NEW SYNTHESES OF FLAVOPEREIRINE AND YOHIMBANES BY ENAMIDE PHOTOCYCLIZATION

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As an extension of the application of enamide photocyclization to the synthesis of protoberberine alkaloids[1], new total syntheses of flavopereirine (6), one of the simplest alkaloids of Strychnos plants, and yohimbanes (11a, b, and c), the basic structures of the alkaloid yohimbine, are described.

SYNTHESIS OF FLAVOPEREIRINE (6)

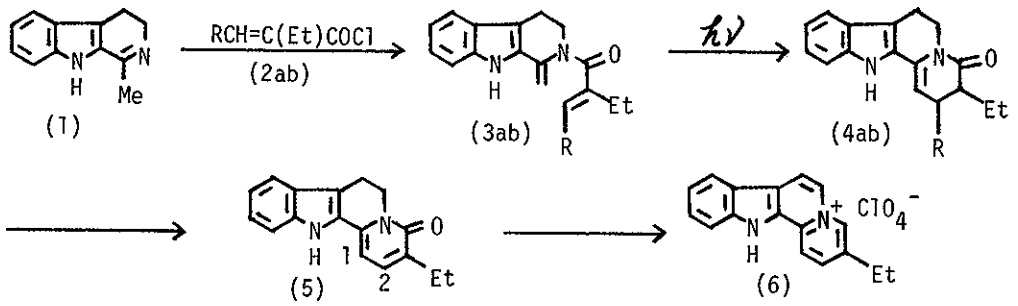
Harmalane (1) was acylated with ethacryloyl chloride (2a) to yield the corresponding enamide (3a) which was so unstable that it was without purification irradiated in a benzene solution with a high pressure mercury lamp at room temperature. However, this

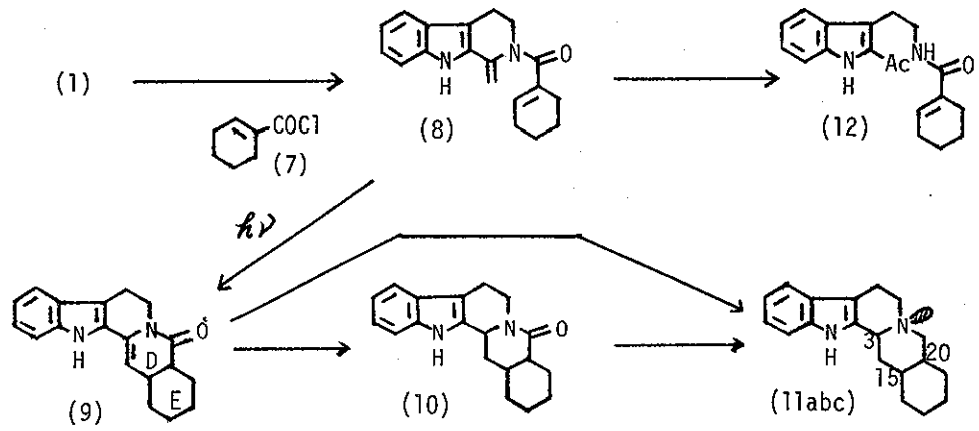
photocyclization proceeded very slowly, taking more than 20 hr to afford a poor yield (7.5 %) of the photocyclized lactam (4a). [i.r. ν 3480 (NH), 1670, 1650 (NCO, C=CN), n.m.r. δ 5.47 (1H, t-like, olefinic H)]. Therefore, we next prepared the enamide (3b) which carried an extra methoxyl group at β-position of the acyl group. As an introduction of a methoxyl group into a β-position of the acyl group of an enamide has been known to facilitate smooth photocyclization[2], the enamide (3b) was thus prepared from harmalane (1) and 3-methoxyethacryloyl chloride (2b). However, the enamide (3b) was found to be so unstable that it was employed without purification for irradiation (8 hr) in a benzene solution to yield the unstable photocyclized lactam (4b), the structure of which was suggested from the n.m.r. spectrum of the crude product [δ 5.87 (1H, d, J=6Hz, olefinic H) and 3.33 (3H, s, OMe)].

Then, the lactam (4b) was treated with 10 % hydrochloric acid at room temperature for a few minutes to afford the stable dehydrolactam (5) in 35 % yield from harmalane (1). The structure of the dehydrolactam (5) was deduced from the n.m.r. spectrum which lost a signal of a methoxyl group in (4b) and showed a new signal of an olefinic proton at δ 6.45 (1H, d, J=8Hz, 2-H). Lithium aluminum hydride reduction of the lactam (5) followed by dehydrogenation with palladium on charcoal at 280-300°C without solvent afforded the fully aromatized compound, isolated as its perchlorate (6), m.p. 301-305°C (lit.[3] m.p. 319-322°C), which was identical with the natural flavopereirine perchlorate upon their comparison.

a, R=H

b, R=OMe





	3	15	20
(11a) Yohimbane	···H	···H	—H
(11b) Epiyohimbane	—H	···H	—H
(11c) Alloyohimbane	···H	···H	···H

SYNTHESIS OF YOHIMBANES (11a, b, and c)

Since the enamide (8), prepared from harmalane (1) with 1-cyclohexene-1-carbonyl chloride (7), was found to be unstable and underwent facile hydrolytic ring opening to the methyl ketone (12) [i.r. ν 3450 (NH), 1670 (COMe), 1640, 1520 (NHCO)], even under usual workup or extraction process, the irradiation was applied to the crude enamide (8) [δ 6.05 (1H, m, olefinic H) and 5.18 (2H, m, olefinic H)] without further purification. However, the photocyclization proceeded very smoothly to afford the photocyclized lactam (9) in a good yield, which showed two spots on t.l.c., thus suggesting an existence of two stereoisomers with respect to the ring junction (D/E).

Catalytic hydrogenation of (9) in the presence of platinum oxide afforded a mixture of three saturated lactams (10a, b, and c) in the ratio of 2 : 1 : 2 which were separated by chromatography and their structures were deduced as isomeric yohimban-21-ones from their spectral evidences [similar absorptions at ν 3450 (NH) and 1620 (NCO) in their i.r. spectra, identical molecular ion peaks at m/e 294, and characteristic n.m.r. signals].

Then, these isomeric yohimban-21-ones (10a, b, and c) were reduced with lithium aluminum hydride to afford the corresponding amines (11a, b, and c) respectively with the combined yield of 27-35 % from harmalane (1). The ratio of the formation of the amines (11a, b, and c) was 3 : 0 : 2 when the lactams (9) as a mixture were reduced with lithium aluminum hydride followed by

sodium borohydride.

The structures of these stereoisomeric yohimbanes (11a, b, and c) as yohimbane, epiyohimbane, and alloyohimbane were established as follows respectively. Yohimbane (11a) was identified upon comparison with the authentic sample prepared according to the known procedure[4] from (±)-yohimbinone which was kindly given by Professor Szantay. Epiyohimbane (11b) and alloyohimbane (11c) were identified upon comparisons of their i.r. spectra with those of the authentic samples[5,6] respectively.

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