Total Synthesis of O-Methylandrocymbine by Photolysis of Diazotised Isoquinoline

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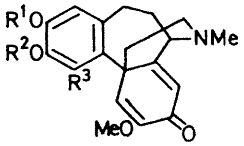
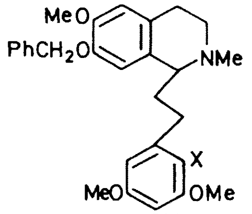
Summary Total synthesis of (±)-*O*-methylandrocymbine (II) by photo-Pschorr reaction of 1-(2-amino-3,4,5-trimethoxyphenethyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (V) is reported.

ANDROCYMBINE, an alkaloid isolated from *Androcymbium melanthioides* together with melanthioidine and colchicine, was assigned structure (I).[2] Recently, *O*-methylandrocymbine (II) was found in *Colchicum autumnale*.[3] In previous papers,[4,5] we reported the synthesis of the homomorphinandienone-type compounds (III) and (IV) by phenol oxidation and by Pschorr reaction. The total synthesis of *O*-methylandrocymbine by a modification of the latter method is now outlined.

Diazotisation of the 2′-aminophenethylisoquinoline (V), followed by thermal decomposition of the resulting diazonium salt (VI), gave the spiroisoquinoline (VII), whose structure was assigned by spectroscopic methods [λ_{max} (MeOH) 283 nm (log ϵ 3·41); τ (in $CDCl_3$) 7·88 (NMe), 6·98 (OMe), 6·27 (OMe), 6·17 (OMe), 6·12 (OMe), 5·14 (OCH_2Ph), 3·85, 3·51, and 3·46 (aromatic protons), and 2·85 (OCH_2Ph); *m/e* 475 (M^+) and 384] and by Hofmann degradation of its *O*-methyl analogue (VIII), b.p. 220°/0·01 mm. (bath temp.) (M^+ 399·2047; required 399·2045), prepared from (VII) *via* the phenolic isoquinoline (IX), to the indene derivative (X), m.p. 176—178° [M^+ 386; τ (in $CDCl_3$), 6·61, (OMe), 6·17 (OMe), 6·14 (OMe), 6·11 (OMe) 6·05 (OMe), 6·55 (2H, d, J 1·7 Hz, H_Y and H_Z), 3·84 (1H, t, J 1·7 Hz, H_X), 4·99 (1H, q, J_{AC} 10·5 Hz, J_{AB} 1·7 Hz, H_A), 4·49 (1H, q, J_{BC} 17·5 Hz, J_{AB} 1·7 Hz, H_B), 3·25 (1H, q, H_C), 3·18 (2H, s, aromatic protons), and 3·09 (1H, s, aromatic proton)] *via* the methine base (XI) [*m/e* 413 (M^+), 355 ($M^+ - CH_2NMe_2$)].

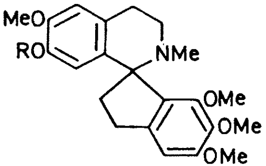
Irradiation of the diazonium salt (VI) (4·8 mmole/l.) with a Hanovia 450w mercury lamp using Pyrex filter at 5—10° for 4 hr. afforded the 2′-hydroxyphenethylisoquinoline (XII) [ν_{max} ($CHCl_3$) 3500 cm^{-1}; λ_{max} (MeOH) 283 nm; (log ϵ 3·74); the expected n.m.r. absorptions for *N*- and *O*-methyl groups together with 3·62, 3·45 and 3·42 (three aromatic protons); *m/e* 493 (M^+), 282, and 191] and *O*-methylandrocymbine. The i.r. and u.v. spectra of the synthetic product were superimposable upon those of natural *O*-methylandrocymbine prepared from androcymbine (I) provided by Professor F. Šantavý, whom we thank.



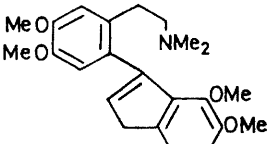


(I) $R^1 = Me, R^2 = H, R^3 = OMe$
(II) $R^1 = R^2 = Me, R^3 = OMe$
(III) $R^1 = R^3 = H, R^2 = Me$
(IV) $R^1 = R^2 = Me, R^3 = H$

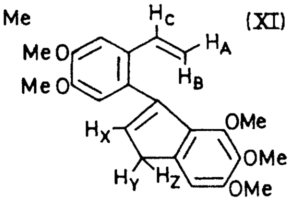
(V) $X = NH_2$
(VI) $X = N_2^+$
(XII) $X = OH$



(VII) $R = CH_2Ph$
(VIII) $R = Me$
(IX) $R = H$



(XI)



(X)

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