[Chem. Pharm. Bull. 24(1) 52 — 55 (1976)]

UDC 547.94.02 : 581.192

Studies on the Erythrina Alkaloids. XI.[1] Alkaloids of *Erythrina crysta-galli* Linn. Structure of a New Alkaloid, Crystamidine

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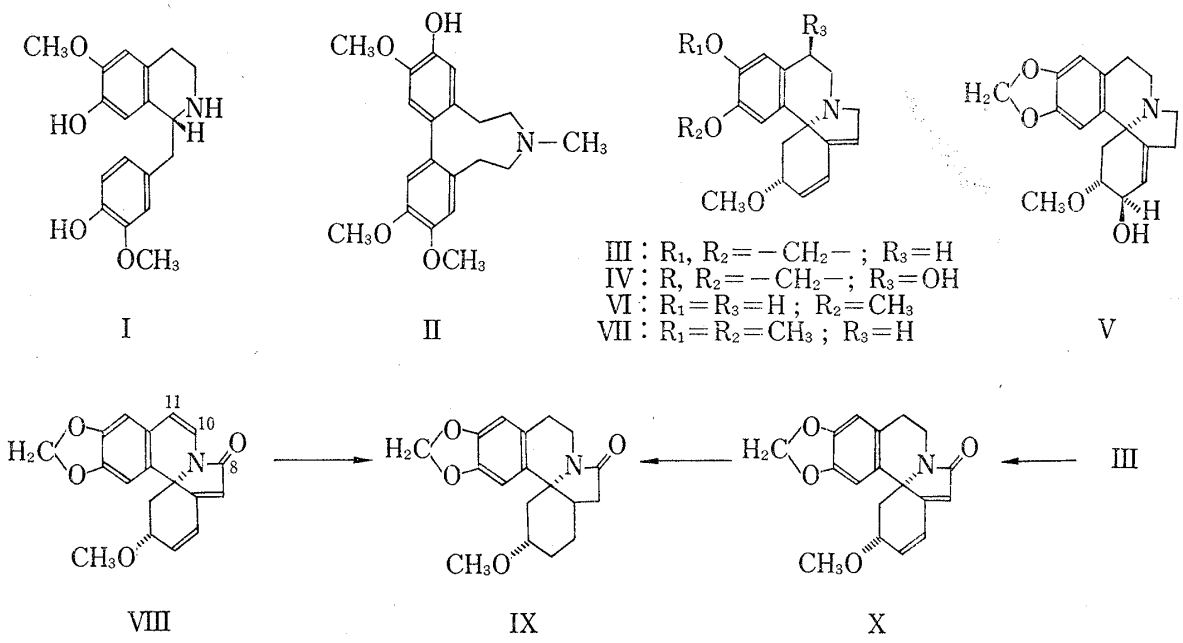
(Received May 10, 1975)

Crystamidine is a new Erythrina alkaloid, which has been isolated from *Erythrina crysta-galli* Linn. (Japanese name: *Hosoba Deiko*) (Leguminosae) along with six known bases, N-nororientaline (I), erybidine (II), erythraline (III), erythrinine (IV), erysodine (VI) and erysotrine (VII). Chemical and spectral investigations of crystamidine showed that it should have the stereostructure (VIII).

In our preceding paper[3] of this series, we described the isolation of two phenolic bases, N-nororientaline (I) and erybidine (II), and three non-phenolic bases, erythraline (III), erythrinine (IV) and erythratine (V) from the leaves, heartwoods, barks and roots of *Erythrina crysta-galli* Linn. cv. *Maruba Deiko* H. Murata (Japanese name: *Maruba Deiko*) (Leguminosae).

In this paper, we present the isolation and characterization of the alkaloidal components of the leaves of *Erythrina crysta-galli* Linn. (Japanese name: *Hosoba Deiko*).

Along with the known Erythrina alkaloids, erysodine (VI), erythraline (III), erythrinine (IV) and erysotrine (VII), a tetrahydrobenzylisoquinoline alkaloid, N-nororientaline (I) and an alkaloid of dibenz[*d*,*f*]azonine-type, erybidine (II), we isolated a new non-phenolic base which we named as crystamidine, and established the structure (VIII).



I II III V

VIII IX X

Chart 1

1) Part X: K. Ito, M. Haruna, and H. Furukawa, *Yakugaku Zasshi*, **95**, 358 (1975).
2) Location: *Yagoto, Tenpaku-ku, Nagoya.*
3) K. Ito, H. Furukawa, M. Haruna, and M. Ito, *Yakugaku Zasshi*, **93**, 1674 (1973).

We have failed in all attempts of crystallization of crystamidine. $[\alpha]_D$: +840° (chloroform). The infrared (IR) spectrum[4] (chloroform) of this base showed the presence of the carbonyl group and aromatic ring by the absorption bands at 1695 and 1490 cm^{-1} respectively. Its ultraviolet (UV) spectrum (λ_{max}^{EtOH} 235 (log ε 4.13), 267 (log ε 4.15) and 357 nm (log ε 3.31))[4] suggested the presence of heteroannular conjugated system in the alkaloid.

The nuclear magnetic resonance (NMR) spectrum[5] in deuterochloroform of crystamidine (Fig. 1) indicated the existence of a methoxyl group (6.71), a methylenedioxy group (4.05), two aromatic protons (3.27, 1H, s; 3.30, 1H, s) which are located at the *para* positions, and three vinyl protons 3.07 (dd, 1H, J=2.5, 10.0 Hz), 3.68 (broad d., 1H, J=10.0 Hz) and 3.93 (broad s., 1H). The mass spectrum[6] showed the significant ions at *m/e* 309 (M^+), 294 (M-15), 278 (M-31) and 276 (M-33, base peak). The fragmentation pattern was typical of that of the Erythrina alkaloid having the 1,6-diene moiety with an additional methoxyl function at C_3.[7]

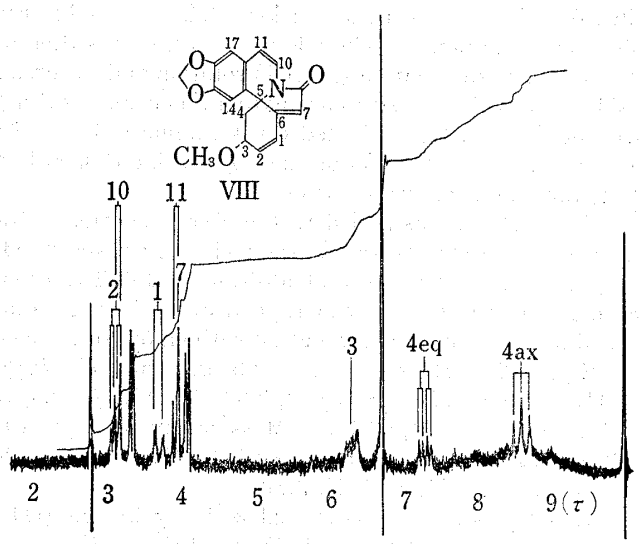


Fig. 1. The 100 MHz NMR Spectrum of Crystamidine (VIII) (in $CDCl_3$)

The position of an absorption band at 1695 cm^{-1} in the IR spectrum of crystamidine suggested the presence of a carbonyl group at C_8-, C_{10}- or C_{11}-position. However the methylene signals assigned to C_{10} and C_{11} in the benzyl proton region were not observed, and two doublets of AB-type at 3.09 (J=7.0 Hz) and 3.89 (J=7.0 Hz) corresponding to one proton appeared in the NMR spectrum. This fact indicates the existence of a double bond between C_{10} and C_{11}, and thereby it is confirmed that the carbonyl group is present at C_8 as an amide carbonyl.

The steric configuration at C_3 is defined on the basis of the signal of C_4-axial proton which appears as a triplet at 8.60 ($J_{4ax,3ax}$=10.0 Hz, $J_{4ax,4eq}$=10.0 Hz). Largeness of the coupling constant between 4ax-H and 3ax-H (J=10.0 Hz) is well consistent with the fact that a hydrogen attached to C_3 is axial, and hence C_3-methoxyl group is equatorial.

Hydrogenation of crystamidine with platinum dioxide in glacial acetic acid afforded hexahydrocrystamidine. This compound showed an absorption band due to amide carbonyl group at 1675 cm^{-1} in its IR spectrum, and no signal based on vinyl proton was observed in the NMR spectrum.

On the other hand, oxidation of erythraline (III) with potassium permanganate-magnesium sulfate,[8] followed by hydrogenation with platinum dioxide provided tetrahydro-8-oxoerythraline (IX) in low yield. The identification of hexahydrocrystamidine and tetrahydro-8-oxoerythraline (IX) suggested that both compounds have the same configuration at C_5 and C_3.

On the basis of the experimental results described above, crystamidine is represented by the formula (VIII).

4) IR spectra were determined by Nippon-Bunko IR-1 Spectrometer and UV spectra — on Perkin-Elmer 202 Spectrophotometer.
5) NMR spectra were measured on Nippon-Denshi PS-100 Spectrometer in $CDCl_3$ with tetramethylsilane as internal standard and chemical shifts were given in τ-value.
6) Mass spectra were determined on Hitachi RMU-6 Mass Spectrometer using a direct inlet system.
7) R.B. Boar and D.A. Widdowson, *J. Chem. Soc.*, (*B*), **1970**, 1591.
8) K. Wada and K. Munakata, *Agr. Biol. Chem.*, **31** 336 (1967).

Experimental[9]

Extraction and Isolation of Alkaloids——Dried leaves of *Erythrina crysta-galli* Linn. (5.6 kg) were milled and extracted with MeOH at 60°. The methanolic extract was evaporated *in vacuo*, and the concentrate was diluted with 5% citric acid solution. The acidified solution was filtered and the filtrate was made alkaline by addition of ammonia. The alkaline solution was then extracted repeatedly with $CHCl_3$. The combined extracts were washed with 5% NaOH solution and water, and dried over Na_2SO_4, followed by evaporation. The residual brownish oil was chromatographed on a silica gel (Mallinckrodt, 100 mesh) column. Elution with benzene–$CHCl_3$ (8: 2) afforded crystamidine (VIII). Successive elution with $CHCl_3$ gave erythraline (III), and erysotrine (VII) was obtained by elution of $CHCl_3$–acetone (7: 3). Further elution with $CHCl_3$–acetone (1: 1) furnished erythrinine (IV).

Solid NH_4Cl was added to the above-mentioned NaOH solution and extracted repeatedly with $CHCl_3$. The combined extracts were washed with water, and dried over anhydrous Na_2SO_4. $CHCl_3$ solution was evaporated *in vacuo* to dryness, and addition of MeOH to the residue deposited crystals of N-nororietaline (I). The mother liquor was chromatographed on a silica gel (Mallinckrodt) column. Elution with chloroform gave erysodine (VI), and further elution with chloroform–acetone (7: 3) afforded erybidine (II).

Erythraline (III)——Yield. 3.01 g. Oil. UV λ_{max}^{EtOH} nm: 232, 290. NMR ($CDCl_3$) τ: 3.22 (s., 1H), 3.36 (s., 1H), 4.10 (s., 2H, $-OCH_2O-$), 3.37 (dd., 1H, $J=2.5$, 10.0 Hz), 4.05 (broad d., 1H, $J=10.0$ Hz), 4.30 (broad s., 1H), 6.67 (s., 3H, OCH_3). Mass Spectrum *m/e*: 297 (M^+), 288, 266 (base peak), 264. HBr-salt: mp 243° (decomp.). $[\alpha]_D^{22}$ +210° ($c=0.5$, EtOH). *Anal.* Calcd. for $C_{18}H_{19}O_3N\cdot HBr$: C, 57.15; H, 5.33; N, 3.70. Found: C, 57.27; H, 5.47; N, 3.79.

This compound was identical with erythraline (III) hydrobromide, previously isolated by us,[10] by the comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

Erysotrine (VII)——Yield. 105 mg. Oil. UV λ_{max}^{EtOH} nm: 229, 280. NMR ($CDCl_3$) τ: 6.18 (s., 3H, OCH_3), 6.25 (s., 3H, OCH_3), 6.68 (s., 3H, OCH_3), 3.44 (dd., 1H, $J=2.0$, 10.0 Hz), 4.02 (broad d., 1H, $J=10.0$ Hz), 4.30 (broad s., 1H), 3.17 (s., 1H), 3.37 (s., 1H), 5.95 (m., 1H), 7.47 (dd., 1H, $J=5.0$, 12.5 Hz), 8.17 (t., 1H, $J=12.5$ Hz). Mass Spectrum *m/e*: 313 (M^+), 298, 282, 280. Picrate: mp 161—162°. $[\alpha]_D^{23}$ +140° ($c=0.4$, EtOH). *Anal.* Calcd. for $C_{18}H_{23}O_3N\cdot C_6H_3O_7N_3$: C, 55.35; H, 4.83; N, 10.33. Found: C, 55.36; H, 4.83; N, 10.35.

This free base was identical with erysotrine (VII) by the comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

Erythrinine (IV)——Yield. 922 mg. mp 202—204°. $[\alpha]_D^{22}$ +205° ($c=0.5$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). UV λ_{max}^{EtOH} nm: 211, 234, 291. NMR ($CDCl_3$) τ: 3.00 (s., 1H), 3.22 (s., 1H), 3.41 (dd., 1H, $J=2.5$, 10.0 Hz), 4.00 (broad d., 1H, $J=10.0$ Hz), 4.28 (broad s., 1H), 5.28 (t., 1H, $J=4.5$ Hz), 6.40 (dd., 1H, $J=4.5$, 13.5 Hz), 7.10 (dd., 1H, $J=4.5$, 13.5 Hz), 4.10 (s., 2H, $-OCH_2O-$), 6.68 (s., 3H, OCH_3). Mass Spectrum *m/e*: 313 (M^+), 295 (M—18), 280 (M—18—15), 264 (M—18—31, base peak), 262 (M—18—33). *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.72; H, 5.98; N, 4.37.

This compound was identical with erythrinine (IV) by the comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

N-Nororientaline (I)——Yield. 4.65 g. mp 101—102°. $[\alpha]_D^{23}$ +42.0° ($c=0.5$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). UV λ_{max}^{EtOH} nm (log ε): 216 (4.03), 230 (4.03), 286 (3.81). NMR ($CDCl_3$) τ: 3.07—3.43 (5H), 5.78 (broad s., 3H, –NH, –OH), 6.17 (s., 3H, OCH_3), 6.18 (s., 3H, OCH_3). Mass Spectrum *m/e*: 315 (M^+), 178 (base peak), 163. *Anal.* Calcd. for ($C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.75; H, 6.48; N; 4.16.

This compound was identical with N-nororientaline (I) by the comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

Erybidine (II)——Yield. 2.04 g. mp 178—180°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH). UV λ_{max}^{EtOH} nm (log ε): 223 (5.24), 2.81 (3.90). NMR ($CDCl_3$) τ: 3.12—3.27 (4H), 6.05 (s., 3H, OCH_3), 6.12 (s., 6H, $2\times OCH_3$), 7.62 (s., 3H, $N-CH_3$). Mass Spectrum *m/e*: 343 (M^+). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.23. Found: C, 69.68; H, 7.32; N, 4.08.

This substance was identical with erybidine (II) by the comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

Erysodine (VI)——Yield. 401 mg. mp 204—205°. $[\alpha]_D^{23}$ +243° ($c=0.5$, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). UV λ_{max}^{EtOH} nm (log ε): 233 (4.14), 284 (3.81). NMR ($CDCl_3$) τ: 3.18 (s., 1H), 3.28 (s., 1H), 3.42 (dd., 1H, $J=2.5$, 10.0 Hz), 3.98 (broad d., 1H, $J=10.0$ Hz), 4.27 (broad s., 1H), 6.25 (s., 3H, OCH_3), 6.68 (s., 3H, OCH_3), 5.93 (m., 1H), 7.45 (dd., 1H, $J=5.5$, 12.0 Hz), 8.15 (t., 1H, $J=12.0$ Hz). Mass Spectrum *m/e*: 299 (M^+), 284 (M-15), 268 (M-31), 266 (M-33). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.08; H, 6.98; N, 4.88.

This compound was identical with erysodine (VI) by the comparison of IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

9) All melting points were determined on the Yanagimoto Micro-Melting point Apparatus and uncorrected.
10) K. Ito, H. Furukawa, and H. Tanaka, *Yakugaku Zasshi*, **93**, 1211 (1973).

Crystamidine (VIII)——Yield. 32 mg. Pale yellow oil. $[\alpha]_D^{23}$ +840° (c=0.5, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (C=O). UV λ_{max}^{EtOH} nm (log ε): 235 (4.13), 267 (4.15), 357 (3.31). NMR ($CDCl_3$) τ: 3.27 (s., 1H), 3.30 (s., 1H), 3.07 (dd., 1H, J=2.5, 10.0 Hz. C_2–H), 3.68 (broad d., 1H, J=10.0 Hz, C_1–H), 3.93 (s., 1H, C_7–H), 3.09 (d., 1H, J=7.0 Hz), 3.89 (d., 1H, J=7.0 Hz), 4.05 (q., 2H, $-OCH_2O-$), 6.71 (s., 3H, OCH_3), 6.27 (m., 1H, C_3–H), 7.28 (dd., 1H, J=5.0, 10.0 Hz, C_{4eq}–H), 8.60 (t., 1H, J=10.0 Hz, C_{4ax}–H). Mass Spectrum m/e: 309 (M^+), 294 (M-15), 278 (M-31), 276 (M-33, base peak).

Hexahydrocrystamidine (IX)——Crystamidine was hydrogenated with hydrogen over PtO_2 (10 mg) in glacial acetic acid (5 ml). Stirring was continued overnight at room temperature, water was added, and the mixture was neutralized with NH_4OH and extracted with ether. The ethereal layer was dried over Na_2SO_4 and evaporated. The residue was purified by the use of alumina (Woelm IV) column chromatography. Yield. 6 mg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (–NHC=O). NMR ($CDCl_3$) τ: 3.30 (s., 1H), 3.46 (s., 1H), 4.14 (s., 2H, $-OCH_2O-$), 6.76 (s., 3H, OCH_3). Mass Spectrum m/e: 315 (M^+).

8-Oxoerythraline (X)——To a solution of 145 mg of erythraline (III) and 400 mg of $MgSO_4 \cdot 7H_2O$ in 70 ml of acetone and 10 ml of water, a solution of 150 mg of $KMnO_4$ in 30 ml of water was added on ice-salt bath with stirring. Further stirring was continued for 20 minutes at room temperature. The excess reagent was decomposed with saturated solution of Na_2SO_3 in 5% H_2SO_4 and solvents were evaporated *in vacuo*. The concentrated solution was acidified with 5% HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and $CHCl_3$ was evaporated. The residue was purified by the alumina column chromatography (elution with benzene). Yield. 52 mg (oil). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665 (C=O). NMR ($CDCl_3$) τ: 3.09 (dd., 1H, J= 2.5, 10.0 Hz), 3.67 (broad d., 1H, J=10.0 Hz), 3.22 (s., 1H), 3.25 (s., 1H), 3.95 (s., 1H), 4.07 (m., 2H, $-OCH_2O-$), 6.65 (s., 3H, OCH_3). Mass Spectrum m/e: 311 (M^+).

Tetrahydro-8-oxoerythraline (hexahydrocrystamidine) (IX)——8-Oxoerythraline (X) (30 mg) was hydrogenated with PtO_2 (10 mg) in glacial acetic acid (5 ml). Stirring was continued overnight at room temperature. The reaction mixture was treated according to the method described above. Yield. 28 mg (oil).

This substance was identical with hexahydrocrystamidine (IX) by comparison of their IR ($CHCl_3$) and NMR ($CDCl_3$) spectra.

Acknowledgement We express our thanks to Dr. H. Murata, Ibusuki, Kagoshima Prefecture for his collection of the plant material. We are also indebted to Misses E. Yoshida and C. Shibata of the Analysis Center of our university for elemental analyses.