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ERYTHRINA STUDIES. PART 1. NOVEL ANTIBACTERIAL FLAVANONES FROM ERYTHRINA SIGMOIDEA

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Summary : Two new flavanones, sigmoidin A and B have been isolated from the Cameroonian medicinal plant Erythrina sigmoidea. The two compounds exhibit significant antibacterial activity against Gram-positive bacteria.

Erythrina alkaloids have attracted attention for decades[1]. The neutral components of this genus have, on the other hand, received very little attention. However, recently, Nakanishi and co-workers[2] isolated from E. abyssinica several flavonoids which displayed noteworthy biological activities. In continuation of our studies on Cameroonian medicinal plants[3] we have investigated the widely used folk medicinal plant, Erythrina sigmoidea[4], and now report the characterisation of two novel antibacterial flavanones from the chloroform extract.

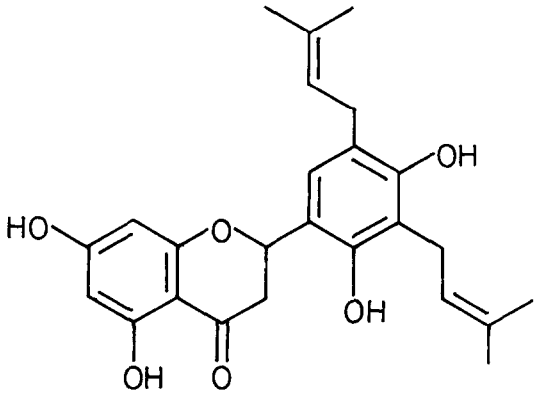
The first compound for which we propose the name sigmoidin A, 1 m.p. 180-181°, was shown to have the composition $C_{25}H_{28}O_6$ by elemental analysis and mass spectral data (M^+ at m/z 424). Colour tests with $FeCl_3$ (green) and magnesium-concentrated hydrochloric acid (pink) together with the u.v. spectral data {λ_{max}^{MeOH} : 288nm (ε 12 000), $\lambda_{max}^{MeOH + NaOMe}$ 323nm (20 900) ; $\lambda_{max}^{MeOH + NaOAc}$: 325nm (18 800) and $\lambda_{max}^{MeOH + AlCl_3}$: 309nm (15 400) (unchanged on addition of HCl} indicated that sigmoidin A was a flavanone bearing at least two hydroxy-groups[5]. Further indication of this skeleton came from the i.r, spectrum of 1 which exhibited strong absorptions at νmax (KBr) 3500 (free OH), 3300-3100 (bonded OH) and 1640 cm^{-1} (chelated C=O). The trimethyl ether of 1, (M^+ 466) from diazomethane methylation gave a green colour with $FeCl_3$ confirming the

presence of a chelated hydroxy-group while acetylation with acetic anhydride-pyridine yielded a tetraacetate which did not respond to the $FeCl_3$ test. Thus sigmoidin A contains four hydroxy-groups. The bathochromic shifts in the u.v. spectrum of 1 induced by NaOMe, NaOAc and $AlCl_3$ are consistent with its formulation as a flavanone hydroxylated at C-5 and C-7[5]. The ^{1}H. n.m.r. spectrum (DMSO-d_6) of 1 confirmed its 5,7-dihydroxylated nature and showed resonances for the characteristic flavanone 2H-3 and H-2 protons at δ 2.80 (1H, dd, J=17Hz and 4Hz, H-3), 3.16 (1H, dd, J=17Hz and 4Hz, H-3) and 5.33 (1H, m, H-2), and four D_2O-exchangeable signals for four hydroxy-groups at δ 7.85, 8.05, 10.40 and 12.01. Further signals at δ 1.67 (12H, bs), 3.24 (4H, d, J=7.5Hz) and 5.28 (2H, ill-defined t) indicated the presence of two 3-methylbut-2-enyl (prenyl) groups. Resonances for three aromatic protons were also observed at δ 5.84 (2H, s) and 6.70 (1H, s). The former were assigned to H-6 and H-8 in accordance with chemical shift data recorded for these two protons[2] while the latter obviously arose from ring-B. It thus follows that sigmoidin A is a 5,7-dihydroxyflavanone bearing four substituents : two hydroxy and two prenyl groups in ring B whose relative positions had to be determined. On biogenetic grounds[6], it was assumed that there would be hydroxylation at C-4'. Furthermore, in sigmoidin tetracetate the H-6 and H-8 singlet at δ 5.84 was split into two symmetric doublets (J=2.5Hz) and shifted to δ 6.65 and 6.8 while the ring-B proton singlet remained almost unchanged at δ 6.68. The absence of any downfield shift for this proton on acetylation indicated that it was not ortho to a hydroxy-group[7,8]. Hence two possible structures 1 and 2 could be assigned to sigmoidin A. Mild formic acid-catalysed cyclisation of sigmoidin A furnished a single dichromano-derivative which lacked prenyl absorption in its ^{1}H n.m.r. spectrum. This result ruled out the possibility of 2 which must give more than two chromano-derivatives in this reaction. Sigmoidin A could therefore be formulated as 1.

The major compound, sigmoidin B, 3, $C_{20}H_{20}O_6$, (M^+ 356) had m.p. 217-218°. Preliminary colour tests showed that 3 was also a hydroxylated flavanone. The i.r. spectrum of 3 (νmax (KBr) 3600, 3450-3150 and 1635 cm^{-1} (chelated C=O) and the u.v. spectrum {λ_{max}^{MeOH} : 288 nm (ε 12900) ; $\lambda_{max}^{MeOH + NaOMe}$: 325 nm (21800) ; $\lambda_{max}^{MeOH + NaOAc}$: 323 (19600) and $\lambda_{max}^{MeOH + AlCl_3}$: 309 nm (16000) unchanged on addition of HCl) further indicated that 3 had the same 5,7-dihydroxylation pattern as sigmoidin A[5]. The ^{1}H n.m.r. spectrum of sigmoidin B (3) was well-resolved and showed besides the characteristic 2H-3 and H-2 resonances {δ 2.84 (1H, dd, J=17 and 4Hz, H-3), 3.20 (1H, dd, J=17 and 4Hz, H-3) and δ 5.40 (1H, ill-defined t, H-2)}, signals for one chelated hydroxy-group at δ 12.02 (1H, s, exchangeable with D_2O) and one 3-methylbut-2-enyl group. Resonances for four aromatic protons were also observed at δ 5.86 (2H, s), 6.61 (1H, d, J=2Hz) and 6.75 (1H, d, J=2H). The former were assigned to H-6 and H-8[2] while the other

two obviously arose arose from ring-B. In agreement with the above spectral data 3 on diazomethane methylation furnished a trimethyl ether and on acetylation, a tetra-acetate. Sigmoidin B 3 therefore differed from sigmoidin A (1) only by having one prenyl group less in ring-B. The establishment of the structure of sigmoidin B thus resolved itself into one of determining the positions of the prenyl and the two hydroxy groups. One of the hydroxy-groups was assigned to C-4' on biogenetic considerations[6]. Treatment of sigmoidin B with 98% formic acid gave a single chromano-derivative (M^+ 356) indicating that the prenyl group was flanked by a single hydroxy-group. The existence of two meta-coupled ring-B protons (^1H n.m.r spectrum vide supra) coupled with the above evidence uniquely defined the B-ring substitution pattern as 3',4'-dihydroxy-5'-(3"-methylbut-2"-enyl). Hence sigmoidin B has the novel structure 5,7,3'4'-tetrahydroxy-5'-(3"-methylbut-2"-enyl)-flavanone 3.

Preliminary antibacterial tests show that sigmoidin A and B strongly inhibited Staphylococcus aureus and Bacillus subtillis at 50 p.p.m. The exact MIC will be published in detail elsewhere.



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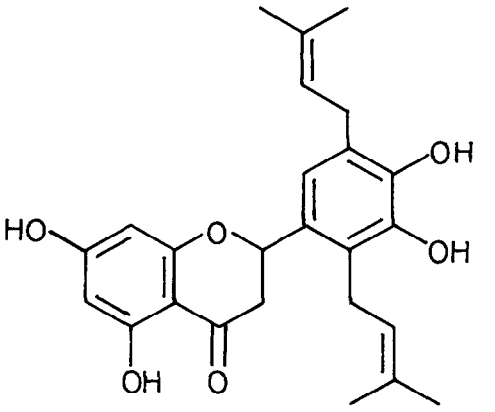

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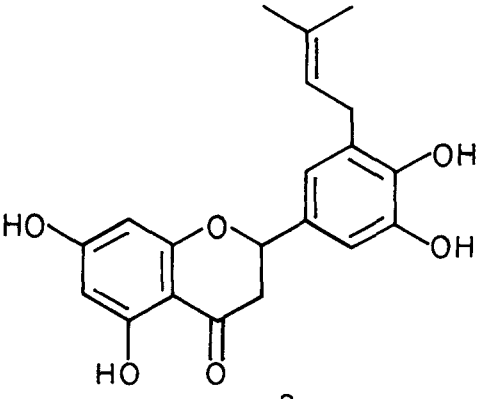

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