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THE TOTAL SYNTHESIS OF THE ALKALOID (±)-1-ACETYLASPIDOALBIDINE

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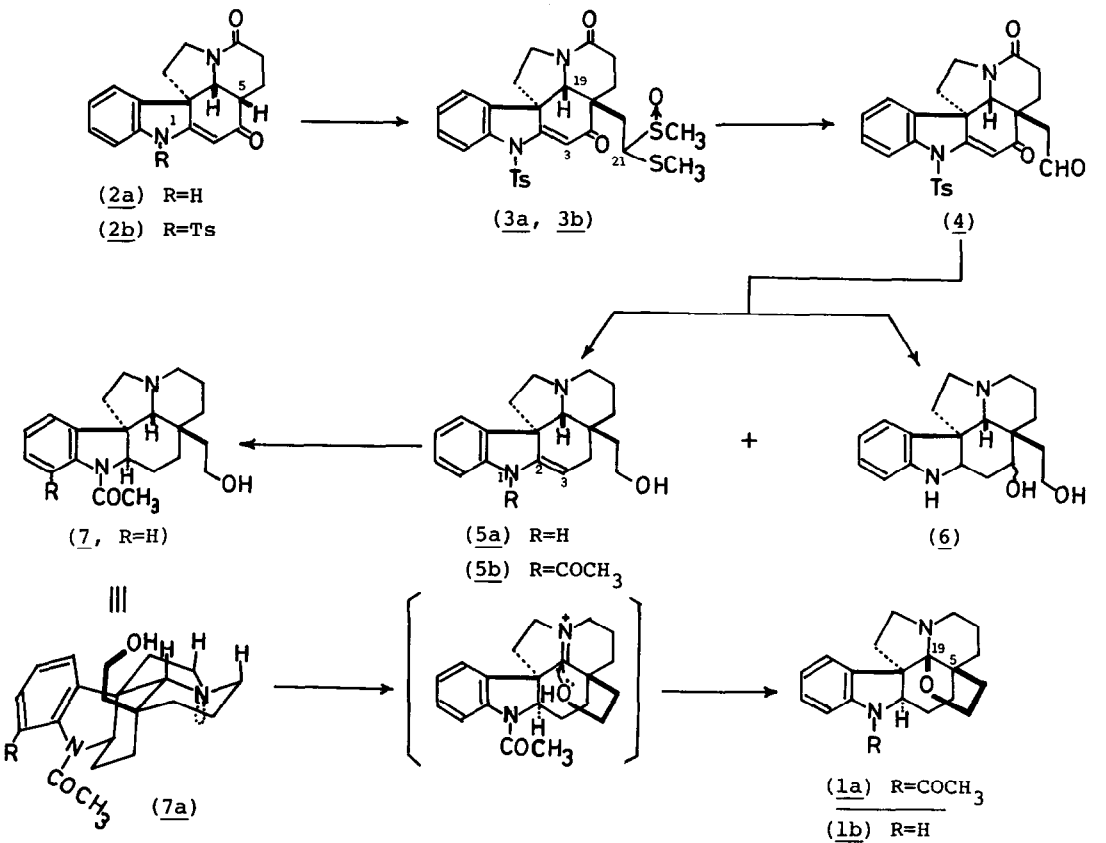
(+)-1-Acetylaspidoalbidine(1a),[1] a representative member of aspidoalbine type of alkaloids,[2] was isolated from *Vallesia dichotoma* RUIZ et PAV, the structure of which was proposed by Djerassi mainly through the combined use of the mass, uv, ir and nmr spectra. Fendleridine[=aspidoalbidine(1b)] was also isolated by Burnell from the seeds of *Aspidosperma fendleri* WOODSON.[3] We wish to communicate the first total synthesis of the former racemic alkaloid[(±)-1a] from our versatile precursor(2b),[4,5] establishing the structure of the alkaloid to be 1a, which involves the two carbon side chain at C-5 in a tetrahydrofuran ring linked with C-19.

It has been already published from this laboratory that the compound(2a) was prepared from 2-hydroxytryptamine and its stereochemistry fully elucidated.[4] The reaction site of this compound(2a) for the Michael condensation was proved to be predominantly located at C-5 by introduction of tosyl group into 1-position.[5,6] The tosyl amide(2b) was thus submitted to the Michael condensation with ketene thioacetal monoxide[7] in the presence of the freshly prepared $LiN[CH(CH_3)_2]_2$ in 1,2-dimethoxyethane under stirring at room temperature for one night to afford the two diastereoisomers, [3a, colorless prisms, mp 163°(dp); MS: m/e 506, 307, 305, 275 and 91(100%), the M^+ peak for MW=570 was not observed; NMR($CDCl_3$): δ2.08(3H, s, $SC\underline{H}_3$), 2.28(3H, s, $SOC\underline{H}_3$), 2.38(3H, s, ar-$C\underline{H}_3$), 3.99(1H, s, C_{19}-$\underline{H}$) and 6.55(1H, s, C_3-$\underline{H}$); 38% yield] and [3b, colorless prisms, mp 163°(dp); MS: m/e 506, 307, 305, 275 and 91(100%), the M^+ peak was not observed; NMR($CDCl_3$): δ2.03(3H, s, $SC\underline{H}_3$), 2.62(3H, s, $SOC\underline{H}_3$), 2.38(3H, s, ar-$C\underline{H}_3$), 3.81(1H, s, C_{19}-$\underline{H}$) and 6.58(1H, s, C_3-$\underline{H}$); 37% yield] after separation by chromatography on alumina. Both diastereoisoemrs(3a and 3b) gave the same



crystalline aldehyde[4, colorless needles, mp 186-187°, MS: m/e 476(M^+), IR: ν_{max}^{nujol} 1720, 1680, 1655, 1630 and 1595 cm^{-1}; NMR($CDCl_3$): δ2.38(3H, s, ar-CH_3), 3.95(1H, s, C_{19}-H), 6.51(3H, s, C_3-H) and 9.26(1H, t, J=2.3 Hz, -CHO); ca. 100% yield] when refluxed with a catalytic amount of 60% perchloric acid in aqueous acetonitrile for 1.5 hr. Therefore, the isomerism of 3a and 3b should be considered to be due to the asymmetry of sulfur atom associated with C-21 carbon. The aldehyde(4) was refluxed with a large excess of $LiAlH_4$ in dimethoxyethane for 1.5 hr to give a rather unstable alcohol[5a, colorless needles (from ethyl acetate), mp 183-184°; MS: m/e 296(M^+), 265 and 166(100%); NMR($CDCl_3$): δ3.47(2H, t, J=6 Hz, -CH_2-(C-21), 5.71(1H, broad s, C_3-H); 38% yield] after separation by chromatography on alumina from the dihydroxyl derivative(6, viscous oil, M^+=314) as a by-product(27% yield). The location of the double bond at C-2

and C-3 in the alcohol(5a) was assigned mainly by the presence of a vinyl proton at δ5.71 in the nmr spectrum and by the fact that the double bond was not reduced with $LiAlH_4$.[8] The alcohol(5a) was reacted with acetyl chloride in a mixture of methylene chloride and 4% NaOH aqueous solution under ice cooling to yield the amorphous acetyl derivative[5b, MS: m/e 338(M^+), 307, 294, 166 (100%), 144, 130, 122 and 109; IR: ν_{max}^{neat} 1640 cm^{-1}; ca. 100% yield], forming the crystalline picrate[mp 223-225°9dp)]. The hydrogenation of 5b with Adams' catalyst at 4 atmospheric pressure of hydrogen gave the reduced alcohol[(7, R=H), amorphous solid; MS: m/e 340(M^+), 312, 296, 281, 168, 144, 140(100%); UV: λ_{max}^{EtOH} nm(log ε) 255(4.09), 283(3.48) and 292(3.41); IR: $\nu_{max}^{CHCl_3}$ 3620, 2800 & 2780 (Bohlmann's absorptions)[9] and 1640 cm^{-1}; NMR($CDCl_3$): δ2.23(3H, s, $NCOCH_3$), 3.54 (2H, t, J=7.5 Hz, $-CH_2-$(C-21)), 4.05(1H, q, C_{20}-H) and 8.10(1H, d, C_{17}-H); ca. 100% yield]. These spectral data were fully consistent with the structure(7, R=H), corresponding to the dehydroxy-derivative of limapodine(7, R=OH),[10] which might be delineated as 7a.[11] The compound(7, R=H) was heated with mercuric acetate in 5% acetic acid at 65-70° for 7 hr[12] to afford (±)-1-acetylaspidoalbidine(1a) as an amorphous powder[dp 235-237°; MS: m/e 338(M^+), 310, 294, 166, 144, 138(100%) and 130; IR: $\nu_{max}^{CHCl_3}$ 1640 cm^{-1}(the absorptions due to the hydroxyl group disappeared with the Bohlmann's bands); UV: λ_{max}^{EtOH} nm(log ε): 254.5(4.10) and 291(3.40); NMR(CD_3COCD_3): δ2.23 & 2.18(3H, N-$COCH_3$) and 4.13(1H, q, C_2-H), 64% yield]. These spectral data were identical with those of the natural alkaloid generously supplied by Professor Djerassi.

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References and Notes

1. (a) K. S. Brown, Jr., H. Budzikiewicz and C. Djerassi, Tetrahedron Letters, 1731 (1963). (b) A. Walser and C. Djerassi, Helv. Chim. Acta, 48, 391 (1965).
2. M. Hesse, "Indolalkaloide in Tabellen, Ergänzungswerk", pp 77-81 (1968), (Springer-Verlag, Berlin).
3. (a) R. H. Burnell, J. D. Medina and W. A. Ayer, Chem. and Ind., 33 (1964).
-- (b) R. H. Burnell, J. D. Medina and W. A. Ayer, Canad. J. Chem., 44, 28 (1966).
4. (a) Y. Ban, T. Ohnuma, M. Nagai, Y. Sendo and T. Oishi, Tetrahedron Letters, 5023 (1972). (b) Y. Ban, Y. Sendo, M. Nagai and T. Oishi, ibid., 5027 (1972). (c) T. Oishi, M. Nagai and Y. Ban, ibid., 491 (1968).
5. (a) T. Ohnuma, T. Oishi and Y. Ban, J. Chem. Soc. Chem. Comm., 301 (1973). (b) T. Ohnuma, K. Seki, T. Oishi and Y. Ban, ibid., 291 (1974).
6. The procedure for tosylation of 2a was improved after the previous publication.[4a] To a solution of 2a(1 mol. equiv.) were added a 20% solution of n-BuLi(1.2 mol. equiv.) in n-hexane and then TsCl(1.1 mol. equiv.). The whole mixture was stirred at room temperature for one night to give the tosyl amide(2b, mp 240-241°, recrystallized from ethyl acetate) in 82% yield after purification by chromatography on alumina.
7. J. L. Hermann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo and R. H. Schlessinger, Tetrahedron Letters, 4711 (1973).
8. The possibility of the equilibration of the double bond between $-N_{(1)}=C_{(2)}-$ and $-C_{(2)}=C_{(3)}-$ seems unlikely, since the double bond was not reduced with $LiAlH_4$. If the indolenine were present during the reduction with $LiAlH_4$, a reduced alcohol(7, NH instead of $N-COCH_3$) should have been generated. The authors acknowledge the discussion on this problem with Dr. G. F. Smith, The University of Manchester, by private communications.
9. F. Bohlmann, Chem. Ber., 91, 2157 (1958).
10. M. Pinar and H. Schmid, Liebigs Ann. Chem., 668, 97 (1963).
11. Cf. H. Budzikiewicz, C. Djerassi and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry. Vol. 1: Alkaloids", p. 103 (1964) (Holden-Day, Inc., San Francisco).
12. Cf. N. J. Leonard and W. K. Musker, J. Am. Chem. Soc., 82, 5148 (1960).