Tetrahedron. Vol. 30, pp. 1047 to 1051. Pergamon Press 1974. Printed in Great Britain

STUDIES ON THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—DXLVI[1]

REGIOSPECIFIC CYCLOADDITION OF A BENZOCYCLOBUTENE DERIVATIVE WITH SCHIFF BASES BY THERMOLYSIS—A NEW METHOD FOR ISOQUINOLINE SYNTHESIS

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(*Received in Japan* 13 *September* 1973; *Received in the UK for publication* 20 *November* 1973)

Abstract—4-Cyano-3-phenylisoquinoline derivatives were prepared by the regiospecific intermolecular thermal cycloaddition reaction between a 1-cyanobenzocyclobutene derivative and Schiff bases.

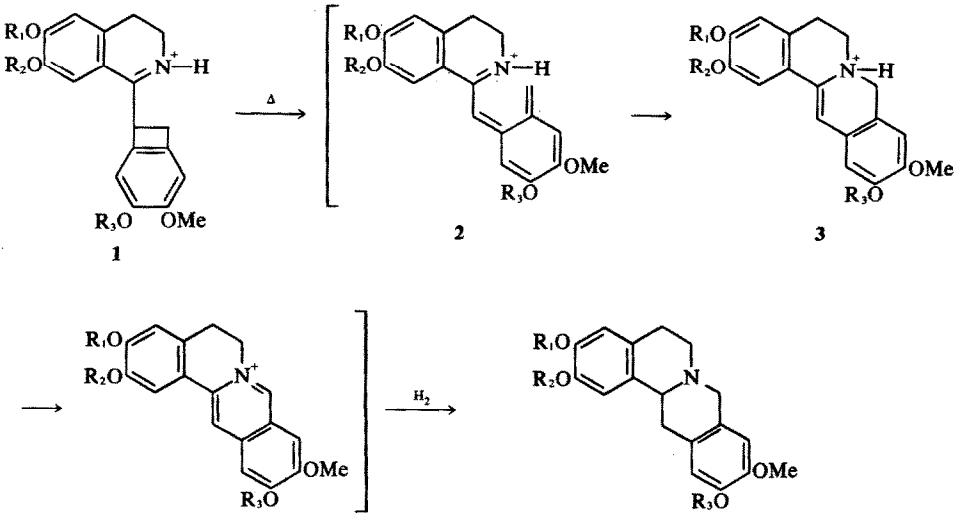
We have recently reported a new synthesis of protoberberine alkaloids (**5a, b, c**)[2a,b,c] and an ochotensine-type model compound (**10**)[3] by the intramolecular thermal rearrangement of benzocyclobutene derivatives.

More recently we found an intermolecular thermal cycloaddition between benzocyclobutenes (**11a, b**) and 3, 4 - dihydroisoquinoline (**13**) to afford 13 - substituted protoberberines (**14a, b**) in excellent yield in a highly regiospecific manner.[4]

As an expansion of the thermal intermolecular cycloaddition of a benzocyclobutene derivative to a C=N double bond, the present study provides a new regiospecific cycloaddition for the synthesis of 3, 4 - disubstituted isoquinoline derivatives.

The reaction of a benzocyclobutene derivative (**11a**) with Schiff bases (**15a, b**) at 150–160° without solvent afforded two compounds, an isoquinoline derivative (**16a, b**) and a dimer of the benzocyclobutene (**11a**), respectively.

The structure of the former isoquinolines (**16a, b**) was deduced from their NMR spectra which showed two pairs of AB type splittings due to two isolated methylene groups eliminating isoquinoline (**17a, b**) as possible structures. However, a stereochemical relationship between C-3 and C-4 substituents could not be made clear since the observed coupling constant (8 Hz) between C-3 and C-4 protons indicated two possible stereostructures with the dihedral angles 0° and 150° (on the basis of



5a: $R_1 = R_2 = R_3 = Me$: Xylopinine
5b: $R_1 = H$, $R_2 = R_3 = Me$: Discretine
5c: $R_1 = Me$, $R_2 = R_3 = H$: Coreximine

CHART 1a

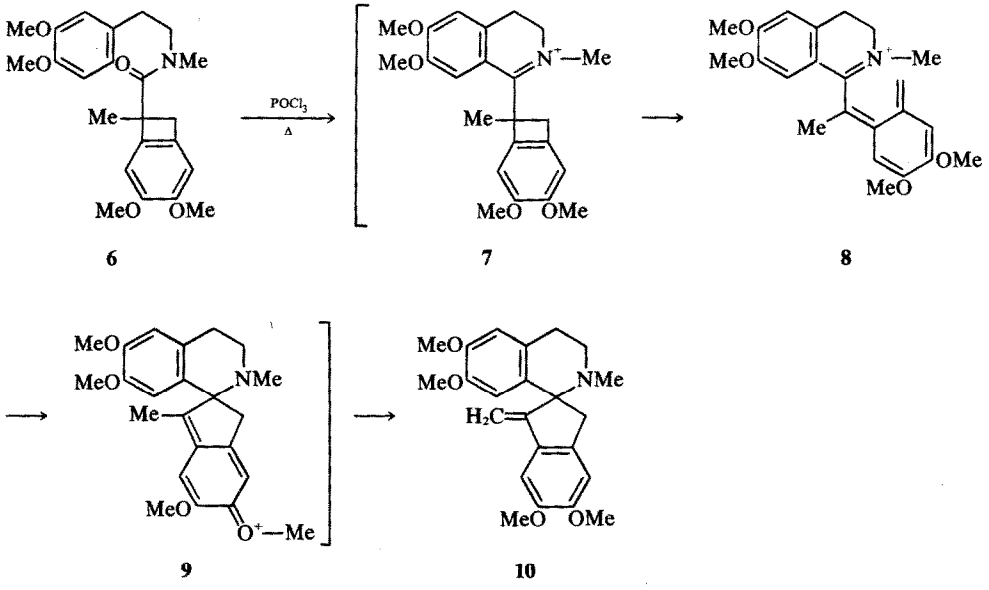


CHART 1b

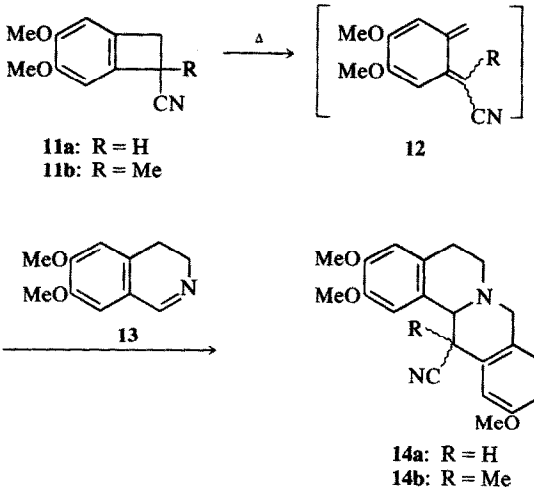


CHART 2

the Karplus equation) which seemed to be almost equally stable from the appropriate model examination. Since the isoquinoline (**16a, b**) was obtained as a single stereostructure, we may conclude that the cycloaddition proceeded in both a regio- and stereospecific manner.

Although a stereochemical assignment could not be made, the benzocyclobutene dimer, which was also obtained quantitatively on heating of **11a** without solvent at 150–160° under an atmosphere of nitrogen, was assigned the dibenzocyclooctene structure (**18**), and not the alternate structure (**19**), since its NMR spectrum showed two broad singlets due to methylene and methine protons at 3·15 ppm and 4·48 ppm. In this case, no interaction between two signals was observed by the decoupling experiment. Furthermore, this assignment may be also supported by a comparison of the ^{13}CMR spectra of the dimer (**18**) and the amide (**20**), in which the observed relative chemical shift of the methine carbons between **18** and **20** was almost identical with that of reported values.[5]

Under the same condition, the reaction of benzocyclobutene (**11a**) with an oxime (**21**) did not give an isoquinoline derivative, but a mixture of the benzocyclobutene dimer (**18**), the half amide (**23**) of **18** and a benzonitrile (**22**) was obtained.

The observed regio- and stereospecific formation

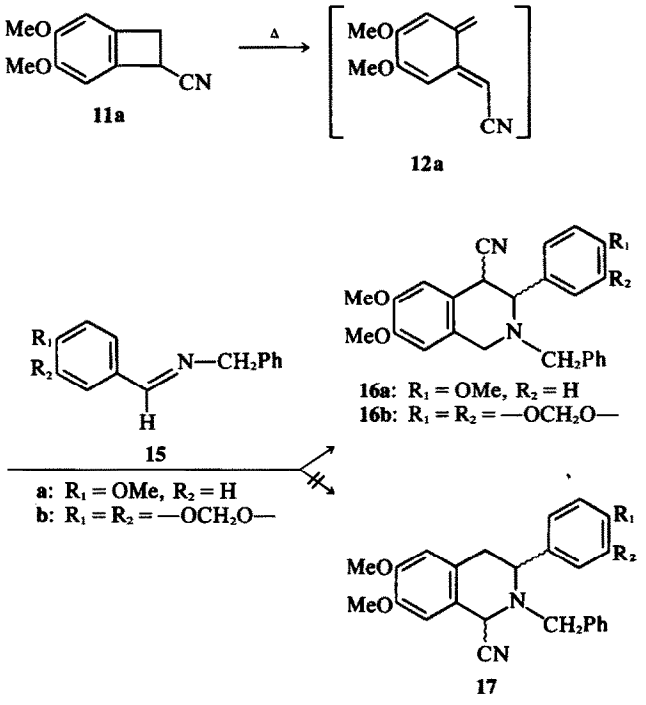


CHART 3

Table 1

Starting materials	Reaction time	Products and yield	NMR data (δ) Methylene protons Chemical shift		Methylene protons Coupling constant	Methine protons Chemical shift		Methine protons Coupling constant
11a + 15a	1 hr	16a + 18	3·18	3·85	J = 14 Hz	3·96	4·26	J = 8 Hz
		16a 41·8% 44·6%	3·52	3·75	J = 16 Hz			
11a + 15b	2 h	16b + 18	3·16	3·89	J = 14 Hz	3·90	4·24	J = 8 Hz
		16b 25·0% 65·2%	3·49	3·77	J = 16 Hz			
11a	2 h	18	3·15		broad s	4·48		broad s
		18 93·1%			(4 Hz)*			(7 Hz)*

*Width at half-height.

of 3, 4 - disubstituted isoquinoline derivatives described herein should be applicable to the synthesis of isoquinoline alkaloids, e.g. the benzophenanthridine alkaloids. An extensive study of the applications of benzocyclobutene derivatives is currently under investigation.

*IR spectra were measured with a Hitachi EPI-3 and UV spectra on a Hitachi 124-spectrophotometer. NMR spectra were measured on a Hitachi H-60 using TMS as an internal standard. The mass spectra were taken with a Hitachi RMU-7.

EXPERIMENTAL*

2 - *Benzyl* - 4 - *cyano* - 1, 2, 3, 4 - *tetrahydro* - 6, 7 - *dimethoxy* - 3 - (4 - *methoxyphenyl*) *isoquinoline* (**16a**). A mixture of the Schiff base **15a** (496·4 mg; 2·2 m mol) and to remove benzocyclobutene derivative **11a** (415·8 mg; 2·2 m mol) was heated at 150–160° for 1 h under an atmosphere of N_2. The mixture was chromatographed on silica gel (40 g) with CH_2Cl_2 to afford 381·4 mg (41·8%) of **16a** as pale yellow plates (from EtOH), m.p. 158·5–160°; IR ($CHCl_3$) 2245 cm^{-1} (CN); NMR ($CDCl_3$) δ 3·52 (2H, d, d, internal chemical shift with 67 Hz, and J = 14 Hz, 2 × methylene protons), 3·64 (2H, d, d, internal chemical shift with 23 Hz, and J = 16 Hz, 2 × methylene protons),

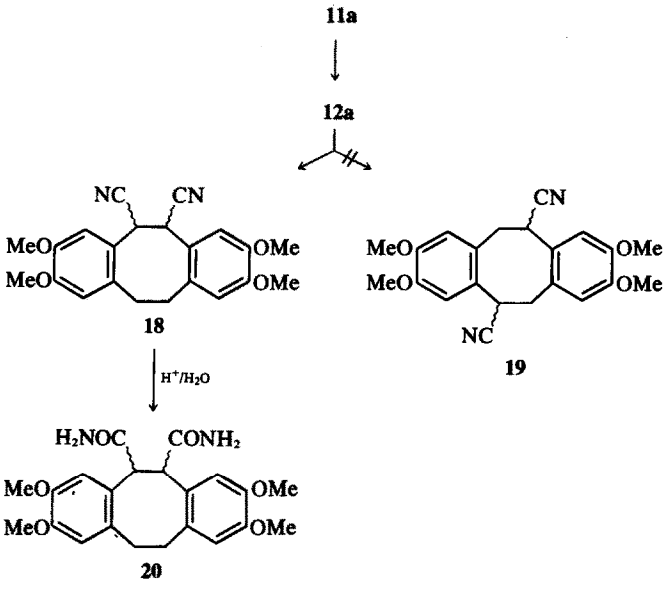


CHART 4

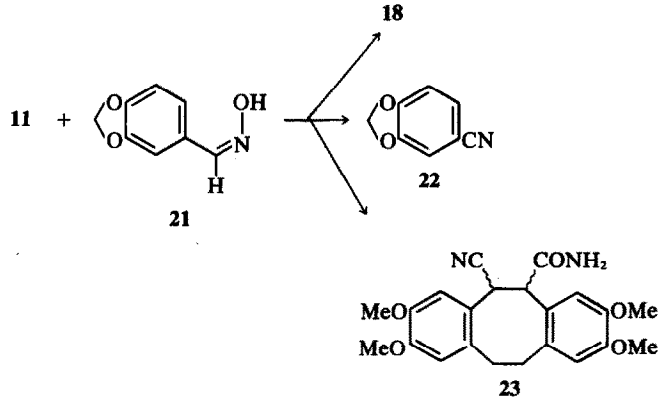


CHART 5

3·80 (6H, s, 2 × OMe), 3·88 (3H, s, OMe), 3·96 and 4·26 (2H, each d, J = 8 Hz, methine protons of C-3 and C-4), 6·49 (1H, s, ArH), 6·88 (2H, s, 2 × ArH), 6·97 (1H, s, ArH), and 7·32 ppm (7H, m, 2 × ArH + $C_6\underline{H}_5CH_2$); *m/e* 414 (M^+). (Calc. for $C_{26}H_{26}N_2O_3$: C, 75·34; H, 6·32; N, 6·76. Found: C, 75·64; H, 6·35; N, 6·90%).

Furthermore, **18** (185·3 mg; 44·6%) was obtained as prisms (benzene–$CHCl_3$), m.p. 100–102·5°; IR ($CHCl_3$) 2245 cm^{-1} (CN); NMR ($CDCl_3$) δ 3·15 (4H, broad s, 2 × methylene protons), 3·79 (12H, s, 4 × OMe), 4·48 (2H, broad s, 2 × methine proton), 6·47 (2H, s, 2 × ArH), 6·64 (2H, s, 2 × ArH), ^{13}CMR ($CDCl_3$) δ 33·06 (—$\underline{C}H_2$—), 39·85 (—$\underline{C}$(CN)H—) and 40·46 (—$\underline{C}$(CN)H—) 55·99 (O$\underline{Me}$), 111·93 and 113·99 ($\underline{Ar}$H), 117·99 (R-$\underline{Ar}$), 118·48 and 121·76 ($\underline{C}$N), 128·31 (R-$\underline{Ar}$), 130·86 ($\underline{Ar}$H), 131·83 (R-$\underline{Ar}$), 147·72, 149·18 and 149·42 (MeO-$\underline{Ar}$); *m/e* 378 (M^+), 189 (M^+-$C_{11}H_{11}NO_2$). (Calc. for $C_{22}H_{22}N_2O_4$: C, 69·82; H, 5·86. Found: C, 69·99; H, 5·95%).

2 - *Benzyl* - 4 - *cyano* - 1, 2, 3, 4 - *tetrahydro* - 6, 7 - *dimethoxy* - 3 - (3, 4 - *methylenedioxyphenyl*) *isoquinoline* (**16b**). A mixture of Schiff base **15b** (1005·1 mg; 4·2 m mol) and **11a** (795 mg; 4·2 m mol) was heated in the similar manner as described above for 2 h. The mixture was chromatographed on silica gel (72 g) with CH_2Cl_2 to afford 423·3 mg of piperonal as needles and 443·8 mg (25·0%) of **16b** as pale yellow needles (from EtOH), m.p. 156–157°; IR ($CHCl_3$) 2245 cm^{-1} (CN); NMR ($CDCl_3$) δ 3·53 (2H, d, d, internal chemical shift with 73 Hz and J = 14 Hz, 2 × methylene protons), 3·63 (2H, d, d, internal chemical shift with 28 Hz, and J = 16 Hz, 2 × methylene protons), 3·80 and 3·88 (6H, each s, 2 × OMe), 3·90 and 4·24 (2H, each d, J = 8 Hz, methine protons of C-3 and C-4), 5·97 (2H, s, —OCH_2O—), 6·49 (1H, s, ArH), 6·87 (4H, m, 4 × ArH), 7·32 (5H, m, $C_6\underline{H}_5CH_2$), ^{13}CMR ($CDCl_3$) δ 39·06 and 53·19 (N—$\underline{C}H_2$—), 55·86 and 58·53 (M$\underline{e}$O), 66·42 (—$\underline{C}$(CN)H—), 101·25 (OCH_2O), 101·25 (R-$\underline{Ar}$), 107·68 and 108·41 (—$\underline{C}$(CN)H—), 109·13, 110·23 and 119·69 ($\underline{Ar}$H), 120·05 ($\underline{C}$N), 121·87 and 122·12 ($\underline{Ar}$H), 126·36 (R-$\underline{Ar}$), 127·21 (p-$\underline{Ar}$H or benzyl group), 128·43 ($\underline{C}_6H_5CH_2$), 131·95 and 138·26 (R-$\underline{Ar}$),

147·84, 148·33 and 148·93 (RO-Ar); *m/e* 428 (M^+). (Calc. for $C_{26}H_{24}N_2O_4$: C, 72·88; H, 5·65; N, 6·54. Found: C, 73·20; H, 5·68; N, 6·58%). Furthermore, 518 mg (65·2%) of **18** was obtained as prisms (benzene–$CHCl_3$), m.p. 100–102·5°, which was identical with the authentic sample.

5, 6 - *Dicyano* - 2, 3, 8, 9 - *tetramethoxydibenzo* [a, e] *cyclooctene* (**18**). The nitrile **11a** (100 mg; 0·53 m mol) was heated under the same conditions as above for 2 h to afford **18** (93·1 mg; 93·1%), identical with the above sample.

5, 6 - *Dicarboxamido* - 2, 3, 8, 9 - *tetramethoxydibenzo* [a, e] *cyclooctene* (**20**). To **18** (207 mg; 0·55 m mol), 2 ml of conc H_2SO_4 was added dropwise under ice-cooling. After standing overnight at room temp, 100 ml of water was added to the mixture, followed by extraction with $CHCl_3$. The extract was washed with water, dried (K_2CO_3), and evaporated to afford 228·6 mg of a pale yellow mass. Recrystallisation from $CHCl_3$–MeOH left 131·6 mg (58·1%) of **20** as granules, m.p. 298–299° (dec.); IR ($CHCl_3$) 3530 and 3415 (amide NH), 1680 cm^{-1} (amide C=O); NMR ($CDCl_3 + CF_3COOH$) δ 3·08 (4H, broad s, 2 × methylene protons), 3·77 (12H, s, 4 × OMe), 4·64 (2H, broad s, 2 × methine proton), 6·51 (2H, s, 2 × ArH), 6·66 (2H, s, 2 × ArH); ^{13}CMR ($CDCl_3 + CF_3COOH$) δ 32·81 and 33·17 (—$\underline{C}H_2$—), 51·36 and 53·15 (>$\underline{C}$H—), 55·86 (Me$\underline{O}$), 109·01 (R-$\underline{Ar}$), 114·35 ($\underline{Ar}$H), 120·42 and 127·09 (R-$\underline{Ar}$), 131·82, 147·23 and 148·08 (MeO$\underline{Ar}$), 178·90 ($\underline{C}ONH_2$); *m/e* 414 (M^+). (Calc. for $C_{22}H_{26}N_2O_6.H_2O$: C, 61·10; H, 6·53; N, 6·48. Found: C, 60·78; H, 6·65; N, 6·57%).

5 - *Carboxamido* - 6 - *cyano* - 2, 3, 8, 9 - *tetramethoxydibenzo* [a, e] *cyclooctene* (**23**). A mixture of **21** (800 mg; 6 m mol) and **11a** (1135 mg; 6 m mol) was heated in a similar manner as described above for 1·5 h. The mixture was chromatographed on silica gel (80 g) with CH_2Cl_2 to afford 295·5 mg (33·5%) of **22** as prisms and 331·0 mg (41·4%) of the starting oxime **21** as pale yellow needles. Furthermore, 263·8 mg (46·5%) of (**18**) was obtained.

Elution with CH_2Cl–$CHCl_3$ (1:3) afforded 472·4 mg (39·8%) of **23** as granules (MeOH–$CHCl_3$), m.p. 288–289° (dec.); IR (KBr) 3470 and 3370 (primary amide NH_2), 2245 (CN), 1690 cm^{-1} (amide C=O); NMR ($CDCl_3 + CF_3COOH$) δ 2·80–3·44 (4H, m, 2 × methylene protons), 3·77 (6H, s, 2 × OMe), 3·80 and 3·83 (6H, each s, 2 × OMe), 4·25 and 4·90 (2H, each d, J = 10 Hz, 2 × methine proton), 6·48 (1H, s, ArH), 6·56 (3H, s, 3 × ArH), 6·48 and 7·56 (2H, each broad s, NH_2); ^{13}CMR ($CDCl_3 + CF_3COOH$) δ 56·11 (Me$\underline{O}$), 108·76 and 109·01 (R-$\underline{Ar}$), 114·47 ($\underline{Ar}$H), 120·29 ($\underline{C}N$), 123·57, 125·27 and 131·21 ($\underline{Ar}$H), 132·06, 148·57 and 148·93 (MeO$\underline{Ar}$), 176·72 ($\underline{C}ONH_2$); *m/e* 396 (M^+). (Calc. for $C_{22}H_{24}N_2O_5$: C, 66·65; H, 6·10; N, 7·07. Found: C, 66·74; H, 6·14; N, 6·93%).

Hydrolysis of **23**. To **23** (10 mg; 0·025 m mol), 0·1 ml conc H_2SO_4 was added under ice-cooling, and the mixture was treated in the same way as in the case of **18** to give 8·2 mg (79·2%) of **20**, identical with the above sample by IR spectrum and TLC.

Acknowledgments—We thank Mr. T. Ohuchi, Miss A. Ujiie, Mrs. A. Satoh, Mrs. C. Koyanagi, Miss R. Kato, and Miss C. Yoshida, Pharmaceutical Institute, Tohoku University, for spectral measurements and microanalyses.

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