HETEROCYCLES, Vol. 3, No. 4, 1975

SYNTHESIS OF N-DEMETHYLFAGARONINE

Ichiya Ninomiya * and Takeaki Naito

Kobe Women's College of Pharmacy
Motoyamakita, Higashinada, Kobe, Japan

and

Hisashi Ishii

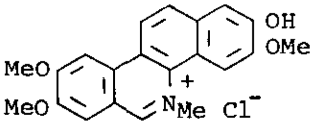
Faculty of Pharmaceutical Sciences, Chiba University
Yayoi-cho, Chiba, Japan

N-Demethylfagaronine (II) was synthesized by the route including the enamide photocyclization.

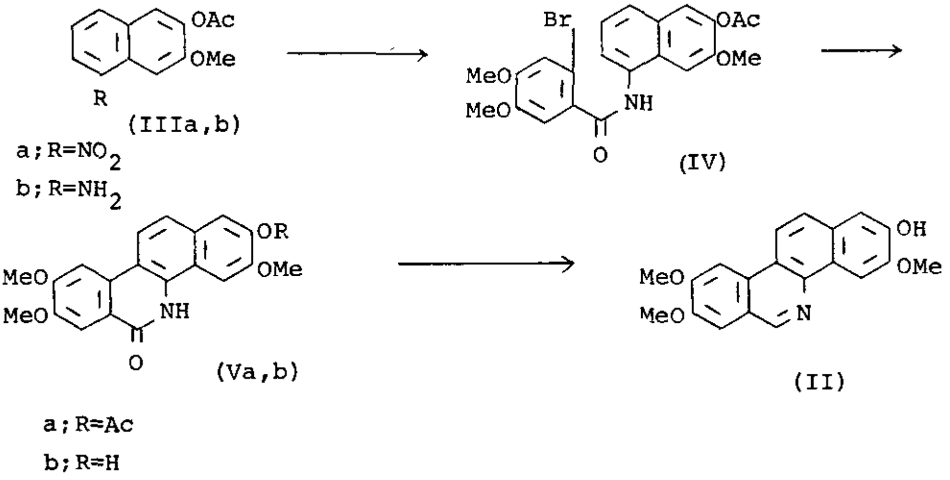
Fagaronine (I), a very active antileukemic alkaloid, was recently isolated[1] from *Fagara zanthoxyloides* and established its structure first from the spectral studies on the N-demethyl derivative (II)[2] and very recently by the synthesis.[3] As an extension of the work for the preparation of the pharmacologically active benzo[c]phenanthridine alkaloids[4], we report a simple synthesis of N-demethylfagaronine (II) by applying the photocyclization of a bromonaphthalide (IV).

Reduction of the acetate (IIIa) of 2-hydroxy-3-methoxy-5-nitronaphthalene, prepared by the Havinga's method[5], with Raney nickel produced the amine (IIIb), which was then treated with 6-bromoveratroyl chloride to afford the naphthalide (IV), m.p. 229-230°, in 78 % yield. Irradiation[6], using a high pressure mercury lamp with a pyrex filter, of a 0.003 M solution of the naphthalide (IV) in benzene-methanol (9:1) in the presence of triethylamine over a period of 5 hr. afforded the lactam (Va), m.p. >300°, in 36 % yield. Reduction of the lactam (Va) with lithium aluminium hydride afforded the corresponding naphthol (Vb), m.p. >300°, m/e 351 (M^+), accompanied by a small amount of the desired phenanthridine (II). However, successive treatment of the lactam (Va) with phosphorous pentachloride, hydrogen on 40 % palladium-charcoal, and potassium hydroxide gave the phenanthridine (II), m.p. 271-273°, (lit. 250°[2], 274-276°[3]) in 33 % yield, which exhibited n.m.r. (δ) (DMSO-d_6) 9.35 (1H, s, 6-H), 8.69 (1H, s, 4-H), 8.57 (1H, d, J=9 Hz, 11-H), 8.15 (1H, s, 7- or 10-H), 7.90 (1H, d, J=9 Hz, 12-H), 7.71 (1H, s, 10- or 7-H), 7.40 (1H, s, 1-H), 4.11, 4.07, and 4.01 (9H, each s, OMe×3), mass m/e 335 (M^+), 334, 320, 306, and 292, and i.r. ν_{max}(Nujol) 3540 (OH) and 1615 (C=N) cm^{-1}. Upon comparisons of these data, this phenanthridine (II) was found to be identical with N-demethylfagaronine. The above process involving the enamide photocyclization therefore provided a convenient route to a group of benzo[c]phenanthridine alkaloids in a sufficient amount for the pharmacological testing.

ACKNOWLEDGEMENT We thank Drs. N. R. Farnsworth and M. Tin-Wa for a sample of (I).



(I)



(IIIa,b)

a; R=NO_2

b; R=NH_2

(IV)

(Va,b)

a; R=Ac

b; R=H

(II)

REFERENCES

1 W. M. Messmer, M. Tin-Wa, H. H. S. Fong, C. Bevelle, N. R. Farnsworth, D. J. Abraham, and J. Trojánek, J. Pharm. Sci., 1972, 61, 1858.

2 M. Tin-Wa, C. L. Bell, C. Bevelle, H. H. S. Fong, and N. R. Farnsworth, J. Pharm. Sci., 1974, 63, 1476.

3 J. P. Gillespie, L. G. Amoros, and F. R. Stermitz, J. Org. Chem., 1974, 39, 3239.

4 I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda, and K. Harada, J. C. S. Perkin I, in the presss.

5 J. Lugtenburg and E. Havinga, Tetrahedron Letters, 1969, 1505.

6 S. V. Kessar, G. Singh, and (Miss) P. Balakrishnan, Tetrahedron Letters, 1974, 2269.

Received, 10th February, 1975