A FORMAL TOTAL SYNTHESIS OF THE ALKALOID YOHIMBINE

Ichiya Ninomiya*, Yukiko Tada, Okiko Miyata, and Takeaki Naito.
Kobe Women's College of Pharmacy
Motoyamakita, Higashinada, Kobe 658, Japan.

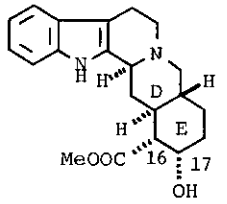
Abstract------- Photocyclization of the enamide (3a), which was readily prepared from harmalane and substituted benzoyl chloride, provided a simple preparation of the key intermediate (4a) for total synthesis of the alkaloid yohimbine.

Synthetic challenge to indole alkaloids has attracted much attention from many chemists. A crucial step in the synthesis of yohimbine (1)[1], a representative of indole alkaloids, would be the stereo-controlled introduction of two functionalized groups into 16- and 17-positions while holding a trans-configuration of D/E ring.

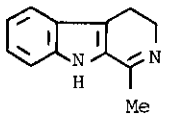
As an extension of our synthetic study on yohimbane[2], a basic structure of the alkaloid, we now report a simple synthesis of the potential intermediate (4a) in the total synthesis of yohimbine which had been described by Kametani and his coworkers.[3]

Harmalane (2) was acylated with 4-methoxy-3-methoxycarbonylbenzoyl chloride[4] to yield the corresponding enamide (3a), which was found to be so unstable that it was without purification irradiated in a benzene solution with a high pressure mercury lamp with a pyrex filter at room temperature. Chromatography of the reaction mixture on silica gel separated two readily crystallized products (4a and 4b) in 5 and 32 % yields respectively. The spectral data of these products [(4a); ir (Nujol) cm^{-1}: 3300, 1700, 1645; nmr ($CDCl_3$) δ : 9.00 (1H, br.s, NH), 8.41 (1H, d, J=9Hz, 19-H), 6.80 (1H, d, J=9Hz, 18-H), 6.58 (1H, s, 14-H), 4.42 (2H, t, J=7Hz, 5-H_2), 4.10 (3H, s, OMe), 3.76 (3H, s, OMe), 3.05 (2H, t, J=7Hz, 6-H_2); m/e 374 (M^+) and (4b): ir ($CHCl_3$) cm^{-1}: 3470, 1700, 1640; nmr ($CDCl_3$) δ : 9.33 (1H, br.s, NH), 9.00 (1H, s, 19-H), 6.68 and 6.75 (each 1H, s, 14- and 16-H), 4.58 (2H, t, J=7Hz, 5-H_2), 3.88 (3H, s, OMe), 3.84 (3H, s, OMe), 3.18 (3H, t, J=7Hz, 6-H_2); m/e 374 (M^+)] confirmed their structures as depicted and the former (4a) was identical with a known key intermediate[3a] to yohimbine upon comparisons with their spectral data.

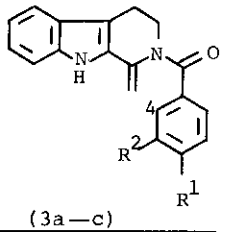
Though a formal total synthesis of yohimbine was thus completed by preparing the key intermediate (4a), non-regiospecificity of photocyclization pushed us to



(1)

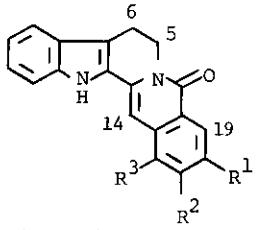


(2)



(3a—c)

	R^1	R^2
a:	-OMe	$-CO_2Me$
b:	-O-N=C(Me)-	
c:	$-OCH_2Ph$	-Ac



(4a—f)

	R^1	R^2	R^3
a:	-H	-OMe	$-CO_2Me$
b:	$-CO_2Me$	-OMe	-H
c:	-H	-O-N=C(Me)-	
d:	-C(Me)=N-O-		-H
e:	-H	-OH	-Ac
f:	-Ac	-OH	-H

investigate the cyclization in search of a suitable enamide for regiospecific photocyclization. We prepared the enamide (3b) having an isoxazole ring which would be expected to cyclize preferably at 4-position due to a comparable degree of aromaticity in the benzisoxazole ring system as in the case of N-(2-naphthoyl)enamine[5] and would also be expected to undergo facile ring cleavage into two functional groups.

Irradiation of the enamide (3b), which was prepared from harmalane and 3-methyl-1,2-benzisoxazole-5-carbonyl chloride[6], afforded a mixture of two types of the lactams (4c and 4d) in 19 and 3 % yields respectively. The structures of these products were established from their spectral data [(4c); ir (Nujol) cm^{-1}: 3330, 1640; nmr (CF_3CO_2H) δ: 8.73 (1H, d, J=10Hz, 19-H), 3.07 (3H, s, N=C-Me); m/e 341 (M^+); and (4d); ir (Nujol) cm^{-1}: 3250, 1640, 1625; nmr (CF_3CO_2H) δ: 8.72 (1H, s, 19-H), 7.50 (1H, s, 16-H), 2.60 (3H, s, N=C-Me); m/e 341 (M^+)] and the following reactions. Hydrogenolysis of (4c and 4d) with 10 % palladium on charcoal in the presence of triethylamine followed by hydrolysis of the resulting imino-phenols afforded the acetyl-phenols (4e and 4f) in good yields, which were identical with the corresponding lactams (4e and 4f) upon comparisons with the samples obtained from photocyclization of the enamide (3c) followed by hydrogenolysis of the benzyl group respectively.

Interestingly, no transposition of an isoxazole ring into oxazole[7] was observed during the course of photocyclization of the enamide (3b).

Finally, another synthetic approaches to this intermediate (4a) from (4e) by the conversion of an acetyl group into a carboxyl group by haloform reaction or treatment with I_2-pyridine[8a], $CuBr_2$-DMSO[8b] , and $CuBr_2$-pyridine[8c] were unsuccessful.

ACKNOWLEDGEMENT

The authors are grateful to Professor T. Kametani for the spectral data. Part of this work was supported by a Grant-in-Aid from the Ministry of Education, Science, and Culture, Japan.

REFERENCES

1) J. P. Kutney in " The Total Synthesis of Natural Products", ed. J. ApSimon, New York, 1977, vol.3, p 273.

2) I. Ninomiya, Y. Tada, T. Kiguchi, O. Yamamoto, and T. Naito, Heterocycles, 1978, 9, 1527.

3) a) T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, Chem. and Pharm. Bull. (Japan), 1975, 23, 2634.
b) T. Kametani, Y. Hirai, and K. Fukumoto, Heterocycles, 1976, 4, 29.

4) a) A. L. Mndzhoyan and A. A. Aroyan, Izvest. Akad. Nauk. Armyan. S. S. S. R., Ser. Khim. Nauk., 1957, 10, 203 [Chem. Abstr., 1958, 52, 7195].
b) G. Orzalesi, R. Selleri, O. Caldini, and R. Fahrizi, Boll. Chim. Farm., 1969, 108, 619. [Chem. Abstr., 1970, 72, 130810m]

5) I. Ninomiya and T. Naito, Kagaku no Ryoiki, special ed., 1979, No.123, p 69.

6) D. H. R. Barton, B. Halpern, Q. N. Porter, and (in part) D. J. Collins, J. Chem. Soc. (C), 1971, 2166.

7) J. P. Ferris, F. R. Antonucci, and R. W. Trimmer, J. Amer. Chem. Soc., 1973, 95, 919.

8) a) N. A. Lund, A. Robertson, and W. B. Whalley, J. Chem. Soc., 1953, 2434.
b) R. T. Major and H. J. Hess, J. Org. Chem., 1958, 23, 1563.
c) L. C. King and G. K. Ostrum, J. Org. Chem., 1964, 29, 3459.

Received, 28th February, 1980