# Regiospecific Cyclisation of 1,2,3,4-Tetrahydro-1-methylene-2-nicotinoyl-β-carbolines: a Synthesis of Naucléfine

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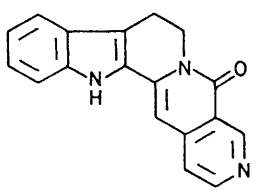
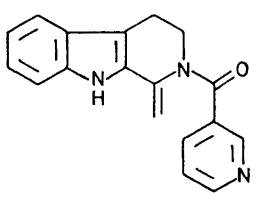
*Summary* The alkaloid naucléfine has been synthesised from 1,2,3,4-tetrahydro-1-methylene-2-nicotinoyl-β-carboline by the action of benzyl bromide, followed by debenzylation; the problem of isomer formation is avoided and the overall yield is 55%.

NAUCLÉFINE (**1**) is a minor alkaloid of certain plants of the genus *Nauclea* (Rubiaceae).[1] The extracts of one such plant *N. parva* Merrill[1a] show activity against the experimental P 388 tumour in mice and as a result there has been interest in the synthesis of naucléfine and its congeners[1,2] in order to determine the source(s) of this activity.

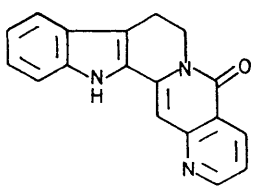
The most efficient route to naucléfine embodies the photocyclisation, and subsequent oxidation, of the enamide (**2**), but it is marred by the concomitant formation of isonaucléfine (**3**) which may only be separated from (**1**) by very careful column chromatography.[3] The enamide (**2**) is prepared from harmalan and nicotinoyl chloride, but we have noted that when excess of nicotinoyl chloride is used the required product is contaminated with a yellow solid



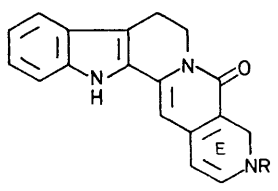

(1)




(2)

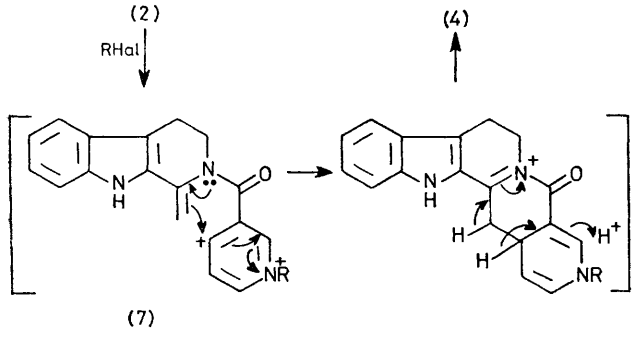



(3)




(4) R = nicotinoyl
(5) R = H
(6) R = benzyl: ring E aromatic

which exhibits i.r. bands corresponding to *two* amide carbonyl groups. This has been shown to be the dihydro-derivative of naucléfine (**4**), and when 2 mol. equiv. of




nicotinoyl chloride are used this is the sole product of the reaction. We envisage its formation as shown (**2** → **4**) assuming that the bulky substituent group on the pyridine N atom of (**7**) now precludes cyclisation other than at C-4 of this unit. This conclusion is supported by the fact that acid treatment of (**2**) gives a mixture of naucléfine and isonaucléfine, the latter predominating (molar ratio 1:6; *cf.* ref. 1a).

Clearly, if the nicotinoyl group of (**4**) could be cleaved by hydrolysis, *etc.* then the parent compound (**5**) should be oxidised easily to naucléfine effecting a regiospecific synthesis. Unfortunately, it has not been found easy to achieve this cleavage, but if the enamide (**2**) is treated with benzyl bromide the only product isolated is the quaternary salt (**6**) which may be *N*-debenzylated by heating in toluene containing acetic acid and sodium acetate to naucléfine (**5**); the yield from (**2**) is 55%. We have been unable to isolate the dihydro-derivative of (**6**); oxidation to the quaternary salt occurs spontaneously during work-up.

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[2] T. Kametani, M. Takeshita, M. Ihara, and K. Fukumoto, *J. Org. Chem.*, 1976, **41**, 2543.
[3] M. Sainsbury and N. L. Uttley, *J.C.S. Perkin I*, 1976, 2416.