A NEW CYTOTOXIC ALKALOID THALIFALANDINE

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Abstract——The new dimeric aporphine-benzylisoquinoline alkaloid thalifalandine (1) from Thalictrum faberi has shown the marked antitumor activity in vitro. Its structure was confirmed by chemical transformation and spectral analysis.

Thalictrum faberi Ulbr. (Ranunculaceae), a plant native to China, is used in Chinese folk medicine as an antiphlogistic, antibacterial and recently in treatment of stomach cancer. This plant has produced a lot of dimeric aporphine-benzylisoquinoline alkaloids[1,2,3]. Thalifalandine (1) is also a component of the plant and shows a significant cytotoxicity against P_{388}, L_{1210} leukemia cells with IC_{50} value 0.7-1.8 ug/ml.

Thalifalandine (1) is one of the minor alkaloids of the plant, and obtained as an amorphous solid (70 mg) from 10 kg of the roots. The UV spectrum of the alkaloid has a maximum at 285 nm with a shoulder at 308 nm, which is typical of most aporphine-benzylisoquinoline dimers. The 400 MHz (FT) NMR spectrum has been summarized around expression 1 and includes two N-methyl, six methoxy and three aromatic proton singlets including deshieled H-11 of aporphine moiety and typical for the four symmetric protons of the benzyl part, as well as the characteristic AA'BB' quartet, so the remaining C-12' should be the terminus of the diaryl ether bridge in the moiety. The NMR spectrum also shows a phenolic group which is supported by the IR spectrum. The mass spectrum of the compound shows a small molecular ion m/z 682 for the formula of $C_{40}H_{46}N_2O_8$ and base peak m/z 206 which suggests that there are two methoxy groups at the isoquinoline part, thus, the phe-

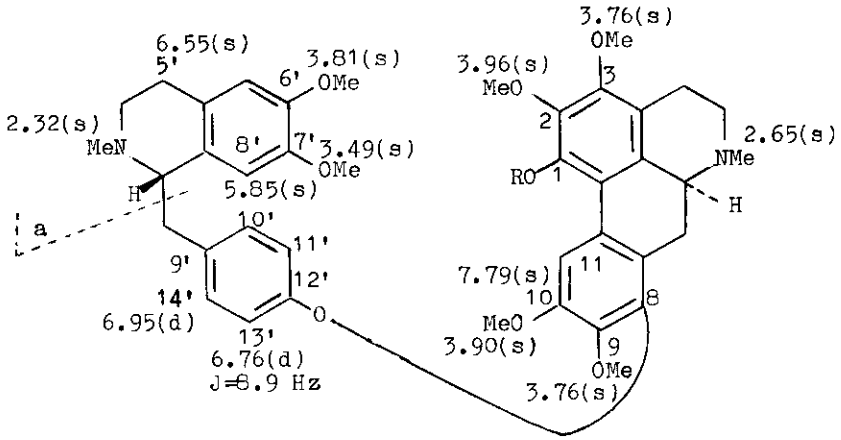
nolic group must be at the aporphine moiety.

The circular dichroism (CD) curve of 1 is also very similar to that of thalifaberine (2), indicating that both the alkaloids possess the identical absolute configuration. O-Methylation of 1 with diazomethane gave 2, which indicated that 1 was an O-demethyl derivative of 2. Thalifarapine (i.e. 3-demethylthalifaberine)[2] is different from 1, thus, the phenolic function of 1 will be at C-1 or C-2, C-9, C-10 position.

In order to establish the position of the phenolic group of 1, the alkaloid was taken to an nuclear Overhauser enhancement (NOE) study at 400 MHz, which was very useful for the structural determination of this kind alkaloids[1,2,3,5]. Irradiation of H-11(δ 7.79) gave 4.2% NOE of C-10 methoxy (δ 3.90), alternatively, irradiation of C-10 methoxy gave 15.4% NOE of H-11, which supported that the diaryl ether terminal could not be at C-10 position. Similarly, the 13.6% NOE shown by the H-8' (δ 5.85) upon irradiation of C-7' methoxy (δ 3.49), 3.0% NOE of C-7' methoxy upon irradiation of H-8', 14.4% NOE of H-5' (δ 6.55) upon irradiation of C-6' methoxy (δ 3.81), and 4.3% NOE of C-6' methoxy upon irradiation of H-5', supported that two methoxy groups of 1 were attached to C-6' and C-7' positions. No signficant NOE between H-11 and every methoxy group except C-10 methoxy to be found, serves to suggest that a methoxy group are absent at C-1, i.e., the phenolic group will be attached to C-1 position. Therefore, new alkaloid must be 1-demethylthalifaberine 1.

Spectral and physiochemical data of 1 are as follows:MS m/z 682 (M^+,about 0.1%), 476 (M-a, 5%),206 (a, 100%); UV λ_{max} (MeOH) nm (log ε) 205 (4.47), 225sh (4.37), 285 (4.03) and 308sh (3.89); λ_{max} (MeOH-NaOH) 204 (4.37), 226sh (4.30), 290 (3.83), 313 (3.95) and 325 (3.95); IR $\nu_{max}^{CHCl_3}$ 3530 cm^{-1}; CD (MeOH) $\Delta\varepsilon$(nm) -7.50 (304), -8.80 (278), +74.97 (243.3);$[\alpha]_D^{14^\circ}$ +83.3° (c o. 375, MeOH).

About fifty aporphine-benzylisoquinoline dimers so far reported in the literature were divided into nine groups[4]. It is interesting that the eight thalifaberine-type dimers as well as several other new members of this type have been obtained from Thalictrum faberi and all of them showed significant cytotoxicity againt P_{388} cell[6].



1 : R=H

2 : R=Me

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Received, 13th May, 1986