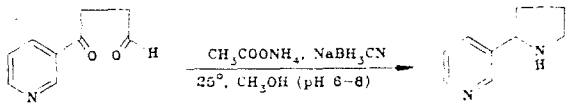
The complex potassium tetracarbonylhydridoferrate and sodium cyanoborohydride are mild and selective reducing agents in the hydroamination of carbonyl compounds. However, insufficient study has thus far been devoted to reactions with the use of the indicated reducing agents. N-substituted piperidines were synthesized in 41-90% yields from equimolar amounts of glutaraldehyde, primary amines, and $KHFe(CO)_4$ [120]. The reaction proceeds at 20°C in alcohol in a stream of carbon monoxide:



R=Alk, Ar, cycloalkyl, hydroxy(amino)alkyl

In conformity with [121], Schiff bases generated in situ from aldehydes and ketones are selectively reduced by a potassium hydride—iron carbonyl complex to amino aldehydes; this is followed by heterocyclization and reduction of the immonium salts. The reaction with the participation of sodium cyanoborohydride is represented by a similar scheme in which the rate-determining step is assumed to be the formation of cycloimmonium structures [122].

Sodium cyanoborohydride — a milder reducing agent than KBH_4 — induces the reductive amination of polyoxo compounds, sometimes even with retention of the oxo functions [123]. Considering the solubility and stability of the reducing agent, the reaction is carried out in methanol, water, and acetonitrile at pH 6-8, since at such pH values the imino group is reduced much more rapidly than the carbonyl group. N-Methylpiperidine was isolated in the form of the picrate in 43% yield via this method from glutaraldehyde and methylamine hydrochloride. Borch and co-workers have demonstrated the applicability of this reaction to the synthesis of nornicotine [122]:



The hydrazination of glutaraldehyde and succinaldehyde in the presence of $NaBH_3CN$ leads to five-, six-, and seven-membered azaheterocycles [124]. 1,1'-Dipiperidyl and 1-pyrrolidinopiperidine were obtained when N-aminopiperidine was used as the nitrogen-containing reagent. Symmetrically substituted hydrazines and aqueous glutaraldehyde form azepine derivatives as a result of cyclization. Tetrasubstituted hydrazines had a high degree of purity; however, their yields did not exceed 36%.

Despite the mild conditions and, in most cases, stereospecificity of hydride amination, its disadvantages are the necessity of using costly reducing agents, the formation of side products, and the relatively small amount of study that has been devoted to it.

Thus the material set forth above correlates the currently known information regarding the synthesis and possible pathways for the formation of azaheterocycles in reductive amination processes. Of the examined variants of hydroamination, preference should be given to catalytic reductive amination. The merits of this method are the use of a cheap reducing agent, viz., molecular hydrogen, selectivity, and stereospecificity. Considering the great practical value of catalytic methods for the synthesis of nitrogen heterocycles, it may be assumed that these studies will be developed further, particularly in the direction of the study of the kinetic principles and mechanisms of the reactions, as well as the selection of new effective catalysts.

LITERATURE CITED

1. R. K. Hill, in: Chemistry of the Alkaloids, Van Nostrand, New York (1970), p. 385.
2. M. D. Mashkovskii, Medicinals [in Russian], Vol. 1, Meditsina, Moscow (1985), pp. 133, 135.
3. I. N. Klochkova, A. P. Kriven'ko, and M. V. Noritsina, Pyrrolidylalkanols [in Russian], Izd. Saratovsk. Univ., Saratov (1979).
4. V. Emerson, in: Organic Reactions [Russian translation], Vol. 5, Inostr. Lit., Moscow (1951), p. 347.
5. V. A. Nekrasova and N. I. Shuikin, Usp. Khim., 34, 1945 (1965).
6. M. I. Yukushkin, Khim. Promst., No. 7, 13 (1966).
7. P. Rylander, Catalytic Hydroamination over Platinum Metals, Academic Press, New York (1967).
8. B. M. Bogoslovskii, in: Reactions and Methods of Investigation of Organic Compounds [in Russian], Vol. 3, GNTIKhL, Moscow (1954), p. 225.
9. M. V. Klyuev and M. L. Khidekel', Usp. Khim., 49, 28 (1980).
10. M. V. Shimanskaya, Ya. F. Oshis, and A. A. Anderson, Khim. Geterotsikl. Soedin., No. 12, 1587 (1983).
11. M. G. Mignonac, Compt. Rend., 169, 237 (1919).
12. J. Jungers and L. Sajus, Kinetic Methods for the Investigation of Chemical Processes [Russian translation], Khimiya, Moscow (1972), p. 400.
13. G. A. Kliger, L. S. Glebov, V. A. Fridman, E. I. Bogolepova, and A. N. Bashkirov, Kinet. Katal., 19, 619 (1978).
14. N. S. Kozlov, V. A. Tarasevich, S. I. Kozintsev, and L. V. Gladkikh, Dokl. Akad. Nauk BSSR, 27, 634 (1983).
15. E. I. Hil'debrand and A. B. Fasman, Raney Catalysts in Organic Chemistry [Russian translation], Nauka, Alma-Ata (1982).
16. A. Skita and F. Keil, Chem. Ber., 62, 1142 (1929).
17. A. Skita and F. Keil, Angew. Chem., 42, 501 (1929).
18. V. G. Kharchenko, A. P. Kriven'ko, O. V. Fedotova, and T. G. Nikolaeva, Khim. Geterotsikl. Soedin., No. 7, 944 (1982).
19. T. G. Nikolaeva, P. V. Reshetov, A. P. Kriven'ko, and V. G. Kharchenko, Khim. Geterotsikl. Soedin., No. 10, 1370 (1983).
20. E. J. Schwoegler and H. Adkins, J. Am. Chem. Soc., 61, 3499 (1939).
21. N. S. Kozlov, in: Heterogeneous Catalysis in the Chemistry of Heterocyclic Compounds [in Russian], Zinatne, Riga (1981), p. 23.
22. N. S. Kozlov, L. I. Moiseenok, and S. I. Kozintsev, in: The Chemistry of Dicarbonyl Compounds [in Russian], Izd. Rizhsk. Politekh. Inst., Riga (1981), p. 114.
23. N. S. Kozlov, L. I. Moiseenok, and S. I. Kozintsev, Khim. Geterotsikl. Soedin., No. 11, 1483 (1979).
24. W. Z. Shilling, US Patent No. 3235562; Ref. Zh. Khim., 13N82 (1967).
25. H. Vakamatsu and M. Takesada, Japanese Patent No. 23344; Ref. Zh. Khim., 12N210 (1975).
26. A. A. Ponomarev and V. A. Sedavkina, USSR Inventor's Certificate No. 192820; Byull. Izobret., No. 6, 28 (1967).
27. A. A. Ponomarev and V. A. Sedavkina, Khim. Geterotsikl. Soedin., No. 5, 809 (1969).
28. V. A. Sedavkina, I. V. Lizak, and L. K. Kulikova, Khim.-farm. Zh., No. 10, 34 (1978).
29. N. I. Shuikin, I. F. Bel'skii, V. M. Shostakovskii, S. N. Khor'kov, and G. K. Gaivoronskii, Dokl. Akad. Nauk SSSR, 153, 628 (1963).
30. Shu-Kung Chu and W. S. Lin, Hua Hsueh, Nos. 3-4, 65 (1970); Chem. Abstr., 74, 87732 (1971)
31. V. A. Sedavkina and N. A. Morozova, Khim. Geterotskikl. Soedin., No. 3, 331 (1972).
32. V. A. Sedavkina, N. A. Morozova, L. K. Kukokova and V. E. Murav'ev, Khim.-farm. Zh., No. 3 33 (1976).
33. V. A. Sedavkina and N. A. Morozova, USSR Inventor's Certificate No. 574440; Byull. Izobret., No. 36, 63 (1977).
34. V. A. Sedavkina and I. V. Lizak, USSR Inventor's Certificate No. 513972; Byull. Izobret., No. 18, 72 (1976).
35. V. A. Sedavkina and G. V. Bespalova, USSR Inventor's Certificate No. 697505; Byull. Izobret., No. 42, 96 (1979).
36. G. V. Bespalova and V. A. Sedavkina, in: Heterogeneous Catalysis in the Chemistry of Heterocyclic Compounds [in Russian], Zinatne, Riga (1981), p. 128.
37. V. A. Sedavkina, I. V. Lizak, L. K. Kulikova, and E. E. Ostroumova, Khim.-farm. Zh., No. 1, 54 (1984).
38. J. Greenstein and M. Winitz, Chemistry of the Amino Acids, Wiley (1961).

39. R. B. Moffat, J. Org. Chem., 14, 862 (1949).
40. W. Reid, US Patent No. 2605266; Chem. Abstr., 47, 5451 (1953).
41. V. G. Bukharov and T. E. Pozdnyakova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1108 (1960).
42. V. A. Sedavkina, N. A. Morozova, G. V. Bespalova, and I. V. Lizak, in: Collection of Lectures of the 3rd International Symposium on Furan Chenistry, Czechoslovakia (1979), p. 232.
43. A. A. Ponomarev and V. A. Sedavkina, Khim. Geterotsikl. Soedin., No. 5, 809 (1969).
44. C. F. Winans, J. Am. Chem. Soc., 61, 3566 (1939).
45. A. A. Ponomarev, N. P. Maslennikova, N. V. Alakina, and A. P. Kriven'ko, Dokl. Akad. Nauk SSSR, 131, 1355 (1960).
46. A. A. Ponomarev, N. P. Maslennikova, and A. P. Kriven'ko, Zh. Obshch. Khim., 31, 958 (1961).
47. A. P. Kriven'ko, Candidate's Dissertation, Saratov (1967).
48. N. I. Shuikin, A. D. Petrov, V. G. Glukhovtsev, I. F. Bel'skii, and G. E. Skobtsova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 1682 (1964).
49. B. V. Passet and V. Ya. Vorob'eva, The Technology of Pharmaceutical-Chemical Preparations and Antibiotics [in Russian], Meditsina, Moscow (1977), p. 282.
50. C. L. Wilson, J. Am. Chem. Soc., 67, 693 (1945).
51. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, Dokl. Akad. Nauk SSSR, 156, 102 (1964).
52. A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, Khim. Geterotsikl. Soedin., No. 6, 923 (1966).
53. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, Khim. Geterotsikl. Soedin., No. 5, 850 (1967).
54. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, USSR Inventor's Certificate No. 158277; Byull. Izobret., No. 21, 15 (1963).
55. A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, USSR Inventor's Certificate No. 176961; Byull. Izobret., No. 24, 22 (1965).
56. A. A. Ponomarev, A. P. Kriven'ko, and M. V. Noritsina, Khim. Geterotsikl. Soedin., No. 6, 787 (1970).
57. A. P. Krivenko and T. G. Nikolaeva (Nickolaeva), in: Collection of Lectures of the 3rd International Symposium on Furan Chemistry, Czechoslovakia (1979), p. 190.
58. A. P. Kriven'ko and T. G. Nikolaeva, in: Materials of the 3rd All-Union Scientific Conference on the Chemistry and Technology of Furan Compounds [in Russian], Zinatne, Riga (1978), p. 119.
59. A. P. Kriven'ko and T. F. Kotenko, Khim. Geterotsikl. Soedin., No. 12, 1639 (1974).
60. I. N. Klochkova and M. V. Noritsina, in: New Methods for the Synthesis and Investigation of Organic Compounds [in Russian], Part 2, Izd. Leningr. Gos. Univ., Leningrad (1979), p. 70.
61. M. V. Noritsina, Candidate's Dissertation, Saratov (1967).
62. A. P. Kriven'ko, T. G. Nikolaeva, A. A. Espenbetov, Yu. T. Struchkov, and V. G. Kharchenko, Khim. Geterotsikl. Soedin., No. 1, 66 (1985).
63. I. N. Klochkova, M. V. Noritsina, and O. Yu. Rastegaev, USSR Inventor's Certificate No. 1049482; Byull. Izobret., No. 39, 27 (1983).
64. M. V. Noritsina, I. N. Klochkova, and T. S. Bykovskaya, Khim. Geterotsikl. Soedin., No. 2, 186 (1976),
65. V. G. Kharchenko, A. P. Kriven'ko, I. A. Markushina, M. V. Noritsina, T. I. Gubina, G. E. Marinicheva, T. G. Nikolaeva, I. N. Klochkova, and N. V. Shulyakovskaya, in: Catalytic Processes in the Liquid Phase [in Russian], Part 2, Alma-Ata (1978), p. 92.
66. I. N. Klochkova, M. V. Moritsina, and L. K. Kulikova, Khim.-farm. Zh., No. 9, 63 (1977).
67. T. G. Nikolaeva and A. P. Kriven'ko, in: The Chemistry and Technology of Furan Compounds [in Russian], Izd. Krasnodarsk. Politekh. Inst., Krasnodar (1982), p. 65.
68. A. P. Kriven'ko, T. G. Nikolaeva, A. A. Espenbetov, N. T. Komyagin, N. N. Sorokin, Yu. T. Struchkov, and V. G. Kharchenko, Khim. Geterotsikl. Soedin., No. 1, 71 (1985).
69. V. M. Potapov, Stereochemistry [in Russian], Khimiya, Moscow (1976), p. 344.
70. M. V. Noritsina (Noritzina) and I. N. Klochkova, in: Collection of Lectures of the 3rd International Symposium on Furan Chemistry, Czechoslovakia (1979), p. 228.
71. D. Chadwick, ibid., p. 39.
72. A. I. Brodskii, The Chemistry of Isotopes [in Russian], Izd. Akad. Nauk SSSR, Moscow (1957), p. 287.
73. I. N. Klochkova, S. A. Lazarev. V. G. Andrianov, Yu. T. Struchkov, G. K. Kravtsova, and M. V. Noritsina, Khim. Geterotsikl. Soedin., No. 2, 222 (1983).

74. M. V. Noritsina, I. N. Klochkova, and N. N. Sorokin, Khim. Geterotsikl. Soedin., No. 12, 1648 (1984).
75. I. F. Bel'skii and N. I. Shuikin, Dokl. Akad. Nauk SSSR, 137, 331 (1961).
76. I. F. Bel'skii, Zh. Obshch. Khim., 32, 2905 (1962).
77. I. F. Bel'skii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 6, 1077 (1962).
78. I. F. Bel'skii, N. I. Shuikin, and G. E. Skobtsova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 1678 (1963).
79. N. I. Shuikin, I. F. Bel'skii, and G. E. Abgaforova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 163 (1965).
80. G. E. Abgaforova, N. I. Shuikin, and I. F. Bel'skii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 734 (1965).
81. V. G. Kharchenko, A. P. Kriven'ko, and T. G. Nikolaeva, USSR Inventor's Certificate No. 1030359; Byull. Izobret., No. 27, 106 (1983).
82. V. G. Kharchenko, A. P. Kriven'ko, and T. G. Nikolaeva, Khim. Geterotsikl. Soedin., No. 11, 1561 (1983).
83. T. G. Nikolaeva and A. P. Kriven'ko, in: Research on the Synthesis and Catalysis of Organic Compounds [in Russian], Vol. 2, Izd. Saratovsk. Univ., Saratov (1983), p. 68.
84. T. G. Nikolaeva and A. P. Kriven'ko, in: Advances in the Chemistry of Nitrogen Heterocycles [in Russian], Rostov-on-Don (1983), p. 55.
85. N. S. Kozlov, L. I. Moiseenok, and S. I. Lozintsev, Dokl. Akad. Nauk SSSR, 252, 1132 (1980).
86. L. I. Moiseenok, in: Materials from the Conference of Young Scientists of the Chemistry Department of Moscow State University Dedicated to the 26th Session of the Communist Party of the Soviet Union [in Russian], Izd. Mosk. Gos. Univ., Moscow (1981), p. 493.
87. N. S. Kozlov, L. P. Dmitriev, and M. I. Kozlyak, Izv. Akad. Nauk Belorussk. SSSR, Ser. Khim., 6, 9 (1977).
88. V. G. Kharchenko and S. N. Chalaya, 1,5-Diketones [in Russian], Izd. Saratovsk. Univ., Satatov (1977), p. 4.
89. O. V. Fedotova, A. P. Kriven'ko, V. G. Kharchenko, and M. N. Tilichenko, Manuscript Deposited in the All-Union Institute of Scientific and Technical Information, No. 2254-76 Dep.; Ref. Zh. Khim., 3Zh257 (1977).
90. A. P. Kriven'ko, T. G. Nikoaleva, O. V. Fedotova, and P. V. Reshetov, in: Nucleophilic Reactions of Carbonyl Compounds [in Russian], Izd. Saratovsk. Iniv., Saratov (1982), p. 56.
91. V. G. Kharchenko, A. P. Kriven'ko (Krivenko), O. V. Fedotova, and T. G. Nikolaeva (Nickolaeva), in: The 7th Symposium on the Chemistry of Heterocyclic Compounds, Czechoslovakia (1981), p. 200.
92. V. G. Kharchenko, A. P. Kriven'ko, T. G. Nikolaeva, and P. V. Reshetov, USSR Inventor's Certificate No. 939442; Byull. Izobret., No. 24, 124 (1982).
93. V. G. Kharchenko, A. P. Kriven'ko, and T. G. Nikolaeva, USSR Inventor's Certificate No. 1057496; Byull. Izobret., No. 44, 102 (1983).
94. V. G. Kharchenko, A. P. Kriven'ko, and T. G. Nikolaeva, USSR Inventor's Certificate No. 1010060; Byull. Izobret., No. 13, 158 (1983).
95. V. G. Kharchenko, N. S. Smirnova, A. P. Kriven'ko, O. V. Fedotova, T. G. Nikolaeva, and L. I. Markova, in: The Chemistry of Dicarbonyl Compounds [in Russian], Izd. Rizhsk. Politekh. Inst., Riga (1981), p. 225.
96. D. H. Johnson, J. Chem. Soc., C, No. 14, 1284 (1967).
97. A. P. Kriven'ko, O. V. Fedotova, P. V. Reshetov, and V. G. Kharchenko, Khim. Geterotsikl. Soedin., No. 12, 1652 (1984).
98. J. Colonge and J. Dreux, Bull. Soc. Chim. Fr., No. 3, 447 (1957).
99. R. Allwin, J. Colonge, R. Crieger, and J. Dreux, Bull. Soc. Chim. Fr., Nos. 8-9, 1178 (1958).
100. M. N. Tilichenko and V. I. Vysotskii, Dokl. Akad. Nauk SSSR, 119, 1162 (1958).
101. M. N. Tilichenko and V. G. Kharchenko, Zh. Obshch. Khim., 29, 2370 (1959).
102. M. N. Tilichenko and V. G. Kharchenko, Zh. Obshch. Khim., 30, 2283 (1960).
103. V. Balian, Chem. Rev., 83, 379 (1983).
104. E. S. Karaulov, A. A. Usol'tsev, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 4, 472 (1976).
105. V. I. Vysotskii and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 3, 383 (1976).
106. T. V. Moskovkina, M. N. Tilichenko, V. M. Kurikenko, and L. P. Fedyaeva-Basova, Khim.-farm. Zh., No. 3, 3 (1973).
107. N. Barbulescu and F. Potmischil, Rev. Chim., (RSR), 14, 1427 (1969).

108. N. Barbulescu and F. Potmischil, Tetrahedron Lett., No. 27, 2309 (1969).
109. N. Barbulescu and F. Potmischil, Rev. Chim. (RSR), 21, 677 (1970).
110. N. Barbulescu and F. Potmischil, Rev. Roum. Chim., 15, 1601 (1970).
111. V. I. Vysotskii and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 3, 376 (1971).
112. L. M. Eremeeva, Yu. V. Vasilenko, V. A. Kaminskii, and M. N. Tilichenko, Khim. Geterotsikl Soedin., No. 10, 1361 (1977).
113. B. D. Tilak, T. Ravindranathan, and X. N. Subbaswami, Indian J. Chem., 6, 422 (1968).
114. V. A. Kaminskii, A. N. Saverchenko, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 11, 1539 (1970).
115. M. N. Tilichenko, V. I. Vysotskii, and V. G. Kharchenko, Uch. Zap. Saratovsk. Gosudarstv. Univ., Ser. Shim., 71, 159 (1959).
116. V. I. Vysotskii, Zh. Org. Khim., 4, 1494 (1968).
117. T. V. Moskovkina, V. A. Kaminskii, V. I. Vysotskii, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 6, 826 (1973).
118. V. I. Vysotskii, Khim. Geterotsikl. Soedin., No. 9, 1236 (1970).
119. V. I. Alekseev, V. A. Kaminskii, and M. N. Tilichenko, Khim. Geterotsikl. Soedin., No. 7, 957 (1976).
120. Y. Watanabe, S. Ch. Shim, T. Mitsudo, M. Yamashita, and Y. Takegami, Chem. Lett., No. 9, 995 (1975).
121. Y. Watanabe, S. Ch. Shim, T. Mitsudo, M. Yamashita, and Y. Takegami, Bull. Chem. Soc. Jpn., 49, 2302 (1976).
122. R. F. Borch. M. D. Bernstein, and H. D. Durst. J. Am. Chem. Soc., 93, 2897 (1971).
123. A. S. Kende, T. J. Bentley, R. A. Mader, and D. Ridge, J. Am. Chem. Soc., 96, 4332 (1974).
124. S. F. Nelson and G. R. Weisman, Tetrahedron Lett., No. 26, 2321 (1973).

2-METHYL-5,6-DIHYDRO-2H-PYRAN IN THE SIMMONS—SMITH REACTION

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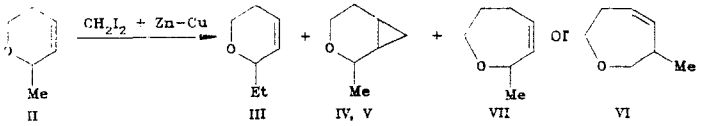
2-Methyl-5,6-dihydro-2H-pyran reacts with the Simmons—Smith reagent to give a mixture of 2-ethyl-5,6-dihydro-2H-pyran, cis- and trans-2-methyl-3-oxabicyclo-[4.1.0]heptanes, and 2-methyl-2,5,6,7- or 3-methyl-2,3,6,7-tetrahydrooxepine in a ratio of 2:2:5:1.

Carbene generated via the Simmons—Smith reaction readily adds to the double bond of 4-methyl-5,6-dihydro-2H-pyran (I) to give the corresponding cycloadduct [1]. We have observed that 2-methyl-5,6-dihydro-2H-pyran (II), which is isomeric to I with respect to the position of the methyl group, reacts with CH_2I_2 and a Zn—Cu couple in a completely different way to give a mixture of four compounds (III-VI) in a ratio of 2:2:5:1.



Considering the fact that the Simmons—Smith reaction is used for the stereospecific cycloaddition of carbene to alkenes [2], this result should be considered to be unexpected.

The overall yield of III-VI when ether is used as the solvent is ~1%, as compared with 8% with tetrahydrofuran (THF) as the solvent vis-à-vis the same very small degree of conversion of the starting II. The reaction products were therefore identified by chromatographic mass spectrometry (Table 1). All of the compounds are isomers, as evidenced by the presence

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