A SYNTHESIS OF 4-CYANO-HEXAHYDRO-1,5-IMINO-3-BENZAZOCINE-7,10-DIONE; A POTENTIAL INTERMEDIATE TO SAFRAMYCIN SYNTHESIS[1]

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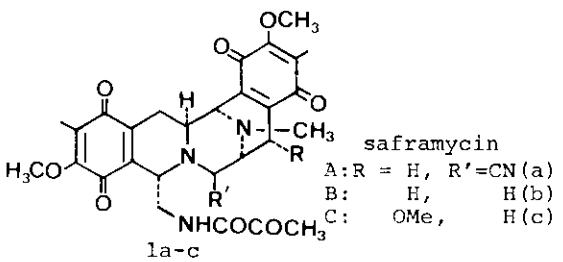
Abstract - A simple and efficient synthesis of 4-cyano-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-8-methyl-3-benzazocine-7,10-dione (2a) is described starting from the corresponding lactam (3). Reduction of the lactam (3) with DIBAH followed by oxidation with HNO_3 and neutralization of the resulting quinone in the presence of KCN afforded an α-aminonitrile derivative as the single product; the stereochemistry of the introduced cyano group being determined to be α-axial.

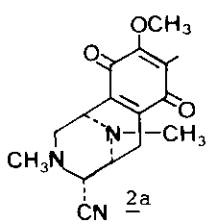
Isoquinolinequinone antibiotics, which include such naturally occurring quinones as cyanocyclines,[2] naphthyridinomycins,[3] saframycins,[4] mimosamycin,[5] mimocin,[6] renieramycins,[7] and renierone,[8] constitute a group of structurally intriguing compounds into which there have so far been a number of synthetic studies.[9]

Our interest in the synthesis towards saframycins (1a-c), which exhibit a wide-spectrum of antimicrobial activity and are active against several types of tumor in mice, resulted in the development of the efficient synthesis of



saframycin
A: R = H, R'=CN (a)
B: H, H (b)
C: OMe, H (c)

1a-c



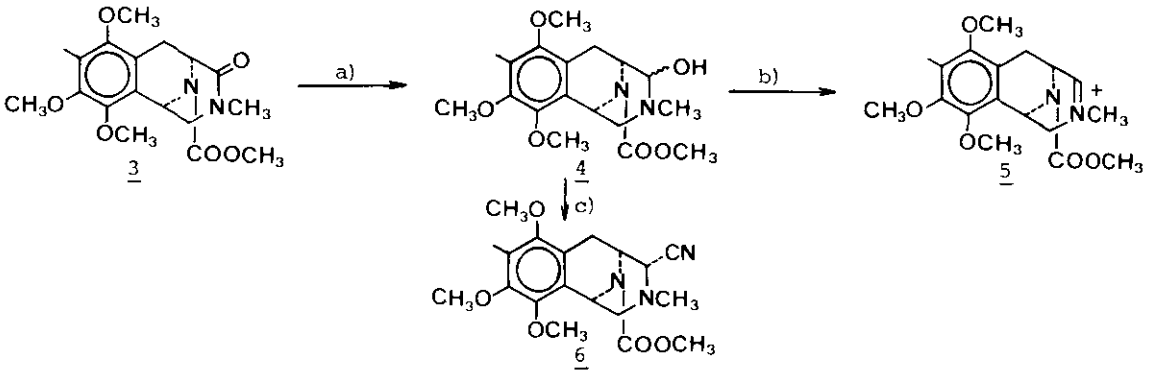
2a

hexahydro-1,5-imino-3-benzazocine derivatives[10], embodying all of the skeletal features of the 'right half' of saframycin.[1]

Saframycin A (1a) is the most potent antineoplastic agent of all saframycins[11] and differs from other saframycin congeners in regard to having a cyano group at C-21 (orientation not known), while the congeners have either a hydroxy group at C-21 or an unsubstituted methylene moiety.
THis paper reports the stereoselective synthesis of the 'right half' of saframycin A.

The lactam (3), 1,2,3,4,5,6-hexahydro-1,5-methoxyimino-8-methyl-7,9,10-trimethoxy-3-benzazocin-4-one,[1] was chosen as a starting material, because its functionality is obviously suitable for the synthetic manipulation to give the desired 4-cyano-1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-8-methyl-3-benzazocine-7,10-dione (2a).
Reduction of the lactam (3), which was readily available from a phenylalanine derivative in three steps,[10] with one equivalent of DIBAH at -78°C in toluene afforded a somewhat unstable and inseparable mixture of α-hydroxyamine (4) almost quantitatively as per the Sanders' protocol.[12]
The IR spectrum of 4 exhibited an absorption band at 3350 cm^{-1} due to a hydroxy group and did not show any of the characteristics for an aldehyde group around 1735 cm^{-1}. The NMR spectrum of the mixture of α-hydroxyamine (4) in $CDCl_3$ showed the common absorption peaks at δ 2.15(s, CH_3), 2.27(s, CH_3), 3.65(s, CH_3), 3.66(s, CH_3), 3.78(s, CH_3), and 3.84(s, CH_3) ppm, but its NMR spectrum in TFA was noteworthy; in a relatively lower field, a proton resonating at δ 8.73 ppm (br s) was coupled with a proton assigned as a C-5 bridge-head proton (δ 5.85, br s) and N-methyl protons resonating at δ 2.27 ppm in $CDCl_3$ were shifted to δ 3.71 ppm as a relatively broad singlet. These resonances, which are reasonably assigned as a methin (at C-4) and an N-methyl attached to an iminium moiety, establish the preferential formation of 5 in acidic medium. Based on the expectation that such a type of ion remains intact by HNO_3 oxidation, HNO_3 was the favored choice for oxidation of a compound having α-hydroxyamine moiety to get a quinone having an iminium moiety.

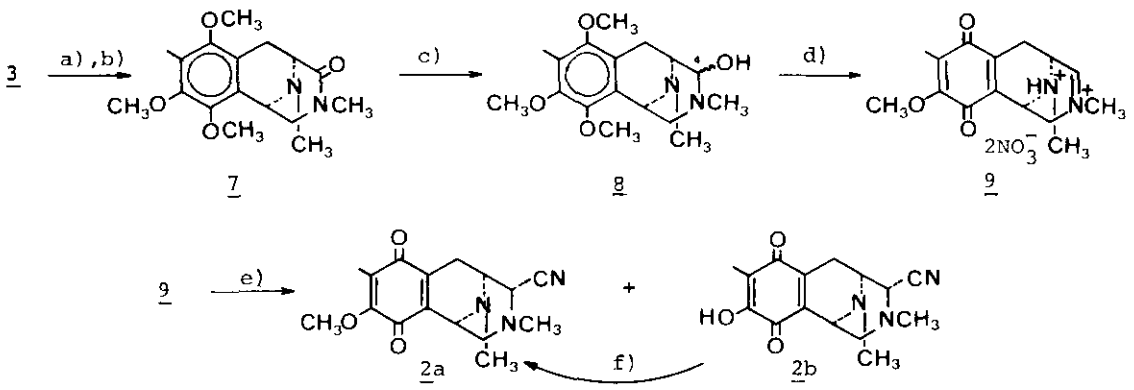
When the epimeric mixture of α-hydroxyamine (4) was treated directly with one equivalent of HCN in DMF for a few minutes at room temperature, aminonitrile (6)[13] was obtained as a single product in 93% yield. This transformation of tertiary lactam thereby provides a convenient method for the preparation of α-aminonitrile.[12]



a)DIBAH/tolu.,-78°C, b)TFA,r.t., c)HCN,pH 5 /DMF

Thus, synthesis of the quinone (2a) - the 'right half' of saframycin A - from compound 3 was performed as shown in Scheme I.

Hydrolysis of 3 with sodium methoxide in methanol followed by Eschweiler-Clarke methylation afforded methylamine (7),[13] in 50 % overall yield and reduction of 7 using the method of Sanders by the action of DIBAH at -78°C afforded, almost quantitatively, 4-hydroxy-1,5-methylimino-3-benzazocine (8)[13] as an epimeric mixture. Upon treatment with 12N-HNO_3[14] below 20°C, hydroxyamine (8) was oxidized with evolution of N_2O_4 to afford a quinone bearing an iminium ion as an HNO_3 salt (9)[13] in up to 80 % yield. When the quinone HNO_3 salt (9) was treated with aqueous $NaHCO_3$ in the presence of one equivalent of KCN, α-aminonitriles (2a and 2b) were formed in 39 and 42 % yield, respectively. The proposed structures of these quinones agreed with analytical and spectral properties.[13] Methylation of 2b with CH_2N_2 yielded, quantitatively, a methoxy derivative identical with 2a.



a)NaOMe/MeOH,refl., b)HCHO/HCOOH,100°C, c)DIBAH/tolu.,-78°C, d)12N-HNO_3,<20°C, e)KCN,$NaHCO_3/H_2O$, f)CH_2N_2/CH_2Cl_2-Et_2O.

Scheme I

Inspection of the NMR data allowed assignment of the stereochemistry of a cyano group as shown in Figure I. From the facts that, in the 400MHz NMR spectrum of 2a, H-4 appeared at δ 3.63 ppm as a double doublet (J=2.5, 0.5Hz) and a W-character type long range coupling between this proton and the equatorial proton at C-2 (δ 2.47 ppm, ddd, J=11.5, 1.9, 0.5 Hz) was ascertained by using a double resonance technique, the orientation of the cyano group at C-4 was determined as α-axial.

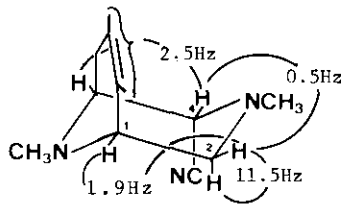
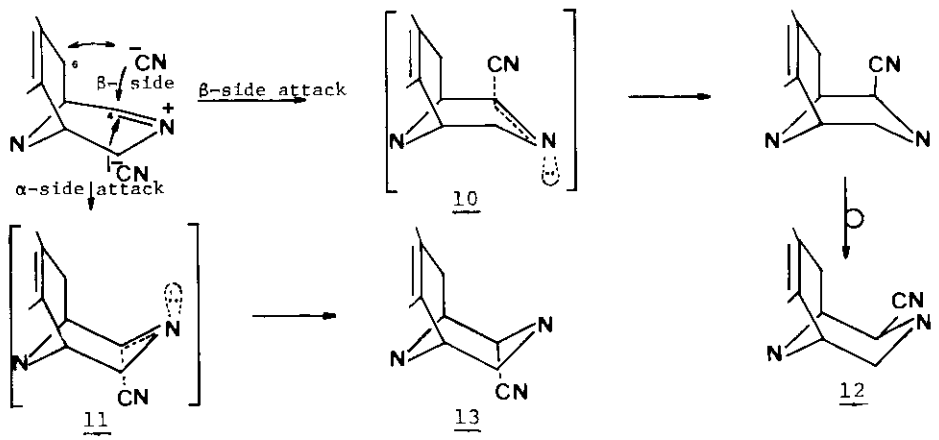


Figure I

Orientation of the cyano group in 6 is also α-axial because, in the NMR spectrum of 6, H-4 appeared at δ 3.73 ppm and its splitting pattern (br d, J= 2.6 Hz) was just like the pattern of H-4 in 2a.

Contrary to expectations,[15] such an α-aminonitrile group as in 6 or 2a was found to be stable under aqueous acidic conditions: for instance, treatment of 6 with 3N-HCl aqueous solution for 1 h at room temperature resulted in recovery of 6 exclusively. Together with this finding, by considering the facts that the α-aminonitrile was produced not only as a single epimer but also as an α-axial isomer in both cases of the conversion of alcohol (4 or 8) into the corresponding nitrile (6 or 2) *via* the iminium ion (5 or 9), respectively, may prove the proceeding of the reaction in a kinetically controlled fashion. As

shown in Scheme II, a cyano anion is able to attack the iminium ion either from the β-side or from the α-side of the molecule and to form 10 or 11 as transition states. But, approach from the α-side may be favorable, because the β-side of the iminium ion is sterically more hindered by the C-6 methylene moiety. Moreover, between these two transition states, in which the formation of a carbon-carbon bond (C_4-CN) and the development of a lone pair on the nitrogen atom are anti-coplanar to each other, 10 is kinetically disfavored because of the inevitable formation of a boat-like transition state. Therefore, it seems certain that the reaction proceeds through 11 and an α-axial type product such as 13 is formed stereoselectively.[16]



Scheme II

Determination of the orientation of the cyano group in saframycin A (1a), which was not clarified till 2a was synthesized, became possible by comparison of the NMR of 1a with that of 2a, the results of which have been reported separately.[17]

ACKNOWLEDGMENT

We wish to express our gratitude to Professor T. Arai for his many invaluable suggestions.

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13) Physicochemical data of compounds synthesized are as follows: 6 (amorph.); $\nu(CHCl_3)$: 2300(w), 1695, 1443 cm^{-1}; $\delta(CDCl_3)$: 2.18 (3H,s), 2.27(3H,s), 2.57 (1H,br d,J=11.7), 2.70(1H,br d,J=18.0), 2.77(1H,dd,J=11.7, 3.5), 3.18(1H,br dd,J=18.0, 7.8), 3.73(1H,d,J=2.6), 3.67, 3.78, 3.83 and 3.90(each 3H,s), 4.85 (1H,br d,J=7.8), 5.43(1H,br s) ppm; m/z: 375(M^+,10), 293(25), 292(100), 278

(9), 257(9), 242(14). Anal. ($C_{19}H_{25}N_3O_5$): C, 60.57(60.79); H, 6.80(6.71); N, 11.06(11.19). 7 (mp 115-116°C); ν(KBr): 1650, 1010, 955 cm^{-1}; δ($CDCl_3$): 2.19, 2.50 and 2.86(each 3H,s), 3.07(1H,dd,J=16.0, 4.6), 3.60(1H,br m), 3.69, 3.82 and 3.90(each 3H,s), 4.02(1H,d,J=4.5), 4.12(1H,br d,J=4.5) ppm; m/z: 320(M^+, 29), 249(21), 248(100), 218(20). Anal. ($C_{17}H_{24}N_2O_4$): C, 63.72(63.73); H, 7.58 (7.55); N, 8.71(8.74). 8 (amorph.); ν(KBr): 3120, 1600(w), 1066, 1027, 755 cm^{-1}; δ($CDCl_3$): 2.19, 2.27 and 2.27(each 3H,s), 3.71, 3.83 and 3.83(each 3H, s), 4.16(1H,br s) ppm; m/z: 322(M^+,13), 250(100), 248(58), 218(17). Anal. ($C_{17}H_{26}N_2O_4$): C, 63.50(63.33); H, 8.18(8.13); N, 8.62(8.69). 9 (hygroscopic); only NMR spectrum could be measured, δ(CF_3COOH): 2.06(3H,s), 3.29 and 3.94 (each 3H,br s, Me), 4.14(3H,s), 5.40(1H,br m), 9.04(1H,br s) ppm. 2a (mp 122-124°C (dec.)); ν(KBr): 2220(w), 1650, 1639, 1620, 1233 cm^{-1}; δ($CDCl_3$, 400MHz): 1.96(3H,s), 2.21(1H,d,J=20.5), 2.29 and 2.32(each 3H,s), 2.46(1H,ddd,J=11.5, 1.9, 0.5), 2.73(1H,dd,J=20.5, 7.5), 2.79(1H,dd, J=11.5, 3.5), 3.32(1H,ddd,J=7.5, 2.5, 1.5), 3.63(1H,dd,J=2.5, 0.5), 3.81(1H,ddd,J=3.5, 1.9, 1.5), 4.02(3H,s) ppm; λ(EtOH): 270nm(ε=13,200); m/z: 301(M^+,18), 219(100), 218(87), 204(47). Anal. ($C_{16}H_{19}N_3O_3$): C, 63.56(63.77); H, 6.47(6.36); N, 13.80(13.94). 2b (mp 180-182°C(dec.)); ν(KBr): 2230(w), 1657, 1640, 1626, 1235, 754 cm^{-1}; δ(DMF-D_7): 1.86, 2.27 and 2.31(each 3H,s), 3.42(1H,m,J=6.3), 3.76(1H,br s), 4.12(1H,d,J=2.5) ppm; m/z: 287(M^+, 7), 205(100), 204(36), 177(10). Anal. ($C_{15}H_{17}N_3O_3$): C, 62.48(62.70); H, 5.96(5.96); N, 14.46(14.62).

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