MASS SPECTROMETERIC STUDY OF THIOCARBAMOYL-SUBSTITUTED 2-AMINOTHIAZOLES AND 2-IMINO-THIAZOLINES.

2.* N-THIAZOLYL- AND N-THIAZOLINYLIDENE-N'-PERACETYL GLYCOSYLTHIOUREAS

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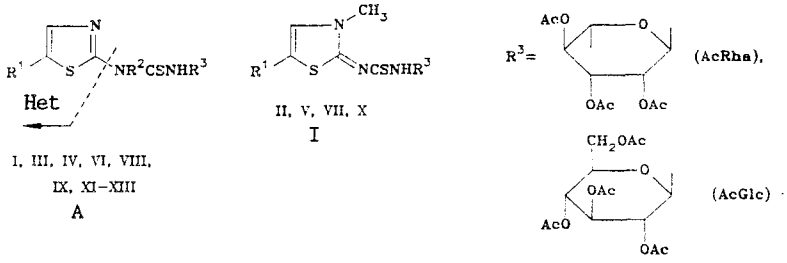
The mass spectra of isomeric peracetylated glycosides, substituted in the $C_{(1)}$-position with thiazolyl and thiazolinylidene thioureido groups, reveal qualitative and quantitative differences in the processes associated with elimination of fragments containing the thioureido functional group. We have studied, in addition to cleavage of the acetoxy groups in the glycosidic units, the fragmentation processes of the carbohydrate unit.

We have previously [1] characterized the mass spectra of alkyl- and alkenylthioureido derivatives of thiazole with amino and imino structures. Our goal in the present paper was to study the mass spectra of isomeric N-thiazolyl- and N-thiazolinylidene-N'-peracetylglycosylthioureas and to analyze the spectral differences associated with the amino- and imino-structures, which are retained upon replacement of alkyl groups by peracetylglycosyl substituents. The overall mass spectral characteristics of this class of compounds is of special interest since these compounds are synthons for the preparation of modified nucleosides [2].



I, II R^1=H, III—V R^1=CH_3, VI—VIII R^1=C_2H_5, IX, X R^1=n-C_3H_7, XI R^1=n-C_4H_9, XII, XIII R^1=n-C_5H_{11}; I, III, VI, VIII, IX, XI—XIII R^2=H, II, IV, V, VII, X R^2=CH_3; I—VII, IX—XII R^3=AcGlc, VIII, XIII R^3=AcRha

Molecular ion peaks (M^+) were detected in the spectra of all of the compounds studied; the stabilities of the molecular ions (W_M) are on the average two orders of magnitude lower than in the corresponding alkyl and alkenyl derivatives [1].

Compared to the analogous aliphatic derivatives, the fragmentation processes in the peracetylated glycosides I-XIII are more complex in nature, due to the existence of competing decay pathways or processes for the carbohydrate unit. Three principal pathways can be discerned for the appearance of daughter or fragment ions: 1) decay via cleavage of the bond between the heterocycle and the thiourea unit in a direction analogous to that observed in the corresponding alkyl(alkenyl)-substituted thioureas [1]; 2) cleavage of the substituents and destruction of the pyranose ring, occurring directly from M^+; 3) cleavage of the NH=R^3

*Communication 1, see [1].

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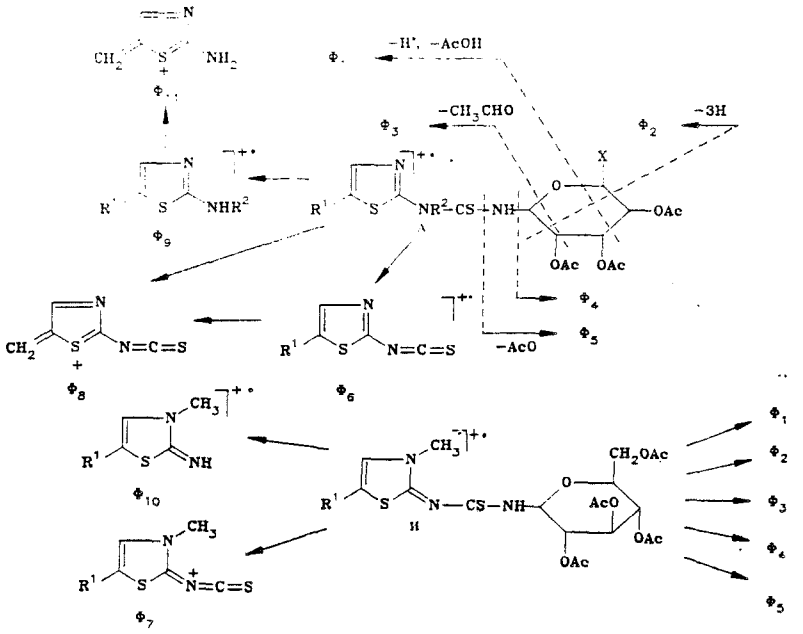
bond with the formation of Φ_4 ions (331* for glucoside acetates, or 273 for rhamnoside acetates), which undergo further decay the same as related acetates of the corresponding monosaccharides [3].



I, III, IV, VI, IX, XI, XII X=CH_2OAc, VIII, XIII X=CH_3

The spectra of most of the compounds investigated herein contain Φ_5 ion peaks (288 or 230). These ions have retained the carbohydrate and part of the thiourea units. R_3NCS fragments and the products of its subsequent decomposition were not detected in these spectra. In addition, most of the spectra also contain 101 and 88 ion peaks, corresponding to the composition $C_4H_7O_2N$ and $C_3H_6O_2N$, respectively, which incorporate the elements of the pyranose ring and the nitrogen atom closest to it.

With respect to the principal analytical peaks characterizing the amino-imino structure, the spectra of compounds I-III and V follow the principles previously elaborated [2]. The most characteristic ions for the amino form (A) are Φ_6 and Φ_9, for the imino form (I) Φ_7. In a quantitative sense, however, in the case of amino compounds there is a substantial increase in the contribution of thiazolylisothiocyanate ion peaks, relative to thiazolylamine ions. This property has a tendency to decrease as the length of the radical R^1 is increased, but parallel with this trend the products of β-cleavage of the alkyl radical, with concomitant formation of Φ_8 and Φ_{11} ions (Table 1), are also observed in the case of amino derivatives; the latter ions Φ_8 and Φ_{11} may possibly possess stable structures, thiazinylisothiocyanate and aminothiazine, respectively. In the spectra of the imino compounds VII and X, which contain $R^1 = C_2H_5$ and C_3H_7, on the other hand, peaks due to fragments associated with β-cleavage of the alkyl chain are not present; this provides an additional factor for the identification of amino- versus imino- structural types.

Comparing the mass spectra of all of the amino derivatives studied, including the data in the previous paper [1], we conclude that the contribution due to Φ_6, given identical R^1 groups, increases as the number of π-bonds in the substituent R^3 increases, in the series CH_3, C_3H_5, AcRha, AcGlc, but only if the molecule contains an easily migrating hydrogen atom (i.e., if $R^2 = H$). If this hydrogen atom is replaced by a methyl group (compound IV), pronounced redistribution of the intensities of the characteristic ion peaks is observed. The maximum peak becomes that due to the Φ_9 ion (128), while the Φ_6 ion peak disappears.

Intense peaks due to $[M - AcOH]^+$, $[M - AcOH, - AcO]^+$, and $[M - 2AcOH, - AcO]^+$ ions are observed in the mass spectra of compounds I-XIII; peaks due to $[M - 2AcOH, - C_2H_2O]^+$ and $[M - 3AcOH, - AcO]^+$ ions, on the other hand comprise only 1-3% relative intensity, and are characteristic primarily of amino-structural type glycosides.

*The numbers given to characterize the ions are their respective m/e values.

TABLE 1. Mass Spectra of Compounds I-XIII

Compound	m/e value (I, %)*										
	M^+	W_M	$[M-AcOH]^+$	$[M-AcOH, AcO]^+$	$[M-2AcOH, -AcO]^+$	Φ_1	Φ_2	Φ_3	Φ_4	$[\Phi_4-AcOH]^+$	$[\Phi_4-AcOH, -C=O]^+$
I	489 (1,1)	0,12	429 (5)	370 (10)	310 (4)	270 (2)	270 (2)	199 (7)	331 (22)		243 (10)
II	503 (0,1)	0,02	443 (9)	384 (5)	324 (3)	284 (3)	284 (3)		331 (17)	271 (8)	
III	503 (1,2)	0,19	443 (4)	384 (9)	324 (3)	284 (13)	284 (13)	213 (2)	331 (23)	271 (4)	243 (11)
IV	517 (2,2)	0,30	457 (1)	398 (2)	338 (1)	298 (5)	298 (5)		331 (34)	271 (4)	
V	517 (1,2)	0,41	457 (21)	398 (10)	338 (4)	298 (5)	298 (5)		331 (2)	271 (1)	
VI	517 (5,5)	0,91	457 (6)	398 (10)	338 (4)	298 (16)	298 (16)	227 (3)	331 (6)	271 (1)	243 (8)
VII	531 (0,3)	0,09	471 (5)	412 (3)	352 (1)	312 (1)	312 (1)		331 (16)	271 (3)	
VIII	459 (6,0)	0,56	399 (13)	340 (14)	280 (10)	298 (21)	240 (2)	227 (7)	273 (42)	213 (12)	185 (13)
IX	531 (0,3)	0,05	471 (2)	412 (2)	352 (2)	312 (3)	312 (3)		331 (4)	271 (3)	243 (10)
X	545 (0.1)	0,03	485 (1)	426 (1)	366 (1)	326 (1)	326 (1)		331 (33)	271 (9)	
XI	545 (0,7)	0,20	485 (1)	426 (1)	366 (1)	326 (2)	326 (2)		331 (5)	271 (1)	243 (2)
XII	559 (3,1)	0,77	499 (4)	440 (9)	380 (3)	340 (12)	340 (12)	269 (2)	331 (3)	271 (1)	243 (6)
XIII	501 (6,9)	0,80	441 (25)	382 (41)	322 (29)	340 (51)	282 (4)	269 (22)	273 (36)	213 (63)	185 (6)

Compound	m/e value (I, %)*									
	$[\Phi_4-AcOH, -CH_2C=O]^+$	$[\Phi_4-2AcOH, -CH_2C=O]^+$	$[AcOCH=CH-CHOAc]^+$	Φ_5	Φ_6	Φ_7	Φ_8	Φ_9	Φ_{10}	Φ_{11}
I		169 (72)	157 (22)	288 (3)	142 (100)			100 (47)		
II	229 (5)	169 (100)	157 (9)	288 (3)		157 (64)			114 (33)	
III		169 (94)		288 (2)	156 (100)			114 (38)		
IV	229 (4)	169 (44)	157 (15)	288 (1)				128 (100)		
V		169 (13)				171 (100)			128 (12)	
VI		169 (19)			170 (96)		155 (100)	128 (28)		113 (42)
VII	229 (2)	169 (100)	157 (3)			185 (66)			142 (77)	
VIII	171 (37)	111 (59)	157 (30)	230 (2)	170 (87)		155 (97)	128 (75)		113 (100)
IX		169 (24)	157 (8)	288 (1)	184 (38)		155 (100)	142 (18)		113 (53)
X	229 (3)	169 (100)	157 (27)	288 (1)		199 (22)			156 (23)	
XI		169 (13)		288 (1)	198 (36)		155 (100)	156 (21)		113 (32)
XII		169 (11)		288 (2)	212 (34)		155 (100)	170 (11)		113 (32)
XIII	171 (16)	111 (44)	157 (14)	230 (4)	212 (27)		155 (69)	170 (44)		113 (100)

*The ions Φ_6-Φ_{11} characterize differences between isomeric structures.

TABLE 2. Characteristics of the Newly Synthesized Compounds

Compound	Molecular formula	mp, °C	Recrystallization solvent	Yield, %
I	$C_{18}H_{23}N_3O_9S_2$	89...90	Benzene	63
II	$C_{19}H_{25}N_3O_9S_2$	96,5...97	Benzene–hexane	46
III	$C_{19}H_{25}N_3O_9S_2$	117...118	Benzene–hexane	78
IV	$C_{20}H_{27}N_3O_9S_2$	133...134,5	Benzene–hexane	95
V	$C_{20}H_{27}N_3O_9S_2$	208...209	Alcohol	90
VI	$C_{20}H_{27}N_3O_9S_2$	154...155	Benzene–hexane	96
VII	$C_{21}H_{29}N_3O_9S_2$	185...187	Alcohol	95
VIII	$C_{18}H_{25}N_3O_7S_2$	85...86,5	Benzene–hexane	89
IX	$C_{21}H_{29}N_3O_9S_2$	160,5...161	Benzene–hexane	77
X	$C_{22}H_{31}N_3O_9S_2$	148...149	Alcohol	97
XI	$C_{22}H_{31}N_3O_9S_2$	154...155	Benzene–hexane	52
XII	$C_{23}H_{33}N_3O_9S_2$	158...159	Benzene–hexane	89
XIII	$C_{21}H_{31}N_3O_7S_2$	81...22	Benzene–hexane	92

In the spectra of all of the glycosides examined there is a peak due to an $[M - 219]^+$ ion (Φ_1 and Φ_2); the ion peak is of variable intensity and its elemental composition suggests the possibility that there are two variations available for cleavage of the carbohydrate unit, as indicated in the fragmentation scheme. The fact that both pathways apparently occur is confirmed by analysis of the spectra of rhamnosides VIII and XIII, where the ions corresponding to the two possible fragmentation types have different mass numbers (298 and 240 in compound VIII, and 340, 282 in compound XIII) and elemental compositions.

In the majority of cases involving amino-structural type compounds, their spectra contain ion peaks due to Φ_3, which are also of variable intensity and which are formed via cleavage of the $C_{(1)}$–O and $C_{(2)}$–$C_{(3)}$ bonds in the carbohydrate unit. Fragmentation along the $C_{(1)}$–$C_{(2)}$ and $C_{(5)}$–O bonds leads to ions of the type Het-NR^2(S)NHC≡O$^+$, which are characteristic of glycosides [4]; peaks due to these ions are observed, however, only in the spectra of compounds XII and XIII (256).

Of the number of ions in the second group which are present in these spectra, a peak due to a fragment of composition $C_7H_9O_4$ (157) deserves attention, since it has a significant intensity in the spectra of most of the compounds examined. The structure of this ion has been discussed previously [3], but the process responsible for its formation has not been investigated. Based on the spectra of the metastable defocused ion Φ_7 in the case of peracetylglucoside VI and peracetylrhamnoside XIII, the nature of the process for its formation can differ substantially. In compound VI the Φ_4 ion undergoes sequential elimination of $C_3H_4O_2$ from $C_{(5)}$, a molecule of AcOH from the $C_{(3)}$ atom, and C_2H_2O. In compound XIII, in contrast, the 157 ion forms via cleavage of a molecule of AcOH from the Φ_4 ion, followed by elimination of a C_3H_4O moiety.

The spectra of compounds VIII and IX also contain a component of the 157 ion, having the composition $C_4H_3N_3S_2$, which corresponds to an ion of the type [Het-NHC(S)NH-R^1]$^+$.

We have thus found that the same diagnostic criteria which were found useful for distinguishing isomeric structures in the case of N-thiazolyl-N'-alkylthioureas [1] are also characteristic of the mass spectra of N-thiazolyl-N'-peracetylglycosylthioureas and their imino analogs (R^1 = H, CH_3). In addition, it has been shown that as the length of the alkyl chain in R^1 is increased, additional mass spectral factors appear which make it possible to distinguish isomeric forms.

EXPERIMENTAL

An MX 1310 mass spectrometer featuring direct sample introduction SVP-5 was used in this study. The ionizing voltage was 50 V, the collector current 40 μA, and the temperature of the injection ampoule and ionization chamber 80-90°C. Accurate mass measurements were made with a resolution capacity of 8000. The calibration substance was perfluorokerosene. Defocusing: E/H = constant; scanning the acceleration voltage 2.0-4.5 kV at a rate of 0.1 kV/sec.

The characteristic properties of the newly synthesized compounds are given in Tables 1 and 2. The results of C, H, N elemental analysis of compounds I-XIII agreed with calculations.

N-Thiazolyl-N'-peracetylglycosylthioureas (I, III, IV, VI, VIII, IX, XI-XIII). To a solution of 5 mmoles 2-aminothiazole or 1,5-substituted aminothiazole in dry benzene or acetone was added with stirring an equivalent amount of tetra-O-acetyl-β-D-glucopyranosylisothiocyanate (compounds I, III, IV, VI, IX, XI, and XII) or tri-O-acetyl-α-L-rhamnopyranosylisothiocyanate (compounds VIII, XIII) in several portions. The reaction mixture was refluxed 1-6 h while the course of the reaction was monitored by TLC; the solution was evaporated to dryness in air, and the residue was worked up with dilute HCl, followed by water, then dried and recrystallized.

N-Thiazolinylidene-N'-peracetylglycosylthioureas (II, V, VII, X). To a suspension of 20 mmoles 2-imino-3-methylthiazoline iodohydrate or its 5-substituted homolog in 25 ml dry acetone was added with stirring an equimolar amount of dry triethylamine followed by portions of 20 mmoles tetra-O-acetyl-β-D-glucopyranosylisothiocyanate; the mixture was refluxed 1-3 h, then evaporated to dryness. The residue was washed with water, dilute HCl, and water again, and then dried and recrystallized.

LITERATURE CITED

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