NOTES

THE REVISED STRUCTURE OF BOTTROMYCIN A2

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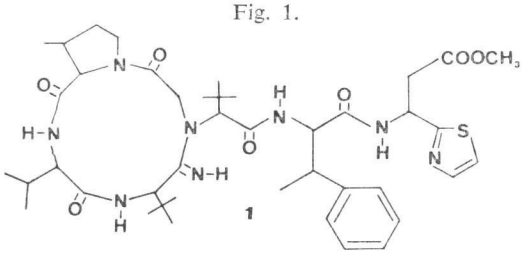
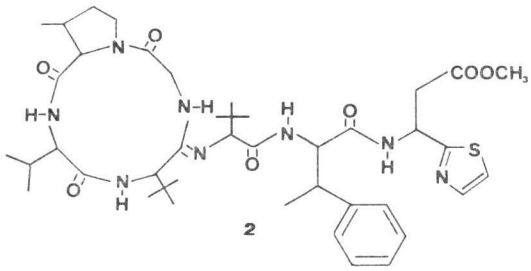
Bottromycin is produced by *Streptomyces bottropensis* and is active against Gram-positive bacteria[1]. Renewed interest in this antibiotic has led to a comparison of its ^{13}C NMR spectrum and EI mass spectrum with those published by TAKAHASHI *et al.*, who proposed structure **1** (Fig. 1) for bottromycin A2[2].

Fig. 1.





The ^{13}C NMR spectra and EI mass spectra of the two antibiotics are identical and therefore the two products share the same structure.

In the course of a study to modify bottromycin chemically, some doubts arose about its structure. Therefore, bottromycin was reinvestigated using ^{1}H, ^{13}C and ^{15}N NMR spectroscopy. The ^{15}N NMR spectrum (Fig. 2) shows 8 resonances. The lowest field resonances can be easily assigned; that at 312.8 ppm to the thiazolidine nitrogen and that at 229.5 ppm to the imino nitrogen of the amidine group[3].

Five resonances are found in the region for amide nitrogens: 135.4, 124.0, 120.0, 112.7 and 109.8 ppm[3]. The chemical shift of the highest field resonance (81.8 ppm) lies between regions for amide and amine nitrogens and is therefore assigned to the amine nitrogen of the amidine group. In a proton-coupled spectrum, 5 resonances show a doublet, four referring to amide nitrogens and one to that at the highest field. On the basis of structure **1**, however, this amine nitrogen should be a singlet and the imino nitrogen a doublet. Apparently, the substitution of the amidine nitrogens is different from that in structure **1** and for that reason structure **2** seems to be more in accordance with the ^{15}N NMR spectrum. On partial acid hydrolysis, **2** will give a tetrapeptide isomeric to that claimed to be obtained from **1**[2]. Treatment with sodium metal in liquid ammonia of this tetrapeptide should lead to the same tetrahydro derivative, from which structure **1** was derived[2]. Structure **2** could be confirmed from the ^{1}H NMR spectrum (250 MHz; $CDCl_3$); the glycine ABC spin system (3.49, 3.69 and 3.92 ppm) is converted into an AB system by addition of

Fig. 2.

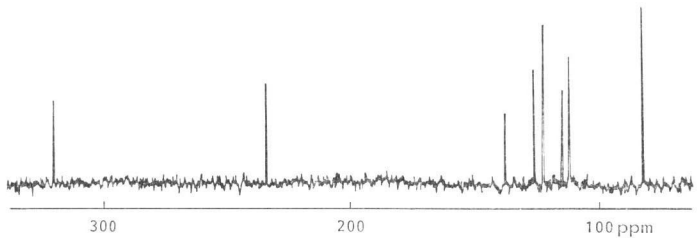
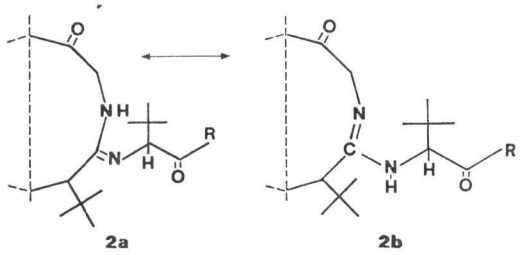


Fig. 3.



2a **2b**

D_2O. In DMSO-d_6, however, two tautomers can be observed, the major one being about 80%. In this major tautomer, only the AB part of the glycine moiety can be detected, but the proton at C-17, which is a singlet in $CDCl_3$, is a doublet, being turned into a singlet on deuteriation. From these data it can be concluded that there is a tautomeric equilibrium between the exo- and endocyclic protonated forms of the amidine group (Fig. 3).

In addition the changes in the ^1H NMR spectrum of the glycine moiety and the proton at C-17, this equilibrium is attended with differences is chemical shift of some other protons of up to 2 ppm, indicating a dramatic change in conformation on transition from **2a** and **2b**. These phenomena will be described in detail elsewhere.

From what has been said above, it follows that the structure of bottromycin A2 should be revised to **2**, which is also in full agreement with the mass spectrometric data obtained by TAKAHASHI *et al.*[2].

References

1) WAISVISZ, J. M.; M. G. VAN DER HOEVEN, J. VAN PEPPEN & W. C. M. ZWENNIS: Bottromycin. I. A new sulfur-containing antibiotic. J. Am. Chem. Soc. 79: 4520~4521, 1957
2) TAKAHASHI, Y.; H. NAGANAWA,T. TAKITA, H. UMEZAWA & S. NAKAMURA: The revised structure of bottromycin A2. J. Antibiotics 29: 1120~1123, 1976
3) WITANOWSKI, M.; L. STEFANIAK & G. A. WEBB: Nitrogen NMR spectroscopy. *In* Annual Reports on NMR Spectroscopy. Vol. 11B, G.A. WEBB, *Ed.*, Academic Press, London, 1981

Note: Due to the rather slow exchange, no ^{15}N NMR spectrum of bottromycin in DMSO could be obtained.