

SYNTHESIS OF N-DEMETHYLFAGARONINE

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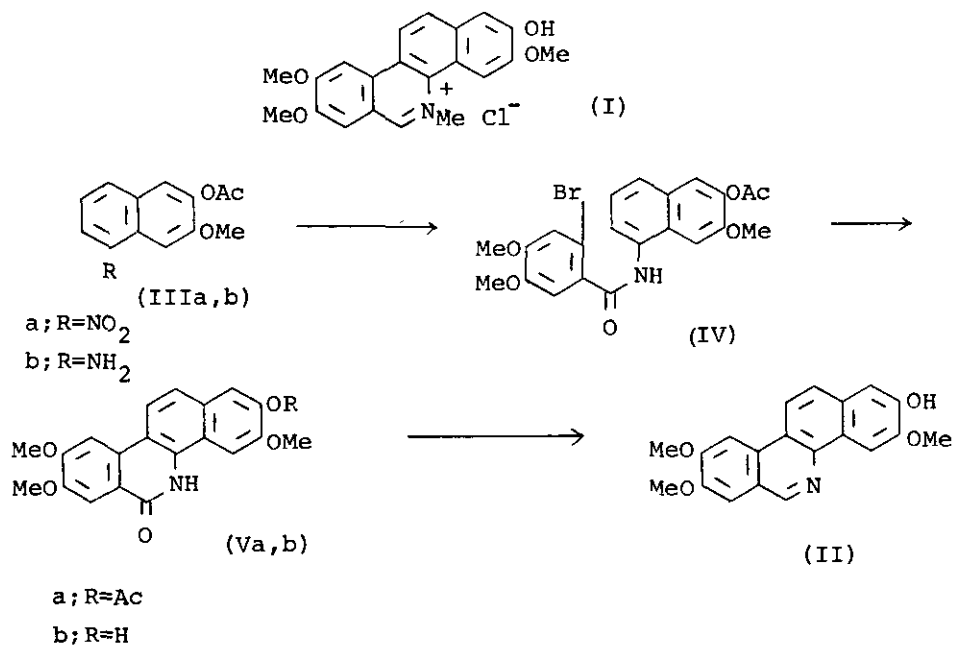
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N-Demethylfagaronine (II) was synthesized by the route including the enamide photocyclization.

Fagaronine (I), a very active antileukemic alkaloid, was recently isolated¹ 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 alkaloids⁴, 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-nitro-naphthalene, prepared by the Havinga's method⁵, with Raney nickel produced the amine (IIIb), which was then treated with 6-bromo-veratroyl chloride to afford the naphthalide (IV), m.p. 229-230°, in 78 % yield. Irradiation⁶, 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-d₆) 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, OMex₃), 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.

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