CYCLIZATION REACTION OF 1-METHYLENE-2-NICOTINOYL-1,2,3,4-TETRAHYDROISOQUINOLINES AND A TOTAL SYNTHESIS OF ALAMARINE

Takeaki Naito, Okiko Miyata, Ichiya Ninomiya*, and Satyesh C. Pakrashi#

Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan and # Indian Institute of Experimental Medicine, Calcutta-700032, India.

Abstract ------- Under photochemical, thermal and acylating conditions, cyclization of 1-methylene-2-nicotinoyltetrahydroisoquinolines was investigated and as a result the alkaloid alamarine was synthesized via the route involving enamide cyclization under both thermal and photochemical conditions.

Pakrashi et al[1] have isolated several alkaloids, alamarine, alangimarine, alangimaridine, and isoalamarine, from Alangium lamarckii Thw., Alangiaceae, grown in India, of which alamarine is a representative of these benzo[a]pyrido[3,4-g]-quinolizine alkaloids, and proposed the structure (3e) for alamarine. We now report the first total synthesis of alamarine (3e) via the route involving enamide cyclization under both thermal and photochemical conditions.

We first investigated the cyclization of the N-nicotinoylenamines (enamides) in the course of our study[2] on the reaction of enamides. Acylation of the 3,4-dihydroisoquinoline (1a) with three kind of the nicotinoyl chlorides in the presence of triethylamine afforded the corresponding enamides (2a, b, and c)[3] in good yields respectively. The cyclizations of these enamides (2a, b, and c) were examined under the conditions of irradiation (low pressure mercury lamp), thermolysis (neat, heating at 195-200°), and acylation (refluxing in benzene in the presence of one molar amount of benzoyl chloride) respectively, and their results were collected in the table.

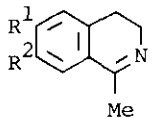
Upon irradiation or thermolysis, the enamides (2a, b, and c) underwent smooth cyclization to result in the predominant formation of the 2,7-naphthyridines (3a, b, and c)[3] along with small amounts of the 1,6-naphthyridines (4a, b, and c)[3]. However, thermal cyclization of the enamide (2a) which is unsubstituted on the pyridine ring resulted in the sole formation of the acyl-migration product (5)[3]. On the other hand, the 1,6-naphthyridines (4b and c) were obtained as a major product from the enamides (2b and c) under acylating condition.

Thus, establishment of a selective synthetic route to either 2,7- or 1,6-naphthyridine pushed us to synthesize the alkaloid alamarine by the application of thermal cyclization of enamides.

Treatment of sodium 5-acetylnicotinate[4] with oxalyl chloride afforded the acid chloride, which without further purification was treated with 7-benzyloxy-3,4-dihydroisoquinoline (1b)[5] to afford the corresponding enamide (2d) as yellow solid, δ 5.10 and 4.27 (each 1H, d, J= 1.5Hz, olefinic H).

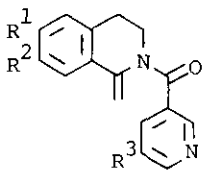
The enamide (2d) was heated in an oil bath at 180-200° for 20 min. and chromatography of the reaction mixture on silica-gel separated two products (3d) and (4d) in 43 and 10 % yields respectively. [(3d); m.p. 198-199°, δ 9.50 and 9.03 (each 1H, s, 2- and 4-H), and 2.67 (3H, s, Ac). (4d); m.p. 218-219° , δ 9.25 and 8.93 (each 1H, d, J= 2Hz, 2- and 4-H), and 2.63 (3H, s, Ac). On the other hand, when the enamide (2d) was irradiated with a low pressure mercury lamp at room temperature for 8 h., a mixture of the products (3d) and (4d) was obtained in 25 and 13 % yields respectively upon chromatographic separation on silica-gel.

Acid catalyzed debenzylation[6] of (3d) followed by reduction with sodium borohydride afforded the alcohol (3e), m.p. 287-289° (lit.[1] 288°) in 85 % yield. Acetylation of (3e) with acetic anhydride afforded the diacetate (3f) as yellow solid, which was identical with alamarine diacetate (3f)[1], prepared from natural alamarine, upon comparisons of their Rf values on t.l.c. and i.r. and n.m.r. spectra. Since alamarine had been converted into alangimarine (3g)[1], this synthesis formally completed the total synthesis of alangimarine.



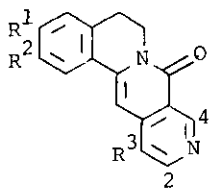
(1ab)

	R^1	R^2
a	OMe	OMe
b	OMe	OCH_2Ph



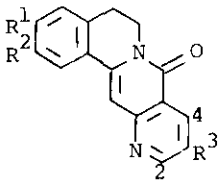
(2a-d)

	R^1	R^2	R^3
a	OMe	OMe	H
b	OMe	OMe	COOEt
c	OMe	OMe	Ac
d	OMe	OCH_2Ph	Ac



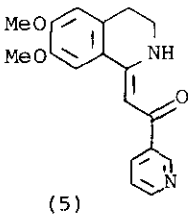
(3a-g)

	R^1	R^2	R^3
a	OMe	OMe	H
b	OMe	OMe	COOEt
c	OMe	OMe	Ac
d	OMe	OCH_2Ph	Ac
e	OMe	OH	-CH(OH)Me
f	OMe	OAc	-CH(OAc)Me
g	OMe	OH	$-CH=CH_2$

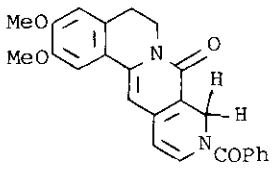


(4a-d)

	R^1	R^2	R^3
a	OMe	OMe	H
b	OMe	OMe	COOEt
c	OMe	OMe	Ac
d	OMe	OCH_2Ph	Ac



(5)



(6)

Table

Conditions		(3abc)	(4abc)	(5)	(6)
Photochemical	a	20	10	--	--
	b	43	22	--	--
	c	39	20	--	--
Thermal	a	--	--	35	--
	b	55	7	--	--
	c	54	10	--	--
Under Acylation	a	10	--	--	20
	b	4	34	--	--
	c	3	24	--	--

ACKNOWLEDGEMENT

The authors are grateful to Professor S. V. Kessar, Panjab University, India, for his kind advice and Dr. M. Sugiura, Kobe Women's College of Pharmacy, for the n.m.r. measurement. The author's appreciation (I.N) also extends to the Ministry of Education, Science and Culture, Japan, for the Research Grant.

REFERENCES

1 S. C. Pakrashi, B. Achari, E. Ali, P. P.Ghosh Dastidar, and R. R. Sinha, Tetrahedron Letters, 1980, 21, 2667.

2a) T. Naito, O. Miyata, and I. Ninomiya, J. Chem. Soc. Chem. Commun., 1979, 517.

b) T. Naito and I. Ninomiya, Heterocycles, 1980, 14, 959.

3 Structures of these products (2, 3, 4, 5, and 6) were firmly established from their spectral evidences.

4 I. Ninomiya, T. Naito, and H. Takasugi, J. Chem. Soc. Perkin I, 1976, 1865.

5a) H. Kondo, H. Kataoka, Y. Hayashi, and T. Uchibori, Itsuu Kenkyusho Nempo, 1958, 9, 1 [Chem. Abstr., 1960, 54, 1399^{e}]

b) I. T. Strukov, Zhur.Obshchei. Khim., 1961, 31, 2709 [Chem. Abstr., 1962, 56, 11567^{e}]

6 A. R. Battersby, R. Southgate, J. Staunton, and M. Hirst, J. Chem. Soc. (C), 1966, 1052.

Received, 19th January, 1981