TOTAL SYNTHESIS OF NAUCLEA ALKALOID NAUCLEFICINE

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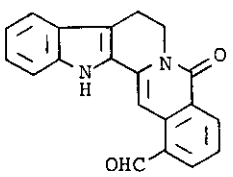
Abstract——— The first total synthesis of naucleficine (1), an alkaloid of Nauclea officinalis, was achieved according to the route involving enamide photocyclization.

In 1984,[1] Mao and his co-workers isolated three new alkaloids, naucleficine (1), nauclefidine, and nauclefoline from the stems of Nauclea officinalis Pierre ex Pitard (Rubiaceae) which grows in the southern part of China and has been used as an anti-inflammatory and anti-bacterial medicinal in Chinese folk medicine. As an extension of our synthetic study on the groups of both yohimbine[2] and heteroyohimbine alkaloids,[3] we now report the first total synthesis of naucleficine (1) by employing enamide photocyclization[4] which makes the alkaloid readily available by a concise method that is well suited to a multigram scale synthesis. In order to apply regioselective photocyclization of the o-methoxy-substituted enamide[5,6] to the synthesis of benz[g]indolo[2,3-a]quinolizine compound having a methoxycarbonyl group at 16-position, we chose harmalane as an imine portion and 2-methoxy-3-methoxycarbonylbenzoic acid as an acyl portion for the preparation of the starting enamide.

The known 2-hydroxyisophthalic acid (2a)[7] was treated with an excessive amount of methyl iodide to give the trimethoxy compound (2b) which was hydrolyzed with one molar amount of potassium hydroxide to afford the corresponding potassium salt of the half ester (2c). Acylation of harmalane with 2-methoxy-3-methoxycarbonylbenzoyl chloride, which was prepared by treatment of the corresponding potassium salt (2c) with thionyl chloride, afforded the desired enamide (3a) in a good yield. The enamide (3a) was so unstable that it was without purification irradiated in three different solvent systems with high pressure mercury lamp with a Pyrex filter at 5-10°C for 1.5 h.

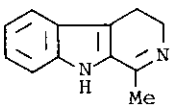
Chromatography of the respective reaction mixture on silica gel separated two readily crystallized products (4a) and (5a) in the yields as shown in Table. These structures were confirmed from the following spectral data. The main product (4a) showed a molecular ion at m/z 344 in mass spectrum and the n.m.r. signals at δ8.70 (br d, J=8 Hz, 19-H), 8.37 (dd, J=8 and 1.5 Hz, 17-H), 8.03 (s, 14-H), 7.45 (t, J=8 Hz, 18-H), and 4.00 (s, COOMe) which established the desirably substituted structure on the ring E of (4a) thus suggesting that the lactam (4a) is identical with oxygambirtannine[8] and would be formed expectedly as a result of photocyclization at the root of the o-methoxyl group followed by elimination of a methanol moiety from the resulting intermediate (B) as documented previously on the o-methoxy-substituted enamides.[5,6] On the other hand, the minor product (5a) showed a molecular ion at m/z 374 in mass spectrum and the n.m.r. signals at δ7.97 (d, J=8 Hz, 17-H), 7.26 (d, J=8 Hz, 16-H), 6.61 (s, 14-H), 4.10 (s, COOMe), and 3.96 (s, OMe) which established the structure of the lactam (5a) having two substituents at both 18- and 19-positions. Although the ratio of preferential formation of the desired lactam (4a) was slightly improved by using either ether or benzene as a solvent for irradiation, it is quite exceptional to have observed that photocyclization of the enamide (3a) showed low regioselectivity in the direction of cyclization though (3a) carries a methoxyl group at o-position. In order to clarify the substituent effect in enamide photocyclization, the enamide (3b) having a methoxycarbonyl group at m-position was prepared from harmalane and the potassium salt (2d) and irradiated. A homogeneous lactam (5b) was obtained as a sole product in a good yield. These evidences on the direction of cyclization in addition to the previously reported regioselective photocyclizations of a number of o-methoxy-substituted enamides[5,6] and anilides[9] would explain regioselectivity of (3a) to (4a) and (5a) as follows: in the case of the enamide having an electron-attracting group such as methoxycarbonyl group in addition to a methoxyl group at o-position, the photocyclization would proceed to afford a mixture of two lactams as a result of the preferential contribution of an excited form (A) over the another form (C). Further study on the substituent effect in the photocyclization of poly-substituted enamides is now in progress.



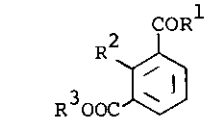
naucleficine (1)

Table

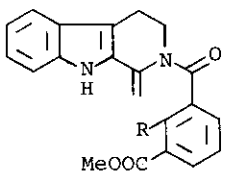
Solvent	Yield (%) (4a)	(5a)
MeCN	53	26
C_6H_6	58	19
Et_2O-MeOH (40 : 1)	56	19



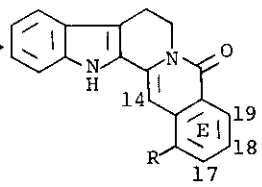
harmalane



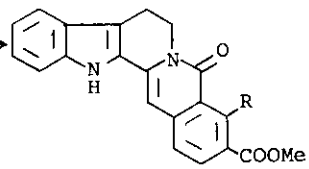
	R^1	R^2	R^3
(2a)	OH	OH	H
(2b)	OMe	OMe	Me
(2c)	OK	OMe	Me
(2d)	OK	H	Me



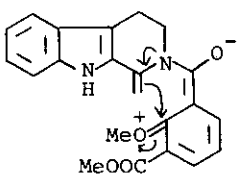
(3a) R=OMe
(3b) R=H



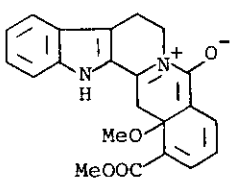
(4a) R=COOMe
(4b) R=CH_2OH



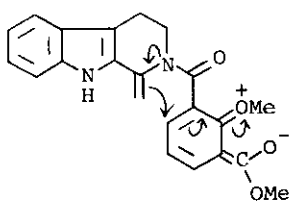
(5a) R=OMe
(5b) R=H



(A)



(B)



(C)

The ester (4a) was reduced with sodium borohydride by refluxing in MeOH-THF to give the alcohol (4b) in quantitative yield, which was then oxidized with manganese dioxide in chloroform to afford the desired aldehyde (1), mp 284-290°C (lit.,[1] lcp. 290-291°C) in 66 % yield. Direct comparison of i.r. and n.m.r. spectra of the synthetic aldehyde (1) with those of the authentic naucleficine established their identity, thus completed the first total synthesis of the alkaloid.

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