THE STRUCTURE OF RIMOCIDIN: MASS SPECTROMETRIC ANALYSIS OF DERIVATIVES OF THE ANTIBIOTIC*

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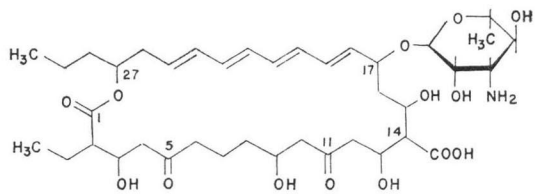
The utility of various derivatives of rimocidin in assigning its structure by means of mass spectrometry is discussed.

The antifungal antibiotic rimocidin had been isolated from the culture of *Streptomyces rimosus* by DAVISSON *et al.*[2] The chemical studies performed by COPE *et al.*[3,4] led to a proposition for the structure of the aglycone moiety. These results had been revised in our laboratory and the structure of rimocidin established as **I** (Fig. 1).[1] One year later, PANDEY and RINEHART[5] confirmed our results.

Results and Discussion

The field desorption mass spectrometry had been successfully applied for the determination of molecular weights of various antibiotics.[6] However, polyene macrolides containing in the molecule an aminosugar moiety did not reveal mass spectra enabling the determination of their molecular weights.[6] Searching for derivatives of rimocidin, simple in preparation, formed in unambiguous reactions and with high yields, we synthesized the methyl esters of N-acetyl-dimethoximes of rimocidin (**II**) and octahydrorimocidin(**III**). Both derivatives preserved the structural features of the parent substances, and their field desorption mass spectra exhibited molecular ions as base peaks at *m/e* 881 and 889 respectively.

Fig. 1. The structure of rimocidin.



I

The N-acetyl-di-methoximino-rimocidin methyl ester (**II**) under treatment with acetic anhydride in pyridine at $-10°C$ yielded a hexa-O-acetyl derivative (**IV**). The electron impact mass spectrum of **IV** (Table 1) exhibited prominent molecular ion at *m/e* 1133 and clusters of elimination ions formed by the loss of acetoxyl, acetic acid, methanol and mycosamine or mycosaminyloxy moieties:

a) P-AcO - *n*-AcOH (1074, 1014, 954, 894)
b) P-AcO - MeOH - *n*-AcOH (1042, 982, 922, 862, 802, 742)
c) P-mycosamine - *n*-AcOH (844, 784, 724, 664, 604)

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Table 1. Ions observed in the EI mass spectrum of N-acetyl-hexa-O-acetyl-di-methoximino-rimocidin methyl ester (IV).

m/e	Relative intensity %	m/e	Relative intensity %	m/e	Relative intensity %	m/e	Relative intensity %	m/e	Relative intensity %	m/e	Relative intensity %
*											
43	100	128	37	541	4	636	3	802	2	982	4
44	37	129	22	543	2	664	2	844	2	983	3
45	81	142	23	573	4	665	2	846	3	1014	3
60	83	156	20	574	2	693	3	862	5	1015	2
84	22	169	21	575	2	694	2	863	2	1042	2
101	37	212	20	604	2	695	2	892	3	1074	2
102	56	230	22	605	2	724	4	894	3	1133	3
110	22	272	94	632	2	725	3	922	6	1134	2
111	25	273	34	633	10	742	3	923	5		
115	23	**		634	5	784	2	924	3		
117	22	497	2	635	4	785	2	954	2		

Ions of relative intensities above: * 20% and ** 2% have been tabularized.

d) P-mycosamine - AcO - *n*-AcOH (785, 725, 665, 605)

e) P-mycosamine - AcO - MeOH - *n*-AcOH (693, 633, 573)

The salient feature of the spectrum in the mass region below *m/e* 300 is the presence of ions derived from the mycosamine moiety: 272, 230, 212, 169, 156, 142, 102 and 101. This part of the spectrum in large measure superimposes with that obtained for N-acetyl-2,4-di-O-acetyl-mycosamine (**V**). The identity of the above-mentioned ions in the spectra of **IV** and **V** had been confirmed by means of high resolution mass spectrometry. Compound **V** had been obtained from the peracetylated derivatives of rimocidin under treatment with hydrogen chloride in methylene chloride at room temperature. We established, that under these conditions only the glycosidic bond in allylic position is cleaved. The mass and NMR spectra of **V** were identical with appropriate spectra of the acetylated aminosugar derived from peracetylated amphotericin B[7]. This gave the evidence for the same ring size and conformation of the mycosamine moieties in both antibiotics.

Further structural informations revealed from the electron impact mass spectra of the hexa-O-trimethylsilyl derivatives of N-acetyl-di-methoximino-methyl esters of rimocidin (**VI**) and octahydrorimocidin (**VII**) as well as N-acetyl-hexa-O-trimethylsilyl-octahydrorimocidin methyl ester (**VIII**). In all these spectra the molecular ions were significant (Table 2). Of dominating intensities in the mass spectra of persilylated derivatives were the ions formed as a result of the elimination of the trimethylsilanol and the substituted aminosugar moieties. Exemplary for that fragmentation could be the

Fig. 2 The structure of N-acetyl-di-methoximino-hexa-O-trimethylsilyl-octahydrorimocidin methyl ester and its main fragmentation pattern in the electron impact mass spectrum.

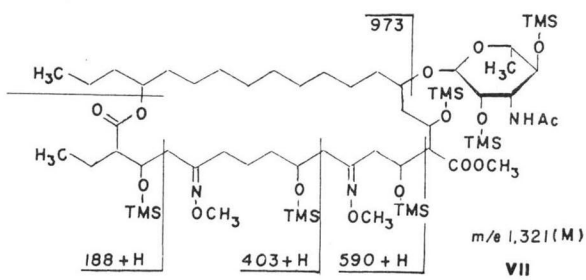

Table 2. Ions observed in the mass spectra of the methyl esters of N-acetyl-di-methoximino-hexa-O-trimethylsilyl-rimocidin (**VI**), N-acetyl-di-methoximino-hexa-O-trimethylsilyl-octahydrorimocidin (**VIII**), and N-acetyl-hexa-O-trimethylsilyl-octahydrorimocidin (**VIII**).

Compound **VI**		Compound **VII**						Compound **VIII**			
m/e	Relative intensity %	*m/e*	Relative intensity %	*m/e*	Relative intensity %	*m/e*	Relative intensity %	*m/e*	Relative intensity %	*m/e*	Relative intensity %
*		*		**				*			
47	22	47	25	469	5	885	5	41	30	915	2
73	92	73	100	476	4	941	2	43	54	916	1
75	84	75	90	478	2	942	3	55	50	1062	1
110	21	89	24	501	6	943	3	57	63	1158	2
117	27	103	26	502	4	944	2	67	24	1159	1
129	28	110	32	559	6	945	3	69	51	1160	1
131	31	116	32	591	6	946	2	71	54	1173	1
133	23	117	38	592	3	971	6	73	45	1174	1
143	35	129	57	593	2	972	5	75	90	1221	1
152	51	130	38	640	2	973	11	81	36	1247	4
171	33	131	50	641	2	974	8	83	38	1248	4
173	25	132	26	642	2	975	5	95	38	1249	3
200	37	133	48	643	2	1014	2	97	36	1250	1
217	21	143	55	646	2	1198	2	98	20	1263	1
242	32	145	28	671	2	1199	2	109	20	1264	1
332	100	147	24	672	2	1200	4	117	22		
333	64	152	71	673	2	1201	4	129	42		
404	25	158	43	695	2	1202	3	130	20		
**		159	26	731	2	1203	2	131	29		
562	2	170	28	732	2	1231	3	143	35		
591	3	171	57	759	3	1232	3	145	24		
756	2	173	71	760	3	1233	2	149	22		
757	3	174	33	761	3	1276	2	152	24		
847	2	175	24	762	4	1277	2	158	20		
875	4	184	38	763	3	1278	2	173	100		
876	4	189	23	764	2	1288	4	195	33		
877	3	200	50	791	6	1289	4	217	98		
952	2	204	28	792	3	1290	5	242	20		
953	2	212	45	793	5	1291	7	285	27		
966	2	217	98	794	3	1292	5	303	37		
981	3	242	62	811	2	1293	5	332	78		
982	2	244	28	823	2	1294	3	333	38		
***		246	31	849	3	1304	4	404	20		
1187	1	247	24	851	4	1305	4	***			
1281	2	258	28	852	3	1306	7	505	3		
1282	2	273	34	853	3	1307	6	523	3		
1283	1	275	26	854	4	1308	4	524	2		
1284	1	303	52	855	5	1309	2	537	2		
1312	1	314	24	856	2	1319	7	555	5		
1313	2	332	83	867	3	1320	7	556	2		
1314	1	333	63	869	3	1321	11	627	1		
		334	35	879	3	1322	10	645	5		
		348	62	880	2	1323	6	646	2		
		404	67	881	27	1324	3	735	1		
		405	48	882	13			825	2		
		406	29	883	22			826	1		
		420	20	884	10						

Ions of relative intensities above: * 20%, ** 2% and *** 1% have been tabularized.

Table 3. Ions observed in the mass spectra of N-acetyl-N-methyl-undeca-O-methyl-tetradecahydrorimocidin (**IX**) and its hexadeuterio analogue (**X**).

m/e	Relative intensity (%) IX	X	m/e	Relative intensity (%×10) IX	X	m/e	Relative intensity (%×10) IX	X	m/e	Relative intensity (%×100) IX	X
*			383	—	11	620	3	—	****	—	15
71	19	17	391	18	—	621	3	—	863	—	15
72	10	16	394	—	10	622	5	—	864	—	20
75	13	11	395	—	10	623	3	—	904	30	—
87	11	12	397	10	—	624	—	3	907	—	8
97	10	—	***			625	—	3	908	—	10
98	—	10	475	3	—	635	8	—	909	—	11
101	17	20	477	4	—	636	4	—	910	—	10
129	31	20	478	—	3	637	7	—	915	45	—
130	—	11	479	—	4	638	4	—	916	30	10
131	27	—	480	—	7	639	3	4	920	30	11
132	—	10	481	3	6	640	—	6	921	—	13
133	—	10	482	—	3	641	—	8	922	—	10
142	11	15	484	—	3	642	—	5	932	30	—
156	11	13	489	3	—	643	—	3	934	30	—
201	23	25	491	4	—	651	3	—	936	50	—
211	10	—	493	4	—	652	6	—	937	30	6
212	—	11	507	4	—	653	7	—	938	—	8
230	100	100	509	5	—	654	6	—	939	—	8
231	12	16	511	—	5	655	3	—	940	—	8
243	23	—	512	—	10	657	—	3	941	—	7
244	—	15	513	—	10	667	3	—	942		10
246	16	17	514	—	5	668	3	—	943	—	6
**	Relative intensity (%×10)		515	—	3	669	4	—	946	15	—
			539	3	—	670	3	—	947	38	—
251	—	31	541	4	—	672	—	5	948	15	—
253	—	10	543	—	5	673	—	8	949	22	—
255	—	10	544	—	9	674	—	4	953	—	5
256	—	15	545	—	9	701	9	—	954	—	6
257	10	—	546	—	5	702	5	—	963	15	—
275	60	—	547	—	3	703	—	6	964	38	—
276	10	18	571	5	—	704	—	14	965	17	—
277	20	18	572	3	—	705	—	19	969	—	5
281	20	—	573	6	—	706	—	8	970	—	5
283	19	32	574	3	—	707	—	3	971	—	5
284	—	12	575	3	3	731	6	—	977	15	—
295	30	—	576	—	6	732	3	—	978	16	—
297	—	10	577	—	8	733	20	—	979	15	—
298	—	11	578	—	5	734	12	—	983	—	3
299	—	10	579	—	3	735	3	—	984	—	2
314	—	10	603	5	—	736	—	4	985	—	3
327	24	—	604	3	—	737	—	8			
329	—	10	605	6	—	738	—	10			
330	—	10	606	3	—	739	—	8			
331	—	11	607	3	4	740	—	4			
339	—	10	608	3	8	834	4	—			
359	11	—	609	—	10	858	4	—			
362	—	10	610	—	6	860	10	—			
364	11	—	611	—	3	861	5	—			
369	—	10	619	3	—	862	4	—			

Ions of relative intensities above * 10%, ** 1%, *** 0.3% and **** 0.03% have been tabularized.

spectrum of **VIII** and the series of ions P-mycosamine - *n*-TMSOH: 825, 735, 654 and 555.

Of prominent intensities were the ions derived from the aminosugar moiety: *m/e* 332, 242 and 152. The presence of significant ions formed by the cleavage of the carbon-carbon and the lactone bonds of the macrolide ring allowed the location of the oxygen functions in the antibiotic: ions at *m/e* 189, 404, 314, 591, 501 and 469 for **VI**, and **VII** (Fig. 2), and 285 and 195 for **VIII**.

The final location of the oxygen functions in rimocidin, including the position of carbonyls, had been assigned upon analysis of the mass spectra of N-acetyl-N-methyl-undeca-O-methyl-tetradecahydrorimocidin (**IX**) and its hexadeuterio analogue (**X**) (Table 3). The most characteristic features of the fragmentation patterns of these compounds had been shown in our previous paper[1].

The utility of various derivatives for elucidation of the structure of the antibiotic should be characterized as following: The simplest derivative of rimocidin which revealed prominent molecular ions in the F.D. mass spectrum was its N-acetyl-di-methoxime-methyl ester; substitution of the ketone with methoxime, the carboxyl with methyl ester, acylation of the amino group and further acetylation or silylation of the hydroxyls afforded derivatives where E.I. mass spectra exhibited prominent molecular ions as well as elimination and fragmentation ions significant for the assignment of the structure of the antibiotic; diagnostic for the placement of the oxygen functions in the molecule of the antibiotic were the E.I. mass spectra of permethylated tetradecahydrorimocidin, its hexadeuterio analogue and the persilylated octahydrorimocidin.

GOLDING *et al.*[8] applied the E.I. high resolution mass spectrometry for the determination of the molecular weights and elemental composition of lagosin, filipin and their decahydro derivatives. More detailed discussion of the mass spectra of persilylated polyene macrolides had been published by HAEGELE and DESIDERIO.[9] The authors prepared these derivatives in the reaction with hexamethyldisilazane-trimethylchlorosilane mixture in pyridine. In these conditions the chromophore of the antibiotic is partially degraded, whereas complete substitution of the hydroxyl groups and minimum decrease of the UV extinction coefficient during the silylation procedure had been achieved by using trimethylsilylimidazol (TSIM) in pyridine or nonpolar solvents like heptane, cyclohexane and carbon tetrachloride*.

The peracetylated derivatives, in contradiction to the persilylated, are stable in polar solvents. That property enables isolation of pure compounds and elucidation of their structure by means of various spectroscopic techniques. The mass spectra of peracetylated derivatives are more complicated as compared to the spectra of trimethylsilyl ethers, however, they had been successfully applied in structure assignment of peracetylated polyene macrolides which do not contain an aminosugar moiety.[9,11]

The permethyl ethers could be obtained for hydrogenated antibiotics and in rather low yields because of the drastic conditions of the reaction. Their advantages are the stability, thermal as well as chemical, and lower molecular weights as compared to the persilyl derivatives. That type of derivatives had been applied in our laboratory for the elucidation of the structure of perimycin A.[12]

Experimental

Instrumental analysis

The mass spectra were obtained on a Varian MAT 711 double focusing spectrometer by means of a direct introduction probe. The instrumental conditions were as follows: (a) electron impact mode—

* Unpublished data obtained by one of us (L.F.) in Dr. E. C. HORNING Laboratory, Institute for Lipid Research, Houston, USA.

electron energy, 70 eV; emission current, 0.8 mA; accelerating voltage, 8 kV; ion source temperature, 250°C; resolution (10% valley definition), 1,000 and 10,000 for exact mass determinations; (b) field desorption mode—wire heating current, 14~18 mA; ion source temperature, 70~100°C, accelerating voltage, 8 kV; extraction voltage, −4 kV.

The ^{1}H NMR spectra were measured on a 80 MHz Tesla BS-487 instrument. The IR and electronic spectra were recorded on UR-10 and UV-VIS Carl Zeiss Jena instruments.

General procedures

Thin-layer chromatography has been performed on DC-Alufolien Kieselgel 60 (Merck). The spots were visualized with cerium sulphate (1%), molybdenic acid (2.5%) in 10% sulphuric acid. The column chromatography has been carried out on silica gel 60 minus 0.063 mm (above 230 mesh ASTM, Merck). Solvents were removed under reduced pressure using a rotatory evaporator. Magnesium sulphate was used as drying agent for the solvents. Solid samples were dried under reduced pressure at room temperature in the presence of phosphorus pentoxide.

The silylation procedure

Five mg of analyzed compound was suspended in 1 ml of toluene - pyridine - N-trimethylsilylimidazole (10: 1: 1, v/v) mixture, left overnight and the solvents removed at room temperature under reduced pressure (0.1 mmHg). Two ml of heptane had been added to the residue, the mixture centrifuged, the supernatant concentrated to 0.2 ml and further used for the mass spectrometric measurements.

Rimocidin

The crude antibiotic ($E^{1\%}_{1cm}$ 380 at 304 nm) had been supplied by Pharmaceutical Works Tarchomin "Polfa" as a fermentation product of a standard strain of *S. rimosus*. It has been purified by means of counter-current distribution in solvent system chloroform - methanol - water (2 : 2 : 1, v/v). After 250 transfers the solvents were concentrated with butanol. The crystalline substance was centrifuged, washed with ethyl ether and dried. $E^{1\%}_{1cm}$ 1,025 at 304 nm, IR: 1010, 1070, 1110, 1140, 1170, 1190, 1270, 1405, 1575, 1630, 1715, 2930, and 3450 cm^{-1}.

N-Acetylrimocidin

Two g of rimocidin was suspended in 10 ml of methanol - pyridine (5 : 1, v/v), cooled to 0°C stirred and a mixture of methanol - pyridine - acetic anhydride (2 : 2 : 1) was added dropwise. The reaction was completed after 3 hours (TLC, solvent system, ethyl acetate - acetic acid - water (4 : 1 : 1, v/v)). The product was precipitated with ethyl ether, washed with ethyl ether, hexane, centrifuged and dried. Yield 1.43 g, $E^{1\%}_{1cm}$ 900 at 304 nm.

N-Acetyl-di-methoximino-rimocidin

To a solution of 400 mg of rimocidin in 6 ml of pyridine, 40 mg of methoxime hydrochloride has been added and left overnight at room temperature. The mixture was poured into 50 ml of butanol, the organic solvent washed with water, concentrated and worked up as described above. Yield 340 mg, $E^{1\%}_{1cm}$ 910 at 304 nm.

N-Acetyl-di-methoximino-rimocidin methyl ester

To a cooled solution of 200 mg of N-acetyl-di-methoximino-rimocidin in 20 ml of methanol a solution of diazomethane in ethyl ether was added dropwise until the substitution of the carboxylic group was completed. The reaction was controlled by means of TLC in the solvent system, chloroform - methanol - water (50 : 30 : 3, v/v). After addition of 10 ml of butanol the solution was concentrated to 5 ml, the product precipitated with hexane - ethyl ether (1 : 1, v/v) and worked up as described for rimocidin. Yield 150 mg, $E^{1\%}_{1cm}$, 890 at 304 nm, F.D. mass spectrum, ions at *m/e* (rel. int): 864 (23%), 866 (23%), 868 (22%), 879 (32%), 880 (86%), 881 (100%), 882 (46%), 889 (22%), 893 (20%), 894 (24%), 895 (27%), 896 (23%).

Octahydrorimocidin

The octahydro derivative of rimocidin had been obtained according to the procedure described by COPE *et al.*[3] The product was purified by means of chromatography on silica gel with the solvent system, chloroform - ethyl acetate - methanol - water (200 : 100 : 40 : 15, v/v).

Methyl esters of octahydrorimocidin, N-acetyloctahydrorimocidin and its dimethoxime

These compounds have been prepared analogically to appropriate derivatives of rimocidin. F.D. mass spectrum of N-acetyl-di-methoximino-octahydrorimocidin methyl ester; *m/e* (rel. int), 855 (26%), 859 (28%), 860 (20%), 885 (28%), 886 (22%), 887 (96%), 888 (80%), 889 (100%), 890 (35%).

Hexa-O-acetyl-di-methoximino-rimocidin methyl ester

To a cooled (−15°C) and stirred solution of 300 mg N-acetyl-di-methoximino-rimocidin methyl ester in 5 ml of pyridine, 20 ml of pyridine - acetate anhydride (2 : 1, v/v) has been added dropwise, the mixture was left for 24 hours at −10°C, and then poured on ice. The product was extracted with chloroform, the solvent washed with water, dried and concentrated. The derivative was precipitated with hexane, centrifuged, washed with hexane and dried. Yield 250 mg, $E^{1\%}_{1cm}$ 750 at 304 nm. It was further purified by means of chromatography on silica gel in the solvent system, chloroform - ethyl acetate (5 : 1, v/v) and the fractions directly used for the mass spectrometric analysis.

N-Acetyl-N-methyl-undeca-O-methyl-tetradecahydrorimocidin

To a stirred suspension of 100 mg of N-acetyloctahydrorimocidin methyl ester in 10 ml of tetrahydrofuran 70 mg of lithium borohydride in 10 ml of tetrahydrofuran has been added and the mixture refluxed for 3 hours. The excess of reducing agent has been decomposed by addition of acetone (10 ml) and methanol (10 ml). The solution was acidified with Dowex 50(H^+), concentrated and purified on silica gel in the solvent system, chloroform - ethyl acetate - methanol - water (100 : 100 : 90 : 15, v/v). Yield 76 mg, F.D. mass spectrum ions at *m/e* (rel. int): 809 (37%), 810 (70%), 811 (100%), 812 (50%), 838 (33%).

The polyol obtained was suspended in 5 ml of tetrahydrofuran and stirred for 48 hours with 300 mg of sodium hydride and 0.3 ml of methyl iodide. The work up was accomplished by addition of 20 ml of benzene, the organic solvent washed successively with water - acetic acid (10 : 1, v/v), water, dried and evaporated. The residue was purified on silica gel in the solvent system, chloroform - ethyl acetate - benzene - methanol (80 : 40 : 30 : 5, v/v) and analyzed directly by means of mass spectrometry.

Acknowledgement

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