COMMUNICATIONS TO THE EDITOR

The Stereochemistry of Micrococcin P₁
Reinvestigated

Sir:

First discovered in 1948 from a strain of Micrococcus found in sewage from the city of Oxford, the isolate that was to be named micrococcin is recorded as the first example of a thiopptide antibiotic, although no work to elucidate the chemical structure of this material was ever reported. An antibiotic with therapeutic activity later obtained from the B. pumilus group of spore-bearing bacillus demonstrated a considerable degree of identity with the antibiotic isolated from Micrococcus, and so was named micrococcin P, in spite of the taxonomic implications. This antibiotic complex, which actually consists of two distinct components present in a 7:1 ratio and designated micrococcin P₁ and P₂, respectively, has more recently been obtained from foodborne Staphylococcus equorum isolated from French Raclette cheese and has been shown to inhibit the growth of the malaria parasite Plasmodium falciparum and ribosomal protein biosynthesis in Gram-positive bacteria, the latter through binding to the complex of protein L11 and 23S rRNA in the bacterial 50S subunit.

A number of exhaustive studies have been conducted to determine the structural identity of the micrococccins, culminating in the Walker-Lukacs proposal which was later revised by Bycroft and Gowland on the basis of chemical and spectroscopic evidence. However, the synthesis of micrococcin P₁ (MP₁) by Ciufolini and Shen in 1999 demonstrated that the Bycroft-Gowland structure did not correspond with the material isolated from the bacillus. Subsequent NMR studies validated the constitution of this thiopeptide antibiotic and concluded that the difference between the natural product and synthetic material was purely stereochemical. A synthetic epimer that differs in the configuration of the isoalaninol residue, has been prepared but the (R)-stereochemistry of this unit is not in doubt. In this manuscript we re-examine some of the original synthetic studies to resolve ambiguities in the absolute configuration of the micrococccin natural products.

The configuration of the valine-derived thiazole residue in micrococcin was assigned by Walker following the reproducible isolation of laevorotatory 2-(1-amino-2-methylpropyl)thiazole-4-carboxylic acid hydrochloride from the hydrolysis products of MP₁. Comparison with synthetic material, prepared by the condensation of L-thioamide with ethyl bromopyruvate followed by hydrolysis of the benzamido N-protecting group, we sought to access valine-derived thiazole 8 by a known alternative route to establish its specific rotation and thus verify Walker’s
original findings (Scheme 1). tert-Butoxycarbonyl protected thiazole 6b (97% ee) was prepared in 97% ee from the corresponding (S)-thioamide 5b and hydrolyzed under basic conditions to give acid 7b in 85% yield. N-Deprotection under acidic conditions gave the required amine hydrochloride, (S)-8, in 98% yield. The specific rotation of (S)-8, measured immediately following its isolation, 20) was found to be laevorotatory, $\left[\alpha\right]_{D}^{23} -7.2$ (c 0.5, H2O) and closely matched hydrolysate 8 obtained by WALKER from MP1 (Scheme 1). 21) This contrasts with the specific rotation of synthetic (S)-8 obtained by WALKER and recorded with a small dextrorotation, $\left[\alpha\right]_{D}^{22} +2.1$ (c 2.5, H2O) or $\left[\alpha\right]_{D}^{25} +5.2$ (c 0.5, H2O). In order to verify the discrepancy in these findings, (R)-thioamide 5b was also prepared according to the established route via (R)-thiazole 6b, isolated in 97% ee, to give the hydrochloride, (R)-8, in 98% overall yield with an equal but opposite specific rotation.

We propose, considering these measurements, that the stereochemistry of the valine-derived thiazole unit in micrococcin P1 should be corrected to S, based upon WALKER’s isolation of laevorotatory hydrochloride 8 from the hydrolysis of MP1. It is now our hope that, on the basis of these studies, the validity of the BYCROFT-GOWLAND structure can be verified by total synthesis.

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References

10) WALKER, J.; A. OLESKER, L. VALENTE, R. RABANAL & G.

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20) The material was found to be completely racemic after 1 day in H\textsubscript{2}O and so must be analysed immediately following isolation.

21) The original specific rotation of thiazole 8 isolated from micrococcin was erroneously reported as dextrorotatory. BROOKES, P.; A. T. FULLER & J. WALKER: Chemistry of micrococcin P. Part I. J. Chem. Soc.: 689–699, 1957. This was corrected subsequently.\textsuperscript{16} In three separate hydrolysis experiments, the specific rotation was found to be laevorotatory at concentrations ranging from c 0.5–2.5.