Tetrahedron Letters No.49, pp. 6215-6219, 1966. Pergamon Press Ltd.
Printed in Great Britain.

STRUCTURE OF FAWCETTIDINE : TRANSFORMATION OF SERRATININE INTO FAWCETTIDINE

H. Ishii, B. Yasui, T. Harayama and Y. Inubushi

Faculty of Pharmaceutical Sciences, Osaka University,
Toyonaka, Osaka-fu, Japan.

(Received 29 September 1966)

Fawcettidine was first isolated by R. H. Burnell[1] from a Jamaican Lycopodium plant, Lycopodium fawcettii Lyloyd et Underwood.

Characterization[1,2] of this base has already been presented; oil, $C_{16}H_{23}ON$, IR ν_{max}^{film} 1740 cm^{-1}, its methiodide, m.p. 223-225°, its picrate, m.p. 222-223° but since then there has been no report on the structure of this alkaloid.

Recently, we have isolated several new alkaloids from Lycopodium serratum THUNB. var. Thunbergii MAKINO growing in Japan and structures of serratinine [I][3] and serratinidine [II][4] have been established.

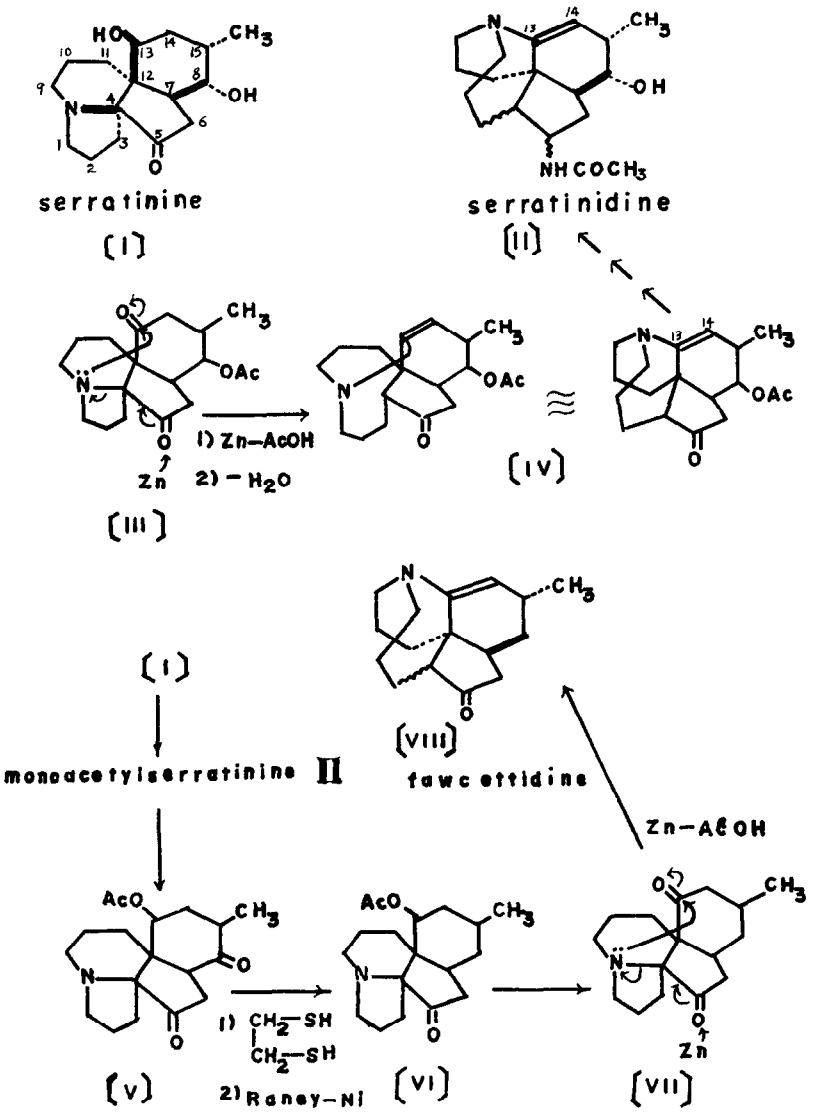
In this communication we wish to report the structure establishment of fawcettidine by means of the chemical transformation of serratinine into fawcettidine [VIII].

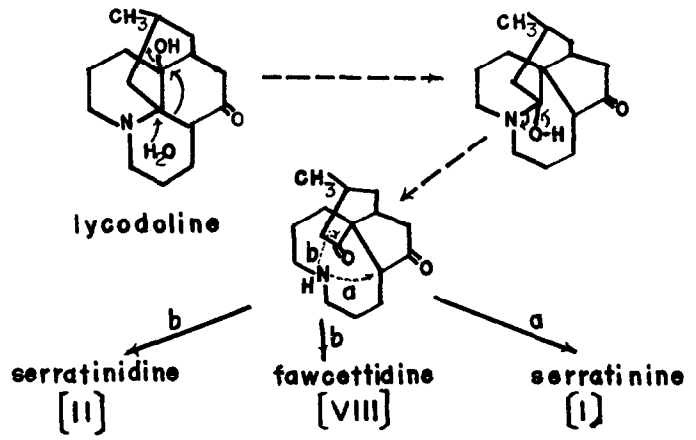
In the preceding communication[4], we described the structure assignment of serratinidine [II] and acetylanhydroaposerratinine [IV], derived from serratinine. The placement of the double bond at C_{13} - C_{14} (enamine structure) in the alkaloids was

based partly on their weak basicity (pKa' 6.4) compared with other tertiary lycopodium alkaloids.

The weak basicity of fawcettidine (pKa' 6.2), the presence of a double bond and its IR absorption band at 1740 cm^{-1} in the literatures[1,2], together with the hypothetical biogenesis of serratinine type alkaloids suggested by us[3,4], led us to suppose that the skeletal structure of fawcettidine would be the same as that of acetylanhydroaposerratinine [IV]. On this assumption, a parallel reduction process applied to the transformation of serratinine into serratinidine nucleus[4] was expected to be available for the present subject. In this case, the compound [VII] would be suitable for the starting material in view of the lack of a hydroxyl group in fawcettidine.

Oxidation of monoacetylserratinine II[3] with Jones' reagent afforded dehydromonoacetylserratinine II [V], $C_{18}H_{25}O_4N$ *1, m.p. 187.5-188°*1, IR ν_{max}^{Nujol} 1730 and 1695 cm^{-1} (five and six membered ketones, acetoxyl carbonyl group). Treatment of [V] with ethanedithiol, followed by desulfurization with Raney nickel, gave acetyl-8-deoxyserratinine [VI], $C_{18}H_{27}O_3N$, m.p. 190-191°, IR ν_{max}^{Nujol} 1740 cm^{-1} (five membered ketone and acetoxyl group). Hydrolysis of this acetate, followed by oxidation with Jones' reagent, furnished 8-deoxy-13-dehydroserratinine [VII], $C_{16}H_{23}O_2N$, m.p. 110-112°, IR ν_{max}^{Nujol} 1737 (five membered ketone) and 1693 cm^{-1}(six membered ketone). Reduction of [VII] with Zn-AcOH afforded an oil, IR ν_{max}^{film} 1737 cm^{-1} (five membered ketone) which was then derived to its crystalline methiodide, m.p. 224-226°, and its picrate, $C_{16}H_{23}ON.C_6H_3O_7N_3$, m.p. 223-225°, IR ν_{max}^{Nujol}


serratinine
(I)
serratinidine
(II)
1) Zn–AcOH
2) – H2O
(III)
(IV)
(I)
monoacetylserratinine II
(VIII)
fawcettidine
Zn–AcOH
1) CH2–SH
CH2–SH
2) Raney–Ni
(V)
(VI)
(VII)



1740 cm^{-1}. It has been reported that reduction of fawcettidine (an oil) with sodium borohydride gave dihydrofawcettidine, m.p. 153-156°, $[\alpha]_D$+ 137°(c, 1.0 in EtOH), no carbonyl band in the infrared[1]. Reduction of [VIII] with the same reagent afforded a dihydro compound, $C_{16}H_{25}ON$, m.p. 156-159°, $[\alpha]_D$+132.8°, (c, 0.78 in EtOH), IR,no carbonyl band.

All these physical constants agreed with those of fawcettidine reported by Burnell[1,2] thus establishing the structure of fawcettidine as [VIII], although no direct comparison was made.

It is of interest to note that serratinine, serratinidine, and fawcettidine may be derived from a common intermediate in biogenesis which is presumed to arise from lycopodine type alkaloids as illustrated in the chart given above. In these possible biogenetic schemes, there is still no experimental ground with regard to the step of formation of the common intermediate from lycodoline but their usefulness lies