

A NEW ANTIBIOTIC, SF-837

Sir :

In the course of our screening to find new antibiotics, we have found an antibiotic SF-837 in culture broth of a new *Streptomyces* species that was named *Streptomyces mycarofaciens* nov. sp.* From the physico-chemical and biological properties described in this communication, antibiotic SF-837 is considered to be a new antibiotic belonging to the macrolide family.

Antibiotic SF-837 is produced in both shaken culture and jar fermentation in a medium containing 3.0% glucose, 1.0% peptone, 0.5% meat extract, 0.4% soluble vegetable protein, 0.3% soybean oil, 0.2% NaCl and 0.3% CaCO₃ (pH 7). Production of the antibiotic reached a maximum after 60~70 hours in jar fermentation.

The culture broth containing antibiotic SF-837 was filtered, the filtrate adjusted to pH 8, and extracted with ethyl acetate. The antibiotic in organic solvent was transferred into H₂O at pH 2, and then re-extracted with ethyl acetate at pH 8. The final organic solvent layer was passed through a column of activated carbon, and the effluents were collected and concentrated to dryness to yield a crude powder. The powder was dissolved in benzene, and purified by silica gel column chromatography using benzene-acetone (4:1) as a developing solvent. The active fractions were combined, and concentrated to dryness.

Antibiotic SF-837 was obtained as a white powder, which melted at 122~124°C. Crystallization from benzene-cyclohexane gave colorless needles, which melted at 155~156°C after drying at 80°C. It is soluble in acid and organic solvents other than alkanes. It gives dark reddish purple color in the erythromycin test¹⁾ with sulfuric acid, and reddish purple color in the carbomycin test¹⁾ with hydrochloric acid, but negative FEHLING, ferric chloride and ninhydrin reactions. Silica gel thin-layer chromatography with various solvent systems showed a single spot in every

case with the following Rf values: 0.45 with benzene-acetone (2:1); 0.67 with *n*-butanol-acetic acid-H₂O (3:1:1); 0.82 with methanol; 0.92 with acetone-H₂O (49:1).

Antibiotic SF-837 is optically active, $[\alpha]_D^{25}$ -67° (*c* 1, ethanol), and exhibits a UV maximum at 232 m μ ($E_{1cm}^{1\%}$ 325) in ethanol.

Analysis Calcd. for C₄₁H₆₇NO₁₅ (813):

C 60.52, H 8.24, N 1.72, O 29.39.

Found:

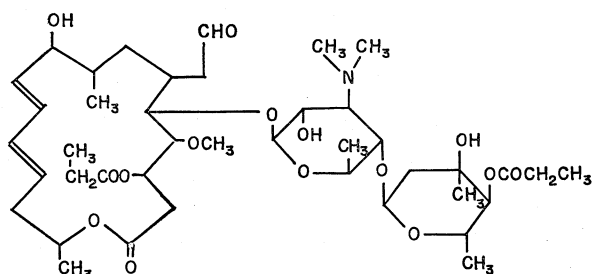
C 60.38, H 8.35, N 1.65, O 29.62.

Supporting the formula, mass spectrometry of the intact antibiotic showed the parent peak at *m/e* 813. Potentiometric titration in 50% ethanol showed an equivalent weight of 830, with p*K*' value of 6.9. As will be reported in a subsequent paper, the following structure is proposed for antibiotic SF-837.

Antibacterial spectrum of antibiotic SF-837 is primarily active against Gram-positive bacteria, and less active against Gram-negative bacteria. On a nutrient agar, it inhibited the growth of *Staphylococcus aureus* 209P at 0.39 mcg/ml, *Bacillus subtilis* ATCC 6633 at 0.39 mcg/ml and *Sarcina lutea* at less than 0.05 mcg/ml. The antibiotic has a low toxicity. Oral administration of 6,000 mg/kg to mice caused no death.

The characteristics mentioned above revealed the macrolide nature of antibiotic SF-837. There have been reported a large number of macrolide antibiotics so far. Among them, the macrolides having a UV maximum at or near 232 m μ include leucomycins A₁~A₉²⁾, spiramycins I~III³⁾, josamycin⁴⁾, tertiomycins A and B⁵⁾ and miamycin⁶⁾. It is found out, however, that antibiotic SF-837 can be clearly distinguished

Fig. 1.



* Detailed taxonomic study of this strain will be published in a separate paper.

from optically inactive miamycin and from the spiramycins which have higher nitrogen contents (3.05~3.1%) and higher pK_a' values (7.6~7.7). Differentiation from the leucomycins, josamycin and tertiomycins was accomplished by direct comparison of R_f values on thin-layer chromatograms. On alumina plates developed with ethyl acetate, antibiotic SF-837 showed the highest R_f value of 0.78, while R_f values of leucomycins, josamycin and tertiomycins are all below 0.66.

Thus, antibiotic SF-837 was differentiated from all known macrolide antibiotics, and, accordingly, concluded to be a new antibiotic. This was finally confirmed by the unique structure of antibiotic SF-837 shown above.

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