[Chem. Pharm. Bull. 20(7)1488—1491(1972)]

UDC 547.94.057 : 547.833.04

Studies on the Syntheses of Heterocyclic Compounds. CDLXXXII.[1] Total Photolytic Synthesis of (±)-Epicrinine[2]

Tetsuji Kametani, Tetsuya Kohno, Ramamurty Charubala, Shiroshi Shibuya, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University[3]

(Received January 10, 1972)

Photolytic intramolecular cyclization of N-(4-hydroxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (Va) gave (±)-oxocrinine (VI). Meerwein–Ponndorf reaction of VI resulted in the exclusive formation of (±)-epicrinine (I), similar to the reduction of VI, employing lithium aluminum hydride. The same reaction of N-(2-hydroxy-3-methoxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (Vb) was also examined.

In a series of investigations on photochemical intramolecular cyclization of phenolic bromo-compounds, it was found that photolysis of N-(4-hydroxy-3-methoxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine gave 2-methoxy-3-oxocrinine, exclusively coupled at the *para*-position, as previously reported.[4]

This result has led to the suggestion that the photochemical reaction of the appropriate N-(4-hydroxyphenethyl)-2-bromobenzylamine derivative would be generally applicable to the laboratory synthesis of the oxocrinine ring system, which would be expected to be a key intermediate to the crinine-type alkaloids. Furthermore, the photolysis of the N-(2-hydroxyphenethyl)-2-bromobenzylamine analogue would give the lycorine-type compound, if the coupling occurs at the *para* position. We have now extended the above hypotheses to the stereospecific synthesis of (±)-epicrinine (I)[5] and (±)-crinine (II)[5,6] *via* 3-oxocrinine (VI), and to the synthesis of lycorine-type compound (VII).

The key reaction in the synthesis of I and II was the photochemical cyclization of N-(4-hydroxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (Va). The compound (Va) was prepared as follows. The Schiff base (IIIa), which was prepared by condensation of 4-benzyloxyphenethylamine with 2-bromo-4,5-methylenedioxybenzaldehyde, was reduced to the corresponding amine (IVa) with sodium borohydride. Debenzylation of IVa with ethanol–concentrated hydrochloric acid (1: 1) afforded the expected amine (Va), which was characterized as hydrochloride. An attempt to effect photochemical cyclization of Va in 50% aqueous ethanolic solution in the presence of sodium hydroxide at room temperature afforded the proposed oxocrinine; irradiation by a Riko 400 W mercury lamp with a Pyrex filter, followed by silica gel column chromatography, gave an oxocrinine (M^+ 269), mp 175—178° (lit.,[7] 177—178°) in 5% yield, which displayed a typical enone system in the infrared (IR) spectrum ($\nu_{max}^{CHCl_3}$ 1675 and 1615 cm^{-1}). These bands indicated the structure of the product to be VI. The nuclear magnetic resonance (NMR) spectrum (τ in $CDCl_3$) revealed two aromatic protons (2.71, 3.46, each singlet), two olefinic protons (2.40, 1H, doublet, J=10 Hz; 3.91,

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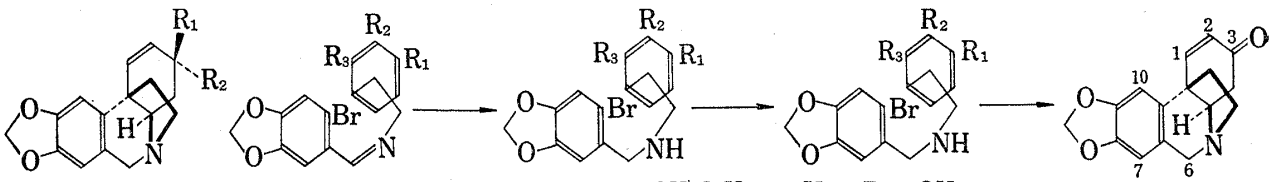
2) One part of this work was reported as a preliminary communication; T. Kametani and T. Kohno, *Tetrahedron Letters*, **1971**, 3155.
3) Location: *Aobayama, Sendai.*
4) T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Chem. Commun.*, **1971**, 774; T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5441 (1971).
5) H. Muxfeldt, R.S. Schneider, and J.B. Mooberry, *J. Am. Chem. Soc.*, **88**, 3670 (1966).
6) H.W. Whitlock, Jr. and G.L. Smith, *J. Am. Chem. Soc.*, **89**, 3600 (1967).
7) R.E. Lyle, E.A. Kielar, J.R. Crowder, and W.C. Wildman, *J. Am. Chem. Soc.*, **82**, 2620 (1960).

1H, doublet, J=10 Hz), methylene protons due to a methylenedioxy group (4.06, 2H, singlet), and two benzylic protons (5.53, 1H, doublet, J=17 Hz, 6.19, 1H, doublet, J=17 Hz). Thus the photochemical cyclization of Va proceeded to give (±)-oxocrinine (VI)[5-7] in one step.

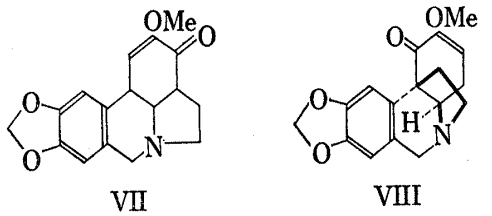
Reduction of VI with lithium aluminum hydride gave (±)-epicrinine (I), as already mentioned by Wildman.[8] On the other hand, as reported by Uyeo,[9] reduction of dihydrooxocrinine using lithium aluminum hydride or aluminum isopropoxide resulted in the exclusive formation of dihydroepicrinine with the former reagent and dihydrocrinine with the latter. Our own attempts, in contrast, to effect Meerwein–Ponndorf reduction of (±)-oxocrinine (VI) resulted only in conversion to (±)-epicrinine (I) without the formation of (±)-crinine (II). Physical and spectral data of I were in good accord with those of an authentic sample. It is of considerable interest that the reduction employing aluminum isopropoxide appears to have produced (±)-epicrinine (I) free from its epimer, (±)-crinine (II). This, of course, suggests the stereospecific synthesis of (±)-epicrinine.



I : R_1=OH, R_2=H
II : R_1=H, R_2=OH
IIIa : R_1=$OCH_2C_6H_5$, R_2=R_3=H
IIIb : R_1=H, R_2=OMe, R_3=$OCH_2C_6H_5$
IVa : R_1=$OCH_2C_6H_5$, R_2=R_3=H
IVb : R_1=H, R_2=OMe, R_3=$OCH_2C_6H_5$
Va : R_1=OH, R_2=R_3=H
Vb : R_1=H, R_2=OMe, R_3=OH
VI

Chart 1

Secondly, we examined the photochemical cyclization of N-(2-hydroxy-3-methoxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (Vb) as follows. The phenolic bromoamine (Vb), which was prepared by the condensation of 2-benzyloxy-3-methoxyphenethylamine with 2-bromo-4,5-methylenedioxybenzaldehyde, followed by reduction and debenzylation, was irradiated and worked up in a manner similar to the above. The compound (M^+ 299) on hand showed the presence of an enone system in the IR spectrum ($\nu_{max}^{CHCl_3}$ 1680 cm^{-1}). Although the NMR spectrum showed a doublet at 4.28 τ, it was not differentiated as a signal due to the olefinic proton at the 1-position of VII or 3-position of VIII.



VII VIII

Chart 2

Further attempts to effect the photochemical reaction of Vb in the presence of an excess of sodium borohydride, followed by oxidation with manganese dioxide, according to Horii's method,[10] were carried out, but only the decomposed products, 2-bromopiperonal and piperonal, were isolated.

Experimental[11]

Schiff Base (IIIa)——A mixture of 11.5 g of 2-bromo-4,5-methylenedioxybenzaldehyde, 11.3 g of 4-benzyloxyphenethylamine and 300 ml of MeOH was refluxed for 1 hr. After cooling, the separated oil was triturated with MeOH to give a solid, which was recrystallized from $CHCl_3$–MeOH to give 19 g of IIIa as

8) W.C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).
9) H. Irie, S. Uyeo, and A. Yoshitake, *Chem. Commun.*, **1966**, 635.
10) Z. Horii, Y. Nakashita, and C. Iwata, *Tetrahedron Letters*, **1971**, 1167.
11) Melting points are uncorrected. IR spectra were recorded with a Hitachi EPI-S_2 spectrophotometer. NMR spectra were determined on a Hitachi R-20 spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi RMU-7 spectrometer (80 eV). Photolysis was carried out with a Riko 400 W mercury lamp with a Pyrex-filter.

colorless needles, mp 103—104.5°. *Anal.* Calcd. for $C_{23}H_{20}O_3NBr$: C, 63.02; H, 4.60; N, 3.20. Found: C, 62.79; H, 4.45; N, 3.19.

N-(4-Benzyloxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (IVa)——To a stirred solution of 19 g of IIIa in 100 ml of $CHCl_3$ and 200 ml of MeOH, 4 g of $NaBH_4$ was added in portions. After stirring for 1 hr at room temperature, the mixture was refluxed for 1 hr and evaporated *in vacuo*. The residue was agitated with 200 ml of water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated to give 19 g of IVa as a pale yellow syrup. Its oxalate, prepared as usual, was recrystallized from MeOH–$CHCl_3$ to give colorless needles, mp 194—196.5°. *Anal.* Calcd. for $C_{23}H_{22}O_3NBr \cdot C_2H_2O_4$: C, 56.51; H, 4.56; N, 2.61. Found: C, 56.75; H, 4.45; N, 2.87.

N-(4-Hydroxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (Va) Hydrochloride——A mixture of 18 g of IVa, 150 ml of EtOH and 150 ml of conc. HCl was heated under reflux for 1 hr and then evaporated *in vacuo*. The remaining dark oil was crystallized from MeOH–ether to give 8.4 g of Va as a powder, the recrystallization of which from MeOH–ether gave colorless needles, mp 234—236° (decomp.). *Anal.* Calcd. for $C_{16}H_{16}O_3NBr$: C, 49.69; H, 4.17; N, 3.62. Found: C, 49.51; H, 4.49; N, 3.44.

(±)-Oxocrinine (VI)——A solution of hydrochloride of 6 g of Va in 1 liter of 50% aqueous EtOH containing 6 g of NaOH was irradiated under stirring for 4 hr at room temperature. The reaction mixture was mixed with an excess of NH_4Cl and extracted with $CHCl_3$ under saturation with NaCl. The $CHCl_3$ extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. The dark brown residue was again extracted with hot $CHCl_3$, and 1.4 g of the soluble portion in $CHCl_3$ was chromatographed on 100 g of silica gel with MeOH–$CHCl_3$ (2:98) as eluant to give the crude enone, which was rechromatographed on 15 g of neutral alumina. Elution with $CHCl_3$ gave 200 mg of the enone (VI) as a glass, the sublimation of which *in vacuo* afforded colorless prisms, mp 175—178° (lit.,[7] 177—178°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675 (C=O), 1615 (C=C). NMR (in $CDCl_3$) τ: 2.71, 3.46 (1H×2, each s, ArH), 2.40 (1H, d, J=10 Hz, 1-H), 3.91 (1H, d, J=10 Hz, 2-H), 4.06 (2H, s, $OC\underline{H}_2O$), 5.53 (1H, d, J=17 Hz, 6-H), 6.19 (1H, d, J=17 Hz, 6-H). *Anal.* Calcd. for $C_{16}H_{15}O_3N$: M^+, 269 *m/e*; C, 71.36; H, 5.61; N, 5.20. Found: M^+ 269 *m/e*; C, 71.07; H, 5.78; N, 5.07.

(±)-Epicrinine——(a) A mixture of 100 mg of VI, 100 ml of dry ether and 120 mg of $LiAlH_4$ was refluxed for 13 hr. After cooling the mixture was treated with EtOAc and 40% KOH as usual; then the ethereal layer separated was washed with water and dried over Na_2SO_4. The aqueous layer was extracted with $CHCl_3$ and the extract was washed with water and dried over Na_2SO_4. The combined extracts were evaporated to give a pale yellow oil, which was triturated with ether, giving 60 mg of I as a powder. Recrystallization from $CHCl_3$ afforded colorless needles, mp 235—239° (decomp.) (lit.,[7] 239°), the IR spectrum of which was identical with that of (±)-epicrinine. NMR (in $CDCl_3$) τ: 3.20, 3.52 (1H×2, each s, ArH), 3.60 (1H, a pair of d, $J_{1,2}$=10 Hz, $J_{1,3}$=2 Hz, 1-H), 4.22 (1H, d, J=10 Hz, 2-H), 4.09 (2H, s, $OC\underline{H}_2O$), 5.58 (1H, d, J=17 Hz, 6-H), 6.23 (1H, d, J=17 Hz, 6-H).

(b) A solution of 300 mg of aluminum isopropoxide and 90 mg of VI in 50 ml of dry toluene was refluxed for 1 hr. After cooling, 25 ml of isopropanol was added and the mixture was then refluxed for an additional 7 hr. The cooled reaction mixture was extracted with 10% HCl. The acidic extract was made alkaline with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated. The remaining oil was chromatographed on 2 g of silicic acid with MeOH–$CHCl_3$ (1:99) to afford 10 mg of the starting material and with MeOH–$CHCl_3$ (2:99) as eluant to give 50 mg of (±)-epicrinine (I), mp 239—240°, the latter of which was completely identical with an authentic sample donated by Prof. Wildman.

Schiff Base (IIIb)——A mixture of 5 g of 2-bromo-4,5-methylenedioxybenzaldehyde, 4.5 g of 2-benzyloxy-3-methoxyphenethylamine, and 150 ml of EtOH was heated on a water-bath for 1 hr. The resulting oil was triturated with hexane to afford a solid, which was recrystallized from hexane to give 7.5 g of IIIb as colorless needles, mp 95—97°. *Anal.* Calcd. for $C_{24}H_{22}O_4NBr$: C, 61.55; H, 4.70; N, 2.99. Found: C, 61.49; H, 4.90; N, 2.96.

N-(2-Benzyloxy-3-methoxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (IVb)——To a solution of 16 g of IIIb in 100 ml of $CHCl_3$ and 200 ml of MeOH was added 8 g of $NaBH_4$ in portions. After stirring for 1 hr at room temperature, the mixture was refluxed for 1 hr and evaporated to dryness. The residue was treated with water and extracted with $CHCl_3$. The $CHCl_3$ extract, after washing with water and drying over Na_2SO_4, was evaporated to give 14 g of IVb as a yellow oil. Its oxalate was recrystallized from MeOH to give colorless needles, mp 166—168°. *Anal.* Calcd. for $C_{24}H_{24}O_4NBr$: C, 55.72; H, 4.64; N, 2.50. Found: C, 55.55; H, 4.71; N, 2.71.

N-(2-Hydroxy-3-methoxyphenethyl)-2-bromo-4,5-methylenedioxybenzylamine (Vb)——A mixture of 12 g of the amine (IVb), 240 ml of EtOH and 120 ml of conc. HCl was refluxed for 2 hr. After removal of the solvent *in vacuo*, the residue was made basic with 28% NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over Na_2SO_4, and evaporated to give 8 g of Vb as a pale brown solid. This was recrystallized from hexane to afford the amine (Vb) as colorless needles, mp 131—133°. *Anal.* Calcd. for $C_{17}H_{18}O_4NBr$: C, 53.68; H, 4.78; N, 3.68. Found: C, 53.64; H, 5.00; N, 3.62.

Photolysis of Compound (Vb)——(a) A solution of 3 g of Vb, 1 liter of 50% aqueous EtOH, and 3 g of NaOH was irradiated under stirring for 6 hr at room temperature. The reaction mixture was con-

centrated to half its volume and the residue was treated with NH_4Cl. It was then extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and evaporated. The resulting brown oil (2 g) was chromatographed on 8 g of silica gel with MeOH–$CHCl_3$ (2:98) as eluant to give 135 mg of the crude enone, which was rechromatographed on 15 g of alumina. Elution with benzene–$CHCl_3$ (60:40) gave 12 mg of the enone as a viscous syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 and 1630. NMR (in $CDCl_3$) τ: 3.45 and 3.52 (2H, each s, ArH), 4.13 (2H, s, $OC\underline{H}_2O$), 4.28 (1H, d, $J=2.5$ Hz, olefinic proton), 6.40 (3H, s, $OC\underline{H}_3$).

(b) A mixture of 3 g of Vb, 1 liter of 50% aqueous EtOH, 3 g of NaOH and 3 g of $NaBH_4$ was irradiated under stirring for 17 hr at room temperature. After addition of NH_4Cl the reaction mixture was saturated with NaCl and then extracted with $CHCl_3$. After evaporation of the extract the remaining oil was again extracted with $CHCl_3$ in order to remove an inorganic material. The $CHCl_3$ extract was washed with saturated NaCl aqueous solution, dried over Na_2SO_4, and evaporated. The resulting dark brown oil (2 g) was chromatographed on 30 g of silica gel with $CHCl_3$ as eluant to remove 0.8 g of the starting material. Further elution with 3% methanolic $CHCl_3$ gave 1 g of an oil, which was oxidised with 7 g of manganese dioxide in 200 ml of $CHCl_3$ under stirring for 6 hr at room temperature. The reaction mixture was filtered to remove the excess of reagent, which was washed with hot $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried over Na_2SO_4, and evaporated. The resulting brown oil (1 g) was chromatographed on 25 g of silica gel with $CHCl_3$ to give 0.2 g of 2-bromopiperonal and with MeOH–$CHCl_3$ (1:99) as eluant to give 0.1 g of piperonal, both of which were identical with authentic samples.

Acknowledgement We are very grateful to Professor W.C. Wildman for providing samples of (±)-epicrinine and vittatine. We also thank Miss A. Kawakami and Miss C. Yoshida for microanalyses, Miss A. Ujiie for the NMR spectral measurement.