

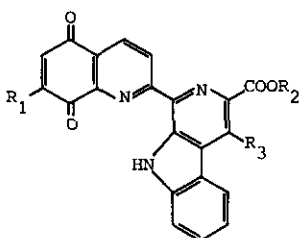
SYNTHETIC APPROACH TO THE ANTITUMOR ANTIBIOTIC LAVENDAMYCIN:

A SYNTHESIS OF DEMETHYLLAVENDAMYCIN METHYL ESTER

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Abstract-----A synthetic approach to the lavendamyacin has been achieved by a formation of β -carboline derivative and oxidation of bromophenol derivative to the quinolinequinone system using cerium ammonium nitrate.

Lavendamyacin, a new antitumor antibiotic isolated from *Streptomyces lavendulae*, strain C22030, was determined by spectroscopic evidences to have structure 1¹. This structure was similar to that of antitumor antibiotic streptonigrin². We have attempted to develop a total synthesis and syntheses of its congeners based on the nonacidic Pictet-Spengler type cyclization of an appropriately substituted quinoline-2-aldehyde 5 with a tryptophan methyl ester 6 to provide a demethyl-lavendamyacin methyl ester 2 via oxidation of bromophenol 11. We now wish to report on this result. Initial study was aimed at the formation of pyridine ring (β -carboline 8)³, which was successfully prepared from 8-benzyloxyquinoline-2-aldehyde 5 (mp 92-93°C)³ with tryptophan methyl ester 6 in benzene under reflux, followed by aromatization with 5% Pd-C in xylene. Then quinolyl- β -carboline 8 (mp 219-220°C) was hydrogenated by 10% Pd-C to give 8-hydroxyquinoline 9 (mp 226-227°C), followed by bromination with 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one 10⁴ to have the desired dibromo-compound 11 (mp 257-259°C) in good yields, respectively. In many oxidizing agents, we have found that cerium ammonium nitrate⁵ in tetrahydrofuran was extremely effective for the oxidation of quinoline 11 to orange red bromoquinolinequinone 4 (mp >300°C). Replacement of the bromine of 4 by

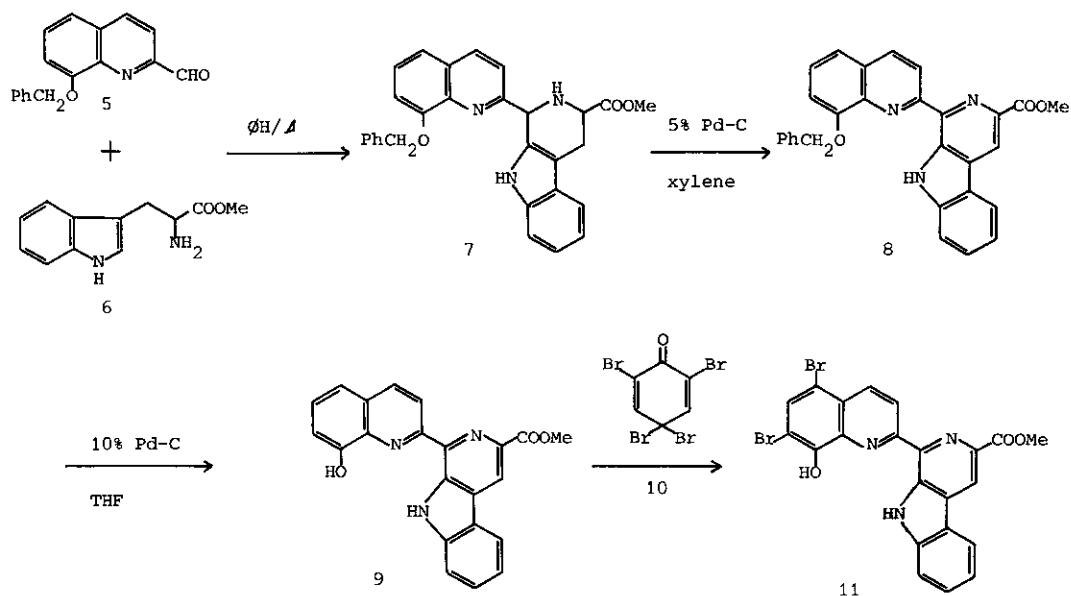


1 : R₁ = NH₂, R₂ = H, R₃ = Me

2 : R₁ = NH₂, R₂ = Me, R₃ = H

3 : R₁ = N₃, R₂ = Me, R₃ = H

4 : R₁ = Br, R₂ = Me, R₃ = H



the sodium azide gave azidoquinolinequinone 3, and reduction of the azide group of 3 with sodium hydrosulfite afforded aminoquinolinequinone 2 (demethylavandamycin methyl ester, m/z 398, mp 250-251°C). Spectroscopic evidences of 2 were similar to those of lavandamycin^{1a,6,7}.

Work is now in progress on 1 and other related compounds.

REFERENCES AND NOTES

- 1) (a) T. W. Doyle, D. M. Balitz, R. E. Grulich, D. E. Nettleton, S. J. Gould, C.-h. Tann and A. E. Moews, *Tetrahedron Letters*, **22**, 4595 (1981). (b) D. M. Balitz, J. A. Bush, W. T. Doyle, F. A. O'Herron and D. E. Nettleton, *J. Antibiotics*, **35**, 259 (1982).
- 2) See review ; (a) S. Hibino, *Heterocycles*, **6**, 1485 (1977). (b) S. J. Gould and S. M. Weinreb, *Fortschr. Chem. Org. Natur.*, **41**, 77 (1982).
- 3) All new compounds gave satisfactory analyses and spectroscopic evidences.
- 4) G. J. Fox, G. Hallas, J. D. Hepworth and K. N. Paskins, *Organic Syntheses*, Vol 55, 20 (1976).
- 5) Oxidation of *p*-bromophenols to *p*-quinone system with cerium ammonium nitrate is first example.
- 6) ¹H-NMR and ¹³C-NMR spectra of AB-aminoquinolinequinone portion were observed as follows:
¹H-NMR (DMSO-D₆/CF₃COOD), δ 5.91 (1H, s, C₆-H); ¹³C-NMR (DMSO-D₆/CF₃COOD), δ 157.8 (C₂), 134.4 (C₃), 124.6 (C₄), 180.5 (C₅), 102.3 (C₆), 150.6 (C₇), 179.8 (C₈).
- 7) We wish to thank Prof. S. J. Gould, Oregon State University for sending ¹³C-NMR spectrum of lavandamycin.

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