MASS SPECTRA OF 3-ARYLIDENE-1H-2,3-DIHYDRO-1,4-BENZODIAZEPIN-2-ONES

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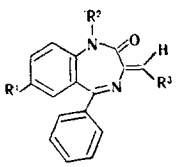
The scheme of the fragmentation of arylidene derivatives of 5-phenyl-1,4-benzodiazepin-2-ones was established by means of high-resolution mass spectrometry. One of the principal fragmentation pathways of these compounds is cleavage of the 2C–3C and 4N–5C bonds to give two fragments. Depending on the substituents in the arylidene portion of the molecule, the charge is localized primarily on one or the other of these fragments. The mechanism of the formation of the $[ArCH_2]^+$ ions observed in the mass spectra of all of the investigated compounds was established on the basis of the mass spectrum of the 1N-deuterium-labeled compound. The specific fragmentation pathways due to the ortho effect of the nitro group are discussed.

Arylidene derivatives of benzodiazepin-2-ones have appreciable pharmacological activity, and some of them are being subjected to biological testing. In this connection, a mass spectrometric study of the series of compounds seemed of great interest. The following series of compounds were investigated:



	R^1	R^2	R^3	W_M*		R^1	R^2	R^3	W_M*
I	H	H	C_6H_5	31,9	VII	Cl	H	p-$C_6H_4NO_2$	27,0
II	CH_3	H	C_6H_5	35,2	VIII	Cl	H	o-$C_6H_4NO_2$	1,2
III	Cl	H	C_6H_5	28,2	IX	Cl	H	p-C_6H_4-i-C_3H_7	29,7
IV	Br	H	C_6H_5	29,1	X	Cl	H	p-$C_6H_4N(CH_3)_2$	57,2
V	Br	D	C_6H_5	—	XI	Cl	H	2-Thienyl	51,6
VI	Cl	H	p-C_6H_4Cl	32,0	XII	Cl	H	2-Pyrrolyl	35,2

The molecular ions of all of the investigated compounds (except for VIII) have high stabilities, and their peaks are the maximum peaks in the mass spectra. The W_M values range from 27.0 to 57.2%, and the fraction of the current of the molecular ions in the total ion current is 1.2% only in the case of VIII. Compound X, in which the strong electron-donor $N(CH_3)_2$ grouping of the R^3 substituent plays a stabilizing role, is characterized by the highest stability. Replacement of it by a nitro group (VII) reduces the stability of the molecule with respect to electron impact by a factor of more than two. The presence in VIII of a nitro group in the ortho position leads to a sharp decrease in the character of the dissociative ionization due to the so-called "ortho effect," in connection with which the mass spectrometric fragmentation of this compound will be thoroughly analyzed separately.

The m/e values and the relative intensities (as a percent of the maximum) of the ion peaks observed in the mass spectra of I-XII are presented in Table 1. Since even the characteristic fragment ions in the mass spectra of the arylidene derivatives have low intensities, ions having intensities up to 3% are included in Table 1.

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TABLE 1. m/e Values and Relative Intensities (in Percent of the Maximum Peak) of the Ion Peaks in the Mass Spectra of I-XII

I. 325 (18,4), 324 (100), 323 (16,1), 296 (6,6), 295 (31,3), 294 (3,0), 247 (20,7), 219 (5,0), 209 (3,4), 208 (35,9), 180 (6,2), 179 (3,0), 153 (3,0), 152 (6,3), 91 (3,3), 78 (19,9), 77 (13,3), 51 (3,7)

II. 339 (21,8), 338 (100), 337 (10,4), 323 (5,7), 310 (7,1), 309 (28,8), 295 (3,2), 261 (21,2), 233 (4,4), 223 (3,4), 222 (35,5), 194 (3,1), 193 (3,2), 165 (4,8), 152 (3,1), 91 (7,8), 77 (7,1), 51 (3,0)

III. 361 (3,7), 360 (27,6), 359 (24,2), 358 (100), 357 (3,9), 331 (9,7), 330 (10,4), 329 (38,2), 328 (6,2), 323 (3,4), 293 (5,4), 283 (3,4), 281 (16,6), 253 (5,5), 244 (5,3), 242 (22,6), 214 (4,8), 213 (3,4), 207 (6,7), 179 (7,1), 178 (15,0), 177 (11,5), 176 (3,2), 165 (4,6), 152 (14,7), 151 (13,6), 150 (3,4), 117 (7,8), 116 (4,8), 91 (12,8), 90 (3,8), 89 (5,1), 77 (15,9), 51 (4,1)

IV. 405 (23,6), 404 (99,2), 403 (24,8), 402 (100), 401 (7,8), 375 (4,7), 374 (19,8), 373 (4,9), 372 (20,1), 361 (3,0), 327 (5,2), 325 (7,1), 295 (3,0), 294 (5,1), 293 (3,7), 285 (8,1), 283 (8,3), 207 (6,1), 179 (5,0), 178 (4,5), 152 (6,0), 151 (6,5), 147 (4,0), 129 (5,7), 128 (17,1), 127 (12,7), 91 (14,1), 77 (6,0), 51 (3,1)

VI. 396 (9,3), 395 (14,5), 394 (67,2), 393 (31,3), 392 (100), 391 (11,6), 366 (4,6), 365 (11,9), 364 (8,9), 363 (17,4), 359 (6,4), 358 (5,1), 357 ((22,1), 330 (3,0), 329 (5,0), 328 (14,3), 327 (11,4), 326 (7,7), 325 (4,3), 317 (3,8), 315 (6,9), 293 (5,7), 292 (4,4), 244 (6,4), 243 (4,5), 242 (26,4), 241 (4,1), 214 (6,2), 213 (4,4), 207 (9,6), 190 (3,0), 179 (7,1), 178 (17,5), 177 (13,2), 176 (3,3), 165 (4,1), 164 (5,4), 163 (4,3), 153 (3,6), 152 (18,2), 151 (19,0), 150 (10,1), 127 (4,8), 126 (5,4), 125 (10,9), 121 (3,4), 119 (13,3), 117 (13,5), 89 (6,6), 78 (3,1), 77 (15,7), 69 (4,2), 51 (4,2)

VII. 406 (5,8), 405 (34,8), 404 (26,2), 403 (100), 402 (9,1), 375 (5,1), 374 (5,5), 373 (9,2), 368 (6,4), 352 (3,0), 330 (3,1), 329 (10,3), 328 (7,0), 327 (6,5), 326 (4,8), 293 (4,8), 292 (3,5), 244 (3,1), 242 (10,5), 214 (3,2), 207 (3,9), 178 (7,2), 177 (5,5), 152 (5,5), 151 (5,6), 77 (6,5)

VIII. 403 (6,7), 389 (3.0), 388 (14,4), 387 (12,2), 386 (49,0), 361 (7,1), 360 (15,0), 359 (23,6), 358 (14,4), 357 (5,4), 344 (3,4), 343 (6,7), 342 (3,2), 332 (9,9), 331 (10,0), 330 (35,4), 329 (8,0), 328 (7,5), 327 (5,9), 326 (4,3), 294 (3,9), 293 (7,2), 292 (11,1), 291 (5,0), 290 (4,2), 283 (4,4), 282 (5,0), 269 (8,6), 268 (5,4), 264 (3,0), 259 (3,0), 258 (11,1), 257 (40,1), 256 (32,5), 255 (100), 254 (12,8), 253 (3,7), 252 (3,4), 244 (14,4), 243 (15,6), 242 (53,6), 241 (42,0), 240 (14,3), 239 (47,2), 238 (3,4), 228 (6,8), 221 (7,0), 216 (3,8), 215 (6,2), 214 (10,5), 213 (13,8), 205 (8,9), 178 (3,3), 177 (3,8), 151 (3,4), 89 (4,2), 77 (4,1)

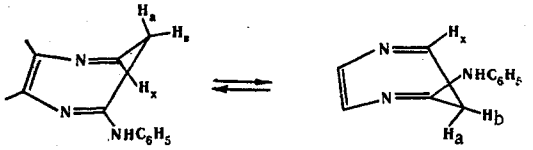
IX. 403 (6,3), 402 (32,4), 401 (29,4), 400 (100), 399 (10,2), 387 (6,6), 386 (7,3), 385 (22,4), 371 (3,7), 360 (3,0), 359 (17,3), 358 (14,6), 357 (61,1), 356 (7,2), 355 (6,4), 329 (7,3), 323 (7,6), 321 (3,2), 244 (3,8), 242 (14,7), 214 (5,8), 213 (3,5), 207 (5,4), 179 (4,8), 178 (11,0), 177 (8,2), 176 (3,3), 159 (8,4), 152 (9,5), 151 (8,1), 144 (5,6), 117 (12,7), 116 (4,1), 115 (7,0), 91 (11,1), 77 (8,4)

X. 404 (7,0), 403 (33,2), 402 (27,6), 401 (100), 400 (5,7), 372 (3,0), 358 (3,6), 357 (3,1), 324 (3,7), 160 (3,3), 159 (23,9), 143 (4,5), 134 (12,3), 77 (3,9)

XI. 367 (6,6), 366 (37,2), 365 (24,3), 364 (100), 363 (5,7), 336 (3,8), 335 (6,0), 329 (3,1), 291 (6,7), 214 (3,0), 207 (3,8), 178 (6,9), 177 (6,8), 152 (7,7), 151 (7,8), 150 (3,0), 122 (4,1), 98 (3,0), 97 (22,5), 96 (3,4), 77 (8,9), 69 (3,2)

XII. 350 (4,0), 349 (28,7), 348 (20,9), 347 (100), 346 (6,5), 319 (5,8), 318 (6,9), 291 (3,2), 243 (3,0), 242 (3,5), 214 (3,0), 179 (3,6), 178 (4,8), 177 (4,2), 151 (6,2), 150 (6,2), 105 (11,5), 97 (4,0), 95 (3,8), 85 (3,4), 84 (3,7), 83 (5,3), 81 (6,7), 80 (37,1), 79 (4,3), 78 (7,3), 77 (9,6), 71 (6,3), 69 (9,3), 67 (6,8), 57 (15,3), 56 (4,7), 55 (12,5), 51 (3,7)

In contrast to 3C-unsubstituted benzodiazepinones [3, 4] and their thio analogs [5], elimination of a hydrogen atom is only slightly characteristic for the molecular ions of the arylidene derivatives. As previously demonstrated in [3, 4], only 7% of the hydrogen from the 3-methyl group and 22% of the hydrogen from the amide nitrogen atom are lost in the formation of $[M - H]^+$ ions in the case of 1,4-benzodiazepin-2-ones. The hydrogen atom is eliminated primarily (70%) from the ortho position of the 5-aryl group with simultaneous cyclization to the 4N atom. Since, according to the data from the mass spectrum of V, the amide hydrogen atom does not participate appreciably in the $M^+ - H\cdot$ process, a similar mechanism for elimination of a hydrogen atom and in the fragmentation of arylidene derivatives of 1,4-benzodiazepin-2-ones can be assumed. The suppression of this process in this case then could have been associated with steric hindrance, which may be due to interaction of the 5-phenyl ring with the aryl group, as a result of which neither ring can draw close to the 4N atom and undergo opening in order to occupy the planar (with respect to the benzodiazepine portion of the molecule) position.



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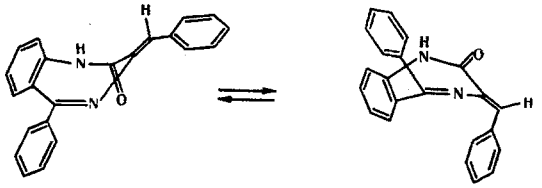
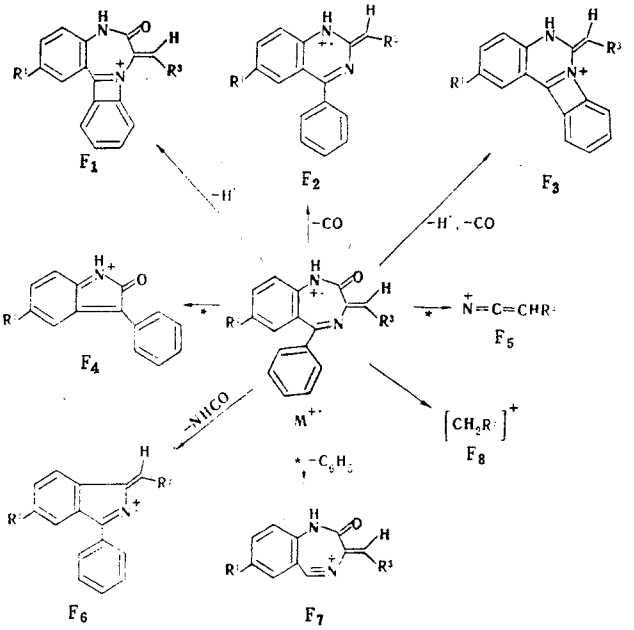
However, on the basis of the PMR spectra it has been established [6] that diazepines exist primarily in the boat form in solutions. Approximately the same rates of inversion and $\Delta G^{\ddagger}$ values were also obtained for 1-CH_3-5-phenyl-7-chloro-1,4-benzodiazepin-2-one [1]. In this case it was shown that the 3-methylene group and the 5-phenyl substituent are always found in a quasi-para orientation. The geometry of the arylidene molecule consequently does not presuppose interaction of the aryl group with the 5-phenyl substituent and, from this point of view, the decrease in the relative intensity of the $[M - H]^+$ ion peaks remains unexplained.



Another explanation for the suppression of elimination of a hydrogen atom by arylidenes can be given proceeding from the ratio of the tautomeric forms of the molecular ion. As demonstrated in the case of 1,4-benzodiazepine-2-thiones [5], elimination of a hydrogen atom is peculiar only to the molecular ions of the eniminethiol tautomeric form. Consequently, in the case of arylidene derivatives the tautomeric equilibrium in the molecular ions is shifted more markedly to favor the lactam tautomer as compared with benzodiazepin-2-ones and their thio analogs, and the ratio of the $[M - H]^+$ and M^+ ion peaks qualitatively determines the magnitude of this shift. The I_{M-H}/I_M values for arylidenes range from 0.04 (III) to 0.16 (I), as compared with 0.24 to 1.24 for benzodiazepin-2-ones (depending on the electronic properties of the substituents in the condensed benzene ring) [3], whereas it is 0.41 for the thio derivatives [5]. The presence in the mass spectra of I-XII of low-intensity (up to 2%) $[M - OH]^+$ ion peaks confirms the conclusion that the molecular ions of arylidenes exist partially in the lactim tautomeric form.

The principal fragmentation pathways of I-VII and IX-XII can be represented by the following scheme:



The elementary compositions of the ions indicated in the scheme were determined for I by means of the high-resolution mass spectrum (see Table 2). In this case it was also established that the ions with m/e 151, 152, 179, and 180 [4] characteristic for benzodiazepine systems in this case also have the compositions, $C_{12}H_7$, $C_{12}H_8$, $C_{13}H_9N$, and $C_{13}H_{10}N$, respectively. The relative intensities in percent relative to the total ion current of the principal fragment ions in the mass spectra of the investigated compounds are presented in Table 3.

TABLE 2. Mass Spectrum of I

High resolution masses observed	High resolution masses calculated	ionic composition	group eliminated	Relative intensity of the ion peak	Ion index
324, 1190	,1262	$C_{22}H_{16}N_2O$	—	100	M+
323, 1144	,1184	$C_{22}H_{15}N_2O$	H	16,1	F_1
317, 1190	,1163	$C_{22}H_{15}N_2$	HO	1,0	
296, 1298	,1313	$C_{21}H_{16}N_2$	CO	6,6	F_2
295, 1235	,1220	$C_{21}H_{15}N_2$	CHO	31,3	F_3
281, 1098	,1133	$C_{21}H_{15}N$	CHNO	1,3	F_6
247, 0781	,0790	$C_{16}H_{11}N_2O$	C_6H_5	20,7	F_7
219, 0880	,0850	$C_{15}H_{11}N_2$	C_7H_5O	5,0	
208, 0784	,0762	$C_{14}H_7NO$	C_8H_6N	35,9	F_4
180, 0826	,0813	$C_{13}H_{10}N$	C_9H_6NO	6,2	
179, 0748	,0735	$C_{13}H_9N$	C_9H_7NO	3,0	
165, 0742	,0704	$C_{13}H_9$	$C_9H_7N_2O$	2,4	
152, 0638	,0625	$C_{12}H_8$	$C_{10}H_8N_2O$	6,3	
151, 0571	,0547	$C_{12}H_7$	$C_{10}H_9N_2O$	2,3	
116, 0569	,0502	C_8H_6N	$C_{14}H_{10}NO$	1,2	F_5
91, 0568	,0548	C_7H_7	$C_{15}H_9N_2O$	3,3	F_8
78, 0501	,0469	C_6H_6	$C_{16}H_{10}N_2O$	19,9	
77, 0419	,0391	C_6H_5	$C_{16}H_{11}N_2O$	13,3	

TABLE 3. Relative Intensities in Percent Relative to the Total Ion Current of the Peaks of Ions F_1-F_8 in the Mass Spectra of the Investigated Compounds

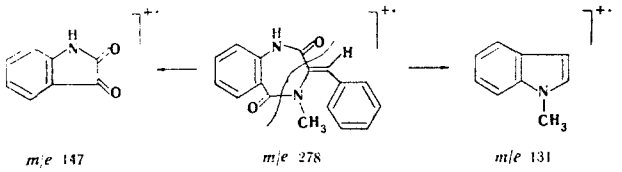
Compound	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
I	5,0	1,0	9,6	10,7	0,03	0,4	6,3	1,0
II	3,1	1,2	9,2	11,2	0,04	0,9	6,8	2,3
III	4,3	3,2	11,5	6,4	1,4	0,7	5,0	3,0
IV	2,8	2,9	7,9	5,3	1,1	1,2	5,2	2,8
VI	3,5	2,6	5,8	5,8	1,4	—	2,2	2,8
VII	3,4	2,8	5,6	4,4	—	—	2,0	1,0
IX	4,5	0,5	0,8	4,1	—	15,8*	2,0	0,5
X	1,1	0,9	1,8	0,5	11,8	—	1,3	6,4
XI	1,0	1,9	2,8	2,0	4,3	—	0,2	6,8
XII	2,0	1,9	2,4	1,2	4,0	0,5	0,3	10,0

*The $[M-43]^+$ ions in the mass spectrum of IX are formed primarily as a result of elimination of an isopropyl radical from substituent R^3.

The deuterium label is completely retained in the case of V during the formation of F_3 ions, and the $[M-HCO]^+$ ions are consequently formed as a result of detachment of H· and CO in different sequences.

One of the principal fragmentation processes of arylidenes is cleavage of the 2C–3C and 4N–5C bonds to give the F_4 ion, which is common to the entire series of compounds (see the scheme above). The intensity of the F_4 ion peak is a maximum in the mass spectra of I and II (10.7 and 11.2%, respectively). It ranges from 4.1 to 6.4% for III, IV, VI, VII, and IX, but, when substituent R_3 contains a heteroatom, the intensity of the F_4 ion peaks decreases sharply, and intense F_5 ion peaks, which show up weakly in other cases (Table 1), are observed in the mass spectra of compounds of this sort (see the above scheme).

A fragmentation process similar to that described above has been observed during a mass spectrometric study of cyclopenine [7]:



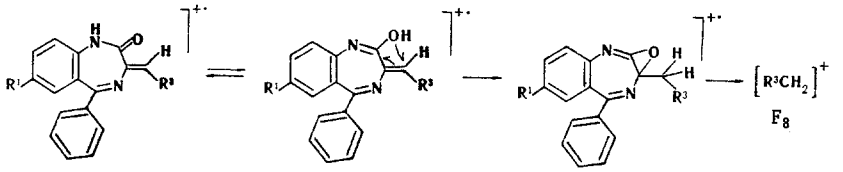
Peaks of both ions were observed in the mass spectrum.

Elimination of an isocyanic acid molecule by the molecular ions of the arylidenes leads to the formation of low-intensity F_6 ion peaks. The deuterium label is completely lost during this process in the case of V.

In addition, splitting out of a phenyl radical is peculiar to the molecular ions of the arylidene derivatives, and peaks of F_7 and $[C_6H_5]^+$ ions are observed in the mass spectra. A process involving the formation of F_7

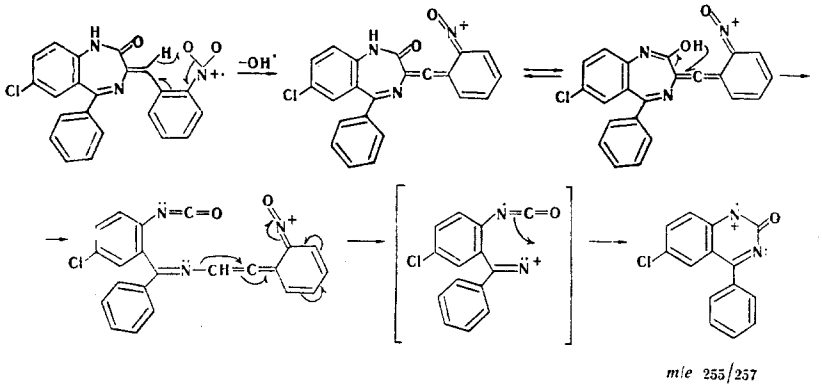
ions in the mass spectra of most of the investigated compounds is confirmed by the corresponding metastable transitions. At the same time, splitting out of substituent R^3 by the molecular ions is uncharacteristic. The peaks of these ions usually do not exceed 2-3% of the maximum peak.

The chief feature of the mass spectrometric fragmentation of the arylidenes is the formation of rearranged $[R^3CH_2]^+$ ions (F_8), the peaks of which are present in all of the investigated mass spectra. Since the peak of the F_8 ion in the mass spectrum of V is completely shifted by 1 amu to the higher m/e side, it is absolutely obvious that the hydrogen atom attached to the amide nitrogen atom participates in the process. The rearrangement mechanism can then be represented by the following probable scheme:



Substituents R^3 have a strong effect on the rate of formation or the stability of the F_8 ions, and if the substituent contains a heteroatom (X-XII), the intensity of the F_8 ion peaks increases markedly (see Table 2). It should be noted that ions of the $[M - R^3CH_2]^+$ type were not observed in the mass spectra of the investigated series of compounds.

As noted above, in the case of VIII (R^3=o-$NO_2C_6H_4$) the nitro group in the ortho position has a specific effect on the fragmentation of the molecular ions. An intense (49%) peak of $[M - OH]^+$ ions is observed in the mass spectrum of VIII, and the maximum peak is the peak of ions with m/e 255, which contain a chlorine atom. Elimination of an OH radical in one step is confirmed by the metastable ion (apparent mass 369.7). It is characteristic for the fragmentation of nitro compounds in which the nitro group is adjacent to atomic groupings containing a hydrogen atom. Since the indicated ions are not observed in the mass spectrum of VII (R^3=p-$NO_2C_6H_4$), it can be assumed that their formation is interdependent in the case of VIII and that these processes can be represented by the following scheme:



m/e 255/257

Thus the fragmentation of 3-arylidene-1H-2,3-dihydro-1,4-benzodiazepinones is subject to a single scheme of mass spectrometric fragmentation, and substituents R^3 play a central role in their dissociative ionization via different fragmentation pathways. The F_4, F_5 and F_8 characteristic ions can be used for the identification of related compounds and also for mass-fragmentographic analysis.

EXPERIMENTAL

The mass spectra were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples at an ionizing voltage of 50 V, an emission current of 1.5 mA, and temperatures of 180-210°. The high-resolution mass spectrum was obtained with a JEOL JMS-01-SG-2 spectrometer. Compounds I-IV and VI-XII were synthesized under the conditions previously described in [8]. Compound V was obtained by means of organomagnesium synthesis. A solution of 0.81 g (2 mmole) of I in anhydrous tetrahydrofuran (THF) was added with cooling to a solution of methylmagnesium iodide, obtained from 0.24 g (10 mmole) of magnesium and 2.42 g (10 mmole) of methyl iodide, in anhydrous THF, and, after 30 min, 2 ml of D_2O was added. The liquid phase was separated by decantation and evaporated with a rotary evaporation, and the product was subjected to mass spectrometric investigation. The mass spectrum showed that 60% of the deuterated derivative was present.

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