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STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—CDXXXVI[1]

PHOTOLYTIC SYNTHESIS OF THE CRININE RING SYSTEM—FORMAL TOTAL SYNTHESIS OF (±)-MARITIDINE[2]

T. KAMETANI, T. KOHNO, S. SHIBUYA and K. FUKUMOTO

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

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Abstract—Photolytic intramolecular cyclisation of 2-bromo-*N*-(4-hydroxy-3-methoxyphenethyl)-4,5-methylenedioxybenzylamine (**3a**) and 2-bromo-5-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxybenzylamine (**3b**) gave 2-methoxy-3-oxocrinine (**4a**) and 8-demethyl-3-oxomaritidine (**5b**), respectively. The latter compound was identical with Schwartz's intermediate[3] to (±)-maritidine.

THERE have been some reports on the biogenetic synthesis of the crinine ring system by phenolic oxidative coupling.[3,4] This method, however, can be regarded as inapplicable to the preparation of the substituted crinine ring with a methylenedioxy group. On the other hand, photolysis of the bromophenolic compounds has been recently provided by Kametani *et al.*[5] as a new synthetic route to some isoquinoline alkaloids such as morphinan and aporphine systems. This photolytic method provides an exceedingly simple synthetic route not only to these alkaloids, but also to the other alkaloid ring systems.

In this paper we describe a one-step synthesis of the crinine ring (**4a**, **5b**) by photolytic intramolecular cyclisation of the bromo-phenolic compounds (**3a**, **3b**). Successful synthesis of **4a** suggests the applicability of this synthetic method to other crinine alkaloids, the substituents of which are replaced with a methylenedioxy group at the C_8 and C_9-positions; and also, the synthesis of **5b**, in particular, represents a formal total synthesis of (±)-maritidine.

As a preliminary experiment to examine the photolytic behaviour of the bromophenolic compound having a methylenedioxy group, we prepared 2-bromo-*N*-(4-hydroxy-3-methoxyphenethyl)-4,5-methylenedioxybenzylamine (**3a**). The Schiff base (**1a**), which was prepared from the condensation of 4-benzyloxy-3-methoxyphenethylamine with 2-bromo-4,5-methylenedioxybenzaldehyde, was reduced to the corresponding amine (**2a**) with $NaBH_4$. Debenzylation of **2a** with ethanolic HCl (1:1) afforded the proposed amine (**3a**). Photolysis of **3a** was carried out in 50% aqueous ethanolic solution in the presence of NaOH at room temperature; irradiation by a Riko 400 W mercury lamp with a Pyrex-filter, followed by silica gel column chromatography, gave an oxocrinine compound (M^+ 299), m.p. 210–212°, in 3·3% yield, which displayed a typical enone system in the IR spectrum (ν_{max} 1685 and 1620 cm^{-1} in $CHCl_3$). These bands indicated the structure of the product to be **4a**. This was supported by the NMR spectrum (τ in $CDCl_3$), which showed two aromatic protons (3·20, 3·59, 2H, each singlet), an olefinic proton (3·69, 1H, singlet), methylene protons due

to a methylenedioxy group (4·17, 2H, singlet), two benzylic protons (5·65, 1H, doublet, $J = 17$ Hz; 6·31 (1H, doublet, $J = 17$ Hz), and Me protons (6·23, 3H, singlet). Thus, we developed a new general synthesis of the crinine ring system, and an attempt to synthesise **5b**, which has already been converted into (±)-maritidine by Schwartz,[3] was carried out by our method as follows.

The starting phenolic bromo-compound (**3b**) was prepared by a procedure similar to the above method: condensation of 5-benzyloxy-2-bromo-4-methoxybenzaldehyde with 4-benzyloxyphenethylamine, followed by $NaBH_4$ reduction, gave the corresponding secondary amine (**2b**) which was debenzylated with ethanolic HCl (1:1) to afford 2-bromo-5-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxybenzylamine (**3b**), characterised as the hydrochloride. Irradiation of **3b** under the same conditions as above, followed by acetylation and isolation with silica gel column chromatography, yielded 8-*O*-acetate (**4b**), m.p. 214–217°, in 3·6% yield. The 8-*O*-acetate (**4b**), $C_{18}H_{19}NO_4$ (M^+ 313), exhibited absorptions characteristic of the *O*-acetyl group and enone system in the IR spectrum (ν_{max} 1755, 1670, and 1615 cm^{-1} in $CHCl_3$). The NMR spectrum (τ in $CDCl_3$) revealed two aromatic protons (3·07, 3·34, 2H, each singlet), two olefinic protons (2·36, 1H, doublet, $J = 10$ Hz; 3·98, 1H, doublet, $J = 10$ Hz), two benzylic protons (5·63, 1H, doublet, $J = 17$ Hz; 6·27, 1H, doublet, $J = 17$ Hz), Me protons (6·21, 3H, singlet), and Me protons due to *O*-Ac group (7·74, 3H, singlet). Deacetylation of **4b** with ethanolic KOH gave the compound **5b** as needles, m.p. 250–252° (decomp.) (lit.,[3] 250–252°), which showed a typical enone system in the IR spectrum (ν_{max} 1670 and 1610 cm^{-1} in KBr). The NMR spectrum [τ in $(CD_3)_2SO$] revealed two aromatic protons (2·91, 3·54, 2H, each singlet) two olefinic protons (1·99, 1H, doublet, $J = 10$ Hz; 4·04, 1H, doublet, $J = 10$ Hz), two benzylic protons (5·81, 1H, doublet, $J = 17$ Hz; the higher field portion of this AB quartet was obscured by other resonances), and Me protons (6·21, 3H, singlet). The physical and spectral data of **5b** were in good accord with those of Schwartz's intermediate to (±)-maritidine.[3]

The above results constitute the formal total synthesis of (±)-maritidine by photolysis and also suggest the applicability of this method to a one-step synthesis of other crinine-type alkaloids having a methylenedioxy group.

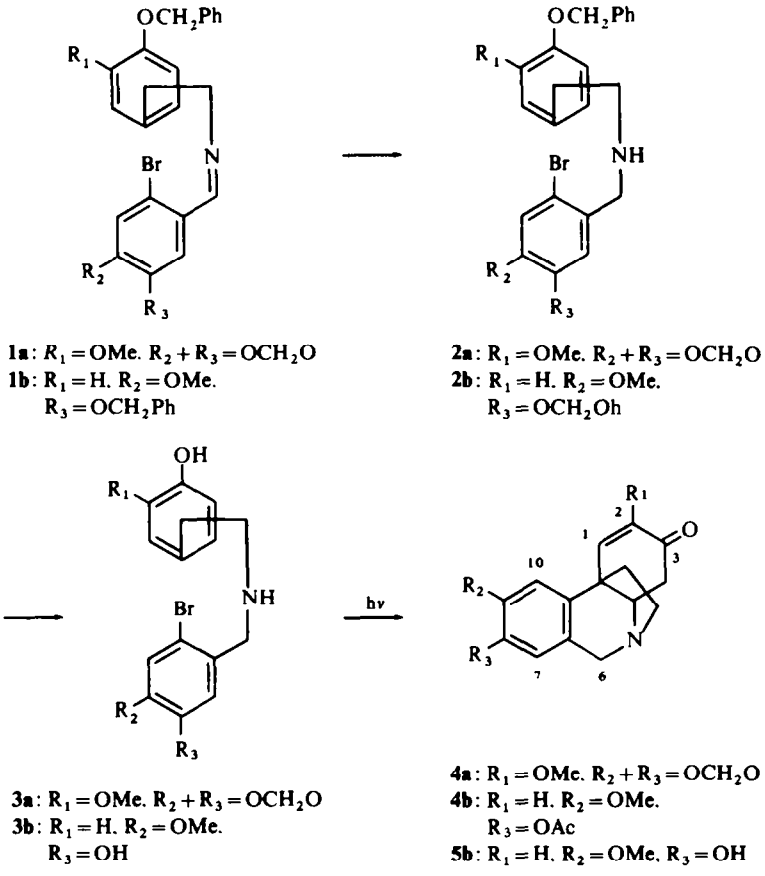
EXPERIMENTAL

M.ps are uncorrected. UV spectra were recorded in 95% EtOH with a Hitachi 124 spectrophotometer. IR spectra were recorded with a Hitachi EPI-S_2 spectrophotometer. NMR spectra were determined on a Hitachi R-20 spectrometer (TMS as internal standard). Mass spectra were determined on a Hitachi RMU-7 spectrometer (80 eV). Photolysis was carried out with a Riko 400 Mercury lamp with a Pyrex-filter.

Schiff base (**1a**). A mixture of 2·5 g of 2-bromo-4,5-methylenedioxybenzaldehyde and 2·5 g of 4-benzyloxy-3-methoxyphenethylamine was heated on a water bath for 30 min. After cooling, the resulting solid was recrystallised from MeOH to give **1a** (4·5 g) as colourless needles, m.p. 102–103°. (Calc. for $C_{24}H_{22}BrNO_4$: C, 61·50; H, 4·74; N, 2·99. Found: C, 61·50; H, 4·70; N, 3·23%).

N-(4-*Benzyloxy*-3-*methoxyphenethyl*)-2-*bromo*-4,5-*methylenedioxybenzylamine* (**2a**). To a solution of 4·5 g of **1a** in $CHCl_3$ (20 ml) and MeOH (80 ml) was added 1·5 g of $NaBH_4$ in portions. After additional stirring for 30 min at room temp., the mixture was refluxed for 30 min and evaporated. The residue was then stirred with H_2O (50 ml) and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure to give a pale yellow oil (**2a**) (4·2 g). Its hydrochloride, was recrystallised from MeOH to give colourless needles, m.p. 194–195°. (Calc. for $C_{24}H_{24}BrNO_4 \cdot HCl$: C, 56·85; H, 4·97; N, 2·76. Found: C, 56·83; H, 5·04; N, 2·96%).

2-*Bromo*-N-(4-*hydroxy*-3-*methoxyphenethyl*)-4,5-*methylenedioxybenzylamine* (**3a**). A mixture of **2a** (4 g), EtOH (30 ml), and conc. HCl (30 ml) was refluxed for 1 hr. After removal of solvent *in vacuo* the remaining



1a: R_1 = OMe. $R_2 + R_3 = OCH_2O$
1b: R_1 = H. R_2 = OMe. $R_3 = OCH_2Ph$

2a: R_1 = OMe. $R_2 + R_3 = OCH_2O$
2b: R_1 = H. R_2 = OMe. $R_3 = OCH_2Oh$

3a: R_1 = OMe. $R_2 + R_3 = OCH_2O$
3b: R_1 = H. R_2 = OMe. R_3 = OH

4a: R_1 = OMe. $R_2 + R_3 = OCH_2O$
4b: R_1 = H. R_2 = OMe. R_3 = OAc
5b: R_1 = H. R_2 = OMe. R_3 = OH

SCHEME 1

solution was made basic with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried (Na_2SO_4), and evaporated to give a pale brown oil (**3a**) (2·5 g). Hydrochloride of **3a** was recrystallised from MeOH to form colourless needles, m.p. 210–212° (decomp.). (Calc. for $C_{17}H_{18}BrNO_4 \cdot HCl$: C, 48·96; H, 4·59; N, 3·35. Found: C, 48·75; H, 4·79; N, 3·44%).

2-Methoxy-3-oxocrinine (**4a**). A solution of **3a** (1·5 g) in 1l of 50% aq. EtOH containing 1·2 g of NaOH was irradiated for 5 hr at room temp. The mixture was concentrated to about 150 ml *in vacuo*, followed by addition of NH_4Cl and saturation with NaCl. and extraction with $CHCl_3$. The $CHCl_3$ extract was washed with satd. aq. NaCl. dried (Na_2SO_4). and evaporated. The remaining brown oil (1·2 g) was chromatographed on silica gel (35 g) with MeOH-$CHCl_3$ (1:99) to give the crude enone (200 mg). rechromatographed on neutral alumina (10 g). The eluant with $CHCl_3$ gave 80 mg of enone as a solid. recrystallised from Et_2O-MeOH to afford 40 mg of **4a** (3·3%) as colourless needles. m.p. 210–212°. λ_{max}: 262 nm (log ε = 3·946). 290 nm (log ε = 3·765). $\nu_{max}^{CHCl_3}$: 1685. 1620 cm^{-1}. NMR ($CDCl_3$) τ: 3·20. 3·59 (1H × 2. each singlet. aromatic protons). 3·69 (1H. singlet. C_1-H). 4·17 (2H. singlet. —O—C<u>H</u>$_2$—O). 5·65 (1H. doublet. J = 17 Hz. C_6—H). 6·31 (1H. doublet. J = 17 Hz. C_6—H). 6·23 (3H. singlet. OC<u>H</u>$_3$). MS M^+ at *m/e* 299. (Calc. for $C_{17}H_{17}NO_4$: C. 68·21; H. 5·73; N. 4·68. Found: C. 68·10; H. 5·66; N. 4·81%).

Schiff base (**1b**). A mixture of 5-benzyloxy-2-bromo-4-methoxybenzaldehyde (9·6 g) and 4-benzyloxyphenethylamine (6·8 g) in MeOH (200 ml) was refluxed for 1 hr. After cooling. the resulting crystals were filtered and recrystallised from MeOH-$CHCl_3$ to afford **1b** (11 g) as colourless needles. m.p. 123–125°. (Calc.for $C_{30}H_{28}NO_3Br$: C. 67·92; H. 5·32; N. 2·64. Found: C. 68·10; H. 5·60; N. 2·63%).

N-(4-Benzyloxyphenethyl)-5-benzyloxy-2-bromo-4-methoxybenzylamine (**2b**). Reduction of 10·6 g of **1b** with $NaBH_4$ (2 g) in the same way as **2a** gave a yellow oil (**2b**) (10 g). Its oxalate was recrystallised from MeOH–$CHCl_3$ to give colourless needles, m.p. 211–212·5°. (Calc. for $C_{30}H_{30}NO_3Br\ C_2H_2O_4$: C, 61·74; H, 5·18; N, 2·25. Found: C, 61·96; H, 5·25; N, 2·26%).

2-Bromo-5-hydroxy-N-(4-hydroxyphenethyl)-4-methoxybenzylamine (**3b**) *Hydrochloride.* A mixture of 9 g of **2b**, EtOH (60 ml) and conc. HCl (50 ml) was refluxed for 1 hr. The dark brown oil obtained upon evaporation of the mixture was crystallised from Et_2O–MeOH to give a pale yellow powder, recrystallised from Et_2O–MeOH, affording **3b**-HCl (3 g) as colourless needles, m.p. 230–232·5° (decomp.). (Calc. for $C_{16}H_{18}NO_3Br{\cdot}HCl$: C, 49·44; H, 4·67; N, 3·60. Found: C, 49·74; H, 5·01; N, 3·86%).

8-O-Acetyl-3-oxomaritidine (**4b**). A solution of 1·5 g of **3b**-HCl in 11 of 5% aq. EtOH containing NaOH (1·5 g) was irradiated with stirring for 5·5 hr at room temp. The mixture was extracted with $CHCl_3$ after addition of NH_4Cl and saturation with NaCl. The $CHCl_3$ extract was washed with satd. aq. NaCl, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The resulting dark red oil (0·4 g) was dissolved in 4 ml of Ac_2O and 5 drops of pyridine. After standing for 7 hr at room temp., the mixture was poured onto crushed ice and left overnight. The resulting oil was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with satd. aq. $NaHCO_3$, H_2O, and dried (Na_2SO_4). Evaporation of solvent gave a dark brown oil (0·45 g), chromatographed on silica gel (15 g) with MeOH–$CHCl_3$ (2:98) to give a pale brown solid. Recrystallisation from Et_2O–MeOH afforded 43 mg of **4a** (3·6%) as colourless needles, m.p. 214–217° (decomp.). $\nu_{max}^{CHCl_3}$: 1755, 1670, 1615 cm^{-1}. NMR ($CDCl_3$): τ3·07, 3·34 (1H × 2, each singlet, aromatic protons), 2·36 (1H, doublet, J = 10 Hz, C_1–H), 3·98 (1H, doublet, J = 10 Hz, C_2–H), 5·63 (1H, doublet, J = 17 Hz, C_6–H), 6·27 (1H, doublet, J = 17 Hz, C_6–H), 6·21 (3H, singlet, —OC$\underline{H}_3$), 7·74 (3H, singlet, –OCOC$\underline{H}_3$). MS M^+ at *m/e* 313. (Calc. for $C_{18}H_{19}NO_4$: C, 68·99; H, 6·11; N, 4·47. Found: C, 68·92; H, 6·13; N, 4·51%).

8-Demethyl-3-oxomaritidine (**5b**). A solution of 30 mg of **4a** in EtOH (5 ml) containing 1·5 ml of 0·1 N KOH was heated under reflux for 30 min, in a current of N_2 and concentrated to about 1 ml *in vacuo*. The remaining solution was diluted with H_2O (5 ml) and extracted with $CHCl_3$ after addition of NH_4Cl. The $CHCl_3$ extract was washed with satd. aq. NaCl, dried (Na_2SO_4), and evaporated to dryness *in vacuo* to afford a pale yellow solid. Recrystallisation from Et_2O-MeOH gave 25 mg of **5b** as colourless needles, m.p. 250–252° (decomp.) (lit.,[3] mp 250–252°, decomp.). λ_{max}: 227 nm (log ε = 4·286), 286 nm (log ε = 3·597). ν_{max}^{KBr}: 1670, 1610 cm^{-1}. NMR [$(CD_3)_2SO$] τ: 2·91, 3·54 (1H × 2, each singlet, aromatic protons), 1·99 (1H, doublet, J = 10 Hz, C_1-H), 4·04 (1H, doublet, J = 10 Hz, C_2–H), 5·81 (1H, doublet, J = 17 Hz, C_6–H; the higher field of this type quartet was obscured by other resonances), 6·21 (3H, singlet, —OC$\underline{H}_3$). (Calc. for $C_{16}H_{17}NO_3$; C, 70·83; H, 6·32; N, 5·16. Found: C, 70·83; H, 6·32; N, 5·17%).

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