Studies on the Syntheses of Heterocyclic Compounds. Part CDXLVI.† Total Photolytic Synthesis of (±)-Androcymbine and (±)-Multifloramine

By **T. Kametani** * and **M. Koizumi**, Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

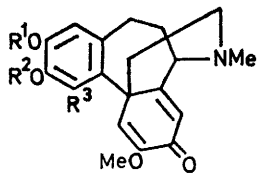
Photolysis of 1-(2-bromo-4-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (8) in the presence of sodium iodide gave (±)-androcymbine (1). When the photolysis was done without sodium iodide, it afforded only multifloramine (10).

ANDROCYMBINE (1) and *O*-methylandrocymbine (2) have been isolated from the leaves of *Androcymbium melanthioides* [1,2] and *Colchicum autumnale*,[3] respectively, together with colchicine (5) and its derivatives. Both alkaloids are key intermediates in the problem of the biosynthesis of colchicine.[4] Previously we have described syntheses for the androcymbine-type compounds (3) and (4); the first by a Pschorr reaction [5] and the second by phenol oxidation.[6] The total synthesis of *O*-methylandrocymbine (2) has been accomplished *via* photolysis of the diazonium salts (6) and (7).[7] Recently

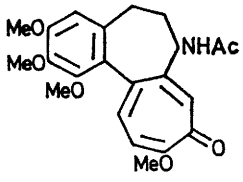
† Part CDXLV, T. Kametani and T. Kohno, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 2102.

[1] J. Hrbek and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1962, **27**, 225.
[2] A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228.
[3] R. Ramage, *Ann. Reports*, 1967, **64***B*, 515.
[4] A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1966, 603.
[5] T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968, 1001; *J. Chem. Soc.* (*C*), 1968, 3084.
[6] T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *Chem. Comm.*, 1968, 1605; *J. Chem. Soc.* (*C*), 1969, 1295.
[7] T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Comm.*, 1970, 1157.

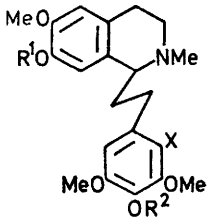
we reported the syntheses [8-10] of various morphinandienone alkaloids by photolysis from (2-bromobenzyl)-isoquinoline derivatives. We now report the total syntheses of (±)-androcymbine (1) and (±)-multifloramine (10) by photolysis of the (2-bromophenethyl)-isoquinoline (8).



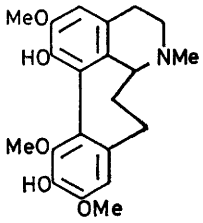
(1) R^1 = Me, R^2 = H, R^3 = OMe
(2) R^1 = R^2 = Me, R^3 = OMe
(3) R^1 = R^2 = Me, R^3 = H
(4) R^1 = R^3 = H, R^2 = Me



(5)



(6) R^1 = R^2 = Me, X = N_2^+
(7) R^1 = CH_2Ph, R^2 = Me, X = N_2^+
(8) R^1 = R^2 = H, X = Br
(9) R^1 = R^2 = CH_2Ph, X = Br



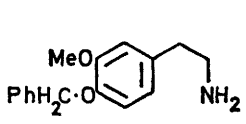
(10)

The starting material (8) was synthesised as follows: esterification of 4-hydroxy-3,5-dimethoxyphenylpropionic acid (12) [11] gave the ester (13), which was brominated to give the methyl 2-bromophenylpropionate (14). Benzylation of the bromo-ester (14) afforded the benzyl compound (15), which was converted into the amide (16) by fusion with 4-benzyloxy-3-methoxyphenethylamine (11). Bischler–Napieralski cyclisation of this amide (16) gave the 3,4-dihydroisoquinoline (17), the methiodide (18) of which was treated with sodium borohydride to afford the bromophenethyl-1,2,3,4-tetrahydro-2-methylisoquinoline (9). This was debenzylated with hydrochloric acid in boiling ethanol.

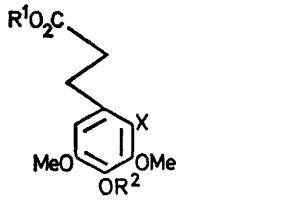
Irradiation of compound (8) with a Riko 400 W mercury lamp (Pyrex filter) was carried out in aqueous alcoholic solution in the presence of sodium hydroxide and sodium iodide at room temperature with stirring for 8 h to give (±)-androcymbine (1) in 0·5% yield, characterised as its methiodide. The structure of this compound was confirmed as follows.

Mass spectrometry (M^+, 371) of the free base and microanalysis of its methiodide confirmed the formula $C_{21}H_{25}NO_5$. The i.r. spectrum ($CHCl_3$) showed bands at 1660, 1635, and 1613 cm^{-1} characteristic of a cross-conjugated cyclohexadienone system, and the u.v. spectrum also supported the presence of this system.

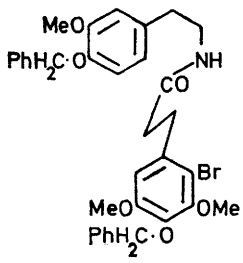
The n.m.r. spectrum ($CDCl_3$) showed one *N*-methyl, one enolic *O*-methyl, and two other *O*-methyl resonances; signals for two olefinic and one aromatic proton were



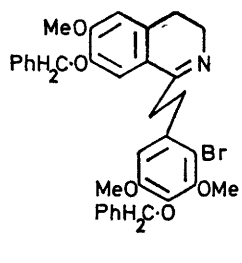
(11)



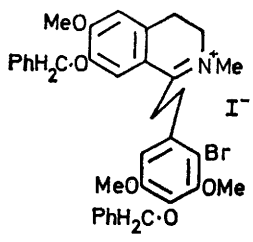
(12) R^1 = R^2 = X = H
(13) R^1 = Me, R^2 = X = H
(14) R^1 = Me, R^2 = H, X = Br
(15) R^1 = Me, R^2 = CH_2Ph, X = Br



(16)



(17)



(18)

observed at τ 3·76 (2H, s) and 3·23 (1H, s), respectively. Direct comparison (i.r., u.v., and n.m.r. spectra) with natural androcymbine, provided by Professor F. Šantavý, revealed the compounds to be identical.

When the foregoing photolysis was done without sodium iodide, it afforded only (±)-multifloramine (10), the (−)-isomer of which has been isolated from *Kreysigia multiflora*.[12] Its u.v. (MeOH) spectrum showed typical absorption [12,13] at 261 and 291 nm, and the n.m.r. ($CDCl_3$) spectrum revealed the expected signals for four methyl groups at τ 7·66, 6·50, and 6·13 (2 × Me) and two aromatic protons at τ 3·45 and 3·4. These data were identical with those for an authentic sample.[13]

EXPERIMENTAL

M.p.s were determined with a Yanagimoto microapparatus (MPS 2). I.r. spectra were measured with a Hitachi EPI-3 recording spectrophotometer, u.v. spectra with a Hitachi EPS-3 recording spectrophotometer, and n.m.r.

[8] T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem and Ind.*, 1971, 818; *J. Chem. Soc.* 1971, 2446.
[9] T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Comm.*, 1971, 724.
[10] T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Tetrahedron*, in the press.
[11] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, 1968, **33**, 690.
[12] A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 450.
[13] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1970, 382.

spectra with a Hitachi R-20 spectrometer, with tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-7 spectrometer.

Methyl 2-Bromo-4-hydroxy-3,5-dimethoxyphenylpropionate (14).—A solution of 4-hydroxy-3,5-dimethoxyphenylpropionic acid (12) [11] (4·0 g) and concentrated sulphuric acid (0·4 ml) in methanol (50 ml) was heated on a water-bath for 10 h. Evaporation left a viscous syrup, an aqueous solution of which was made basic with saturated sodium hydrogen carbonate and extracted with ether. The extract was washed with saturated sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated to give methyl 4-hydroxy-3,5-dimethoxyphenylpropionate (13) (3 g) as a pale brownish viscous syrup, $\nu_{max.}$ ($CHCl_3$) 3500 (OH) and 1726 cm^{-1} (C=O), τ ($CDCl_3$) 6·36 (3H, s, CO_2Me), 6·19 (6H, s, 2 × OMe), and 3·61 (2H, s, ArH). To a mixture of the ester (13) (2·4 g), potassium acetate (1 g), and chloroform (24 ml) a solution of bromine (1·6 g) in chloroform (4 ml) was added dropwise during 20 min at 20° with stirring, and stirring was continued for a further 1 h at the same temperature. After decomposition of the excess of bromine with saturated sodium thiosulphate solution, the chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to afford the *ester* (14) as a brown oil (2·2 g), b.p. 182—183° at 0·7 mmHg (Found: C, 44·8; H, 4·35. $C_{12}H_{15}BrO_5$ requires C, 45·15; H, 4·75%), $\nu_{max.}$ ($CHCl_3$) 3500 (OH) and 1725 cm^{-1} (C=O), τ ($CDCl_3$) 6·33 (3H, s, CO_2Me), 6·15 (3H, s, OMe), 6·11 (3H, s, OMe), and 3·4 (1H, s, ArH).

Methyl 4-Benzyloxy-2-bromo-3,5-dimethoxyphenylpropionate (15).—A mixture of the bromo-compound (14) (2·9 g), benzyl chloride (1·3 g), potassium carbonate (1·4 g), and methanol (30 ml) was heated under reflux for 15 h. Inorganic material was filtered off and the filtrate was evaporated to give the crude product (3·5 g), which was distilled *in vacuo* to afford the *ester* (15) as a viscous syrup (2 g), b.p. 170—172° at 0·4 mmHg (Found: C, 55·8; H, 5·05. $C_{19}H_{21}BrO_5$ requires C, 55·75; H, 5·15%), $\nu_{max.}$ ($CHCl_3$) 1722 cm^{-1} (C=O), τ ($CDCl_3$) 6·35 (3H, s, CO_2Me), 6·21 (3H, s, OMe), 6·13 (3H, s, OMe), 5·02 (2H, s, O·CH_2Ph), 3·4 (1H, s, ArH), and 2·72 (5H, s, O·CH_2·C_6H_5).

N-(4-*Benzyloxy*-3-*methoxyphenethyl*)-4-*benzyloxy*-2-*bromo*-3,5-*dimethoxyphenylpropionamide* (16).—A mixture of 4-benzyloxy-3-methoxyphenethylamine (11) (3·8 g) and the ester (15) (2·5 g) was heated at 180° for 2·5 h under a current of nitrogen. The cooled mixture was dissolved in chloroform; the solution was washed with 10% hydrochloric acid, 5% sodium hydroxide, and water, dried (Na_2SO_4), and evaporated to leave a brown viscous syrup, which was subjected to silica gel (30 g) chromatography. Elution with chloroform gave the amide (16) (2·7 g) as a pale yellow viscous syrup. Methanol (0·5 ml) was added to induce crystallisation. Filtration, followed by recrystallisation from benzene–hexane, gave yellow *needles*, m.p. 100—101° (Found: C, 64·1; H, 5·8; N, 2·25. $C_{34}H_{36}BrNO_6$ requires C, 64·35; H, 5·7; N, 2·2%), $\nu_{max.}$ ($CHCl_3$) 1660 cm^{-1} (C=O), τ ($CDCl_3$) 6·28 (3H, s, OMe), 6·22 (3H, s, OMe), 6·17 (3H, s, OMe), 5·05 (2H, s, O·CH_2Ph), and 4·96 (2H, s, O·CH_2Ph).

7-*Benzyloxy*-1-(4-*benzyloxy*-2-*bromo*-3,5-*dimethoxyphenethyl*)-3,4-*dihydro*-6-*methoxyisoquinoline* (17).—A mixture of the amide (16) (3 g), phosphoryl chloride (3 ml), and dry chloroform (30 ml) was refluxed for 1·5 h and the solvent was then distilled off. The residue was poured into an excess of hexane and the separated solid afforded the 3,4-*dihydroisoquinoline* (17) *hydrochloride* (2·5 g) as needles, m.p. 148—149° (from chloroform–hexane) (Found: C, 62·5; H, 5·7; N, 2·15. $C_{34}H_{34}BrNO_5$,HCl requires C, 62·65; H, 5·25; N, 2·15%), $\nu_{max.}$ ($CHCl_3$) 1642 cm^{-1} ($C=\overset{+}{N}$).

7-*Benzyloxy*-1-(4-*benzyloxy*-2-*bromo*-3,5-*dimethoxyphenethyl*)-3,4-*dihydro*-6-*methoxyisoquinoline Methiodide* (18).—To the 3,4-dihydroisoquinoline (17) [prepared from the hydrochloride (2·5 g)] was added methyl iodide (6 ml), and the mixture was set aside overnight at room temperature. The excess of methyl iodide was then distilled off and the residue was recrystallised from methanol–ether to give the *methiodide* (18) as pale brown needles (2·5 g), m.p. 121—123° (Found: C, 55·35; H, 5·15; N, 2·0. $C_{34}H_{34}BrNO_5$,CH_3I requires C, 55·4; H, 4·9; N, 1·85%), $\nu_{max.}$ ($CHCl_3$) 1627 ($C=\overset{+}{N}$).

7-*Benzyloxy*-1-(4-*benzyloxy*-2-*bromo*-3,5-*dimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*methylisoquinoline* (9).—To a stirred solution of the methiodide (18) (2·5 g) in methanol (150 ml), sodium borohydride (2·5 g) was added in small portions within 30 min. Stirring was continued for 1 h, the solvent was evaporated off, and the residue was diluted with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The remaining syrup was distilled *in vacuo* to give a viscous syrup (9) (1·7 g), b.p. 230—233° at 0·05 mmHg (Found: N, 2·2. $C_{35}H_{38}BrNO_5$ requires N, 2·3%), τ ($CDCl_3$) 7·57 (3H, s, NMe), 6·29 (3H, s, OMe), 6·22 (3H, s, OMe), 6·19 (3H, s, OMe), 5·09 (2H, s, O·CH_2Ph), 5·01 (2H, s, O·CH_2Ph), and 3·58, 3·51, and 3·44 (3H, each s, ArH).

1-(2-*Bromo*-4-*hydroxy*-3,5-*dimethoxyphenethyl*)-1,2,3,4-*tetrahydro*-7-*hydroxy*-6-*methoxy*-2-*methylisoquinoline* (8).—A mixture of the isoquinoline (9) (2·2 g), concentrated hydrochloric acid (25 ml), and ethanol (25 ml) was refluxed for 3 h. The solvent was evaporated off and the residue was basified with 10% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a pale brown viscous syrup (1·4 g), $\nu_{max.}$ ($CHCl_3$) 3500 cm^{-1} (OH), τ ($CDCl_3$) 7·56 (3H, s, NMe), 6·22 (9H, s, 2 × OMe), 4·6br (2H, s, 2 × OH), and 3·68, 3·54, and 3·44 (3H, each s, ArH), which was used without purification.

Photolysis of the Isoquinoline Derivative (8).—(*a*) A cooled mixture of the isoquinoline (8) (1·4 g), sodium hydroxide (0·8 g), sodium iodide (0·8 g), ethanol (50 ml), and water (850 ml) was irradiated for 7 h with a Riko 400 W high-pressure mercury lamp (Pyrex filter). After the addition of an excess of ammonium chloride, the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave a brownish syrup (1·1 g), which was chromatographed on silica gel (25 g) with chloroform [fractions (50 ml) 1—20, monitored by i.r. and u.v. spectra] and chloroform–methanol (99 : 1 v/v; fractions 21—72) as eluants. Fractions 49—62 yielded a brown viscous syrup (41 mg), which was again chromatographed on alumina (5 g); the column was eluted successively with benzene [fractions (50 ml) 1—4], benzene–chloroform (95 : 5 v/v; fractions 5—12), benzene–chloroform (90 : 10 v/v; fractions 13—16), benzene–chloroform (80 : 20 v/v; fractions 17—23), benzene–chloroform (70 : 30 v/v; fractions 24—32), benzene–chloroform (50 : 50 v/v; fractions 33—43), and benzene–chloroform (25 : 75 v/v;

fractions 43—53). Fractions 45—52 were combined and distilled to give (±)-androcymbine (1) (7 mg) as a pale yellow viscous syrup; its methiodide gave pale yellow *needles*, m.p. 246—248° (from methanol–ether) (Found: C, 51·65; H, 5·6; N, 2·95. $C_{21}H_{25}NO_5,CH_3I$ requires C, 51·45; H, 5·5; N, 2·75%), $\lambda_{max.}$ (MeOH) (free base) 240 279 nm (log ε 4·18 and 3·62), $\nu_{max.}$ ($CHCl_3$) 3500 (OH), 1660, 1635, and 1613 cm^{-1} (cyclohexadienone), τ ($CDCl_3$) 7·62 (3H, s, NMe), 6·39 (3H, s, OMe), 6·19 (3H, s, OMe), 5·99 (3H, s, OMe), 3·76 (1H, s, ArH), and 3·76 and 3·23 (2H, each s, olefinic H), *m/e* 371·171 (M^+; $C_{21}H_{25}NO_5$ requires *M*, 371·173).

(*b*) A mixture of the isoquinoline (8) (2·26 g), sodium hydroxide (2·5 g), ethanol (20 ml), and water (850 ml) was irradiated under the same conditions as in (*a*). The crude product (1·9 g) was chromatographed on silica gel (50 g) with chloroform containing 3% methanol as eluant (inspection by t.l.c. and i.r. and u.v. spectra) to give (±)-multifloramine (10) (34 mg), m.p. 190° (lit.,[13] 190°) (from ether–hexane), $\lambda_{max.}$ (MeOH) 261 and 291 nm (log ε 4·25 and 4·025), $\nu_{max.}$ ($CHCl_3$) 3450 cm^{-1} (OH), τ ($CDCl_3$) 7·66 (3H, s, NMe), 6·5 (3H, s, OMe), 6·13 (6H, s, 2 × OMe), and 3·45 and 3·4 (2H, each s, ArH). The spectral data were identical with those of an authentic sample.[13]

We thank Professor F. Šantavý, Palacký University, Czechoslovakia, for a gift of natural androcymbine. We also thank Mr. T. Ohuchi, Miss Y. Tadano, Miss A. Ujiie, Miss A. Kawakami, Miss C. Yoshida, Miss R. Kato, Miss T. Yoshida, and Miss R. Suzuki for microanalyses and spectral measurements.

[1/1348 *Received*, *August 2nd*, 1971]