

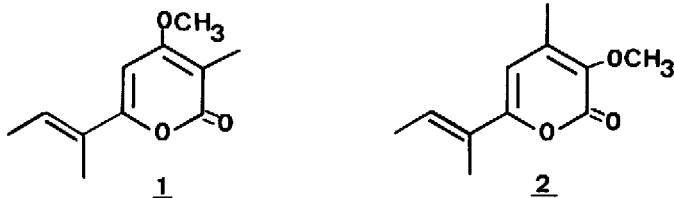
SYNTHESIS OF THE ANTIBIOTIC MONOTERPENOID NECTRIAPYRONE

Torsten Reffstrup and Per M. Boll

Department of Chemistry, Odense University, DK-5000 Odense, Denmark

(Received in UK 29 March 1976; accepted for publication 16 April 1976)

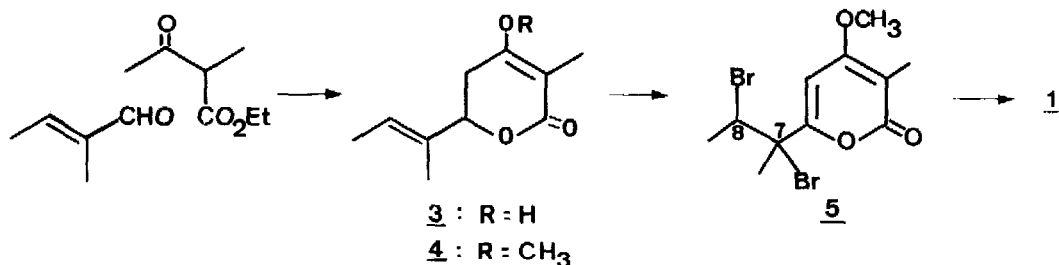
Nectriapyrone is a monoterpeneoid α -pyrone isolated from Gyrostroma missouriense Seeler, the imperfect stage of Thyronectria missouriensis Seaver. On the basis of the chemical and spectral data nectriapyrone has been assigned structure 1. Another structure (2), biogenetically possible, has also been taken into consideration, but was rejected on the basis of shifts in the NMR-spectrum induced by $\text{Eu}(\text{FOD})_3$.¹



Nectriapyrone being the first monoterpeneoid α -pyrone isolated poses an interesting biogenetic problem, since naturally occurring α -pyrones usually appear to be acetogenins. Therefore, a confirmation of the structure assignment is of interest.

We report a total synthesis of nectriapyrone which involves as the key step the one-step construction of the corresponding 4-hydroxy-5,6-dihydro-2-pyrone (3) based upon the reaction of the dianion of ethyl 2-methylacetoacetate with tiglic aldehyde. This step has recently been described by us.² Treatment of (3) with excess of diazomethane gave after preparative tlc (silica gel, ether as eluent, $R_F=0.74$) the methoxy derivative (4) with m.p. 79-80 °C in 51 % yield. Bromination of 4 with N-bromosuccinimide resulted not in a 5- or 6-bromo derivative; but in accordance with an earlier reported bromination of a structurally

related compound,² the dibromo derivative (5) was isolated in 45 % yield: m.p. 134.5 - 137 °C, UV (EtOH) 312 nm (ϵ 5800), PMR (CDCl₃): δ 1.92 (s, 3 H), 1.95 (d, 3 H, J 7 Hz), 2.10 (s, 3 H), 3.81 (s, 3 H), 5.03 (q, H), 6.30 (s, H). Treatment



of 5 with Zn in ether/glacial acetic acid at 0 °C afforded after preparative tlc (silica gel, ether-light petroleum (1:1) as eluent, R_F =0.40) 4-methoxy-3-methyl-6-(1-methyl-1-propenyl)-2-pyrone of m.p. 99 - 102 °C (36 % yield). This compound was shown identical to authentic nectriapyrone from m.p., M.S., 270 MHz PMR, UV and IR.

Spectral evidence has suggested that the two methyl groups on the side chain of nectriapyrone are situated cis.¹ It is puzzling fact that our synthesis of nectriapyrone results in the isolation of only one compound with the proposed E-geometry of the side chain. When 4 is treated with NBS to give 5, two asymmetric centers are created and two diastereomeric d,l-pairs are expected to be formed. Only one is isolated, which means that either we have only been able to isolate one of the d,l-pairs formed or the reaction is stereospecific. Although we have stated that the bromination involves reaction at as well the 5- as the 6-position followed by two allylic rearrangements,² nothing definite can be stated concerning the mechanism. The last step, the conversion of 5 to 1, is considered as being a cis-debromination, which makes it possible to propose the following configuration for 5: (7R,8R)(7S,8S).

We thank Dr. M. S. R. Nair for IR and UV spectra as well as for a sample of authentic nectriapyrone and we are indebted to Dr. Jonas Pedersen for recording a 270 MHz spectrum of our synthetic nectriapyrone.

1. M. S. R. Nair and T. Carey, *Tetrahedron Lett.* 1655 (1975).
2. T. Reffstrup and P. M. Boll, *Acta Chem. Scand.*, in press. Cf. D. Seebach and H. Meyer, *Angew. Chem.* 86, 40 (1974).