Pergamon

Tetrahedron Letters 40 (1999) 7197–7200

TETRAHEDRON LETTERS

21-α-Cyano-3-isorauniticine: a spurious heteroyohimbine structure assignment

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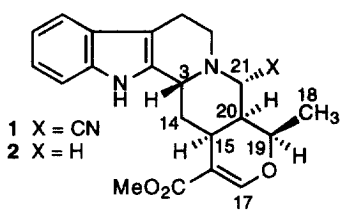
Received 12 July 1999; accepted 27 July 1999

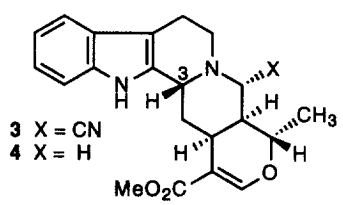
Abstract

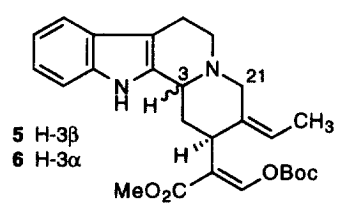
A claim by Lounasmaa and Hanhinen to have synthesised a biogenetic intermediate to heteroyohimbine alkaloids, 3-iso-19-epicathenamine, isolated as the cyano adduct, 21-α-cyano-3-isorauniticine, is wrong; the product is now shown by n.O.e. difference spectra to be in reality the known 21-α-cyano-akuammigine. Their "correction" of the latter structure is thus proven to be totally invalid.

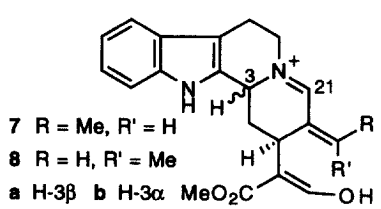
Key words: Alkaloids, biogenesis, indole, NMR, stereochemistry

In a recent publication[1] Lounasmaa and Hanhinen claimed to have prepared 21-α-cyano-3-isorauniticine **1** in 20% yield from Polonovski-Potier reaction[2] of the N-oxide of (±)-*Z*-O-Boc-3-epigeissoschizine **5** *via* a C-21 iminium intermediate **7a**, cyclisation and trapping of the resultant 3-iso-19-epicathenamine with cyanide. Furthermore, on the basis of a comparison of ^{1}H-NMR data, they also claimed that their product was identical with the 21-α-cyanoheteroyohimbine that several years ago we had obtained by hydrolysis of vincoside and characterised as 21-(*S*)-cyano-akuammigine **3**.[3,4] Without any further justification, they stated categorically that our structure assignment was wrong. To say the least, we were surprised at this assertion, since our assignment appeared secure, involving *inter alia* a straightforward reductive cleavage of the cyanide to afford a product identical with natural akuammigine **4**.









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0040-4039/99/$ - see front matter
PII: S0040-4039(99)01564-6

Since the epimeric alkaloids 3-isorauniticine **2** and akuammigine **4** differ only in the configuration at C-19, the same must apply to the corresponding 21-α-cyano derivatives **1** and **3**. Their paper revealed no experimental evidence for the purported C-19 stereochemistry of their product - neither an analogous reduction to 3-isorauniticine nor any relevant spectroscopic data - merely an uncorroborated statement that an intermediate such as **7a** with a Z-ethylidene (like their starting material **5**) is involved. Hence, either the two products are different, or if they are the same, one structure assignment must be wrong.

Although their product was racemic and ours was a single enantiomer, the ^{1}H-NMR spectroscopic data were essentially identical (within instrumental error).[1,3] We have now obtained the ^{13}C-NMR spectrum for an original sample of our compound and found that this also corresponds to their published data.[1] On this basis, we concur that in all likelihood the two compounds have the same structure and relative stereochemistry.

With regard to the configuration at C-19, it is not possible to differentiate between **1** and **3** from the observed coupling of ~1 Hz in the NMR spectrum between H-19 and H-20, since the dihedral angle is similar in both cases. However, in contrast to the alkaloids **2** and **4**, which are conformationally mobile,[5] the presence of an equatorial 21-cyano group effectively leads to 'locked' conformations for both **1** (Figure 1) and **3** (Figure 2). For example, to form the latter, attack by cyanide on the iminium intermediate (Figure 3) necessarily occurs axially at C-21 from the less hindered underside, but the resulting 1,3-diaxial interaction with the indole moiety is relieved by ring flip to the much more stable conformation in Figure 2, which then predominates. Consequently, nuclear Overhauser enhancement spectroscopy should provide the crucial information about the spatial environment of H-19 and Me-18. We duly obtained n.O.e. difference spectra (at 400 Mhz) on our compound and the key results are summarised in the Table.

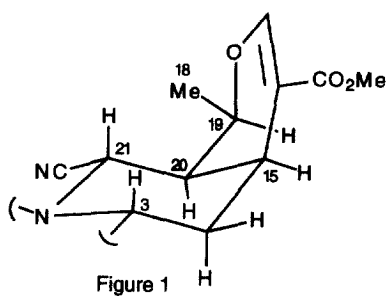

Figure 1

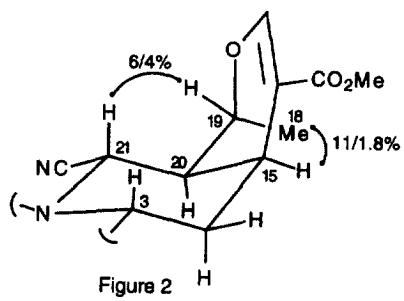

Figure 2

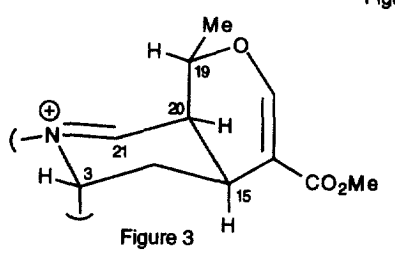

Figure 3

Table

N.O.e. data for 21-α-cyano-akuammigine

	Enhancement				
Irradiated H	H-15 %	H_3-18 %	H-19 %	H-20 %	H-21 %
H-15	-	1.8	0	6	-
H_3-18	11	-	18	-	0
H-19	0	2.5	-	8	4
H-21	-	0	6	-	-

In particular, irradiation of Me-18 gave a substantial enhancement of 11% for H-15 (1.8% for the reverse) and none for H-21; irradiation of H-19 gave 4% enhancement for H-21 and none for H-15; irradiation of H-21 gave 6% enhancement for H-19 and none for Me-18. These data are only compatible with the 21-α-cyano-akuammigine structure **3** as depicted in Figure 2, since for the alternative structure **1** (Figure 1) interactions would have been expected between H-21 and Me-18, and between H-19 and H-15, with none between Me-18 and H-15 or H-21 and H-19. We have thus confirmed, yet again, that our structure is 21-*S*-cyano-akuammigine **3** and hence that Lounasmaa's product must be the corresponding racemate of **3** and *not* the purported 21-α-cyano-3-isorauniticine **1**.

We are at a loss to understand why Lounasmaa and Hanhinen did not use the above standard NMR methodology, and also chose to ignore our simple chemical correlation with akuammigine by reduction of **3** with sodium borohydride in ethanol, which they could have repeated. Again, we had also isolated akuammigine *directly* by using hydride instead of cyanide as trapping agent for the intermediate 3-isocathenamine.[6] Apparently, they preferred to proceed on the naive assumption that the *Z* configuration of the ethylidene in *Z*-3-isogeissoschizine **5** would be retained throughout. For 21-dehydro intermediates such as **7** and **8** which are involved here, there is ample evidence and mechanistic study of ready *E/Z* equilibration as, for example, in cathenamine/19-epicathenamine interconversions.[2,4,7]

Ironically, Lounasmaa and co-workers themselves provide significant clues to the real situation in a previous paper![8] In a similar Polonovski-Potier procedure, formation of 21-α-cyanotetrahydroalstonine[3§] (**3**, H-3α) with H-19β configuration as the *major* product from *Z*-geissoschizine **6** (together with a *minor* amount of 19-epi-ajmalicine with H-19α) was attributed to isomerisation of a *Z*-21-dehydro intermediate **7b** to an *E*-ethylidene **8b**. Our rationalisation[4,5] of stereochemical control in cyclisation to heteroyohimbines, *i.e.* that H-19α requires a *Z*-alkene and H-19β an *E*-alkene, was then used (without attribution) to account for the production of both C-19 configurations. Obviously, a similar *Z/E* isomerization of **7a** to **8a** has likewise occurred in the 3-epi series, resulting in a low yield of **3** from **5**.

§ N.B. There are two errors in ref. 3: in the ^{1}H-NMR data τ8.37 should read τ8.57 (δ1.43), and the bond to CN in structure 7 should be hatched.

It is indeed feasible that in their reaction some 21-cyano-3-isorauniticine may have been produced from intermediate **7a**, but they certainly have not isolated it. Mere assertion is no substitute for sound experimental data: their presumptuous claim to "correct" our structure assignment for 21-cyano-akuammigine is completely without foundation. Incidentally, the status of all vincoside (H-3β) derivatives, including 3-isocathenamine and 3-iso-19-epicathenamine, as actual biogenetic precursors *in vivo* is dubious. No incorporation of vincoside has been achieved, whereas, in addition to the expected H-3α(*S*) indole alkaloids, various H-3β(*R*) indole alkaloids have also been shown to be biosynthesised from strictosidine (H-3α) *via* an oxidation/reduction process at C-3.[9]

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