Tetrahedron Letters No. 46, pp 4393 - 4394, 1971. Pergamon Press. Printed in Great Britain.

ONE-STEP SYNTHESIS OF HALFORDINOL

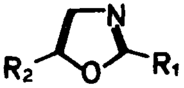
Tadamasa Onaka

ITSUU Laboratory, Tamagawa 2-28-10, Setagaya-ku, Tokyo, Japan

(Received in Japan 20 September 1971; received in UK for publication 12 October 1971)

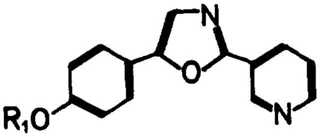
Five naturally occurring bases with an oxazole ring have been known to date, all bearing substituent at 2 and 5 position[1-4] and because of their relatively simple structure most of them have been synthesized.[1,2,5] All of these syntheses, however, used the Robinson-Gabriel synthesis[6] and not by the application of Fisher oxazole synthesis.[7] Robinson-Gabriel synthesis is reliable but it is a multi-step elaboration and the overall yield is often poor. Fisher's method, on the contrary, might provide 2,5-disubstituted oxazoles in one step and applicability of this process to the synthesis of above alkaloids was examined.

Halfordinol (IIa), the mother compound of oxazole alkaloids of Rutaceae, was selected as the objective molecule for the synthesis. Though this base had been synthesized by Brossi and Wenis by way of Robinson-Gabriel method, overall yield was as poor as 0.62%, after 5 steps of troublesome elaboration including a chromatographic separation.[5]



I

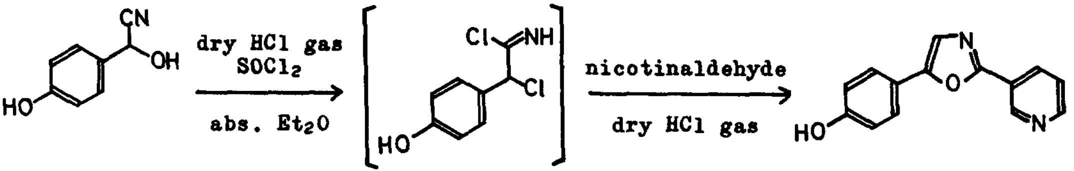
	R_1	R_2	Alkaloid	Lit.
Ia	3,4-diMeOPh-CH=CH-	p-anisyl	annuloline	1.
Ib	Me	β-indolyl	pimprinine	2.



II

	R_1	Alkaloid	Lit.
IIa	H	halfordinol	3.
IIb	$Me_2C(OH)CH(OH)CH_2$-	halfordine	3.
IIc	$Me_2C{=}CHCH_2$-	-	4.

When the Fisher synthesis is used to prepare halfordinol (IIa) from p-hydroxymandelonitrile (III) and nicotinaldehyde, there is a possibility that two different aldehydes and two cyanohydrins may be simultaneously present, if one takes account of the dissociation of III to aldehyde and HCN and of a recombination of HCN with nicotinaldehyde. The addition of $SOCl_2$ to III, however, may prevent the dissociation of cyanhydrin to aldehyde and, hence, may constitute a reliable modification of Fisher oxazole synthesis.



III

IIa

Dry HCl gas was passed and saturated in an ice-cold solution of freshly prepared crystals of 0.94 g of p-hydroxymandelonitrile8) (III) in 45 ml of anhydrous ether. After an addition of 1.12 g of $SOCl_2$, the reaction mixture was stirred for 10 min. with external cooling. Then an addition of 0.75 g of nicotinaldehyde was followed and the reaction mixture was saturated with dry HCl once again. After standing at room temperature for 2 days, the reaction mixture was poured into water and the separated organic layer was further extracted with aq. HCl. Neutralization of the combined aqueous layers with Na_2CO_3 resulted in the precipitation of halfordinol (IIa) which was collected on a filter and recrystallized from methanol to fine cream needles of mp 254-5° (lit. 255-5°3)); yield, 248 mg (16.5%). Mixed mp determination, thin-layer chromatographic behavior, and IR(KBr) spectral comparison with the authentic sample prepared from natural N-methylhalfordinium chloride,3) proved the identity of both samples. Mp (99-100°; Lit. 99-100°) and NMR spectrum of methyl ether of synthesized halfordinol also agreed well with the reported one.3)

These experiments clearly indicate the utility of present modification of Fisher's method for the synthesis of oxazole alkaloids. More particularly, the oxazole alkaloid of Rutaceae (e.g. IIb and IIc), whose synthesis has not been recorded, should easily be derived from halfordinol which can now be obtained in a sufficient quantity.

<u>Acknowledgment</u> The author expresses his deep gratitude to Dr. M. Natsume and Professor Emeritus E. Ochiai for their valuable advice and encouragement throughout this work. Grateful thanks are due to Prof. W. D. Crow of Canberra for generous supply of N-methylhalfordinium chloride.

References

1. R. S. Karimoto, B. Axelrod, J. Wolinsky and E. D. Schall: Tetrahedron Letters, 1962, No. 3, 83.
2. B. S. Joshi, W. I. Taylor, D. S. Bhate and S. S. Karmarkar: Tetrahedron, 19, 1437 (1963).
3. W. D. Crow and J. H. Hodgkin: Tetrahedron Letters, 1963, No. 2, 85; Austr. J. Chem., 17, 119 (1964).
4. D. L. Dreyer: J. Org. Chem., 33, 3958 (1968).
5. A. Brossi and E. Wenis: J. Heterocycl. Chem., 2, 310 (1965).
6. J. W. cornforth: "Heterocyclic Compounds" ed. by R. C. Elderfield, Vol. 5, p. 302. J. Wiley, New York (1957).
7. Idem: ibid. p. 309.
8. K. Ladenburg, K. Folkers and R. T. Major: J. Am. Chem. Soc., 58, 1292 (1936).