Communications to the editor

THE STRUCTURE OF RIMOCIDIN

Sir:

Rimocidin is an antifungal antibiotic isolated from the culture of *Streptomyces rimosus*[1]. The partial structure of the antibiotic including the structure of its aglycone moiety (Fig. 1) was postulated by COPE *et al.*[2,3] The data obtained in our laboratory prompted us to revise the structure of rimocidin aglycone and enabled us to postulate the complete structure of the antibiotic (Fig. 2).

Fig. 1. The structure of rimocidinolide according to COPE *et al.*[3]

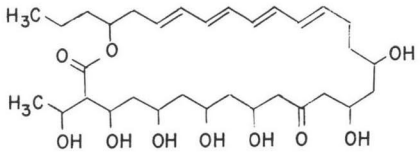
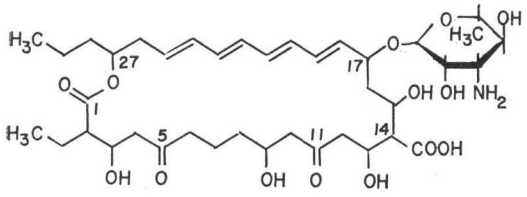


Fig. 2. The structure of rimocidin **I**.



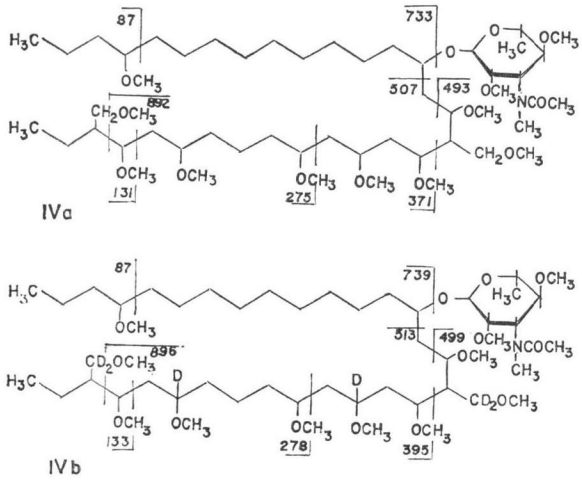
Rimocidin (**I**),* its methoxime, octahydrorimocidin and their N-acetylated derivatives dissolved in methanol react with diazomethane yielding appropriate methyl esters. Their IR spectra exhibited characteristic shift of the carbonyl oscillation band as compared to the parent compounds (up to 1730 cm^{-1}) with simultaneous disappearence of the carboxylate ion band (at 1580 cm^{-1}). The presence of one carboxyl group in the molecule was established by potentiometric titration of N-acetyloctahydrorimocidin (neutralization equivalent 804).

In all known polyene macrolides the mycosamine moiety is attached to the aglycone in allylic position to the chromophore. These substances treated with a diluted solution of hydrogen chloride in methanol yield free aminosugar, whereas the cleavage of the glycosidic bond of hydrogenated substances needs drastic conditions and provides the methyl glycosides only.[4] Rimocidin reacts analogically, which points to a similar attachment of the mycosamine moiety. Formation of a pentaenal **II** (λ_{max}377 nm and ϵ=50,000, ν cm^{-1} 1670 -C=C-CHO $\delta(CDCl_3)$; 6.25 -C=CH, 9.4 -CHO) under treatment of the antibiotic with 1 N sodium hydroxide in water following the procedure of PANDEY *et al.*,[5] assigns the presence of a substituted oxygen function at C17. The structure of **II** was defined as 13-hydroxyhexadecanpenta-2,4,6,8,10-enal on the basis of spectroscopic data of its O-acetylmethoxime **III**. The product **III** was formed upon treatment of **II** with O-methylhydroxylamine hydrochloride in pyridine, followed by treatment with acetic anhydride and exhibited: λ_{max}314, 346, 364, 386 nm, ϵ= 115,000 at 364 nm, $\delta(CDCl_3)$, 1.9 -COOCH$_3$, 3.9=NOCH$_3$, 7.65 -CH=NOCH$_3$, electron impact mass spectrum ions at *m/e* 317 (P), 257 (P-60), 226 (P-60-31), 202 and 115 (cleavage of the C 12-13 bond). The carbon skeleton of rimocidin and the positions of the oxygen functions were established on the basis of the mass spectral data with the permethylated tetradecahydro derivative (**IVa**) and its hexadeuterium analog (**IVb**) obtained in following sequence of reactions: 1. N-acetylation (acetic anhydride in methanol), 2. hydrogenation (H_2/Pd in methanol), 3. esterification (diazomethane in methanol-ether), 4. reduction (lithium borohydride or lithium borodeuteride in tetrahydrofuran), 5. methylation (methyl iodide, sodium hydride in tetrahydrofuran). The molecular ions of **IVa** and **IVb** were determined by means of mass spectrometry using field desorption technique as 979 and 985 respectively, and

* Rimocidin was supplied by Pharmaceutical Works Tarchomin POLFA as a crude fermentation product of a standard strain of *S. rimosus*. It was purified by means of counter-current distribution (chloroform-methanol-water, 2:2:1 v/v, k=0.8; $E^{1\%}_{1cm}$=1025 at 304 nm) and shown to be identical with an authentic sample received from Medical Research Laboratories Pfizer Pharmaceuticals.

The mass spectra were measured on a Varian MAT 711 instrument.

Fig. 3. The structure of tetradecahydrorimocidin IVa and its hexadeuterio analog IVb.



the main diagnostic pattern of the electron impact spectra are shown on Fig. 3. The proposed structure of the antibiotic was documented upon analysis of the mass spectra of the methyl ester of N-acetyldimethoxime-rimocidin **V** and its derivatives: peracetylated **VI** (acetic anhydride in pyridine, −10°C) and persililated **VII** (trimethylsilylimidazol in pyridine-cyclohexane). The product **V** was the simplest derivative of the whole molecule exhibiting prominent ions at the molecular region using the field desorption technique: the highest intensity peak was found at *m/e* 881. The electron impact spectra of **VI** and **VII** are characterized by the presence of the molecular ions at *m/e* 1133 and 1313 respectively and by fragmentation patterns fully consistent with the proposed localization of all functions in the molecule of rimocidin. The compound VI treated with hydrogen chloride dissolved in methylene chloride yielded 2,3,4-triacetylmycosamine **VIII**. Identical mass and NMR spectra of **VIII** and triacetylmycosamine derived from nystatin[4] point the same ring size and conformation of the aminosugar moiety in both antibiotics.

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