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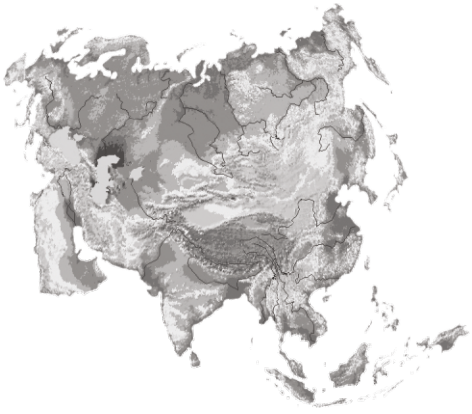

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Stereochemical Peculiarities of the Products of Condensation of Piperidine-4-one with Aromatic Aldehydes

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Abstract

This paper presents the results of investigations on conformation peculiarities of the condensation products of piperidine-4-ones containing arylidene, hydroxyarylmethyl as well as both arylidene and hydroxyarylmethyl substituents. Synthesized α, β-unsaturated ketones can be used to investigate conformation of cycles fixing a conjugated system of carbonyl and double bonds. Synthesis of α, β-unsaturated piperidine-4-ones was carried out according to the reaction of Claisen-Schmidt by condensation of piperidine-4-ones with aromatic aldehydes. The reaction was carried out in methanol medium in the presence of an alkaline agent. High resolution ^{1}H and ^{13}C NMR resonance assignments and conformational assignments were carried out for four 3- arylidene or hydroxyarylmethyl and 3-arylidene-5- hydroxyarylmethyl substituted piperidine-4-ones (1-4). As a result of the initial aldol condensation of piperidine-4-ones with aromatic aldehydes an aryloxymethyl group in the intermediate compound can have both an equatorial and axial position. Conformation of a conjugated system proved to be electronically effected by the presence of nitrogen atom in the heterocycle. At the same time, conformation peculiarities of α, β-unsaturated ketones under study are developed at the stage of their synthesis. This is explained by the fact that in the course of the reaction there appears a new sp^2-centre, this resulting in our case in the change of the conformation of "a chair". There takes place flattening of the structure and fixation of s-cis conformation. Furfurilidene substituent is conjugated with a carbonyl group, there forms a planar structure including 2, 3, 4 and 5 atoms of hydrogen of piperidine cycle and furfurilidene substituent and there exist two isomers with cis- (A) and trans- (B) position of a furyl ring at double bond in relation to a carbonyl group.

1. Introduction

Many piperidine derivatives are found to posses biological activity and form an essential part of the molecular structure of important drugs. It is well known that a number of heterocyclic compounds containing nitrogen exhibited a wide variety of biological activity. Also, in recent years, the high therapeutic properties of the heterocyclic compounds have attached the attention of pharmaceutical chemists to synthesize a large number of novel synthetic compounds. Among these compounds piperidines, pyridines, quinazolinone derivatives have become especially noteworthy in recent years [1].

Most of piperidine compounds are known to exist in chair conformation. Electron withdrawing groups (-NO, -CHO, -COR, and -CONHPh) introduced at the nitrogen atom profoundly affect the conformations of the heterocyclic rings and orientation of the substituents at piperidine ring. Recently attention has been focused on the application of the piperidine derivatives as prospective biophotonic materials. Since the pharmacological properties and the reactivity depend on their stereochemistry, efforts were made for the development of new synthetic techniques leading to stereoselective piperidines and their characterization. The NMR technique is a versatile tool for the structural elucidation of most of the organic compounds and useful for the conformational analysis also. ^{1}H NMR and ^{13}C NMR techniques have been extensively applied in deriving stereodynamical information about a wide variety of systems. They give information about the influence of electronic and conformational effects

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on chemical shifts and coupling constants (J). Vicinal coupling constant values have been used for the conformational analysis which can give an indication of the orientation of the substituents. They also described the change in electronegativity of a particular group or atom on the ring causes a major change in chemical shifts on the ring carbons and their associated protons [2–4].

The Claisen-Schmidt reaction (crossed-aldol reaction) is a condensation reaction of aldehydes and carbonyl compounds leading to β-hydroxycarbonyl compounds and it has played an important role in synthetic organic chemistry. Subsequent dehydration of the β-hydroxycarbonyl compounds afford α-alkylidene or α-arylidene compounds. Although studies on the Claisen-Schmidt reaction have been focused on α-alkylidene- and α-arylidene-carbonyl compounds, interest in α, α′-bisalkylidene and α, α′-bisarylidene-carbonyl compounds is increasing. Particularly, α, α′-bis-(substitutedbenzylidene)-cycloalkanones have been attracting much more attention, not only due to their intriguing biological activities such as antiangiogenic, quinine reductase inducer, arginine methyltransferase inhibitor, cytotoxicity, cholesterol-lowering activity, uses in agrochemicals, pharmaceuticals and perfumes [5].

With the aim to search and create new potentially biologically active compounds as well as to study the reactivity of aromatic aldehydes in the reaction of Claisen-Schmidt depending on the nature of the substituent in the aromatic fragment, we synthesized piperidine-4-ones containing arylidene substituents in α-position [6].

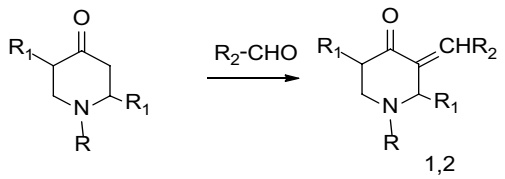
The use of aldol-crotonic condensation reaction makes it possible to introduce a great number of compounds possessing CH-acidity [7]. Piperidine ketones were used as a methylene component. Commercially available aromatic aldehydes: furfural, benzaldehyde were used as a carbonyl component. It is stated that introduction of an aromatic fragment into molecules of some heterocycles results in the improvement of their antitumor and other therapeutical properties [8]. Taking all this into account, one can expect the presence of interesting physiological properties in some representatives of for the first synthesized by us nitrous heterocyclic ketones containing in their structure an aromatic fragment conjugated with an internal multiple carbon-carbon bond.

2. Materials and methods of investigation

The individuality and structure of the synthesized compounds were verified by the data of NMR and IR- spectroscopy. IR spectra of synthesized compounds were recorded on Specord 75 spectrometer IR, in a KBr tablet, in a solution of chloroform and carbon tetrachloride. NMR spectra were recorded on Bruker DRX400 spectrometer with an operating frequency of 400 MHz at a temperature of 25 °C, solvents – CD_3OD, DMSO-d6, $CDCl_3$ and chemical shifts of protons are expressed in δ, ppm.

3. Experimental results and discussion

Synthesis of α, β-unsaturated piperidine-4-ones was carried out according to the reaction of Claisen-Schmidt [9] by condensation of piperidine-4-ones with furfural and benzaldehyde. The reaction was carried out in methanol medium in the presence of an alkaline agent:



1,2

R=H, R_1=CH_3 ,R_2=Fu (1)

R=R_1=CH_3, R_2=C_6H_5 (2)

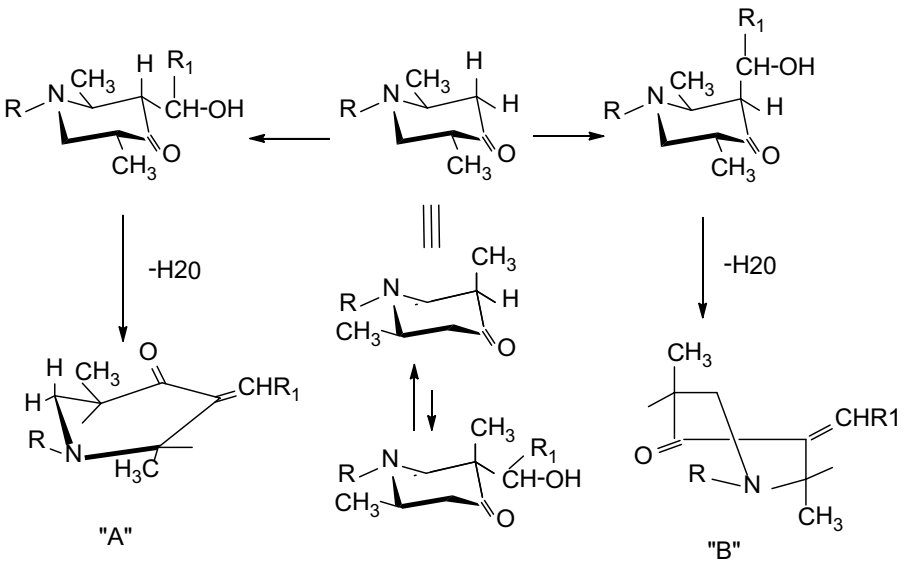
1,2,5-Trimetyl-3-benzylidenepiperidine-4-one (2) was synthesized with the yield of 95.0% by condensation of equimolecular amounts of 1,2,5-trimethylpiperidine-4-one with benzaldehyde in the presence of 15% solution of potassium hydroxide. The product – white crystals with the melting point 162–164 °C – is soluble in benzene, acetone and insoluble in water.

In IR-spectra of compounds (1,2), the frequencies 1665–1685 cm^{-1} refer to stretching vibrations of a carbonyl group and conjugated with carbonyl C=C bonds have absorption bands in the field of 1595–1610 cm^{-1}. The intensity of bands of the multiple carbon-carbon bonds is higher than that of the conjugated carbonyl group [8]. The absorption bands at 3100–3050 cm^{-1} refer to stretching vibrations of =CH bond of aromatic radical. In the field of 1580 cm^{-1}, the absorption band of planar vibrations appears only if benzene ring is conjugated with an unsaturated group as it takes place in compounds (1, 2). The intensity of absorption bands in the field of 1600, 1580 and 1500 cm^{-1} increases due to conjugation of an aryl fragment with a multiple carbon-carbon bond. In the field of 770–730 cm^{-1}, there appear intensive absorption bands conditioned by out-of-plane deformation vibrations. The bands at 730, 735 and 885 cm^{-1} correspond to deformation vibrations of CH-bond of a furan cycle in compound (1). The stretching vibrations of an ether bond of a furyl ring are at 1225–1245 cm^{-1}.

As a result of the initial aldol condensation of piperidine-4-ones with aromatic aldehydes an aryloxymethyl group in the intermediate compound can have both an equatorial and axial position. Depending on this, the formed final product of crotonic condensation must have a different spatial structure [10, 11, 12–14].

The presence of nitrogen atom in the heterocycle exerts an electronic effect on conformation of the conjugated system. At the same time, conformation peculiarities of α, β-unsaturated ketones under study develop already at the stage of their synthesis [10]. This is explained by the fact that in the course of the reaction there appears a new sp^2-centre, this resulting in our case in the change of the conformation of "a chair". There takes place flattening of the structure and fixation of s-cis conformation.

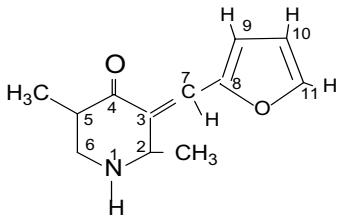
s-cis conformation was confirmed by us on the basis of the data on IR-spectra. In the spectra of compounds (1, 2), the intensity of a conjugated double bond is higher than that of carbonyl group which is characteristic of s-cis conformation. Besides, out-of-plane deformation vibrations of protons of a conjugated multiple carbon-carbon bond play an important role in identification of the structure of vinylene ketones. According to the literature data, in the spectra of compounds in the field of 728–675cm^{-1} one can observe absorption bands conditioned by out-of-plane vibrations of α-hydrogen of a multiple bond. As, in our case, the lability of π-system is disturbed and s-cis conformation is fixed, absorption bands in the field of 990-965 cm^{-1} are not observed.



Partially flattened semi-chair form (A), which is formed when an aryloxymethyl group takes an equatorial α-position, has s-cis configuration of these bonds, while form (B), which can be formed due to sterically hampered axial position of the aryloxymethyl group, must have a trans-configuration of π-bonds. Potential energy of conformer (B) due to spatial repulsion interactions of electrons of nitrogen atoms and π-electrons of the conjugated system of C=O and C=C bonds is higher than the energy of conformer (A) which has no electrostatic interaction. Hence, structure (A) is more profitable from point of view of energy.

2,5-Dimethyl-3-furfurilidenepiperidine-4-one (1) was obtained by condensation of 2,5-dimethylpiperidine-4-one with the excess of furfural in the presence of 15% solution of potassium hydroxide. The target product – 2,5-dimethyl-3-furfurilidenepiperidine-4-one (1) is a yellow powderlike substance with the melting point 99.5–101 °C with the yield of 60–65%.

In ^{1}H NMR spectrum of it in deuterochloroform all 15 protons were identified (Table 1).



1

The most weak field signals of protons at double bond the reference of which can be made on the basis of their multiplicity and tabulated chemical shifts of hydrogen atoms of furan cycle are: δ 7.38 ppm of α-proton, 6.30 ppm of β-proton, $^{\alpha\beta}$J – 1.7-2.0 Hz, $^{\beta\beta}$J – 3.3-3.5 Hz, $^{\alpha\beta}$J – 0.4-0.9 Hz.

Table 1

^{1}H NMR spectrum of 2,5-dimethyl-3-furfurilidenepiperidine-4-one (1)

Chemical shifts of protons, δ from TMS (ppm)									
2-CH_3	5-CH_3	1-H	2-H	5-H	6-H	7-H	9-H	10-H	11-H
1.37 d	1.13 d	2.11 s	4.86 q	2.44 dq	3.05 318 dd	7.06 s	6.6 d	6.47 dd	7.53 d

J, Hz						
2-H, 2-CH_3	5-H, 5-CH_3	5-H, 6-H^a	5-H, 5-H^b	6-H^a, 6-H^b	9-H, 10-H	10-H, 11-H
6.9	6.9	6.9	10.5	13.7	3.3	2.0

Proton (11H) of furyl cycle in *α*-position to oxygen atom has the most weak field signal – doublet δ 7.52 ppm and J is 2.0 Hz. The signal of proton (7H) at double bond which is not in the furyl cycle has a somewhat less chemical shift δ 7.26 ppm. In less weak field are signals of α-protons (10H) of furyl cycle-vicinal to α-proton has chemical shift *δ* 6.47 ppm, doublet of doublets with J 3.3 and 2.0 Hz and neighboring to it β-proton (9H) with 6.6 ppm, doublet with J 3.3 Hz.

The signal of proton 2H of piperidine cycle is in the medium field – quartet 4.86 ppm with splitting 6.9 Hz from 2CH_3 protons (δ 1.37). The signal of the second methyl group 5CH_3 is a doublet with a chemical shift 1.13 ppm and J 6.9 Hz. Protons 6H are doublets of doublets with a chemical shift 3.18 ppm (J 13.7 Hz and 10.5 Hz) and 3.5 ppm (J 13.7 Hz and 6.9 Hz) (J 13.7 Hz is a geminal constant, other constants are splitting from 5H).

Thus, we stated the structure of 2.5-dimethyl-3-furfurilidenepiperidine-4-one (1). As its yield is quite high (up to 65%) and 2,5-dimethyl-3-furfurilidenepiperidine-4-one is mainly (90%) a trans -isomer, we may suppose that methyl groups in this compound are in a trans-position too. Spatial orientation of methyl group in position 5 is determined by the character of spin-spin interaction of proton 5H with protons 6_a and 6_e. In case of equatorial position of 5CH_3 group, hydrogen atom 5H has an axial orientation and J of it with 6H_a proton is of the order 2-4 Hz.

In ^{1}H NMR spectrum of compound (1) under study (Table 1) one of the constants is equal to 10.5 Hz, this being in agreement with their diaxial position, however, the second constant is equal to almost 7 Hz. This fact makes us suppose that position of 5H proton to the second 6H proton is not typically axial-equatorial. On the other hand, a very large chemical shift of 2H proton – 4.86 ppm attracts attention. In the derivatives of piperidine-4-ones, the chemical shift of α-protons makes up ~ 2.7 ppm [11]. As furfurilidene substituent is conjugated with a carbonyl group, there forms a planar structure including 2, 3, 4 and 5 atoms of hydrogen of piperidine cycle and furfurilidene substituent. And there may exist two isomers with cis- (A) and trans- (B) position of a furyl ring at double bond in relation to a carbonyl group (the plane part of the molecule is shown by thickened lines of bonds).

From the presented models it is seen that in each of the structures there takes place a strong repulsion interaction of valence unbound atoms – of oxygen and furyl in structure (A) and 2CH_3-group and furyl in structure (B). To avoid these repulsion interactions, the molecule can take a rotameric conformation where the plane of a furyl ring would be perpendicular to the plane of conjugation of a double carbon-carbon bond and a carbonyl group. But this would result in the loss of conjugation and significant increase in free energy of the molecule.

In case of isomer (B) there may be another way of eliminating spatial stresses. If we look at the geometry of a piperidine cycle, we will see that position of a carbonyl group and double bond makes the piperidine cycle similar to that of cyclohexene where three bonds are in one plane and two bonds can freely change their position in relation to the plane part of the cycle (Fig. 1).

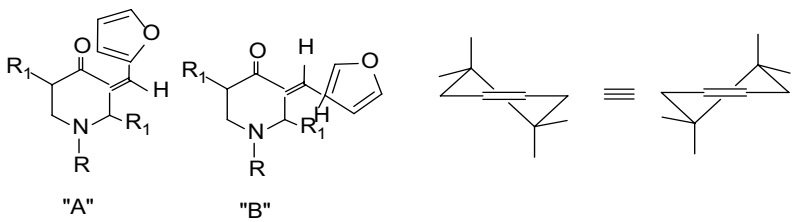


Fig. 1. Geometric isomerism.

In the course of condensation of 1,2,5-trimethylpiperidine-4-one and benzaldehyde we managed to obtain a product of aldol addition – 1,2,5-trimethyl-3-hydroxyphenylmethylpiperidine-4-one (3).

^{1}H NMR spectrum of the compound in $CDCl_3$ (3) is not informative due to superposition of signals of different protons (protons 3H and 5H, $6H_a$ and $6H_e$) (Table 2). However, duplication of the signal of $5CH_3$ and the presence of the signal of proton in α-position to the hydroxyl group (a doublet with a chemical shift of 5.37 ppm and J 4Hz is splitting from proton 3H) indicate the fact that this compound is a monophenylhydroxymethyl derivative according to position 3 of piperidine cycle.

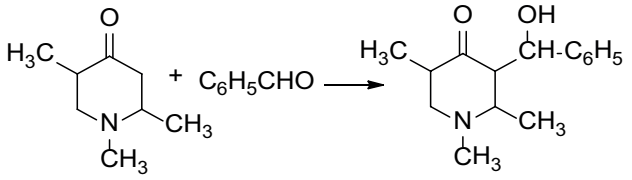


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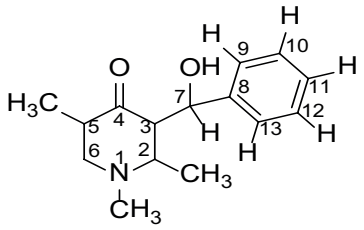
Table 2

^{1}H NMR spectrum of 1,2,5-trimethyl-3-hydroxyphenylmethylpiperidine-4-one (3)

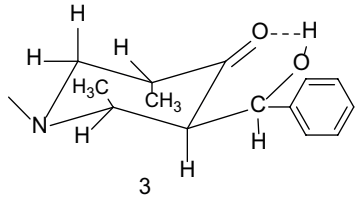
		Chemical shifts of protons , δ from TMS (ppm)						
CH3-N	2-H	2-CH3	3-H	C_6H_5	5-CH3	5-H	6-H	7-H
2.49 s	3.45 m	0.95 d	2.4-2.6 m	7.30 m	0.93 d	2.4-2.6 m	2.9-3.0	5.37 d
		J, Hz						
		2-H, 2-CH3		3H, 7-H			5-H, 5-CH3	
		6.6		4.0			5.0	

^{13}C NMR spectrum allows to determine the structure and conformation of this compound (3). In ^{13}C NMR spectrum there are signals of nuclei of carbon atoms of piperidine cycle respectively with chemical shifts 62.8; 43.3; 208.8; 41.1; 60.6 ppm, phenyl cycle with chemical shifts 141.5; 128.0; 125.3 and 127.5, carbonyl carbon – 75.0 ppm, N-CH_3 – 54.6 ppm and two methyl groups 2C and 5C with chemical shift 11.2 and 9.5 ppm.

A small chemical shift of carbons of 2- and 5-methyl groups indicate their trans-diaxial position [12, 15]. This may be due to the fact that phenylhydroxymethyl radical being in cis-position to methyl group $2CH_3$ takes an equatorial position because of its large volume.



This is confirmed by a large chemical shift of methylol carbon. The structure and conformation of this compound are as follows:



3

This structure is also confirmed by IR spectrum of compound (3) written down in CCl_4: due to formation of hydrogen bond the vibration frequency of OH bond decreased to 2980 cm^{-1} and that of the carbonyl group – to 1645 cm^{-1}. The absence of the effect of dilution on the absorption frequency of the hydroxyl group is confirmed by the intramolecular character of hydrogen bond.

During condensation of 1,2,5-trimethylpiperidine-4-one with furfural in the ratio 1:2 in the presence of potassium hydroxide the reaction product was deposited after a hall an hour mixing, the alkaline agent was washed out and product was recrystallized. Using this method of treatment we managed to obtain 1,2,5-trimethyl-3-furfurilidene-5-hydroxyfurylmethylpiperidine-4-one (4) with the yield up to 65% in the form of a white crystalline substance with the melting point 125–127 °C.

According to ^{1}H NMR spectrum the obtained product (4) contains two furyl cycles (Table 3). As condensation proceeds only in α-position of ketone, compound (4) is a 5-furylhydroxymethyl derivative of 1,2,5-trimethyl-3-furfuilidenepiperidine-4-one. All signals of hydrogen atoms which are characteristic for furfuilidenepiperidine-4-one are almost in the same places of the spectrum (the difference in chemical shifts is, as a rule, about 0.1 ppm), but there is no signal of proton 5H and conditioned by it splitting of protons 6H and $5CH_3$. There are signals characteristic of the furylhydroxymethyl fragment. A signal of proton in α-position to the hydroxyl group – a singlet with a chemical shift of 4.86 ppm; signals of the furyl cycle, probably due to the

absence of conjugation of the furyl cycle with the double bond, almost coincide with the shifts – 7.40 ppm for α-proton, 6.70 ppm for vicinal to it β-proton and 6.31 ppm for the second β-proton (for furyls – 7.38 and 6.30 ppm, respectively). As earlier, these protons were correlated according to the constants of their spin-spin interaction (Table 3).

Close values of chemical shifts of protons of mono- and difuryl derivative allow to suppose that the latter has the same conformation that the first one. The probability of conformation with quasi-diaxial methyls increases on account of the tendency of a large, branched in α-position furyl-hydroxymethyl substituent to take a quasi-equatorial orientation for decreasing repulsion interaction with atoms of the piperidine cycle.

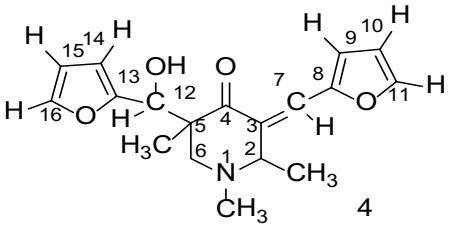


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Table 3

^{1}H NMR spectrum of 1,2,5-trimethyl-3-furfurilidene-5-hydroxyfurylmethylpiperidine-4-one ($CDCl_3$)

Chemical shifts of protons , δ (ppm)						
CH3-N	2-H	2-CH_3	5-CH_3	6-H^{a}	6-H^{b}	7-H
2.52 s	4.7 q	1.27 d	0.88 s	3.09 d	2.93 d	7.38 s
9-H	10-H	11-H	12-H	14-H	15-H	16-H
6.71 d	6.51 dd	7.58 d	4.80 s	6.31 d	6.36 dd	7.40 d
J, Hz						
2H-, 2-CH3	6H^{a}, 6H^{b}	9-H, 10-H	10-H, 11-H	14-H,15-H	15-H, 16-H	
6.4	15.0	3.4	1.8	3.1	1.8	

4. Conclusions

Thus, when studying condensation of piperidin ketones with aromatic aldehydes under the condition of Claisen-Schmidt reaction, for the first time the products of aldol addition were obtained. α, β-unsaturated piperidine ketones with internal multiple bond were obtained. Their structure and conformation were determined by ^{1}H and ^{13}C NMR methods.

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