Studies on the Syntheses of Heterocyclic Compounds. Part 796.† A New Synthesis of Isochroman-3-ones from Benzocyclobutenes; an Application to a Total Synthesis of Sendaverine

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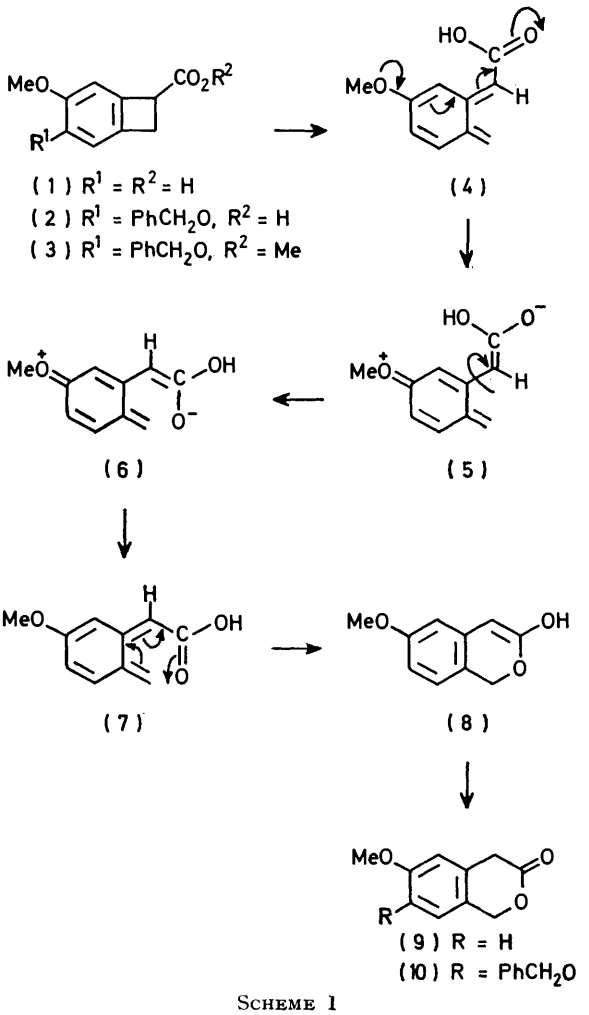
Thermolysis of the methoxylated benzocyclobutene-1-carboxylic acids (1) and (2) forms the isochroman-3-ones (9) and (10); compound (10) has been converted into the isoquinoline alkaloid sendaverine (20) *via* the *N*-(4-methoxybenzyl)-2-hydroxymethylphenylacetamide (17) and the *N*-(4-methoxybenzyl)-2-hydroxymethylphenethylamine (18).

BENZOCYCLOBUTENES [1] have been effectively utilised as starting materials for the synthesis of polycyclic natural products.[2] The key reaction in these syntheses is an inter- or intra-molecular cycloaddition reaction of *o*-quinodimethanes, generated *in situ* by the thermolysis of benzocyclobutenes, with olefins or imines.[3,4] Moreover, an electrocyclic reaction of *o*-quinodimethanes has been applied to the synthesis of protoberberine alkaloids [5] and the yohimbane system.[6] In the latter case, the diene system in *o*-quinodimethanes reacted with an imine group by a 6π process to give an isoquinoline ring, whereas most electrocyclic reactions of the 6π type have been found in hexatriene systems.[7,8] In this paper we report a new type of thermal electrocyclic reaction in the 6π system, consisting of C=C–C=C–C=O, derived from benzocyclobutene-1-carboxylic acids, to form a pyran derivative,[9] which corresponds to the reverse reaction of the conversion of isochroman-3-ones into benzocyclobutenes; [10] we also describe a total synthesis of the 2-benzylisoquinoline alkaloid sendaverine (20),[11,12] by application of this new reaction.

RESULTS AND DISCUSSION

Heating 5-methoxybenzocyclobutene-1-carboxylic acid (1) [6] at 150—160 °C for 45 min gave a neutral compound, m.p. 70—71 °C, molecular formula $C_{10}H_{10}O_3$, which showed a lactonic carbonyl absorption at 1 735 cm^{-1} in the i.r. spectrum ($CHCl_3$), and two pairs of methylene protons as singlets at δ 3.66 and 5.24 in the n.m.r. spectrum ($CDCl_3$). This indicated the product to be 6-methoxyisochroman-3-one (9), and the spectral data are identical to those reported for (9).[13] Formation of this product could be explained as follows; electrocyclic reaction of (1) provides the more stable *E*-form of the *o*-quinodimethane (4) [4,9,14] which by tautomerisation provides the *Z*-form (7), *via* intermediates (5) and (6).[15] The isochroman-3-one (9) could be formed by electrocyclic reaction of the 6π system in (7) by way of enol lactol (8). Thus we have discovered a new type of thermal 6π electrocyclic reaction, and our attention turned to the total synthesis of natural products by application of this reaction.

The key starting material, 4-benzyloxy-5-methoxybenzocyclobutene-1-carboxylic acid (2), was prepared by a standard method as follows.[5,6] 6-Bromobenzylisovanillin (11) [16] was subjected to Knoevenagel reaction with cyanoacetic acid in the presence of pyridine to give the α-cyanocinnamic acid (12) in 62% yield. This was reduced with sodium borohydride, followed by decarboxylation of the resulting dihydrocinnamic acid (13) by heating at 170 °C, to afford, in 64% yield, the phenylpropiononitrile (14). Treatment of the nitrile (14) with freshly prepared potassium amide in liquid ammonia



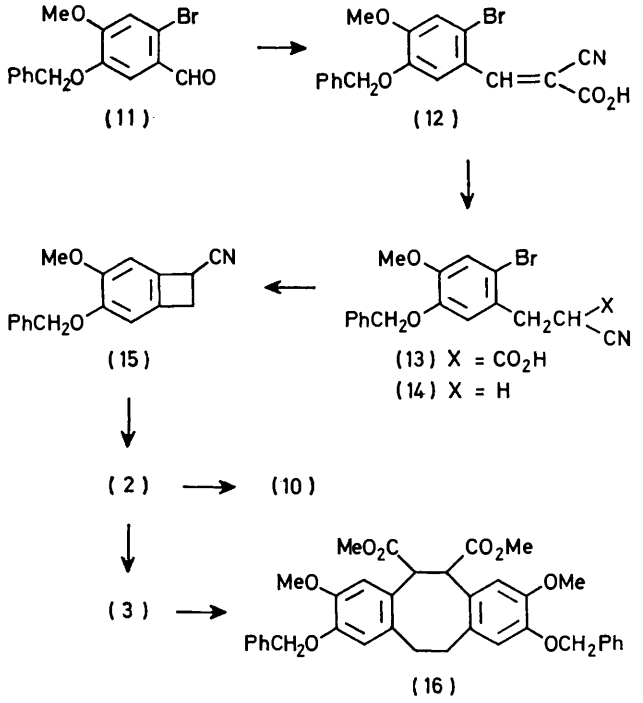
SCHEME 1

† Part 795, T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru, and T. Nakamura, *J. Pharm. Soc. Japan*, 1979, **99**, 752.

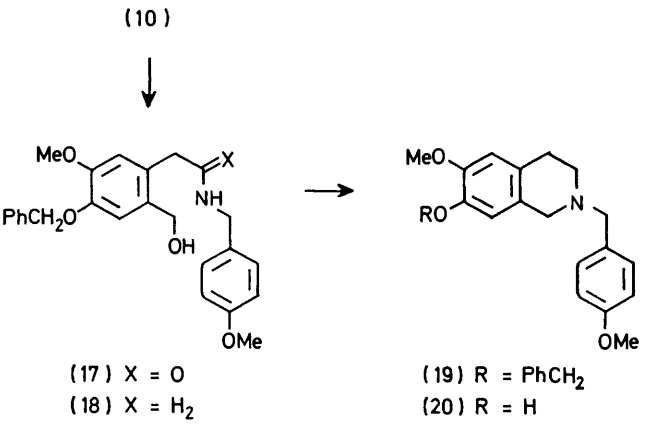
gave the 1-cyanobenzocyclobutene (15) in 67% yield, which on hydrolysis with ethanolic potassium hydroxide furnished the benzocyclobutene-1-carboxylic acid (2) in 91.5% yield. Methylation of this carboxylic acid with diazomethane yielded the corresponding ester (3).

Thermolysis of the benzocyclobutene-1-carboxylic acid (2) was carried out at 170 °C without solvent to give the expected isochroman-3-one (10) in 41.7% yield. However, the same reaction of the ester (3) surprisingly afforded a dimer (*m/e* 596), whose structure was tentatively assigned as (16) from spectroscopic evidence. This type of dimer has been previously prepared by Oppolzer,[17] and also in this laboratory,[18] by the thermolysis of 1-substituted benzocyclobutenes.

Conversion of this isochroman-3-one into a tetrahydroisoquinoline was carried out by the method of Brossi.[19] Heating the isochroman-3-one (10) with 4-methoxybenzylamine at 180 °C for 1 h gave the *N*-4-methoxybenzyl-2-hydroxymethylphenylacetamide (17), in 86.6% yield, showing hydroxy and secondary amide group absorption at 3 460, 3 350, and 1 650 cm^{-1} in the i.r. spectrum. Reduction of the amide (17) with lithium aluminium hydride in boiling tetrahydrofuran afforded the amino-alcohol (18), which, without purification, was treated with thionyl chloride in hot benzene and then with ammonia to produce, in 16% yield, *O*-benzylsendaverine (19), m.p. 92—93 °C, identical to an authentic sample [20] on the basis of its m.p. (lit.,[20] m.p. 92—93 °C), and i.r. and n.m.r. spectral comparison. Finally, debenzylation of (19) was carried out with ethanolic hydrochloric acid [20] giving sendaverine (20) in almost quantitative yield, also identical in all respects to an authentic sample.[11]



SCHEME 2



SCHEME 3

Thus, we have developed a new synthetic route to sendaverine, involving thermolysis of a benzocyclobutene through an isochroman-3-one, and this route could be applied to the synthesis of other types of isoquinoline alkaloids.

EXPERIMENTAL

M.p.s were taken with a Yanagimoto micro melting point apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 recording spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX 60 spectrometer, and mass spectra with a Hitachi M-52G.

6-Methoxyisochroman-3-one (9).—5-Methoxybenzocyclobutene-1-carboxylic acid (1) (200 mg) was heated at 150—160 °C for 45 min in a current of nitrogen, and the reaction product was then subjected to column chromatography on silica gel (20 g). Elution with chloroform gave an oil, which was purified by sublimation at 135—140 °C (3 mmHg) to afford the *isochroman-3-one* (9) (96 mg, 48%) as needles, m.p. 70—71 °C (lit.,[13] m.p. 70—71 °C) (Found: C, 67.5; H, 5.95. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.65%); $\nu_{max.}$ ($CHCl_3$) 1 735 cm^{-1} (CO); δ ($CDCl_3$) 3.66 (2 H, s, CH_2CO), 3.80 (3 H, s, OMe), 5.24 (2 H, s, CH_2O), and 6.73—7.06 (3 H, aryl).

β-(5-Benzyloxy-2-bromo-4-methoxy)-α-cyanocinnamic Acid (12).—A mixture of 6-bromobenzylisovanillin (11) (32 g), cyanoacetic acid (8.5 g), pyridine (100 ml), ammonium acetate (2.5 g), and toluene (250 ml) was heated under reflux using a Dean and Stark apparatus. After a calculated amount of water had been separated, the mixture was acidified with 10% HCl. The separated solid was extracted with ethyl acetate, and the extract was washed with water, dried (Na_2SO_4), and evaporated to give the *α-cyanocinnamic acid* (12) (24.1 g, 62%) as pale yellow needles (from ethyl acetate), m.p. 234—235 °C (Found: C, 55.9; H, 3.75; N, 3.45. $C_{18}H_{14}BrNO_4$ requires C, 55.7; H, 3.65; N, 3.6%); $\nu_{max.}$ (Nujol) 2 190 (CN) and 1 690 cm^{-1} (CO_2H); δ (DMSO) 3.94 (3 H, s, OMe), 5.12 (2 H, s, OCH_2Ph), 7.45 (6 H, br s, aryl and OCH_2Ph), 8.06 (1 H, s, aryl), and 8.50 (1 H, s, Ar–CH=C).

β-(5-Benzyloxy-2-bromo-4-methoxy)-α-cyanophenylpropionic Acid (13).—To a solution of the above cinnamic acid (12) (20 g) in a mixture of methanol (200 ml) and saturated aqueous sodium hydrogencarbonate (100 ml) was added in small portions sodium borohydride (10 g) with stirring at room temperature. After stirring for 0.5 h at room temperature, methanol was distilled off, and the residue was

diluted with water and then acidified with 10% hydrochloric acid. The separated solid was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated to give the *phenylpropionic acid* (13) (15.8 g, 78.6%) as needles (from ethanol–ether), m.p. 91—92 °C (Found: C, 52.45; H, 4.2; N, 3.4. $C_{18}H_{16}BrNO_4 \cdot H_2O$ requires C, 52.95; H, 3.9; N, 3.6%); $\nu_{max.}$ ($CHCl_3$) 2 250 (CN) and 1 735 cm^{-1} (CO_2H); δ (DMSO) 3.33—3.53 (3 H, m, $ArCH_2CH$), 3.94 (3 H, s, OMe), 5.20 (2 H, s, OCH_2Ph), 7.00 (1 H, s, aryl), 7.15 (1 H, s, aryl), and 7.38 (5 H, s, OCH_2Ph).

β-(5-Benzyloxy-2-bromo-4-methoxyphenyl)propiononitrile (14).—A solution of the phenylpropionic acid (13) (20 g) in dimethylacetamide (40 ml) was heated at 170 °C for 1 h, evolution of the calculated amount of carbon dioxide being observed. After the reaction, the mixture was poured into an excess of water and the separated oil was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *phenylpropiononitrile* (14) (14.4 g, 81.4%) as needles (from benzene–hexane), m.p. 120—121 °C (Found: C, 58.9; H, 4.65; N, 3.95. $C_{17}H_{16}BrNO_2$ requires C, 58.95; H, 4.6; N, 4.05%); $\nu_{max.}$ ($CHCl_3$) 2 250 cm^{-1} (CN); δ ($CDCl_3$) 2.45—3.30 (4 H, m, CH_2CH_2), 3.92 (3 H, s, OMe), 5.21 (2 H, s, OCH_2Ph), 6.96 (1 H, s, aryl), 7.28 (1 H, s, aryl), and 7.40 (5 H, s, OCH_2Ph); *m/e* 345 and 347 (M^+).

4-Benzyloxy-1-cyano-5-methoxybenzocyclobutene (15).—To a solution of potassium amide [from potassium (2.95 g) in liquid ammonia] in freshly distilled liquid ammonia (1 l) was added the phenylpropiononitrile (14) (5.9 g) in small portions and the mixture was stirred for 2 h at −33 °C. After the addition of crystalline ammonium chloride (16 g), the excess of ammonia was allowed to evaporate. The residue was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), evaporated, and the residue recrystallised from ethanol to give the *1-cyanobenzocyclobutene* (15) (3.05 g, 67.3%) as prisms, m.p. 101—102 °C (Found: C, 76.75; H, 5.7; N, 5.25. $C_{17}H_{15}NO_2$ requires C, 76.95; H, 5.7; N, 5.3%); $\nu_{max.}$ ($CHCl_3$) 2 245 cm^{-1} (CN); δ ($CDCl_3$) 3.50—3.73 (2 H, m, $ArCH_2CH$), 3.95 (3 H, s, OMe), 4.25 (1 H, t, *J* 4 Hz, ArCHCN), 5.25 (2 H, s, OCH_2Ph), 6.86 (1 H, s, aryl), 7.00 (1 H, s, aryl), and 7.48 (5 H, s, OCH_2Ph); *m/e* 265 (M^+).

4-Benzyloxy-5-methoxybenzocyclobutene-1-carboxylic Acid (2).—A solution of the 1-cyanobenzocyclobutene (15) (3 g) in a saturated ethanolic potassium hydroxide solution (30 ml) [21] was refluxed for 3 h. After the mixture had been poured into water (150 ml), the resulting aqueous layer was acidified with 10% HCl and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to give the *benzocyclobutene-1-carboxylic acid* (2) (2.94 g, 91.5%) as needles (from benzene), m.p. 124—126 °C (Found: C, 70.45; H, 5.63. $C_{17}H_{16}O_4 \cdot 0.33H_2O$ requires C, 70.35; H, 5.55%); $\nu_{max.}$ ($CHCl_3$) 1 700 cm^{-1} (CO_2H); δ ($CDCl_3$) 3.45 (2 H, d, *J* 4 Hz, $ArCH_2CH$), 3.95 (3 H, s, OMe), 4.25 (1 H, t, *J* 4 Hz, ArCHCN), 5.25 (2 H, s, OCH_2Ph), 6.90 (1 H, s, aryl), 7.00 (1 H, s, aryl), and 7.46 (5 H, s, OCH_2Ph); *m/e* 284 (M^+).

7-Benzyloxy-6-methoxyisochroman-3-one (10).—The above carboxylic acid (2) (2.97 g) was heated at 170 °C for 1 h under a nitrogen atmosphere and worked-up as described in the case of (9) to give the *isochroman-3-one* (10) (1.24 g, 41.7%) as pale yellow needles (from benzene–hexane), m.p. 140—141 °C (Found: C, 72.05; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.65%); $\nu_{max.}$ ($CHCl_3$) 1 735 cm^{-1} (CO); δ ($CHCl_3$–DMSO) 3.74 (2 H, s, CH_2CO), 4.00 (3 H, s, OMe), 5.26 (2 H, s, OCH_2Ph), 5.73 (2 H, s, $ArCH_2OCO$), 6.98 (1 H, s, aryl), 7.03 (1 H, s, aryl), and 7.60 (5 H, s, OCH_2Ph).

Methyl 4-Benzyloxy-5-methoxybenzocyclobutene-1-carboxylate (3).—An excess of diazomethane in ether was added to a solution of the benzocyclobutene-1-carboxylic acid (2) (100 mg) in methanol with ice-cooling, and the resulting mixture was set aside overnight at room temperature. After evaporation of all the solvents, the residue was dissolved in ether, and the organic layer was washed with 5% sodium hydrogencarbonate solution and water, dried (Na_2SO_4), and evaporated to give the *methyl ester* (3) (81 mg, 77.2%) as crystals, m.p. 106—107 °C (from ether–hexane) (Found: C, 72.2; H, 6.05. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.1%); $\nu_{max.}$ ($CHCl_3$) 1 700 cm^{-1} (CO_2Me); δ ($CDCl_3$) 3.31 (2 H, m, $ArCH_2CH$), 3.72 (3 H, s, CO_2Me), 3.87 (3 H, s, OMe), 4.12 (1 H, t, *J* 4 Hz, $ArCHCH_2$), 5.00 (2 H, s, OCH_2Ph), 6.62 (1 H, s, aryl), 6.72 (1 H, s, aryl), and 7.35 (5 H, s, OCH_2Ph).

Thermolysis of Methyl 4-Benzyloxy-5-methoxybenzocyclobutene-1-carboxylate (3).—The ester (3) (75 mg) was heated at 170 °C for 2 h in a current of nitrogen. After cooling, the reaction product was dissolved in chloroform. The organic layer was washed with 5% sodium hydrogencarbonate solution and water, dried (Na_2SO_4), and evaporated. The residue was subjected to column chromatography on silica gel and eluted with hexane–benzene (1 : 1 v/v) to give the *cyclo-octadiene* (16) (19.5 g, 13%) as crystals (from hexane), m.p. 78—79 °C (Found: C, 72.25; H, 6.15. $C_{36}H_{36}O_8$ requires C, 72.45; H, 6.1%); $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1} (CO_2Me); δ ($CDCl_3$) 3.10 (4 H, br, 2 × $ArCH_2CH$), 3.68 (6 H, s, 2 × CO_2Me), 3.78 (6 H, s, 2 × OMe), 4.66 (2 H, br s, 2 × $ArCH_2CHAr$), 5.03 (4 H, s, 2 × OCH_2Ph), 6.33 (2 H, s, 2 × aryl), 6.45 (2 H, s, 2 × aryl), and 7.26 (10 H, s, 2 × OCH_2Ph); *m/e* 596 (M^+).

N-(4-Methoxybenzyl)-4-benzyloxy-2-hydroxymethyl-5-methoxyphenylacetamide (17).—A mixture of the isochroman-3-one (10) (0.5 g) and 4-methoxybenzylamine (0.425 g) was heated at 180 °C for 1 h in a current of nitrogen and then dissolved in benzene. The benzene solution was washed with 10% hydrochloric acid and water, dried (Na_2SO_4), and the solvent distilled off to give the *amide* (17) (0.615 g, 86.6%) as needles (from benzene–hexane), m.p. 128—129 °C (Found: C, 70.65; H, 6.25; N, 3.25. $C_{25}H_{27}NO_5 \cdot 0.25H_2O$ requires C, 70.5; H, 6.4; N, 3.3%); $\nu_{max.}$ ($CHCl_3$) 3 460 (OH), 3 350 (NH), and 1 650 cm^{-1} (CO); δ ($CDCl_3$) 3.35 (2 H, s, $ArCH_2CO$), 3.75 (3 H, s, OMe), 3.82 (3 H, s, OMe), 4.13 (1 H, d, *J* 19 Hz, ArCHH–NH), 4.46 (1 H, d, *J* 19 Hz, ArCHH–NH), 4.51 (2 H, s, $ArCH_2OH$), 5.10 (2 H, s, OCH_2Ph), and 6.69—7.53 (11 H, aryl); *m/e* 421 (M^+).

O-Benzylsendaverine (19).—To a suspension of lithium aluminium hydride (100 mg) in dry tetrahydrofuran (20 ml) was added dropwise a solution of the amide (17) (200 mg) in dry tetrahydrofuran with stirring at room temperature, and the mixture was refluxed for 6 h with stirring in a current of nitrogen. After the reaction, the excess of reagent was decomposed with wet ether and the separated solid was filtered off. The filtrate was evaporated to leave a syrup, column chromatography of which on silica gel, using methanol–chloroform (1 : 9 v/v) as eluant, gave the *amine* (18) (90.3 mg, 46.55%) as a syrup; δ ($CDCl_3$) 2.84 (4 H, m, $ArCH_2CH_2N$), 3.62 (2 H, s, $ArCH_2N$), 3.77 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.48 (2 H, s, $ArCH_2OH$), 5.13 (2 H, s, OCH_2Ph), 6.84 (2 H, d, *J* 8 Hz, aryl), 6.72 (1 H, s, aryl), 7.02 (2 H, d, *J* 8 Hz, aryl), 7.11 (1 H, s, aryl), and 7.44 (5 H, s, OCH_2Ph); *m/e* 407 (M^+).

To a solution of the crude amine (18) (55 mg) in dry benzene (10 ml) was added five drops of thionyl chloride, and the mixture was refluxed for 2 h. After evaporation of the solvent and reagent *in vacuo*, the residue was dissolved in chloroform. This solution was shaken vigorously with 10% ammonia, then washed with water, dried (Na_2SO_4), and evaporated to leave a syrup, which was purified by column chromatography on silica gel. The chloroform–methanol (99 : 1 v/v) eluate gave *O*-benzylsendaverine (19) (18 mg, 34.24%) as prisms (from hexane), m.p. 92—93 °C (lit.,[20] m.p. 92—93 °C), whose i.r. and n.m.r. spectra were superimposable upon those of the authentic sample.[20]

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