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MASS-SPECTROMETRIC STUDY OF THE CYCLIZATION REACTIONS OF DIAZOKETONES.

8.* 1-DIAZO-3,4-EPOXY-4-ARYLBUTAN-2-ONES

A. T. Lebedev, P. A. Sharbatyan, A. G. Kazaryan,
T. P. Pokidova, V. G. Kartsev, and V. S. Petrosyan

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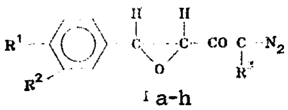
284.4'235.2

An analysis of the mass spectra of 1-diazo-3,4-epoxy-4-arylbutanones has shown that the molecular ions of these compounds lose a molecule of nitrogen and that the $[M - N_2]^+$ ions formed cyclize to form hydroxyfuran structures, whose further fragmentation determines the whole picture of the dissociative ionization of the compounds investigated under electron impact. The majority of the $[M - N_2]^+$ ions have the form of the cyclic intermediate formed in the first step of the cyclization process. It cannot, however, be ruled out that a certain portion of the $[M - N_2]^+$ ions are stabilized as a result of a Wolff rearrangement and do not cyclize at all.

We previously [2] showed that under electron impact in the gaseous phase diazoketones which contain a heteroatom or a heteroatomic grouping in their chain eliminate a nitrogen molecule and cyclize to form heterocyclic systems owing to the practicable cooperation of the heteroatom, rather than decompose according to a mechanism involving a Wolff rearrangement [3, 4]. Since the action of acids on diazoketones in solutions produces similar products [5, 6], it was concluded that it would be possible to predict the direction of this reaction on the basis of mass-spectrometric data. The results of the treatment of phthaloyldipeptide derivatives of diazomethane with acidic reagents completely correspond to the predictions made on the basis of the mass spectra of these compounds [2, 7].

Continuing this investigation, we studied the mass spectra of a series of arylepoxydiazoketones I, whose conversions in solutions were not previously investigated.



I a-h

I a $R^1=H$, b $R^1=CH_3$, c, h $R^1=OCH_3$, d $R^1=NO_2$, e $R^1=F$, f, g $R^1=Cl$; a—f $R^2=R^3=H$, g $R^2=H$, $R^3=D$; h $R^2=OCH_3$, $R^3=H$

The first step of the fragmentation of these compounds under electron impact, as would be expected [1, 2], is the elimination of a nitrogen molecule. This results in the formation of $[M - N_2]^+$ ions, whose structure makes it possible to draw a conclusion regarding the direction of the reactions of diazoketones with acidic reagents, which is the main goal of the present work. The possible structures of the $[M - N_2]^+$ ions (see Scheme 1) can be suggested on the basis of the preceding investigations [1, 2] and the data in [3, 4].

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*For report 7 see [1].

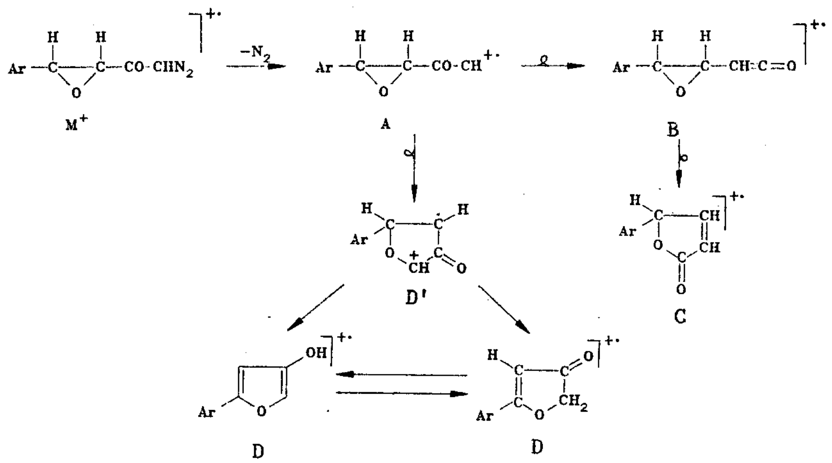
M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 17-22, January, 1986. Original article submitted December 4, 1984.

TABLE 1. Intensities of the Peaks of the Characteristic Fragment Ions in the Mass Spectra of Diazoketones I in the Total Ion Current

Compound	M^+	$[M-N_2]^+$	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	105	69
I a	—	0,6	1,1	2,0	4,3	—	3,5	0,9	3,2	7,0	0,5	7,1	21,6	6,0
I b	0,1	1,3	1,1	1,4	4,2	0,1	2,8	0,5	2,0	6,6	0,9	17,0	20,1	3,2
I c	0,4	1,45	1,2	0,9	4,2	0,4	1,8	0,3	1,4	6,2	1,3	15,9	18,5	—
I d	—	4,0	0,3	1,1	1,5		0,7	1,4	3,5	0,7	—	7,7	1,1	0,6
I e	—	2,1	4,0	1,1	3,1	0,1	2,7	1,0	6,7	10,7	0,6	5,9	2,1	10,2
I f	0,1	0,5	0,5	0,4	1,6	—	1,2	0,2	3,5	5,6	0,2	11,6	9,9	6,6
I g	0,4	0,8	0,4	1,1	4,6	0,4	1,3	0,7	1,0	3,6	0,8	15,8	5,7	0,8
I h	0,3	7,9	—	2,5	3,4	0,2	6,5	1,5	1,6	8,5	0,8	5,8	7,1	5,0

The ions of type A with a linear structure are unstable and are stabilized either as a result of a Wolff rearrangement (ion B) or as a result of intramolecular cyclization (intermediate D' and ions of type D). Ketene B can also cyclize to form ion C [8]. It should be noted that both intramolecular cyclization and a Wolff rearrangement can take place simultaneously with the elimination of a molecule of nitrogen and can, in fact, initiate this process.

Scheme 1



The molecular ions (M^+ of compounds I, like M^+ of the previously studied diazoketones [2], are unstable. The intensity of the peaks for M^+ does not exceed 0.5% of the total ion current,* and the presence of electron-acceptor substituents in the benzene ring (NO_2, F) results in the complete disappearance of the peak of this ion. Nevertheless, the formation of $[M - CHN\ ]^+$ fragments with an intensity of 0.1-0.2% and of $[COCHN_2]^+$ which has a mass-to-charge ratio equal to 69† (see Table 1), proves that diazo compounds I form M^+, i.e., ionization of the diazo compounds, rather than the products of their thermal decomposition, particularly the ketenes, occurs under the conditions of our experiment [3, 4].

An analysis of the fragmentation paths of the $[M - N_2]^+$ ions allows us to conclude that they mainly have a cyclic structure (form D, see Scheme 1). Some of the $[M - N\ ]^+$ ions decompose prior to the migration of the hydrogen ion (the D'-D transition) and the formation of the hydroxyfuran pseudomolecular ion. Ion D can exist in two principal tautomeric forms: a keto and an enol form. In the case of 4-isopropyl-3-hydroxy-4,5-dihydrofuran, the enol form is predominant in the gaseous phase [9]; therefore, it may be postulated that in the case of diazo compounds I, the majority of the ions of type D will have the enol form, since additional stabilization of such a structure is caused by the formation of the aromatic furan system.

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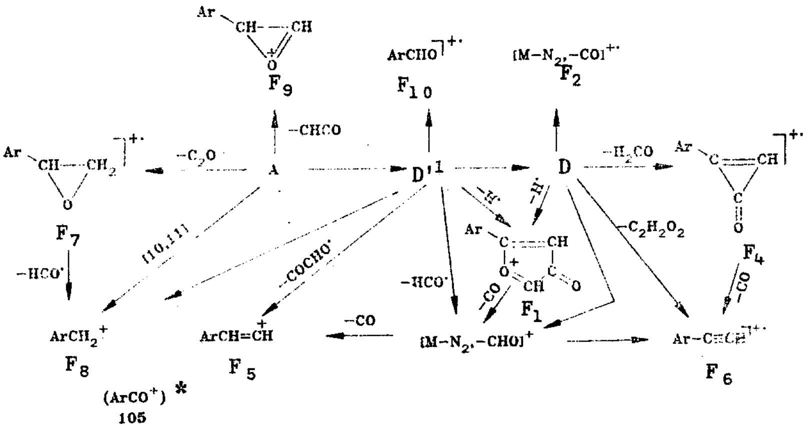
*The fraction of the ions of a particular type in the total ion current is given in percent.
†The formation of this ion form M^+ in the case of compound I is confirmed by the peak of the metastable ion with an apparent mass of 21.4. Here and in the following, the numbers characterizing an ion determine the value of m/z.

The main directions of the fragmentation of the $[M - N_2]^+$ ions of diazoketones I may be represented by the general scheme

Scheme 2



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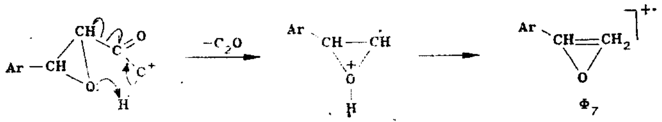
*The genetic relationship of these ions was not established.

The structures of ions F_1, F_2, F_3, F_8, and F_9 may be represented differently, if it is postulated that the first step in the transformation of the $[M - N_2]^+$ ions is a Wolff rearrangement [3, 4]. However, other experimental findings attest to the fact that the majority of the $[M - N_2]^+$ ions (and possibly all of them) are stabilized as a result of intramolecular cyclization.

First, the Wolff rearrangement does not result in the destruction of the epoxy ring; therefore, peaks of ions characteristic of the decomposition of aromatic epoxy compounds should be observed in the mass spectra of diazoketones I. In the mass spectra of phenyl epoxides the peaks of the $ArCH^+$ and ArC^+ ions have the maximum intensities [10]. In the case of diazoketones I, the peaks of these ions have intensities below 0.5%,* attesting to the destruction of the epoxy ring in the initial steps of the fragmentation. On the other hand, the peak of the $ArCHO^{+\cdot}$ ions (F_{10}), which has the maximum intensity in the mass spectra of the compounds investigated, is practically absent in the mass spectra of aryl epoxides [10] and arylepoxyketones [11]. The proves the impossibility of its formation from linear ions A and B (see Scheme 1), while the decomposition of intermediate D' with the formation of such an ion is very favorable.

Second, the Wolff rearrangement does not account for the formation of ion F_5 (see Scheme 2), while its appearance from intermediate D' as a result of the elimination of a COCHO particle or from ion F_3 (elimination of a CO molecule) is not impeded. In addition, the formation of ions of type F_6 as a result of the elimination of a $COCH_2O$ particle from the $[M - N_2]^{\cdot +}$ ion in one or two steps, as was observed in the mass spectra of 1,3-oxazin-5-ones [12] and 4,5-dihydro-3-oxofurans [9], confirms the cyclic structure of D for these ions.

Third, an additional mass-spectroscopic finding which confirms the cyclization of the $[M - N_2]^+$ ion is the formation of the fragments of type F_7. As a result of the attack of the oxygen atom of the epoxy ring at the methine group, which bears a positive charge and a free electron, the lone pair of the oxygen atom can form a bond either with the carbon atom (the electrophilic center) (this results in the formation of intermediate D') or with the acidic proton of the methine group with the subsequent cleavage of a C—C bond and the formation of fragment F_7.



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*An exception is compound Ie, for which the intensities of the peaks of these fragments are 5.5 and 4.5%, respectively. They are also sufficiently intense in the mass spectra of unsubstituted diazoketone Ia (1.7 and 2.2%, respectively).

Electron-acceptor substituents in the aromatic ring increase the acidity of the methine group. This is reflected in the increases in the relative intensities of the peaks of the F_7 ions in the mass spectra of compounds Id-f (see Table 1).

In order to refine the fragmentation scheme, we synthesized compound Ig with deuteration at the diazo group. The calculation of the intensities of the peaks in the mass spectrum of this compound showed that the deuterium label is completely retained in ion F_1, while 30% of it is lost in F_3. Therefore, the $[M - N_2]^+$ ions eliminate the benzyl hydrogen atom, and such elimination can occur either from intermediate D' or from linear forms A and B of the $[M - N]^+$ ion [10, 11].

The F_3 ions apparently form along several paths. The successive elimination of a hydrogen atom and a molecule of CO from the $[M - N_2]^+$ ion does not result in the loss of the deuterium label. The elimination of an $HCO^{\cdot}$ radical is the main process in the fragmentation of furans [13, 14]. The fragmentation of diazoketone Ig according to such a mechanism should result in the complete loss of the deuterium label in the case of the existence of ion D exclusively in the enol form and in its partial loss when the keto form of this ion is present. The partial loss of the deuterium label may also be the result of the elimination of a hydrogen atom from ion F_2. It is not possible to evaluate the contribution of each of these paths to the formation of ion F_3; however, the experimental findings presented can be explained only when the $[M - N_2]^+$ ions are assumed to have a cyclic structure. In this case, the structure of fragment F_3 can vary as a function of the mechanism for its formation and is, therefore, not presented in the scheme.

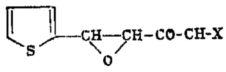
It is known 14 that substituents in positions 2 and 5 of the furan ring (R) can result in the appearance of an alternative direction of fragmentation: An $RCO^{\cdot}$ radical is eliminated along with an $HCO^{\cdot}$ radical. In the case of diazoketones I, position 5 in the furan ring formed is occupied by an aryl substituent. The electronic properties of the substituents in the benzene ring play an important role in the competitive elimination of the $HCO^{\cdot}$ and $RCO^{\cdot}$ radicals. For example, in the mass spectra of compounds Ia-c with electron-donor substituents, the peak of the $[M - N_2 - RCO]$ ion is not observed at all. Electron-acceptor substituents (compounds Id-f) make this fragmentation path competitive. The mass spectra of these compounds display peaks for the corresponding ion 55 with relative intensities equal to 4.6, 1.0, and 1.0%, respectively. As was shown in [13, 14], this ion has a cyclic cyclopropane structure.

The cyclic structure of the $[M - N_2]^+$ ions is also confirmed by the formation of the F_4 fragments as a result of the elimination of a molecule of formaldehyde from the keto form of ion D or an $HCO^{\cdot}$ radical from ion F_1.

Nevertheless, all the mass-spectrometric findings described do not allow us to completely discount the possibility of a Wolff rearrangement; therefore, it should be assumed that the formation of ketene ions of type B according to a mechanism involving a Wolff rearrangement [3, 4] may be a process which competes with the intramolecular cyclization and takes place for some of the $[M - N_2]^+$ ions.

Cleavage of the $C_{(2)}-C_{(3)}$ bond in M^+ results in the formation of ions F_9 and 69, and the mass spectra of diazoketones I display peaks for both these ions (see Table 1), i.e., these fragments have similar ionization energies [15, 16].

Substituents in the benzene ring do not alter the principal fragmentation paths. The behavior of fluorinated derivative Ie is anomalous. The peaks of ions F_8 and 69 have the maximum intensities in the mass spectrum of this compound; the peaks of the $ArCH^{+\cdot}$ and ArC^+ fragments (5.5 and 4.1%), which are characteristic of the fragmentation of aryl epoxides [10], are also intense. The intensity of the peak of ion F_7 is also increased (see Table 1). Such a sharp increase in the number of M^+ ions decomposing along paths not associated with the initial formation of a furan ring indisputably reduces the proportion of $[M - N_2]^+$ ions in form D to the total number of ionized molecules of this compound in comparison to the other compounds of type I.



Ii X=N_2;IIi X=H_2

TABLE 2. Mass Spectra of Compounds Ia-i

Compound	Values of m/z* (relative intensities of ion peaks as percentages of the maximum)
Ia	131 (19,4), 120 (15,0), 106 (36,2), 105 (100), 103 (16,3), 91 (32,2), 78 (12,5), 77 (54,0), 69 (30,1), 51 (25,0)
Ib	145 (21,3), 120 (84,2), 119 (100), 117 (13,3), 105 (33,0), 92 (19,4), 91 (63,8), 69 (17,0), 65 (51,4), 41 (16,4)
Ic	161 (24,9), 159 (10,8), 137 (13,1), 136 (85,7), 135 (100), 121 (33,3), 91 (13,9), 78 (10,1), 77 (31,7), 51 (19,9)
Id	205 (51,6), 165 (45,7), 151 (100), 118 (33,8), 105 (70,4), 102 (37,3), 89 (38,3), 90 (36,9), 77 (36,9), 55 (59,6)
Ie	177 (40,3), 149 (30,8), 138 (66,7), 124 (55,0), 109 (100), 108 (51,8), 107 (33,0), 101 (49,0), 95 (68,9), 69 (95,5)
If	159 (30,5), 154 (28,2), 142 (62,9), 141 (80,4), 140 (100), 139 (85,0), 125 (48,1), 110 (27,6), 89 (43,4), 69 (57,1)
Ig†	160 (14,2), 142 (30,4), 141 (43,2), 140 (87,8), 139 (100), 138 (27,0), 125 (33,1), 111 (21,6), 89 (28,3), 70 (14,8)
Ih	191 (28,9), 189 (15,9), 166 (100), 165 (36,4), 151 (23,0), 95 (23,8), 79 (13,4), 77 (21,9), 63 (11,3), 51 (16,7)
Ii	166 (91,9), 138 (29,5), 137 (39,6), 112 (68,4), 111 (83,2), 110 (26,2), 109 (76,5), 97 (100), 69 (57,7), 65 (22,8)

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*The 10 most intense peaks are given.

†The spectrum was obtained on an MKh-1303 mass spectrometer.

The behavior of epoxythiophene Ii is similar to that of the compounds described. The mass spectrum of this compound differs significantly from the spectrum of epoxyketone IIi, which has a similar structure [17], and all the fragments are described well by the general scheme for the fragmentation of diazoketones I presented, i.e., in this case, too, the epoxy ring opens and a cyclic furan ion forms.

Thus, an analysis of the mass spectra of diazoketones I showed that the M^+ ions of these compounds lose a molecule of nitrogen and the $[M - N_2]^+$ ions formed undergo cyclization with the formation of hydroxy furan structures, whose further fragmentation determines the entire picture of the dissociative ionization of the compounds investigated under electron impact. The majority of the $[M - N_2]^+$ ions have the form of the cyclic intermediate formed in the first step of the cyclization process. It cannot, however, be ruled out that a certain portion of the $[M - N_2]^+$ ions are stabilized as a result of a Wolff rearrangement and do not cyclize at all. On the basis of the investigation carried out, it may be postulated that cyclic furan systems will form when the diazoketones studied are reacted with solutions of acids. In the case of fluorinated derivative Ie, secondary reactions with the formation of other products are possible.

EXPERIMENTAL

All the compounds investigated were synthesized at the Chernogolovka Branch of the Institute of Chemical Physics of the Academy of Sciences of the USSR. The mass spectra of diazoketones Ia-h were obtained on an LKB-2091 mass spectrometer (Sweden) with the use of a system for the direct admission of the sample into the ion source. The temperature of the samples was 60-140°C, and the energy of the ionizing electrons was 70eV. The mass spectra of compounds If and Ig were additionally recorded under identical conditions (the temperature was 100°C, and the energy of the ionizing electrons was 50 eV) on an MKh-1303 mass spectrometer with a similar admission system. The deuterated form of compound Ig was obtained by holding diazoketone If in deuteromethanol (CD_3OD) for 24 h with further evaporation of the solvent and recrystallization of the deuterated derivative from deuteromethanol.

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SYNTHESIS OF 2-, 6-, AND 7-AMINOMETHYL DERIVATIVES IN THE 4,5-DIHYDROXYBENZOFURAN SERIES

A. N. Grinev,* V. M. Lyubchanskaya, L. S. Sarkisova,
L. M. Alekseeva, and Yu. N. Sheinker

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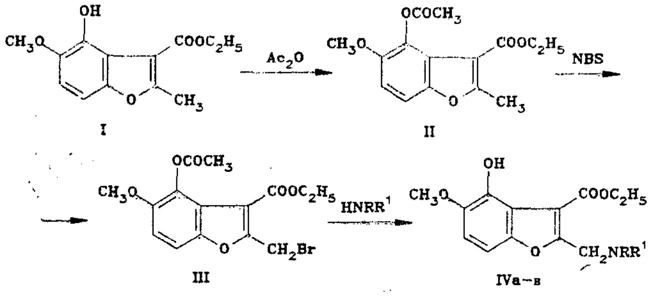
543.422.25

The 2-, 6-, and 7-aminomethyl derivatives have been synthesized from derivatives of 4-hydroxy-5-methoxy- and 4-methoxy-4-hydroxybenzofuran. 2-Methyl-3-carbethoxy-5-methoxy-7-dimethylaminomethylbenzofuran has been converted into the 7-cyanomethyl derivative.

Aminomethyl derivatives of benzofuran are of definite interest in the area of the search for drugs. One of them, viz., 2-phenyl-3-carbethoxy-4-dimethylaminomethyl-5-hydroxybenzofuran hydrochloride (phenykoberan), has found application in the practice of medicine [1]. We recently synthesized derivatives of 4-hydroxy-5-methoxy- and 4-methoxy-5-hydroxybenzofuran [2]. In the present work, we have used them as a basis for obtaining various, primarily the 2-, 6-, and 7-aminomethyl, derivatives.

The bromination of 2-methyl-3-carbethoxy-4-acetoxy-5-methoxybenzofuran (II) by N-bromosuccinimide in the presence of benzoyl peroxide gives 2-bromomethyl derivative III, and 2-dimethylaminomethyl-2-piperidinomethyl-, and 2-isopropylaminomethyl-4-hydroxy-5-methoxybenzofuran (IVa-c) are obtained by reacting the corresponding amines with III. When III is reacted with an excess of the amines, elimination of the acetyl group is observed along with the replacement of bromine by the residue of the amine.



IV a $R=R^1=CH_3$, b $R+R^1=(CH_2)_5$, c $R=H$, $R^1=CH(CH_3)_2$

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*Deceased.

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