Studies on the Syntheses of Heterocyclic Compounds. Part CCCXV.† Modified Total Synthesis of (±)-Galanthamine through Phenol Oxidation [1]

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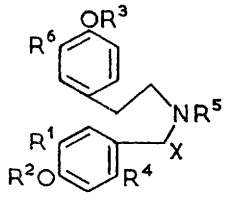
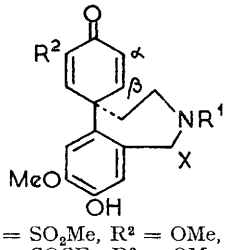
Oxidation of 2-bromo-5-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxy-*N*-methylbenzamide (VIII) with ferricyanide afforded the narwedine-type enone (X) in an excellent yield (40%). Reduction of (X) with lithium aluminium hydride gave (±)-galanthamine (II) and (±)-epigalanthamine (XXI) in yields of 50 and 40% respectively. Oxidation of (II) with manganese dioxide afforded (±)-narwedine (XIX) This work also constitutes a formal synthesis of (±)-lycoramine.

Among various types of alkaloid which can, formally, be derived through phenolic oxidative coupling, those of the *Amaryllidaceae*, including galanthamine,[2] are notable. Barton and Cohen [3] have recognised that these alkaloids could be regarded as derived from the common precursor, norbelladine (I), and this theory has been extensively studied by tracer experiments.[4] Norbelladine type compounds are readily available, and considerable effort has been put into the synthesis of *Amaryllidaceae* alkaloids along the biogenetic pathway. Only a single *in vitro* analogy for this general scheme has however been provided: [4] the total synthesis of galanthamine (II) (1·4%) by phenol oxidation of the diphenolic amine (III). The low yield may be due to attack by the nitrogen lone-pair upon the αβ-unsaturated ketone formed in the first step of oxidation to give an indole system, which could not undergo coupling of aromatic nuclei. Abramovitch [5] and Franck [6] have independently reported that the yields of similar coupling reactions are greatly improved by protection of the basic nitrogen of the starting materials, (IV) and (V), by formation of amides. Cyclisations then proceeded preferentially with '*para–para* coupling' to give the compounds (VI) and (VII) respectively.

We have investigated the oxidation of 2-bromo-5-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxy-*N*-methylbenzamide (VIII) in the expectation that the bromine atom would inhibit the coupling *para* to the hydroxy-group and favour *ortho* coupling with the formation of the dienone (IX) which might be expected to undergo an intramolecular ether formation to give the narwedine-type enone (X). The starting material



(I) $R^1 = OH$, $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $X = H_2$
(III) $R^1 = OH$, $R^3 = R^4 = R^6 = H$, $R^2 = R^5 = Me$, $X = H_2$
(IV) $R^1 = OH$, $R^3 = R^4 = H$, $R^2 = Me$, $R^5 = SO_2Me$, $R^6 = OMe$, $X = H_2$
(V) $R^1 = OH$, $R^3 = R^4 = H$, $R^6 = OMe$, $R^5 = COCF_3$, $X = H_2$
(VIII) $R^1 = OH$, $R^2 = R^5 = Me$, $R^3 = R^6 = H$, $R^4 = Br$, $X = O$
(XVIII) $R^1 = OCH_2Ph$, $R^3 = CH_3Ph$, $R^2 = R^5 = Me$, $R^6 = H$, $R^4 = Br$, $X = O$



(VI) $R^1 = SO_2Me$, $R^2 = OMe$, $X = H_2$
(VII) $R^1 = COCF_3$, $R^2 = OMe$, $X = H_2$
(XX) $R^1 = Me$, $R^2 = H$, $X = O$

† Part CCCXIV, T. Kametani, M. Koizumi, and K. Fukomoto, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 1809.

[1] Preliminary communication, T. Kametani, K. Yamaki, H. Yagi, and K. Fukumoto, *Chem. Comm.*, 1969, 425.

[2] W. C. Wildman in 'The Alkaloids,' ed. R. H. F. Manske vol. XI, Academic Press, New York, 1968, ch. 10 and refs. cited therein; T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids,' Hirokawa Publishing Company, Inc. and Elsevier Publishing Company, Tokyo. 1968, pp. 196, 296.

[3] D. H. R. Barton and T. Cohen, 'Festschr. A. Stoll,' Birkhauser, Basel, 1957, 117; D. H. R. Barton, *Proc. Chem. Soc.*, 1963, 293.

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

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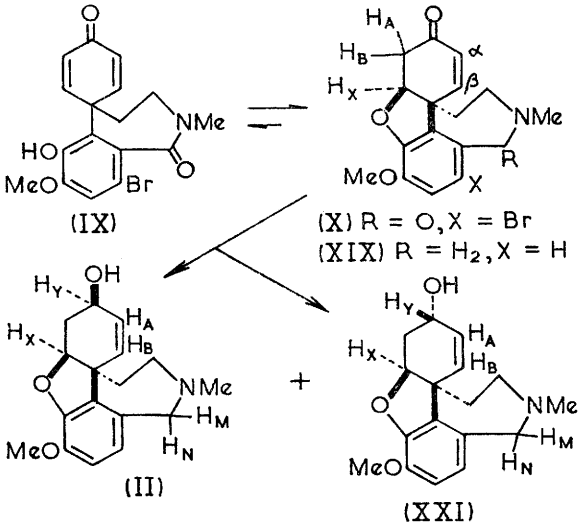
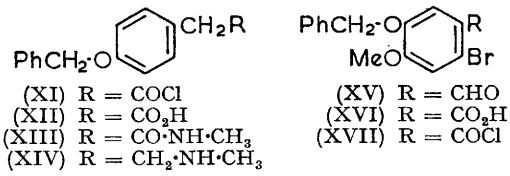
[6] B. Franck, J. Lubs, and G. Dunkelmann, *Angew. Chem.*, 1967, **79**, 989.

(VIII) was prepared as follows. Schotten–Baumann reaction of methylamine with the chloride (XI), which was prepared from the acid (XII) [7] by the action of thionyl chloride in pyridine, afforded the amide (XIII). Reduction of this amide with lithium aluminium hydride afforded the secondary amine (XIV). In the meantime, 2-bromo-*O*-benzylisovanillin (XV) [8] was oxidised to give the acid (XVI), which was then chlorinated with thionyl chloride to give the acid chloride (XVII). Schotten–Baumann reaction of the amine (XIV) with the acid chloride (XVII) gave the amide (XVIII), which when debenzylated with ethanolic hydrobromic acid gave the diphenolic amide (VIII).





The best conditions for phenol oxidation of the amide (VIII) involved a two-phase system of chloroform and aqueous potassium ferricyanide with sodium hydrogen carbonate at 60° for 1·5 hr. By this method the narwedine-type enone (X),* $C_{17}H_{16}BrNO_4$, m.p. 252—253°, was obtained consistently in an analytically pure state with an excellent yield (40%). Its i.r. spectrum showed enone absorption at 1682 and 1621 cm.$^{-1}$ and an amide carbonyl band at 1641 cm.$^{-1}$; the u.v. spectrum ($\lambda_{max.}$ 224, 265sh, and 313 mμ) also supported the presence of this system. The n.m.r. spectrum showed the *N*-methyl (τ 6·78) and *O*-methyl (6·10) signals as singlets. The α- (τ 4·10) and β-olefinic protons (τ 3·65) gave rise to the expected AB quartet ($J_{\alpha\beta}$ 10·5 c./sec.). However, each of the β-components was split further into doublets (J 2 c./sec.), coupled with the methine proton H_X (τ 5·18) through four σ bonds. Irradiation at the frequency of the methine proton H_X caused the β-proton quartet to collapse to a doublet (J 10·5 c./sec.), thus confirming the source of this long-range coupling. The methylene proton was shown at τ 6·83 and 7·25 as two pairs of quartets with coupling of the two non-equivalent protons (J 20 c./sec.) and coupling with the neighbouring methine proton (J 3·5 c./sec.). A single aromatic proton was shown at τ 2·89 as a singlet. The coupling constants and spin systems were confirmed by decoupling experiments; these data are quite similar to Kirby's [9] for narwedine (XIX).

Besides the enone (X), a small amount of the dienone (XX) was obtained. The i.r. spectrum of this compound showed a hydroxy-absorption at 3450 cm.$^{-1}$, dienone absorptions at 1660 and 1625, and an amide carbonyl band at 1640 cm.$^{-1}$. Precedents for this type of debromination are well known.[8,10] Reduction of (X) with lithium aluminium hydride gave a stereoisomeric mixture of carbinols, which were separated by alumina column chromatography to give (±)-galanthamine (II) (50%), m.p. 121—123°, and (±)-epigalanthamine (XXI) (40%), m.p. 199°.

The i.r. spectrum of (II) showed a phenolic hydroxy-absorption at 3575 cm.$^{-1}$, about 55 cm.$^{-1}$ to lower wavelength than the main hydroxy-band of (XXI) in dilute solution. Its n.m.r. spectrum showed two methyl singlets at τ 7·61 (NMe) and 6·18 (OMe), methylene signals for H_M and H_N at 6·34 and 5·90 as two doublets with geminal coupling (J 15·5 c./sec.), two methine signals for H_Y and H_X at 5·88 and 5·41 as multiplets, two olefinic signals at 4·05 (H_A) and 3·91 (H_B) as distorted doublets with fine structures (J_{cis} 10·5 c./sec.), and the aromatic protons at 3·91 as a singlet.

On the other hand, the n.m.r. spectrum of (XXI) showed two methyl singlets at 7·65 (NMe) and 6·18 (OMe), methylene signals for H_M and H_N at 6·41 and 5·92 as two doublets (J 15·5 c./sec.), two methine signals for H_X and H_Y at 5·54 as overlapping multiplets, and two olefinic signals at 4·23 (H_A) and 3·96 (H_B) as distorted doublets with fine structure (J_{cis} 10·5 c./sec.). The coupling constants and spin systems were confirmed by spin-decoupling experiments.

The physical and spectral data of these two carbinols were in good accord with those in the literature.[4,11,12] Moreover, the i.r. and n.m.r. spectra of natural galanthamine, donated by Prof. S. Uyeo of Kyoto University, were identical with those of the synthetic sample.

Further oxidation of (±)-galanthamine (II) with manganese dioxide gave (±)-narwedine (XIX).[4] Since the galanthamine has already been converted into

* All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only one enantiomer is depicted.

[7] D. D. Vaghani and J. R. Merchant, *J. Chem. Soc.*, 1961, 1066.

[8] A. H. Jackson and J. A. Martin, *J. Chem. Soc.* (*C*), 1966, 2061.

[9] G. W. Kirby and H. P. Tiwari, *J. Chem. Soc.*, 1964, 4655.

[10] T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, 1969, **25**, 3667.

[11] L. Bubewa-Iwanowa, *Ber.*, 1962, **95**, 1348.

[12] W. Döpke and H. Dolmer, *Naturwiss.*, 1965, **52**, 60.

lycoramine,[4] this work also constitutes the formal synthesis of (±)-lycoramine.

EXPERIMENTAL

I.r. spectra were measured with a type EPI-3 Hitachi recording spectrophotometer, and n.m.r. spectra with a Hitachi H-60 spectrometer with deuteriochloroform as solvent and tetramethylsilane as internal reference unless otherwise noted. Mass spectra were measured with a Hitachi RMU-7 mass spectrometer.

4-Benzyloxyphenyl-N-methylacetamide (XIII).—To a solution of methylamine (40 g.) and sodium hydroxide (25 g.) in water (200 ml.) was added dropwise a solution of acid chloride (XI) (20 g.) [obtained by chlorination of 4-benzyloxyphenylacetic acid [7] (XII) in the presence of thionyl chloride in pyridine according to the usual method] in chloroform (100 ml.) at room temperature with stirring within 30 min. The chloroform layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give the *amide* (XIII), which afforded colourless needles (17·8 g.), m.p. 103—104° (from benzene) [Found: C, 75·7; H, 6·6; N, 5·35. $C_{16}H_{17}NO_2$ requires C, 75·25; H, 6·6; N, 5·35%], $\nu_{max.}$ ($CHCl_3$) 3390 (NH) and 1655 (C=O) cm.$^{-1}$.

5-Benzyloxy-N-methylphenethylamine (XIV).—To a mixture of lithium aluminium hydride (9·6 g.) and dry tetrahydrofuran (200 ml.) under reflux was added dropwise a solution of the amide (XIII) (16 g.) in dry tetrahydrofuran (200 ml.) with stirring. Stirring was continued under reflux for a further 6 hr. The mixture was then decomposed gradually with saturated Rochelle salt solution and filtered. Evaporation of the solvent, followed by addition of water (100 ml.), gave a mixture which was extracted with chloroform (3 × 100 ml.). The extract was washed with water, dried (Na_2SO_4), and evaporated to give a pale brownish syrup, which was characterised as its hydrochloride. Recrystallisation from methanol–ether gave the amine (14·8 g.) as colourless *needles*, m.p. 163—165° (Found: C, 66·05; H, 7·1; N, 4·85. $C_{16}H_{19}NO,HCl,0·67H_2O$ requires C, 66·2; H, 7·4; N, 4·85%).

5-Benzyloxy-2-bromo-4-methoxybenzoic Acid (XVI).—To a mixture of 5-benzyloxy-2-bromo-4-methoxybenzaldehyde [8] (XV) (29 g.) and a solution of silver nitrate (58 g.) in water (250 ml.) under reflux at 100—110° was added dropwise 40% sodium hydroxide solution (90 ml.) with stirring. Stirring was then continued for a further 1 hr. The mixture was filtered hot, and the filtrate was acidified with concentrated hydrochloric acid and extracted with ether (300 ml.). The extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to give the acid, which yielded colourless *needles* (27·2 g.), m.p. 185° (from ethanol) (Found: C, 53·5; H, 3·65. $C_{15}H_{13}BrO_4$ requires C, 53·45; H, 3·9%), $\nu_{max.}$ (KBr) 1680 cm.$^{-1}$ (CO).

5-Benzyloxy-N-(4-benzyloxyphenethyl)-2-bromo-4-methoxy-N-methylbenzamide (XVIII).—To a mixture of the amine (XIV) (11·8 g.), 10% sodium hydroxide solution (80 ml.), and chloroform (50 ml.) was added dropwise a solution of acid chloride (XVII) (18 g.) [prepared from the acid (XVI) as usual] in chloroform (50 ml.) at room temperature with stirring. Stirring was continued for 30 min., then the solvent layer was separated, washed with water, and dried (Na_2SO_4). Evaporation gave a brown oil (24 g.), $\nu_{max.}$ ($CHCl_3$) 1625 cm.$^{-1}$ (C=O), which could not be crystallised and therefore was used without purification.

2-Bromo-5-hydroxy-N-(4-hydroxyphenethyl)-4-methoxy-N-methylbenzamide (VIII).—A mixture of (XVIII) (24 g.), ethanol (200 ml.), and 48% hydrobromic acid (400 ml.) was heated at 55° for 1 hr. After removal of the solvent, the residue was basified with concentrated ammonia and the crystals precipitated gave the *amide* (VIII) (10·2 g.) as colourless prisms, m.p. 288—289° (from ethanol) (Found: C, 52·7; H, 4·75; N, 3·6. $C_{17}H_{18}BrNO_4,0·25H_2O$ requires C, 52·4; H, 4·85; N, 3·65%).

Phenol Oxidation of (VIII).—To a solution of (VIII) (2 g.) in chloroform (500 ml.) was added rapidly a mixture of potassium ferricyanide (9·8 g.) and 5% sodium hydrogen carbonate solution (100 ml.) with vigorous stirring at 60°; stirring was then continued for 1·5 hr. The chloroform layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give a brown syrup (1·2 g.), which was chromatographed on silica gel (20 g.) with chloroform as eluant.

Evaporation of the first chloroform eluate gave the narwedine-type enone (X) which gave colourless *prisms* (0·86 g., 40%), m.p. 252—253° (from benzene–hexane) (Found: C, 54·05; H, 4·1; N, 3·75. $C_{17}H_{16}BrNO_4$ requires C, 54·0; H, 4·25; N, 3·75%), $\nu_{max.}$ ($CHCl_3$) 1682, 1641, and 1621 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 224, 265sh, and 313 mμ (log ε 4·06, 3·28, and 2·14), τ 6·78 (s, NMe), 6·10 (s, OMe), 3·65 (q, H_β, J 10·5 and 2 c./sec.), 4·10 (d, H_α, J 10·5 c./sec.), 5·18 (m, H_X), 6·83 and 7·25 (each q, H_A and H_B, J 20 and 3·5 c./sec.), and 2·89 (s, aromatic proton).

Elution with 1% methanol–chloroform gave a pale yellow syrup (20 mg.) which was again chromatographed on alumina (5 g.). Elution with 3% methanol–chloroform gave the dienone (XXI) (8 mg.) as a colourless syrup, *m/e* 299 (M^+), $\nu_{max.}$ ($CHCl_3$) 3450, 1660, 1640, and 1625 cm.$^{-1}$.

(±)-Galanthamine (II) *and (±)-Epigalanthamine* (XXI).—To a stirred suspension of lithium aluminium hydride (400 mg.) in tetrahydrofuran (20 ml.) was added dropwise a solution of the enone (X) (150 mg.) in tetrahydrofuran (30 ml.) within 30 min. at room temperature. The mixture was then refluxed on a water-bath for 10 hr. with stirring. Ethyl acetate and water were added to decompose the excess of reagent, and the supernatant liquid was decanted. The remaining paste of aluminium salts was extracted with chloroform, and the extract and supernatant liquid were combined, dried (Na_2SO_4), and evaporated to give a colourless syrup (110 mg.), which was chromatographed on alumina. Elution with ethyl acetate–benzene (1 : 1) gave crystals which yielded (±)-galanthamine (II) as colourless needles (57 mg., 50%), m.p. 121—123° (from ether) (lit.,[4] 121—123°) (Found: C, 70·85; H, 7·4; N, 4·75. Calc. for $C_{17}H_{21}NO_3$: C, 71·05; H, 7·4; N, 4·9%), $\lambda_{max.}$ (EtOH) 234 and 290 mμ (log ε 3·78 and 3·72), $\nu_{max.}$ ($CHCl_3$) 3575 cm.$^{-1}$ (OH), τ (Varian H-100) 7·61 (s, NMe), 6·34 (d, H_M or H_N, J 15·5 c./sec.), 6·18 (s, OMe), 5·90 (d, H_N or H_M, J 15·5 c./sec.), 5·88 (m, H_Y), 5·41 (m, H_X), 4·05 (distorted d with fine structure, H_A, J 10·5 c./sec.), 3·91 (distorted d with fine structure, H_B, J 10·5 c./sec.), and 3·36 (s, 2 aromatic protons), *m/e* 287·152 (M^+) (calc. M, 287·152), 270 (M − OH), 244·131 (M − $COCH_3$; calc. 244·133), 230 and 216. Its i.r. ($CHCl_3$) and n.m.r. spectra were identical with those of natural galanthamine. The column was then washed with chloroform; subsequent elution with ethanol–chloroform (1 : 19) gave crystals which gave (±)-epigalanthamine (XXI) (45 mg., 40%) as colourless needles, m.p. 199° (from ethanol) (lit.,[4] 199°) (Found: N, 5·1. Calc. for $C_{17}H_{21}NO_3$: N, 4·9%), $\lambda_{max.}$ (EtOH) 234 and 290 mμ (log ε 3·80 and 3·28), $\nu_{max.}$ ($CDCl_3$) 3630 cm.$^{-1}$ (OH), τ (Varian H-100) 7·65 (s,

NMe), 6·41 (d, H_M or H_N, J 15·5 c./sec.), 6·18 (s, OMe), 5·92 (d, H_M or H_N, J 15·5 c./sec.), 5·54 (m, H_X and H_Y), 4·23 (distorted d with fine structure, H_A, J 10·5 c./sec.), 3·96 (distorted d with fine structure, H_B, J 10·5 c./sec.), 3·44 (d, aromatic proton, J 7 c./sec.), and 3·34 (d, aromatic proton, J 7 c./sec.), *m/e* 287 (M^+), 270, 244, 230, and 216.

(±)-*Narwedine* (IX).—(±)-Galanthamine (II) (30 mg.), oxidised with active manganese dioxide (300 mg.) in chloroform (20 ml.) in the usual way,[4] gave (±)-narwedine (II) (20 mg.), m.p. 188—190° (lit.,[4] 186—190°), after sublimation at 150—160°/10^{-4} mm.; *m/e* 285·134 (M^+, calc. 285·136), 270, 256, 242, and 206, $\lambda_{max.}$ (EtOH) 225, 265, and 295 mμ (log ε 4·22, 3·55, and 3·08), $\nu_{max.}$ ($CHCl_3$) 1680 and 1630 $cm.^{-1}$, τ 7·57 (s, NMe), 5·28 (m, H_X), 4·00 (d, H_α, J 10·5 c./sec.), 3·05 (q, H_β, J 10·5 and 2 c./sec.), and 3·33 (s, aromatic protons).

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