

Studies on the Syntheses of Heterocyclic Compounds. Part CDLXVI.¹ Synthesis of Narwedine-type Enones by Photochemical Cyclisation

By T. Kametani,* K. Yamaki, T. Terui, S. Shibuya, and K. Fukumoto, Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Irradiation of 4-benzyloxy-2-bromo-3-hydroxy-*N*-(4-hydroxyphenethyl)-*N*-methylbenzamide (26) and of 2-bromo-3-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxy-*N*-methylbenzamide (28) afforded the narwedine-type enones (4) and (3), respectively. The former enone (4) was also synthesised by phenolic oxidation of 4-benzyloxy-3-hydroxy-*N*-(4-hydroxyphenethyl)-*N*-methylbenzamide (24).

NARWEDINE (1),² derived from norbelladine (20) through phenolic oxidative coupling, has been synthesised from the amine (21)³ by a route analogous to the biogenetic pathway. We have previously reported syntheses of this type of enone [(2) and (3)] by phenolic oxidative coupling of diphenolic amides [(22) and (29)].^{4,5} Since narwedine-type enones could be key intermediates in syntheses of galanthamine-type *Amaryllidaceae* alkaloids

[(5)—(7)],³⁻⁵ we have investigated a simple and new general method for their synthesis. We now report the syntheses of the new narwedine-type enone (4) by phenolic oxidation of the amide (24) and by irradiation of the bromophenolic amide (26).

Phenolic oxidation of 4-benzyloxy-3-hydroxy-*N*-(4-hydroxyphenethyl)-*N*-methylbenzamide (24) was examined first, since it was expected that coupling might

¹ Part CDLXV, T. Kametani *et al.*, *J. Pharm. Soc. Japan*, 1972, **92**, 431.

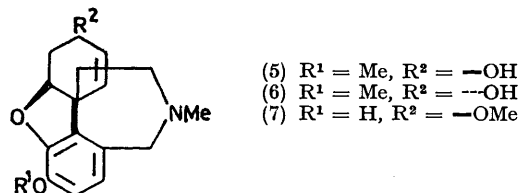
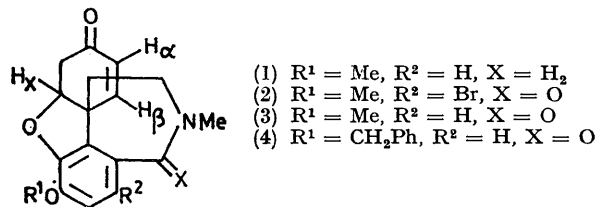
² T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa (Tokyo) and Elsevier (Amsterdam), 1968, p. 96.

³ D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806.

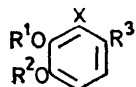
⁴ T. Kametani, K. Yamagi, H. Yagi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1969, 2602.

⁵ T. Kametani, K. Shishido, E. Hayashi, C. Seino, T. Kohno, S. Shibuya, and K. Fukumoto, *J. Org. Chem.*, 1971, **36**, 1295.

occur at two positions, *ortho* and *para* to the hydroxy-group. Schotten-Baumann reaction of 4-hydroxyphenethylamine with 3-acetoxy-4-benzyloxybenzoyl chloride (11), prepared from the acid (10) by way of 4-benzyloxy-3-hydroxybenzoic acid (9), afforded the



corresponding amide (23), deacetylation of which gave the diphenolic amide (24). Phenolic oxidation of this amide (24) with potassium ferricyanide then gave the narwedine-type enone (4) and the dienone (31). The n.m.r. spectrum of the former (4) showed signals for the α - and β -olefinic protons at δ 5.88 and 6.42 p.p.m., respectively, in accord with the expected coupling mode, and the signals due to aromatic protons similar to those of compound (3) were observed at δ 6.96 and 7.48 p.p.m. (doublet). This narwedine-type enone was also synthesised by irradiation⁶ of the phenolic bromo-amide (26), which was prepared in the usual



- (8) $R^1 = X = \text{H}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{CHO}$
 (9) $R^1 = X = \text{H}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{CO}_2\text{H}$
 (10) $R^1 = \text{Ac}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{CO}_2\text{H}, X = \text{H}$
 (11) $R^1 = \text{Ac}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{COCl}, X = \text{H}$
 (12) $R^1 = \text{H}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{CHO}, X = \text{Br}$
 (13) $R^1 = \text{H}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{CO}_2\text{H}, X = \text{Br}$
 (14) $R^1 = \text{Ac}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{CO}_2\text{H}, X = \text{Br}$
 (15) $R^1 = \text{Ac}, R^2 = \text{CH}_2\text{Ph}, R^3 = \text{COCl}, X = \text{Br}$
 (16) $R^1 = \text{H}, R^2 = \text{Me}, R^3 = \text{CHO}, X = \text{Br}$
 (17) $R^1 = \text{CH}_2\text{Ph}, R^2 = \text{Me}, R^3 = \text{CHO}, X = \text{Br}$
 (18) $R^1 = \text{CH}_2\text{Ph}, R^2 = \text{Me}, R^3 = \text{CO}_2\text{H}, X = \text{Br}$
 (19) $R^1 = \text{CH}_2\text{Ph}, R^2 = \text{Me}, R^3 = \text{COCl}, X = \text{Br}$
 (20) $R^1 = R^2 = X = \text{H}, R^3 = p\text{-HO}\cdot\text{C}_6\text{H}_4\cdot[\text{CH}_2]_2\cdot\text{NH}\cdot\text{CH}_2$
 (21) $R^1 = X = \text{H}, R^2 = \text{Me}, R^3 = p\text{-HO}\cdot\text{C}_6\text{H}_4\cdot[\text{CH}_2]_2\cdot\text{NMe}\cdot\text{CH}_2$

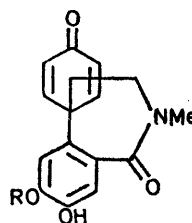
manner as follows. Schotten-Baumann reaction of 4-hydroxyphenethylamine with 3-acetoxy-4-benzyloxy-2-bromobenzoyl chloride (15), prepared from the acid (14) by way of 4-benzyloxy-2-bromo-3-hydroxybenzoic acid (13), afforded the corresponding amide (25), deacetylation of which under basic conditions gave the diphenolic bromo-amide (26). Irradiation of the amide (26) with a Hanovia 450 W mercury lamp (Pyrex filter) gave the enone (4).

This photochemical cyclisation was then applied to the synthesis of the enone (3), which had previously been

obtained by phenolic oxidation of the amide (29). The amide (28) was prepared by debenzoylation of the amide (27), derived by condensation of 4-benzyloxy-*N*-methylphenethylamine with 3-benzyloxy-2-bromo-4-methoxybenzoyl chloride (19) (see Experimental section). The product (3) obtained on irradiation of compound (28) showed the α - and β -olefinic proton signals at δ 5.87 and 6.37 p.p.m., respectively (charac-



- (22) $R^1 = R^2 = X = \text{H}, R^3 = \text{Me}, Y = \text{Br}$
 (23) $R^1 = X = Y = \text{H}, R^2 = \text{Ac}, R^3 = \text{CH}_2\text{Ph}$
 (24) $R^1 = R^2 = X = Y = \text{H}, R^3 = \text{CH}_2\text{Ph}$
 (25) $R^1 = Y = \text{H}, R^2 = \text{Ac}, R^3 = \text{CH}_2\text{Ph}, X = \text{Br}$
 (26) $R^1 = R^2 = Y = \text{H}, R^3 = \text{CH}_2\text{Ph}, X = \text{Br}$
 (27) $R^1 = R^2 = \text{CH}_2\text{Ph}, R^3 = \text{Me}, X = \text{Br}, Y = \text{H}$
 (28) $R^1 = R^2 = Y = \text{H}, R^3 = \text{Me}, X = \text{Br}$
 (29) $R^1 = R^2 = X = Y = \text{H}, R^3 = \text{Me}$



- (30) $R = \text{Me}$
 (31) $R = \text{CH}_2\text{Ph}$

teristic of narwedine-type enones) in its n.m.r. spectrum. It was identical [i.r. (in chloroform), n.m.r. (in deuteriochloroform), and mass spectra] with an authentic specimen.⁵

Since the enone (3) had already been converted into galanthamine (5), this work constitutes a formal synthesis of (\pm)-galanthamine.

EXPERIMENTAL

I.r. spectra were measured with a Shimadzu recording spectrometer, and n.m.r. spectra with a Hitachi R-20 spectrometer (deuteriochloroform as solvent and tetramethylsilane as internal reference). Mass spectra were taken with a Hitachi RMU-7 spectrometer.

4-Benzyloxy-3-hydroxybenzoic Acid (9).—To a stirred suspension of silver oxide [from silver nitrate (17 g) and sodium hydroxide (4.4 g)] in 10% sodium hydroxide solution (200 ml) was added 4-benzyloxy-3-hydroxybenzaldehyde (8) (22.8 g) at 55–60° within 20 min. Inorganic material was filtered off and the filtrate was made acidic with 15% hydrochloric acid. The precipitate gave the acid (9) (15.4 g) as *needles*, m.p. 188–189° (from benzene) (Found: C, 68.9; H, 4.9. $\text{C}_{14}\text{H}_{12}\text{O}_4$ requires C, 68.8; H, 4.95%).

3-Acetoxy-4-benzyloxybenzoic Acid (10).—A mixture of the acid (9) (12 g), sodium acetate (12 g), and acetic anhydride (100 ml) was refluxed for 1 h at 120–130°. The excess of acetic anhydride was removed and the residue was poured into water and extracted with ether. The

⁶ T. Kametani, T. Kohno, S. Shibuya, and K. Fukumoto, *Chem. Comm.*, 1971, 774; T. Kametani and T. Kohno, *Tetrahedron Letters*, 1971, 3155.

extract was washed with water, dried (Na_2SO_4), and evaporated. The resulting solid afforded the acid (10) (12.0 g) as *prisms*, m.p. 211° (from ethanol) (Found: C, 72.5; H, 5.4. $\text{C}_{16}\text{H}_{14}\text{O}_5$ requires C, 72.5; H, 5.3%).

3-Acetoxy-4-benzyloxy-N-(4-hydroxyphenethyl)-N-methylbenzamide (23).—A mixture of the acid (10) (6.5 g), thionyl chloride (3 g), pyridine (1 g), and dry benzene (100 ml) was refluxed for 2 h. Evaporation left the acid chloride (11), a solution of which in chloroform (60 ml) was added dropwise to a mixture of 4-hydroxy-N-methylphenethylamine hydrochloride (4.2 g), water (100 ml), and 7.5% sodium hydrogen carbonate (60 ml) at room temperature with stirring. Stirring was continued for 0.5 h, then the organic layer was separated, washed with 5% hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue afforded the amide (23) (8.6 g) as *prisms*, m.p. 98° (from ether) (Found: C, 71.45; H, 5.85. $\text{C}_{25}\text{H}_{25}\text{NO}_5$ requires C, 71.6; H, 6.0%), ν_{max} (CHCl_3) 3652 (OH), 1775 (O-COMe), and 1620 cm^{-1} (CO-NMe), δ (CDCl_3) 2.20 (3H, s, O-COMe), 3.01 (3H, s, NMe), 5.01 (2H, s, O- CH_2Ph), 6.45–7.02 (7H, m, ArH), and 7.31 p.p.m. (5H, s, ArH).

4-Benzyloxy-3-hydroxy-N-(4-hydroxyphenethyl)-N-methylbenzamide (24).—A mixture of the amide (23) (8.0 g), sodium hydroxide (3.6 g), water (60 ml), and ethanol (40 ml) was heated at 85–92° for 2 h. The solvent was removed and the residue was diluted with water (100 ml), acidified with concentrated hydrochloric acid, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the amide (24) (7.0 g) as a pale yellowish oil, which was chromatographed on silica gel (120 g) (chloroform as eluant). The amide (24) (5.8 g) formed *needles*, m.p. 137–138° (from benzene-hexane) (Found: C, 73.45; H, 5.95; N, 3.6. $\text{C}_{23}\text{H}_{23}\text{NO}_4$ requires C, 73.2; H, 6.15; N, 3.7%), ν_{max} (CHCl_3) 3570 (OH) and 1620 cm^{-1} (CO), δ (CDCl_3) 2.90 (3H, s, NMe), 4.96 (2H, s, O- CH_2Ph), 6.5–6.98 (7H, m, ArH), and 7.29 p.p.m. (5H, ArH).

Phenolic Oxidation of the Amide (24).—A mixture of the amide (24) (2.4 g), chloroform (200 ml), sodium hydrogen carbonate (36 g), potassium ferricyanide (13.2 g), and water (300 ml) was stirred at 50° for 2 h. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated to leave a viscous oil (1.4 g); this was chromatographed on silica gel (25 g). Elution with methanol-chloroform (0.5 : 99.5 v/v) afforded the *narwedine-type enone* (4) (58 mg) as *needles*, m.p. 208–209° (from ether) (Found: C, 73.7; H, 5.5; N, 3.8. $\text{C}_{23}\text{H}_{21}\text{NO}_4$ requires C, 73.6; H, 5.65; N, 3.75%), *m/e* 375 (M^+) and 332 ($M - 43$), ν_{max} (CHCl_3) 1685, 1635, and 1615 cm^{-1} (enone system), δ (CDCl_3) 3.22 (3H, s, NMe), 5.20 (2H, s, O- CH_2Ph), 4.86 (1H, m, H_X), 5.88 (1H, d, J 10 Hz, H_Z), 6.42 (1H, d, J 10 Hz, H_β), 6.96 and 7.48 (2H, each d, J 8 Hz, ArH), and 7.4 p.p.m. (5H, s, Ar-H). Elution with methanol-chloroform (1 : 99) then gave the *dienone* (31) (40 mg) as *needles*, m.p. 193–194° (from ether) (Found: C, 73.6; H, 5.6; N, 3.7. $\text{C}_{23}\text{H}_{21}\text{NO}_4$ requires C, 73.6; H, 5.65; N, 3.75%), *m/e* 375 (M^+), ν_{max} (CHCl_3) 3570 (OH), 1660, 1638, and 1620 cm^{-1} (C=O), δ (CDCl_3) 3.19 (3H, s, NMe), 5.10 (2H, s, O- CH_2Ph), 6.22 and 7.0 (4H, each d, J 11 Hz, α - and β -olefinic H), 6.69 and 7.5 (2H, each s, ArH), and 7.37 p.p.m. (5H, s, ArH).

4-Benzyloxy-2-bromo-3-hydroxybenzoic Acid (13).—To a stirred solution of the acid (9) (6 g) in acetic acid (100 ml) was added a solution of bromine (4 g) in acetic acid (50 ml) in the presence of sodium acetate (2 g) at room temperature.

Stirring was continued for 2 h, then the mixture was poured into water, and extracted with chloroform. The extract was washed with 2% sodium thiosulphate solution and then water, dried (Na_2SO_4), and evaporated. The residue gave the acid (13) (6.9 g) as *needles*, m.p. 81–83° (from ethanol-hexane) (Found: C, 52.2; H, 3.15. $\text{C}_{14}\text{H}_{11}\text{BrNO}_4$ requires C, 52.0; H, 3.4%).

3-Acetoxy-4-benzyloxy-2-bromobenzoic Acid (14).—A mixture of the acid (13) (5.8 g), sodium acetate (6.0 g), and acetic anhydride (80 ml) was refluxed for 1 h. The excess of acetic anhydride was evaporated off and the residue was poured into water (100 ml) and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The solid afforded the acid (14) (4.9 g) as *prisms*, m.p. 147–148° (from ethanol) (Found: C, 52.4; H, 3.5. $\text{C}_{16}\text{H}_{13}\text{BrO}_5$ requires C, 52.6; H, 3.6%).

3-Acetoxy-4-benzyloxy-2-bromo-N-(4-hydroxyphenethyl)-N-methylbenzamide (25).—A mixture of the acid (14) (4.2 g), thionyl chloride (1.8 g), pyridine (0.4 g), and dry benzene (60 ml) was refluxed for 2 h. Evaporation left the acid chloride (15), a solution of which in chloroform (50 ml) was added dropwise to a stirred mixture of 4-hydroxy-N-methylphenethylamine hydrochloride (2.3 g), sodium hydrogen carbonate (2.6 g), and water (130 ml). Stirring was continued for 0.5 h, then the organic layer was separated and washed with 5% hydrochloric acid and water, dried (Na_2SO_4), and evaporated to afford a pale yellowish oil (4.6 g), which was chromatographed on silica gel (60 g) (chloroform as eluant). The amide (25) (3.5 g) was a syrup, ν_{max} (CHCl_3) 3625 (OH), 1770 (OAc), and 1620 cm^{-1} (CO-N<), δ (CDCl_3) 2.22 (3H, s, OAc), 2.98 (3H, s, NMe), 4.98 (2H, s, O- CH_2Ph), 6.55–7.00 (6H, m, ArH), and 7.32 p.p.m. (5H, s, ArH), which was used without further purification for the following reaction because of difficulty in crystallisation.

4-Benzyloxy-2-bromo-3-hydroxy-N-(4-hydroxyphenethyl)-N-methylbenzamide (26).—A mixture of the amide (25) (3.25 g), ethanol (25 ml), sodium hydroxide (1.8 g), and water (30 ml) was heated at 85–95° for 2 h. The solvent was largely removed and the resulting solution was diluted with water, made acidic with concentrated hydrochloric acid and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The solid afforded the amide (26) (2.4 g) as *needles*, m.p. 139° (from benzene-hexane) (Found: N, 3.2. $\text{C}_{23}\text{H}_{23}\text{BrNO}_4$ requires N, 3.05%), ν_{max} (CHCl_3) 3500 (OH) and 1620 cm^{-1} (CO-N<), δ (CDCl_3) 2.96 (3H, s, NMe), 5.00 (2H, s, O- CH_2Ph), and 7.37 p.p.m. (5H, s, ArH).

Irradiation of the Amide (26).—A mixture of the amide (26) (1.3 g), sodium hydroxide (1.2 g), and water (1 l) was irradiated with a Hanovia 450 W mercury lamp fitted with a Pyrex filter for 6 h. An excess of crystalline ammonium chloride was added and the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brownish oil (400 mg), which was chromatographed on silica gel (10 g). Elution with methanol-chloroform (0.5 : 99.5 v/v) afforded the enone (4) (10 mg), identical (spectroscopic data) with the specimen prepared from compound (24).

3-Benzyloxy-2-bromo-4-methoxybenzaldehyde (17).—A mixture of the aldehyde (16) (32 g), benzyl chloride (18 g), sodium hydroxide (5.6 g), and methanol (300 ml) was refluxed for 4 h, then evaporated. The residue was diluted with water and extracted with benzene. The extract was washed with 10% sodium hydroxide and water,

dried (Na_2SO_4), and evaporated. The remaining solid afforded the aldehyde (17) (28 g) as *needles*, m.p. 77–78° (from ethanol) (Found: C, 56.2; H, 4.0. $\text{C}_{16}\text{H}_{13}\text{BrO}_3$ requires C, 56.1; H, 4.1%).

3-Benzoyloxy-2-bromo-4-methoxybenzoic Acid (18).—To a stirred mixture of the aldehyde (17) (14 g), silver nitrate (28 g), and water (150 ml) was added 40% sodium hydroxide (45 ml) at 90°. Stirring was continued for 1 h at the same temperature, then inorganic material was filtered off. The filtrate was made acidic with concentrated hydrochloric acid. The acid (18) was precipitated and formed *prisms* (11.5 g), m.p. 175–176° (from ethanol) (Found: C, 53.5; H, 3.7. $\text{C}_{15}\text{H}_{13}\text{BrO}_4$ requires C, 53.4; H, 3.9%).

3-Benzoyloxy-N-(4-benzoyloxyphenethyl)-2-bromo-4-methoxy-N-methylbenzamide (27).—A mixture of the acid (18) (8.4 g), thionyl chloride (3.6 g), pyridine (0.6 g), and benzene (120 ml) was refluxed for 1.5 h. Evaporation left the acid chloride (19), a solution of which in chloroform (50 ml) was added dropwise to a stirred mixture of 4-benzoyloxy-N-methylphenethylamine (6.0 g), 10% sodium hydroxide (40 ml), and chloroform (50 ml) at room temperature. After the addition, stirring was continued for 1 h, and the organic layer was separated, washed with water, and dried (Na_2SO_4). Evaporation afforded a yellowish oil (12.7 g), which was chromatographed on silica gel (120 g) (chloroform as eluant). The amide (27) (11.2 g) was a viscous syrup, ν_{max} (CHCl_3) 1625 cm^{-1} (C=O), $\delta(\text{CDCl}_3)$ 2.96 (3H, s, NMe), 3.74 (3H, s, OMe), 4.93 (4H, s, O- CH_2 Ph), 7.15–6.50 (6H, m, ArH), and 7.26 p.p.m. (10H, s, ArH).

2-Bromo-3-hydroxy-N-(4-hydroxyphenethyl)-4-methoxy-N-

methylbenzamide (28).—A mixture of the amide (27) (11.0 g), concentrated hydrochloric acid (120 ml), and ethanol (120 ml) was refluxed for 4 h, then evaporated. The residue gave the amide (28) (5.8 g) as *prisms*, m.p. 253–256° (from ethanol) (Found: C, 53.5; H, 4.8; N, 3.5. $\text{C}_{17}\text{H}_{18}\text{BrNO}_4$ requires C, 53.7; H, 4.8; N, 3.7%).

Irradiation of the Amide (28).—A water-cooled solution of the amide (28) (2.0 g) in 0.2% sodium hydroxide (1 l) was irradiated with a Hanovia 450 W mercury lamp fitted with a Pyrex filter for 8 h. Crystalline ammonium chloride was added and the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brownish oil (120 mg). The reaction was repeated with 3 g of the amide (28) to give an oil (250 mg). The combined crude product (370 mg) was chromatographed on silica gel (10 g). Elution with methanol-chloroform (0.5:99.5 v/v) gave the enone (3) (16 mg) as *prisms*, m.p. 268–270° (lit.,⁵ 269–271°) (from benzene-n-hexane), identical (spectroscopic data) with an authentic specimen,⁵ ν_{max} (CHCl_3) 1685, 1635 and 1615 cm^{-1} (C=O and C=C), $\delta(\text{CDCl}_3)$ 3.21 (3H, s, NMe), 3.90 (3H, s, OMe), 4.92 (1H, m, H_α), 5.89 (1H, d, J 10.5 Hz, H_α), 6.38 (1H, d, J 10.5 and 2 Hz, H_β), and 6.91 and 7.51 p.p.m. (2H, each d, J 10 Hz, ArH), m/e 299 (M^+).

We thank Miss A. Kawakami, Miss C. Yoshida, Miss R. Kato, Miss T. Yoshida, Miss A. Ujiie, and Mr. T. Ohuchi for microanalyses, spectral measurements, and technical assistance.

[1/2494 Received, 30th December, 1971]