Total Syntheses of (−)-*O*-Methylandrocymbine, (−)-Kreysigine, and Alkaloid CC-10 Methyl Ether †

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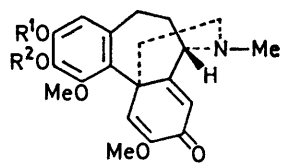
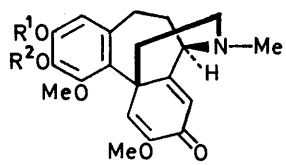
(−)-*O*-Methylandrocymbine (1) was obtained from (−)-1-(2-bromo-3,4,5-trimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (13a) by irradiation. The corresponding (+)-phenolic bromoisoquinoline (13b) gave alkaloid CC-10 methyl ether [(+)-*O*-methylandrocymbine] (3) and (−)-kreysigine (6).

(−)-*O*-METHYLANDROCYMBINE (1) is a homomorphinandienone-type alkaloid isolated from *Colchicum autumnale*,[1] and has been derived by methylation of androcymbine [2] (2) with dizomethane. (+)-*O*-Methylandrocymbine (3), its optical antipode, has been obtained by methylation of alkaloid CC-10 (4), isolated from *Colchicum cornigerum*.[3] Racemic kreysigine (5) has been isolated from *Kreysigia multiflora*;[4] the optically active form, (−)-kreysigine (6), was later found in *Bulbocodium vernum L.*[5]

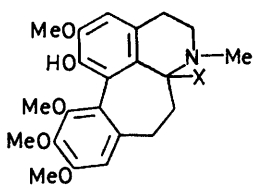
Recently Battersby [3] reported that *O*-methylandrocymbine is a key precursor of colchicine (8) and related alkaloids, implying that these tropolone derivatives are to be classed as highly modified 1-phenethylisoquinoline systems. We have previously [6,7] reported syntheses of (±)-*O*-methylandrocymbine and (±)-kreysigine by iradiation of the 2′-bromophenethylisoquinoline (9) and by a photo-Pschorr reaction of the diazonium salt of the 2′-aminophenethylisoquinoline (10). We now describe the total syntheses of (−)-*O*-methylandrocymbine (1), (−)-kreysigine (6), and their optical antipodes (3) and



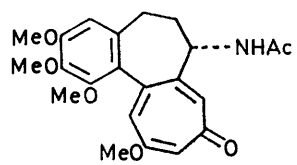
(1) $R^1 = R^2 = Me$
(2) $R^1 = Me$, $R^2 = H$



(3) $R^1 = R^2 = Me$
(4) $R^1 = H$, $R^2 = Me$



(5) X = ⁓ H
(6) X = ◀ H
(7) X = ···· H



(8)

(7) from the optically active 2′-bromophenethylisoquinolines (13a and b) by the former method.

† Part CDLXXV of ' Studies on the Syntheses of Heterocyclic Compounds,' Part CDLXXIV, T. Kametani, S. Takano, and H. Takeda, *J. Pharm. Soc. Japan.*, 1972, **92**, 743.

[1] R. Ramage, *Ann. Reports*, 1967, **64***B*, 515.
[2] A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228.
[3] A. R. Battersby, R. Ramage, A. F. Cameron, C. Hannaway, and F. Šantavý, *J. Chem. Soc.* (*C*), 1971, 3514.

The (±)-2′-bromophenethylisoquinoline [6] (11) was readily resolved with di-*p*-toluoyltartaric acid. The (−)-compound (12a), obtained from the (−)-di-*p*-toluoyltartrate, showed two positive Cotton effects, at 290 and 250 nm, and the (+)-base (12b), recovered from the (+)-di-*p*-toluoyltartrate, showed two negative Cotton effects at the same positions (Figure 1). It has been

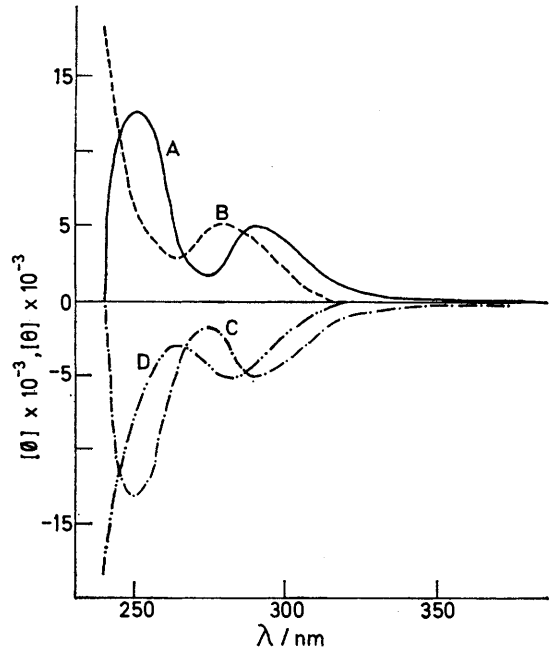
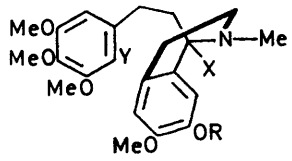


FIGURE 1 O.r.d. (A) and c.d. (B) curves of compound (12a) and o.r.d. (C) and c.d. (D) curves of compound (12b) (in methanol)

reported [8] that in 1-phenethyltetrahydroisoquinoline derivatives, the *S*-series show two positive Cotton effects, at 290 and 245 nm, whereas the *R*-series have double negative curves. We therefore expected that the (−)-base (12a) (*S*-configuration) would be converted into (−)-*O*-methylandrocymbine (1), whereas the (+)-isomer (12b) (*R*-configuration) would give the optical antipode (3) of natural *O*-methylandrocymbine and (−)-kreysigine (6).

[4] G. M. Badger and R. B. Bradbury, *J. Chem. Soc.*, 1960, 445.
[5] F. Šantavý, P. Sedmera, G. Snatzke, and T. Reichstein, *Helv. Chim. Acta*, 1971, **54**, 1084.
[6] T. Kametani, Y. Satoh, S. Shibuya, M. Koizumi, and K. Fukumoto, *J. Org. Chem.*, 1971, **36**, 3733.
[7] T. Kametani, M. Koizumi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1971, 1792.
[8] A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 678.

The (−)-2′-bromophenethylisoquinoline (12a) was debenzylated with ethanolic hydrochloric acid and the resulting phenolic bromoisoquinoline (13a) in ethanol was irradiated with a Hanovia 450 W mercury lamp



(9) R = H, X = ~~ H, Y = Br
(10) R = CH_2Ph, X = ~~ H, Y = NH_2
(11) R = CH_2Ph, X = ~~ H, Y = Br
(12a) R = CH_2Ph, X = ◀ H, Y = Br
(12b) R = CH_2Ph, X = ▮▮▮ H, Y = Br
(13a) R = H, X = ◀ H, Y = Br
(13b) R = H, X = ▮▮▮ H, Y = Br

(Pyrex filter) at room temperature for 7 h to give (−)-*O*-methylandrocymbine (1) and (+)-kreysigine (7). The (+)-2′-bromophenethylisoquinoline (12b) was similarly converted into (+)-*O*-methylandrocymbine (3) and (−)-kreysigine (6).

Both the (−)-enantiomeric compounds were shown to be identical with *O*-methylandrocymbine derived from natural androcymbine and with kreysigine prepared by

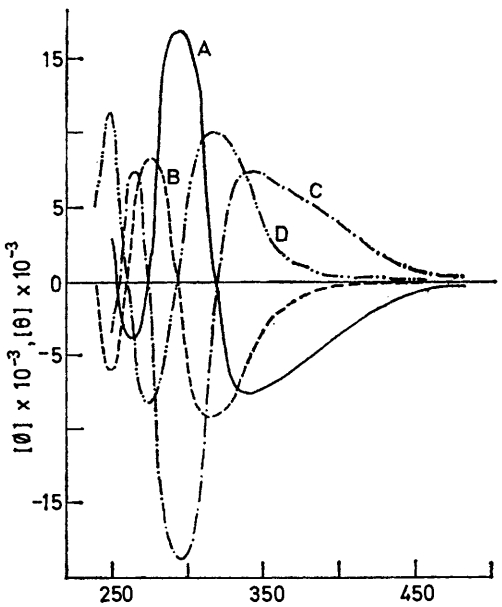


FIGURE 2 O.r.d. (A) and c.d. (B) curves of (−)-*O*-methylandrocymbine (1) and o.r.d. (C) and c.d. (D) curves of (+)-*O*-methylandrocymbine (3) (in methanol)

photo-Pschorr reaction, respectively, by spectral comparisons.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto microapparatus. I.r. and u.v. spectra were taken with Hitachi EPI-3 and EPS-3 recording spectrophotometers, respectively. Mass spectra were measured with a Hitachi RMU-7 spectrometer. N.m.r. spectra were measured with a Hitachi R-20 spectrometer for solutions in deuteriochloroform with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO PIP-SL automatic polarimeter. O.r.d. and c.d. curves were

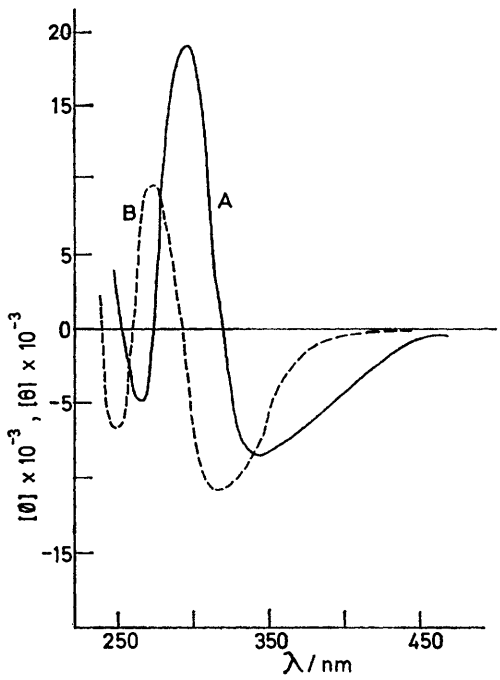


FIGURE 3 O.r.d. (A) and c.d. (B) curves of natural *O*-methylandrocymbine (in methanol)

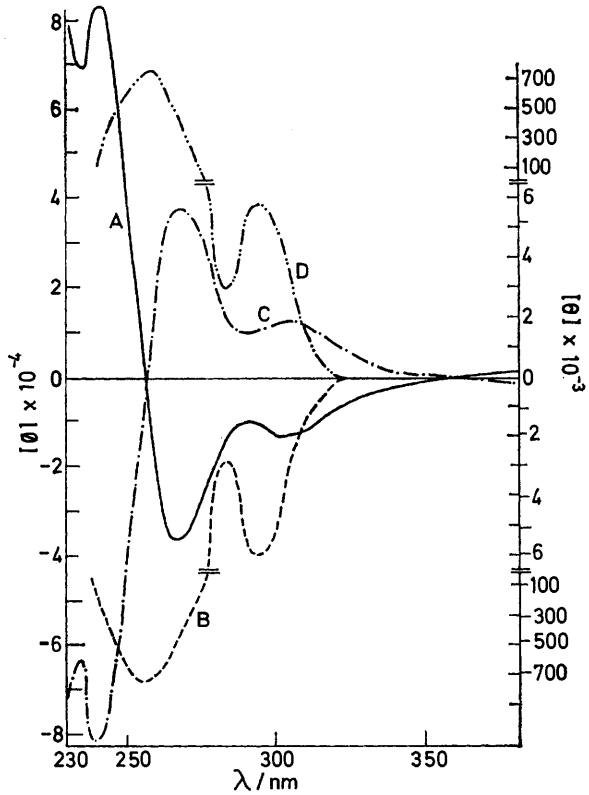


FIGURE 4 O.r.d. (A) and c.d. (B) curves of (+)-kreysigine (7) and o.r.d. (C) and c.d. (D) curves of (−)-kreysigine (6) (in methanol)

measured for solutions in methanol with a JASCO/UV-5 spectropolarimeter (*l* 0·1 and 0·02 dm).

(−)- *and* (+)-7-*Benzyloxy*-1-(2-*bromo*-3,4,5-*trimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methylisoquinolines* (12a *and* b).—(−)-Di-*p*-toluoyltartaric acid (13 g) was added to a solution of the base (9) (9 g) in acetone (300 ml). The salt which crystallised afforded the (−)-2′-*bromophenethylisoquinoline* (−)-*di*-p-*toluoyltartrate* (7·8 g), m.p. 158—159° (from methanol), $[\alpha]_D^{15}$ +46·1° (*c* 0·40 in MeOH) (Found: C, 62·6; H, 5·6; N, 1·65. $C_{49}H_{52}BrNO_{13}$ requires C, 62·4; H, 5·55; N, 1·5%). To a solution of this salt (7·5 g) in chloroform (*ca.* 200 ml) was added 10% sodium carbonate solution, and the mixture was shaken for a few minutes. The chloroform layer was separated, washed with water, and dried (K_2CO_3). Removal of the solvent left a yellowish solid, which crystallised from n-hexane to give the (−)-2′-*bromophenethylisoquinoline* (12a) (3 g) as needles, m.p. 94—95° (Found: C, 62·45; H, 6·3; N, 2·55. $C_{29}H_{34}BrNO_5$ requires C, 62·6; H, 6·15; N, 2·5%), $[\alpha]_D^{15}$ −22° (*c* 0·42 in MeOH), $\nu_{max.}$ ($CHCl_3$) 2780 cm^{-1} (NCH_3). The mother liquors from the salt of the (−)-base were worked up for the free base (5 g) and this was treated with (+)-di-*p*-toluoyltartaric acid (7·5 g) in acetone (200 ml). The salt which crystallised afforded the (+)-2′-*bromophenethylisoquinoline* (+)-*di*-p-*toluoyltartrate* (7·2 g) as needles, m.p. 158—159° (from methanol) (Found: C, 62·2; H, 5·55; N, 1·7%), $[\alpha]_D^{15}$ −46° (*c* 0·40 in MeOH). This salt gave the (+)-2′-*bromophenethylisoquinoline* (12b) (3 g) as needles, m.p. 94—95° (from n-hexane) (Found: C, 62·8; H, 5·95; N, 2·7%), $[\alpha]_D^{20}$ +23° (*c* 0·50 in MeOH), $\nu_{max.}$ ($CHCl_3$) 2780 cm^{-1} (NCH_3).

(−)- *and* (+)-1-(2-*Bromo*-3,4,5-*trimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (13a *and* b).—A mixture of the preceding isoquinoline (12a) (3 g), concentrated hydrochloric acid (30 ml), and ethanol (30 ml) was refluxed for 5 h. The usual work-up [6] gave compound (13a) (2·5 g) as a yellowish oil, which was difficult to crystallise and therefore used in the following reaction without purification [$\nu_{max.}$ ($CHCl_3$) 3510 (OH) and 2730 cm^{-1} (NCH_3)].

Similar treatment of compound (12b) (3 g) gave compound (13b) (2·5 g) as a yellowish oil, $\nu_{max.}$ ($CHCl_3$) 3510 (OH) and 2730 cm^{-1} (NCH_3).

Irradiation of the Phenolic Bromophenethylisoquinoline (13a).—A stirred water-cooled mixture of the phenolic isoquinoline (13a) (2·5 g), sodium hydroxide (0·7 g), ethanol (200 ml), and water (800 ml) was irradiated with a 450 W Hanovia mercury lamp (Pyrex filter) for 7 h. The usual work-up [6] left a brownish oil (2·2 g), which was chromatographed on silica gel (50 g) with methanol–chloroform (1 : 99) as eluant to give a dienone fraction (750 mg). Further chromatography on silica gel (10 g) with chloroform–methanol (99 : 1) as eluant afforded the dienone (300 mg), which was rechromatographed on neutral alumina (10 g). Elution with benzene–chloroform (9 : 1) gave (−)-*O*-methylandrocymbine (1) (45 mg), identical (spectroscopic data) with an authentic specimen.[7] Further elution after collection of the dienone fraction in the first chromatography afforded (+)-kreysigine (7) (80 mg), m.p. 112—113° (from ether), $[\alpha]_D^{15}$ +60° (*c* 0·40 in $CHCl_3$), otherwise identical spectroscopic data) with an authentic specimen.[6]

Photolysis of Irradiation of the Phenolic Bromophenethylisoquinoline (13b).—Similar irradiation of compound (13b), followed by chromatography as in the case of (13a), gave (+)-*O*-methylandrocymbine (3) (35 mg), identical (spectroscopic data) with an authentic specimen apart from the o.r.d. and c.d. spectra.[7] Chloroform eluted (−)-kreysigine (6) (80 mg), $[\alpha]_D^{15}$ −65° (*c* 0·40 in $CHCl_3$), otherwise identical (spectroscopic data) with an authentic specimen.[6]

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