MASS SPECTROMETRIC STUDY OF 2-KETO(THIO)TETRAHYDROPYRIMIDINE DERIVATIVES

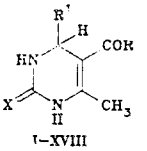
E. E. Stashenko, P. I. Zakharov,
V. G. Pleshakov, and B. S. Subbotin

UDC 543.51:547.853.7'854

The fragmentation pathways of 2-keto(thio)-6-methyl-5-carbethoxy(acetyl)-4-aryl-1,2,3,4-tetrahydropyrimidines were established using high resolution mass spectra and DADI spectra. An unusual rearrangement was observed, which involves cyclization of the aryl substituent in the 4 position with the oxygen of an ester group and elimination of a C_2H_5 radical.

Derivatives of 2-keto(thio)-1,2,3,4-tetrahydropyrimidines are potentially biologically active substances and also synthons for production of new heterocyclic compounds. In this respect, it is necessary to study their dissociative ionization in order to find a correlation between the structural data of the compounds and their mass spectra. The fragmentation of various pyrimidine derivatives has been studied in sufficient detail [1-3] and differs substantially from the mass spectral behavior of their hydrogenated analogs.

Earlier the decomposition patterns of uracil, thymine, and their derivatives [4, 5], and also of a few substituted 2-oxotetrahydropyrimidines [6] were found. In this work, the effects of the type of heteroatom in the 2 position of the tetrahydropyrimidine ring and the substituent in the ring on the stability of the molecular ion (M^+) and the character of its decomposition upon electron impact are studied for 2-keto(thio)-6-methyl-5-carbethoxy(acetyl)-4-aryl-1,2,3,4-tetrahydropyrimidines I-XVIII, which were not examined earlier:



I–XVIII

I—XI X=O, XII—XVIII X=S, I—III, XII R=CH_3, IV—XI, XIII—XVIII R=OC_2H_5; I, VI, XIII R^1=α-furyl II, VII, XIV R^1=C_6H_5, III, XI, XII, XVI R^1=C_6H_4-Br-*p*; IV R^1=CH_3, V R^1=CH=CHC_6H_5, VIII R^1=C_6H_4—OH-*p*, IX R^1=C_6H_3—OH-*p*, —OCH_3-*m*, X R^1=C_6H_3—OCH_3-*p*, —OCH_3-*m*, XV R^1=C_6H_4—OCH_3-*p*, XVII R^1=β-pyridyl XVIII R^1=γ-pyridyl

The M^+ peaks of I-XVIII have high to medium intensities (Table 1). Comparison of their stabilities (W_M) indicates that replacement of the carbonyl group in the tetrahydropyrimidines III, VI, VII, and XI by a thiocarbonyl increases W_M by 2-3 times (Table 2). This fact can be explained by the additional stability of the M^+ of XII-XIV, and XVI due to the lower electronegativity of the sulfur by comparison to the oxygen atom.

Replacement of the acetyl group in the 5 position of the tetrahydropyrimidines I-III and XII by a carbethoxy leads to a decrease in W_M by 1.5-2 times for compounds VI, VII, XI, and XVI. This is related to the appearance of additional decomposition pathways for M^+, involving elimination of the ester group. Introduction of electron-donating substituents in the benzene ring at atom $C_{(4)}$ of the tetrahydropyrimidine ring for VIII-X and XV increases the stability of M^+ while the presence of a Br atom lowers the W_M value for III, XI, and XVI by comparison to the unsubstituted analogs (Table 2).

P. Lumumba Peoples' Friendship University, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 360-365, March, 1989. Original article submitted September 24, 1987; revision submitted November 30, 1987.

0009-3122/89/2503-0301 $12.50

TABLE 1. Mass Spectra of Compounds I-XVIII*

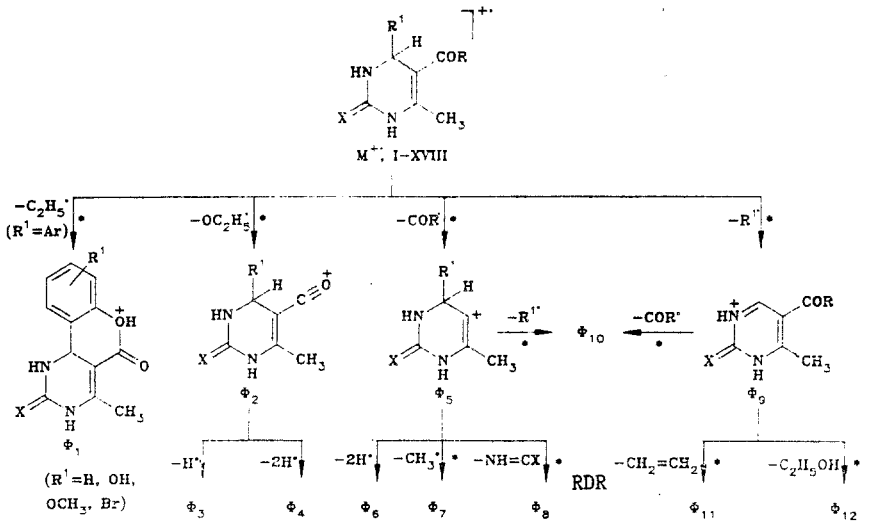
Compound	m/z value (I_{rel}, %) **
I	110 (8), 134 (17), 149 (13), 153 (15), 166 (22), 177 (100), 191 (22), 203 (24), 205 (14), 219 (13), 220 (M^+, 71)
II	51 (13), 77 (16), 110 (10), 144 (8), 153 (100), 172 (3), 185 (2), 187 (34), 215 (29), 229 (54), 230 (M^+, 71)
III	110 (14), 115 (8), 153 (100), *222* (13), 229 (11), *250** (2), *263* (1), *265* (18), *293* (22), *307* (31), *308* (M^+, 33)
IV	82 (7), 110 (17), 125 (10), 137 (41), 151 (5), 153 (15), 155 (58), 169 (7), 183 (100), 197 (7), 198 (M^+, 11)
V	110 (21), 115 (18), 137 (19), 155 (35), 183 (50), 211 (20), 213 (66), 240 (19), 257 (100), 285 (16), 286 (M^+, 99)
VI	110 (18), 134 (13), 155 (16), 162 (13), 177 (100), 183 (10), 203 (14), 205 (22), 221 (95), 233 (16), 250 (M^+, 56)
VI***	67 (6), 121 (14), 134 (1), 137 (4), 155 (10), 162 (7), 174 (4), 183 (24), 205 (3), 221 (5), 251 (MH^+, 100), 343 (MH + glycerin, 19)
VII	77 (22), 110 (10), 137 (22), 144 (6), 155 (40), 183 (100), 187 (40), 215 (9), 231 (51), 259 (4), 260 (M^+, 26)
VIII	110 (18), 137 (18), 155 (32), 183 (59), 201 (13), 203 (65), 231 (11), 247 (100), 261 (6), 275 (7), 276 (M^+, 31)
IX	110 (17), 137 (26), 155 (45), 183 (73), 231 (18), 233 (59), 260 (16), 261 (14), 277 (100), 305 (10), 306 (M^+, 47)
X	110 (19), 137 (31), 138 (29), 155 (43), 183 (83), 245 (17), 247 (65), 275 (15), 291 (100), 319 (11), 320 (M^+, 63)
XI	110 (14), 137 (22), 155 (35), 183 (100), 259 (4), *265* (23), *293* (6), *309* (35), *323* (2), *337* (3), *338* (M^+, 13)
XII	110 (26), 126 (6), *155* (4), 169 (100), *222* (8), 245 (9), *266* (5), *281* (26), *309* (20), *323* (40), *324* (M^+, 76)
XIII	126 (6), 134 (16), 153 (6), 178 (9), 193 (100), 199 (5), 221 (11), 237 (54), 249 (5), 265 (5), 266 (M^+, 98)
XIV	77 (20), 144 (12), 153 (13), 171 (31), 188 (9), 199 (100), 201 (11), 203 (47), 231 (11), 247 (55), 276 (M^+, 72)
XIV***	77 (8), 144 (5), 153 (5), 171 (9), 188 (3), 199 (17), 201 (3), 203 (5), 245 (8), 247 (9), 277 (MH^+, 100)
XV	126 (16), 153 (9), 171 (21), 175 (10), 199 (58), 218 (18), 231 (10), 233 (87), 261 (10), 277 (100), 306 (M^+, 82)
XVI	77 (5), 126 (11), 153 (11), *155* (13), 171 (29), 199 (100), 275 (2), *281* (32), *309* (7), *325* (49), *354* (M^+, 44)
XVII	79 (15), 145 (13), 153 (14), 171 (34), 189 (6), 199 (100), 204 (35), 232 (7), 248 (54), 276 (4), 277 (M^+, 85)
XVIII	78 (9), 126 (4), 145 (8), 153 (15), 171 (35), 189 (5), 199 (100), 204 (20), 232 (8), 248 (27), 277 (M^+, 73)

*The values of the molecular ion, M^+, and the 10 most intense peaks are given.
**m/z values calculated for ^{79}Br are given in italics.
***Spectrum obtained by fast atom bombardment.

Decomposition of the compounds studied is distinguished by low selectivity ($S_{1/2}$ = 5-10).* Analysis of their mass spectra, establishing the sequence of fragmentation by direct analysis of daughter ions (DADI) for I, VII, and XVII, and also the measurement of exact masses allow the dissociative ionization of 2-keto(thio)-1,2,3,4-tetrahydropyrimidines I-XVIII to be represented by the general scheme (see scheme on following page).

Fragmentation of compounds IV-XI and XIII-XVIII, which contain a carbethoxy group in the 5 position, is accompanied by elimination of C_2H_5 and OC_2H_5 radicals. The high intensity of the $[M - C_2H_5]^+$ fragment peak is characteristic only for the 4-aryl-substituted tetrahydropyrimidines and is explained by cyclization of the carbonyl group with the aromatic nucleus of the R^1 substituent, which leads to the formation of the stable cyclic structure Φ_1 (scheme). Such cyclization is not possible upon fragmentation of the 4-methyltetrahydropyrimidine IV since the ion peak of Φ_1 in this case has low intensity (Table 2). It is interesting to note that the analogous trend is also observed upon formation of the $[M - C_2H_5]^+$ fragments in the decomposition process of 2- and 4-aryl(alkyl)-3,5-diethoxycarbonyl-1,4-dihydropyridines [7, 8]. The ion peaks $[M - COR^1]^+$ and $[M - R^1]^+$ which are observed in the mass spectra of I-XVIII have high intensity and relay information on the

*Selectivity of decomposition, $S_{1/2}$, is defined as the number of peaks in the spectrum, the total intensities of which are 50% of the total ion current.



nature of the substituent in the 4 and 5 positions of the ring. The Φ_5 ion is further decomposed in two basic directions. The first is caused by aromatization of the tetrahydropyrimidine ring and results in the appearance of the Φ_6 and Φ_7 fragments (scheme). The second direction is related to the retrodiene decomposition of the ring (RDR), which is explained by the formation of the $[\Phi_5 - NH{=}CX]^+$ ion, the appearance of which in the mass spectra of I-XVIII allows the nature of the heteroatom X to be defined. It is interesting to note that RDR occurs even in the first step of dissociative ionization during the fragmentation of uracil and thymine [4, 5].

The $[M - R^1]^+$ ion is further decomposed, similarly eliminating a molecule of ethylene and ethanol from the carbethoxy group, which leads to the formation of the Φ_{11} and Φ_{12} fragments. Their elemental composition was confirmed by high resolution mass spectra of VII and XIV (Table 3). The Φ_{10} ion, as analysis of the DADI spectra of I, VII, and XVII showed, is formed by loss of R^1 and COR radicals from the Φ_5 and Φ_9 fragments, respectively.

The decomposition of 2-keto(thio)-1,2,3,4-tetrahydropyrimidines I-XVIII is sensitive to structural changes in their molecules and can be used for analytical purposes. If the phenyl substituent R^1 in the 4 position of the tetrahydropyrimidine ring is not substituted or contains an electron-accepting group on the ring, then the $C_{(4)}-R^1$ bond is markedly weakened and the $[M - R^1]^+$ peak is observed with maximal intensity (Table 2). Loss of the

TABLE 2. Intensities of Characteristic Fragment Peaks in the Mass Spectra of Compounds I-XVIII

Compound	M^+ (W_M)	$S_{1/2}$	Σ_{50}, % Total ion content														
			$[M-H]^+$	$[M-CH_3]^+$	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9	Φ_{10}	Φ_{11}	Φ_{12}	R^{1+}
I	11,7	10	1,9	2,1	—	—	—	—	14,8	0,7	1,3	2,5	2.2	1,2	—	—	1,6
II	14,0	5	10,2	5,5	—	—	—	—	6,4	0,4	0,6	1,5	18,9	1,9	—	—	3,0
III	10,3	6	9,5	6,9	—	—	—	—	5,7	0,3	0,6	1,0	15,3	2,1	—	—	1,2
IV	3.0	5	1,9	13,5	1,9	4,1	—	1,4	2,7	—	2,3	1,8	13,5	2,3	15.7	11,1	—
V	13,4	8	1,9	0,2	13,3	1,7	2,2	0,8	7,8	2,4	0,5	0,8	5,9	2,5	4.2	2,3	1,2
VI	6,9	10	0,8	0,2	6,2	2,4	0,8	1,5	10,8	0,9	1,4	1,4	1,1	1,9	1,7	1,4	1,4
VII	5,8	5	0,7	0,5	9,6	1,7	1,7	0,9	7,5	1,9	1,1	1,1	18,7	1,9	7,5	4,1	4,1
VIII	5,8	6	1,1	0,9	16,2	1,8	1,5	1,3	10,5	2,1	0,8	1,0	9,5	2,9	5.2	2,9	0,6
IX	6,0	9	1,1	0,7	11,3	1.6	1,8	0,9	6,6	2,0	1,8	0,5	8,2	1,9	5,1	2.9	0,5
X	7,2	9	1,1	0,9	9,9	1,5	1,5	1,4	6,4	1,7	1,1	0,4	8,2	1,9	4,2	3,1	0,5
XI	4,3	8	0,9	0,6	10,6	1,6	1,4	0,7	6,2	0,9	0,9	0,6	14,5	2,0	5,1	3,2	1,2
XII	19,8	5	10,0	5,1	—	—	—	—	6,4	—	1,3	1,9	12,6	0,8	—	—	1,1
XIII	16.9	6	0,9	0,3	7,4	1,9	0,4	0,9	17,2	0,8	1,6	2,9	0,9	1,0	0.7	1,0	1,6
XIV	12.4	7	0,7	0,3	7,9	1,4	0,6	0,5	6,8	1,6	1,3	1,7	14,4	1,2	4,5	1,9	2,9
XV	12,8	6	1,2	0.5	13,2	1.3	1,0	0,9	11,5	1,3	2,4	1,3	7,7	2,1	2.8	1,2	0,5
XVI	11,6	6	1,1	0.5	12,9	1,8	0,5	0,5	8,4	0,6	1,1	1,1	13,2	1,5	3,8	1,5	0,7
XVII	12,7	6	0,6	0,3	8,1	1,0	0,3	0,4	5,2	0,7	0,9	1,9	15,0	0,7	5,1	2,1	1.8
XVIII	13,8	6	0,6	0,4	5,1	1,5	0,8	0,6	3,8	0,8	0,9	1,6	18,9	0,8	6.6	2,8	0,7

TABLE 3. Elemental Composition of Characteristic Ions of Compounds I, IV, VI, VII, IX, XIII, XIV, and XVII from High Resolution Mass Spectra

Compound	M+	Exact mass: found	Exact mass: calculated	Elemental composition	Ion	Relative intensities of isobaric ions
I	203	203.0832	203.0818	$C_{11}H_{11}N_2O_2$	$[M-OH]^+$	
	191	191.0824	191.0818	$C_{10}H_{11}N_2O_2$	$[M-CHO]^+$	
	177	177.0663	177.0662	$C_9H_9N_2O_2$	Φ_5	
	166	166.0750	166.0740	$C_8H_{10}N_2O_2$	$[M-C_3H_2O]^+$	
IV	169	169.0600	169.0611	$C_7H_9N_2O_3$	Φ_1	
	155	155.0454	155.0455	$C_6H_7N_2O_3$	Φ_{11}	
VI	221	221.0559	221.0560	$C_{10}H_9N_2O_4$	Φ_1	3
		221.0921	221.0923	$C_{11}H_{13}N_2O_3$	$[M-CHO]^+$	2
VII	172	172.0640	172.0635	$C_{10}H_8N_2O$	Φ_7	3
		172.0773	172.0760	$C_{11}H_{10}NO$	$[M-OC_2H_5,\ -NHCO]^+$	1
	155	155.0459	155.0455	$C_6H_7N_2O_3$	Φ_{11}	
	137	137.0343	137.0350	$C_6H_5N_2O_2$	Φ_{12}	
IX	190	190.0826	190.0860	$C_{11}H_{12}NO_2$	Φ_8	
	110	110.0482	110.0479	$C_5H_6N_2O$	Φ_{10}	
XIII	249	249.0703	249.0695	$C_{12}H_{13}N_2O_2S$	$[M-OH]^+$	
	237	237.0326	237.0332	$C_{10}H_9N_2O_3S$	Φ_1	4
		237.0690	237.0695	$C_{11}H_{13}N_2O_2S$	$[M-CHO]^+$	1
XIV	171	171.0259	171.0227	$C_6H_7N_2O_2S$	Φ_{11}	
	153	153.0102	153.0122	$C_6H_5N_2OS$	Φ_{12}	
	144	144.0798	144.0811	$C_{10}H_{10}N$	Φ_8	
XIV	126	126.0243	126.0251	$C_5H_6N_2S$	Φ_{10}	1
		126.0012	126.0013	C_5H_4NOS	$[M-C_6H_5,\ -C_2H_5OH,\ -HCN]^+$	1
XVII	202	202.0449	202.0438	$C_{10}H_8N_3S$	Φ_6	
	189	189.0371	189.0360	$C_9H_7N_3S$	Φ_7	3
		189.0647	189.0662	$C_{10}H_9N_2O_2$	$[M-C_2H_5,\ -NHCS]^+$	1

C_2H_5 radical becomes the dominant decomposition direction of VIII-X and XV upon introduction of electron-donating groups into the aromatic ring of the R^1 substituent. The driving force for formation of the $[M - C_2H_5]^+$ fragment is the subsequent cyclization of the carbonyl group with the aromatic nucleus so that the increase in its nucleophilicity facilitates the indicated process.

Fragmentation of the tetrahydropyrimidines I, VI, and XIII which contain the α-furyl radical is characterized by formation of the $[M - COR]^+$ ion with maximal intensity independent of the nature of the R and X substituents. The low intensity of the $[M - R^1]^+$ fragment indicates a strengthening of the bond between the tetrahydropyrimidine ring and the furyl substituent. Besides this, peaks explained by the dissociation of a furan ring are observed in the mass spectra of these compounds (Table 3).

Compounds I-XVIII are slightly volatile substances and their mass spectra must be taken at high temperatures (>250°C) which can cause thermal effects related to decomposition of the molecules upon ionization. Thus, we used the fast atom bombardment method (FAB) which does not require preliminary vaporization of the sample by heating [9]. Peaks of the protonated molecular ions (MH^+) have maximal intensity in the mass spectra of VI and XIV obtained by FAB. Decomposition of VI also leads to formation of the cluster ion [M + glycerin]$^+$ with m/z 343 (Table 1). The dominant fragmentation direction of VI and XIV upon FAB is loss of the R^1 radical and subsequent decay of the $[M - R^1]^+$ ion which is formed. Formation of the Φ_1 and Φ_2 fragments, which are related to the dissociation of the carbethoxy group, is unexpectedly strongly suppressed by comparison to the electron impact mass spectra. Since these ions cannot be products of thermal decomposition, this fact is explained by the ionization conditions of FAB.

EXPERIMENTAL

Mass spectra were obtained on a LKB-2091 using an ionizing potential of 70 V, a cathodic emission current of 300 μA, an acceleration potential of 3 kV, and a temperature program

(10°C/min; 50-300°C). Exact masses were determined on a Varian MAT-311A instrument with resolution of 10000 by peak comparison. DADI spectra were obtained on a Varian MAT-112 instrument by direct sample introduction in the source at an electron energy of 70 eV and an ionization chamber temperature of 180°C. Spectra of VI and XIV, obtained by FAB, were taken on a Varian MAT-311A instrument. A beam of ionized Xe with 1-3 W power, accelerating potential of 3 kV, and a glycerine matrix were used for ionization of samples.

Substituted 2-keto(thio)-1,2,3,4-tetrahydropyrimidines I-XVIII were obtained according to [10, 11]. Their identity, composition, and structure were confirmed by elemental analysis, IR, UV, PMR, and mass spectra.

The authors thank O. S. Anisimova and V. G. Zhil'nikova for the DADI and FAB spectra.

LITERATURE CITED

1. L. Yu. Ivanovskya, M. I. Gorfinkel, V. F. Sedova, and Z. D. Duhovenko, Org. Mass Spectrom., 7, 911 (1973).
2. T. Kate et al., Org. Mass Spectrom., 9, 981 (1974).
3. X. Hasapis et al., Tetrahedron, 35, 2087 (1979).
4. E. Falch, Acta Chem. Scand., 24, 137 (1970).
5. C. Fenselau and S. Y. Wang, Tetrahedron, 25, 2853 (1969).
6. L. Yu. Ivanovskaya, V. F. Sedova, M. I. Gorfinkel', and V. P. Mamaev, Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 4, 123 (1969).
7. E. L. Esmans, R. A. Domisse, and F. C. Alder-Weikeldt, Org. Mass Spectrom., 10, 854 (1975).
8. A. Selva, A. Gennaro, and P. Caramella, Org. Mass Spectrom., 11, 117 (1976).
9. G. D. Tantsyrev and V. A. Saraev, Secondary Ion and Ion-Photon Emission [in Russian], Khar'kov (1980), p. 73.
10. P. Biginelli, Berichte, 24, 1317 (1981).
11. K. Folkers, H. J. Harwood, and T. B. Johnson, J. Am. Chem. Soc., 54, 3751 (1932).

DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN BRIDGEHEAD POSITIONS.

17.* EFFECT OF SUBSTITUENTS IN BENZO[b]-1,4-DIAZABICYCLO[2.2.2]-OCTENE ON PROTON AFFINITY AND OPENING BY CHLOROFORMATE ESTER

A. A. Gall', S. O. Doronina,
G. V. Shishkin, A. A. Voityuk,
and A. A. Bliznyuk

UDC 547.863.13'895'493:541.6:543.422.25

The reaction of benzo[1',2'-b]-1,4-diazabicyclo[2.2.2]octene with chloroformate ester is accompanied by opening of the diazabicyclo fragment and addition of chloroformate ester. A nitro group in the 4' position lowers the rate constant for opening by 40 times in comparison to the unsubstituted heterocycle, while a 4' methoxy group practically does not affect the reaction rate. The ratio of the 6- and 7- substituted 1-(β-chloroethyl)-4-ethoxycarbonyl-1,2,3,4-tetrahydroquinoxalines which are formed agrees with a quantum chemical calculation of the proton affinity and indicates a principally inductive effect of the substituents on the reactivity of the heteroatoms.

*For Communication 16, see [1].

Institute of Bioorganic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 366-371, March, 1989. Original article submitted July 21, 1987; revision submitted January 6, 1988.

0009-3122/89/2503-0305 $12.50