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GARDNERIA ALKALOIDS II.[1)]

THE STRUCTURES OF GARDNERINE, GARDNUTINE AND HYDROXYGARDNUTINE[2)]

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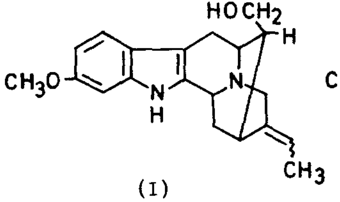
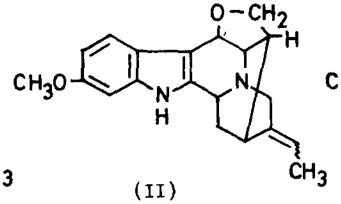
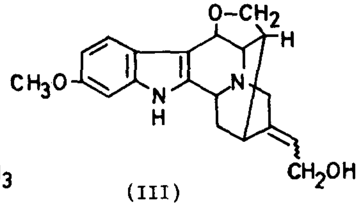
We have described previously the isolation of four kinds of indole alkaloids, gardneramine, gardnerine, gardnutine and hydroxygardnutine from the dry roots and stems of Gardneria nutans Sieb. et Zucc. (Hōraikazura).[2)] From the following chemical and spectroscopical data, the structures of gardnerine, gardnutine and hydroxygardnutine were elucidated to be I, II, and III, respectively.


(I)


(II)


(III)

Gardnerine(I): m.p. 243-244°, $C_{20}H_{24}O_2N_2$:H_2O, $(\alpha)_D^{25}$- 29.4, Pka 7.36, UV λ_{max}^{MeOH} mμ (log ε); 228.5, 268.5 and 298 (4.56, 3.70 and 3.77) (2,3-disubstituted 6-methoxyindole chromophore). Presence of the functional groups (1 x double bond, 1 x C-OH, 1 x OCH_3 and 1 x $C-CH_3$) was evidenced by the following experiments; (i) acetylation with Ac_2O/Py gave the mono-acetate, m.p. 218-219°, $C_{22}H_{26}O_3N_2$(M^+ 366), which by hydrolysis regenarated gardnerine(I); (ii) catalytic reduction over Adam's catalyst yielded the corresponding 19,20-dihydrogardnerine as an isomeric mixture, m.p. 230-240°, $C_{20}H_{26}O_2N_2$; (iii) the dihydrogardnerine yielded both acetic acid and propionic acid by Kuhn-Roth method, while gardnerine(I) gave only acetic acid by this method.

NMR spectrum[3)] of the mono-acetate of gardnerine indicated the presence of an ethylidene group (8.4τ, 3H,d. and 4.79τ, 1H,q. with J=7 cps) and a methoxy group (6.3τ, 3H,s.). The mass spectrum of I showed strong peaks at m/e 324(M^+ 56%), 323(M-1 57%), 306($M-H_2O$ 59%), 293($M-CH_2OH$ 36%), 212(16%), 199(84%) and 198(100%).

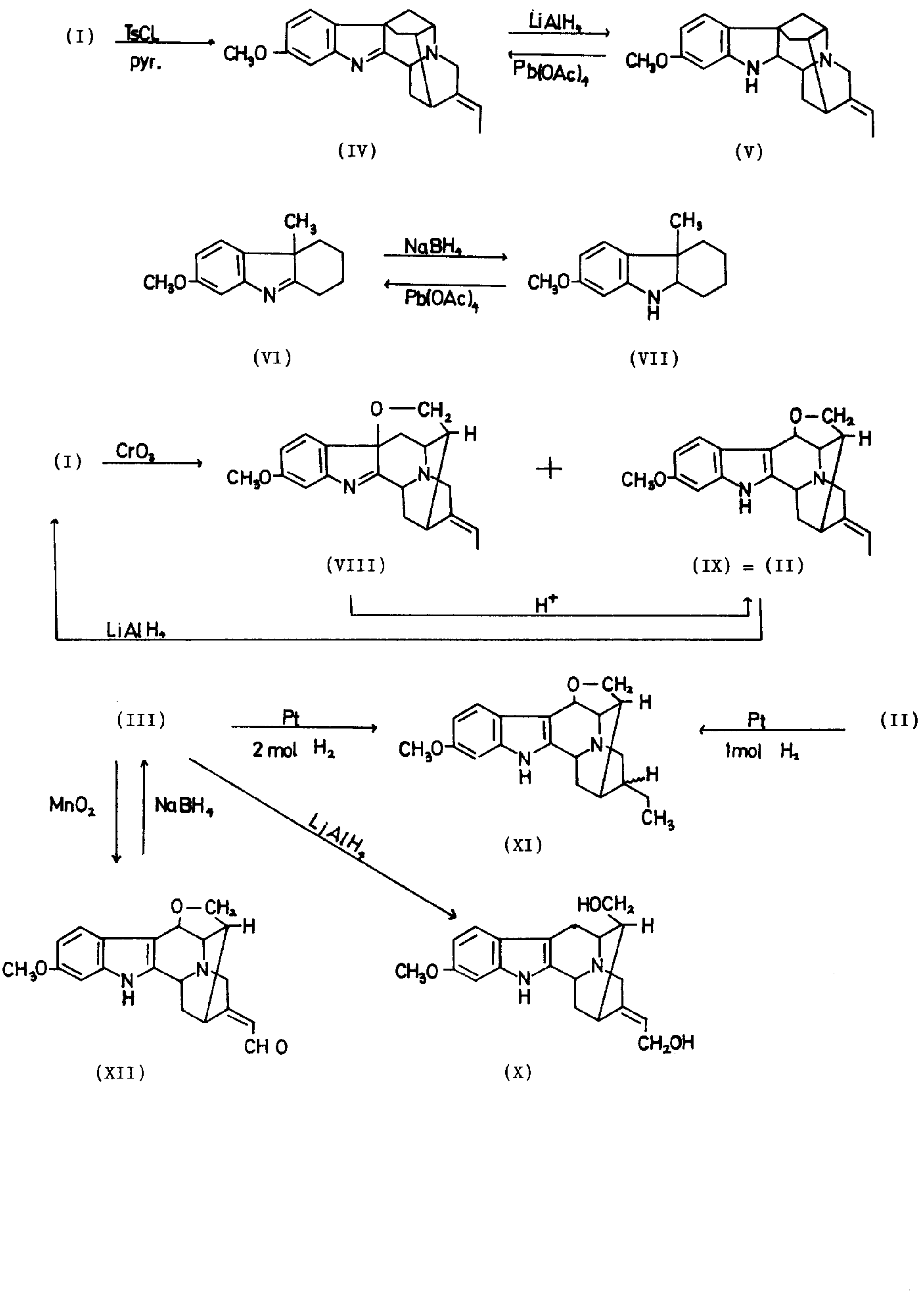
These data seem to suggest that gardnerine is closely related to polyneuridine[4)] and, therefore, structure I can tentatively be postulated to gardnerine. The correctness of this tentative assignment is provided by the following experiments.

Upon treatment with p-toluenesulfonylchloride in pyridine, gardnerine(I) afforded in high yield an indolenine derivative, m.p. 141-142°(IV), $C_{20}H_{22}O\ N_2$ (M^+; 306). This type of ring closure reaction was first described by W.I. Taylor et al.[5)] in the chemistry of the ajmaline series. Upon reduction with $LiAlH_4$, IV was transformed solely into an indoline derivative(V), m.p. 79-81°, $C_{20}H_{24}O\ N_2$ (M^+; 308), UV,$\lambda_{max.}^{MeOH}$mμ (log ε):295(3.66), which by oxidation with $Pb(OAc)_4$ reverted to IV. A similar interconversion between VI and VII was made as a model experiment for these transformations (IV $\rightleftarrows$ V). Upon oxidation with CrO_3-H_2SO_4 in acetone, gardnerine(I) gave rise to two compounds, VIII, m.p. 151-152°, $C_{20}H_{22}O_2N_2$, and IX, m.p.319-320°, $C_{20}H_{22}O_2N_2$. Since treatment of the former product (VIII) with strong acid gave the latter product (IX), the primary oxidation product in this experiment was surely VIII. An analogous transformation was observed by Taylor's group in the $Pb(OAc)_4$ oxidation of 21-deoxyajmalol A.[6)]

Upon reduction with $LiAlH_4$, the latter oxidation product(IX) regenerated gardnerine(I). Leete has observed an analogous simple transformation of 3-hydroxymethylindole to skatole by utilizing the same reagent.[7)] On the basis of these experiments, structure I is assigned to gardnerine.

The definite determination of the ethylidene group stereochemistry as well as the absolute configuration of gardnerine awaits a further study.

Gardnutine (II): m.p. 319-320°, $C_{20}H_{22}O_2N_2$ (M^+; 322), $(\alpha)_D^{25}$+30.3, Pka 5.77. The uv spectrum of gardnutine (II) $\lambda_{max.}^{MeOH}$ mμ(log ε): 223.5, 260, 295 and 302 (4.63, 3.64, 3.73 and 3.63sh.) is similar to that of gardnerine (I). The ir spectrum ($\nu_{max.}^{KBr}$ cm^{-1}; 3200) was superimposable to that of the oxidation product(IX) of gardnerine (I) obtained as above. The identity between II and IX was further confirmed by mixed melting point determination and optical rotation measurement. It should be stressed at this stage that gardnutine is a rare example of the 6-oxygenated indole alkaloids.[8)]


(I)
TsCl
pyr.
CH3O
N
(IV)
LiAlH4
Pb(OAc)4
CH3O
N
H
(V)
CH3
CH3O
N
(VI)
NaBH4
Pb(OAc)4
CH3
CH3O
N
H
(VII)
(I)
CrO3
O — CH2
H
CH3O
N
(VIII)
+
O—CH2
H
CH3O
N
H
(IX) = (II)
H+
LiAlH4
(III)
Pt
2 mol H2
O—CH2
H
CH3O
N
H
H
CH3
(XI)
Pt
1mol H2
(II)
MnO2
NaBH4
LiAlH4
O—CH2
H
CH3O
N
H
CH O
(XII)
HOCH2
H
CH3O
N
H
CH2OH
(X)

Hydroxygardnutine (III): m.p. 311-312°, $C_{20}H_{22}O_3N_2$(M^+; 338), $(\alpha)_D^{25}$+36.2, Pka 5.64, IR $\nu_{max.}^{KBr}$ cm^{-1}; 3200 and 3580, functional groups: no C-CH_3, 1 x OCH_3 and C-OH (monoacetat, m.p. 278-280°, M^+380, $C_{22}H_{24}O_4N_2$). The uv spectrum of the alkaloid (III) $\lambda_{max.}^{MeOH}$mμ (log ε): 223, 260.5, 295 and 301 (4.61, 3.69, 3.79 and 3.70sh.) is similar to those of gardnerine (I) and gardnutine (II). Upon reduction with $LiAlH_4$, III was transformed into a dihydroxy derivative (X), m.p. 162°,(M^+ 340, $C_{20}H_{24}O_3N_2$), which gave the diacetate, m.p. 182-183° (M^+ 424, $C_{24}H_{28}O_5N_2$). The nmr spectrum of the diacetate showed signals at 5.41τ (2H,d) and 4.57τ (1H,t) with J=7 cps., indicating the presence of acetoxyethlidene group (AcO-CH_2-CH=C). The presence of an allylic alcohol group in III was confirmed chemically by its hydrogenolysis to 19,20-dihydrogardnutine (XI) m.p. 294-296° (M^+ 324, $C_{20}H_{24}O_2N_2$), $(\alpha)_D^{25}$-41.1. The same dihydrocompound (XI) was also obtained by direct catalytic hydrogenation of gardnutine (II) using one mole equivalent of hydrogen and Adam's catalyst. Therfore, the structure of hydroxygardnutine can now be represented as III. This assignment was further confirmed by the fact that III was oxidized by MnO_2 to an α,β-unsaturated aldehyde(XII), m.p.310°(M^+336, $C_{20}H_{20}O_2N_2$), NMR(DMSO-D_6) 4.02τ(1H,d, $=C\underline{H}-CHO$) and 0.17τ(1H,d, $=CH-C\underline{H}O$) with J=7.0 cps., which, in turn, regenerated hydroxygardnutine(III) by $NaBH_4$ reduction.

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