Syntheses of Homoaporphine-type Compounds by Phenolic Oxidative Coupling

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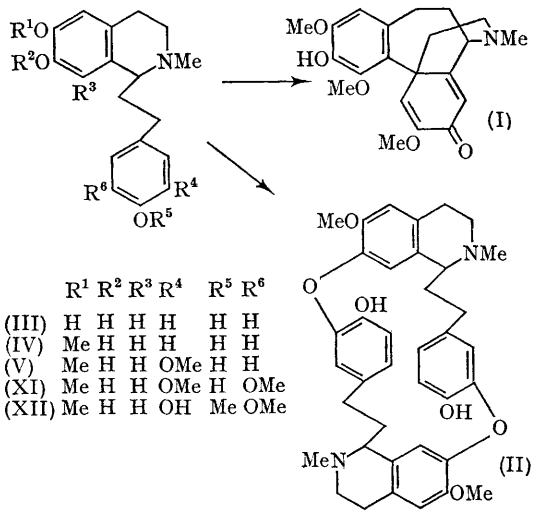
ANDROCYMBINE (I) and melanthioidine (II) can be derived biogenetically from 1-phenethyltetrahydroisoquinoline (III) by phenolic oxidative coupling.[1-3]



	R^1	R^2	R^3	R^4	R^5	R^6
(III)	H	H	H	H	H	H
(IV)	Me	H	H	H	H	H
(V)	Me	H	H	OMe	H	H
(XI)	Me	H	H	OMe	H	OMe
(XII)	Me	H	H	OH	Me	OMe

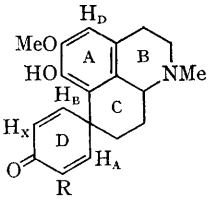
We have been studying the phenolic oxidative coupling reactions of the phenethylisoquinolines in order to obtain androcymbine (I) and melanthioidine (II). Very recently Battersby and his co-workers have reported that phenolic oxidative coupling of phenethylisoquinoline (XI) leads to dienone (XIII), whose dienone–phenol rearrangement gives homoaporphine, multifloramine (XIV), which is a novel alkaloid isolated from *Kreysigia multiflora* by the same authors.[4] This work prompted us to report our independent results on oxidation of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxyphenethyl)-6-methoxy-2-methylisoquinoline (IV) and its methoxy-analogues (V and XI).

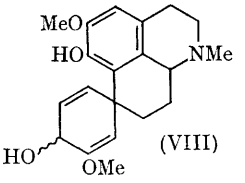
The phenethylisoquinolines (IV), (V), and (XI), prepared by standard methods,† were oxidized with potassium ferricyanide in a two-phase system consisting of 8% aqueous ammonium acetate solution and chloroform or with aqueous ferric chloride solution to give homoproaphorphines.

The oxidation of the first isoquinoline (IV) gave a dienone (VI), m.p. 248—249° (decomp.) [1·0% yield with $K_3Fe(CN)_6$, 19·0% yield with $FeCl_3$], whose structure was confirmed by the following evidence. The molecular formula, $C_{19}H_{21}O_3N$, was supported by microanalysis and mass spectrometry (M^+, 311; *m/e* $M-1$, $M-17$, $M-28$, $M-29$, $M-43$, $M-71$), and it showed ν_{max} 1600, 1619, 1657 (in KBr) and 3500 cm.$^{-1}$ (in $CHCl_3$); λ_{max} 235, 290 (log ϵ, 4·53, 3·66) (in MeOH); its n.m.r. spectrum (τ in $CDCl_3$) showed the expected methyl resonances at 7·55 (NMe) and 6·20 (OMe) as singlets, olefinic protons at 3·55—3·90 (2H; $\alpha\alpha'$) and 2·80—3·30 (2H; $\beta\beta'$) as two AB type quartets, and a singlet at 3·44 for single aromatic proton in the H_D position. These facts well support the dienone structure (VI).

† Satisfactory analyses were obtained for all new compounds described herein.

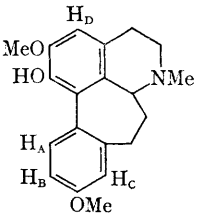
On the other hand, the second isoquinoline (V) gave a mixture of two isomeric dienones (VIIa and VIIb), from which both compounds were separated by recrystallization from benzene. One of them,





(VIII)

(VI) R=H
(VIIa) R=OMe
(VIIb) R=OMe
(XIII) R=H_X=OMe



(IX)
(X) H_B=OH
(XIV) H_A=OMe, H_B=OH

colourless prisms, m.p. 156—158° (decomp.) (VIIa), [3·5—4·5% yield with $K_3Fe(CN)_6$, 19·1% yield with $FeCl_3$] had a molecular formula, $C_{20}H_{23}O_4N,\frac{1}{2}C_6H_6$‡ [microanalysis and mass spectrometry (M^+; 341, m/e; $M-1$, $M-17$, $M-28$, $M-29$, $M-43$] and showed ν_{max} 1608, 1634, 1658, and 3495 cm.$^{-1}$ (in $CHCl_3$); λ_{max} 234, 286 (log ϵ, 4·406, 4·20) (in MeOH); its n.m.r. spectrum (τ in $CDCl_3$) showed the methyl resonances at 7·57 (NMe), 6·24 (aromatic OMe), and 6·45 (olefinic OMe), and a singlet at 3·47 due to single aromatic proton of H_D-position. In addition, there appeared a doublet at 4·02 (1H, H_A; J_{AB} = 2·5 c./sec.), a doublet at 3·72 (1H, H_X; J_{BX} = 10 c./sec.), and a pair of doublets centred at 3·14 (1H, H_B, coupled with H_A and H_X). The other dienone (VIIb), colourless prisms, $C_{20}H_{23}O_4N,\frac{1}{2}C_6H_6$,‡ m.p. 193—195°, [4·8% yield with $K_3Fe(CN)_6$, 17·5% yield with $FeCl_3$] was very similar to the former product (VIIa) in the u.v. (λ_{max} 244, 289 (log ϵ, 4·12, 3·80) (in MeOH)], i.r. [1608, 1636, 1658, and 3495 cm.$^{-1}$ (in $CHCl_3$)] and mass spectra, but there was a little difference in the n.m.r. spectrum (τ in $CDCl_3$); for it showed the methyl resonances at 7·58 (NMe), 6·26 (aromatic OMe) and 6·40 (olefinic OMe), aromatic proton at 3·48, and olefinic proton at 4·20 (1H, H_A; a doublet, J_{AB} = 2·5 c./sec.), 3·81 (1H, H_X, a doublet, J_{BX} = 10 c./sec.) and 3·0 (1H, H_B, a pair of doublets, coupled with H_A and H_X). One dienone should have the methoxy-group of ring D lying above the general plane of rings A, B, and C and the methoxy-group of ring D in the other dienone was below the general plane, though which is which is not yet clear. The oxidation of the third isoquinoline (XI) gave the same dienone (XIII), m.p. 176—178° (decomp.),‡ [18·0% yield with $FeCl_3$] [i.r. ν_{max} 1618, 1656, and 3500 (in $CHCl_3$), u.v. λ_{max} 278 (log ϵ, 4·03) (in MeOH)], whose n.m.r. data were identical with that of Battersby's sample.[4]

Reduction of VIIa with $NaBH_4$ afforded a dienol (VIII), m.p. 122—123°, [ν_{max} 1638 and 3495 (in $CHCl_3$); λ_{max} 290 (in MeOH)] which underwent dienol–benzene rearrangement with a methanolic hydrogen chloride solution to give the homoaporphine (IX), m.p. 170—175°. This structure was assigned as (IX) from the spectral evidences: the i.r. and u.v. spectra showed ν_{max} 3505 (in $CHCl_3$) and λ_{max} 260, 290 (in MeOH), respectively, and n.m.r. spectrum (τ in $CDCl_3$) revealed the following peaks, 7·61 (NMe), 6·19 (OMe), 4·14 (OH), 3·41 (1H, H_D, singlet), 3·20 (1H, H_C, doublet, J_{BC} = 2·3 c./sec.), 3·17 (1H, H_B, a pair of doublets, J_{AB} = 7·7, J_{BC} = 2·3 c./sec.), 2·55 (1H, H_A, doublet, J_{AB} = 7·7 c./sec.).

The dienone (VIIa) was subjected to dienone–phenol rearrangement with concentrated hydrochloric acid–acetic acid to afford an another phenolic base, m.p. 185—187°, whose structure was tentatively assigned as structure (X) by spectroscopic methods; i.r.: ν_{max} 3505 (in $CHCl_3$), u.v.: λ_{max} 264, 291 (in MeOH), and n.m.r. (p.p.m. in $CF_3{\cdot}CO_2H$) 4·00 (2 OMe), 6·88, 6·98, 7·25 (singlets, aromatic protons).

Attempts to obtain an androcymbine-type compound by phenolic oxidation of isoquinoline (XII) were unsuccessful. The above oxidation, followed by rearrangement, provides an interesting result from the point of biosynthesis of the homoaporphine alkaloids.

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‡ The benzene of this solvate was identified by its n.m.r. (τ 2·67 3H singlet) and mass spectra (m/e 78).

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[2] A. R. Battersby and R. B. Herbert, *Chem. Comm.*, 1965, 415.
[3] A. R. Battersby, R. B. Herbert, Z. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1966, 603.
[4] A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 450.