CRASSIFOLAZONINE, A NEW TYPE OF DIBENZ[d,f]AZONINE ALKALOID

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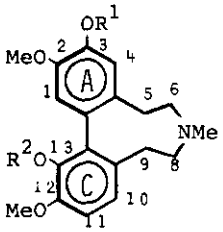
Abstract — The isolation of crassifolazonine, a dibenzazonine with a new type of tetrasubstitution pattern at 2,3,12,13 positions is described. This is the first example of a dibenzazonine possibly derived from a diphenolic benzylisoquinoline by an ortho-para coupling.

The dibenzazonines are a small group of alkaloids found in Menispermaceae and Leguminosae plants which have the general structure 1. Three of them are trisubstituted at 2,11 and 12 carbons, and two tetrasubstituted at 2,4,11 and 12, and 2,3,11 and 12[1]. Very recently, two new examples isolated from Papaver bracteatum[2] have been found which are trisubstituted at positions 1,2 and 12, and 1,2 and 11. In this communication we describe the isolation of crassifolazonine[3] 1a from Corydalis claviculata (L.) DC.(Fumariaceae). This alkaloid is the first 2,3,12,13-tetrasubstituted diphenolic dibenzazonine reported to date.

Crassifolazonine 1a was obtained as colourless crystals, mp 160-162°C(hexane-benzene). It is an optically active substance with $[\alpha]_D^{20}$ -50° (c 0.06, $CHCl_3$). Its UV spectrum showed two bands at λ_{max}(EtOH) 232 and 286 nm, characteristic of the twisted biphenyl system present in the dibenzazonine alkaloids[1]. A bathochromic shift was observed upon addition of base [λ_{max}(EtOH+NaOH) 232 and 300 nm] indicating the phenolic nature of the alkaloid. Its pmr spectrum(250MHz,$CDCl_3$,δ) exhibited in the aromatic region a pair of doublets due to two ortho coupled protons and two singlets for two para protons (Fig.I). In addition, there is a broad signal at 5.88 and a broad singlet at 5.36(W1/2=11.4 Hz), which both disappeared with D_2O; two singlets due to methoxyl groups; a complex aliphatic region between 2.63 and 2.36 (8H); and a singlet at 2.29 for an N-methyl group. Its ^{13}C-NMR spectrum (62.83MHz,$CDCl_3$, δ) showed characteristic signals for the saturated carbons of the azonine ring, which appeared as triplets at 33.83, 34.21, 57.97 and 58.14. In addition, two quartets at 47.32 (N-Me) and 55.94 (2x OMe) were also observed. The aromatic region exhibited four doublets (110.15, 112.21, 115.69 and 120.04), four singlets due to non-oxygenated quaternary carbons (126.90, 127.70, 134.22 and 134.91) and four singlets due to quaternary carbons bound to oxygen (142.59, 144.91, 145.04 and 145.55).

All the above data clearly suggested a dibenzazonine structure with two methoxyl and two hydroxyl groups as substituents. Its molecular formula $C_{19}H_{23}O_4N$ was



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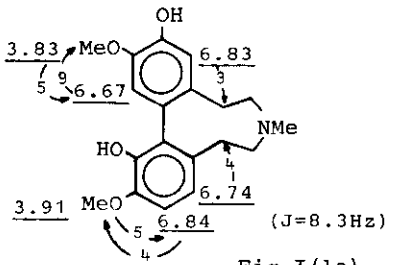
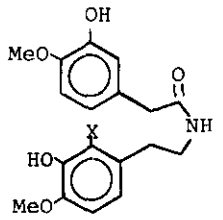
a, $R^1=R^2=H$
b, $R^1=Me, R^2=H$
c, $R^1=R^2=Me$
d, $R^1=R^2=Ac$

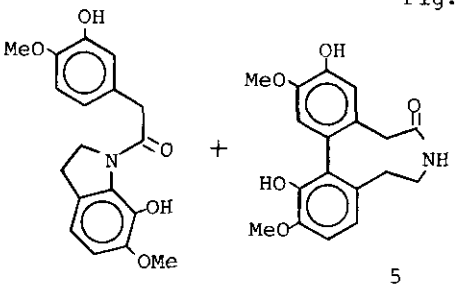


(J=8.3Hz)

Fig.I(1a)



2, X=Br
3, X=H



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confirmed by mass spectrometry, which showed the molecular ion at m/e 329(100%). The location of substituents as in structure 1a was based on nuclear Overhauser effect difference spectroscopy experiments (Fig. I)[4]. Further support for the structure of crassifolazonine 1a was obtained by its O-methylation with diazomethane, which afforded a mixture of the trimethoxy derivative 1b and the permethylated compound 1c[5], and it was separated by tlc. Compound 1c showed a singlet at δ 3.51 attributable to a methoxy group at C-13, which should appear at higher field in the dibenzazonines due to a shielding effect by ring A of their twisted biphenylic system. The absence of this signal in the trimethoxy derivative 1b and in crassifolazonine 1a proves that they both have a phenolic substituent at C-13. This assignment for crassifolazonine was confirmed from its diacetyl derivative 1d, which was obtained in the usual way (Ac_2O/Py), as it also showed a high field acetoxyl group at 1.96 (C_{13}-OAc) while the other appeared at 2.30.

Final proof for the proposed structure of crassifolazonine was obtained by its total synthesis, the key step being a photochemically induced biphenyl bond formation from the amide 2. Its irradiation in an alkaline methanolic solution with Vycor filtered light (200 W medium pressure mercury lamp) for 2.5 h under Ar, gave indoline 4[6] (7 %) and the cyclized amide 5 (10 %), which were separated from large amounts of the initial substance 2 and its reduced derivative 3. Indoline 4 probably arises from a nucleophilic attack of the amide anion on the intermediate aryl radical, as has been observed in similar cases[7]. Diborane reduction of 5, followed by N-methylation ($H-CHO/NaBH_4$) gave a product which was

identical with natural crassifolazonine, thus firmly establishing structure 1a for the alkaloid.

From a biogenetic view point the new substitution pattern present in 1a can be considered as the result of an ortho-para coupling of crassifoline, which is also present in the plant[8]. Other routes such as a para-ortho coupling of protosinomenine via the same neoproaporphine, which has been suggested for the biosynthesis of the 1,2,10,11-tetrasubstituted aporphine corydine[9], can also be envisioned. Protosinomenine has been postulated as the precursor of erybidine[1], a 2,3,11,12-tetrasubstituted dibenzazonine, through a para-para coupling. Reticuline has also been considered as the precursor of dibenzazonine alkaloids[2].

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5. 3-O-methylcrassifolazonine 1b; pmr (250 MHz, $CDCl_3$, δ): 6.86 and 6.75 (AB system, J=8.3 Hz, 2H, H-11 and H-10 respectively), 6.78 (s, 1H, H-4), 6.68 (s, 1H, H-1), 5.38 (broad s, 1H, OH), 3.92 (s, 6H, 2 x OMe), 3.83 (s, 3H, OMe), 2.32 (s, 3H, NMe) and 2.4-2.8 (m, 8H, 4 x CH_2).
3,13-O,O'-dimethylcrassifolazonine 1c; pmr (250 MHz, $CDCl_3$, δ): 6.96 and 6.91 (AB system, J=8.4 Hz, 2H, H-10 and H-11), 6.74 (s, 1H), 6.66 (s, 1H), 3.93 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.51 (s, 3H, OMe at C-13), 2.36 (s, 3H, NMe) and 2.4-2.8 (m, 4 x CH_2).

6. Indoline 4 crystallized as colourless prisms mp 192-194°C (Cl_2CH_2); pmr (250 MHz, $CDCl_3$, δ): 11.53 (s, 1H, OH), 6.87 (m, 3H), 6.66 and 6.59 (AB system, J=8 Hz, 2H), 5.66 (s, 1H, OH), 4.03 (t, J=8 Hz, 2H, $-CH_2N-$), 3.88 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.79(s, 2H, $-CH_2CO-$) and 3.01 (t, J=8 Hz, 2H, $Ar-CH_2-$); MS, m/e (%): 329 (M^+, 2), 165 (100), 164 (2), 151 (3) and 137 (40); IR (KBr): 3380, 2400-2560, 1630, 1600 and 1570 cm^{-1}; UV λ_{max}^{EtOH} (log ε): 228 (4.52) and 274 (4.11), $\lambda_{max}^{EtOH/NaOH}$: 220 (4.80), 240 sh (4.44) and 296 (4.00) nm.

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