Regioselectivity in the Thermal 1,2-Cycloaddition of Benzocyclobutenes to 3,4-Dihydroisoquinolines

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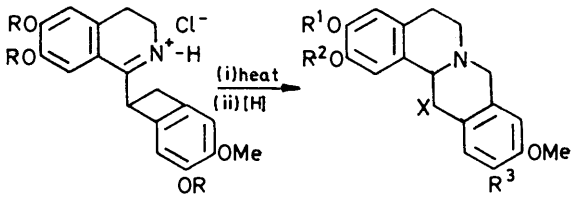
Thermolysis of 1,2-dihydro-4,5-dimethoxybenzocyclobuten-1-ol (7a) in the presence of 3,4-dihydro-6,7-dimethoxyisoquinoline (8), followed by reduction of the product with sodium borohydride, gave the berbine alkaloid xylopinine (2a). Regioselectivity in the cycloaddition of benzocyclobutenes to the 3,4-dihydroisoquinoline system is described.

It is well known that heating benzocyclobutenes [1] produces reactive *o*-quinodimethanes, which condense intra- or inter-molecularly with olefins to give tetralin derivatives.[2,3] We have extended this reaction to the synthesis of the isoquinoline ring system by intramolecular condensation of the *o*-quinodimethane with an imine function, and have developed a new synthetic method for the berbine-type alkaloids, xylopinine (2a), discretine (2b), and coreximine (2c), involving thermolysis of the resulting (1,2-dihydrobenzocyclobuten-1-yl)-3,4-dihydroisoquinolines (1), followed by reduction.[4]



(1)

(2) a; $R^1=R^2=Me$, $R^3=OMe$, X = H
b; $R^1=H$, $R^2=Me$, $R^3=OMe$, X = H
c; $R^1=Me$, $R^2=H$, $R^3=OH$, X = H
d; $R^1=R^2=Me$, $R^3=H$, X = H
e; $R^1=R^2=Me$, $R^3=OMe$, X = CN
f; $R^1=R^2=Me$, $R^3=NH_2$, X = H

Scheme 1

This type of berbine formation suggested that it was possible to synthesise isoquinoline derivatives by intermolecular cycloaddition of *o*-quinodimethanes to imines.[5] We therefore investigated the reaction of the benzocyclobutenols (7) with a 3,4-dihydroisoquinoline and here report a new and regioselective total synthesis of xylopinine (2a).

1,2-Dihydro-4,5-dimethoxybenzocyclobutene-1-carbonitrile (3a) [4a] was treated with 33% hydrogen peroxide and sodium hydroxide at 60° to give the amide (4a), which was subjected to a Hofmann rearrangement with potassium hypobromite at 70° to afford the amine (5a). Oxidation of this amine with potassium permanganate in the presence of calcium sulphate at room temperature for 1 h yielded the cyclobutenone (6a), which was reduced with sodium borohydride at 0° to give the benzocyclobutenol (7a).

A mixture of the benzocyclobutenol (7a) and 3,4-dihydro-6,7-dimethoxyisoquinoline (8) in benzene was heated for 6 h to give the expected protoberberine (12a) in 52% yield which was easily characterised as the chloride, identical with authentic material.[4a] Reduction of this chloride with sodium borohydride afforded xylopinine (2a), spectroscopically identical with an authentic sample.[4a]

The mechanism of formation of the protoberberine (12a) could involve cycloaddition of the *o*-quinodimethane (9a), derived from (7a), to the 3,4-dihydroisoquinoline (8) to give the 8-hydroxyberbine (10a), which could then undergo dehydration followed by thermal dehydrogenation. However, another possible pathway through the intermediate (11a) was also envisaged. In order to clarify which was the preferred route, we examined the thermolysis of 1,2-dihydro-5-methoxybenzocyclobuten-1-ol (7b) [synthesised from (3b) through compounds (4b), (5b), and (6b) by the same method as for (7a)] in the presence of the 3,4-dihydroisoquinoline (8). In a cycloaddition of the *o*-quinodimethane (9b) to the 3,4-dihydroisoquinoline (8), attack by the methylene system on C-1 of structure (8) (first mechanism) would lead to the 10-methoxyprotoberberine (12b), whereas attack by the methine system would result in the 11-methoxyprotoberberine (12c). Only compound (12b) was formed. This product (12b) was identified by spectral comparison of the reduction product with the 2,3,10-trimethoxyberbine (2d), which was synthesised by deamination of 11-amino-2,3,10-trimethoxyberbine (2f) [6] (by treatment with nitrous acid and then hypophosphorous acid). Therefore, the reaction of the benzocyclobutenols (7) with 3,4-dihydroisoquinoline (8) proceeds regioselectively to form the 8-hydroxyberbines (10) by the first reaction mechanism.

From this finding and from the formation of the 13-cyanoberbine (2e) [5] by cycloaddition of the 1-cyanobenzocyclobutene (3a) to the 3,4-dihydroisoquinoline (8), we conclude that the cycloaddition of the benzocyclobutenes to 3,4-dihydroisoquinolines proceeds regio-

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[5] T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *J. Org. Chem.*, 1974, **39**, 447.
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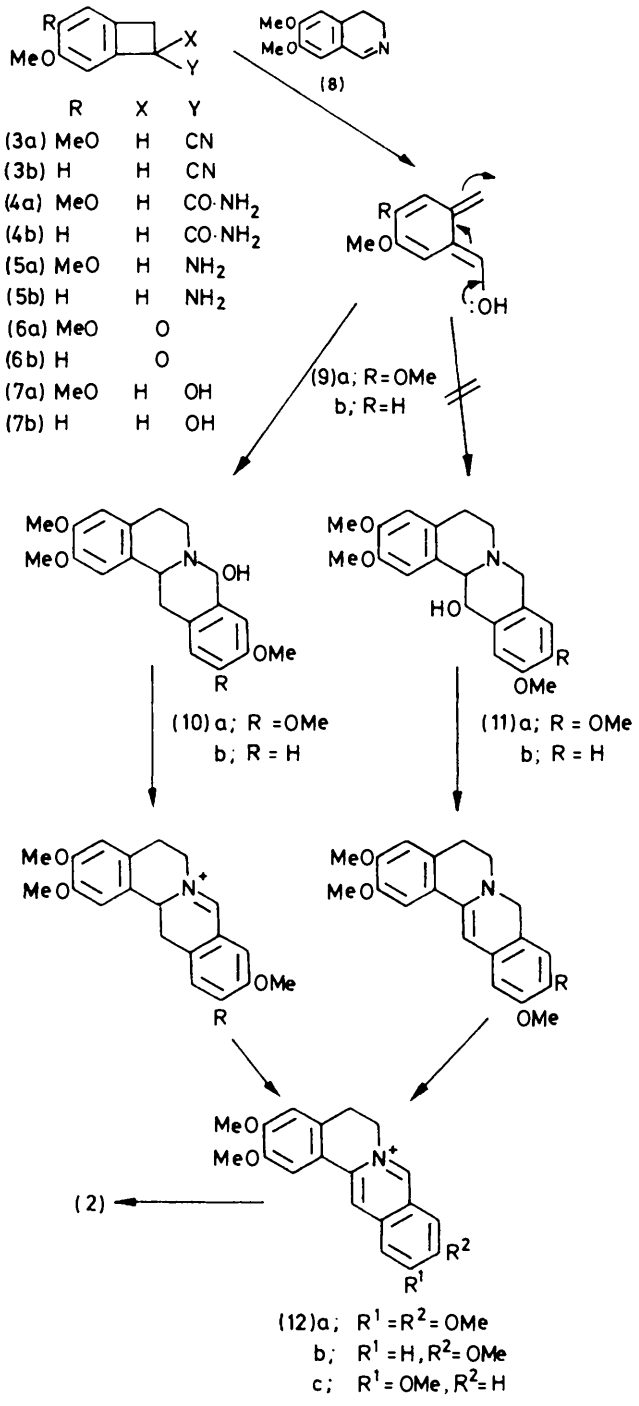
selectively and that the direction of cycloaddition depends on the *E*-effect of the substituent on the cyclobutene ring.



SCHEME 2

EXPERIMENTAL

M.p.s were measured with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were measured with a Hitachi 215 grating spectrophotometer, n.m.r. spectra with a Hitachi H-60 spectrometer (with tetramethylsilane as internal standard), mass spectra with a Hitachi RMU-7 spectrometer, and u.v. spectra with a Hitachi 124 spectrometer.

1,2-*Dihydro*-4,5-*dimethoxybenzocyclobutene*-1-*carboxamide* (4a).—1,2-Dihydro-4,5-dimethoxybenzocyclobutene-1-carbonitrile (3a) (1 g, 5·3 mmol) was added to 33% hydrogen peroxide (1·5 ml, 12 mmol) and 20% sodium hydroxide (1·5 ml), and the mixture was stirred for 15 min at room temperature. After addition of methanol (10 ml) at 15°, the mixture was stirred for 15 min at 60°, and then mixed with water (20 ml) to precipitate a solid, which was separated by filtration and recrystallised from dichloromethane–n-hexane to give *needles* (0·84 g, 76%), m.p. 146—147° (Found: C, 62·55; H, 6·1; N, 6·4. $C_{11}H_{13}NO_3,0{\cdot}25H_2O$ requires C, 62·4; H, 6·3; N, 6·3%), $\nu_{max.}$ (KBr) 3400 (NH_2), 3220 (NH_2), and 1668 cm^{-1} (CO), δ [$(CD_3)_2SO$] 3·13 (2H, d, *J* 3·5 Hz, CH_2), 3·66 (6H, s, 2 × OCH_3), 4·00 (1H, t, *J* 3·5 Hz, CH), 6·25 (1H, s, ArH), and 6·80 (1H, s, ArH).

1,2-*Dihydro*-5-*methoxybenzocyclobutene*-1-*carboxamide* (4b). — 1,2-Dihydro-5-methoxybenzocyclobutene-1-carbonitrile (3b) (0·25 g, 1·6 mmol) was similarly treated with 33% hydrogen peroxide (0·4 ml, 4·5 mmol) and 20% sodium hydroxide (0·4 ml, 2 mmol) to give the *amide* (4b) (0·21 g, 75%) as needles, m.p. 157—158° (from dichloromethane–n-hexane) (Found: C, 67·75; H, 6·5; N, 7·6. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·25; N, 7·9%), $\nu_{max.}$ ($CHCl_3$) 3520 (NH_2), 3410 (NH_2), and 1670 (CO) cm^{-1}, δ [$(CD_3)_2SO$] 3·16 (2H, d, *J* 3·5 Hz, CH_2), 3·68 (3H, s, OCH_3), 4·05 (1H, t, *J* 3·5 Hz, CH), 6·60—7·00 (3H, m, ArH), and 7·01—7·50br (2H, NH_2).

1-*Amino*-1,2-*dihydro*-4,5-*dimethoxybenzocyclobutene* (5a)—To a mixture of potassium hydroxide (0·35 g, 6·2 mmol), bromine (352 mg, 2·2 mmol), and water (3·3 ml) was added the amide (4a) (500 mg, 2·4 mmol) at 0°, and the mixture was stirred for 15 min at 0° and then for 15 min at 70°. After cooling, solid potassium carbonate was added and the mixture was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* below 20° to leave the amine (5a), characterised as the *oxalate* (475 mg, 74·1%) which formed needles (from methanol), m.p. 176—178° (Found: C, 57·6; H, 6·3; N, 6·0. $C_{10}H_{13}NO_2,0{\cdot}5C_2H_2O_4,0{\cdot}5H_2O$ requires C, 57·8; H, 6·4; N, 6·1%), $\nu_{max.}$ ($CHCl_3$) (free base) 3380 (NH_2) cm^{-1}, δ ($CDCl_3$) (free base) 2·69 (1H, dd, *J* 15 and 2 Hz, HC*H*), 3·50 (1H, dd, *J* 15 and 4 Hz, *H*CH), 3·82 (6H, s, 2 × OCH_3), 4·48 (1H, dd, *J* 4 and 2 Hz, CH), 6·81 (1H, s, ArH), and 6·92 (1H, s, ArH).

1-*Amino*-1,2-*dihydro*-5-*methoxybenzocyclobutene* (5b).—The amide (4b) (200 mg, 1·2 mmol) was similarly treated with potassium hydroxide (67·5 mg, 3·6 mmol), bromine (190 mg, 1·2 mmol), and water (3·3 ml) to give the amine (5b), the *oxalate* (84 mg, 23·3%) of which formed needles (from methanol), m.p. 190—191° (Found: C, 54·5; H, 5·6; N, 5·5. $C_{10}H_{11}NO,C_2H_2O_4,0{\cdot}5H_2O$ requires C, 54·2; H, 5·6; N, 5·75%), $\nu_{max.}$ ($CHCl_3$) (free base) 3400 (NH_2) cm^{-1}, δ ($CDCl_3$) (free base) 1·85br (2H, NH_2), 2·68 (1H, dd, *J* 13·5 and 3 Hz, HC*H*), 3·62 (1H, dd, *J* 13·5 and 5·5 Hz, *H*CH), 3·72 (3H, s, OCH_3), 4·46 (1H, dd, *J* 5·5 and 3 Hz, CH), and 6·07—7·03 (3H, m, ArH).

4,5-*Dimethoxybenzocyclobuten*-1(2H)-*one* (6a).—To a mixture of the amine (5a) [prepared from its oxalate (100 mg, 0·37 mmol) and 20% potassium hydroxide (3 ml) in chloroform], calcium sulphate (83 mg), water (1 ml), and t-butyl alcohol (1 ml), potassium permanganate (118 mg, 0·74 mmol) was added in small portions with stirring, and the mixture was then stirred for 1 h at room temperature.

After addition of water (20 ml), the mixture was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to leave a yellow solid, which was sublimed at 140° and 0·05 mmHg to give the *ketone* (6a) (25 mg, 35%) as plates, m.p. 142—143° (Found: C, 67·85; H, 6·15. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·65%), $\nu_{max.}$ ($CHCl_3$) 1782 cm^{-1} (CO), $\lambda_{max.}$ (MeOH) 317, 294, and 262 nm, δ ($CDCl_3$) 3·84 (5H, s, OCH_3 and CH_2), 3·96 (3H, s, OCH_3), 6·82 (1H, ArH), and 7·01 (1H, s, ArH), *m/e* 178 (M^+).

5-*Methoxybenzocyclobuten*-1(2H)-*one* (6b).—The amine (5b) [prepared from its oxalate (200 mg, 0·84 mmol) as before] was similarly oxidised with potassium permanganate (236 mg, 0·96 mmol) in the presence of calcium sulphate (166 mg) in water (2 ml) and t-butyl alcohol (2 ml) to give the ketone (6b) (65 mg, 57%) as a syrup, $\nu_{max.}$ ($CHCl_3$) 1795 (CO) and 1775 cm^{-1} (CO), δ ($CDCl_3$) 3·75 (3H, s, OCH_3), 3·82 (2H, s, CH_2), and 6·72—7·42 (3H, m, ArH), characterised as the 2,4-*dinitrophenylhydrazone*, reddish needles (from chloroform–ethanol), m.p. 222—238° (Found: C, 54·95; H, 3·8. $C_{15}H_{12}N_4O_5$ requires C, 54·9; H, 3·7%).

1,2-*Dihydro*-4,5-*dimethoxybenzocyclobuten*-1-*ol* (7a).—To a solution of the ketone (6a) (100 mg, 0·56 mmol) in methanol (5 ml) sodium borohydride (23 mg, 0·62 mmol) was added in portions during 15 min at 0°, and the mixture was stirred for 1 h at 0°. After addition of acetic acid (37·2 mg) and water (10 ml), the mixture was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* below 30° to give the *alcohol* (7a) (63 mg, 62%) as needles (from dichloromethane–n-hexane), m.p. 104—105° (Found: C, 66·1; H, 6·6. $C_{10}H_{12}O_3$ requires C, 66·65; H, 6·7%), $\nu_{max.}$ ($CHCl_3$) 3600 cm^{-1} (OH), δ ($CDCl_3$) 2·88 (1H, dd, *J* 14 and 2·5 Hz, HC*H*), 3·84 (1H, dd, *J* 14 and 6 Hz, *H*CH), 3·80 (6H, s, 2 × OCH_3), 5·12 (1H, dd, *J* 6 and 2·5 Hz), 6·63 (1H, s, ArH), and 6·78 (1H, s, ArH).

1,2-*Dihydro*-5-*methoxybenzocyclobuten*-1-*ol* (7b).—The ketone (6b) (370 mg, 2·72 mmol) was similarly reduced with sodium borohydride (95 mg, 2·56 mmol) in methanol (20 ml) to give the alcohol (7b) (320 mg, 86·4%) as an oil, $\nu_{max.}$ ($CHCl_3$) 3600 cm^{-1} (OH), δ ($CDCl_3$) 2·78 (1H, dd, *J* 13·5 and 1·5 Hz, HC*H*), 3·34 (1H, dd, *J* 13·5 and 3·5 Hz, *H*CH), 3·62 (3H, s, OCH_3), 5·01 (1H, dd, *J* 3·5 and 1·5 Hz), and 6·60—6·96 (3H, m, ArH), *m/e* 150 (M^+).

2,3,10,11-*Tetramethoxyprotoberberine Chloride* (12a).—A solution of the benzocyclobutenol (7a) (90 mg, 0·5 mmol) and 3,4-dihydro-6,7-dimethoxyisoquinoline (8) (96 mg, 0·5 mmol) in benzene (10 ml) was refluxed for 5 h. After cooling, the separated solid was collected by filtration, washed with ether, and converted into the chloride (12a) (98 mg, 52%), obtained as yellow needles (from methanol), m.p. 207—208° (lit.,[4a] 207—208°), identical (m.p. and spectra) with an authentic sample,[4a] $\nu_{max.}$ (KBr) 1630 cm^{-1} (C=$\overset{+}{N}$), δ ($CF_3{\cdot}CO_2H$), 3·35 (2H, t, *J* 6·5 Hz, Ar$CH_2{\cdot}CH_2$), 4·07, 4·13, 4·18, and 4·24 (each 3H, s, OCH_3), 4·88 (2H, t, *J* 6·5 Hz, $CH_2{\cdot}CH_2{\cdot}\overset{+}{N}$), and 7·05, 7·51, 7·56, 7·62, 8·42, and 9·14 (each 1H, s, ArH).

2,3,10-*Trimethoxyprotoberberine Chloride* (12b).—A solution of the benzocyclobutenol (7b) (200 mg, 1·33 mmol) and the 3,4-dihydroisoquinoline (8) (250 mg, 1·3 mmol) in benzene (20 ml) was treated similarly to give the *protoberberine chloride* (12b) as hygroscopic yellow needles (from methanol–ether), m.p. 300—302° (Found: N, 3·4. $C_{20}H_{20}ClNO_3$ requires N, 3·9%), $\nu_{max.}$ (KBr) 1620 cm^{-1} (C=$\overset{+}{N}$), *m/e* 322 (M^+ — Cl).

Xylopinine (2,3,10,11-*Tetramethoxyberbine*) (2a).—To a solution of the protoberberine chloride (12a) (94 mg, 0·25 mmol) in methanol (5 ml) sodium borohydride (19 mg, 0·5 mmol) was added in portions at 0°, and the mixture was stirred at room temperature for 15 min and then refluxed for 15 min. Methanol was removed by distillation and the residue was decomposed with water (10 ml) and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give xylopinine (2a) (71 mg, 81·5%) as yellow needles (from methanol), m.p. 152—153° (lit.,[4a] 150—151·5°), identical (spectra) with an authentic specimen.[4a]

2,3,10-*Trimethoxyberbine* (2d).—(a) *By reduction of the protoberberine chloride* (12b). Sodium borohydride (10 mg) was added to a solution of the protoberberine chloride (12b) (32 mg) in methanol (5 ml) at 0°, and the mixture was treated as before to give a yellow viscous syrup, which was chromatographed on silica gel (2 g). Elution with chloroform–methanol (99 : 1 v/v) gave the berbine (2e) (11 mg) as a yellow viscous syrup, $\nu_{max.}$ ($CHCl_3$) 2850—2750 cm^{-1} (Bohlmann bands), δ ($CDCl_3$) 2·50—3·18 (6H, m, 3 × CH_2), 3·72, 3·82, and 3·84 (each 3H, s, OCH_3), and 6·56—7·12 (5H, m, ArH), the hydrochloride of which formed yellow *needles* (from methanol), m.p. 226—227° (Found: C, 65·85; H, 6·85; N, 3·65. $C_{20}H_{24}ClNO_3{,}0{\cdot}25H_2O$ requires C, 65·55; H, 6·75; N, 3·8%). The spectral data of the free base and the m.p. of the hydrochloride were identical with those of samples prepared by deamination of the aminoberbine (2f); *m/e* 325 (M^+ — HCl), 324, 190, and 134.

(b) *By deamination of the aminoberbine* (2f). To a solution of 11-amino-2,3,10-trimethoxyberbine (2f) (100 mg, 0·29 mmol) in N-sulphuric acid (3 ml), 5% sodium nitrite (1 ml) was added dropwise at 0—5° during 15 min and the mixture was stirred for 1 h at 0°. After addition of 30% hypophosphorous acid (0·2 ml, 4 mmol) at 0° with stirring, the mixture was stirred for 2 h at 0° and then left at room temperature for 2 days. The mixture was made alkaline with concentrated ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to leave a brown oil (53 mg), which was subjected to silica gel (1 g) chromatography. Elution with chloroform–methanol (99 : 1 v/v) gave the berbine (2d) (37 mg, 36%); hydrochloride, m.p. 226—229°).

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