A FACILE SYNTHESIS OF DESOXYSESBNINE. AN APPROACH TO THE SESBA-NINE SKELETON.

Martinus J. Wanner, Gerrit-Jan Koomen and Upendra K. Pandit.*

Organic Chemistry Laboratory, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS AMSTERDAM, The Netherlands.

Abstract. Reaction of ethyl cyclopentanecarboxylate anion with N-benzylnicotinamide salt leads to the formation of the spiro-tricyclic skeleton of sesbanine.

The alkaloid sesbanine, isolated from the extracts of the seeds of Sesbania drummondii has been shown to possess the novel structure 1, which contains the spirocyclic 2,7-naphthyridine nucleus. The reported anti-leukemic properties of the alkaloid, coupled with its low content in the extracts, makes the availability of the alkaloid and its analogues via total synthetic route very desirable. As a part of our programme on the development of potential carcinostatic compounds we have directed our attention to a practical synthesis of sesbanine. The recent report by Kende and Demuth prompts us, at this stage, to disclose our convenient synthesis of the sesbanine skeleton.

Our strategy for the construction of the tricyclic framework of sesbanine anticipated that the coupling of an appropriately substituted cyclopentyl ester with a suitably activated nicotinamide derivative, would provide a precursor which should possess the desired functionality for its elaboration to sesbanine. In order to test this basic scheme, the anion of ethyl cyclopentanecarboxylate was allowed to react with N-benzylnicotinamide (2) (LDA/THF, -30°, 4 h), whereupon the crystalline spirocyclopentyl naphthyridine 3a was obtained in 51% yield. It should be remarked that the aforementioned procedure provides the complete tricyclic skeleton of sesbanine in one practical step, from readily available starting materials. The desired oxidation and substitution level of the 2,7-naphthyridine nucleus was achieved via the two-step sequence 3a → 4a → 5a. Oxidation of 3a was carried out by reaction with 1-ethoxycarbonylmethylenequinolinium bromide (CHCl₃, room temp., 3h) to yield 4a (75%). Subsequent hydrogenation (Pd/C, 10%, CH₃OH, 1 atm, 3 h) resulted in debenzylation to give crystalline 5a (53%). That the scope of the initial coupling reaction leading to the spirocyclic system could be extended to function-
alized cyclopentyl esters, was illustrated by the reaction of the Schiffs base of p-bromoaniline and 2-cyclopentanonecarboxylate ester with 2 (NaH/THF; addition to the Schiffs base anion at -76° followed by warming to 20°), which resulted in the formation of 3b (97%). Attempts to achieve an analogous reaction between methyl 2-cyclopentanonecarboxylate and N-benzylnicotinamide, led, however, to the formation of a new tricyclic product 3c. In a reaction sequence similar to the one described for 3a, the naphthyridine derivative 3b was oxidized and debenzylated to 5b.

The total synthesis of sesbanine via the appropriately substituted (optically active) cyclopentane derivative is currently under way and the detailed results will be presented elsewhere. The extremely facile synthesis of the spirocyclopentyl 2,7-naphthyridine system, described in this report, allows an entry to a wide variety of analogues and derivatives of the alkaloid.

References.
4. 3a M.p. 174-178°. IR(KBr): 3200, 1700, 1670, 1660, 1580 cm⁻¹. ¹H NMR(DMSO-d₆): δ 1.5-1.8 (m, 4H); 2.0-2.5 (m, 2H); 3.7-3.8 (m, H₄a); 4.45 (s, -CH₂Ph); 4.58 (d x d, J=2, J=8, H₄); 6.14 (d x d x d, J=1.5, J=2, J=8, H₃); 7.22 (d, J=1.5, H₆); 7.31 (s, Ph-H), 10.1 (broad, N-H). MS(70 eV): 308 (M⁺).
5. 4a: M.p. 220-230°. IR(KBr): 3580, 3370, 1725, 1700, 1640 cm⁻¹. ¹H NMR (CD₂OD): δ 1.7-2.8 (m, 4 x CH₂), 5.95 (s, CH₂Ph); 7.45 (s, Ph-H), 8.20 (d, J=7, H₃); 9.08 (d x d, J=2, J=7, H₆); 9.53 (d, J=2, H₈).
6. 5a: M.p. 204-207°. IR(CHCl₃): 3360 (N-H), 1720, 1700, 1600 cm⁻¹. ¹H NMR (DMSO-d₆): δ 1.5-2.5 (m, 4 x CH₂); 7.56 (d, J=5.5, H₃); 8.75 (d, J=5.5, H₆); 9.08 (s, H₈); 11.35 (broad, N-H).
7. 3b: Yellow glass. IR(CHCl₃): 3400, 1705, 1685, 1660 and 1580 cm⁻¹. ¹H NMR (CDCl₃): δ 1.5-3.0 (m, 6H, -CH₂CH₂CH₂⁻); 4.38 (s, CH₂Ph); 4.56 (d x d, J=2.5, J=8, H₄); 4.64-4.70 (m, H₄a); 5.90 (d x d x d, J=2, J=2.5, J=8, H₆); 6.62 (d, J=9, 2H, 2 x H₉A⁺); 7.1-7.5 (m, 8H, Ph-H + H₈ + 2 x H₉A⁺); 8.25 (broad, N-H).
8. The tricyclic product has been identified as A. Details about the reaction leading to A will be described in a separate communication.

9. 4b: M.p. 215-218° (80%). IR(KBr): 3400, 1720, 1705, 1670, 1640 cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.0-3.0 (m, 6H, -CH₂CH₂CH₂-); 6.04 (s, -CH₂Ph); 6.8-7.7 (m, Ph-H and Ar-H); 8.02 (d, J=7, H₅); 9.2 (d x d, J=2, J=7, H₆); 9.63 (d, J=2, H₇).

5b: Glass. IR(CHCl₃): 3380, 1720, 1700, 1675 and 1600 cm⁻¹. ¹H NMR(CDCl₃): 1.7-3.2 (m, 6H, -CH₂CH₂CH₂-); 6.52 (d, J=9, 2 x H₁Ar); 7.2 (d, J=6, H₅); 7.37 (d, J=9, 2 x H₂Ar); 8.85 (d, H₆); 9.49 (s, H₇).

Received, 10th March, 1980