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STUDIES OF THE SYNTHESES OF HETEROCYCLIC COMPOUNDS—CDXCIV

A TOTAL SYNTHESIS OF (±)-XYLOPININE BY THERMOLYSIS

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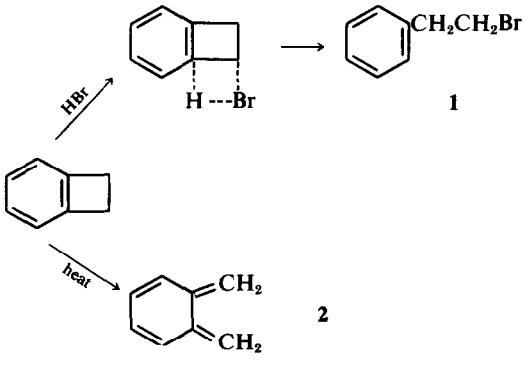
Abstract—Thermolysis of the hydrochloride (**12**) of 3,4-dihydro-6,7-dimethoxy-1-(4,5-dimethoxybenzocyclobutenyl)isoquinoline in bromobenzene or dichlorobenzene, followed by catalytic hydrogenation, gave (±)-xylopinine (**16**) in good yield.

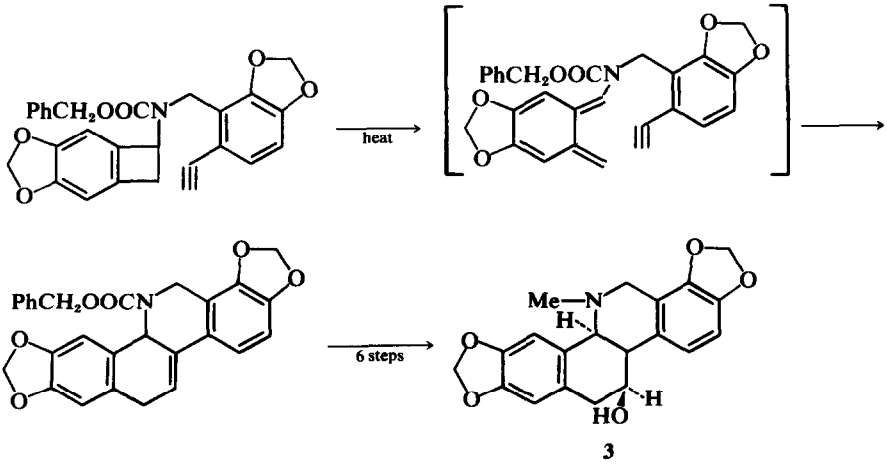
Since the synthesis of a benzocyclobutene derivative by Finkelstein[2] in 1959 and its re-investigation by Cava and Napier[3] in 1965, this strained compound has been shown to undergo many interesting reactions. For example, heating benzocyclobutene with hydrobromic acid gives β-phenethyl bromide[4] (**1**) and its thermolysis affords *o*-quinodimethane (**2**), which is formed as an unstable intermediate by cleavage at the β-position.[5]



Oppolzer examined the intramolecular cycloadditions of *o*-quinodimethanes[6] and the thermal rearrangement of *N*-(1-benzocyclobutenyl)vinylacetamide and reported the first total synthesis of (±)-chelidonine (**3**).[7,8]

We were interested in finding out if the same type of rearrangement could occur with *o*-quinodimethane derivative **13**, giving dihydroprotoberberine (**15**) *via* (**14**), the catalytic hydrogenation of which would give (±)-xylopinine (**16**). Regarding the synthesis of xylopinine a number of procedures have been reported,[9] but this type of total synthesis has not yet been reported. Here we describe these results.

In order to test the above speculation, the benzocyclobutenylisoquinoline (**12**) was synthesized as follows. Reduction of the cinnamic acid derivative **5**,[10] (obtained by Knoevenagel reaction of 6-bromoveratraldehyde (**4**) with cyanoacetic acid), with $NaBH_4$ in the presence of saturated $NaHCO_3$ aq[11] gave the expected hydrocinnamic acid derivative **6** in 95·2% yield. Decarboxylation of **6** was attempted by heating without solvent under reduced



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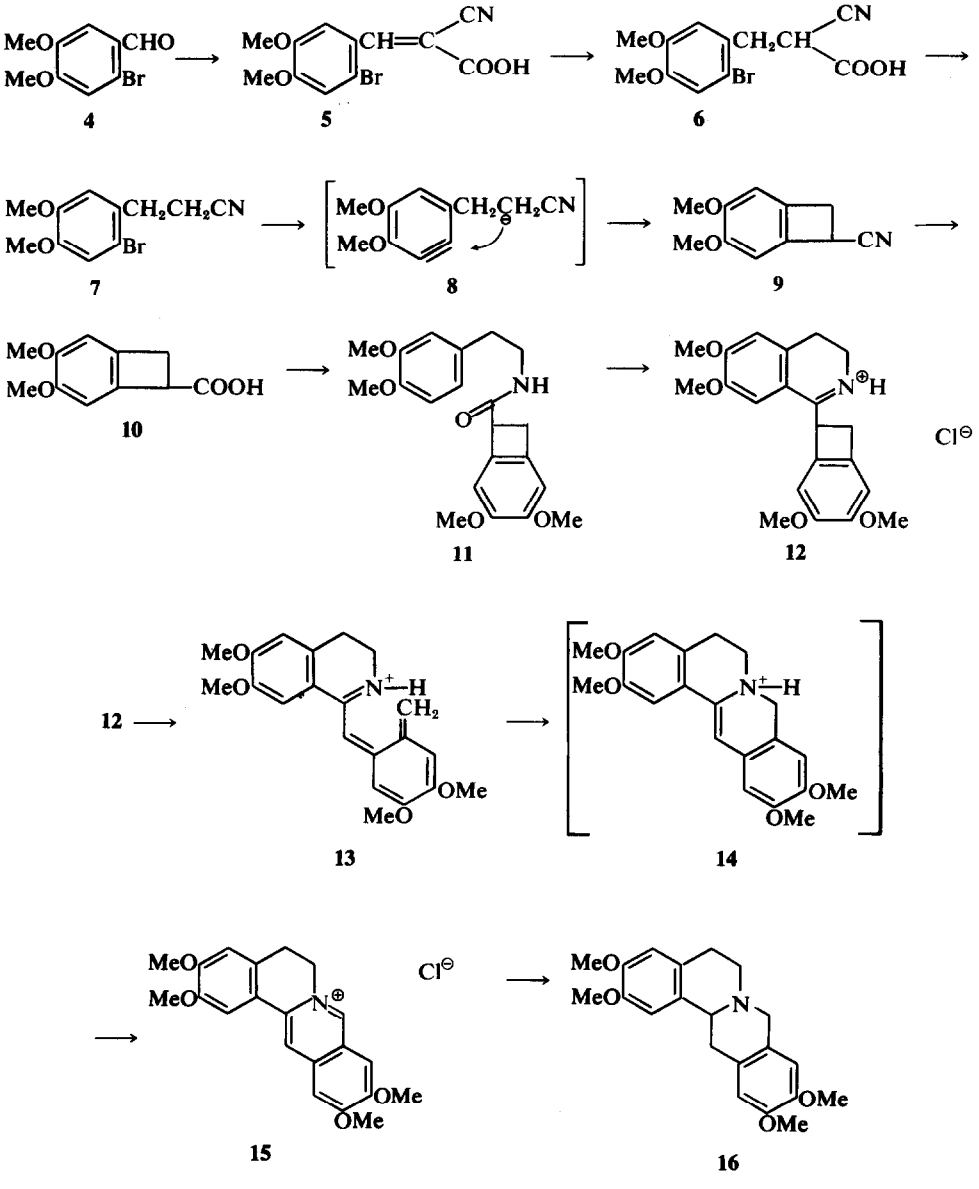
pressure, or by heating in DMF or biphenyl ether, but both failed. But treatment of **6** in hexamethyltriamide phosphate[12] successfully afforded hydrocinnamonitrile **7** within a few minutes in 85% yield. In this case the use of dimethylacetamide as solvent[13,14] also gave **7** in 95% yield. Treatment of **7** with 4 equimolar amounts of $NaNH_2$ in liquid NH_3 according to the Bunnett procedure[15] gave benzocyclobutene derivative **9** perhaps due to the benzyne reaction *via* intermediate **8** in 73·7% yield.[5]

Hydrolysis of nitrile **9** with KOH according to Cava's method[16] yielded the corresponding acid (**10**, 90·9%), which was condensed with 3,4-dimethoxyphenethylamine with dicyclohexylcarbodiimide in dichloromethane[17] to give amide **11** (82·7%). The Bischler-Napieralski reaction of **11** with phosphoryl chloride in benzene afforded the hydrochloride **12** of 3,4-dihydroisoquinoline derivative in 98·4% yield. Since the free base of **12** was unstable, the above hydrochloride **12** was used in the following reaction after purification.

Thermolysis of the hydrochloride **12** in bromobenzene at 150–160° for 18 min under a current of N_2 afforded, in 90% yield, our expected protoberberinium chloride **15**, which would be formed by dehydrogenation of intermediate **14**. In this case, even though dichlorobenzene was used as solvent, the same result was obtained. Catalytic hydrogena-



tion of the chloride (**15**) in the presence of Adams' platinum gave (±)-xylopinine (**16**), namely (±)-norcoralydine, in 90% yield, which was identical with authentic sample.[18]

This protoberberine alkaloid synthesis is such that if a suitable benzocyclobutene derivative could be obtained the above procedure would prove more convenient than the method of Mannich[19,20a–b] as regards synthetic steps and yields.

EXPERIMENTAL

M.p.'s are uncorrected and were determined on a Yanagimoto microapparatus (MP-S2). IR spectra were measured with a Hitachi EPI-3 and NMR spectra were measured on a Hitachi H-60 in $CDCl_3$ using TMS as an internal standard. The mass spectra were taken with a Hitachi RMU-7.

2-Bromo-4,5-dimethoxycyanocinnamic acid (**5**). A mixture of 13·5 g of 2-bromo-4,5-dimethoxybenzaldehyde (**4**), 4·4 g of cyanoacetic acid, 0·5 g of ammonium acetate, 50 ml of benzene, and 11 ml of pyridine was heated under reflux using a Stark and Dean apparatus. After a calculated amount of water (0·9 ml) had separated the mixture was cooled and crystals which separated were collected to give 15·45 g (72·2%) of pale yellow needles as pyridine salt of **5**; IR (nujol) 2200 (CN), 1670 cm^{-1} (C=O); NMR ($CDCl_3$+DMSO) δ 3·97 (6H, s, 2 × OMe), 8·70 – 6·80 (7H, m, 2-H, 5-H, py 5-H), 8·58 (1H, s, Ar—CH=C—).

After acidification of the above pyridine salt with 10% HCl work-up, followed by recrystallization from EtOH-DMF, gave acid **5** as pale yellow needles: m.p. 272–272·5° (decomp.); IR (nujol) 2200 (CN), 1700 cm^{-1} (C=O); NMR (DMSO) δ 3·86 (3H, s, OMe), 3·92 (3H, s, OMe), 7·42 (1H, s, 5-H), 7·92 (1H, s, 2-H), 8·47 (1H, s, Ar—CH=C—); *m/e* 311 (M^+), 313 (M^+ +2, isotope peak). (Calc for $C_{12}H_{10}BrNO_4$: C, 46·15; H, 3·21; N, 4·49. Found: C, 46·08; H, 3·01; N, 4·48%.)

β-(2-Bromo-4,5-dimethoxyphenyl)-α-cyanopropionic acid (**6**). To a soln of 58 g of the pyridine salt of the above acid **5** in 1·1 liter of sat $NaHCO_3$ aq 15 g of $NaBH_4$ was added in small portions with stirring at room temp. After addition, the stirring was continued for 0·5 hr. After the mixture had been acidified with 10% HCl, the precipitate was collected to give 44·45 g (95·2%) of **6** as colorless crystals: m.p. 166·5–168°; IR (nujol) 2250 (CN), 1735 cm^{-1} (C=O); NMR (DMSO) δ 3·5–3·05 (2H, m, Ar—CH_2—), 3·78 (6H, s, 2 × OMe), 4·30 (1H, q, J = 6 Hz, Ar—CH_2—C*H*—), 7·10 (1H, s, 5-H), 7·16 (1H, s, 2-H); (CF_3COOH) δ 3·85 – 3·10 (2H, m, Ar—CH_2—), 3·97 (6H, s, 2 × OMe), 4·35 (1H, q, J = 6 Hz, Ar—CH_2—C*H*—), 7·07 (1H, s, 5-H), 7·25 (1H, s, 2-H); *m/e* 313 (M^+), 315 (M^+ +2, isotope peak).

Recrystallization from C_6H_6-DMF gave acid **6** as colorless plates: m.p. 171–172°; IR (nujol) 2250 (CN), 1725 cm^{-1} (=O); NMR (pyridine-d_5)* δ 2·67 (1·5 H, s, NMe), 2·72 (1·5 H, s, NMe), 3·95 – 3·18 (2H, m, Ar—CH_2—), 3·70 (3H, s, OMe), 3·73 (3H, s, OMe), 4·37 (1H, q, J = 6 Hz, Ar—CH—CH<), 8·02 (½H, s, C*H*O), 12·12 (1H, s, COO*H*). (Calc for $C_{12}H_{12}BrNO_4 \cdot \frac{1}{2}C_3H_7NO$: C, 46·22; H, 4·42; N, 5·99. Found: C, 46·55; H, 4·12; N, 6·39%.)

*In order to prove this compound to be a dimethylformamide adduct, the NMR spectrum was measured in pyridine-d_5.

2-Bromo-4,5-dimethoxyhydrocinnamonitrile (**7**). (*a*) *decarboxylation in hexamethyltriamide phosphate.* A suspension of 1 g of cyanoacetic acid **6** in 2 ml of hexamethyltriamide phosphate was heated at 170° for 30 min, evolution of the calculated amount of CO_2 being observed. The mixture was mixed with water, acidified with HCl and $CHCl_3$ extracted. The extract was water washed, dried (Na_2SO_4), and evaporated to give a syrup, which was recrystallized from EtOH to give 0·9 g (85%) of nitrile **7** as colorless prisms: m.p. 79–80°; IR ($CHCl_3$) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 3·20 – 2·45 (4H, m, CH_2—CH_2), 3·85 (6H, s, OMe), 6·78 (1H, s, 5-H), 6·98 (1H, s, 2-H); *m/e* 269 (M^+), 271 (M^+ +2, isotope peak). (Calc for $C_{11}H_{12}BrNO_2$: C, 48·89; H, 4·44; N, 5·19. Found: C, 49·11; H, 4·32; N, 5·19%.)

(*b*) *Decarboxylation in dimethylacetamide.* A suspension of 1 g of the acid **6** in 2 ml of dimethylacetamide was heated at 170° and evolution of the calculated amount of CO_2 ceased after 10 min. The mixture was poured into water and set aside overnight. Crystals separated and were collected, washed with water and hexane, and recrystallized (EtOH) to give 0·8 g (95%) of nitrile **7** as colorless needles: m.p. 79·8–80°, the spectral data of which were identical with the sample prepared by method (*a*).

1-Cyano-4,5-dimethoxybenzocyclobutene (**9**). To a soln of $NaNH_2$, prepared from 200 ml of liquid NH_3 and 1 g Na ($FeCl_3$ catalyst) 5·4 g of nitrile **7** was added in portions and the mixture stirred at room temp for 2 hr. After evaporation of excess NH_3, 2 g NH_4Cl and 200 ml of water were added in portions. After standing at room temp, greyish crystals separated and were collected and recrystallized (EtOH) to give 2·75 g (73·8%) of cyclobutene **9** as colorless prisms, the Beilstein test of which was negative: m.p. 84·5–85°; IR ($CHCl_3$) 2250 cm^{-1} (CN); NMR ($CDCl_3$) δ 3·52 (2H, d, J = 4 Hz, CH_2), 3·84 (6H, s, 2 × OMe), 4·15 (1H, t, J = 4 Hz, 1-H), 6·68 (1H, s, 3-H), 6·77 (1H, s, 6-H); (benzene) δ 2·98 (2H, d, J = 4 Hz, CH_2), 3·35 (3H, s, OMe), 3·38 (3H, s, OMe), 3·55 (1H, t, J = 4 Hz, CH); *m/e* 189 (M^+).

4,5-Dimethoxybenzocyclobutene-1-carboxylic acid (**10**). A soln of 1·5 g of cyclobutene **9** in 6 ml of sat ethanolic KOH was kept at room temp overnight and the mixture then refluxed with 2 ml water for 3 h. After the mixture had been poured into 50 ml of water, the resulting alkaline layer was ether washed and acidified with HCl to precipitate a colorless powder, which was recrystallized from benzene to give 1·5 g (90·9%) of acid **10** as colorless plates: m.p. 142·5–143°; IR ($CHCl_3$) 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3·38 (2H, d, J = 4 Hz, CH_2), 3·83 (6H, s, 2 × OMe), 4·24 (1H, t, J = 4 Hz, CH), 6·68 (1H, s, 3-H), 6·75 (1H, s, 6-H), 10·80 (1H, s, COOH); *m/e* 208 (M^+). (Calc for $C_{11}H_{12}O_4$: C, 63·46; H, 5·77. Found: C, 63·69; H, 5·74%.)

N-(3,4-Dimethoxyphenethyl)-4,5-dimethoxybenzocyclobutene-1-carboxamide (**11**). To a soln of 5·43 g of 3,4-dimethoxyphenethylamine and 6·24 g of acid **10** in 120 ml of CH_2Cl_2 was added 6·8 g of dicyclohexylcarbodiimide at room temp with stirring and the mixture stirred for 2 h. After removal of an insoluble material, the filtrate was diluted with 200 ml of CH_2Cl_2. The organic layer was separated, washed with 2% HCl, 5% $NaHCO_3$ and water, and dried (Na_2SO_4). Evaporation of solvent, followed by trituration with benzene, gave a colorless powder, the recrystallization of which from benzene-hexane afforded 9·2 g (82·7%) of amide **11** as colorless needles: m.p. 108–109·5°; IR ($CHCl_3$) 3370 (NH), 1650 cm^{-1} (C=O), NMR

($CDCl_3$) δ 2·73 (2H, t, $J = 7$ Hz, CH_2), 3·05 (1H, a pair of doublets, $J = 13$ Hz, 3 Hz, CH_2, the lower-field portion of another proton of this methylene was obscured by the other methylene groups), 3·42 (2H, t, $J = 7$ Hz, CH_2), 3·78 (3H, s, OMe), 3·89 (9H, s, 3 × OMe), 4·03 (1H, a pair of doublets, $J = 5$ Hz, 3Hz, CH_2), 6·52 (1H, s, ArH), 6·64 (2H, s, ArH), 6·68 (2H, s, ArH); *m/e* 371 (M^+). (Calc. for $C_{21}H_{25}NO_5$: C, 67·92; H, 6·74; N, 3·77. Found: C, 68·03; H, 6·98; N, 4·12%.)

3,4-Dihydro-6,7-dimethoxy-1-(4,5-dimethoxybenzocyclobutenyl)isoquinoline hydrochloride (**12**). A mixture of 7·7 g of amide **11**, 5 g of phosphoryl chloride and 100 ml of dry benzene was refluxed for 2 h. After addition of excess hexane to the mixture, yellow crystals separated on cooling. Recrystallization from EtOH-hexane gave 8·0 g (98·4%) of hydrochloride (**12**) of 3,4-dihydroisoquinoline as yellow needles: m.p. 189–190°; IR (nujol) spectrum showed no absorption due to amide carbonyl group; NMR (DMSO) δ 3·75 (3H, s, OMe), 3·92 (9H, s, 3 × OMe), 5·51 br (1H, s, $\geqslant N^+H$), 6·90 (1H, s, ArH), 7·00 (1H, s, ArH), 7·17 (1H, s, ArH), 7·45 (1H, s, ArH); *m/e* 353 (M^+). (Calc for $C_{21}H_{24}ClNO_4$: C, 64·70; H, 6·16; N, 3·60. Found: C, 64·65; H, 6·42; N, 3·60%.)

The above hydrochloride (**12**) was made basic with ammonia and treated in a usual manner to give pale yellow crystals: m.p. 135–136° (decomp.), recrystallization difficult because of instability; NMR ($CDCl_3$) δ 2·58 (2H, t, $J = 7·5$ Hz, CH_2), 3·72–3·35 (4H, m, 2 × CH_2), 3·82 (6H, s, 2 × OMe), 3·85 (3H, s, OMe), 3·90 (3H, s, OMe), 4·72 br (1H, s, CH), 6·70 (3H, s, 3 × ArH), 7·07 (1H, s, ArH); *m/e* 353 (M^+).

2,3,10,11-Tetramethoxyprotoberberinium chloride (**15**). (*a*) *thermolysis in bromobenzene*. A suspension of 0·5 g of chloride **12** in 10 ml bromobenzene was heated at 150–160° in a current of N_2 for 18 min. After excess hexane had been added to the mixture, pale yellow crystals separated and were recrystallized (MeOH) to give 0·45 g (90%) of the ammonium chloride **15** as needles: m.p. 207–208°; IR (nujol) 1610 cm^{-1} ($>\overset{+}{N}=C$); NMR (CF_3COOH) δ 3·35 (2H, t, $J = 6·5$ Hz, 5-CH_2), 4·07 (9H, s, OMe, 2 × MeOH as solvated MeOH), 4·13 (3H, s, OMe), 4·18 (3H, s, OMe), 4·24 (3H, s, OMe), 4·88 (2H, t, $J = 6·5$ Hz, 6-CH_2), 7·05 (1H, s, ArH), 7·51 (1H, s, ArH), 7·56 (1H, s, ArH), 7·62 (1H, s, ArH), 8·42 (1H, s, ArH), 9·14 (1H, s, ArH); *m/e* 352 (M^+—Cl). (Calc. for $C_{21}H_{22}ClNO_4$, $2CH_3OH$: C, 61·11; H, 6·69; N, 3·10. Found: C, 61·07; H, 6·01; N, 2·81%.)

(*b*) *Thermolysis in o-dichlorobenzene*. Treatment of 100 mg of **15** in 15 ml of *o*-dichlorobenzene at 150–160° for 19 min, followed by the same work-up as method (*a*), gave 96·5 mg of **12**. The recrystallization from MeOH gave pale yellow needles, m.p. 207–208°, identical with the above sample.

(±)-Xylopinine (**16**) [*(±)-Norcoralydine*]. A soln of 50 mg of the chloride **15** in 10 ml of MeOH was hydrogenated in the presence of 53 mg of PtO in a current of H_2 until uptake of a calculated amount of H_2 ceased. After removal of catalyst, the filtrate was evaporated to give 45 mg (90%) of the hydrochloride of (±)-xylopinine (**16**) as a pale yellow syrup, which was recrystallized from MeOH-ether to give pale yellow needles: m.p. 213–214°. (Calc for $C_{21}H_{26}ClNO_4$: N, 3·57. Found: N, 3·45%.) A soln of the above hydrochloride was made basic with 10% ammonia and $CHCl_3$ extracted. The extract was water washed, dried (Na_2SO_4) and evaporated to give a syrup, which crystallized from EtOH as pale yellow plates: m.p. 150–151·5° [lit., m.p. 147–148°;[18] m.p. 145–145·5°;[20a] m.p. 157–158°;[21] m.p. 151·5–152·5°[22]], the IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of which were superimposable upon those of authentic sample. Recrystallization of the hydrobromide gave pale yellow needles: m.p. 217–218°. (Calc for $C_{21}H_{26}BrNO_4$: C, 57·80; H, 5·96; N, 3·21. Found: C, 57·73; H, 5·89; N, 3·45%.)

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