A Novel Synthesis of an Ochotensine-type Isoquinoline By Thermolysis

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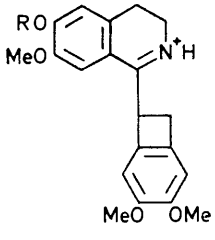
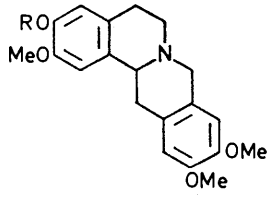
A novel synthesis of an ochotensine-type isoquinoline, by thermolysis of a benzocyclobutene intermediate, is described.

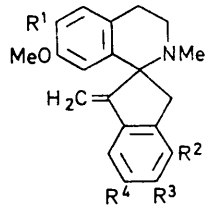
RECENTLY we described the preparation of (±)-xylopinine (2) and (±)-discretine (3) from the benzocyclobutenyl precursor (1) by thermal rearrangement.[1] As an extension of this method, we now report a novel synthesis of the spiro-benzylisoquinoline (4), which is structurally related to the alkaloid ochotensine (5).



(1)



(2) R = Me
(3) R = H



(4) $R^1 = R^3 = R^4 = OMe, R^2 = H$
(5) $R^1 = OH, R^2R^3 = O{\cdot}CH_2{\cdot}O, R^4 = H$
(6) $R^1 = OMe, R^2 = H, R^3 = R^4 = OH$

Ochotensine (5) is the parent of a small family of isoquinoline alkaloids found in *Corydalis ochotensis*. Degradative [2] and synthetic [3] investigations have confirmed its unique skeletal structure.

Consideration of the proposed mode of biogenesis and the model biogenetic transformation reported by Shamma and Jones [4] [smooth conversion of the protoberberine methide (7) *via* (9) into the diphenol (6) in basic aqueous solution] led us to prepare the 1-benzocyclobutenylisoquinolinium salt (10) as a key intermediate for the synthesis of an ochotensine-type compound (4). The rationale for the synthesis of (4) was the expectation that compound (10) would thermally rearrange *via* the *o*-quinodimethane (8b), since this intermediate is the dimethyl derivative of (8a), which was the postulated intermediate in the synthesis by Shamma and Jones.[4]

Treatment of the known cyanobenzocyclobutene (11) [1a,5] with methyl iodide in the presence of sodium amide[6] in refluxing benzene for 30 h afforded the methyl-substituted derivative (12) in 41% yield, accompanied by 23·2% of the starting material. Hydrolysis of (12) was readily accomplished by the procedure of Cava [7] to provide the acid (13) in 82·4% yield. Condensation of (13) with an equimolar amount of 3,4-dimethoxy-*N*-methylphenethylamine in the presence of dicyclo-

[1] T. Kametani, K. Ogasawara, and T. Takahashi, (*a*) *J.C.S. Chem. Comm.*, 1972, 675; (*b*) *Tetrahedron*, 1973, **29**, 73; (*c*) T. Kametani, Y. Hirai, F. Satoh, K. Ogasawara, and K. Fukumoto, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 907.

[2] S. McLean and M.-S. Lin, *Tetrahedron Letters*, 1964, 3819.

[3] (*a*) S. McLean, M.-S. Lin, and J. Whelan, *Tetrahedron Letters*, 1968, 2425; (*b*) H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc.* (*C*), 1968, 3051; (*c*) T. Kametani S. Takano, S. Hibino, and T. Terui, *J. Heterocyclic Chem.*, 1969, **6**, 49.

[4] M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 4009; 1970, **92**, 4943.

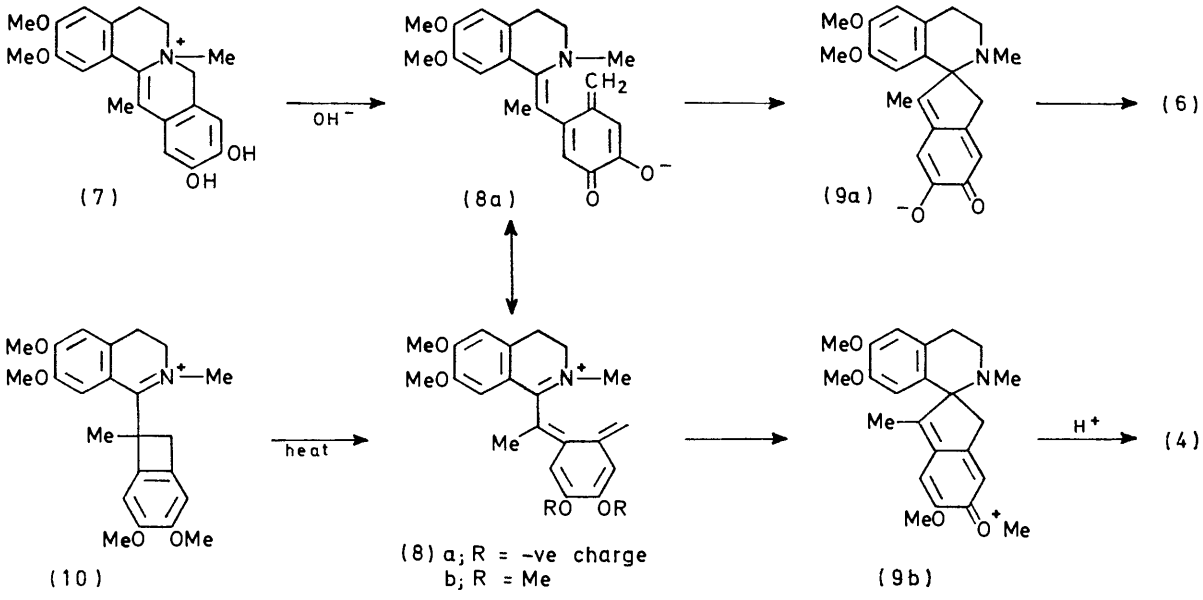
[5] I. L. Klundt, *Chem. Rev.*, 1970, **70**, 471.

[6] J. A. Skorcz and F. E. Kaminski, *J. Medicin. Chem.*, 1965, **8**, 732.

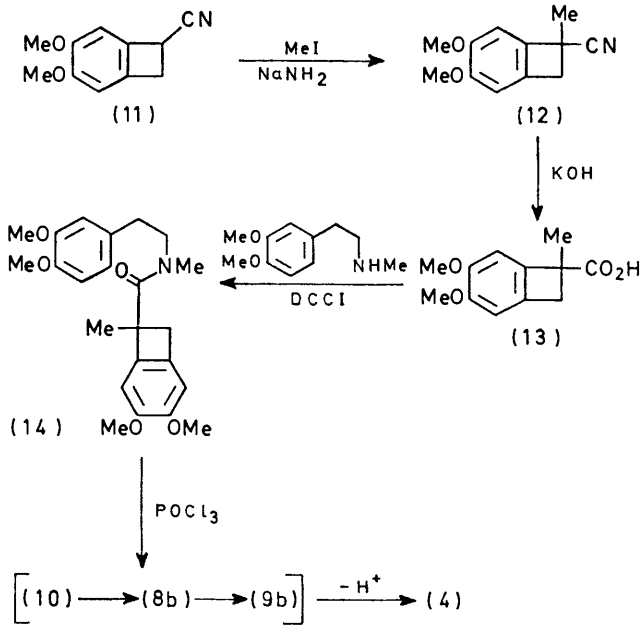
[7] M. P. Cava and M. J. Mitchell, *J. Org. Chem.*, 1962, **27**, 631.

hexylcarbodi-imide [8] in methylene chloride at room temperature gave the amide (14) in 51·6% yield.

Bischler–Napieralski reaction of the amide (14) with 2 mol. equiv. of phosphoryl chloride in boiling benzene for 22 h did not yield the expected intermediate (10), but afforded the spiro-benzylisoquinoline (4) in 14·0% yield,



accompanied by 35% of the starting amide (14). The formation of (4) was confirmed by its n.m.r. spectrum, which showed two sharp singlets at δ 4·85 and 5·52, typical of the exocyclic methylene group of ochotensine-type compounds.[2]



This transformation represents a convenient entry into the ochotensine class of alkaloids.

[8] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.

EXPERIMENTAL

N.m.r. spectra were recorded with Hitachi H-60 and JNM PS-100 spectrometers, and mass spectra with a Hitachi RMU-7 spectrometer.

4,5-Dimethoxy-1-methylbenzocyclobutene-1-carbonitrile (12).—To a mixture of the nitrile (11) [1b] (21·9 g, 116 mmol), methyl iodide (33·09 g, 232 mmol), and dry benzene (22 ml), sodamide (9 g, 231 mmol) was added in portions at less than 40°. The mixture was then refluxed for 30 h with stirring, cooled and poured onto water. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on silica gel (400 g) with benzene–chloroform (3 : 1) to give a crystalline mass. Recrystallisation from ethanol afforded the *nitrile* (12) as needles (9·6 g, 41·0%), m.p. 72·5—73° (Found: C, 70·5; H, 6·5; N, 6·65. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·54; N, 6·9%), $\nu_{max.}$ ($CHCl_3$) 2220 cm^{-1}, δ($CDCl_3$) 1·73 (3H, s, CMe) 3·41 (2H, dd, separation 21 Hz, *J* 14 Hz), 3·84 (6H, s, 2 × OMe), and 6·68 and 6·75 (2H, each s, 2 × aromatic H), *m/e* 203 (M^+).

4,5-Dimethoxy-1-methylbenzocyclobutene-1-carboxylic Acid (13).—A mixture of the nitrile (12) (500 mg, 2·46 mmol) and saturated ethanolic potassium hydroxide solution (2·1 ml) was set aside for 20 h at room temperature, then was refluxed with more water (0·7 ml). After cooling, the mixture was poured into water (17·5 ml) and made acidic with dilute hydrochloric acid. The crude material which separated afforded the *acid* (13) as needles (450 mg, 82·4%), m.p. 91·5—92° (from benzene–hexane) (Found: C, 62·5; H, 6·55. $C_{12}H_{14}O_4,0{\cdot}5H_2O$ requires C, 62·3; H, 6·55%), $\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1}, δ ($CDCl_3$) 1·68 (3H, s, CMe), 3·21 (2H, dd, separation 29 Hz, *J* 14 Hz), 3·84 (6H, s, 2 × OMe), 6·71 and 6·75 (2H, each s, 2 × aromatic H), and 8·08br (1H, s, disappeared with D_2O ,CO_2H), *m/e* 222 (M^+).

N-3,4-Dimethoxyphenethyl-4,5-dimethoxy-N,1-dimethylbenzocyclobutene-1-carboxamide (14).—To a solution of 3,4-dimethoxy-*N*-methylphenethylamine (485·7 mg, 2·4 mmol) and the acid (13) (553·2 mg, 2·4 mmol) in methylene chloride (10 ml) was added dicyclohexylcarbodi-imide

(536·4 mg, 2·6 mmol) with stirring at room temperature. After stirring for 3 h at room temperature the separated solid was filtered off and the filtrate was washed with 2% hydrochloric acid, water, 5% sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to give an oil (1 g). This was chromatographed on silica gel (40 g) with methylene chloride to afford the *amide* (14) as an oil (510·5 mg, 51·6%) (Found: C, 68·6; H, 7·55; N, 3·4. $C_{23}H_{29}NO_5$ requires C, 69·15; H, 7·32; N, 3·5%), $\nu_{max.}$ 1620 cm^{-1}, $\delta(CDCl_3)$ 1·64 (3H, s, CMe), 2·91 (3H, s, NMe), 2·60—3·70 (6H, m, 3 × CH_2), 3·80 (9H, s, 3 × OMe), 3·83 (3H, s, OMe), 6·62 (1H, s, aromatic H), 6·72 (3H, s, 3 × aromatic H), and 6·95 (1H, s, aromatic H), *m/e* 399 (M^+).

1′,2,2′,3,3′,4′-Hexahydro-5,6,6′,7′-tetramethoxy-2′-methyl-1-methylenespiro[indene-2,1′-isoquinoline] (4).—A mixture of the amide (14) (1 g, 2·5 mmol), phosphoryl chloride (766·8 mg, 5·0 mmol), and dry benzene (30 ml) was refluxed for 22 h. Separation of the organic layer by decantation, followed by evaporation, gave a residue, which was made alkaline with ammonia and extracted with methylene chloride. The extract was washed with water, dried (K_2CO_3), and evaporated to give an oil (550 mg), which was chromatographed on silica gel (15 g). Elution with methylene chloride (30 ml) gave the starting amide (14) (345·9 mg, 35·0%). Further elution with methylene chloride (50 ml) and chloroform–methylene chloride (1 : 3) afforded crude (4) (100 mg). The material left after decantation was made basic with ammonia and extracted with methylene chloride. The extract was washed with water, dried (K_2CO_3), and evaporated to give a brown oil (370 mg), which was chromatographed on silica gel to crude (4) (50 mg).

The combined crude product was rechromatographed on silica gel with methylene chloride as eluant to give a pale brown amorphous *powder* (4) (132·5 mg, 14·0%), m.p. 46—49° (Found: C, 72·65; H, 7·55; N, 3·3. $C_{23}H_{27}NO_4$ requires C, 72·4; H, 7·15; N, 3·65%), $\nu_{max.}$ ($CHCl_3$) 850 cm^{-1}, $\delta(CDCl_3)$ 2·16 (3H, s, NMe), 2·66—3·56 (6H, m, 3 × CH_2), 3·59, 3·82, 3·88, and 3·92 (12H, each s, 4 × OMe), 4·85 (1H, s, vinylic H), 5·52 (1H, s, vinylic H), and 6·24, 6·49, 6·71, and 6·97 (4H, each s, 4 × aromatic H), *m/e* 381 (M^+).

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