Tetrahedron Letters No.19, pp. 1489-1492, 1969. Pergamon Press. Printed in Great Britain.

GARDNERIA ALKALOID III.[1]

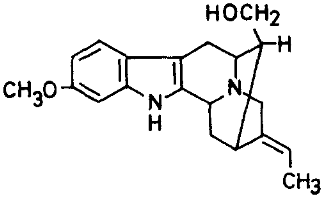
ON THE ABSOLUTE CONFIGURATION OF GARDNERINE.[2]

S.Sakai, A.Kubo, T.Hamamoto, M.Wakabayashi, K.Takahashi, Y.Ohtani and J.Haginiwa

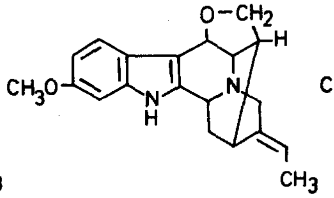
Faculty of Pharmaceutical Sciences, Chiba University, Chiba, Japan

(Received in Japan 22 February 1969; received in UK for publication 17 March 1969)

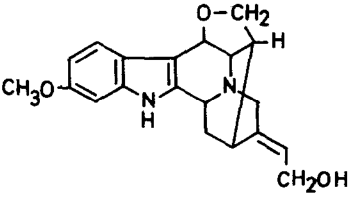
As reported in the previous papers,[1,3] we have isolated three new indole alkaloids[4] gardnerine(I), gardnutine(II) and hydroxygardnutine(III) from Gardneria nutans Sieb. et Zucc. (Loganiaceae) to which we have assigned the structures (I),(II) and (III). Since the latter two alkaloids (II and III) were correlated chemically with gardnerine(I), it has been concluded that all three alkaloids (I - III) have the same carbon skeleton.



(I)



(II)



(III)

In the course of these studies, we have successfully interrelated gardnerine(I) to ajmaline (of established absolute configuration[5]) by two different routes (A and B). The present communication reports these results.

Route A (Chart 1): As described in the previous paper,[1] gardnerine gave the ring closed compound(IV) by treatment with TsCl/Py. The action of BCl_3 in dichloromethane solution converted the ring closed compound(IV) to the expected demethyl phenolic compound(V) m.p. 261-263°, $(\alpha)_D^{26}$ + 67.1, $C_{19}H_{20}O\,N_2$:0.5 H_2O(M^+ 292), in 89% yield. The phenolic compound(V) was refluxed with 1-phenyl-2-chlorotetrazole in acetone solution in the presence of K_2CO_3 for 44 hrs.

From the reaction mixture, the tetrazole ether(VI) m.p. 232-233°, $(\alpha)_D^{26.5}$+ 6.5, $C_{26}H_{24}O\,N_6$ (M^+ 436) was isolated in 95% yield. In order to obtain the desoxy compound(VII), catalytic reduction of tetrazole ether(VI) over Pd/charcoal was attempted, but under these conditions[6] the desired product was not obtained. However, under stronger hydrogenolysis conditions using Adam's catalyst in acetic acid solution at 60°C, the deoxy compound(VII) was generated in poor yield (9%) after alumina column chromatography. This compound(VII) m.p. 76-83°, $C_{19}H_{24}N_2$ ($M^{+}\cdot 280$) was, however, found to be contaminated with isomers at C-2 or/and C-20 position. The impure desoxy compound(VII) was oxidized with $Pb(OAc)_4$ in benzene solution to the pure 1,2-dehydro-derivative(VIII) m.p. 188-189.5°, $C_{19}H_{22}N_2$ (M^{+} 278). The compound(VIII) was found to be identical with 17,21-dideoxy-1-demethyl-1,2-dehydroajmaline obtained from ajmaline by Bartlett et al [5)] by mixed melting point determination as well by the comparison of IR, NMR, Mass and ORD spectra.

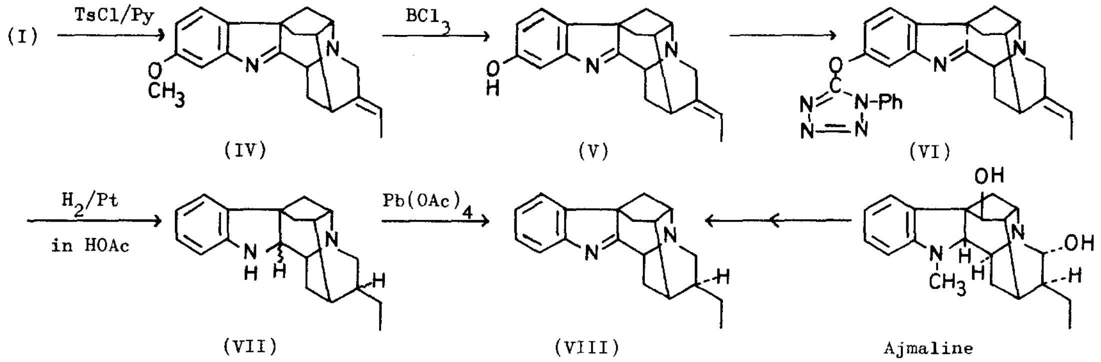


Chart 1.

Route B (Charts 2 and 3): Upon reduction with $LiAlH_4$, the ring closed compound(IV) gave rise to indoline derivative(IX) in high yield as described in the previous paper.[1)] Treatment of IX with methanesulfonylchloride in pyridine solution resulted in the formation of the corrsponding N-mesyl-derivative(X) m.p. 215-216°, $C_{21}H_{26}O_3N_2S$ (M^{+} 386) in 83% yield,which, in turn, was converted by the action of BCl_3 to the demethylated phenol compound(XI) m.p. 175-185°, $C_{20}H_{24}O_3N_2S{:}0.5C_6H_6$ (M^{+} 372) in nearly quantative yield. The action of CH_2N_2 on the phenol(XI) regenerated the parent N-mesyl-derivative(X). The phenol(XI) was converted to tetrazolether derivative(XII) m.p. 124-126°, $C_{27}H_{28}O_3N_6S$ (M^{+} 516), and the latter compound(XII) was catalytically reduced to the desmethoxy-19,20-dihydro derivative(XIII) m.p. 83-102°, $C_{20}H_{26}O_2N_2S{:}H_2O$

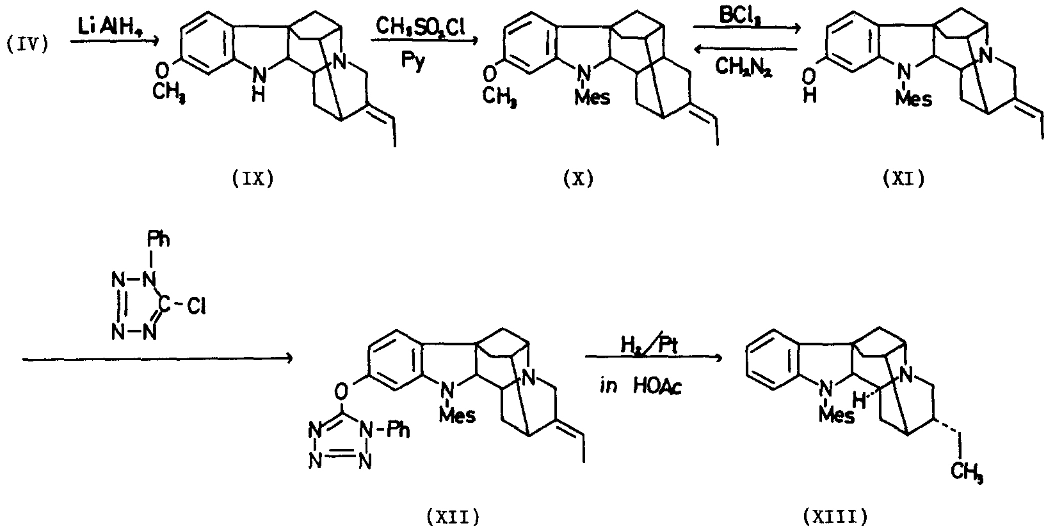


Chart 2.

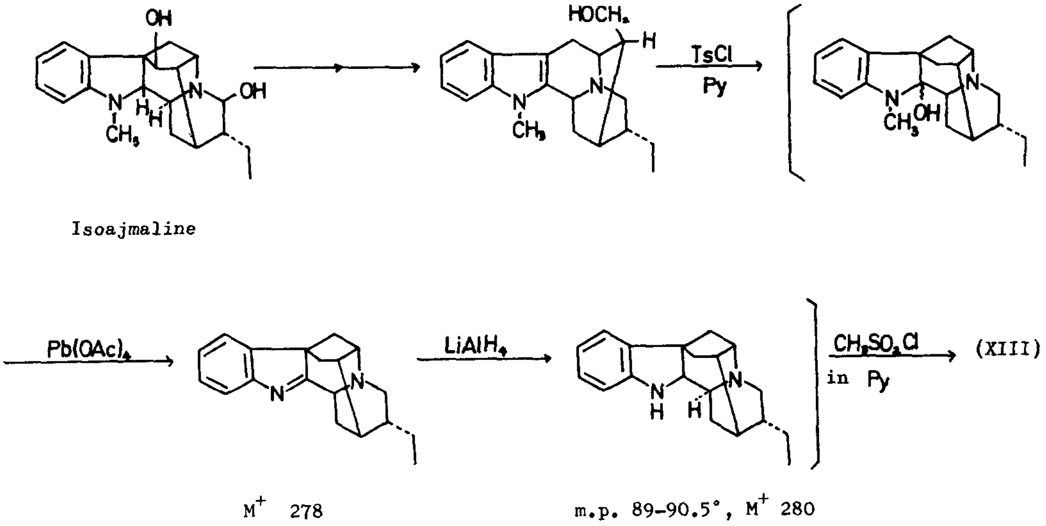


Chart 3.

(M^+ 358) in 61% yield. On the other hand, the same desmethoxy compound(XIII) was obtained from isoajmaline(7) through 21-deoxyisoajmalol-A(XIV)(5) as shown in Chart 3. The two desmethoxy compounds were found to be identical by mixed melting point determination as well as by the comparison of their UV, IR, NMR and ORD spectra. The geometry of the C-18 methyl attached to the ethylidene group was demostrated to be that of other sarpagine alkaloids(8) by NOE experiment. The signal due to the C-15 hydrogen group (6.88τ) of gardnutine(II) (in $DMSO\text{-}D_6+F_3CCOOH$) in NMR spectrum showed increase in the integration value by 13% when irradiated at the C-18 methyl group(8.31τ). Thus the structures and the absclute configurations of gardnerine (I), gardnutine (II) and hydroxygardnutine (III)(9) are established as shown.

Acknowledgement A part of the expences of this work was supported by a Grant-in-Aid from the Ministry of Education, Japan, for which the authors wish to express their gratitude. We are also grateful to Hitach Chem. Co. for a sample of ajmaline.

REFERENCES

1) Part II: S.Sakai, A.Kubo and J.Haginiwa ; Tetrahedron Letters 1969, in the press.

2) This work was presented at 12th Symposium on the chemistry of natural products, Sendai, Oct. 1968. Symposium papers, p. 74.

3) Part I: J.Haginiwa, S.Sakai, A.Kubo and T.Hamamoto; Yakugaku Zasshi, 87, 1484 (1967).

4) Another alkaloid, gardneramine, has also been isolated. The structure of this alkaloid is under investigation.

5) M.F.Bartlett, R.Sklar, W.I.Taylor, E.Schlittler, R.L.S.Amai, Peter Beak, N.V.Bringi and Ernest Wenkert; J. Am. Chem. Soc. 84, 622 (1962).
M.F.Bartlett, B.F.Lambert and W.I.Taylor; J. Am. Chem. Soc. 86, 729 (1964).

6) W.J.Musliner and J.W.Gates,Jr.; J.Am. Chem. Soc. 88, 4271 (1966).

7) Similarly, ajmaline was transformed to the corresponding desmethoxy compound, amorphous (HCl-salt, m.p. 290-293°), which was surely the diasteroisomer of XIII at the C-20 position.

8) J.C.Nouls, P.Wollast, J.C.Braekman, G.Van Binst, J.Pecher and R.H.Martn; Tetrahedron Letters; 2731 (1968).

9) Though this compound (III) has not been subjected to the above NOE experiment, biogenetic considerations require that it have the same etl.ylidene geometry as (I) and (II).