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# Aromatization Reactions of Castanospermine Tetraacetate

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*Abstract*

The Polonovski reaction of castanospermine tetraacetate *N*-oxide with acetic anhydride gave (±)-1-acetoxy-8-hydroxy-2,3-dihydro-1*H*-indolizinium acetate (10) by aromatization of the piperidine ring. *N*-Bromosuccinimide oxidation of castanospermine tetraacetate gave a low yield (4%) of (+)-2-bromo-5,6,7,8-tetrahydroindolizine-6,7,8-triyl triacetate (13), by aromatization of the pyrrolidine ring.

## Introduction

Castanospermine (1), the major alkaloid from the seed of the Australian tree *Castanospermum australe* (black bean, Moreton Bay chestnut),[1] is a potent inhibitor of the enzyme α-glucosidase I,[2,3] and it shows some anti-HIV activity both *in vitro*[4] and *in vivo*.[5] The molecule is highly lipophobic, and the anti-HIV activity can be improved significantly by increasing the lipophilicity of the molecule by partial esterification.[6,7] In the present work, we attempted to find routes to lipophilic derivatives of (1) by functionalization at a carbon atom (C 3, C 5 or C 8a). The idea was to generate one of the corresponding iminium cations (3) (Scheme 1) by oxidation of castanospermine tetraacetate (2), and then to add a carbanion which could provide or lead to a lipophilic chain. This plan was, however, frustrated by the aromatization reactions described below.

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[6] Sunkara, P. S., Taylor, D. L., Kang, M. S., Bowlin, T. L., Liu, P. S., Tyms, A. S., and Sjoerdsma, A., *Lancet*, 1989, 1206.
[7] Ruprecht, R. M., Bernard, L. D., Bronson, R., Gama Sosa, M. A., and Mullaney, S., *J. Acquired Immune Defic. Syndr.*, 1991, **4**, 48.

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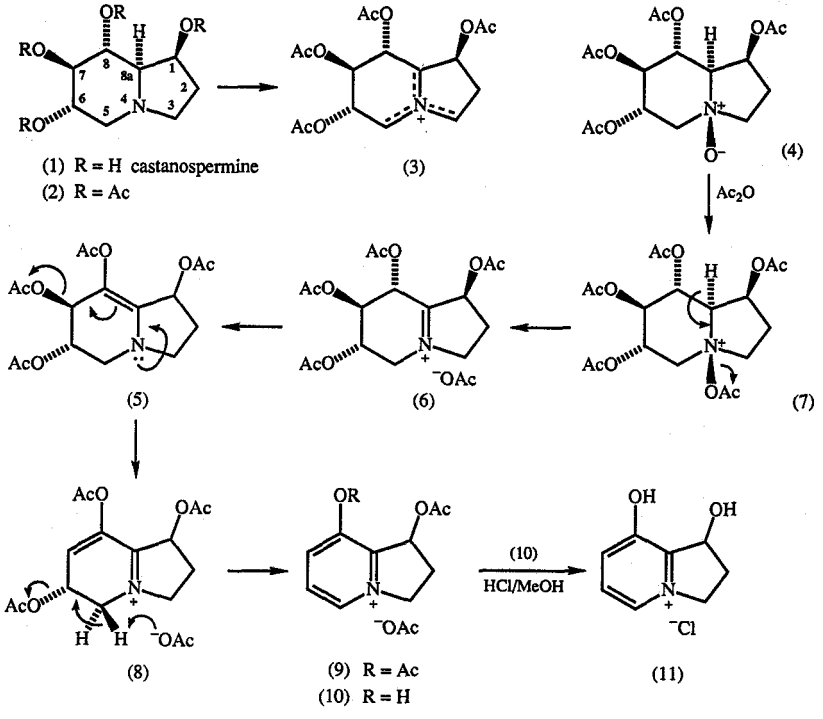
Reactions of castanospermine tetraacetate with active manganese dioxide or with 2,3-dichloro-5,6-dicyanobenzoquinone were not productive; with mercuric acetate in 5% aqueous acetic acid, oxidation occurred but no product was isolated. However, the Polonovski reaction[8] of the tetraacetate *N*-oxide (4) with acetic anhydride, and the bromination of the tetraacetate (2) with *N*-bromosuccinimide, led to products of aromatization of the piperidine ring and of the pyrrolidine ring, respectively.




Scheme 1

## Results and Discussion

Oxidation of the tetraacetate (2) with *m*-chloroperoxybenzoic acid gave the crystalline *N*-oxide (4) (56%). It is assumed that in this oxidation the stereochemistry of the ring junction of (1)[1] is retained to give the 4,8a-*trans* *N*-oxide; this is consistent with the ease of elimination in the subsequent Polonovski reaction under mild conditions. Treatment of the *N*-oxide (4) with acetic anhydride at room temperature for 7 days gave a viscous oil which showed infrared, ultraviolet and $^1$H n.m.r. spectra consistent with the indolizinium acetate structure (10). Brief treatment of (10) with methanolic hydrochloric acid afforded the crystalline dihydroxyindolizinium chloride (11). The 300 MHz $^1$H n.m.r. spectrum of the chloride (11) in $CD_3OD$ was similar, particularly in the aromatic region, to a 90 MHz spectrum of 8-hydroxy-2,3-dihydro-1*H*-indolizinium chloride,[9] kindly sent to us by Professor T. Shono (Kyoto University). The composition $C_8H_{10}ClNO_2$ for (11) was confirmed by microanalysis; mass spectrometry showed

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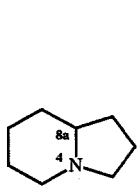
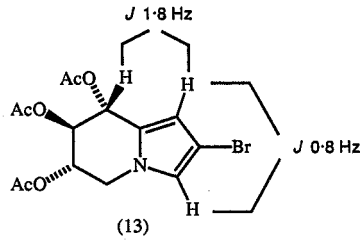
an ion of *m/z* 151 corresponding to the loss of hydrogen chloride. The indolizinium chloride (11) was racemic, and it appears that racemization occurred in the primary Polonovski reaction product (6) rather than in the eventual elimination products (9) and (10), because the latter did not undergo deuterium exchange at C 1 in $CD_3COOD$ containing sodium acetate during 14 days.

We suggest that in the Polonovski reaction the initial *N*-acetoxyperhydroindolizinium ion (7) undergoes diaxial elimination of acetic acid to give the 4,8a-iminium ion (6) which could equilibrate with the 1,8a-enamine (leading to racemization) and with the 7,8a-enamine (5). The enamine (5) could undergo elimination of acetate as shown to give (8). Aromatization is then completed by *trans*-5,6-elimination of acetic acid to give compound (9). The probability of initial 4,8a-iminium ion formation is based on the related mercuric acetate oxidation of $\delta$-coniceine (12) which gives only the corresponding 4,8a-iminium ion.[10]

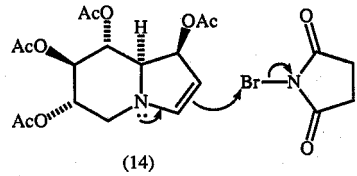
Oxidation of castanospermine tetraacetate (2) with 1 equiv. of *N*-bromosuccinimide in carbon tetrachloride, under irradiation from a tungsten lamp, led to a rapid reaction and precipitation of the hydrobromide of (2). The other product, however, was elusive, apparently because it was unstable to traces of acid. The reaction was rerun in the presence of 4 equiv. of anhydrous potassium carbonate, and, after recovery of (2) (90%), a crystalline brominated product, m.p. 112°, was obtained in 4% yield. Mass spectrometry and microanalysis established the composition $C_{14}H_{16}BrNO_6$, and the compound was optically active, $[\alpha]_D^{20}$ +3·2°. $^1$H n.m.r. spectrometry showed that the six-membered ring was probably intact, with three secondary acetoxy groups. Two downfield protons at $\delta$ 6·28 and 6·63 appeared to be *meta*-coupled ($J$ 0·8 Hz) in an aromatic ring. Further n.m.r. evidence summarized in the Experimental section is consistent only with the pyrrolic structure (13).




(12)




(13)




(14)

Bromination of *N*-substituted pyrroles with *N*-bromosuccinimide occurs at an $\alpha$-position;[11] the location of bromine in a $\beta$-position in (13) thus suggests that this $\beta$-bromine is introduced before aromatization, perhaps through attack on the 2,3-enamine (14). This in turn requires initial (? radical) attack by *N*-bromosuccinimide at H 3 of the tetraacetate (2). Aromatization could be completed by elimination of the *trans*-related H 8a and the 1-acetoxy group. All attempts to improve the yield of the bromo compound (13) by varying reactant ratios were fruitless.

[10] Leonard, N. J., Middleton, W. J., Thomas, P. D., and Choudhury, D., *J. Org. Chem.*, 1956, **21**, 344.
[11] Gilow, H. M., and Burton, D. E., *J. Org. Chem.*, 1981, **46**, 2221.

## Experimental

Melting points are uncorrected. Microanalyses were carried out by the National Analytical Laboratory, Melbourne. Infrared spectra were recorded with a Perkin–Elmer 1600 Fourier-transform spectrophotometer. Optical rotations were obtained with a Perkin–Elmer 141 polarimeter. N.m.r. spectra were measured with a Bruker AC200, or with a Bruker AM300 spectrometer. Chemical shifts ($\delta$) are in ppm from internal $SiMe_4$. Carbon resonances were assigned by use of a DEPT or J-MOD XH pulse sequence. Mass spectra were measured at 70 eV with a VG Micromass 7070F spectrometer with an INCOS 2400 data system or, with a VG TRIO-1 g.c./m.s. instrument. Ultraviolet spectra were recorded on a Hitachi 150-20 spectrophotometer. Analytical thin-layer chromatography (t.l.c.) was carried out on silica-coated plastic slides (Machery-Nagel Polygram SilG/u.v. 254). Flash chromatography was carried out with Merck Kieselgel 60 (230–400 mesh). Light petroleum refers to fractions of b.p. 60–75°.

*(1S,6S,7R,8R,8aR)-Octahydroindolizine-1,6,7,8-tetrayl Tetraacetate (2)**

Castanospermine (1) (2·49 g, 13·2 mmol) was added to a stirred solution of acetic anhydride (9·55 g, 71·3 mmol) and pyridine (60 ml) at room temperature. After 20 h the reaction mixture was poured into ice-cold water (100 ml) and extracted with dichloromethane (5×50 ml). The combined organic extracts were dried ($MgSO_4$) and filtered. Evaporation of the filtrate under vacuum gave a colourless solid (4·65 g) which showed several components on t.l.c., and which was purified by flash chromatography (silica, ethyl acetate/light petroleum, from 1:4 to 1:1). Recrystallization of the principal product from light petroleum yielded (1*S*,6*S*,7*R*,8*R*,8a*R*)-octahydroindolizine-1,6,7,8-tetrayl tetraacetate (4·11 g, 87%) as colourless crystals, m.p. 115°, $[\alpha]_D^{20}$ +40·3°, $[\alpha]_{578}^{20}$ +42·1°, $[\alpha]_{546}^{20}$ +48·2°, $[\alpha]_{436}^{20}$ +81·8°, $[\alpha]_{365}^{20}$ +122·3° (*c*, 0·7 in $CHCl_3$) (Found: C, 53·7; H, 6·4; N, 3·7. $C_{16}H_{23}NO_8$ requires C, 53·8; H, 6·5; N, 3·9%). $\nu_{max}$ (KBr) 2975m, 2835w, 1745s, 1733s, 1632w, 1438w, 1374s, 1250s, 1235s, 1137m, 1030s, 906m, 809m $cm^{-1}$. $^1H$ n.m.r. ($CDCl_3$, 300 MHz) $\delta$ 1·85, m, H 2$\alpha$; 1·97, 2·02, 2·03, 2·05, 4×Me; 2·13, m, H 5$\alpha$; 2·0–2·4, m, H 2$\beta$,3$\alpha$,8a; 3·23, m, H 3$\beta$; 3·40, dd, *J* 10·4, 4·3 Hz, H 5$\beta$; 5·08, m, H 6,7; 5·21, m, H 8; 5·37, m, H 1. $^{13}C$ n.m.r. ($CDCl_3$, 50·3 MHz) $\delta$ 20·50, 20·55, 20·62, 20·85, 4×Me; 31·5, C 2; 51·8, C 3; 52·7, C 5; 68·0, C 8; 68·3, C 8a; 70·0 and 74·9, C 6,7; 70·9, C 1; 169·5, 169·7, 2×CO; 170·3, 2×CO. Mass spectrum *m/z* (M absent), 297 (M−60, 8%), 238 (71), 237 (37), 235 (44), 196 (41), 194 (42), 178 (100), 164 (26), 152 (38), 136 (57), 134 (22), 111 (18), 109 (23), 82 (37), 79 (18), 69 (33), 57 (20).

*(1S,6S,7R,8R,8aR)-Octahydroindolizine-1,6,7,8-tetrayl Tetraacetate* N*-Oxide (4)*

*m*-Chloroperoxybenzoic acid (1·61 g, 9·34 mmol) was added in small portions to a stirred solution of castanospermine tetraacetate (2) (2·61 g, 7·31 mmol) in dichloromethane (30 ml). After 20 h the solvent was evaporated and water (50 ml) was added. The resulting mixture was extracted with ether (15×30 ml) to remove *m*-chlorobenzoic acid and the aqueous layer was evaporated under vacuum to give a colourless solid. Recrystallization from propan-2-ol yielded *(1S,6S,7R,8R,8aR)-octahydroindolizine-1,6,7,8-tetrayl tetraacetate* N*-oxide* (4) (1·52 g, 56%), m.p. 137–138°, $[\alpha]_D^{20}$ +0°, $[\alpha]_{578}^{20}$ +0·5°, $[\alpha]_{546}^{20}$ +6·2°, $[\alpha]_{436}^{20}$ +38·0°, $[\alpha]_{365}^{20}$ +77·8°, (*c*, 0·6 in MeOH) (Found: C, 51·2; H, 6·5; N, 3·4. $C_{16}H_{23}NO_9$ requires C, 51·5; H, 6·2; N, 3·7%). $\nu_{max}$ (KBr) 3646m (partial hydrate?), 3093s(br), 1753s, 1650w, 1432m, 1376m, 1217s(br), 1131m, 1056m, 1037m, 900m, 803w, 602w $cm^{-1}$. $^1H$ n.m.r. ($D_2O$, 300 MHz) $\delta$ 2·05, 2·06, 2×Me; 2·08, 2×Me; 2·45, m, and 2·78, m, H 2,2; 3·47–3·63, m, H 3,5; 3·72, apparent t, $J \approx 9·5$ Hz, H 8a; 3·95–4·06, m, H 3,5; 5·40, t, *J* 9·2 Hz, 1H, 5·64, m, 1H, and 5·68–5·78, m, 2H, H 1,6,7,8. $^{13}C$ n.m.r. ($D_2O$, 75 MHz) $\delta$ 20·0, 2×Me; 20·1, 20·3, 2×Me; 30·2, C 2; 61·8, C 3; 67·3, C 5; 66·1, 68·1, 68·9, 74·2, C 1,6,7,8; 74·3, C 8a; 172·3, 172·4, 173·0, 173·2, 4×CO. Mass spectrum *m/z* (M absent), 314 (M−59, 4%), 297 (4), 238 (25), 237 (16), 236 (18), 194 (15), 178 (35), 134 (18), 133 (41), 104 (19), 60 (100).

* Castanospermine tetraacetate has been reported in the literature[1] but full characterization has not been described.

*(±)-1-Acetoxy-8-hydroxy-2,3-dihydro-1H-indolizinium Acetate (10)*

Castanospermine tetraacetate *N*-oxide (4) (1·55 g, 4·16 mmol) was dissolved in acetic anhydride (20 ml) and allowed to stand at room temperature for 7 days. The mixture was evaporated under vacuum to give crude (±)-1-acetoxy-8-hydroxy-2,3-dihydro-1*H*-indolizinium acetate (10) (0·70 g, 90%) as a dark brown oil which was dissolved in ethyl acetate and passed through a Sephadex LH-2-100 column. Evaporation of the eluate under vacuum yielded a viscous pale brown oil. $\nu_{max}$ (film) 3422m, 1737s, 1670m, 1597m, 1413s, 1259s, 1093s, 1057s $cm^{-1}$. $\lambda_{max}$ (ethanol) 220 ($\log\epsilon$ 4·12), 259 (3·77), 332 nm (3·69). $^1H$ n.m.r. ($CDCl_3$, 200 MHz) $\delta$ 2·06, s, Me; 2·10, s, Me; 2·40, m, and 2·75, m, H 2,2; 4·61–4·84, m, H 3,3; 6·43, dd, *J* 6·8, 1·4 Hz, H 1; 7·41, dd, *J* 8·6, 5·5 Hz, H 6; 7·52, d, *J* 5·0 Hz, H 5; 7·58, d, *J* 8·6 Hz, H 7.

*(±)-1,8-Dihydroxy-2,3-dihydro-1H-indolizinium Chloride (11)*

Concentrated hydrochloric acid (2 ml) was added to a solution of (±)-1-acetoxy-8-hydroxy-2,3-dihydro-1*H*-indolizinium acetate (10) (399 mg, 1·58 mmol) in methanol (10 ml). After 0·5 h the solution was evaporated under vacuum to yield a brown solid. Recrystallization from methanol/ether afforded *(±)-1,8-dihydroxy-2,3-dihydro-1H-indolizinium chloride* (11) (159 mg, 54%) as a light brown solid, m.p. 185–186°, $[\alpha]_D^{20}$ −0·1°, $[\alpha]_{365}^{20}$ +1·1°, (*c*, 1·1 in MeOH) (Found: C, 51·0; H, 5·6; N, 7·4. $C_8H_{10}ClNO_2$ requires C, 51·2; H, 5·4; N, 7·5%). $\nu_{max}$ (KBr) 3294s, 3084s, 2985–2697s(br), 1591s, 1510s, 1471s, 1450s, 1369s, 1318s, 1263m, 1232m, 1083s, 1005s, 923m, 811s $cm^{-1}$. $\lambda_{max}$ (ethanol) 218 ($\log\epsilon$ 4·32), 258 (3·98), 329 nm (3·84). $^1H$ n.m.r. ($CD_3OD$, 300 MHz) $\delta$ 2·35, m, and 2·76, m, H 2,2; 4·74–5·05, m, H 3,3; 5·65, dd, *J* 7·0, 2·9 Hz, H 1; 7·80–7·89, m, H 6,7; 8·39, d, *J* 5·8 Hz, H 5. $^1H$ n.m.r. ($D_2O$/DCl/$D_2SO_4$, 200 MHz) ($\delta$ values relative to external $SiMe_4$ capillary tube) 1·62, m, and 2·10, m, H 2,2; 3·97, m, and 4·22, m, H 3,3; 4·97, dd, *J* 7·6, 4·0 Hz, H 1; 7·05, dd, *J* 8·6, 5·7 Hz, H 6; 7·20, d, *J* 8·5 Hz, H 7; 7·56, d, *J* 5·6 Hz, H 5. $^{13}C$ n.m.r. ($D_2O$/DCl/$D_2SO_4$) $\delta$ 30·6, C 2; 57·4, C 3; 71·0, C 1; 128·8, 131·8, 132·7, C 5,6,7; 153·7, C 8; (C 8a not observed). Mass spectrum *m/z* 151 (M−HCl, 38%), 150 (15), 134 (18), 133 (40), 122 (11), 104 (36), 95 (100), 94 (41), 78 (15), 67 (38), 66 (19), 51 (15).

*Attempted Deuterium Exchange of (±)-1-Acetoxy-8-hydroxy-2,3-dihydro-1H-indolizinium Acetate with $CD_3COOD$*

Anhydrous sodium acetate (2 mg) was added to a solution of indolizinium acetate (10) (20 mg) in $^2H_4$-acetic acid (0·4 ml). $^1H$ n.m.r. spectra recorded at 0, 3 and 14 days after mixing showed a slow transformation ($t_{1/2} \approx 3$ days) from the spectrum of (10) to that of the 1,8-dihydroxy system (11), but with no loss of $^1H$ signal from H 1.

*(6S,7R,8R)-2-Bromo-5,6,7,8-tetrahydroindolizine-6,7,8-triyl Triacetate (13)*

*N*-Bromosuccinimide (251 mg, 1·41 mmol) and anhydrous potassium carbonate (780 mg, 4×1·4 mmol) were added to a solution of castanospermine tetraacetate (500 mg, 1·40 mmol) in carbon tetrachloride (8 ml). The mixture was stirred and irradiated with a 60 W tungsten lamp for 3·5 h, and then filtered, and the solid was washed with carbon tetrachloride. The filtrate was evaporated and the green residue was stabilized by addition of a drop of triethylamine. Flash chromatography (silica, ethyl acetate/light petroleum, 1 : 4) yielded first a greenish-yellow oil (65 mg) followed by castanospermine tetraacetate (450 mg, 90% recovery). The oil was stabilized with a trace of triethylamine; it slowly crystallized at 0°, and recrystallization from ethyl acetate/light petroleum gave *(6S,7R,8R)-2-bromo-5,6,7,8-tetrahydroindolizine-6,7,8-triyl triacetate* (13) (20 mg, 4%) as colourless crystals, m.p. 111–112°, $[\alpha]_D^{20}$ +3·2° (*c*, 0·60 in $CHCl_3$) (Found: C, 45·3; H, 3·9; N, 3·6. $C_{14}H_{16}BrNO_6$ requires C, 44·9; H, 4·3; N, 3·7%). $\lambda_{max}$ (ethanol) 221 nm, ($\log\epsilon$ 3·48). $\nu_{max}$ 3129w, 3018w, 2962w, 1740s, 1653w, 1492m, 1428m, 1372s, 1302m, 1250s, 1226s, 1179m, 1074m, 1049s, 1019s, 970m, 926m, 871m, 807m, 769w, 693w, 641m, 604m $cm^{-1}$. $^1H$ n.m.r. ($CDCl_3$, 300 MHz) $\delta$ 2·08, 2·09, 2·10, 3×s, 3×Me; 4·04, dd, *J* 13·1, 5·0 Hz, and 4·25, dd, *J* 13·1, 4·2 Hz, H 5,5; 5·20–5·25, m, H 6; 5·39, dd,

*J* 6·0, 3·6 Hz, H7; 5·94, dd, *J* 3·6, 1·8 Hz, H8; 6·28, dd, *J* 1·8, 0·8 Hz, H1; 6·63, d, *J* 0·8 Hz, H3. $^{13}C$ n.m.r. ($CDCl_3$, 50·3 MHz) $\delta$ 20·7 and 21·0, 3×Me; 45·4, C5; 65·1, C6; 66·7, C7; 68·7, C8; 97·2, C2; 112·5, C1; 120·2, C3; 125·2, C8a; 169·2, 169·7, 169·8, 3×CO. Mass spectrum *m/z* 375 and 373 (M, <1%), 273 (30), 271 (32), 214 (60), 212 (100), 133 (40), 104 (10).

**Acknowledgment**

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