# Reaction of 1,2-Dihydrobenzocyclobutene-1-carbonitriles with Methyl Acrylate as an Unsymmetric Dienophile

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Thermolysis of the 1,2-dihydrobenzocyclobutene-1-carbonitriles (11) and (12) in the presence of methyl acrylate gives in each case two stereoisomeric 1-cyano-2-methoxycarbonyltetralins [(16) and (17), and (18) and (19), respectively]. The *cis*-isomer (19) was converted into the more stable *trans*-isomer (17) by treatment with sodium hydride.

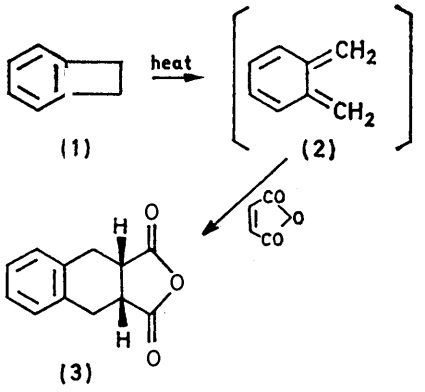
PREVIOUSLY we have reported [1-4] novel syntheses of isoquinoline alkaloids by an electrocyclic reaction of 1,2-dihydrobenzocyclobuten-1-yl-3,4-dihydroisoquinolines and a cycloaddition reaction of 1,2-dihydrobenzocyclobutenes with 3,4-dihydroisoquinolines. In these reactions, *o*-quinodimethanes [*cf.* (2)] were postulated as intermediates which can easily react stereoselectively and regioselectively with imines to afford quinolizine derivatives. *o*-Quinodimethanes can also act as dienes in Diels–Alder reactions.[5-8] For instance, the reaction of benzocyclobutene (1) with maleic anhydride affords the adduct (3).[5]

We were interested in whether a similar reaction of a 1,2-dihydrobenzocyclobutene with an unsymmetric dienophile would proceed regioselectively and/or stereoselectively to form tetralin derivatives, and examined the thermal reaction of 1,2-dihydro-5-methoxybenzocyclobutene-1-carbonitrile (11) [9] and its 3-methyl analogue (12) with methyl acrylate as an unsymmetric olefin in the absence or presence of toluene-*p*-sulphonic acid.

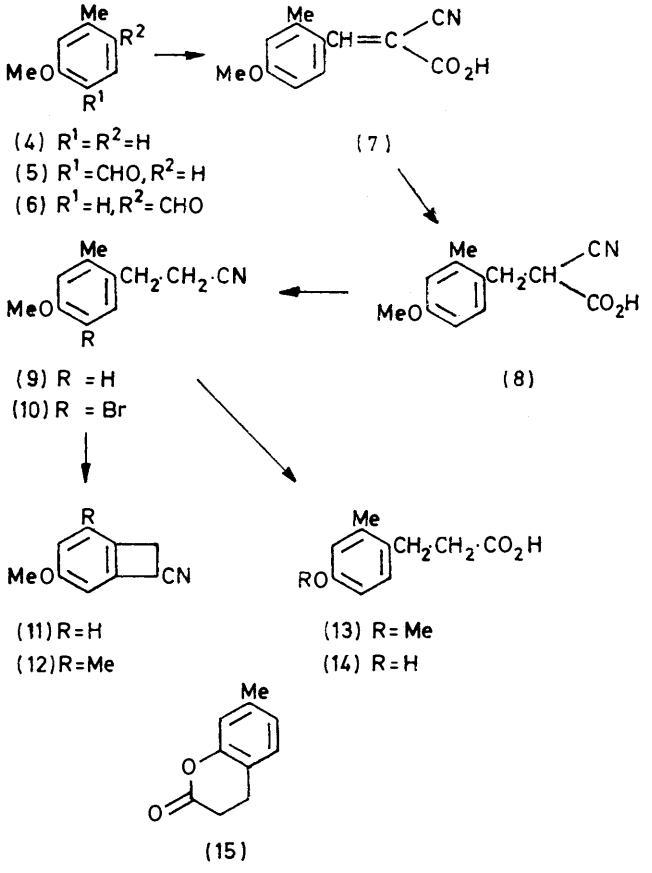
The benzocyclobutenes (11) and (12) were made by the route shown in the Scheme. Thermolysis of the benzocyclobutene (12) in the presence of an excess of methyl acrylate in refluxing toluene for 3 h gave two isomeric tetralin derivatives in the ratio 1 : 1, separated by silica gel chromatography. The eluted second product was transformed into that eluted first by treatment with sodium hydride in benzene, but the reverse process was not observed under the same conditions. The methine protons at C–1 and C–2 in the first product resonated at δ 4.34 (d, *J* 9 Hz) and 3.06 (dt, *J* 9 and 4 Hz), respectively, whereas the C–1 proton in the second

[1] T. Kametani, K. Ogasawara, and T. Takahashi, *J.C.S. Chem. Comm.*, 1972, **675**; *Tetrahedron*, 1973, **29**, 73.
[2] T. Kametani, Y. Hirai, F. Satoh, K. Ogasawara, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 907; T. Kametani, Y. Kato, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 1043; *J.C.S. Perkin I*, 1974, 1712.
[3] T. Kametani, T. Takahashi, and K. Ogasawara, *J.C.S. Perkin I*, 1973, 1464.
[4] T. Kametani, M. Takemura, K. Ogasawara, and K. Fukumoto, *J. Heterocyclic Chem.*, 1974, **11**, 179.
[5] F. R. Jensen, W. E. Coleman, and A. J. Berlin, *Tetrahedron Letters*, 1962, 15.
[6] M. P. Cava and M. J. Mitchell, *J. Amer. Chem. Soc.*, 1955, **81**, 5409.
[7] M. P. Cava, A. A. Deana, and K. Muth, *J. Amer. Chem. Soc.*, 1959, **81**, 6458.
[8] M. P. Cava, R. L. Shirley, and B. W. Erickson, *J. Org. Chem.*, 1962, **27**, 755.
[9] T. Kametani, M. Kajiwara, and K. Fukumoto, *Tetrahedron*, 1974, **30**, 1035.

compound resonated at δ 4.26 (d, *J* 4 Hz). These observations showed that the first compound had the




*trans*-configuration (17) and the second the *cis*-configuration (19). To confirm this fact the hexahydrobenz-[*e*]isoindolone derivatives (20) and (21) were synthesised




SCHEME

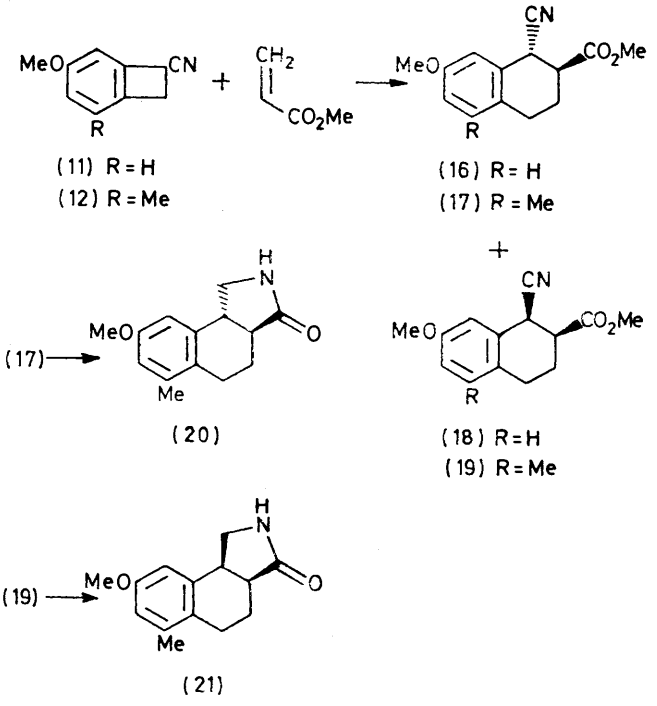
by catalytic reduction of the tetralin derivatives (17) and (19), respectively, in the presence of Raney nickel.

[10] J. Sauer, *Angew. Chem.*, 1967, **79**, 76.

[11] N. P. Buu-Hoi, N. D. Xuong, M. Sy, G. Lejeune, and N. B. Tien, *Bull. Soc. chim. France*, 1955, **240**, 224.

The i.r. spectra of the lactams showed no cyano-absorption but possessed amide bonds at 3 450 and 1 700 $cm^{-1}$, indicating the presence of a five-membered lactam ring. The m.p. of a mixture of (20) with (21) showed a depression. Similar results have been reported [10] in the reaction of penta-2,4-dienoic acid with acrylic acid.

When the reaction was carried out in the presence of a trace of toluene-*p*-sulphonic acid, the ratio of the compound (19) to (17) was increased.




Similarly, the reaction of the benzocyclobutene (11) with methyl acrylate gave the *trans*- (16) and the *cis*-tetralin (18) in the ratio 1 : 1, and the reaction in the presence of toluene-*p*-sulphonic acid afforded the *cis*-compound (18) as the major product.

The fact that these reactions are regioselective but not stereoselective suggests that they proceed stepwise through diradical or ionic intermediates, stabilised by the presence of a methoxycarbonyl group.

## EXPERIMENTAL

M.p.s were measured with a Yanagimoto microapparatus, i.r. spectra with a Hitachi EPI-3 recording spectrophotometer, and n.m.r. spectra with a JEOL JNM-PMX 60 or JEOL PS-100 spectrophotometer.

*α-Cyano-4-methoxy-2-methylcinnamic Acid* (7).—A mixture of the aldehydes (5) and (6) [11,12] (50 g), cyanoacetic acid (35 g), ammonium acetate (25 g), and dry benzene (200 ml) was refluxed for 4 h. After cooling, the precipitate was collected, then washed with 10% hydrochloric acid and water and dried to afford the *acid* (7) as pale yellowish needles (53 g), m.p. 225—228° (from methanol) (Found: C, 66.5; H. 5.0; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.35;

[12] K. E. Harding, E. J. Leopold, A. M. Hudrlik, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1974, **96**, 2540.

H, 5.1; N, 6.45%), $\nu_{max.}$ (KBr), 2 230 (CN), 1 675 (C=O) and 1 605 (C=C) $cm^{-1}$, δ ($CDCl_3$) 2.20 (3 H, s, $ArCH_3$), 3.75 (3 H, s, OMe), 6.30—6.80 (3 H, ArH), and 8.03 (1 H, s, ArCH).

α-*Cyano*-β-(4-*methoxy*-2-*methylphenyl*)*propionic Acid* (8).—To a solution of the acid (7) (43.4 g) and sodium hydrogen carbonate (11.4 g) in water (400 ml), sodium borohydride (11.4 g) was added in small portions with stirring at 0 °C. Stirring was continued for 2 h at room temperature, and the mixture was then acidified with 10% hydrochloric acid and extracted with ether. The extract layer was washed with water, dried ($Na_2SO_4$), and evaporated to give the *cyanopropionic acid* (8) as needles (32 g), m.p. 97—98° (from benzene–hexane) (Found: C, 65.55; H, 5.8; N, 6.45. $C_{12}H_{13}NO_3$ requires C, 65.75; H, 6.0; N, 6.4%), $\nu_{max.}$ ($CHCl_3$) 2 250 (CN) and 1 720 (C=O) $cm^{-1}$, δ ($CDCl_3$) 2.33 (3 H, s, $ArCH_3$), 3.10—3.40 (2 H, m, $ArCH_2$), 3.80 (3 H, s, OMe), 6.70—7.20 (3 H, ArH), and 7.36 (1 H, s. $CO_2H$).

3-(4-*Methoxy*-2-*methylphenyl*)*propiononitrile* (9).—A solution of the acid (8) (32 g) in *NN*-dimethylacetamide (64 ml) was heated at 150 °C until evolution of the calculated amount of carbon dioxide had ceased. The mixture was poured into water and extracted with ether. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give the *nitrile* (9) as an oil, b.p. 147° at 5 mmHg (Found: C, 75.35; H, 7.3; N, 7.85. $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0%), $\nu_{max.}$ ($CHCl_3$) 2 250 $cm^{-1}$ (CN), δ ($CCl_4$) 2.27 (3 H, s, $ArCH_3$), 2.40—2.93 (4 H, m, $CH_2{\cdot}CH_2$), 3.70 (3 H, s, OMe), and 6.50—7.06 (3 H, ArH).

3-(5-*Bromo*-4-*methoxy*-2-*methylphenyl*)*propiononitrile* (10).—To a mixture of the nitrile (9) (21 g), anhydrous sodium acetate (9.8 g), and chloroform (100 ml), a solution of bromine (23.2 g) in chloroform (50 ml) was added dropwise with stirring at room temperature. Stirring was continued for 3 h at the same temperature and the mixture was then washed with water. The solution was dried ($Na_2SO_4$) and evaporated to give the *bromo-derivative* (10) as needles (23.5 g), m.p. 82—83° (from ethanol) (Found: C, 52.25; H, 4.85; N, 5.45. $C_{11}H_{12}BrNO$,0.5 $H_2O$ requires C, 52.2; H, 5.0; N, 5.55%), $\nu_{max.}$ ($CHCl_3$) 2 250 $cm^{-1}$ (CN), δ ($CDCl_3$) 2.30 (3 H, s, $ArCH_3$), 2.33—3.00 (4 H, m, $CH_2{\cdot}CH_2$), 3.82 (3 H, s, OMe), 6.63 (1 H, s, ArH), and 7.20 (1 H, s, ArH).

1,2-*Dihydro*-5-*methoxy*-3-*methylbenzocyclobutene*-1-*carbonitrile* (12).—To a stirred solution of sodamide [from sodium (7.8 g)] in liquid ammonia (1.52 l) the nitrile (10) (21 g) was added in small portions. Stirring was continued for 5 h at room temperature, and the excess of sodium amide was then decomposed with crystalline ammonium chloride. The mixture was diluted with water and extracted with ether. The extract was washed with water, dried ($Na_2SO_4$), and evaporated. The resulting brownish oil (16.5 g) was chromatographed on silica gel (200 g). Elution with benzene (fractions 2—5; each 200 ml) gave the *benzocyclobutene* (12) as prisms (5.5 g), m.p. 96—97° (from ethanol) (Found: C, 76.6; H, 6.5; N, 8.1. $C_{11}H_{11}NO$ requires C, 76.25; H, 6.4; N, 8.1%), $\nu_{max.}$ ($CHCl_3$) 2 250 $cm^{-1}$ (CN), δ ($CCl_4$) 2.66 (3 H, s, $ArCH_3$), 3.42 (2 H, d, *J* 4 Hz, $ArCH_2$), 3.78 (3 H, s, OMe), 4.03 (1 H, t, *J* 4 Hz, CH·CN), and 6.50br (2 H, s, ArH).

β-(4-*Methoxy*-2-*methylphenyl*)*propionic Acid* (13).—A solution of the propiononitrile (9) (200 mg) in ethanolic 10% potassium hydroxide (10 ml) was refluxed for 5 h. The solvent was removed and the residue was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water, dried ($Na_2SO_4$), and evaporated to give the acid (13) as leaflets (132 mg), m.p. 97—98° (lit.,[13] 105°) (from water) (Found: C, 67,55; H, 7.0. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.25%), $\nu_{max.}$ ($CHCl_3$) 1 700 $cm^{-1}$ (C=O).

β-(4-*Hydroxy*-2-*methylphenyl*)*propionic Acid* (14).—A mixture of the acid (13) (200 mg), acetic anhydride (2 ml), and 47% hydrobromic acid (5 ml) was refluxed for 4 h and then diluted with water (20 ml). The mixture was extracted with ether, washed with water, dried ($Na_2SO_4$), and evaporated to give the phenolic carboxylic acid (14) as a powder (165 mg), m.p. 101—102° (lit.,[13] 103°) (from benzene–n–hexane), $\nu_{max.}$ ($CHCl_3$) 3 500 (OH) and 1 710 $cm^{-1}$ (C=O), δ ($CDCl_3$–$CD_3OD$) 2.30 (3 H, s, $ArCH_3$), 2.50—3.10 (4 H, m, $CH_2{\cdot}CH_2$), and 6.50—7.16 (3 H, ArH), *m/e* 180 ($M^+$).

*Thermolysis of* 1,2-*Dihydro*-5-*methoxybenzocyclobutene*-1-*carbonitrile with Methyl Acrylate.*—A mixture of the benzocyclobutene (11) (1.6 g), methyl acrylate (4.3 g), dry toluene (20 ml), and a catalytic amount of toluene-*p*-sulphonic acid was gradually heated in a sealed tube. Heating was continued for 2 h at 190 °C, then the cooled mixture was diluted with benzene. The organic layer was washed with water, dried ($Na_2SO_4$), and evaporated to give a brownish gum (5.7 g), which was chromatographed on silica gel (150 g). Eluation with n-hexane–benzene (1 : 1 v/v) (fractions 12—18; each 150 ml) gave trans-*methyl* 1-*cyano*-7-*methoxytetralin*-2-*carboxylate* (16) as needles (270 mg), m.p. 92—93° (from ethanol) (Found: C, 68.85; H, 6.05; N, 5.9. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.15; N, 5.7%), $\nu_{max.}$ ($CHCl_3$) 2 250 (CN) and 1 730 (C=O) $cm^{-1}$, δ ($CDCl_3$) 1.80—2.40 (2 H, m, $ArCH_2{\cdot}CH_2$), 2.80 (2 H, t, *J* 6 Hz, $ArCH_2$), 3.08 (1 H, d, t, *J* 9 and 4 Hz, $CH{\cdot}CO_2Me$), 3.78 and 3.80 (6 H, each s, OMe and $CO_2Me$), 4.32 (1 H, d, *J* 9 Hz, CH·CN), and 6.72—7.04 (3 H, ArH). Fractions 21—35 gave the cis-*isomer* (18) as needles (1.47 g), m.p. 99—100° (from ethanol) (Found: C, 68.55; H, 5.95; N, 5.75%), $\nu_{max.}$ ($CHCl_3$) 2 250 (CN) and 1 730 (C=O) $cm^{-1}$, δ ($CDCl_3$) 2.10—2.45 (2 H, m, $ArCH_2{\cdot}CH_2$), 2.80—2.96 (3 H, m, $ArCH_2$ and $CH{\cdot}CO_2Me$), 3.75 and 3.80 (6 H, each s, OMe and $CO_2Me$), 4.27 (1 H, d, *J* 4 Hz, CH·CN), and 6.74—7.06 (3 H, ArH).

*Thermolysis of the Benzocyclobutene* (11) *with Methyl Acrylate without Catalyst.*—A mixture of the benzocyclobutene (11) (1.2 g), methyl acrylate (5.0 g), and dry toluene (20 ml) was heated at 190 °C for 3 h. The mixture was diluted with benzene, then washed with water, dried ($Na_2SO_4$), and evaporated. The resulting gum (5.2 g) was chromatographed on silica gel (150 g). Elution as above gave the *trans*- (16) and the *cis*-tetralin (18) in yields of 480 and 560 mg, respectively.

*Thermolysis of* 1,2-*Dihydro*-5-*methoxy*-3-*methylbenzocyclobutene*-1-*carbonitrile* (12) *with Methyl Acrylate.*—Heating a mixture of the benzocyclobutene (12) (1.7 g), methyl acrylate (4.7 g), dry toluene (20 ml), and a catalytic amount of toluene-*p*-sulphonic acid as in the case of (11) gave a brownish gum (5.9 g), which was chromatographed on silica gel (150 g). Elution with benzene (fractions 23—29; each 150 ml) gave trans-*methyl* 1-*cyano*-7-*methoxy*-5-*methyltetralin*-2-*carboxylate* (17) (320 mg) as needles, m.p. 96—97° (from ethanol) (Found: C, 69.3; H, 6.4; N, 5.5. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%), $\nu_{max.}$ ($CHCl_3$) 2 240 (CN) and 1 720 (C=O) $cm^{-1}$, δ ($CCl_4$) 1.84—2.40 (2 H, m, $ArCH_2{\cdot}CH_2$), 2.20 (3 H, s, $ArCH_3$), 2.66 (1 H, dt, *J* 9 and 4 Hz, $CH{\cdot}CO_2Me$), 3.78 (6 H, s, OMe and $CO_2Me$), 4.34 (1 H,

[13] P. C. Mukharji and P. K. S. Gupta, *Chem. and Ind.*, 1970, 533.

d, *J* 9 Hz, CH·CN), 6.68 (1 H, d, *J* 1.5 Hz, ArH), and 6.78 (1 H, d, *J* 1.5 Hz, ArH).

Fractions 30—42 gave the cis-*isomer* (19) as needles (1.32 g), m.p. 87—88° (from ethanol) (Found: C, 69.2; H, 6.3; N, 5.4%), $\nu_{max.}$ ($CHCl_3$) 2 240 (CN) and 1 720 (C=O) $cm^{-1}$, δ ($CDCl_3$) 2.12 (3 H, s, $ArCH_3$), 2.00—3.20 (5 H, m, $ArCH_2{\cdot}CH_2$ and $CH{\cdot}CO_2Me$), 3.76 and 3.80 (6 H, each s, OMe and $CO_2Me$), and 4.26 (1 H, d, *J* 4 Hz, CH·CN).

Heating a mixture of the benzocyclobutene (12) (1.0 g), methyl acrylate (4.0 g), and dry toluene (20 ml) without toluene-*p*-sulphonic acid gave the corresponding *trans*-(17) and *cis*-tetralin derivatives (19) in the ratio 1 : 1 (460 and 520 mg).

*Conversion of the* cis-*Isomer* (19) *into the* trans-*Isomer* (17).—A mixture of the *cis*-tetralin (19) (100 mg), sodium hydride (50% in oil; 20 mg), and dry benzene was refluxed for 2 h, cooled, and poured into ice–water. The organic layer was separated, then washed with water, dried ($Na_2SO_4$), and evaporated to give the *trans*-isomer (17) (85 mg), identical with the authentic sample.

trans-1,2,3a,4,5,9b-*Hexahydro*-8-*methoxy*-6-*methylbenz*[e]-*isoindol*-3-*one* (20).—A mixture of the tetralin (17) (1 g), Raney nickel (2 g), and ethanol (50 ml) saturated with ammonia gas was hydrogenated in an autoclave with shaking at an internal pressure of 70 kg $cm^{-2}$ of hydrogen. After absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was evaporated. The residue was extracted with benzene. The extract was washed with water, saturated aqueous sodium hydrogen carbonate, 10% hydrochloric acid, and water, dried ($Na_2SO_4$), and evaporated to give the *lactam* (20) (700 mg) as needles, m.p. 195—196° (from ethanol) (Found: C, 69.65; H, 7.2. $C_{14}H_{17}NO_2,0.5H_2O$ requires C, 69.95; H, 7.55%), $\nu_{max.}$ ($CHCl_3$) 3 450 (NH) and 1 700 (C=O) $cm^{-1}$, δ ($CDCl_3$) 2.20 (3 H, s, $ArCH_3$), 3.68 (3 H, s, OMe), 6.34 (1 H, d, *J* 2 Hz, ArH), and 6.58 (1 H, *J* 2 Hz, ArH).

Hydrogenation of the tetralin (19) (1 g) in the same manner gave the cis-*lactam* (21) (740 mg) as needles, m.p. 234—235° (from ethanol) (Found: C, 72.5; H, 7.45; N, 6.15. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.05%), $\nu_{max.}$ ($CHCl_3$) 3 450 (NH) and 1 700 (C=O) $cm^{-1}$, δ ($CDCl_3$) 2.21 (3 H, s, $ArCH_3$), 3.72 (3 H, s, OMe), 6.28 (1 H, d, *J* 2 Hz, ArH), and 6.58 (1 H, d, *J* 2 Hz, ArH).

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