A New Stereoselective Synthesis of (±)-Crinan, Basic Ring System of the Alkaloid Crinine

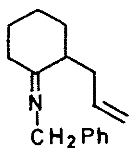
By I. NINOMIYA,* T. NAITO, and T. KIGUCHI
(*Kobe Women's College of Pharmacy, Motoyama, Higashinada, Kobe, Japan*)

Summary (±)-Crinan, the basic ring system of crinine, has been synthesized through stereoselective photocyclization.

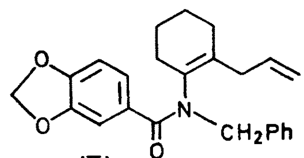
CRINAN, 8,9-methylenedioxy-1,2,3,4,4a,5,6,11b-octahydro-5, 10b-ethanophenanthridine, the ring system of crinine,[1] which is a representative of the widely occurring Amaryllidaceae alkaloids, has been synthesized recently by two groups.[2] The present investigation was undertaken in order to synthesize (±)-crinan stereoselectively applying the photocyclization of an *N*-benzoyl-enamine.[3]

2-Allylcyclohexanone was treated with benzylamine to give the imine (I), which was immediately acylated with piperonyloyl chloride. Purification by chromatography on silica gel afforded the *N*-acyl-enamine (II), b.p. 200°/2 × 10^{-3} mm Hg, ν_{max} ($CHCl_3$) 1630—1600 (broad), 995, 940, and 920 cm^{-1}; n.m.r. δ ($CDCl_3$): 5·95 (2H, s, OCH_2O), 5·8—4·6 (3H, $\cdot CH{:}CH_2$), 4·95 and 4·6 (2H, AB-type q, *J* 14Hz, $N\cdot CH_2Ph$), and 2·9—2·0 p.p.m. (2H, broad 8 lines, $:C\cdot CH_2\cdot CH{:}CH_2$).

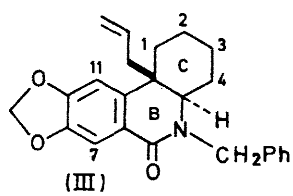
A methanolic solution (0·02 M) of (II) was irradiated with a low-pressure mercury lamp at room temperature for 15 h. Chromatography of the reaction mixture on silica gel afforded a readily crystallized compound (III), m.p. 157—158°, in 15% yield. The structure and stereochemistry of (III) were established from spectral data: ν_{max} (Nujol) 1640, 1615, 995, 930, and 910 cm^{-1}; n.m.r. δ ($CDCl_3$); 7·7 (1H, s, 7-H), 6·65 (1H, s, 11-H), 6·0 (2H, s, OCH_2O), 5·4 and 4·4 (2H, AB-type q, *J* 16Hz, $N\cdot CH_2Ph$), 5·9—4·7 (3H, $\cdot CH{:}CH_2$), 3·7



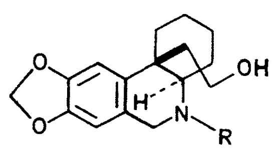
(I)



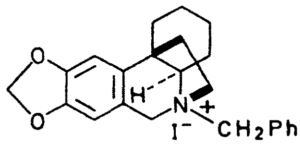
(II)



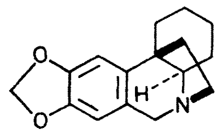
(III)



(IVa) R = CH2Ph
(IVb) R = H



(V)



(VI)

† All m.ps and b.ps are uncorrected; satisfactory analyses were obtained on the compounds described.

(1H, d-d, *J* 11 and 5Hz, 4a-H), and 2·4 p.p.m. (2H, broad d, *J* 6·5Hz, $\cdot CH_2\cdot CH:CH_2$), which unequivocally established the orientation of cyclization as that shown in structure (III). Assignment of the B/C *trans* ring juncture to (III) was deduced on the basis that this type of photocyclization should afford only the *trans*-isomer if it followed the electrocyclic mechanism suggested previously,[4] and the identity with crinan of the final product (VI) derived from the photoproduct (III).

Ozonolysis of (III) followed by lithium aluminium hydride reduction afforded the amino-alcohol (IVa), m.p. 190—191°, in 54% yield. Debenzylation of (IVa) with 40% Pd–C afforded the *N*-nor-amino-alcohol (IVb) in good yield. Treatment of (IVb) with thionyl chloride in dioxan was accompanied by spontaneous ring closure to give (±)-crinan (VI), which was homogeneous and whose i.r. spectrum was identical with that of an authentic sample.[1] Its hydrochloride had m.p. 252—254° (dec.) On the other hand, the amino-alcohol (IVa) was converted in good yield into the iodide (V) on heating under reflux with toluene-*p*-sulphonyl chloride in pyridine followed by treatment with aqueous potassium iodide. This salt, m.p. 188—191°, was then subjected to hydrogenolysis with 40% Pd–C, affording (±)-crinan together with a considerable amount of the starting material. This synthesis confirms the stereochemistry of the compounds involved and therefore the stereoselectivity of the photocyclization to the *trans*-fused ring system as in (III), and offers a promising approach to total synthesis of the alkaloids of this group,[5] which have additional substituents only on C-1 and/or C-2.

We thank Prof. W. C. Wildman for providing us with the i.r. spectrum of (−)-crinan.

(*Received, October 30th*, 1970; *Com.* 1887.)

[1] W. C. Wildman, "The Alkaloids" ed. R. H. F. Manske, Academic Press, New York, 1960, Vol. VI, p. 290.
[2] H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *J. Amer. Chem. Soc.*, 1966, **88**, 3670; W. C. Wildman, *ibid.*, 1958, **80**, 2567.
[3] I. Ninomiya, T. Naito, and T. Mori, *Tetrahedron Letters*, 1969, 2259, 3643.
[4] I. Ninomiya, T. Naito, and T. Mori, Abstracts of the 2nd. Symposium on Heterocyclic Chemistry, Nagasaki, November, 1969, p. 177.
[5] T. Kametani, "The Chemistry of the Isoquinoline Alkaloids" Hirokawa, Tokyo, 1968, p. 176.