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STUDIES ON THE SERIES OF AZOLES AND AZINES.

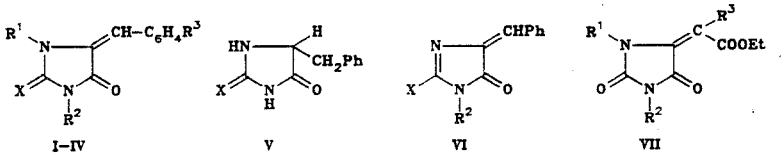
65.* MASS SPECTRA OF 5-ARYLIDENE-, 5-ETHOXYCARBONYLMETHYLENE-HYDANTOINS AND THEIR DERIVATIVES

V. S. Mirzoryan, R. G. Melik-Ogandzhanyan, T. N. Rusavskaya, G. V. Rutkovskii, and B. A. Ivin

UDC 543.51:547.783.07

The mass spectra of 5-m- and p-substituted benzylidenehydantoins, their thio analogs and 5-carbethoxymethylenehydantoins with a substituent at the α-carbon atom of the side chain were studied. The fragmentation of the molecular ions of 5-arylidenehydantoins proceeds in one direction, splitting of the X=C–NR–C=O fragment, irrespective of the substituent in the benzene ring. The peak intensity of the fragmentary ions formed from the molecular ions is linearly dependent on the σ-constants of the substituent. The direction of the fragmentation of 5-ethoxycarbonylmethylenehydantoins markedly depends on the substituent at the α-carbon atom in the side chain that determines the stability of the hydantoin ring and the carboethoxyl group. The fragmentation of these compounds under electron impact proceeds by five paths, related to splitting of fragments $O=C_{(2)}NCH_{(4)}=O$, C_2H_4, C_2H_5O, C_2H_5OH, and $COOC_2H_5$.

The mass spectra of hydantoins, their aryl, alkyl, and thio derivatives were fairly thoroughly investigated in [2-4]. Depending on the nature of the substituent, the fragmentation of these compounds under electron impact can proceed by three paths: with the splitting of the fragments $X=C_{(2)}N_{(3)}RC_{(4)}=O$ (X = O, S), NHCO or CO, respectively. Data on the



I–IV V VI VII

I, III, Va X=O, II, IV, Vb X=S, VIa,b X=MeS; I, II $R^1=R^2=H$; a $R^2=4\text{-}NO_2$; b R^3=3-Br; c R^3=3-Cl; d R^3=3-COOH; e R^3=4-Br; f R^3=4-Cl; g R^3=4-I; h R^3=3-OH; i R^3=2-OMe; j $R^3=H$; k R^3=4-Me; l R^3=4-OMe; m R^3=3-OMe–4-OH; n R^3=3-OMe; o $R^3=4\text{-}NEt_2$; III, IV a R^1=Me, $R^2=R^3=H$; b $R^1=R^3=H$, R^2=Me; VI a $R^2=H$; b R^2=Me; VII a-i $R^1=R^2=H$, a $R^3=NO_2$; b R^3=Cl; c R^3=F; d $R^3=H$; e R^3=Ph; f R^3=Me; g R^2=OMe; h R^2=OPh; i R^3=OH; j $R^2=R^3=H$, R^1=Me; k $R^1=R^3=H$, R^2=Me; l $R^1=H$, R^2=Me, R^3=Ph; m $R^1=R^2$=Me, R^3=OPh

*See [1] for Communication 64.

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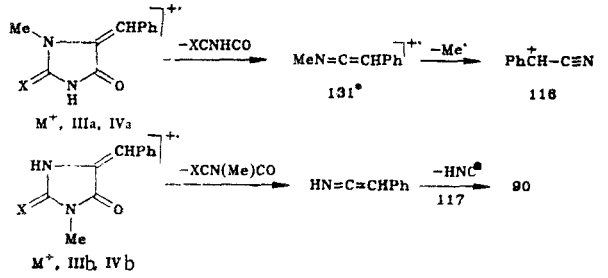
fragmentation of hydantoins with a $C_{(5)}=C_{(\alpha)}$ double bond are not available. For this reason and also to identify this group of hydantoins, we studied the mass spectra of a series of 5-arylidenehydantoins (Ib-m), their thio analogs (IIa-o), certain N-methyl derivatives (III, IV), 5-benzylhydantoins (V) and α-substituted-5-(ethoxycarbonylmethylene)hydantoins (VII).

The fragmentation of 1- and 3-methyl-5-benzylidenehydantoins (III, IV) is extraordinarily simple (Scheme 1, Table 1) and corresponds to the data in [2] on the splitting of the $X=C_{(2)}-N_{(3)}R_{(3)}-C_{(4)}=O$ fragment from the molecular ions of the simpler hydantoins [2] at the first stage of the fragmentation. This is indicated by the presence of peaks 117* in the spectra of 3-methylhydantoins(IIIb, IVb) and peaks of ions 131 in the spectra of 1-methyl derivatives (IIIa, IVa). Usually the ions decompose further with splitting of Me and HCN, respectively.

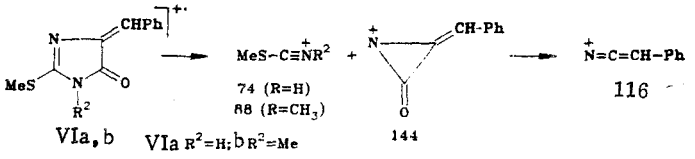
Scheme 1



For benzylhydantoins Va, b, the rupture of the $C_{(5)}-C_{(\alpha)}$ bond at the first stage of fragmentation with localization of the charge on the benzyl fragment is characteristic. As a result ion 91 is formed (see Table 1).

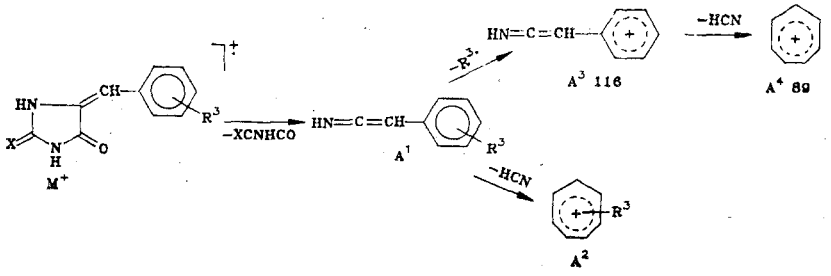
The fragmentation of the molecular ions of the S-methyl derivatives VIa, b of benzylidenehydantoin IIj, differs, as expected, from the fragmentation of N-methylhydantoins III, IV: in the spectra of compounds VIa, b there are no very intense peaks of ions 74 or 88 and 144, which are formed according to Scheme 2.

Scheme 2



Thus, if 5-arylidenehydantoins have, in fact, the structure attributed to them, they can be identified mass-spectrometrically by the presence of peaks of ions $[M - XC_{(2)}N_{(3)}C_{(4)}O]$ and from the absence of peaks of ions C_7H_5R and RC_7H_5NCCO. It was found that the mass spectra of all the arylidenehydantoins I and II are characterized by molecular ion peaks with a maximum intensity in all cases. The only exception is (3-carboxybenzylidene)hydantoin (Id) (see Table 1). The preferential path of the fragmentation of the molecular ions of these compounds is the elimination of the $X=C_{(2)}N_{(3)}HC_{(4)}=O$ groups (see Scheme 3) with the formation of ion A^1. In each case this is confirmed by a metastable transition (Table 1). The stability of the main fragmentary ion A^1 decreases proportionally to increase in the electron-donor

Scheme 3



*Here and below in the text, the m/z values are given under the formulas of the ions.

TABLE 1. Mass Spectra of 5-Arylidenehydantoins (I-IV) and Their Derivatives (V, VI)

Compound	$M^{+\cdot}$	Ions characteristic for main paths of fragmentation				Other ions
		A^1	A^2	A^3	A^4	
Ib	266 (100) 268 (98)	195 (58) 197 (55)	—	116 (55)	89 (65)	
Ic	222 (100) 224 (34)	151 (62) 153 (22)	124 (5) 126 (2)	116 (38)	89 (37)	m^*=102,5
Id	232 (97)	161 (100)	—	116 (55)	89 (36)	231 (26), 230 (10), 213 (16), 188 (13), 166 (44), 162 (22), 144 (50), 143 (33), 142 (22), 136 (10), 135 (11), 117 (50), 115 (32), 106 (10), 105 (12), 90 (33), 44 (96); m^*=195,8
Ie	266 (100) 268 (96)	195 (55) 197 (52)	—	116 (20)	89 (44)	m^*=142,5
If	222 (100) 224 (35)	151 (58) 153 (25)	124 (12) 126 (4)	116 (21)	89 (36)	m^*=102,5
Ig	314 (100)	243 (61)	—	116 (37)	89 (50)	
Ih	204 (100)	133 (72)	105 (24)	—	—	203 (22), 132 (24), 104 (23), 78 (40), 77 (24); m^*=84,5
Ii	218 (100)	147 (42)	120 (7)	—	—	187 (32), 152 (6), 132 (42); m^*=159,5
Ij	188 (100)	117 (64)	90 (22)	116 (10)	89 (8)	187 (20), 118 (30), 80 (22)
Ik	202 (100)	131 (71)	104 (24)	116 (6)	—	130 (25), 103 (16), 96 (4), 91 (6), 78 (6), 77 (3); m^*=84,5
Il	218 (100)	147 (50)	—	—	—	203 (3), 132 (46), 104 (3), 77 (10); m^*=118,5, 99,5
Im	234 (100)	163 (41)	—	—	—	148 (20), 120 (60), 106 (8)
IIa	249 (100)	162 (45)	—	116 (26)	89 (25)	250 (27), 219 (27), 163 (26), 132 (28), 131 (5), 88 (9)
IIb	282 (100) 284 (96)	195 (90) 197 (87)	—	116 (80)	89 (91)	286 (10); m^*=102,5
IIc	288 (100) 240 (33)	151 (90) 153 (30)	—	116 (60)	89 (72)	241 (10)
IIh	220 (100)	133 (40)	—	—	—	222 (13), 221 (21), 219 (10), 203 (11), 160 (6), 134 (13), 107 (12), 88 (6), 78 (5)
IIi	234 (100)	147 (60)	120 (20)	—	—	236 (8), 235 (20), 233 (42), 148 (8), 121 (20), 88 (40)
IIj	204 (100)	117 (66)	90 (33)	116 (21)	89 (25)	205 (33), 118 (25); m^*=67,5
IIk	218 (100)	131 (95)	104 (20)	116 (18)	89 (5)	220 (12), 219 (20), 217 (32), 192 (20), 130 (18), 91 (25), 59 (15)
IIl	234 (100)	147 (48)	—	—	—	236 (8), 235 (18), 148 (8), 133 (4), 132 (39), 88 (3); m^*=118,5, 92,5
IIm	275 (100)	118 (3)	—	—	—	276 (30), 261 (32), 260 (100), 246 (8), 232 (11), 231 (14), 214 (7), 187 (7), 173 (16), 162 (9), 144 (21); m^*=206,5, 246,3
IIIa	202 (100)	131 (46)	—	116 (38)	—	m^*=102,5, 84,5
IIIb	202 (100)	117 (29)	—	116 (19)	89 (18)	118 (25), 90 (32)
IVa	218 (100)	131 (50)	—	116 (22)	—	174 (10)
IVb	218 (100)	117 (72)	—	116 (20)	89 (27)	220 (13), 219 (36), 118 (18), 91 (19), 90 (36)
Va	190 (23)	—	—	—	—	92 (15), 91 (100)
Vb	206 (32)	—	—	—	—	92 (15), 91 (100)
VIa	218 (100)	—	—	—	—	220 (12), 219 (35), 144 (3), 117 (71), 116 (17), 90 (16), 89 (8), 74 (43)
VIb	232 (100)	—	—	—	—	234 (16), 233 (32), 217 (10), 199 (10), 144 (16), 142 (17), 130 (8), 125 (7), 117 (16), 116 (25), 88 (75)

ability of the substituent in the benzene ring. As expected, the intensities of peaks A^3 and A^4 116 and 89 are also linearly dependent on the σ-constants of the substituents.

Table 2 and Scheme 4 show that the mass spectrometric fragmentation of 5-ethoxycarbonylmethylenehydantoins VII is much more complex than in the case of 5-arylidenehydantoins and their derivatives I-VI. The spectra of all compounds studied contain molecular ion peaks,

TABLE 2. Mass Spectra of Substituted 5-Carbethoxymethylidenehydantoins and Their Derivatives (VIIa-m)

Compound	M+	Ions characteristic for main paths of fragmentation												Other ions
		A^1	A^2	A^3	B^1	B^2	B^3	B^4	C^1	C^2	D^1	D^2	D^3	E	
VIIa	229 (100)	158 (3)	130 (3)	201 (72)	201 (72)	157 (6)	—	114 (26)	184 (50)	113 (3)	183 (35)	—	—	156 (6)	230 (15), 212 (11), 211 (6), 202 (5), 200 (10), 199 (10), 185 (10), 182 (7), 171 (10), 169 (6), 168 (6), 167 (6), 165 (24), 142 (6), 141 (30), 140 (28), 139 (26), 138 (11), 128 (8), 127 (7), 126 (7), 125 (36), 124 (13), 115 (14), 112 (11), 100 (6), 89 (7), 82 (5), 71 (14), 45 (18), 44 (12)
VIIb	218/220 (100/40)	147/149 (40/15)	119/121 (96/35)	75/77 (12/5)	190/192 (92/33)	146/148 (55/33)	118/120 (8/4)	103/105 (14/6)	173/175 (30/10)	102/104 (10/4)	172/174 (12/6)	—	—	—	118 (8), 71 (14); m^*=165,5, 112,2
VIIc	202 (100)	131 (38)	103 (90)	59 (15)	174 (34)	130 (31)	102 (10)	87 (7)	157 (15)	86 (12)	156 (3)	—	—	—	203 (13), 176 (6), 159 (4), 158 (10), 132 (3), 126 (10), 104 (7), 85 (8), 60 (6); m^*=149,8, 122,2, 97,2, 84,9, 80,9
VIIc-D	204 (40)	132 (40)	104 (44)	60 (10)	176 (20)	132 (45)	104 (44)	88 (4)	159 (18)	87 (9)	157 (12)	—	—	—	205 (10), 203 (100), 202 (98), 177 (3), 175 (45), 174 (42), 160 (11), 158 (16), 156 (7), 133 (5), 131 (72), 130 (31), 127 (7), 126 (8), 105 (3), 103 (65), 88 (4), 59 (9)
VIId	184 (85)	113 (28)	85 (38)	41 (10)	156 (80)	112 (74)	—	69 (15)	139 (100)	68 (34)	138 (20)	—	—	111 (4)	185 (14), 157 (12), 141 (21), 140 (26), 126 (30); m^*=132,5, 106,3, 90,2
VIIe	260 (100)	—	—	117 (33)	—	188 (6)	160 (4)	—	215 (40)	144 (32)	214 (96)	171 (72)	186 (11)	187 (14)	261 (20), 213 (23), 172 (14), 170 (10), 161 (13), 143 (62), 118 (20), 116 (30), 115 (35), 105 (6), 104 (8), 89 (25), 77 (3); m^*=176,1, 136,6, 119,5, 92,5
VIIe-D	262 (38)	—	—	118 (27)	—	190 (1)	—	—	217 (12)	145 (8)	215 (63)	171 (80)	187 (14)	189 (6)	263 (6), 261 (12), 260 (100), 216 (28), 214 (100), 213 (36), 188 (10), 186 (13), 172 (16), 170 (12), 161 (7), 143 (54), 119 (8), 117 (20), 116 (28), 115 (32), 90 (9), 89 (24), 77 (3)
VIIf	198 (50)	—	—	—	—	—	98 (4)	—	153 (27)	82 (8)	152 (100)	—	124 (62)	125 (8)	199 (10), 151 (10), 99 (6), 81 (7), 71 (8), 55 (8); m^*=116,1, 101,2
VIIf-D	200 (35)	—	—	—	—	—	100 (5)	—	155 (25)	—	154 (60)	—	126 (42)	127 (7)	199 (52), 198 (35), 153 (100), 152 (75), 125 (75), 124 (50), 99 (5), 98 (7), 83 (20), 82 (25), 81 (25), 72 (7), 71 (9), 56 (6), 55 (10)
VIIg	214 (100)	143 (22)	115 (36)	71 (18)	186 (4)	142 (10)	114 (3)	99 (4)	168 (8)	—	168 (35)	125 (10)	140 (40)	141 (15)	215 (100), 185 (43), 167 (6), 139 (20), 138 (4), 127 (26), 126 (10), 113 (13), 112 (5), 100 (3), 97 (3); m^*=159,7; 131,8, 116,2, 93,1, 90,2
VIIh	276 (100)	—	—	—	—	—	—	—	231 (3)	—	230 (3)	—	202 (26)	203 (41)	278 (8), 277 (22), 204 (10), 159 (21), 155 (7), 105 (3), 104 (10), 103 (4), 94 (30), 77 (4); m^*=149,3, 124,5
VIIh-D	278 (47)	—	—	—	—	—	—	—	—	—	231 (3)	—	203 (35)	205 (15)	279 (8), 277 (100), 276 (68), 204 (32), 202 (27), 160 (7), 159 (25), 131 (6), 105 (10), 104 (7), 103 (6), 95 (24), 94 (47), 71 (3)
VIIi	200 (38)	—	—	—	172 (18)	128 (4)	100 (4)	—	—	—	—	—	—	127 (26)	201 (5), 144 (36), 126 (100), 110 (10), 99 (8), 98 (20), 71 (6), 55 (12), 44 (25); m^*=147,5, 120,5, 103,6, 92,3, 76,1
VIIj	198 (38)	127 (3)	99 (16)	55 (45)	170 (6)	126 (38)	98 (7)	83 (16)	153 (100)	82 (95)	152 (88)	109 (15)	—	125 (5)	514 (17), 81 (18), 68 (14); m^*=145,9
VIIk	198 (52)	113 (3)	85 (32)	41 (25)	170 (25)	126 (55)	—	69 (14)	153 (100)	68 (88)	152 (15)	95 (22)	—	125 (4)	154 (22), 67 (24), 58 (30); m^*=145,9, 103,1, 118,2
VIIl	274 (100)	—	—	—	—	—	—	—	229 (27)	144 (19)	228 (95)	—	200 (29)	201 (20)	275 (24), 227 (31), 202 (25), 172 (13), 171 (43), 170 (6), 161 (10), 156 (17), 143 (39), 129 (10), 117 (27), 116 (17), 115 (6), 90 (10); m^*=189,7, 175,5
VIIm	304 (100)	—	—	—	—	—	—	—	259 (6)	174 (3)	—	—	—	231 (68)	306 (5), 305 (22), 247 (3), 232 (15), 218 (3), 217 (5), 189 (8), 183 (6), 174 (3), 173 (6), 155 (8), 154 (16), 153 (7), 146 (3), 127 (3), 126 (12), 118 (8), 105 (22), 94 (10), 78 (10), 42 (8); m^*=75,5

*VIIc-D, VIIe-D, VIIf-D, VIIh-D $R^1 = R^2 = D$.

the intensity of which is markedly dependent on the nature of the substituent and the exocyclic $C_{(\alpha)}$ atom. Further fragmentation of the molecular ions proceeds along at least five main paths (Scheme 4).

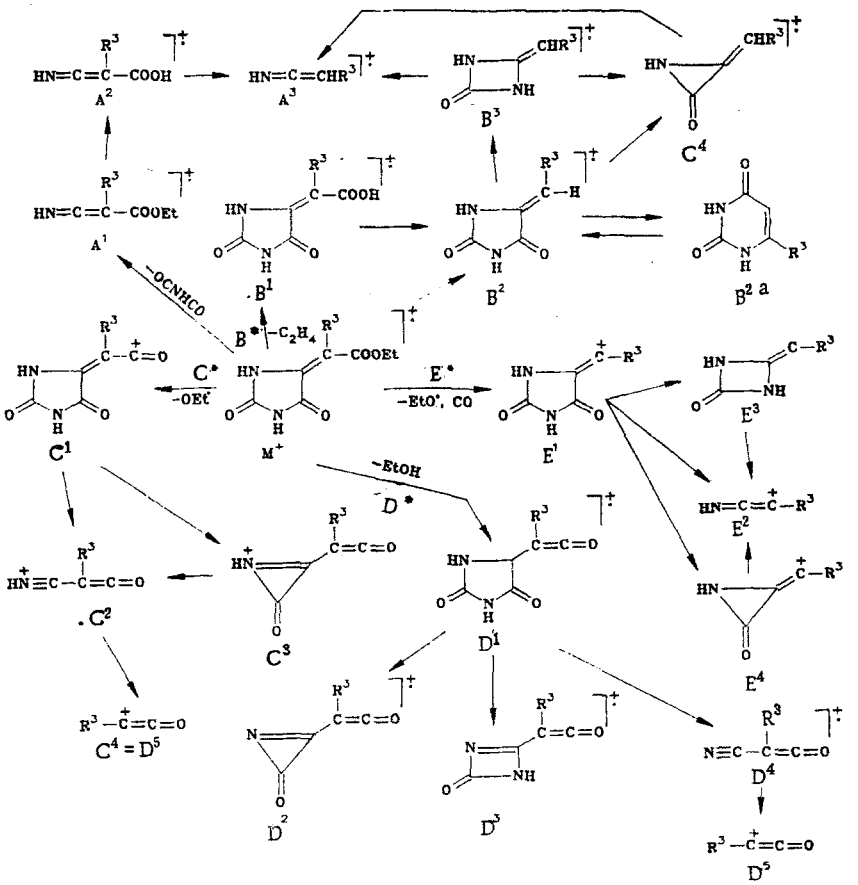
The first path is the splitting of the OCNHCO group (A), which is the main path in the case of 5-benzylidenehydantoins (I), is evident only for a few compounds (VIIb, d, g, j, k), and only in the spectra of fluoro- and chloro(ethoxycarbonylmethylene)hydantoins (VIIb, c), the peaks of ions A^1-A^3 have a high intensity.

The second path (B) is characterized by splitting of an ethylene molecule from the carbethoxyl group (the McLafferty rearrangement), leading to the formation of pseudomolecular ion B^1 (which in all cases is confirmed by the appearance of a metastable ion in the spectrum). Similarly to ion A^1 in the first path, ion B^1 loses the OCNHCO fragment or is decarboxylated, converting into ion B^2. In principle, ion B^2 can isomerize into ion B^{2a}, representing a molecular ion recorded during fragmentation of uracils under electron impact [5]. Unfortunately the conditions used for recording the spectrum did not make it possible for us to estimate this process, since in the spectra obtained, the intensity of ion B^2 (or B^{2a}) is low. Path B is characteristic of compounds VIIa-e, g, i-k. The peak intensity of ions B^2 increases proportionally to increase in the electron-donor properties of the substituent which clearly facilitate the decarboxylation of ion B^1.

The third path (C), the most general one (only the α-hydroxy derivative (VIIi) is an exception) begins with splitting of radical EtO: from the molecular ion. The peak intensity of cation C^1 thus formed decreases with increase in the electron-donor properties of the substituent at $C_{(\alpha)}$. Similarly to the molecular ion, ions B^1 and B^2, ion C^1 splits the OCNHCO or HNCO fragments (similarly as observed in the case of uracils [5]), to form ions C^2 and C^3, respectively.

The fourth path (D) includes the elimination of an ethanol molecule from the molecular ion. To clarify the mechanism of this process, we studied the mass spectra of 1,3-dideutero- and N-methyl derivatives of (ethoxycarbonylmethylene)hydantoins (VIIe, f, h, m). It was found that in the case of compounds VIId, f, g, j, k, the elimination of ethanol proceeds

Scheme 4



with splitting of a hydrogen atom from the substituent at $C_{(\alpha)}$, while in compounds VIIe, h, ℓ, hydrogen is split from the NH groups of the hydantoin ring.

The fifth path (E) occurs when a carboethoxyl group is split from the molecular ion, which leads to the formation of ion E^1. The intensity of its corresponding peaks increases proportionally to increase in the electron donor properties of the substituent at $C_{(\alpha)}$. The last fragmentation of ion E^1 proceeds in the same way as for other ions containing a hydantoin ring.

Table 2 shows that Scheme 4 does not completely describe the fragmentation of 5-(ethoxycarbonylmethylene)hydantoins (VII) under electron impact. The molecular ion of each of them is unique to a certain extent, which is due mainly, as already noted, to the influence of the substituent on the stability of the carbethoxy group, the hydantoin ring, the strength of the $C_{(5)}=C_{(\alpha)}$ bond and the possible splitting or fragmentation of the substituent itself. Thus, in the spectrum of the α-nitro derivative VIIa, very intense peaks of ions are observed, which are formed as a result of the elimination of nitro and nitroso compounds from the molecular and fragmentary ions, characteristic of nitro compounds. It is natural that the fragmentary ions thus formed decompose further, leading to the appearance of a large number of peaks in the spectrum, which are often fairly intense. In the spectrum of this compound there are also peaks of ions (M − 29) and (M − 17), corresponding to the elimination of the Et and OH groups. These are not observed in the spectra of other compounds in this group.

In the spectra of α-phenoxy-α-(ethoxycarbonyl)methylenehydantoins (VIIh, m) and the deutero derivative, in contrast to other compounds, including α-methoxyhydantoin VIIg, peaks are observed which correspond to ions formed as a result of splitting of a substituent, the phenoxy group, with migration of hydrogen atom from ring NH group.

It should here be noted that at not one of the fragmentation stages are halogens eliminated from the molecular ions of chloro- and fluoro(ethoxycarbonyl)methylenehydantoins VIIb, c.

In the spectrum of the α-hydroxy derivative VIIi there is an intense ion peak, corresponding to the elimination of CO and C_2H_4 fragments from the molecular ion, but this does not occur in the case of other compounds VII.

In all the cases studied, the character of the fragmentation of N-methyl(ethoxycarbonylmethylene)hydantoins (VIIj-m) is similar to that of the corresponding compounds unsubstituted at the nitrogen atom.

Thus, the observed character of the mass-spectrometric fragmentation of 5-arylidenehydantoins (I) and their 2-thio analogs (II) is due to selective elimination of the X=C–NH–C=O fragment and is independent of the nature the substituent at $C_{(2)}$ and also in the benzene ring. This ring also determines the intensity of the decomposition of the fragmentary ions. Replacement of the benzene ring or hydrogen at $C_{(\alpha)}$ in the carbethoxyl group leads to a much more complex fragmentation scheme as a result of a noticeable change in the stability of the hydantoin ring and ease of fragmentation of the carboxyl group itself, change in its stability under the influence of the substituent at $C_{(\alpha)}$ and fragmentation of the substituent itself. However, one of the main fragmentation processes of the molecular ions of (ethoxycarbonyl)methylenehydantoins or fragmentary ions containing a hydantoin ring is splitting of the O=C–NR–C=O fragment.

EXPERIMENTAL

We have already described [7] the synthesis and the confirmation of the structure of the compounds studied.

The mass spectra were recorded on an MX-1303 spectrometer at a ionization voltage of 30 eV, emission current of 150 μA, temperature of the ionic source of 150°C, with direct introduction of the sample. The temperature of the introduction of the samples into the ionic source was 100-125°C.

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ACYCLIC ANALOGS OF NUCLEOSIDES. SYNTHESIS OF HYDROXYALKYL DERIVATIVES OF 2-TRIFLUOROMETHYL- AND 2-TRIFLUOROMETHYLTHIOBENZIMIDAZOLE

A. É. Yavorskii, A. V. Stetsenko, I. V. Gogoman, V. N. Boiko, S. G. Zavgorodnii, A. I. Sobko, V. N. Tatskaya, V. G. Kvachev, and V. L. Florent'ev

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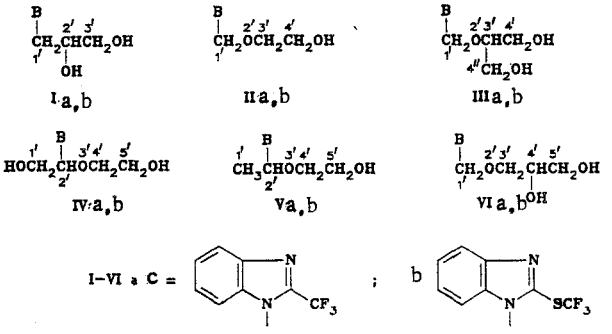
1-(2,3-Dihydroxypropyl)-, 1-(4-hydroxy-2-oxabutyl)-, 1-(3-hydroxymethyl-4-hydroxy-2-oxabutyl)-, 1-(1,5-dihydroxy-3-oxa-2-pentyl)-, 1-(5-hydroxy-3-oxa-2-pentyl)-, and 1-(4,5-dihydroxy-2-oxapentyl)-2-trifluoromethyl- and -2-trifluoromethylthiobenzimidazoles were obtained by condensation of trimethylsilyl derivatives of 2-substituted benzimidazoles with alkylating agents in the presence of $SnCl_4$ or by direct alkylation of the sodium salts of the heterocycles.

A great deal of attention is currently being directed to the study of acyclic analogs of nucleosides [1]. Continuing our previously commenced investigation [2] of the relationship between the structure and biological activity of analogs of nucleosides modified with respect to the sugar and heterocyclic base we studied the effect of the conjunction of the hydrophilic groupings of hydroxyalkyl substituents and hydrophobic substituents in the heterocyclic base on the biological activity of acyclic analogs of nucleosides. In this connection we synthesized a number of derivatives of 2-trifluoromethyl- and 2-trifluoromethylthiobenzimidazole:



2-Trifluoromethylbenzimidazole (VIIa) was obtained by the method in [3], while 2-trifluoromethylthiobenzimidazole (VIIb) was synthesized from 2-mercaptobenzimidazole:

Institute of Molecular Biology, Academy of Sciences of the USSR, Moscow 117984. T. G. Shevchenko Kiev State University, Kiev 252601. Ukrainian Scientific-Research Veterinary Institute, Kiev. All-Union Scientific-Research Institute of Biotechnology, Ministry of the Medical and Microbiological Industry of the USSR, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 632-636, May, 1988. Original article submitted November 14, 1986; revision submitted October 8, 1987.

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