IWAMIDE: A NEW PHENOLIC AMIDE DERIVED FROM A QUATERNARY BENZO[c]PHENANTHRIDINE ALKALOID[1)]

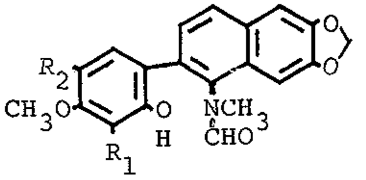
Tsutomu Ishikawa and Hisashi Ishii*

Faculty of Pharmaceutical Sciences, Chiba University,
1-33, Yayoi-cho, Chiba, Japan

The structure of iwamide (I) was established by the fact that decarine (II) was chemically transformed into iwamide (I) using Baeyer-Villiger like oxidation of an immonium group.

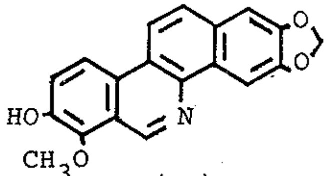
In the course of our studies on the chemical constituents of Rutaceous plants, we[2)] have isolated a new phenolic amide (I) as a minor component of the bark of *Xanthoxylum arnottianum* Maxim. (Japanese name: Iwa-zansho), in 0.00086 % yield. We wish to designate this compound as iwamide (I) and report here its structural establishment due to chemical interconversion of decarine[3)] (II), a tertiary benzo[c]phenanthridine alkaloid, into iwamide (I) using Baeyer-Villiger like oxidation of an immonium group.

Iwamide (I) is a phenolic amide isolated as colourless prisms, mp 271-273° (from CHCl$_3$-MeOH). [$C_{20}H_{17}O_6N$[4)] (M^+: at m/e

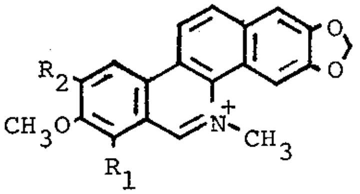


(III) : R_1=OCH_3, R_2=H

(IV) : R_1=H, R_2=OCH_3



(II)



(V) : R_1=OCH_3, R_2=H

(VI) : R_1=H, R_2=OCH_3

367)]. It shows the following spectral properties: ir ν_{max}^{KBr} cm^{-1}: 3480(OH), 1646(C=O); nmr($CDCl_3$ + CD_3OD) δ: 2.97(3H, s, NCH_3), 3.82(3H, s, OCH_3), 6.05(2H, s, OCH_2O), 6.43(1H, d J=9.0 Hz, aromatic H), 6.66(1H, d, J=9.0 Hz, aromatic H), 7.00(1H, s, aromatic H), 7.18(1H, s, aromatic H), 7.27(1H, d, J=9.0 Hz, aromatic H), 7.71(1H, d, J=9.0 Hz, aromatic H), 8.07(1H, s, CHO).

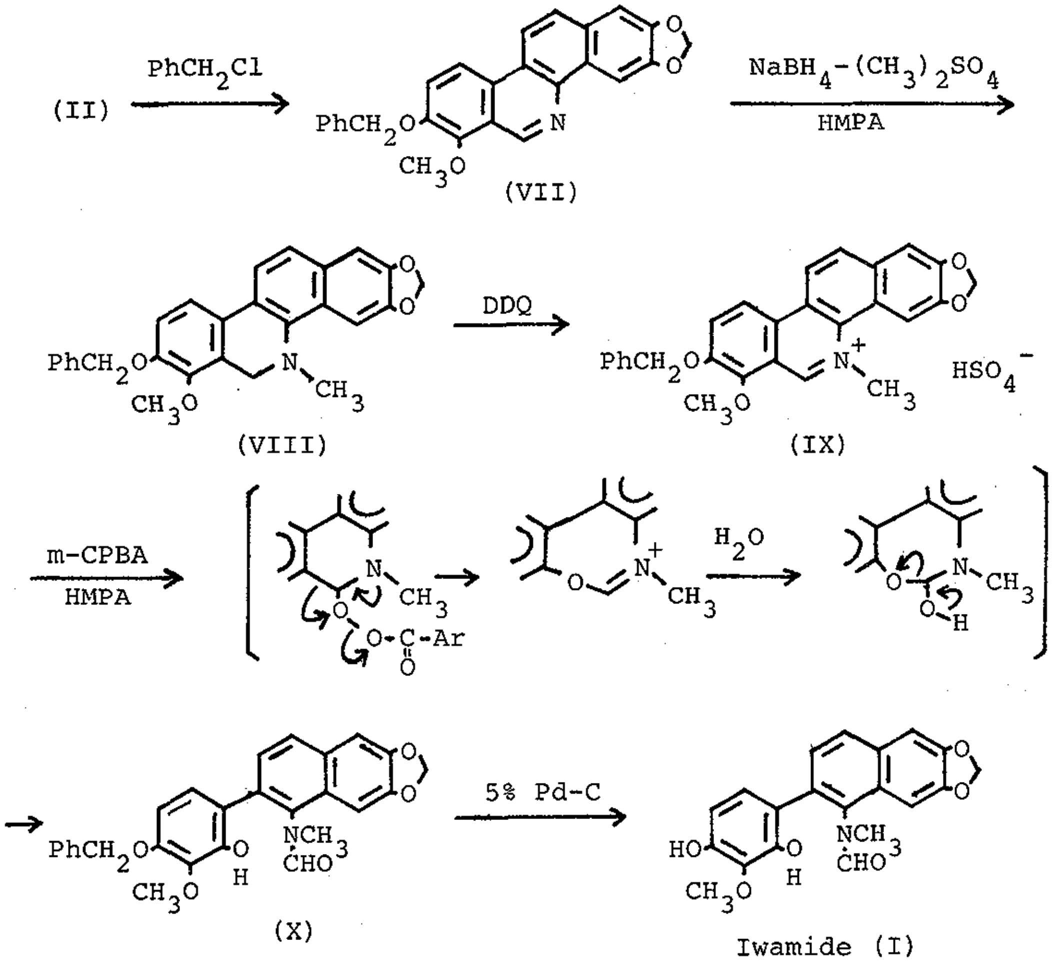
In the previous paper,[5)] we reported the natural occurrence of a new type of amides, arnottianamide (III) and isoarnottianamide (IV), which were supposed to be formed by Baeyer-Villiger like oxidation of an immonium group of quaternary benzo[c]-phenanthridine alkaloids, chelerythrine (V) and nitidine (VI) respectively. We, furthermore, showed that this type of reaction took place in a test tube.

The presence of a formyl proton at δ 8.07 as a 1H singlet and an N-methyl signal at δ 2.97 as a 3H singlet in the NMR spectrum of iwamide (I) suggested that this amide (I) could be belonged to the arnottianamide-isoarnottianamide group. Taking into consideration that decarine[3] (II) was obtained as a phenolic tertiaty base from the same plant,[5] we could imagine that iwamide (I) was formed by quaternarization of decarine (II) followed by Baeyer-Villiger like oxidation of an immonium group in the plant body.

Treatment of decarine (II) with benzylchloride gave benzyl decarine (VII) as pale yellow needles, mp 218-220° (from benzene-MeOH), in 81.3 % yield. [$C_{26}H_{19}O_4N$[4]; nmr($CDCl_3$) δ: 4.12(3H, s, OCH_3), 5.24(2H, s, OCH_2Ph), 6.04(2H, s, OCH_2O), 7.20(1H, s, aromatic H), 7.30-7.60(6H, m, aromatic H), 7.75(1H, d, J=9.0 Hz, aromatic H), 8.21(1H, d, J=9.0 Hz, aromatic H), 8.24(1H, d, J= 9.0 Hz, aromatic H), 8.66(1H, s, aromatic H), 9.68(1H, s, aromatic H)].

Since quaternarization of a nitrogen of a pyridine nucleus with an alkyl reagent gave sometimes a mixture of a quaternary base and salt of the starting tertiary base, we attempt to improve this step of the reaction sequence. A solution of benzyl decarine (VII) in hexamethylphosphoric triamide (HMPA) was treated with $NaBH_4$ and dimethyl sulfate to give N-methyl dihydro-derivative (VIII) as colourless fine needles, mp 183.5-185.5° (from benzene-MeOH), in 98.8 % yield. [$C_{27}H_{23}O_4N$[4]; nmr($CDCl_3$) δ: 2.58(3H, s, NCH_3), 3.91(3H, s, OCH_3), 4.29(2H, s, $ArCH_2N<$), 5.15 (2H, s, OCH_2Ph), 6.00(2H, s, OCH_2O), 6.95(1H, d, J=9.0 Hz, aromatic H), 7.08(1H, s, aromatic H), 7.30-7.55(7H, m, aromatic H), 7.65(1H, s, aromatic H), 7.67(1H, d, J=9.0 Hz, aromatic H)].

Oxidation of N-methyl dihydro-derivative (VIII) with DDQ



gave a desired quaternary salt which was obtained as sulfate (IX), orange needles, mp 260-265° (from MeOH), in 50.4 % yield. [nmr(CF_3CO_2H) δ: 4.28(3H, s, OCH_3), 4.93(3H, s, NCH_3), 5.29(2H, s, OCH_2Ph), 6.06(2H, s, OCH_2O), 7.18-7.36(6H, m, aromatic H), 7.84(1H, s, aromatic H), 7.96(2H, d, J=8.0 Hz, aromatic H), 8.33(2H, d, J=8.0 Hz, aromatic H), 9.51(1H, s, $ArCH=N^+$)].

Treatment of the sulfate (IX) in HMPA with m-chloroperbenzoic acid afforded benzyl iwamide (X) as colourless prisms, mp 249-252° (from $CHCl_3$-MeOH), in 77.9 % yield. [$C_{27}H_{23}O_6N$[4] (M^+: at m/e 457); ir ν_{max}^{KBr} 1675(C=O); nmr($CDCl_3$) δ: 2.99(3H, s, NCH_3), 3.97(3H, s, OCH_3), 5.12(2H, s, OCH_2Ph), 5.99(1H, s, OH), 6.05(2H, s, OCH_2O), 6.58(1H, d, J=8.5 Hz, aromatic H), 6.78(1H, d, J=8.5 Hz, aromatic H), 7.08(1H, s, aromatic H), 7.19(1H, s, aromatic H), 7.36-7.53(6H, m, aromatic H), 7.73(1H, d, J=8.5 Hz, aromatic H), 8.17(1H, s, CHO)].

A benzyl-protecting group was removed via hydrogenolysis using 5 % palladium on charcol to give colourless prisms, mp 267-268.5°, in 97.6 % yield. This was identified with a sample of iwamide (I) which was obtained from the natural source. This result was enough to establish the structure of iwamide to be shown by the formula (I).

REFERENCES

1 This paper constitutes Part XXXII of Chemical Constituents of Rutaceous Plants. [Part XXXI: H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, Yakugaku Zasshi, submitted for publication].

2 H. Ishii, T. Ishikawa, and J. Haginiwa, Yakugaku Zasshi, in preparation.

3 J. Vaquett, J. L. Pousset, R. R. Paris, and A. Cavé, Phytochemistry, 1974, **13**, 1257.

4 The compound gave satisfactory elemental analysis for the formula given.

5 H. Ishii, T. Ishikawa, S.-T. Lu, and I.-S. Chen, Tetrahedron letters, 1976, 1203.

Received, 2nd August, 1976