SYNTHESIS OF MIMOSAMYCIN (2,6-DIMETHYL-7-METHOXY-3,5,8-ISOQUINOLINETRIONE)

Hiroshi Fukumi, Hideshi Kurihara, and Hiroshi Mishima
Central Research Laboratories, Sankyo Co., Ltd., Shinagawa-ku, Tokyo, Japan

Streptomyces lavendulae No. 314 produces mimosamycin, which is responsible for the antibiotic activity on mycobacteria including streptomycin-resistant strains of human tubercle bacilli, in addition to chlorocarcins A, B, and C.

The structure of mimosamycin was determined to be 2,6-dimethyl-7-methoxy-3,5,8-isoquinolinetrione by X-ray crystallographic study. The characteristic feature of the structure is a heterocyclic quinone consisted of 3,5,8-isoquinolinetrione, which has been never found in the literature .

A starting material, 6-methyl-7-isoquinolinol, was prepared in 80% over-all yield in five steps from m-methoxytolualdehyde by the application of the method of Jackson et al. Oxydation of 6-methyl-7-isoquinolinol with oxygen in the presence of cupric acetate and morpholine gave 3,5-dimorpholino-6-methyl-7,8-isoquinolinedione. Upon treatment with sulfuric acid-methanol followed by diazomethane, the o-quinone was converted to 7-methoxy-6-methyl-3-morpholino-5,8-isoquinolinedione. Reductive acetylation with zinc-acetic acid and acetic anhydride gave 5,8-diacetoxy-7-methoxy-6-methyl-3-morpholinoisoquinoline, which was quaternized at isoquinoline nitrogen with methyl iodide. In this N-methylation reaction, no concurrent N-methylation of morpholine nitrogen was observed. Treatment of the iodomethylate with silver oxide gave rise to in one-step 2,6-dimethyl-7-methoxy-3,5,8-isoquinolinetrione, which was identified with a specimen of natural mimosamycin by mixed mp and the comparison of IR, UV, NMR, and MS spectra and Rf value of TLC.