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GARDNERIA ALKALOIDS -X

STRUCTURE OF GARDMULTINE, A NOVEL TYPE BISINDOLE ALKALOID

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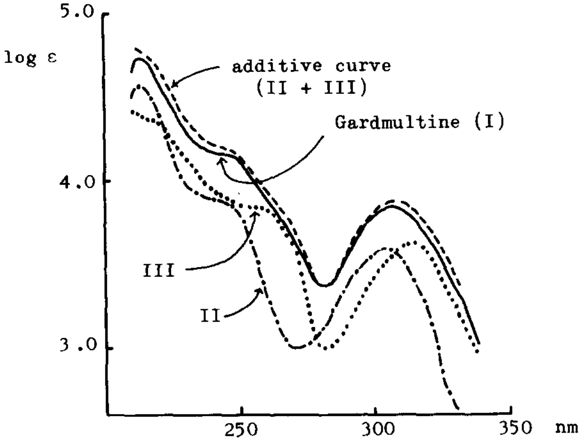
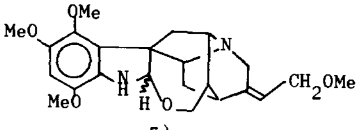
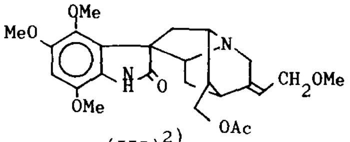
In 1970, we reported the chemical and physical properties of a new dimeric indole alkaloid from Gardneria multiflora under a tentative name of alkaloid E.1) In this communication, the structure of this base, now named gardmultine (I), is described.

Gardmultine (I), $C_{45}H_{54}O_{10}N_4 \cdot 1/2\ H_2O$, mp.283-285°, has seven methoxyl groups, six being aromatic and one aliphatic. IR spectrum of I shows the absorption bands due to oxindole NH and C=O at 3420 and 1713 cm^{-1} respectively, and its UV absorption curve (λ_{max}^{MeOH} 213(4.76), 247 (4.17) and 305(3.84) nm) shows close resemblance to an additive curve of absorptions of 4,5,7-trimethoxy indoline and the corresponding oxindole chromophores.



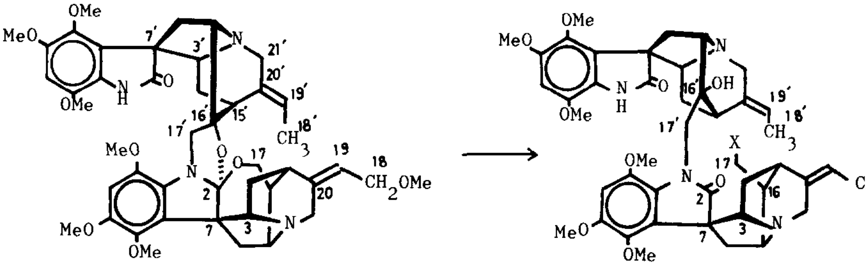


(II)5)



(III)2)

When treated with hot acetic acid, I gave an amorphous acetic acid addition product (IV), (NMR δ 2.02,3H,s.,-OAc), whose UV spectrum is oxindolic. It is well known that in acidic or basic conditions, many of natural 7-spiro oxindole alkaloids epimerise at $C_{(7)}$ and/or $C_{(3)}$ to give diastereomeric mixtures.[6] On the above acetic acid treatment, however, the resulted oxindole (IV) showed no evidence of epimerization, indicating that the both monomeric components were oxindoles with quinuclidine moieties at $C_{(7)}$, in which participation of $N_{(b)}$ was not effective because of its bridge head nature.[2,3] This conclusion is quite reasonable from the biogenetic viewpoint, for all monomeric oxindoles and their congeners in Gardneria plants have the same basic skeleton.



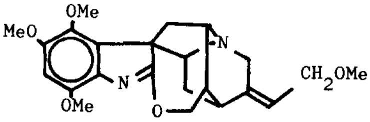
Gardmultine (I)

IV X= OAc

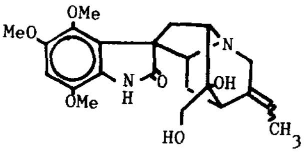
VII X= Cl

VIII X= OH

Structures of the side chain double bonds were revealed by NMR spectrum of I. A singlet signal (3H) due to an aliphatic methoxyl group and a triplet (1H) due to $C_{(19)}$-H are observed at δ 3.28 and 5.26, respectively, the latter of which changes to singlet on irradiation at δ 3.84 ($C_{(18)}$-H_2). These findings are in good accordance with the observation we encountered in our work of gardneramine (V)[2], thus suggesting that one monomeric component is V. On the other hand, a doublet methyl signal is observed at δ 0.88 (J=6.8 Hz) in the NMR spectrum of I. Double resonance experiment proved its coupling with an olefinic proton at δ 4.95 (q., J=6.8 Hz, with fine splitting due to allylic coupling with $C_{(21')}$-H_2). This proved the presence of an ethylidene side chain, and suggested that the cooccurring base, chitosenine (VI)[4], might be the other half of the bisindole (I). It is interesting to note that the olefinic methyl is highly shielded. Inspection of the presented structure (I) by using a molecular model clearly shows that the plane of the aromatic ring of gardneramine moiety is situated just above the $C_{(18')}$-methyl group. (vide infra.)

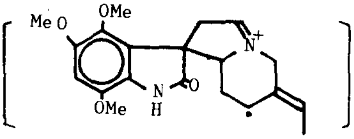


V

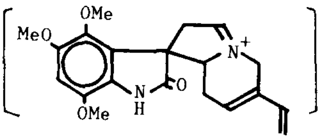


VI

The mass spectrum of I gave supporting evidence for the structure (I). Besides the expected molecular ion peak at m/e 810, two complemental peaks were observed at m/e 412 (22%) and m/e 398 (100%), the former corresponding to gardneramine (V) and the latter to dehydrated chitosenine (VI). Two intense fragments at m/e 356(48%) and m/e 355 (100%) can be depicted as shown below. These peaks are characteristic to chitosenine derivatives.[4)]

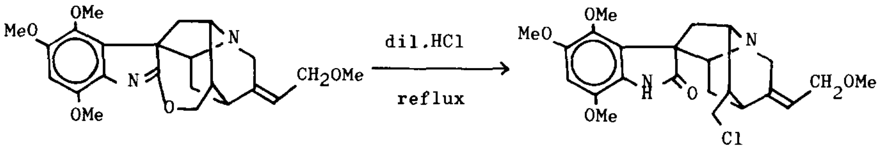


m/e 356



m/e 355

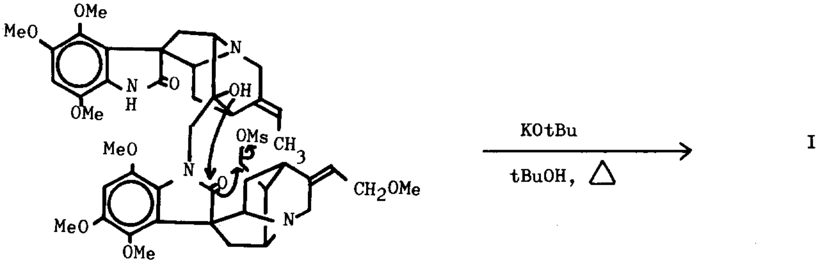
Though inactive to acylating agents or various kinds of bases, gardmultine (I) reacts readily with acids. Thus, when treated with dilute hydrochloric acid, gardmultine (I) yielded a well characterized oxindole (VII). Elemental analysis and the molecular ion peak at m/e 845 in its mass spectrum proved its molecular formula as $C_{45}H_{55}O_{10}N_4Cl$. The UV spectrum (λ_{max}^{EtOH} 220 (4.69) , 255 (4.18) and 313 (3.93) nm) clearly indicated that VII possesses two identical and non interacting chromophores of 4,5,7-trimethoxy oxindole in its molecule. Quite interesting to note is the fact that one molecule of hydrochloric acid adds to I with concomitant formation of oxindole chromophore. A closely similar reaction has been found to occur when gardneramine (V) was heated in dilute hydrochloric acid. In the NMR spectrum of VII, a doublet (3H) signal due to $C_{(18')}$-methyl appeared at δ 1.43 (J= 6.5 Hz), normal position for an olefinic methyl. The same signal appeared at δ 0.88 in I as stated above, and the change in chemical shift values here observed can be reasonably explained by conformational mobility of VII, in which the $C_{(18')}$-methyl group is freed from shielding effect of the aromatic ring of the gardneramine moiety.



(V) (X)

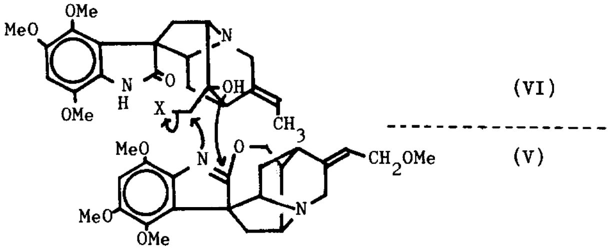
When I was heated in formic acid and subsequently treated with ethanolic potassium hydroxide, diol (VIII) was given as a powder (m/e 828, M^+). Mesylation in pyridine with mesylchloride followed by purification using preparative TLC gave mono methanesulfonate (IX) (m/e 811,

(M^+- OMs); $\nu_{max}^{CHCl_3}$ 1349 and 1185 cm^{-1} (OMs); NMR δ 3.09 ($3H,s.,OSO_2\underline{CH_3}$)). The mother base, gardmultine (I), was regenerated from IX on heating in tert.BuOH in the presence of KOtBu.



(IX)

These and other data were compatible only with the gross structure (I) for gardmultine. Formation of I in the living plants could be rationalised by condensation of gardneramine (V) and chitosenine (VI) (or their equivalents) according to the manner as shown below.



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6) For example see: J.E.Saxton, in "The Alkaloids" ed. R.H.F.Manske, Academic Press, New York, London, 1965, Vol.VIII, p.67.