CLAISEN REARRANGEMENT OF ALKOXYQUINOL-2-ONES IN MASS SPECTROMETRY

Ya. V. Rashkes, I. A. Bessonova, and S. Yu. Yunusov

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In a preceding paper [1] it was shown that under the conditions of mass spectrometry, a Claisen rearrangement (CR) of the alkaloid bucharaine (I) and of the aldehyde bucharainal takes place. In spite of the fact that with a change in the temperature of the inlet tube from 110 to 60°C considerable changes in the mass spectra were recorded, it was impossible to establish unambiguously whether the rearrangement processes are purely thermal or whether some role is played by electron impact. A number of facts indicated a change in the nature of the rearrangement at various temperatures. According to authors who have studied the mechanism of the CR [2], the product of γ inversion that is first formed then rearranges into a compound in which the β atom of the initial allyl chain adds to the ortho position of the aromatic ring (anomalous rearrangement).

To check whether the behavior of O-allyl ethers in mass spectrometry corresponds to these ideas, we have carefully studied the spectra of bucharaine acetonide (II) [3] together with the spectra of the products of the CR prepared under laboratory conditions [4].

The mass spectra of the products of anomalous rearrangement (III-V), subsequently called the β-CR, and the products of γ inversion (γ-CR) (VII, VIII), taken at 90-110°C, contain, with a few exceptions, the same set of peaks differing in their relative intensities. The spectrum of (II) is closer to the spectra of (III-V) than of (VII, VIII).

Let us consider the main fragments of the molecules of the model compounds (III-V, VII, VIII) in connection with the characteristics of the structures of each of them. The maximum intensity of the peak with m/e 242 in the spectrum of the phenol (III) is due to the fact that the splitting off of a dioxolane ring from M^+ is activated by the double bond in the allyl position. The splitting off of the side chain from the dihydrofuranoquinolone system of (IV) and (V) leads to the appearance of a stable oxonium ion with m/e 214 [1], as a result of which the latter is the strongest in these spectra. Under the conditions of mass spectrometry, obviously, the interconversion (III) $\rightleftharpoons$ (IV, V) takes place and therefore all three spectra show the peaks of both ions with m/e 242 and 214. The formation of ions with m/e 214 in the spectra of the products of γ-CR (VII and VIII) is favorable, since this process is caused by the cleavage of a bond in the β position to the aromatic system. In this case, the ion with m/e 214 is accompanied by an ion with m/e 215, obviously obtained by the migration of a hydrogen atom to the position of detachment of the side chain. In agreement with this, one of the methyl groups is split off, forming ions with m/e 200 (m* = 186.0).

Let us now consider the initial bucharaine acetonide (II). 4-Hydroxyquinol-2-one with m/e 161 or its protonated analog with m/e 162 must be characteristic for its structure. As can be seen from Fig. 1, the peaks shown, although they are fairly strong, nevertheless are weaker than the peaks with m/e 242 and 214. The maximum intensity of the peak with m/e 242 cannot be explained by the assumption that the cleavage of the corresponding C–C bond of the side chain is favored by the propinquity of the dioxolane ring. Thus, in the spectrum of dihydrobucharaine acetonide (VI) the analogous peak of the ion M–129 [3] with m/e 244 has a very low intensity. At the same time, in this spectrum the peak of an ion with m/e 162 is the maximum peak.

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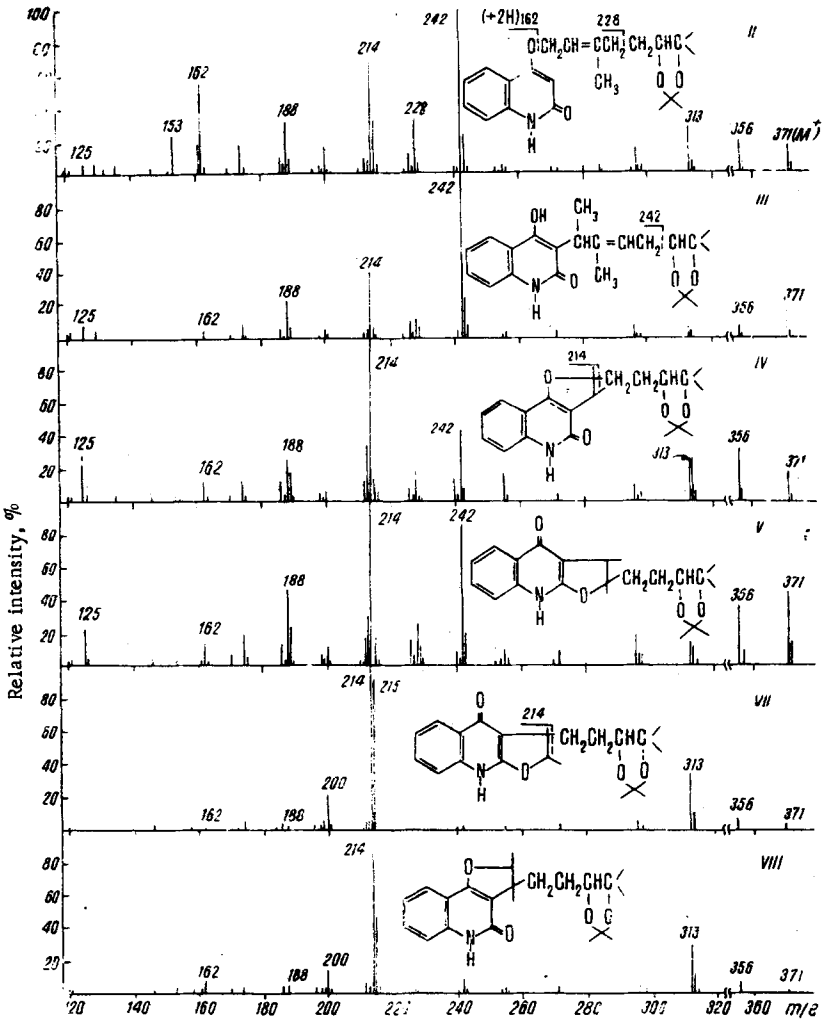


Fig. 1. Mass spectra of compounds (II-V, VII, and VIII) at 90-110°C.

Hence, the similarity of the mass spectrum of the acetonide (II) to the spectra of the products of CR obtained chemically can be explained by the occurrence of side rearrangements in the mass spectrometer. It was mentioned above that the spectrum of (II) resembles the spectra of (III-V) more than those of (VII) and (VIII). Consequently, on mass spectrometry, products of β-CR are formed predominantly. In the spectrum of (II) there are some features characterizing the fragmentation of part of its molecule in the form of an allyl ether. These are, in particular, the peaks with m/e 161 and 162. In the spectra of (III-V) and (VII, VIII), the ion with m/e 162 is small, since its formation takes place through the stage of α cleavage with respect to an aromatic system.

For the molecule of (II), cleavage of the side chain between the two methylene groups is favorable, in view of which the corresponding peak with m/e 228 in the spectrum of (II) has a greater intensity than in the other spectra. The peak of an ion with m/e 153 arising by the detachment of a ArÒ and a molecule of acetone from the molecular ion serves as an analytical peak characterizing the O-allyl system of (II). This ion is essentially similar to the ion with m/e 85 in the spectra of the acetonides of foliosidine and evoxine [3], with the difference that the ion with m/e 153 contains an additional isoprene unit (68 amu). The ion under consideration loses a molecule of water and is converted into an ion with m/e 135. The molecules of (III-V) form the corresponding ions by α cleavage, and therefore in their spectra the ions with m/e 153 and 135 have a low intensity. In the spectra of (III-V) the ions with m/e 125 have a greater intensity; these can be obtained as the result of β cleavage with the splitting off of $ArCHCH_3$ and acetone. The appearance of an ion with m/e 125 from the molecular ions of the cyclic products (IV and V) is preceded by the opening of the dihydrofuran ring. A similar process is not characteristic for the products of γ-CP (VII and VIII). The only indications showing the presence of compounds of type (VII) and (VIII) are the previously mentioned high intensities of the peaks with m/e 215 and 200. The features are actually found in the spectrum of (II)

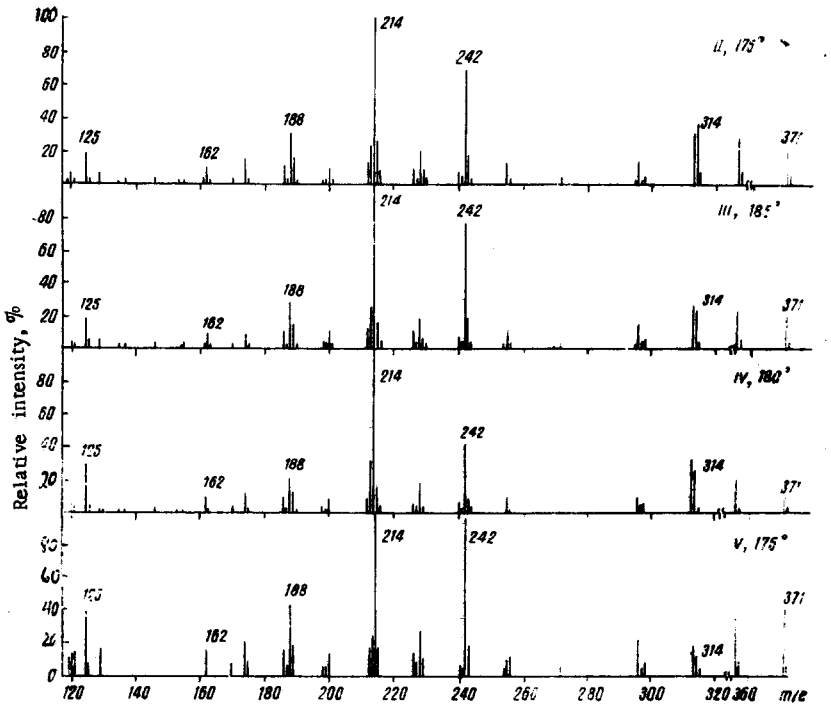


Fig. 2. Mass spectra of compounds (II-V) at 175-185°C.

taken at 100°C. Thus, the ratio of the intensities of the peaks with m/e 215 and 214 in the spectrum of (II) is approximately 15% greater than the similar ratio in the spectra of (III-V).

Unfortunately, the vapor pressure of the acetonide (II) at temperatures below 100°C is insufficient to obtain a high-quality spectrum showing a greater contribution of the initial O-allyl form or of the product of γ inversion. We measured the spectra of the acetonides (II-V) at elevated temperatures (175-185°C). Under these conditions (Fig. 2) the characteristic features of the O-allyl form disappear from the spectrum of (II), and in the spectrum of (III) the ratio of the intensities of the peaks of ions with m/e 214 and 242 change greatly, and both spectra become very similar to the spectra of (IV) and (V), which in turn, change only slightly with a rise in the temperature. The conclusion suggests itself that on intensified heating the bulk of the molecules of (II) passing through a stage of the formation of a phenolic compound then undergo ring-closure to form the dihydrofuroquinolones (IV and V). No traces of (VII and VIII) – the products of γ inversion (increased intensities of the peaks with m/e 215 and 200) – are observed in these spectra. Another characteristic property of the spectra of the cyclic products of β-CR may be mentioned – the increase in the intensity of the peak of the furanoquinolone ion with m/e 213. In the spectra of (VII and VIII) it has a far smaller value. Thus, the ratio between the intensities of the ions with m/e 215 (dihydrofuranoquinolone) and 213 permits an idea to be gained, to some extent, of the contributions of the products of β- and γ-CRs to the mixture of substances formed in mass spectrometry in the analysis of the acetonide (II).

We have studied the mass spectrum of N-methylbucharaine acetonide (IX). At 120°C, the peaks of ions with m/e 256 and 228 have a relatively low intensity in this spectrum (Fig. 3), showing the formation of products of β-CR. In relation to these, the intensity of the peak of an ion with m/e 242, characterizing the decomposition of the O-allyl form of (IX) rises considerably. The persistence of large amounts of unrearranged molecules of (IX) is also indicated by the maximum intensity of the peak of protonated 2,4-dihydroxy-1-methylquinoline with m/e 176. In addition to this, the growth of the peak with m/e 229 can be seen which confirms the presence of the products of γ inversion. The combination of the above-mentioned facts permits the conclusion that in the N-methyl derivative (IX) at the same temperature a relatively smaller number of molecules undergoes CR and the amount of products of γ inversion increases.

With a rise in the temperature of the inlet system to 180°C, the following changes take place in the spectrum of (IX): the intensities of the peaks with m/e 176, 175, and 153 fall sharply, the intensities of the peaks with m/e 242 and 229 also decrease considerably, and the peaks with m/e 228 and 256 become much stronger. Consequently, under the given conditions for the admission of (IX) the bulk of the sample is converted into the product of β-CR.

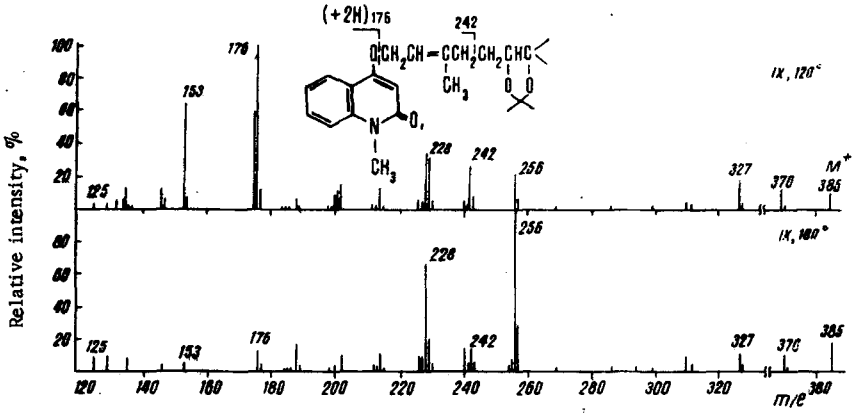
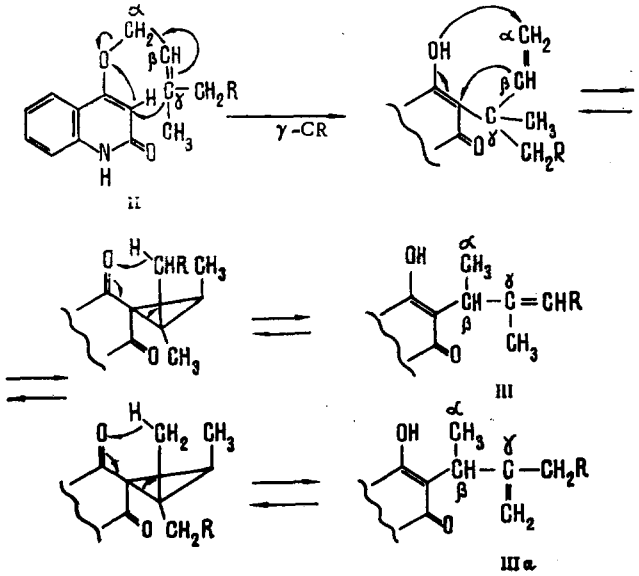


Fig. 3. Mass spectra of N-methylbucharaine acetonide at 120 and 180°C.

A study of the spectra of deuterated samples gave us a considerable amount of information on the nature of the occurrence of CR in mass spectrometry. Having previously [1] observed an additional shift of the peaks in the spectrum of the D-analog of bucharaine (I) by 3 amu, we ascribed to it ring-chain tautomerism of the side-chain of (I). The appearance of a cyclic form of the molecule of bucharaine acetonide (II) is impossible. Nevertheless, even when it was briefly immersed in deuteromethanol, in the spectrum of a sample freed from the bulk of the CD_3OD in the lock system of the mass spectrometer an additional shift of the peak of M^+ by 2 amu was readily observed. This fact can be explained in the following way. Within the framework of the generally accepted approach to the mechanism of γ inversion [2], taking place as a [3,3]-sigmatropic rearrangement [4] (see Scheme), one hydrogen atom migrates from the ortho position. Then, as a result of 1,5-migration of hydrogen in the intermediate spirocyclopropyl derivative of 2,4-dihydroxyquinoline and the subsequent cleavage of the C_3-C_γ bond, the products of β-CR (III) and (IIIa) may arise (we could not isolate the latter). Thus, at this stage of the transformation yet another mobile hydrogen atom appears which is responsible for the additional shift of M^+ in the mass spectrum.

On applying the procedure for the calculation of the spectra of deutero analogs that we have developed, we found that in the spectra of (I) and (II) on passing from the ions M^+ to the ions $M-15$ a considerable part of the isotopic label is lost. This is apparently explained by the fact that at this stage of the formation of the spirocyclopropyl derivative,the hydrogen from 4−OH, which could have been replaced by deuterism before this, passes to C_α, and the CH_3 group so arising is readily split off under electron impact.



The analogous treatment of spectra of the D-analogs of the isomerized compounds (III) and (V) shows the absence of a redistribution of the percentages of the ions in the groups of peaks of M^+ and $M-15$. Consequently, if the tube contained residues of CD_3OD, when a thermal CR took place in it up to two hydrogen

TABLE 1. Mass Numbers and Relative Intensities (%) of the Main Peaks in the Mass Spectra of Compounds (X-XIII)

Compound	T, °C	m/e				
		229 (M^+)	214	186	161	69
X	120	18	5	4	100	34
X	180	47	100	13	2	5
XI	100	42	100	15	8	5

Compound	T, °C	m/e				
		273 (M^+)	258	230	205	69
XII	115	3	—	—	100	18
XII	205	73	100	10	48	16
XIII	110	90	100	8	11	8

atoms would be additionally replaced by deuterism. On recording a section of the mass spectrum in the range from 40-30 m/e at the moment of introduction of the sample and in the subsequent 5-10 min, it was found that a sufficient amount of deuteromethanol remained in the sample for the replacement of the migrating hydrogen atoms.

We also heated a solution of the acetonide (II) in CD_3OD in a sealed tube at 105°C for a day, which led to the appearance in the spectrum of the ions M^+, each including six excess deuterium atoms. It is obvious that a CR took place even before the introduction of the sample into the mass spectrometer as a consequence of the prolonged heating. In view of the fact that the transitions shown in the Scheme are reversible [2], the additional atoms accumulate because of the isotope effect.

Thus, to show the thermal nature of the CR of the acetonides (II) and (IX), the method of deuterating the samples was varied. In parallel with the evaporation of the nondeuterated acetonide, a current of CD_3OD was admitted into the ionization chamber from a separate reservoir, in view of which the molecules of (II) and deuteromethanol could exchange their mobile hydrogen atoms only on the heated surfaces of the ion source. The D-containing ions recorded in this way are formed from the desorbed acetonide molecules.

When experiments were carried out under similar conditions at a temperature of 110°C, in the spectrum of (III) the peak of M^+ shifted by 2 amu (NH and OH at C_4) and in the spectrum of (IV) it shifted by 1 amu (NH). If a sample of bucharaine acetonide (II) present in the tube partially underwent a CR under the action of heat with the formation of products (III-V) and (VII, VIII), its spectrum should contain a certain amount of M+2 ions [through the appearance of the phenolic form (III)]. Such a shift is actually observed in the analysis of the acetonide (II) deuterated by an independent method. With a rise in the temperature of the experiment to 175°C, the peak of the ion M+2 in the spectrum of (II) sharply decreases in intensity, which can be explained by the ring-closure of the phenolic form and the formation of the nonphenolic products (IV) and (V) in the tube. By analyzing the spectrum of the model phenol (III) deuterated under the same conditions, we established that with a rise in the temperature from 110 to 190°, the proportion of M + 2 ions likewise falls sharply:

T, °C	D = 0, %	D = 1, %	D = 2, %
III (110)	14	47	39
III (190)	55	37	8

This confirms the appearance of a dihydrofuran derivative before electron impact under thermal conditions.

When the model dihydrofuranoquinolone (IV) was deuterated by the contact method, no additional shift was observed in its spectrum. Consequently, under the action of heat this form does not isomerize, and the closure of a hydrofuran ring leading, as shown above, to the formation of ions with m/e 125 takes place as the result of electron impact. We may note that with any method of deuteration of the acetonide (II), the ion with m/e 153 characterizing the contribution of the O-allyl form does not bear any traces of isotopic label. This shows that the mass spectrum of bucharaine acetonide (II) is the spectrum of a complex mixture of O- and C-allyl derivatives, and also of the products of the cyclization of the latter.

Other Examples of the Occurrence of CR in the Mass Spectrometer. The ease of occurrence of the CR of bucharaine and its derivatives under the conditions of the inlet system of a mass spectrometer induced us to study the behavior of some other O-allyl ethers. The detection of such processes during analysis would also have a methodical value for the selection of the conditions for recording mass spectra. We limited ourselves to derivatives of quinol-2-one. Information on the mass spectra of the alkaloids ravenine (the γ,γ-dimethylallyl ether of 4-hydroxy-1-methylquinol-2-one) and of ravenoline, which is the product of the β-CR of the first compound, has been given by Paul and Bose [6]. The absence of information of the relative intensities of the main ions in the mass spectra of ravenine and ravenoline does not permit us to judge whether CR took place during the recording of the spectrum of the former. We have performed the synthesis of norravenine (X) by the condensation of 2,4-dihydroxyquinoline with 1-chloro-3-methylbut-2-ene (obtained by A. Kakharov). The mass spectrum of (X) (Table 1) recorded at 120°C confirms the O-allyl nature of this compound. The ion of a phenol with m/e 161 is the maximum ion, and an ion with m/e 69 and

the composition C_5H_9 formed in the localization of the charge on the side chain has a considerably intensity. In the anomalous CR of (X) performed under themal conditions, the C-allyl compound (XI) is obtained. The mass spectrum of (XI) differs sharply from the spectrum of (X) by an increase in the stability of the molecular ion, the 100% intensity of the ion M−15, and the manifold decrease in the peak with m/e 161. Consequently, at temperatures of the inlet system of 100-120°C absolutely no CR of (X) takes place. On raising the temperature of the experiment to 180°C, the spectrum of (X) was obtained, showing that under these conditions norravenine is converted completely into norravenoline (XI).

The γ,γ-dimethylallyl ether of 8-hydroxy-4-methoxy-1-methylquinol-2-one (XII) was synthesized by a similar method. Its spectrum, taken at 115°C, is typical for allyl aromatic ethers [7] and is characterized by the maximum peak of the ion M−68 and a peak at 69 amu. With a rise in the temperature of the inlet system to 170°C, the main features of the spectrum (XII) are preserved, while marked changes take place at temperatures above 200°C: the intensity of M^+ increases severalfold and the peak of the M−15 ion becomes the maximum peak, while the M−68 peak with m/e 205 also remains fairly strong. The results of a comparison of this spectrum with the spectrum of 7-(α,β-dimethylallyl)-8-hydroxy-4-methoxy-1-methylquinol-2-one (see Table 1) obtained from (XII) in the laboratory show that even under such severe conditions the rearranged form (XIII) is present in admixture with a certain amount of the initial O-allyl ether (XII).

The examples of mass spectrometric rearrangements that have been given enable us to recommend a more careful approach to the interpretation of the spectra of O-allyl ethers and also the use of the lowest possible temperature of the inlet system for analyzing these compounds.

Furthermore, from all the material considered it may be concluded that the occurrence of CR under mass spectrometric conditions both for compounds having different substituents in the same position of the quinolinone nucleus and for substances of the same substituents in different positions requires different amounts of thermal energy. The results obtained agree with the quantum-mechanical calculations of V. N. Zvolinskii and M. E. Perel'son [8], who established that in the molecule of quinol-2-one position 3 possesses the highest reactivity index (RI) in all types of reactions and that position 7 is the least reactive. This can explain the difference in the functions for the occurrence of the CR of compounds (X) and (XII) in the mass spectrometer.

EXPERIMENTAL

The mass spectra of all the compounds were obtained on an MKh-1303 instrument fitted with a device for the direct introduction of the sample into the ion source; ionizing voltage 40 V.

The methods for obtaining the compounds have been described elsewhere: (II) in [3], and (III-V, VII, VIII) in [4]. The NMR spectra were taken on a JNM-4H-100/100 MHz instrument (solution in deuterochloroform, τ scale).

N-Methylbucharaine Acetonide (IX). A mixture of 1 g of bucharaine acetonide, 9 ml of methyl iodide, 4.5 g of anhydrous potassium carbonate, and 300 ml of dry acetone was heated for 6 h. When the filtrate was concentrated, a crystalline precipitate deposited, which was chromatographed on alumina. The first chloroform eluates gave substance (IX) with mp 99-100°C (from acetone). On TLC it gave one spot.

Norravenine (X). A mixture of 0.47 g of 2,4-dihydroxyquinoline, 300 ml of dry acetone, 4 g of anhydrous potassium carbonate, and 7 ml of 1-chloro-3-methylbut-2-ene was heated for 20 h. Then it was filtered, the filtrate was evaporated, and the residue was dried and dissolved in ether. The solution was washed with alkali and was then concentrated to give crystals (0.2 g with mp 163°C from ethanol).

NMR spectrum: −2.53 (1H, broadened singlet, NH); 2.13 (1H, doublet, H_5); 2.50-3.00 (3H, multiplet, $H_{6,7,8}$); 4.04 (1H, singlet, H_3); 4.51 (1H, triplet, $-CH=$); 5.39 (2H, doublet, $-O-CH_2-$); 8.23 and 8.29 (6H, singlets, 3H each, $=C\begin{matrix}CH_3\\CH_3\end{matrix}$).

Claisen Rearrangement of X. Compound (X) (50 mg) was heated until it melted and, after cooling, it was treated with a 4% solution of caustic soda. The alkaline solution was washed with ether and was then saturated with ammonium chloride and extracted with ether. The ethereal extract was evaporated, and the residue consisted of substance (XI) in the form of an ion. The ether used for washing the alkaline solution contained the initial base.

γ,γ-Dimethylallyl Ether of 8-Hydroxy-4-methoxy-1-methylquinol-2-one (XII). This was obtained from 0.3 g of 8-hydroxy-4-methoxy-1-methylquinol-2-one and 2 ml of 1-chloro-3-methylbut-2-ene in quantitative yield by the method described above. The substance crystallized in the form of prisms with mp 110°C (from acetone).

NMR spectrum: 2.252 (1H) and 3.00 (2H) (ABX system from H_5 and $H_{6,7}$, respectively); 4.06 (1H, singlet, H_3); 4.57 (1H, triplet, $-CH=$); 5.53 (2H, doublet, $-O-CH_2-$); 6.17 (6H, singlet, $N-CH_3$ and $O-CH_3$); 8.28 and 8.36 (6H, two singlets, 3H each, $=C\begin{matrix}CH_3\\CH_3\end{matrix}$).

Claisen Rearrangement of (XII). This was performed in the same way as the Claisen rearrangement of (X). The alkaline solution yielded crystals of (XIII) with mp 140°C (from aqueous acetone).

CONCLUSIONS

Claisen rearrangements of bucharaine acetonide and its N-methyl derivative take place in the inlet system of a mass spectrometer at 90-110°C. At 180°C, an anomalous rearrangement is the main process, accompanied by the formation of dihydrofuranoquinolinone derivatives.

A similar process is observed in the γ,γ-dimethylallyl ethers of some hydroxyqinol-2-ones.

LITERATURE CITED

1. Ya. V. Rashkes, Z. Sh. Faizutdinova, I. A. Bessonova, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 577 (1970).
2. E. N. Marvell, D. R. Anderson, and J. Ong., J.Org. Chem., 27, 1109 (1962); A. Jefferson and F. Scheinmann, Quart. Rev., 22, 391 (1968).
3. Ya. V. Rashkes, I. A. Bessonova, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 336 (1972).
4. I. A. Bessonova, Ya. V. Rashkes, and S. Yu. Yunusov, Khim. Prirodn. Soedin., 358 (1974).
5. R. Woodward and R. Hoffman, The Conservation of Orbital Symmetry, Academic Press, New York (1970); G. B. Gill, Quart. Rev., 22, 338 (1968).
6. B. D. Paul and P. K. Bose, J. Indian Chem. Soc., 45, 552 (1968); Indian J. Chem., 7, 678 (1969).
7. N. S. Vul'fson, V. I. Zaretskii, and V. G. Zaikin, Dokl. Akad. Nauk. SSSR, 155, 1104 (1964).
8. V. N. Zvolinskii, M. E. Perel'son, and Yu. N. Sheinker, Teoret. Éksperim., Khim., 6, 250 (1970).