Mass Spectra of Diketopiperazines derived from Aranotin and Related Metabolites

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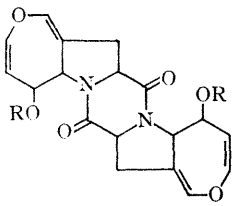
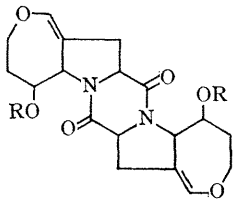
Summary The mass spectra of twenty diketopiperazines reveal four general modes of cleavage.

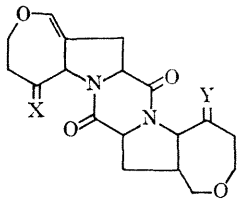
THE mass spectra of metabolites[1] containing the disulphide-bridged diketopiperazine moiety do not seem to show a common fragmentation pattern. However, the mass spectra of the diketopiperazines† obtained by desulphurization of these metabolites lend themselves to a simple but general diagnosis, and the data presented here can be used effectively in structural problems.



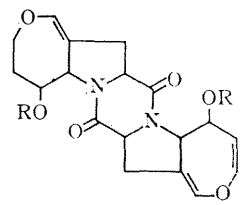
(2) R=Ac (3) R=H



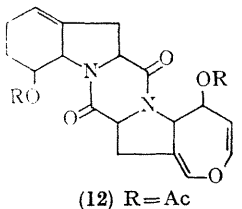
(4) R=Ac (5) R=H



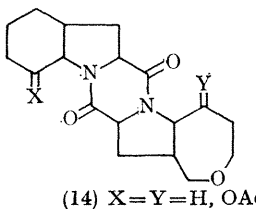
(6) X=Y=H, OAc
(7) X=Y=H, OH
(8) X=Y=O
(11) X=O, Y=H, OCH_2·SMe



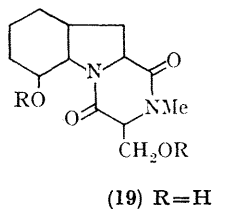
(9) R=Ac
(10) R=H



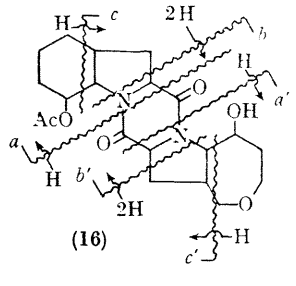
(12) R=Ac
(13) R=H)



(14) X=Y=H, OAc
(15) X=Y=H, OH
(16) X=H, OAc; Y=H, OH
(17) X=Y=O
(18) X—H, OCH_2·SMe; Y=O



(19) R=H
(20) R=Ac



(16)

Molecular ions are evident in the mass spectra of gliotoxin[2c] and sporidesmin,[4] but not in mass spectra of acetylaranotin[1] and acetylapoaranotin.[5] A comparison of the mass spectra of nineteen desulphurized derivatives, (2—20) obtained from acetylaranotin, acetylapoaranotin, and gliotoxin, along with the model prolylproline diketopiperazine (1), show a remarkably consistent fragmentation pattern.

All the diketopiperazines examined show a molecular ion. There are four general modes of cleavage in diketopiperazines, and these are exemplified above for (16). Elimination of CO or CHO, amine fragmentation (*a* and *a'*), diketopiperazine fragmentation (*b* and *b'*), and elimination of the ring adjacent to the prolyl moiety (*c* and *c'*). The last two fragmentations are observed only in saturated diketopiperazines. The diketopiperazines (1), (7), (8), (15), (16), and (17) show peaks due to $M^+ - CO$ ions. However, the compounds (2), (3), (9), (10), (12), and (13) give rise to peaks due to $M^+ - CHO$. The amine fragment which arises from cleavage *a* and *a'* is present in the mass spectra of all the diketopiperazines. In amine fragments containing a readily expellable group, peaks due to the amine fragment are not present, but peaks due to the amine fragment which has expelled its substituent are observed [(2) and (4)]. These two amine fragments constitute the most important diagnostic evidence for structure elucidation of diketopiperazines. This fragmentation occurs with the transfer of one hydrogen from the rest of the molecule. In symmetrical diketopiperazines (1—8), fragmentation *a* and *a'* give identical amine fragments while in unsymmetrical diketopiperazines (9—20) the cleavage *a* and *a'* yield two amine fragments (Table). Similarly, in symmetrical saturated diketopiperazines fragmentations *b*, *b'* and *c*, *c'* afford identical fragments, respectively, while unsymmetrical saturated diketopiperazines yield different fragments. The fragmentations *b*, *b'* and *c*, *c'* take place with the transfer of 2H and 1H, respectively, from the rest of the molecule. An analysis of the mass spectra of the deuteriated alcohols (3), (5), (7), (10), (13), (15), (16), and (19) reveal that peaks arising from fragmentations *a*, *a'*; *b*, *b'*;

† The mass spectra of diketopiperazines (2,5-dioxopiperazines, cyclodipeptides) have not been examined in detail, though some work has been done in this field.[2] The closely related amino-acids and peptides have been studied exhaustively.[3]

and *c*, *c* show increments in mass consistent with a mechanism involving the hydroxyl hydrogen in the hydrogen transfer in the above three cleavages. However, the ratio of the intensity of M^+ to that of the fragments arising from cleavage *a*, *a'*; *b*, *b'*; and *c*, *c'* of both the deuteriated and undeuteriated alcohols indicates that the above mechanism is not the sole mode of hydrogen transfer.

Hydrolysis of acetate (14) with methanolic potassium carbonate afforded the diol (15) as the major product. The n.m.r. spectrum of the minor, less polar, product is consistent with a monoacetate of (15), but it is impossible to decide from the n.m.r. evidence which of the acetyl groups had been preferentially hydrolysed. An analysis of its mass spectrum firmly established the structure of the monoacetate as (16). Similarly, the location of the sulphur-containing substituent in (18) was again established from its mass spectrum.

Mass spectra data of diketopiperazines[a]

	%	Molecular ion composition	Base peak (100%) *m/e*	Fragment *a*, *a'* *m/e*	Fragment *a*, *a'* — substituent *m/e*	%	Fragment *b*, *b'* *m/e*	%	Fragment *c*, *c'* *m/e*	%
(1)[b]	100	$C_{10}H_{14}O_2N_2$	194	70	67					
(2)[b]	3	$C_{22}H_{22}O_8N_2$	80			134	45			
(3)[b]	6	$C_{18}H_{18}O_6N_2$	340	152	14	134	73			
(4)[b]	7	$C_{22}H_{26}O_8N_2$	43			136	50			
(5)[b]	100	$C_{18}H_{22}O_6N_2$	362	154	15	136	20			
(6)	21	$C_{22}H_{30}O_8N_2$	390	198	18	138	31	282	5	321	17
(7)[b]	71	$C_{18}H_{26}O_6N_2$	279	156	27	138	8	240	22	279	100
(8)[b,c]	90	$C_{18}H_{22}O_6N_2$	306	154	58	126	70			277	18
(9)[b]	2	$C_{22}H_{24}O_8N_2$	384	196	3	136	60				
						134	50				
(10)	30	$C_{18}H_{20}O_6N_2$	342	154	15	136	39				
				152	23	134	38				
(11)[b,d]	1	$C_{20}H_{28}O_6N_2S$	348	154	38	126	2	238	13	277	73
						138	4				
(12)[b]	9	$C_{22}H_{24}O_7N_2$	368	180	20	120	51				
						134	41				
(13)[b]	22	$C_{18}H_{20}O_5N_2$	315	138	22	120	80				
				152	2	134	15				
(14)[b]	12	$C_{22}H_{30}O_7N_2$	374	182	30	122	40	226	4	305	10
				198	8	138	29	282	4		
(15)	45	$C_{18}H_{26}O_5N_2$	263	140	24	122	14	224	17	263	100
				156	12	138	10	240	88	279	15
(16)[b]	100	$C_{20}H_{28}O_6N_2$	392	182	19	122	33	266	5	305	81
				156	13	138	16	240	4		
(17)	97	$C_{18}H_{22}O_5N_2$	110	138	72	110	100	222	11	261	18
				154	23	126	81	238	3		
(18)[b]	2	$C_{20}H_{28}O_5N_2S$	304			122	31				
				154	60	126	24	238	12		
(19)[b]	7	$C_{13}H_{20}O_4N_2$	158	140	25	122	10				
				74	26			158	100	197	25
(20)	20	$C_{17}H_{24}O_6N_2$	292	182	20	122	32				
				116	20			200	27	239	9

[a] The n.m.r., i.r., and u.v. spectra of all diketopiperazines were consistent with the assigned structures. All the compounds gave correct elemental analysis, except the acetates (6), (14), and (20). These acetates resisted crystallization. However, they were chromatographically homogenous, and their corresponding alcohols were crystalline.

[b] The high-resolution mass spectra of these compounds gave correct composition of all ions mentioned in the table, within the error of ± 5 millimass units.

[c] There was no peak due to fragment *b*, but a peak at *m/e* 210 (40%) with composition $C_{10}H_{14}O_3N_2$ was present.

[d] There was no peak due to fragment *c*, but a peak at *m/e* 263 (29%) with composition $C_{14}H_{19}O_2N_2$ was present.

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[5] N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Letters*, 1968, 4467.