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STRUCTURE OF CORYDALIDZINE, A NEW ALKALOID FROM CORYDALIS KOIDZUMIANA

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A tertiary diphenolic alkaloid corydalidzine has been isolated from Formosan Corydalis koidzumiana Ohwi along with twelve known alkaloids including l-scoulerine, corydaline, sanguinarine and protopine[1].

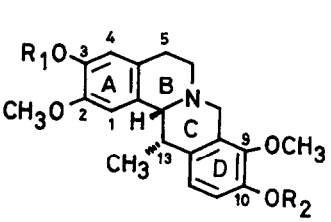
This paper describes the structure determination of the new alkaloid by spectroscopic methods and synthesis.

Corydalidzine (I), $C_{20}H_{23}O_4N$, mp 209-210° (in vacuo)[2], $[\alpha]_D^{23}$ +333° (MeOH), UV λ_{max}^{EtOH} nm (log ε): 211.5(4.46), 225(4.27 sh.), 283.5(3.78), IR ν_{max}^{Nujol} cm^{-1}: 3475, was supposed to be a tetrahydroprotoberberine alkaloid[3]. Its NMR spectrum [4] showed signals due to one secondary methyl group (δ 0.83, d, J=7Hz), two methoxyl groups (δ 3.74, s and δ 3.75, s), four aromatic protons (δ 6.51, 1H, s and δ 6.71, 3H, s), and two hydroxyl groups (δ 8.65, 1H, s and δ 8.94, 1H, s) disappearing on addition of D_2O. The mass spectrum of the alkaloid had a molecular ion at m/e 341 and typical fragment ions of tetrahydroprotoberberine skeleton[5] at m/e 178 and 164. Methylation of corydalidzine with diazomethane gave corydaline (II)[6] confirming the absolute structure of the alkaloid except the location of two methoxyl and two hydroxyl groups.

NOE experiments revealed the substitution pattern of the A ring of corydalidzine. Irradiation at δ 2.50 which was assigned to one of the C-5 benzylic protons[7] increased the intensity of the signal at δ 6.51 by 10% indicating this signal to be attributed to C-4 aromatic proton. Irradiation of the hydroxyl signal at δ 8.65 also caused the increase of the area of the signal at δ 6.51 by 11%, while that at δ 6.71 was unaffected. Thus the hydroxyl group whose signal appears at δ 8.65 must be located at C-3 and consequently the methoxyl group on the A ring at C-2. The aromatic proton signals of corydalidzine showed only two singlets at δ 6.71(3H) and δ 6.51(1H) and no AB quartet was observed, suggesting that the D ring of corydalidzine could be substituted with C-9 methoxyl and C-10 hydroxyl groups[8,9].

However, in the mass spectrum of corydalidzine, the fragment peak at m/e 163 was weak

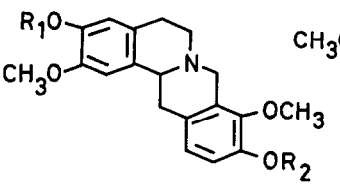
compared with that due to ion b (m/e 164)[5,8]. The results of high resolution mass spectrum revealed that the peak at m/e 163 was not due to ion c but to the fragment formed from ion a through the elimination of a methyl radical. The absence of the peak of ion c could be due to the presence of C-13 methyl group because the fragmentation pattern of the compound (III), having no substituent at C-13, was completely in agreement with the reported data[5,8].



I , $R_1=R_2=H$

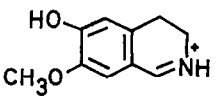
II, $R_1=R_2=CH_3$

IV, $R_1=H$, $R_2=CH_3$

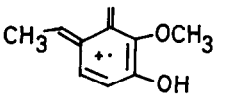


III, $R_1=R_2=H$

V , $R_1=H$, $R_2=CH_3$

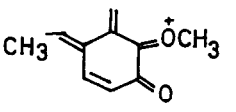


ion a
m/e 178



ion b
m/e 164

m/e 163
($C_9H_9O_2N$)



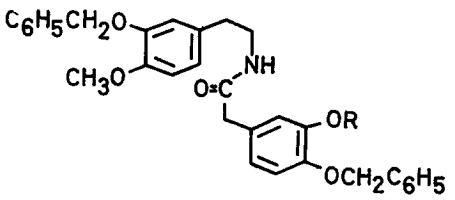
ion c
m/e 163

The Gibbs' test of corydalidzine was negative although isoquinoline alkaloids, having a hydroxyl group at C-6 position, give positive reaction[10]. This phenomenon could also be attributed to the effect of C-13 methyl as corybulbine (IV), having the same substitution pattern of the A ring, is negative while corypalmine (V), is positive to the test. Accordingly, the NMR assignment of the substitution pattern of the D ring described above would be reasonable. We thus infer that the structure of corydalidzine be represented as I. This structure was finally confirmed by the following synthesis of dl-corydalidzine as shown in Chart 1.

Condensation of 3-benzyloxy-4-methoxyphenethylamine with 4-benzyloxy-3-hydroxyphenylacetic acid gave the amide (VI), mp 128-129°, which was converted into VII, mp 51-52°. Bischler-Napieralski cyclisation of VII followed by reduction with sodium borohydride gave 1-(4-benzyloxy-3-hydroxybenzyl)-1,2,3,4-tetrahydro-6-benzyloxy-7-methoxyisoquinoline (VIII), mp 137-139°. A solution of hydrochloride of VIII and 37% formalin was allowed to stand at pH 6.4 at room temperature overnight. The reaction products were tetrahydroprotoberberines (IX), mp 87-90° and (X), mp 169.5-170.5°. The main product (IX) was methylated with diazomethane to give the dimethoxy derivative (XI), mp 146-148.5°. Oxidation of XI with mercuric acetate gave the quaternary base (XII), mp 210° (decomp.), which was converted into the acetone adduct (XIII). Heating XIII with CH_3I in a sealed tube for 16 hours followed by reduction with sodium

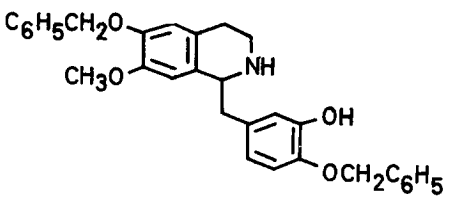
borohydride gave XIV, mp 155-156.5°, whose B/C ring juncture was found to be trans from the chemical shift (60 MHz, in $CDCl_3$) of C-13 methyl group[7] (δ 0.95, d, J=7Hz). Debenzylation of XIV gave a phenolic dl-base (I), mp 156-157.5° (in vacuo)[2], which was identical with natural corydalidzine in TLC, UV, NMR and mass spectra.

This is the first example of natural 3,10-dihydroxytetrahydroprtoberberine.

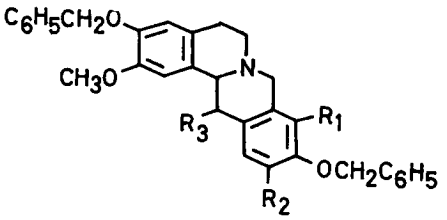


VI , R=H

VII, R=$COOC_2H_5$



VIII

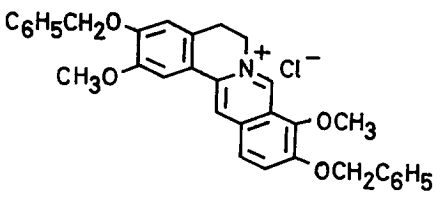


IX , R_1=OH, R_2=R_3=H

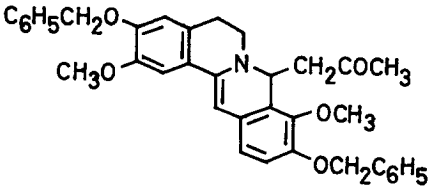
X , R_1=R_3=H, R_2=OH

XI , R_1=OCH_3, R_2=R_3=H

XIV, R_1=OCH_3, R_2=H, R_3=CH_3



XII



XIII

Chart 1

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2. Melting point of the sample placed in a vacuum capillary.
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