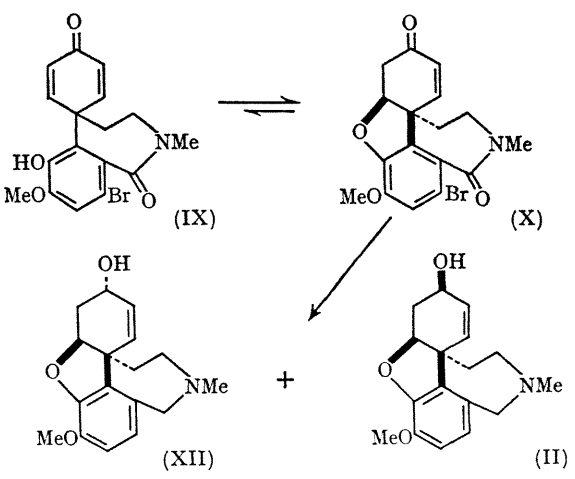
Modified Total Synthesis of (±)-Galanthamine through Phenol Oxidation

By T. KAMETANI,* K. YAMAKI, H. YAGI, and K. FUKOMUTO

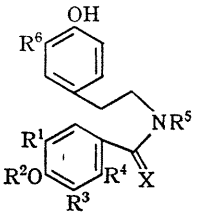
(*Pharmaceutical Institute, School of Medicine, Tohoku University, No. 85, Kitayobancho, Sendai, Japan*)

BARTON and COHEN[1] recognised that the *Amaryllidaceae* alkaloids could be regarded as derived from the common precursor, norbelladine (I), and this important theory has been extensively studied by tracer experiments.[2] An *in vitro* analogy has been provided by Barton and Kirby,[3] who performed the total synthesis (in low yield, 1·4%) of galanthamine (II) by phenol oxidation of the diphenolic amine (III). Abramovitch[4] and Franck[5] independently reported that the yield of similar coupling reactions was greatly improved by protection of the nitrogen in starting materials, (IV) and (V), by amide formation. However, cyclisation occurred preferentially with *para–para*-coupling to give compounds (VI) and (VII), respectively.

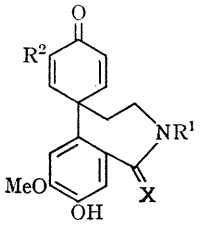
We have investigated the oxidation of 2-bromo-5-hydroxy-*N*-(4-hydroxyphenethyl)-4-methoxy-*N*-methylbenzamide (VIII)† in the expectation that the bromine atom would inhibit coupling *para* to the hydroxy-group and favour *ortho*-coupling, with formation of the dienone (IX)



† The preparation of (VIII) follows conventional procedure and will be described in the full paper, together with its analytical and spectroscopic data.



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



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

which would be expected to undergo intramolecular ether formation to yield the narwedine-type enone (X).

The best conditions found for phenol oxidation of compound (VIII) involved a two-phase system of chloroform and aqueous potassium ferricyanide with sodium hydrogen carbonate at 60°. By this method, the narwedine-type enone (X),§ $C_{17}H_{16}BrNO_4$, m.p. 252—253° was obtained consistently a pure state in excellent yield (40%).

Besides the above enone (IX), a small amount of the dienone (XI) was obtained and the precedents of this type of debromination are well known.[6] Reduction of (X) with lithium aluminium hydride gave a stereoisomeric mixture of the carbinols, which were separated by alumina column chromatography to give (±)-galanthamine (II) (50%), m.p. 121—123° (lit.,[3] m.p. 121—123°) and (±)-epigalanthamine (XII) (40%), m.p. 199° (lit.,[3] m.p. 199°).

The physical and spectral data of these two carbinols were in good accord with those in literature.[3,7] Moreover, the i.r. and n.m.r. spectra of natural galanthamine (donated by Prof. S. Uyeo, Kyoto University) were superimposable on those of our synthetic galanthamine.

Since galanthamine has already been converted into narwedine and lycoramine,[3] this work also constitutes the syntheses of these alkaloids.

(*Received, February 25th*, 1969; *Com.* 269.)

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

§ All the compounds described had spectroscopic properties consistent with the structures shown. Details will be reported in the full paper.

[1] D. H. R. Barton and T. Cohen, 'Festschrift Arthur Stoll', Birkhauser, Basel, 1957, p. 117; D. H. R. Barton Hugo Muller Lecture), *Proc. Chem. Soc.*, 1963, 293.
[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.
[3] D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806.
[4] R. A. Abramovitch and S. Takahashi, *Chem. and Ind.*, 1963, 1039.
[5] B. Franck, J. Lubs, and G. Dunkelmann, *Angew. Chem.*, 1967, **79**, 989.
[6] H. Jackson and J. A. Martin, *J. Chem. Soc.* (*C*), 1966, 2061; T. Kametani, T. Sugahara, H. Yagi, and K. Fukumoto, *Tetrahedron*, in the press.
[7] G. W. Kirby and H. P. Tiwari, *J. Chem. Soc.*, 1964, 4655.