[Chem. Pharm. Bull. 22(9)2108—2112(1974)]

UDC 547.94.057 : 581.192

Studies on the Erythrina Alkaloids. VIII.[1] Alkaloids of *Erythrina* X *bidwillii* Lindl. (4).[2] Synthesis of Erybidine by Photochemical Reaction

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(Received February 28, 1974)

Irradiation of methanolic solution of amide (VIII) by a 100 W high pressure mercury lamp in the presence of sodium hydroxide afforded a mixture of three phenolic irradiation products, whose structures were proved to be IX, X and XI respectively on the basis of chemical and spectral studies.

Among these photocyclization products, X was reducted with sodium borohydride and boron trifluoride to provide the amine (XIII), which was converted with formalin and sodium borohydride to erybidine (I).

In our preceding paper,[2] we reported the structural elucidation of a new alkaloid, erybidine (I), which was isolated from the leaves of *Erythrina* X *bidwillii* Lindl. (Leguminosae); erybidine was shown to be 5,6,8,9-tetrahydro-2,11,12-trimethoxy-7-methyl-dibenz[*d*,*f*]azonin-3-ol on the basis of some degradation experiments and also by direct comparison with an authentic specimen prepared by methylation of erysodienol with Rodionov reagent.

The chemistry of dibenzazonine system of erybidine may have important implications for the biosynthesis of Erythrina alkaloids.[4] Furthermore, recent report[5] has also descrived novel synthesis of O-methylerybidine using facile conversions of the benzylisoquinoline derivative to neoproerythrinadienone and hence to dibenzazonine.

The present paper is concerned with a convenient synthesis of the dibenzazonine system which is based on the photochemical intramolecular coupling of bromo derivative of N-phenethyl phenylacetamide and on further conversion to erybidine.

The key compound (VIII) in the synthesis of erybidine was prepared as follows. 6-Bromo-3,4-dimethoxybenzyl alcohol (II)[6] was converted with thionyl chloride to the corresponding chloride (III). It was converted into IV with sodium cyanide in dimethyl sulfoxide, which was hydrolyzed to give V. This compound (V) was heated with 3-benzyloxy-4-methoxyphenethylamine (VI)[7] in xylene to afford amide (VII). Debenzylation of this amide (VII) with ethanolic hydrochloric acid yielded the expected compound (VIII).

Irradiation of methanolic solution of VIII by a 100 W high pressure mercury lamp in the presence of sodium hydroxide and in a stream of nitrogen afforded a mixture of three phenolic irradiation products,[8] which was subjected to chromatographical separation on silica gel. The structures of these products were confirmed respectively as IX, X and XI on the basis of chemical and spectral studies as follows.

The substance (IX), mp 218—220°, $C_{19}H_{21}O_5N$, was eluted as the first chromatographical fraction. The infrared (IR) spectrum ($CHCl_3$) of this compound shows the hydroxyl band

1) Part VII: K. Ito, H. Furukawa and M. Haruna, *Yakugaku Zasshi*, **93**, 1617 (1973).
2) Part III: K. Ito, H. Furukawa, H. Tanaka and T. Rai, *Yakugaku Zasshi*, **93**, 1218 (1973).
3) Location: *Yagoto-urayama, Tenpaku-cho, Showa-ku, Nagoya.*
4) D.H.R. Barton, R.B. Boar and D.A. Widdowson, *J. Chem. Soc.*, (*C*), 1213 (1970).
5) S.M. Kupchan, A.J. Liepa, V. Kameswaran and R.F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973).
6) R. Pschorr, *Ann. Chem.*, **391**, 23 (1912).
7) E. Späth, A. Orechoff and F. Kuffmer, *Chem. Ber.*, **67**, 1214 (1934).
8) Any non-phenolic compound was not found.

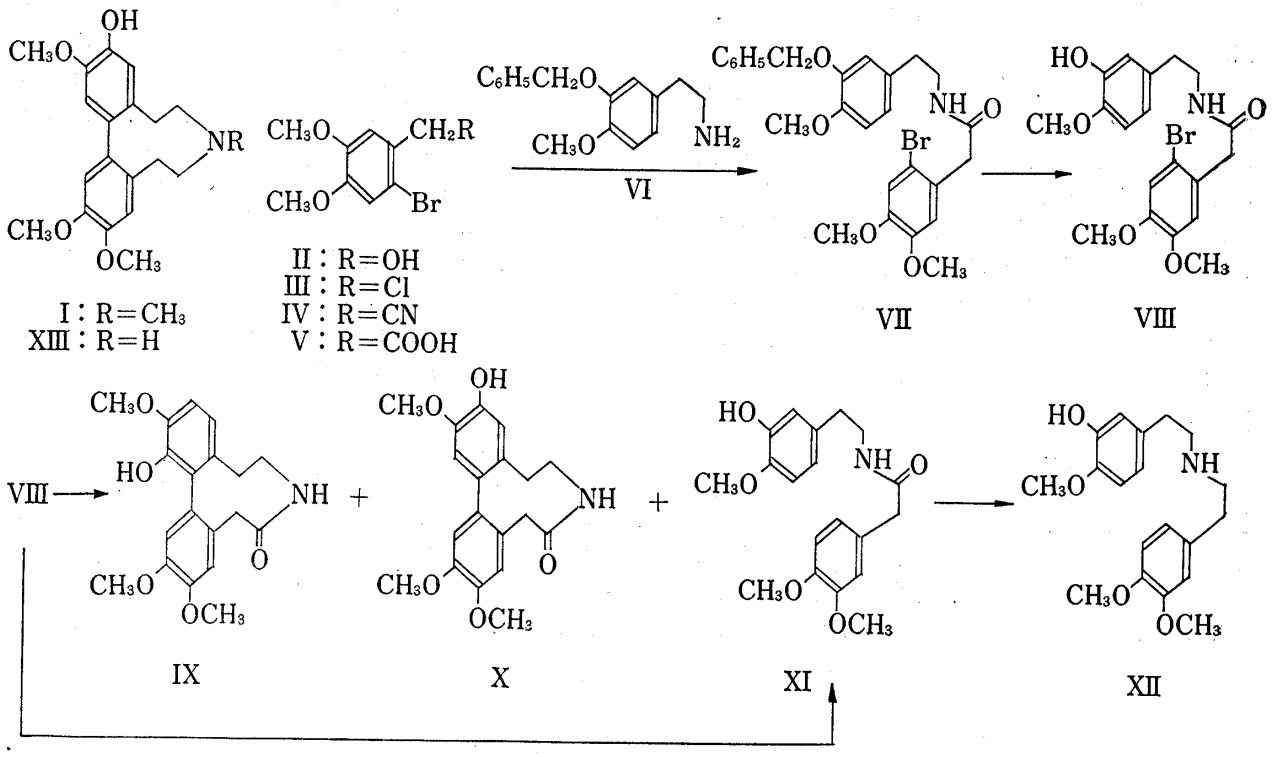

Chart 1

at 3550 cm^{-1} (broad) and the amide band at 3400 and 1660 cm^{-1}, and its ultraviolet (UV) spectrum (λ_{max}^{EtOH} 230 and 280 nm) displayed the presence of a typical biphenyl ring system. These absorption bands indicate that this substance has a dibenzazonine system in the molecule. The nuclear magnetic resonance (NMR) spectrum (τ in $CDCl_3$)[9] of (IX) revealed three methoxyl protons (6.15, 6.08, 6.05, each singlet), also a hydroxyl proton and an imino proton of amide group.[10] In the low-field region, the presence of two aromatic protons (3.23, 3.13, each singlet) and a pair of AB-doublets (3.25, 2.93, J=8 Hz) characteristic of the *ortho* coupling on aromatic protons were exhibited. Therefore, all of these data supports the structure of this substance to be 5,6,9-trihydro-8-oxo-2,11,12-trimethoxy-7*H*-dibenz[*d*,*f*]azonin-1-ol; namely it would be inferred that coupling has occurred at the *ortho* position to hydroxyl group in VIII.

As the secondarily eluted product (X), mp 225—227°, $C_{19}H_{21}O_5N$, shows the same ultraviolet spectrum as that of IX, it has also a dibenzazonine system. Its NMR spectrum ($CDCl_3$) indicated the similar signal pattern as that of IX except for aromatic protons. In the aromatic proton region this substance (X) exhibited the presence of four singlet protons (3.40, 3.36, 3.34, 2.80), thus indicating the coupling at the *para* position to hydroxyl group in VIII. Then these data display that this substance is found to be 5,6,9-trihydro-8-oxo-2,11,12-trimethoxy-7H-dibenz[*d*,*f*]azonin-3-ol and represented by the formula (X).

The third elution product (XI), oil, which is negative to the Beilstein's test, showed the hydroxyl band at 3540 cm^{-1} (broad) and the amide band at 3400 cm^{-1}, 1660 cm^{-1} in its IR spectrum ($CHCl_3$). The NMR spectrum ($CDCl_3$) indicated the presence of three methoxyl protons (6.15, 6.10, each singlet), one-methylelne protons (6.50, singlet) and six aromatic protons (3.60—3.30, multiplet). Furthermore, triplets due to two-methylene protons in phenethylamine portion (7.33, 6.60, J=6.5 Hz) were observed. From these data this compound would be anticipated to be a phenolic amide derivative (XI), which was formed by

9) NMR spectra were determined on the Varian A-60 A spectrometer using tetramethylsilane as an internal standard.

10) The hydroxyl proton and imino proton of amide group disappeared on addition of deuterium oxide.

elimination of bromine atom from VIII. In order to clarify the structure (XI) of this substance, it was submitted to hydroboration of sodium borohydride and boron trifluoride in tetrahydrofuran. The elemental analyses of the resulting product were corresponding to $C_{19}H_{25}O_4N$ and its IR spectrum showed disappearance of the carbonyl group in VIII. These data supported this substance to be a bisphenethylamine derivative (XII). Subsequently, catalytic hydrogenation of VIII with palladium-charcoal in methanol solution gave the corresponding bromine-free amide derivative (XI), which was spectroscopically identical with this irradiation product. Accordingly, this compound has been determined to be (N-3-hydroxy-4-methoxyphenethyl)-2-(3,4-dimethoxyphenyl) acetamide.

In the case of photolysis carried out under the same conditions as described above except that a 10 W low pressure lamp was used, phenolic amide (VIII) affored three same irradiation products (IX, X and XI) respectively.[11] However, the yield of desirable amide (X) was extremely poor.

Finally, a photocyclization product (X) was utilized for conversion to erybidine. Namely, X was reduced with sodium borohydride and boron trifluoride in tetrahydrofuran to afford the corresponding amine (XIII), which was converted with formalin and sodium borohydride quantitatively into I. Direct comparison of this compound (I) with natural erybidine[2] revealed that two compounds were comletely identical. Thus, we have accomplished the total photolytic synthesis of erybidine.

Experimental[12]

6-Bromo-3,4-dimethoxybenzyl Chloride (III)——To a stirred solution of II (4.5 g) dissolved in benzene (30 ml), $SOCl_2$ (2.5 ml) was added dropwise under cooling with ice water. After stirring overnight at room temperature, the reaction mixture was warmed for 30 min at 60°, and poured into ice water (30 ml). Benzene layer was separated and aqueous layer was extracted with ether. The benzene and ethereal layer were combined and dried over Na_2SO_4, followed by evaporation. The residue was recrystallized from benzene. Colorless needles, mp 62—63° (4.2 g). *Anal.* Calcd. for $C_9H_{10}O_2BrCl$: C, 40.69; H, 3.63. Found: C, 40.70; H, 3.80.

6-Bromo-3,4-dimethoxybenzyl Cyanide (IV)——To a stirred solution of NaCN (3 g) dissolved in DMSO (50 ml), a solution of III (10 g) dissolved in DMSO (30 ml) was added dropwise and the reaction mixture was heated for 2.5 hr at 90°. After cooling water was added to this mixture, which was extracted with ether. Ethereal layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene. Colorless prisms, mp 89—90° (9.2 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN). *Anal.* Calcd. for $C_{10}H_{10}O_2NBr$: C, 46.87; H, 3.94; N, 5.46. Found: C, 46.88; H, 3.80; N, 5.32.

6-Bromo-3,4-dimethoxyphenylacetic Acid (V)——A mixture of IV (4 g), NaOH (1.5 g), water (25 ml) and methylselsolve (5 ml) was heated under reflux for 3 hr. After cooling water was added to the reaction mixture, which was washed with ether and neutralized with HCl, followed by extraction with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene. Colorless needles. mp 115—116°[13] (3.7 g). *Anal.* Calcd. for $C_{10}H_{11}O_4Br$: C, 43.65; H, 4.03. Found: C, 43.39; H, 3.87.

N-(3-Benzyloxy-4-methoxyphenethyl)-2-(6-bromo-3,4-dimethoxyphenyl)acetamide (VII)——A mixture of VI (4.5 g), V (4 g) and xylene (70 ml) was heated under reflux for 2.5 hr. The reaction mixture was evaporated to dryness and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed in turn with dil. HCl, dil. NaOH and water, and dried over Na_2SO_4, followed by evaporation. The residue was crystallized from ethyl acetate. Colorless needles. mp 141° (3.4 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH–CO), 1660 (NH–CO). *Anal.* Calcd. for $C_{26}H_{28}O_5NBr$: C, 60.71; H, 5.49; N, 2.72. Found: C, 60.46; H, 5.40; N, 2.64.

N-(3-Hydroxy-4-methoxyphenethyl)-2-(6-bromo-3,4-dimethoxyphenyl)acetamide (VIII)——A solution of VII (2 g) dissolved in 20% HCl (50 ml) and EtOH (50 ml) was heated under reflux for 2 hr. After cooling the reaction mixture was evaporated and dissolved in $CHCl_3$. The $CHCl_3$ solution was extracted with dil. aqueous NaOH. The NaOH layer was washed several times with ether and neutralized with HCl, followed by extraction with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene. Colorless needles. mp 172° (0.9 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 3420 (NH–CO),

11) In this case any non-phenolic compound was not obtained.
12) Melting points are uncorrected.
13) This compound showed a melting point of (V) reported in the literature.[6]

1660 (NH–CO). *Anal.* Calcd. for $C_{19}H_{22}O_5NBr$: C, 53.78; H, 5.22; N, 3.30. Found: C, 53.78; H, 5.08; N, 3.14.

Photolysis of N-(3-Hydroxy-4-methoxyphenethyl)-2-(6-bromo-3,4-dimethoxyphenyl)acetamide (VIII) with High Pressure Mercury Lamp——A solution of VIII (200 mg) and NaOH (500 mg) in MeOH (200 ml) was irradiated by 100 W high pressure mercury lamp, equipped with a quartz water-cooling jacket, in a steady stream of nitrogen for 3 hr. The red-colored solution after irradiation was evaporated *in vacuo* and washed with ether, followed by neutralization with HCl and extraction with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated to leave a deep brownish oil. This oil was chromatographed on a silica gel column and eluted with $CHCl_3$.

The fraction eluted primarily with $CHCl_3$ was evaporated and the residue was recrystallized from benzene. Colorless plates. mp 218—220° (20 mg) (5,6,9-trihydro-8-oxo-2,11,12-trimethoxy-7*H*-dibenz[*d*,*f*]azonin-1-ol (IX)). TLC (silica gel/$CHCl_3$–acetone (1: 1), Rf=0.56). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 3400 (NH–CO), 1660 (NH–CO). UV λ_{max}^{EtOH} nm (log ε): 230 (4.16), 285 (3.73). NMR ($CDCl_3$) τ: 6.15, 6.08, 6.05 (9H, 3×s., 3×OCH_3), 4.52 (1H, s., NH or OH), 4.20 (1H, br. s., OH or NH), 3.25 (1H, d., J=8 Hz, arom. H), 3.23 (1H, s., arom. H), 3.13 (1H, s., arom. H), 2.93 (1H, d., J=8 Hz, arom. H). Mass Spectrum *m/e*[14]: 343 (M^+), 314, 286, 271, 256, 255, 211. *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.59; H, 6.14; N, 3.90.

The fraction eluted secondarily with $CHCl_3$ was evaporated and the residue was recrystallized from benzene. Colorless needles. mp 225—227° (46 mg) (5,6,9-trihydro-8-oxo-2,11,12-trimethoxy-7*H*-dibenz[*d*,*f*]-azonin-3-ol (X)). TLC (silica gel/$CHCl_3$–acetone (1: 1), Rf=0.50). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 3400 (NH–CO), 1650 (NH–CO). UV λ_{max}^{EtOH} nm (log ε): 232 (4.21), 283 (3.85). NMR ($CDCl_3$) τ: 6.16 (6H, s., 2×OCH_3), 6.08 (3H, s., OCH_3), 4.22 (1H, s., NH or OH), 4.06 (1H, br. s., OH or NH), 3.40, 3.36, 3.34, 2.80 (4H, 4×s., 4×arom. H). Mass Spectrum *m/e*: 343 (M^+), 314, 286, 271, 256, 255, 211. *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.21; H, 6.33; N, 3.94.

The last fraction was evaporated and the residue was obtained as colorless oil (10 mg) (N-(3-hydroxy-4-methoxyphenethyl)-2-(3,4-dimethoxyphenyl) acetamide (XI)). TLC (silica gel/$CHCl_3$–acetone (1: 1), Rf=0.69). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (OH), 3400 (NH–CO), 1660 (NH–CO). NMR ($CDCl_3$) τ: 7.33 (2H, t., J=6.5 Hz, $C_6H_5CH_2CH_2N$), 6.60 (2H, t., J=6.5 Hz, $C_6H_5CH_2CH_2N$), 6.50 (2H, s., $C_6H_5CH_2CO$), 6.15 (3H, s., OCH_3), 6.10 (6H, s., 2×OCH_3), 3.60—3.30 (6H, m., 6×arom. H). Mass Spectrum *m/e*: 345 (M^+), 195, 151, 150.

Photolysis of (VIII) with Low Pressure Lamp——A solution of VIII (100 mg) and NaOH (200 mg) in MeOH (200 mg) was irradiated by 10 W low pressure lamp in a steady stream of nitrogen for 8 hr. The reaction mixture was treated by the method described above. IX (3 mg), X (5 mg) and XI (10 mg) were obtained. These compounds were identical respectively with those, which were synthesized by high pressure mercury lamp, by mixed melting point, and by the comparison of IR and NMR spectra.

3-Hydroxy-N-(3,4-dimethoxyphenethyl)-4-methoxyphenethylamine (XII)——To a stirred solution of XI (50 mg) in THF (20 ml) was added slowly solid $NaBH_4$ (50 mg) under ice cooling in an atmosphere of nitrogen and to this stirred mixture was added dropwise a solution of BF_3-etherate (0.1 ml). Stirring was continued for overnight at room temperature and then the mixture was decomposed with EtOH, water and conc. HCl consecutively, followed by evaporation to dryness. The resulting brownish oil was neutralized with NH_4OH and extracted with ether. The ethereal layer was dried over Na_2SO_4 and evaporated. The residue was obtained as a colorless oil (45 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). NMR ($CDCl_3$) τ: 7.48—6.96 (8H, m., 4×$-CH_2-$), 6.16 (3H, s., OCH_3), 6.12 (6H, s., 2×OCH_3), 5.72 (2H, br. s., NH and OH), 3.49—3.08 (6H, 6×arom. H). Mass Spectrum *m/e*: 331 (M^+), 208, 195, 194, 181, 180 (base peak), 166, 165, 152, 151, 137. Its oxalate was recrystallized from MeOH. Colorless needles. mp 182°. *Anal.* Calcd. for $C_{19}H_{25}O_4N \cdot C_2H_2O_4$: C, 59.85; H, 6.46; N, 3.32. Found: C, 59.98; H, 6.46; N, 3.21.

Catalytic Hydrogenation of VIII——VIII (150 mg) was hydrogenated with 10% Pd-charcoal (100 mg) and conc. HCl (5 drops) in MeOH (30 ml). The reduction mixture was filtered and evaporated, followed by dissolution in $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. The residue was obtained as a colorless oil (105 mg). This substance was identical with XI, obtained by the above described photolysis, by the comparison of IR ($CHCl_3$), NMR ($CDCl_3$) and mass spectra.

5,6,8,9-Tetrahydro-2,11,12-trimethoxy-7*H*-dibenz[*d*,*f*]azonin-3-ol (XIII)——To a stirred solution of X (68 mg) dissolved in THF (30 ml) was added gradually $NaBH_4$ (100 mg) under cooling with ice water in a stream of nitrogen and to this ice-chilled stirred mixture was added dropwise a solution of BF_3-etherate (0.5 ml). The resulting mixture was stirred overnight at room temperature and decomposed in turn with EtOH, water and conc. HCl, followed by evaporation to dryness. The residual brownish oil was neutralized with NH_4OH and extracted with ether. The ethereal layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from a mixed solution of acetone and MeOH. Colorless needles. mp 194—196° (44 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). NMR (DMSO) τ: 6.22 (6H, s., 2×OCH_3), 6.17 (3H, s., OCH_3), 3.32 (1H, s., arom. H), 3.28 (2H, s., 2×arom. H), 3.12 (1H, s., arom. H). Mass Spectrum *m/e*: 329 (M^+), 314, 287, 286, 285, 272, 257, 256, 255. *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.03; H, 7.11; N, 3.96.

14) Mass spectra were determined on the Hitachi RMU-6 mass spectrometer using a direct inlet system.

5,6,8,9-Tetrahydro-2,11,12-trimethoxy-7-methyl-dibenz[*d*,*f*]azonin-3-ol (Erybidine) (I)——To a stirred solution of XIII (40 mg) in MeOH (10 ml) was added dropwise 37% HCHO (0.1 ml). After the resulting mixture was stirred for 30 min at room temperature, $NaBH_4$ (200 mg) was added gradually and then stirred for 30 min. After evaporation of MeOH the oily residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. The residue was recrystallized from EtOH. Colorless needles. mp 176—178° (38 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560 (OH). NMR ($CDCl_3$) τ: 7.66 (3H, s., NCH_3), 6.14 (6H, s., $2\times OCH_3$), 6.08 (3H, s., OCH_3), 3.32, 3.31, 3.28, 3.20 (4H, $4\times$s., $4\times$arom. H). Mass Spectrum *m/e*: 343 (M^+), 328, 300, 286, 285, 256, 255.

This compound was completely identical with natural erybidine, previously isolated by us,[2] by mixed melting point, and by comparison of IR ($CHCl_3$), NMR ($CDCl_3$) and mass spectra.

Acknowledgement The authors are indebted to Miss T. Shibata of the Analysis Center of this university for elemental analyses.