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

AN ALTERNATIVE SYNTHESIS OF THE PROTOBERBERINE RING SYSTEM

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Abstract—The reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (**11**) with 1-bromobenzocyclobutene (**10**) gave, in one step, 2,3-dimethoxyprotoberberinium bromide (**15**), which was easily converted into the tetrahydroprotoberberine (**16**).

It is well known that the benzocyclobutenes,[2,3] which have an internal strain,[4] undergo many interesting reactions. For example, heating the benzocyclobutene (**1**) afforded the *o*-quinodimethane (**2**) as an unstable intermediate by an electrocyclic reaction,[5] which then reacted with a dienophile system in an intra- or intermolecular mode to give the tetralin derivative (**3**).[6]

Bromination of benzocyclobutenol (**9**)[11] with triphenylphosphine dibromide[12] gave 1-bromobenzocyclobutene (**10**),[13] which was heated with 3,4-dihydro-6,7-dimethoxyisoquinoline (**11**) without solvent on a water bath for 20 h to give, surprisingly, the desired protoberberinium salt (**15**), but not the corresponding 2-(1-benzocyclobutenyl)-3,4-dihydroisoquinoline (**12**). The structure of **15** was

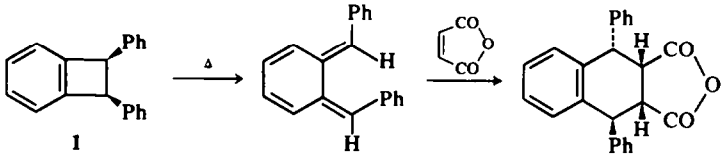

CHART 1

Based on this finding, we have also investigated the thermolysis of benzocyclobutenes and found that heating 1-benzocyclobutenyl-3,4-dihydroisoquinoline hydrochloride (**4**) in bromobenzene or dichlorobenzene, followed by catalytic hydrogenation of the resulting protoberberine (**5**), gave (±)-xylopinine (**6**) in good yield.[7] This reaction was also applied to the total synthesis of the tetrahydroprotoberberine alkaloids, discretine (**7**)[8] and coreximine (**8**).[9]

We were interested in determining whether the same type of rearrangement could occur with the *o*-quinodimethane derivative (**13**), derived by thermolysis of 2-(1-benzocyclobutenyl)-3,4-dihydroisoquinolinium salt (**12**), to give protoberberine (**15**)[7-9] or dihydroprotoberberine (**14**). Regarding the synthesis of the protoberberine and tetrahydroprotoberberine derivatives, a number of procedures have been reported,[10] but since this type of synthesis has not yet been reported, we now wish to describe these results.

determined by spectroscopic and chemical methods; the mass spectrum showed a molecular ion at *m/e* 292 ($M^+ - Br$), and the UV spectrum [λ_{max} (MeOH) 335, 276, 270, 255 and 250sh nm] revealed this product to have a protoberberine system.[14] Although the product (**15**) showed no change on heating in boiling dichlorobenzene it is easily reduced to the tetrahydroberberine base (M^+, *m/e* 295) which showed the typical fragmentation pattern in the mass spectrum (*m/e* 191 and 104) due to the tetrahydroprotoberberine.[15] The IR spectrum also revealed the Bohlmann bands in the region of 2850–2750 cm^{-1}.[16] These facts indicate that the product from 1-bromobenzocyclobutene (**10**) and 3,4-dihydroisoquinoline (**11**) should be the protoberberine (**15**), which was also supported by direct comparison of the tetrahydroprotoberberine (**16**) with an authentic specimen synthesised by Zymalkowski's method[14] from N-homovetatryl-2-hydroxymethylphenylacetamide. Since quaternary isoquinolinium salts having a benzocyclobutene

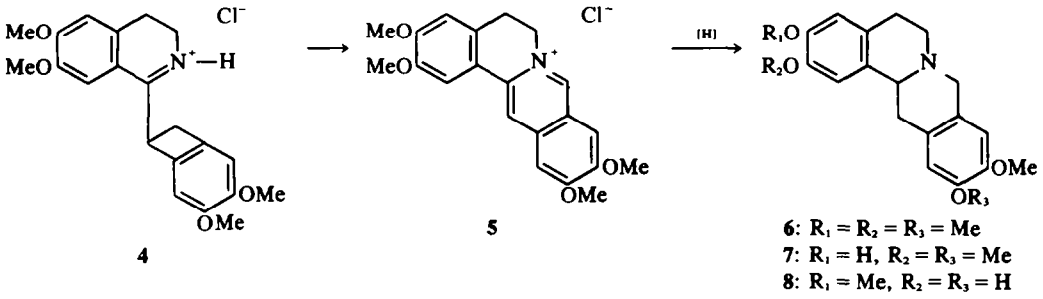

CHART 2

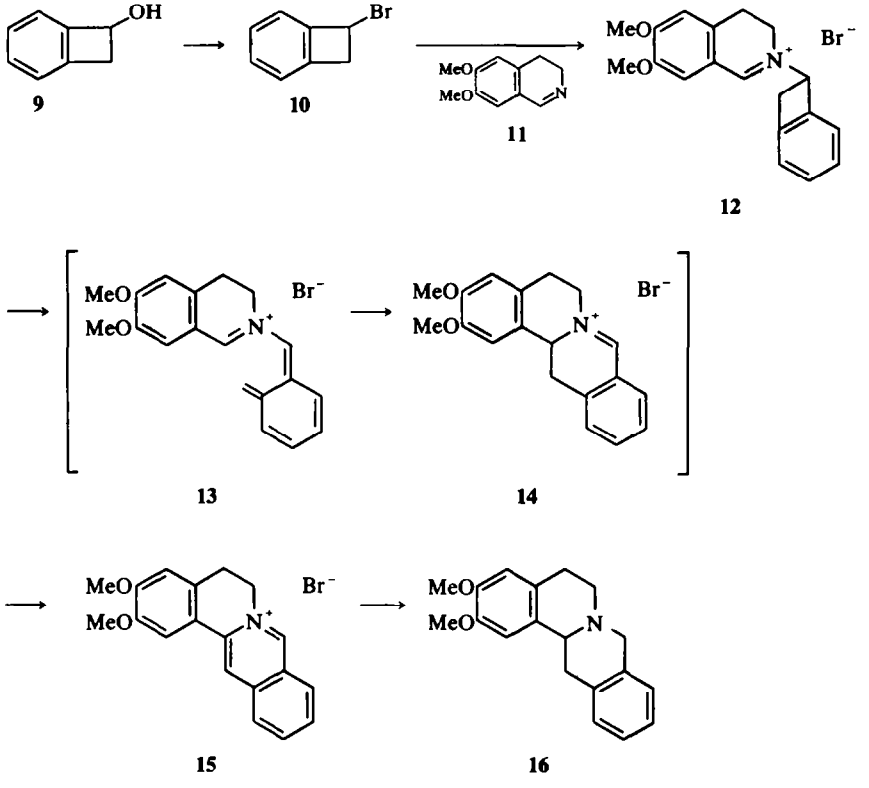

CHART 3

system would readily cleave to *o*-quinodimethanes,[17] it is reasonable to postulate that the quaternary salt **12** is transformed into protoberberine (**15**) via the unstable dihydroprotoberberine (**14**)[14] derived by cyclization of *o*-quinodimethane (**13**) as shown in Chart 3. However, an intermolecular cycloaddition can not be ruled out for the formation of protoberberine.[18] Thus, benzocyclobutene (**10**) could be thermally converted into *o*-quinodimethane (**17**), which reacts with 3,4-dihydroisoquinoline (**11**) to form the bromotetrahydroprotoberberine (**18** and/or **19**) that converts into the dihydroprotoberberine (**20** and/or **14**) as shown in Chart 4.

This transformation demonstrates a facile and simple entry into the synthesis of protoberberine type compounds.

EXPERIMENTAL

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.

1-*Bromobenzocyclobutene* (**10**). A soln of **9**[11] (120 mg) in 5 ml of dry CCl_4 was added dropwise to a suspension of triphenylphosphine dibromide[12] in 20 ml dry CCl_4 (prepared from 500 mg of triphenylphosphine and 320 mg of

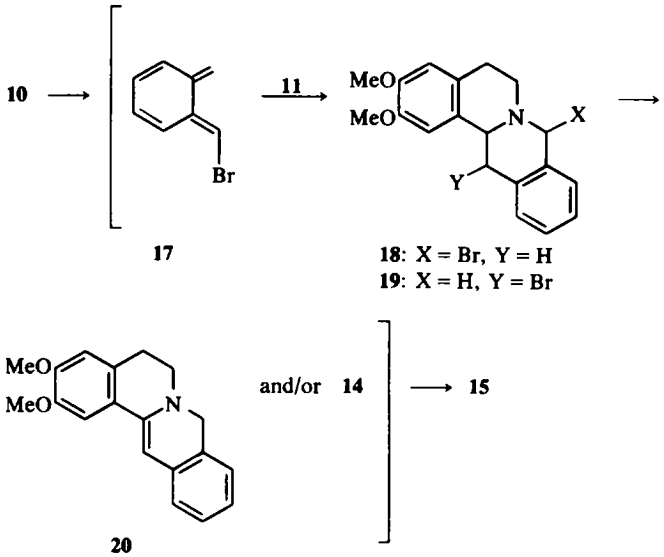

CHART 4

Br_2 in 20 ml of dry CCl_4) with stirring at room temp. The mixture was stirred for 50 min at the same temp and then refluxed for 20 min. The material which separated was filtered off, and the filtrate was evaporated *in vacuo* to leave a residue, which was subjected to silica gel (5 g) column chromatography. The benzene eluant gave 146 mg (79%) of **10** as a colorless oil: NMR ($CDCl_3$) δ 3·55 (1H, dd, J_{gem} = 15 Hz, J_{vic} = 2 Hz, —CH_2—), 3·60 (1H, dd, J_{gem} = 15 Hz, J_{vic} = 5 Hz, —CH_2—), 5·27 (1H, q, J = 5 and 2 Hz, —CHBr—), and 7·14 (4H, m, ArH).

2,3-*Dimethoxyprotoberberinium bromide* (**15**). A mixture of **10** (450 mg) and **11** (480 mg) was heated on a water bath for 20 h. The yellow crystals which separated were collected by filtration and recrystallised from MeOH–ether to give 230 mg (31%) of **15** as yellow needles; m.p. > 250°; IR (KBr) 1640 cm^{-1} (>C=N+<); UV λ_{max} (MeOH) (log ϵ) 335 (4·46), 276 (4·41), 270 (4·41), 255 (4·48), 250sh (4·47), 232·5 (4·52) nm; *m/e* 292 (M^+ – Br). Calc. for $C_{19}H_{18}BrNO_2.0{\cdot}5\,H_2O$: C, 59·85; H, 5·02; N, 3·68. Found: C, 60·32; H, 4·67; N, 3·68%).

The bromide (**15**) was treated with 10% NH_4OH and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to leave a residue, which was treated with conc HCl to give the protoberberinium chloride as yellow needles after recrystallisation from 2N–HCl and then MeOH–ether; m.p. > 250°. (Calc. for $C_{19}H_{18}ClNO_2.0{\cdot}5\,H_2O$: C, 67·75; H, 5·69; N, 4·16. Found: C, 67·50; H, 5·47; N, 4·28%).

7,8,13,13a - *Tetrahydro* - 2,3 - *dimethoxyprotoberberine* (**16**). To a soln of **15** (120 mg) in 10 ml of MeOH was added in small portions 50 mg of $NaBH_4$ with stirring under ice cooling, and the mixture was stirred for 0·5 h at room temp. After refluxing for 15 min, the solvent was distilled *in vacuo* to give a white residue, which was decomposed with 20 ml water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on 3 g of silica gel eluting with $CHCl_3$–MeOH (v/v 99:1) to give 95 mg of **16** as a yellowish orange oil; the IR (2850–2750 cm^{-1}; Bohlmann bands) and NMR spectra were superimposable with those of the authentic sample.[14] UV λ_{max} (MeOH) 286, 281 and 272; *m/e* 295 (M^+), 191 and 104; NMR (DMSO-d_6) δ 3·69 (3H, s, OMe), 3·72 (3H, s, OMe), 3·85 (1H, distorted t, J = 3 Hz, 13a-H), 6·60 (1H, s, ArH), 6·80 (1H, s, ArH), and 7·06 (4H, s, 4 × ArH).

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REFERENCES

[1]Part DXLIV, T. Kametani, F. F. Ebetino and K. Fukumoto, *Tetrahedron Letters* 5229 (1973)
[2]H. Finkelstein, *Ber. Dtsch. Chem. Ges.* **43**, 1528 (1910)
[3]I. L. Klundt, *Chem. Revs.* **70**, 471 (1970)
[4]Y. Hata, *Chemistry of the High Strained Compounds*, Kagaku Dojin, Tokyo (1972)
[5]R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press (1970)
[6]R. Huisgen and H. Seidel, *Tetrahedron Letters* 3381 (1964); G. Quinkert, K. Opitz, W. W. Wiersdorff and M. Finke, *Ibid.* 3009 (1965)
[7]T. Kametani, K. Ogasawara and T. Takahashi, *Chem. Comm.* 675 (1972); *Tetrahedron* **29**, 73 (1973)
[8]T. Kametani, Y. Hirai, F. Satoh, K. Ogasawara and K. Fukumoto, *Chem. Pharm. Bull. Tokyo* **21**, 907 (1973)
[9]T. Kametani, M. Takemura, K. Ogasawara and K. Fukumoto, *J. Heterocyclic Chem.* in press
[10]M. Shamma, *The Isoquinoline Alkaloids*, pp. 271–284. Academic Press, New York (1972)
[11]H. H. Wassermann and J. Solodar, *J. Am. Chem. Soc.* **87**, 4002 (1965)
[12]L. Horner, P. V. Subramaniam and K. Eiben, *Liebigs Ann.* **714**, 91 (1968)
[13]M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.* **80**, 2255 (1958)
[14]W. Meise and F. Zymalkowski, *Arch. Pharm.* **304**, 175 (1971)

[15]M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk and C. Djerassi, *J. Am. Chem. Soc.* **85**, 2807 (1963)
[16]F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958)
[17]T. Kametani, T. Takahashi and K. Ogasawara, *Tetrahedron Letters* 4847 (1972)
[18]T. Kametani, T. Takahashi, T. Honda, K. Ogasawara and K. Fukumoto, *J. Org. Chem.* in press.