Alkaloid Biosynthesis. Part XVII.[1,2] The Structure and Chemistry of Androcymbine †

By **A. R. Battersby** *‡ and **R. B. Herbert**, Robert Robinson Laboratories, University of Liverpool, Liverpool L69 3BX
L. Pijewska and **F. Šantavý**, The Chemical Institute, Medical Faculty, Palacký University, Olomouc, Czechoslovakia
P. Sedmera, Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague

The structure and absolute stereochemistry of androcymbine (3) are proved by spectroscopic study and by reductive cleavage of its *O*-methyl ether to a 1-phenethylisoquinoline, which is synthesised. Emphasis is given (*a*) to the importance of *O*-methylandrocymbine in relation to colchicine biosynthesis and (*b*) to the status of androcymbine as the forerunner of a new class of 1-phenethylisoquinoline alkaloids.

THE biosynthesis of colchicine (1) in *Colchicum autumnale* has been studied extensively; the results were best interpreted [1,3,4] by considering a cyclohexadienone such as (2), or some close relative, to be a key biochemical intermediate. This was subsequently supported by a different labelling experiment.[5] It was therefore of great interest when androcymbine, isolated from *Androcymbium melanthioides*,[6] was found to be a dienone; this plant contains colchicine and closely related tropolones in addition to androcymbine, the major base. The conviction that androcymbine is of biosynthetic importance for colchicine was strengthened by the close botanical relationship between *C. autumnale* and *A. melanthioides*; both species fall into the sub-family *Wurmbaeoideae* of the Liliaceae family. The common interest of the Czechoslovakian and British groups in androcymbine led to joint research which established the novel structure (3) for this alkaloid.

The molecular formula $C_{21}H_{25}NO_5$ for androcymbine, assigned on the basis of elemental analysis,[6] was confirmed by accurate mass measurement. Mild acetylation converted the alkaloid into a basic mono-*O*-acetate which was clearly a phenolic acetate ($\nu_{max.}$ 1760 cm^{-1}). It follows that the nitrogen atom is tertiary, and this was supported by the formation of androcymbine methiodide, involving simple addition of the elements of methyl iodide. Methylation of the phenolic hydroxy-group of androcymbine with methyl toluene-*p*-sulphonate

† This paper is also regarded as Part LXXVII of the series 'Substances from Plants of the Sub-family *Wurmbaeoideae* and their Derivatives' [Part LXXVI, *J. Chem. Soc.* (*C*), 1971, 3514] and as Part II of the series '1-Phenethylisoquinoline Alkaloids' [Part I, *J. Chem. Soc.* (*C*), 1967, 1739].

‡ *Present address:* University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

[1] Part XVI, A. R. Battersby, T. A. Dobson, D. M. Foulkes, and R. B. Herbert, preceding paper.

[2] Preliminary report, A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228.

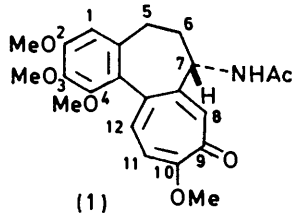
[3] A. R. Battersby, R. Binks, and D. A. Yeowell, *Proc. Chem. Soc.*, 1964, 86; A. R. Battersby and R. B. Herbert, *ibid.*, p. 260.

[4] A. R. Battersby, R. Binks, J. J. Reynolds, and D. A. Yeowell, *J. Chem. Soc.*, 1964, 4257.

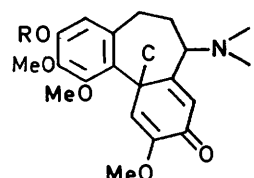
[5] E. Leete, *Tetrahedron Letters*, 1965, 333.

[6] J. Hrbek, jun., and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1962, **27**, 255; L. Pijewska, J. L. Kaul, H. Potěšilová, R. K. Joshi, and F. Šantavý, *ibid.*, 1967, **32**, 158.

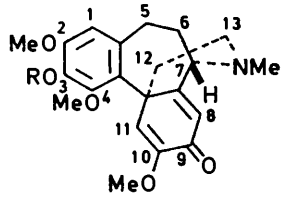
and sodium hydride [7] or with diazomethane gave the same ether, shown by mass spectrometry to be a mono-*O*-methyl derivative. Permanganate oxidation of this product afforded 3,4,5-trimethoxyphthalic anhydride;



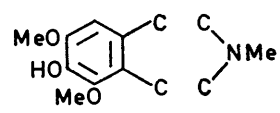
(1)



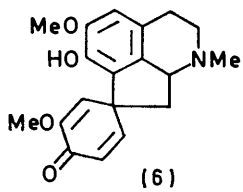
(2)



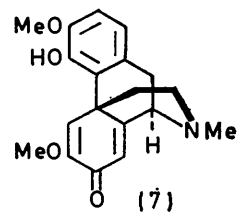
(3) R = H
(4) R = Me



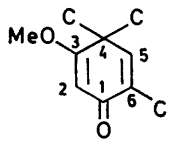
(5)



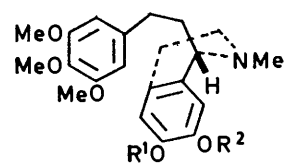
(6)



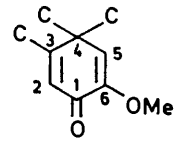
(7)



(8)



(10) R^1 = Me, R^2 = H
(11) R^1 = Me, R^2 = CH_2Ph
(12) R^1 = H, R^2 = Me
(13) R^1 = CH_2Ph, R^2 = Me



(9)

similar oxidation of *O*-ethylandrocymbine led to 3,5-dimethoxy-4-ethoxyphthalic anhydride. The partial structure (5) was thus established for androcymbine and supporting evidence was adduced later.

I.r. absorptions at 1665, 1635, and 1615 cm^{-1} in the spectrum of androcymbine are characteristic of an unsymmetrical, cross-conjugated dienone system. They resemble closely those shown by orientalinone [8] (6) and salutaridine [9] (7). Further, the half-wave potentials observed when androcymbine was reduced polarographically ($E_{\frac{1}{2}}$ — 1·31 V in Britton and Robinson buffer, pH 8·00) matched those given by known cyclohexadienones.[10] Reduction of androcymbine with borohydride or by catalytic hydrogenation gave products which in each case lacked dienone i.r. absorption. The hydrogenation proceeded in two stages: rapid absorption of 2 mol. equiv. of hydrogen was followed by a slower uptake of 1 mol. equiv. The u.v. absorption of androcymbine indicated that the aromatic and dienone chromophores are isolated one from the other.

The foregoing structural deductions were confirmed and extended by analysis of the n.m.r. spectrum of androcymbine (see Experimental section). Signals were immediately apparent corresponding to one olefinic proton, one *N*-methyl group, two aryl methoxy-groups, and one further methoxy-group in an environment similar to the methoxy-groups attached to the dienone systems of orientalinone [8] (6) and salutaridine [9] (7). A two-proton singlet at τ 3·73 became two singlets (1H each) when the solvent was changed to deuterium oxide containing sodium deuterioxide or deuteriochloroform–hexadeuterioacetone. This established that the original singlet at τ 3·73 arises by fortuitous overlap of the signal from the lone aromatic proton [see structure (5)], which should be affected by ionisation of the phenolic hydroxy-group,[11] with a singlet corresponding to an olefinic proton.* Thus, there are *two* signals arising from olefinic protons which have different shifts and each is a *singlet*. It is known [12] that the signals corresponding to two protons on a substituted cyclohexadienone ring show appreciable spin–spin coupling when they are located in any of the following arrangements: (*a*) on adjacent carbon atoms, (*b*) on positions 2 and 6, (*c*) on positions 3 and 5 [see structure (8)]. The absence of such coupling in the spectrum from androcymbine limits the substitution pattern of the dienone system to part structures (8) and (9). No reasonable full constitutions follow from the former but when the latter is combined with (5) and biogenetic considerations are taken into account, structure (3) appears probable for androcymbine. This accommodates all the foregoing information and also is in keeping with the appearance of unresolved signals in the n.m.r. spectrum of androcymbine (in addition to those already discussed) corresponding to nine protons, of which five are deshielded.

Structure (3) for androcymbine was tested by reductive fission of *O*-methylandrocymbine (4) with sodium in liquid ammonia, a reaction which has been used [13] to

* Alternatively, it could be argued that the shifted signal is that from the olefinic proton. If so, this would not affect the subsequent interpretation.

[7] *E.g.*, H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, 1960, **82**, 3368.

[8] A. R. Battersby, J. H. Clements, and T. H. Brown, *J. Chem. Soc.*, 1965, 4550.

[9] D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 1965, 2423.

[10] M. Maturová, L. Hruban, F. Šantavý, and W. Wiegrebe, *Arch. Pharm.*, 1965, **298**, 209.

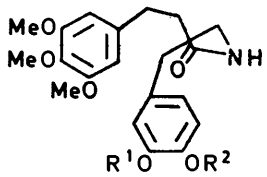
[11] *E.g.*, W. H. Baarschers and K. G. R. Pachler, *Tetrahedron Letters*, 1965, 3451.

[12] W. von Philipsborn, Habilitationsschrift, University of Zürich, 1962; see also ref. 8 and L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *J. Chem. Soc.*, 1966, 1676.

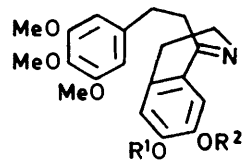
[13] M. P. Cava, K. Nomura, R. H. Schlessinger, K. T. Buck, B. Douglas, R. F. Raffauf, and J. A. Weissbach, *Chem. and Ind.*, 1964, 282.

cleave 4-arylcyclohexadienones; on the basis of structure (4) for *O*-methylandrocymbine, the product was expected to be the isoquinoline (10). The mass spectrum of the product showed a molecular ion at *m/e* 387 and the base peak at *m/e* 192, in accord with structure (10); the n.m.r. spectrum was entirely consistent with this assignment. Rigorous proof of structure was gained by the following syntheses.

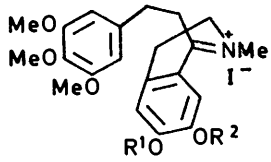
The acid chloride derived from 3-(3,4,5-trimethoxyphenyl)propionic acid [14] reacted with 4-benzyloxy-3-methoxyphenethylamine [15] to give the amide (14). This was converted by phosphoryl chloride into the



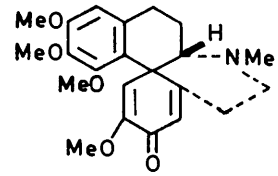
(14) $R^1 = Me, R^2 = CH_2Ph$
(15) $R^1 = CH_2Ph, R^2 = Me$



(16) $R^1 = Me, R^2 = CH_2Ph$
(17) $R^1 = CH_2Ph, R^2 = Me$



(18) $R^1 = Me, R^2 = CH_2Ph$
(19) $R^1 = CH_2Ph, R^2 = Me$



(20)

dihydroisoquinoline (16), which yielded the methiodide (18). Reduction with borohydride then gave the base [as (11)] from which the *O*-benzyl group was cleaved by acid to give the desired phenol [as (10)]. This was identical, apart from optical activity, with the reduction product from *O*-methylandrocymbine.

Only one doubt remained. Structure (20) for *O*-methylandrocymbine can accommodate all the foregoing data save that the product from reductive cleavage would be (12) rather than (10). There seemed a chance that (12) might be difficult to distinguish from (10); accordingly compound (12) was synthesised unambiguously for comparison. The reaction sequence was similar to that used to prepare (10), but in this case 3-benzyloxy-4-methoxyphenethylamine was one of the necessary starting materials. Though the u.v. and mass spectra of the final product [as (12)] were closely similar to those derived from the isomer [as (10)], there were clear differences in the i.r. and n.m.r. spectra of the two bases, in their t.l.c. behaviour, and in the properties of their salts. It was thus firmly established that the degradation product from *O*-methylandrocymbine is the base (10); hence structure (4) follows for the original dienone.

The reduction product (10) from *O*-methylandrocymbine was optically active; its o.r.d. curve showed a positive Cotton effect over the range 278—265 nm. This is known [16] to correspond to the illustrated *S*-configuration. Interlocking evidence came from the o.r.d. curves of androcymbine (3) and salutaridine (7), which were related as mirror images over the observed region 400—260 nm; the absolute stereochemistry of salutaridine is rigorously established.[9] The configuration of androcymbine is thus as shown in structure (3), which now gives the complete constitution of this alkaloid.

At the time this work was completed, androcymbine was an entirely novel structure in being based upon the 1-phenethylisoquinoline system [*e.g.* (10)]. The view [2] that it was the first representative of a new class of alkaloids has been amply confirmed by the discovery of 1-phenethylisoquinoline analogues of (*a*) the bisbenzylisoquinolines (melanthioidine [17]), (*b*) the aporphines (kreysigine, floramultine, and multifloramine [18]), (*c*) the morphine group (kresiginine [19] ≡ Alkaloid CC-21), and (*d*) the *Erythrina* alkaloids (schelhammerine and relatives [20]). The parent 1-phenethylisoquinoline system has also recently been found.[21] Some structural types which are familiar in the 1-benzylisoquinoline series (*e.g.* protoberberines) are missing from the foregoing list; opportunities to fill the gaps thus remain.

The close relationship of *O*-methylandrocymbine (4) to colchicine (1), including correspondence of absolute stereochemistry, emphasised the probable biosynthetic importance of the former for the latter. The way in which the problem of colchicine biosynthesis was laid open by the experimental test of this relationship is described in the following paper.[22]

EXPERIMENTAL

For general directions, see ref. 23.

Androcymbine (3) *and its Derivatives.*—Androcymbine, $C_{21}H_{25}NO_5$, m.p. 199—201°, showed $[\alpha]_D^{22}$ −260° ($CHCl_3$); *m/e* 371 (M^+, 100%), 356 (16), 342 (18), 340 (16), 328 (10),

[14] H. Rapoport and J. E. Campion, *J. Amer. Chem. Soc.*, 1956, **73**, 1417.
[15] M. K. Jain, *J. Chem. Soc.*, 1962, 2203.
[16] A. R. Battersby, I. R. C. Bick, W. Klyne, J. P. Jennings, P. M. Scopes, and M. J. Vernengo, *J. Chem. Soc.*, 1965, 2239; A. Brossi and F. Burkhardt, *Helv. Chim. Acta*, 1961, **44**, 1558; A. Rheiner and A. Brossi, *Experientia*, 1964, **20**, 288.
[17] A. R. Battersby, R. B. Herbert, and F. Šantavý, *Chem. Comm.*, 1965, 415; A. R. Battersby, R. B. Herbert, L. Mo, and F. Šantavý, *J. Chem. Soc.* (*C*), 1967, 1739.
[18] A. R. Battersby, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 450; A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *ibid.*, p. 934.
[19] A. R. Battersby, M. H. G. Munro, R. Bradbury, and F. Šantavý, *Chem. Comm.*, 1968, 695; J. Fredrichsons, M. F. Mackay, and A. Mc L. Lathieson, *Tetrahedron Letters*, 1968, 2887; N. K. Hart, S. R. Johns, J. A. Lamberton, and J. K. Saunders, *ibid.*, p. 2891; A. F. Beecham, N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 2829.
[20] S. R. Johns, C. Kowala, J. A. Lamberton, A. A. Sioumis, and J. A. Wunderlich, *Chem. Comm.*, 1968, 1102; S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 2219; W. Langlois, B. C. Das, P. Potier, and L. Lacombe, *Bull. Soc. chim. France*, 1970, 3535.
[21] A. R. Battersby, R. Ramage, A. F. Cameron, C. Hannaway, and F. Šantavý, *J. Chem. Soc.* (*C*), 1971, 3514.
[22] A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, following paper.
[23] A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc.* (*C*), 1969, 721.

and 210 (31); $\nu_{max.}$ 3550, 1670, 1645, and 1615 cm^{-1}; $\lambda_{max.}$ 280 (log ε 3·70), 241 (4·28), and 211 nm (4·60); o.r.d. (MeOH) $[\phi]_{337}$ −13,500tr, $[\phi]_{292}$ +27,000pk, $[\phi]_{258}$ −23,200tr {*cf.* salutaridine (7) $[\phi]_{355}$ +1810pk, $[\phi]_{306}$ −4200tr, $[\phi]_{278}$ +16,200pk}; τ 3·14 (1H, s, olefinic), 3·73 (2H, s, overlapping aryl H and olefinic), 6·00 (3H, s, OMe), 6·21 (3H, s, OMe), 6·39 (3H, s, OMe), and 7·66 (3H, s, NMe) [in $CDCl_3$–$(CD_3)_2CO$ the signal at τ 3·73 was replaced by two singlets at τ 3·67 and 3·73; the other signals occurred at 3·12, 5·95, 6·17, 6·36, and 7·63, respectively; irradiation at τ 6·36 caused an increase (NOE) of 19—23% in the τ 3·12 signal].

Treatment of androcymbine (4 mg) with pyridine (0·05 ml) and acetic anhydride (0·2 ml) for 16 h at 20° followed by evaporation gave *O*-acetylandrocymbine, homogeneous by t.l.c. (silica; 10% methanol–chloroform); $\nu_{max.}$ 1760 cm^{-1}, *m/e* 413 (M^+, 100%), 398 (8), 370 (14), and 252 (11).

A solution of androcymbine (0·2 g) in methanol (3 ml) and methyl iodide (2 ml) was heated under reflux for 3 h. Conversion into *androcymbine methiodide* was then complete and the product crystallised from acetone or methanol; m.p. 273—275° (Found: C, 51·1; H, 5·2; I, 26·1; N, 2·45. $C_{22}H_{28}INO$ requires C, 51·5; H, 5·5; I, 24·7; N, 2·7%).

Androcymbine (50 mg) was heated under reflux for 3 h in ethanol (2 ml) and pyridine (1 ml) with hydroxylamine hydrochloride (50 mg). The solvents were evaporated off, water was added, the solution was made basic with ammonium hydroxide, and the product was extracted with chloroform. It crystallised from methanol–chloroform to give *androcymbine oxime* (Found: N, 6·6. $C_{21}H_{26}N_2O_5$ requires N, 7·2%), m.p. 168—170°, $[\alpha]_D^{22}$ −266° ± 5° (*c* 0·46 in EtOH); τ 3·14 (1H, s, olefinic), 3·77 and 3·87 (each 1H, s, aryl H and olefinic), 6·0, 6·18, and 6·37 (each 3H, s, OMe), and 7·65 (3H, s, NMe).

O-Methylandrocymbine (4).—Sodium hydride (50% dispersion in oil) was added in portions to androcymbine (0·3 g) in anhydrous dimethylformamide (3 ml) until fresh additions of the hydride caused no effervescence. Methyl toluene-*p*-sulphonate (0·15 g) was then added and the mixture was kept at 20° for 2 days. The solvent was evaporated off, water was added to the residue, and the solution was adjusted to pH 6 with acetic acid before extraction with chloroform. Evaporation of the dried extracts afforded a gum which (t.l.c.) contained one major component, the remainder being starting material. Chromatography, initially in benzene, on neutral alumina (activity I; 15 × 1·5 cm; elution with increasing proportions of chloroform in benzene) gave unchanged androcymbine (100 mg) and *O-methylandrocymbine* (192 mg), *m/e* 385 (M^+, 100%), 370 (16), 356 (18), 354 (15), and 224 (12); $\nu_{max.}$ 1612, 1635, and 1660 cm^{-1}; τ 3·20 (1H, s, olefinic), 3·68 and 3·73 (1H each, s, aryl H and olefinic), 5·99, 6·17, and 6·38 (each 3H, s, OMe), and 7·64 (3H, s, NMe).

O-Methylandrocymbine picrate crystallised from methanol; m.p. 157—161° (decomp.) (Found: C, 54·9; H, 5·0; N, 9·0. $C_{28}H_{30}N_4O_{12}$ requires C, 54·8; H, 4·9; N, 9·1%). The recovered base showed $[\alpha]_D^{20}$ −295° ($CHCl_3$).

An alternative preparation involved treatment of androcymbine (10 mg) in the minimum volume of methanol with an excess of ethereal diazomethane at 20° for 20 h. Evaporation of the solvent left a residue which was almost pure *O*-methylandrocymbine (by t.l.c. and i.r. spectroscopy).

Oxidation of O-*Methyl- and* O-*Ethyl-androcymbine*.—Both oxidations were carried out and the products worked up as for the oxidation of *O*-ethyl-3-demethyldemecolcine.[24] *O*-Methylandrocymbine (150 mg) afforded 3,4,5-trimethoxyphthalic anhydride (5 mg), m.p. and mixed m.p. 141—143°. Similarly, oxidation of *O*-ethylandrocymbine (200 mg) gave 4-ethoxy-3,5-dimethoxyphthalic anhydride (27 mg), m.p. and mixed m.p. 115—118° which was converted into the corresponding *N*-ethylimide (4 mg), m.p. and mixed m.p. 89—91°. Both products were identified by direct comparison with authentic specimens[25] of m.p. 116—118° and 90—91°, respectively.

Reductive Cleavage of O-*Methylandrocymbine* (4).—To a solution of sodium (184 mg) in liquid ammonia at −45 ± 5° was added *O*-methylandrocymbine (184 mg) in dry toluene (2·5 ml with 2 × 0·5 ml washings). More sodium was added during and after the addition of the dienone to maintain the blue colour of the solution. After 2 h, ammonium chloride (1·5 g) was added, the ammonia was evaporated off, and water was added to the residue. The aqueous solution was extracted with ether and with chloroform and the combined extracts were extracted with aqueous 1% potassium hydroxide, washed with water, dried, and evaporated to give mainly *O*-methylandrocymbine (70 mg). This was reduced again and worked up as before.

The aqueous alkaline solutions from both reductions were treated with a large excess of ammonium chloride and extracted with chloroform to give an almost homogeneous gum (82 mg), which, purified by preparative t.l.c. yielded (*S*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methyl*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline*. This product did not crystallise, and the picrate, picrolonate, perchlorate, and oxalate were amorphous [Found: M^+, 387·201(0). $C_{22}H_{29}NO_5$ requires *M*, 387·204(5)], *m/e* 387 (M^+), 372, 206, 192 (base peak, at least 1000 times larger than the others), and 177; τ 3·37 (1H, s, aryl H), 3·48 (1H, s, aryl H), 3·63 (2H, s, aryl H), 6·18 (12H, s, 4 × OMe), and 7·56 (3H, s, NMe); $\nu_{max.}$ 3550 cm^{-1}; $\lambda_{max.}$ (MeOH) 225 (log ε 4·11) and 285 nm (3·55); $\lambda_{max.}$ (NaOH–MeOH) 225 and 300 nm; $[\alpha]_D^{26}$ +32·9° (*c* 0·29 in $CHCl_3$); o.r.d. (MeOH) $[\phi]_{278}$ +4900pk, $[\phi]_{265}$ +2500tr, $[\phi]_{255}$ +3680!.

N-(4-*Benzyloxy*-3-*methoxyphenethyl*)-3-(3,4,5-*trimethoxyphenyl*)*propionamide* (14).—Dimethylformamide (0·1 g) was added to a suspension of 3-(3,4,5-trimethoxyphenyl)-propionic acid[14] (5 g) in anhydrous benzene (30 ml) containing oxalyl chloride (6 g). After the solid had dissolved and the effervescence ceased, the solvents were evaporated off and the residue was treated with 4-benzyloxy-3-methoxyphenethylamine (5·62 g) in ether (25 ml). Aqueous potassium hydroxide (1·3 g in 20 ml) was added and the mixture was shaken for 1 h with addition of more potassium hydroxide solution as necessary to hold the pH above 8. Chloroform and water were then added, the mixture was shaken, and the organic layer was washed in sequence with water, dilute hydrochloric acid, and water and finally dried. Evaporation gave the *amide* (14) (6·7 g), m.p. 104—105·5° (from ethyl acetate) (Found: C, 69·8; H, 6·7. $C_{28}H_{33}NO_6$ requires C, 70·1; H, 6·9%).

7-*Benzyloxy*-3,4-*dihydro*-6-*methoxy*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (16).—A solution of the foregoing amide (0·3 g) in dry toluene (6 ml) was heated for 1 h at 100° (bath) with phosphoryl chloride (0·15 ml) and then evaporated. The residue, in the minimum volume of warm ethanol, was treated with concentrated hydrochloric acid

[24] F. Šantavý, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2237.
[25] F. Šantavý, M. Talas, and O. Tělupilová, *Coll. Czech. Chem. Comm.*, 1953, **18**, 710.

(0·15 ml); the *dihydroisoquinoline hydrochloride* separated (273 mg); m.p. 202—203° (from ethanol) (Found: C, 67·2; H, 6·5. $C_{28}H_{32}ClNO_5$ requires C, 67·5; H, 6·4%).

7-*Benzyloxy*-3,4-*dihydro*-6-*methoxy*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline Methiodide* (18).—The base was recovered from the foregoing salt (0·2 g) into ethyl acetate in the usual way; the solvent was evaporated off and the residue dissolved in methyl iodide (8 ml). After 18 h at 20°, the *methiodide* was collected (310 mg) and recrystallised from propan-2-ol; m.p. 156—157° (decomp.) (Found: C, 58·0; H, 6·0. $C_{29}H_{34}INO_5$ requires C, 57·7; H, 5·7%).

(RS)-7-*Benzyloxy*-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methyl*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (11).—An excess of sodium borohydride was added in portions to a suspension of the foregoing methiodide (0·31 g) in propan-2-ol (10 ml) until the solid dissolved. The solvent was then evaporated off and water was added to the residue, followed by hydrochloric acid (to pH 1) and aqueous sodium hydroxide (to >pH 10). Extraction with chloroform gave the product as a gum which was treated in methanol with picric acid (1·1 equiv.); the (RS)-*tetrahydroisoquinoline picrate* was recrystallised from methanol (yield 326 mg); m.p. 152·5—153·5° (Found: C, 59·6, 59·7; H, 5·4, 5·2; N, 8·0. $C_{35}H_{38}N_4O_{11},CH_3OH$ requires C, 59·8; H, 5·8; N, 7·8%).

(RS)-7-*Hydroxy*-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methyl*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (10).—A solution of the foregoing picrate (0·3 g) in chloroform was passed through a short column of neutral alumina (activity III) and the column was washed with chloroform. Evaporation of the eluates left a gum which was heated under reflux for 20 min with ethanol (4 ml) and concentrated hydrochloric acid (4 ml). The ethanol was evaporated off and the solution was then diluted with water and made basic with solid sodium hydrogen carbonate. Extraction with chloroform yielded the phenol as a gum which was converted in ethanol into the (RS)-*tetrahydroisoquinoline picrolonate* (265 mg), m.p. 182—183° (from ethanol) (Found: C, 59·0; H, 6·2; N, 10·5. $C_{32}H_{37}N_5O_{10}$ requires C, 59·0; H, 5·7; N, 10·7%); $\nu_{max.}$ for recovered base 3550 cm^{-1}, with complete i.r. spectrum identical with that of the reduction product from *O*-methylandrocymbine; τ 3·37 (1H, s, aryl H), 3·48 (1H, s, aryl H), 3·63 (2H, s, aryl H), 6·18 (12H, s, 4 × OMe), and 7·56 (3H, s, NMe); *m/e* 387 (M^+), 372, 206, 192 (enormous base peak), and 177. This product, and the reduction product from *O*-methylandrocymbine were indistinguishable by t.l.c. on silica gel in 10% methanol–benzene and in 10% and 20% methanol–chloroform and they gave identical colour reactions on the plates when sprayed with ferric chloride, concentrated nitric acid, iodine, potassium permanganate, or diazotised sulphanilic acid (strong purple colour).

(RS)-1,2,3,4-*Tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methyl*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (12).—The synthesis followed, without significant change, the foregoing synthesis used for the 7-hydroxy-6-methoxy-isomer. Only the yields of intermediates and characterisations are therefore recorded.

(*a*) N-(3-*Benzyloxy*-4-*methoxyphenethyl*)-3-(3,4,5-*trimethoxyphenyl*)*propionamide* (15), yield 60%, m.p. 101—103° (from ethyl acetate) (Found: C, 70·3; H, 6·9. $C_{28}H_{33}NO_6$ requires C, 70·1; H, 6·9%).

(*b*) 6-*Benzyloxy*-3,4-*dihydro*-7-*methoxy*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (17), yield of *hydrochloride* 81%, m.p. 212—213° (from ethanolic hydrogen chloride) (Found: C, 67·7; H, 6·4. $C_{28}H_{32}ClNO_5$ requires C, 67·5; H, 6·4%).

(*c*) 6-*Benzyloxy*-3,4-*dihydro*-7-*methoxy*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline methiodide* (19), yield quantitative, m.p. 175·5—178·5 (from propan-2-ol) (Found: C, 57·4; H, 5·6. $C_{29}H_{34}INO_5$ requires C, 57·7; H, 5·7%).

(*d*) (RS)-6-*Benzyloxy*-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methyl*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (13), yield 75% as *picrolonate*, m.p. 159—160° (from ethanol) (Found: C, 62·9; H, 6·0; N, 9·4. $C_{39}H_{43}N_5O_{10}$ requires C, 63·2; H, 5·8; N, 9·4%).

(*e*) (RS)-1,2,3,4-*Tetrahydro*-6-*hydroxy*-7-*methoxy*-2-*methyl*-1-(3,4,5-*trimethoxyphenethyl*)*isoquinoline* (12), yield 90% as *picrolonate*, m.p. 178—180·5° (from ethanol) (Found: C, 59·3; H, 5·7; N, 10·6. $C_{32}H_{37}N_5O_{10}$ requires C, 59·0; H, 5·7; N, 10·7%); *m/e* 387 (M^+), 372, 206, and 192 (enormous base peak); τ (for the base) 3·39 (1H, s, aryl H), 3·51 (1H, s, aryl H), 3·61 (2H, s, aryl H), 6·20 (12H, s, 4 × OMe), and 7·53 (3H, s, NMe). The i.r. spectrum differed from that of the reduction product from *O*-methylandrocymbine. This base also differed from the reduction product in its t.l.c. behaviour (silica gel; 10% or 20% methanol–chloroform) and its colour reaction with diazotised sulphanilic acid (orange colour).

We thank Dr. P. M. Scopes and Professor W. Klyne (Westfield College) for the o.r.d. measurements, and Dr. R. A. Baxter (Monsanto Chemicals Ltd.) for gifts of chemicals.

[2/279 *Received*, 8*th February*, 1972]