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FARFUGINE, A NEW PYRROLIZIDINE ALKALOID ISOLATED FROM FARFUGIUM JAPONICUM KITAM.

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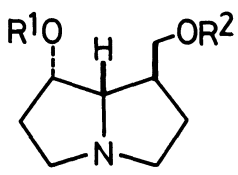
A new pyrrolizidine alkaloid, farfugine (1) was isolated from Farfugium japonicum Kitam. and the structure including absolute stereochemistry was elucidated by chemical and spectroscopic evidence.

In connection with our studies on pyrrolizidine alkaloids in the plants of Compositae family, we have investigated the alkaloidal components of Farfugium japonicum Kitam. (Tsuwabuki in Japanese), from which isolation of senkirkine has been reported previously[1]. Herein we wish to report isolation and structure determination of a new pyrrolizidine alkaloid, farfugine (1), the necine of which was proved to be (+)-turneforcidine (3). It is worthy of note that only the (-)-enantiomer of turneforcidine has so far been known among pyrrolizidine alkaloids,[2] and farfugine (1) is the first example of the alkaloid that possesses the (+)-enantiomer of turneforcidine as necine base.

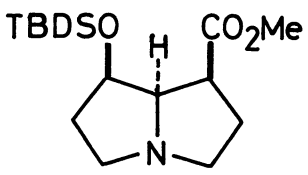
The alkaloidal fraction obtained from the ethanolic extract of the dried plant was chromatographed on aluminum oxide with $CHCl_3$ - MeOH (100:1 to 4:1) and further purified by preparative TLC on aluminum oxide with $CHCl_3$ - MeOH (100:1) to afford a new alkaloid, farfugine (1)[3,4], $C_{13}H_{21}NO_3$, colorless oil [picrate, mp 156.5-157.5 °C (EtOH)], $[\alpha]_D^{23}$ +23° (c 0.54, EtOH) (0.001% dry weight). The spectral (IR, ^{1}H-NMR, and mass) properties[4] of 1 suggested that 1 might be a monoester pyrrolizidine alkaloid consisting of angelic acid and 7-hydroxy-1-hydroxymethylpyrrolizidine. Acetylation of farfugine (1) (Ac_2O - Py, room temp , 4 h) gave a monoacetate 2[3,5], which showed a one-proton multiplet at δ 5.18 in the ^{1}H-NMR spectrum, revealing the presence of a secondary hydroxyl group in 1. Alkaline hydrolysis of the acetate 2 [50% KOH - EtOH (1:2), room temp , 2 h] afforded angelic acid, which was identified



1 R^1 = H, R^2 = -CO(Me)=CH(Me)

2 R^1 = Ac, R^2 = -CO(Me)=CH(Me)

3 R^1 = R^2 = H



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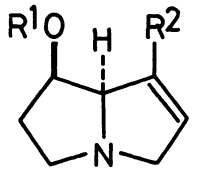
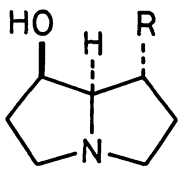


4 R^1 = H, R^2 = CH_2OH

5 R^1 = H, R^2 = CO_2Me

6 R^1 = $Si(Me)_2{}^tBu$, R^2 = CO_2Me



8 R = CO_2Me

9 R = CH_2OH

10 R = CH_2OCO(Me)=CH(Me)

as the p-bromophenacyl ester[3,5] and a necine[3,5], $C_8H_{15}NO_2$, colorless oil. The structure of the necine was deduced to be turneforcidine [(9) or its enantiomer 3] by comparison of the spectral (^{1}H-NMR and mass) data of the necine with those of natural 9. From the evidence described above, the structure of farfugine was deduced to be 9-angelylturneforcidine [(1) or (10)]. In order to establish the structure of farfugine (1) including the absolute stereochemistry, transformation of (+)-retronecine (4) into 10 was performed. An unsaturated ester 5[3,5,6] [mp 118.5-120.0 °C, $[\alpha]_D^{23}$ +30.3° (c 1.27, EtOH)] (Lit.[6] mp 122 °C) derived from (+)-retronecine (4)[7] was converted into the silyl ether 6[3,5] (cololess oil) (TBDSCl - DMAP - Et_3N, DMF, 40 °C, 23 h) in 76% yield after purification[8a]. Hydrogenation of the silyl ether 6 (Pd/C, EtOH, room temp., 1 h) yielded the saturated ester 7[3,5] (colorless oil) in 87% yield after purification[8b]. Epimerization of the carbomethoxyl group in 7 (KO^{t}Am, ^{t}AmOH - benzene, 60 °C, 1.5 h) followed by hydrolysis of the silyl ether group (HCl - MeOH, room temp , 50 min) gave the hydroxy ester 8[3,5] (colorless oil) in 77% yield after purification[8a]. Reduction of the ester 8 ($LiAlH_4$, THF, 0 °C, 20 min) afforded (-)-turneforcidine (9)[3,5,6] [mp 119-120 °C, $[\alpha]_D^{23}$ -12° (c 0.82, MeOH)][Lit.[6] mp 118-120 °C, $[\alpha]_D^{20}$ -12.5° (c 1.3, MeOH)] in 92% yield after purification[8c]. The spectral (IR, ^{1}H-NMR, and mass) properties of synthetic 9 were identical to those of natural 9. Selective esterification of the primary hydroxyl group in 9 with angelyl chloride[9] (Py - THF, -20 °C, 1 h) gave (-)-9-angelylturneforcidine (10)[3,5], colorless oil [picrate, mp 157-158 °C (EtOH)], $[\alpha]_D^{21}$ -22° (c 0.68, EtOH), in 59% yield after purification[8d]. While the spectral (IR, ^{1}H-NMR, and mass) and chromatographic properties of synthetic 10 was completely identical to those of farfugine (1), the sign of the optical rotation of 10 was found to be opposite to that of farfugine (1), indicating the absolute structure of farfugine to be represented by 1.

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References

1) T. Furuya, K. Murakami, and M. Hikichi, Phytochem., 10, 3306 (1971).

2) For a review, see D. J. Robins, Fortschr. Chem. org. Naturstoffe, 41, 115-203 (1982).

3) Satisfactory microanalyses or high resolution mass spectra were obtained for this compound.

4) 1: IR ($CHCl_3$) 3340, 1705, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.91 (3H, m), 2.00 (3H, dq, J=7.0, 1.5 Hz), 1.50-2.40 (4H, m), 2.55 (OH), 2.40-3.00 (3H, m), 3.05-3.45 (3H, m), 4.00-4.30 (3H, m), 6.09 (1H, qq, J=7.0, 1.5 Hz); MS m/z 239(M^+).

5) Satisfactory IR, ^{1}H-NMR, and mass spectra were obtained for this compound.

6) A. J. Aasen and C. C. J. Culvenor, Aust. J. Chem., 22, 2657 (1969).

7) (+)-Retronecine (4) was obtained by hydrolysis of an alkaloid monocrotaline.[10]

8) By chromatography on: a) Al_2O_3 with Et_2O-MeOH-conc NH_3 (100:5:1); b) SiO_2 with $CHCl_3$-MeOH-conc NH_3 (70:10:1); c) Al_2O_3 with EtOAc-MeOH-conc NH_3 (100:10:1 to 20:4:1). d) By preparative TLC on SiO_2 with $CHCl_3$-MeOH-conc NH_3 (100:20:1).

9) Angelic acid[11] was converted [i. n-BuLi, THF, -78 °C; ii. $(COCl)_2$, -78 °C → 0 °C, 1.5 h] to the acyl chloride, which was used instantly without isolation.

10) R. Adams and E. F. Rogers, J. Am. Chem. Soc., 61, 2815 (1939).

11) R. E. Buckels and G. V. Mock, J. Org. Chem., 15, 680 (1950).

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