HETEROCYCLES, Vol. 5, 1976

A TOTAL SYNTHESIS OF (±)-FENDLERIDINE

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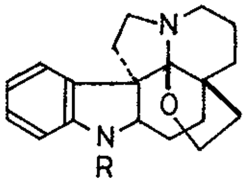
The oxidative cyclization of the aminoalcohol(7) with mercuric acetate gave (±)-fendleridine(1a). In this synthetic course, the reduction product of N-tosyl vinylogous amide(3) with lithium aluminum hydride was now further purified, and the former assignment of the structure(4) was revised to be 5, based upon the chemical and spectroscopic evidences.

Fendleridine(1a=aspidoalbidine) is a minor alkaloid isolated from the seeds of the Venezuelan tree *Aspidosperma fendleri* Woodson, by Burnell *et al.*,[1] which constitutes a parent member of aspidoalbine type of alkaloids.[2] Although the total synthesis of (±)-1-acetylaspidoalbidine(1b), the N-acetyl derivative of fendleridine, was achieved in this laboratory,[3] we describe a total synthesis of (±)-fendleridine(1a) in this communication, since the synthetic sample of the former (1b) was proved to be rather sensitive to acid treatment, suggesting the difficulty to overcome in the satisfactory deacetylation of 1b on hydrolysis, which had been substantially realized by Djerassi.[4]

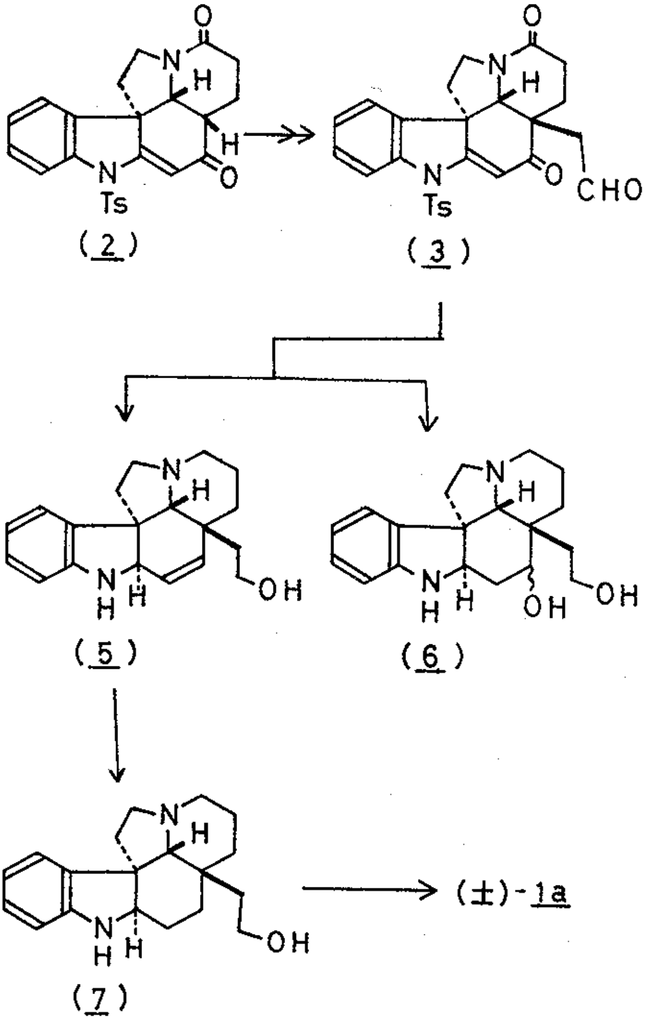
It was reported in our previous communication that the aldehyde(3) was refluxed with a large excess of $LiAlH_4$ in dimethoxyethane to give a rather unstable alcohol[4, mp 183-184°; MS: m/e 296(M^+)] and the dihydroxy derivative[6, viscous oil, MS: m/e 314(M^+)].[3] We carried out the further purification of these products in the present work. Repeated recrystallizations of the former product from ethyl acetate were made to finally give the stable colorless needles, mp 193-194°, which were submitted to the nmr analysis(100 MHz), demonstrating a multiplet centered at δ 5.71 due to two vinyl protons($-C\underline{H}=C\underline{H}-$) and one proton signal as a doublet centered at δ 4.06($J=4$ Hz, $-N-C\underline{H}_X-CH_A=CH_B-$). The decoupling experiment established the present assignment of an ABX system for these protons which are only compatible with the structure(5).[5]

In the other studies of this series, we happened to obtain the N-tosyl-enamine[9, mp 233-234°; MS: m/e 420(M^+); NMR ($CDCl_3$) δ: 6.38(1H, q, J=8 Hz and 3 Hz, C_3-H)] by the selective hydrogenation of 8(mp 228-231°).[6] For further confirmation of the above assignment of the formula(5) by chemical means, the compound(9) was subjected to the reduction with $LiAlH_4$ under the same condition as above to provide the



(1a) R = H

(1b) R = Ac



(2)

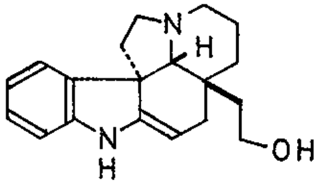
(3)

(5)

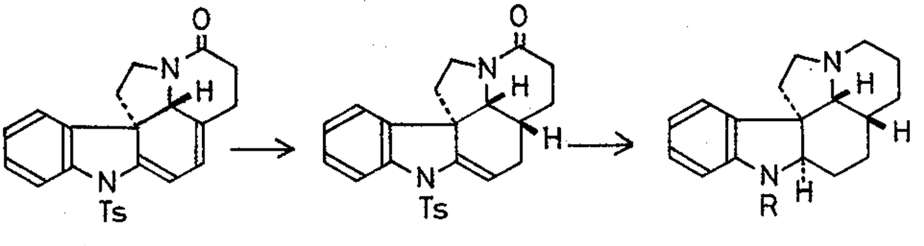
(6)

(7)

(±)-1a



(4)



(8)

(9)

(10a) R = H

(10b) R = Ac

indoline[10a, colorless resin; MS: m/e 254(M^+); UV: λ_{max}^{EtOH} 249, 292 nm] as a sole product without any formation of an enamine.[7] This experiment strongly suggests that the double bond of the enamines of this type like 4 and 9 should be reduced to the saturated bond under these conditions.

Based upon these results, the structure of the reduction product of 3 with $LiAlH_4$, which had been previously assigned the formula(4), should be revised to be 5.[8]

The alcohol(5) was hydrogenated over Adams' catalyst in ethyl acetate under atmospheric pressure of hydrogen to afford the saturated alcohol(7, mp 216-217°), which without a protecting group at N(a), was heated with excess mercuric acetate in 5% aqueous acetic acid at 75° for 40-45 hr. The crude product was purified by preparative thin layer chromatography on alumina eluted with a mixed solvent(methylene chloride - ethyl acetate =1:3) to afford (±)-fendleridine(1a) as a colorless resin[MS: m/e 296(M^+), 268, 252, 144, 138(100%) and 130; UV: λ_{max}^{EtOH} 245 and 295 nm], which were identical with the spectral data of the natural alkaloid.[9]

ACKNOWLEDGEMENT We thank Professor Em. S. Sugasawa, University of Tokyo, for his valuable suggestion and encouragement throughout this work. This work was supported by Grants-in-Aid for Scientific(No. 047007) and Cancer(No. 001503) Research from the Ministry of Education, Science and Culture, Japan, and by a Grant from the Mitsubishi Foundation, which are gratefully acknowledged.

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3. Y. Ban, T. Ohnuma, K. Seki and T. Oishi, Tetrahedron Letters, 1975, 727.
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5. On irradiation at δ 4.06(H_x), the multiplet at δ 5.71 collapsed to an AB type of quartet(δ 5.64, d, J=10.5 Hz, H_A and δ 5.78, d, J=10.5 Hz, H_B). The doublet at δ 4.06 collapsed to a singlet on irradiation at the H_B frequency.
6. Y. Ban, Y. Honma and T. Oishi, Tetrahedron Letters, 1976, 1111.
7. The indoline(10a) was acetylated with acetic anhydride-pyridine to afford 10b, which was identical with the authentic sample. (Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo and T. Oishi, Tetrahedron Letters, 1972, 5023).
8. Dr. G. F. Smith, The University of Manchester, frankly threw doubt on the former assignment[formula(4)] by private communication. His advice is gratefully acknowledged.
9. The physical properties of the natural alkaloid(1a) are: Mp 185-186°; UV: λ_{max}^{EtOH} 242 nm(ε 7300) and 293 nm(ε 3050); MS(m/e): 296(M^+), 268, 252, 144, 138(100%) and 130.[1] We tried to have the authentic sample of the natural "fendleridine" for direct comparison, but unfortunately it was not available.

Received, 27th May, 1976