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STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF SAFRAMYCIN: I. A SYNTHESIS OF HEXAHYDRO-1,5-IMINO-3-BENZAZOCIN-7,10-DIONE.

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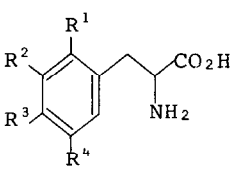
Summary: A short-step synthesis of 2, the right-hand half of antibiotic saframycin (1), is described. The key steps of this synthesis are the acid catalyzed intramolecular double cyclization of 4 and the oxidative demethylation of 7 to the quinone (2).

Saframycins (1)[1] were isolated from the culture filtrate of Streptomyces lavendulae No. 314[2] and have attracted considerable interest due to their antitumor activities.[3] They have a unique skeleton which apparently contains 1,3'-dimeric structure of two isoquinoline quinones.[4] In connection with these biological activities, we have been much interested in synthesizing a new ring system, hexahydro-1,5-imino-3-benzazocin-7,10-dione (2a, b), as a target towards a total synthesis of 1.

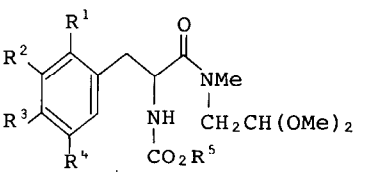
In the preceding paper,[5] we reported efficient synthetic routes to hexahydro-1,5-imino-3-benzazocine derivatives (5), which contain the desired carbon skeleton in themselves, starting from readily available phenylalanine derivatives (3).

According to this procedure, the amide (4a, b) was obtained from an amino acid (3a, b)[6] in good yield. Refluxing of 4a, b in trifluoroacetic acid led directly to the doubly cyclized product (5a, b).[7] This reaction was completed within 1.5 hr in nearly quantitative yield (5a: 91%, 5b: 96%).



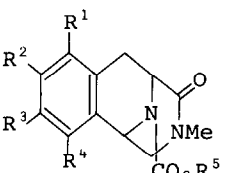
3

R^1=OMe, R^2= H, R^3=OMe, R^4=OMe
R^1=OMe, R^2=Me, R^3=OMe, R^4=OMe



4

a, b (R^5=Me)



5

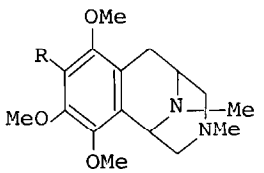
a, b

Reduction of two carbonyl groups in 5a, b was accomplished by $LiAlH_4$ in refluxing ether to obtain the amine (6a, b) in high yield (6a: 85%, 6b: 87%).

Among several methods for oxidative demethylation of hydroquinone dimethyl ether derivatives to quinones,[8] the oxidation with HNO_3 was chosen for the fol-

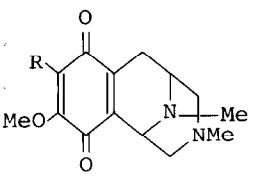
lowing reasons: 1) using HNO_3, a p-quinone may be predominantly produced,[9] 2) in an aqueous acidic medium, a reaction of compounds having amino functions, such as 6a, b, should be carried out in homogeneous conditions. Oxidation of 6a with 6N-HNO_3 proceeded at room temperature to yield $2HNO_3$ salts of 2a selectively as yellow precipitates in 75% yield. Oxidation of 6b to the quinone 2b was accomplished under more severe conditions, namely in conc. HNO_3 at room temperature, to give $2HNO_3$ salts, mp. 124-126° (dec.) in 71% yield. The structure of the quinone (2a, b)[10] was fully supported by physicochemical data.

The UV spectra of 2a, b showed typical p-quinone type absorptions [2a: λ_{max}^{EtOH} 269 nm(log ε=4.19), 2b: λ_{max}^{EtOH} 271 nm(log ε=4.13)].

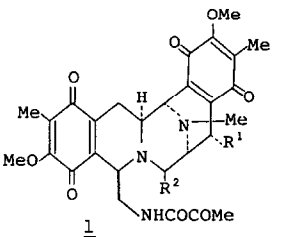


6

a R=H
b R=Me



2



1

a R^1= H , R^2=CN
b R^1= H , R^2= H
c R^1=OMe, R^2= H

Further synthetic studies towards saframycins are under investigation. The biological properties of 2a, b will be reported elsewhere.

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7. 5a; m.p. 146-148°. m/z: 350(M^+, 62), 278(100), 263(44). ν(KBr): 1703, 1665 cm^{-1}. δ($CDCl_3$): 2.38(3H, s), 2.83(1H, dd, J=17.2, 6.0Hz), 3.11(1H, dd, J=17.2, 2.0Hz), 3.26(1H, dd, J=11.2, 6.0Hz), 3.74, 3.79, 3.88 and 3.88(each 3H, s), 4.95(1H, br.m), 5.61(1H, br.m), 6.45(1H, s) ppm. 5b; m.p. 110-112°. m/z: 364(M^+, 38), 292(100), 277(33). ν(KBr); 1712, 1667 cm^{-1}. δ($CDCl_3$): 2.18(3H, s), 2.86(3H, s), 3.15(3H, m), 3.68, 3.76, 3.82 and 3.89(each 3H, s), 4.98(1H, br.m), 5.56(1H, br.m) ppm.
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10. 2a(free base); m.p. 152-153°. m/z: 262(M^+, 71), 204(47), 58(100). ν(KBr): 1667, 1648, 1633, 1612 cm^{-1}. δ($CDCl_3$): 2.13(3H, s), 2.28(3H, s), 2.40(2H, m), 2.60(3H, m), 3.05(1H, m), 3.81(3H, s), 3.84(1H, br.m), 5.89(1H, s) ppm. 2b(free base); m.p. 108-110°. m/z: 276(M^+, 75), 218(45), 58(100). ν(KBr): 1653, 1630, 1605 cm^{-1}. δ($CDCl_3$): 1.94, 2.16 and 2.29(each 3H, s), 3.07(1H, br.m), 3.80(1H, br.m), 4.00(3H, s) ppm.

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