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Alkaloids of *Cephalotaxus harringtonia* var. *drupacea*. 11-Hydroxycephalotaxine and Drupacine[1a]

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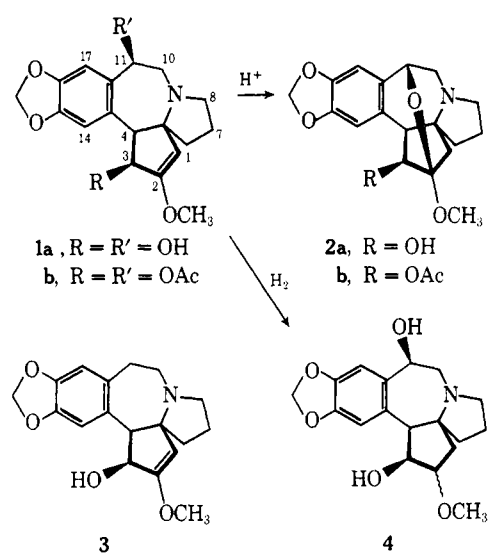
Two isomeric alkaloids, 11-hydroxycephalotaxine and drupacine, have been isolated from *Cephalotaxus harringtonia* var. *drupacea* (Sieb. + Zucc.) Koidzumi. Evidence is presented to show that these alkaloids are represented by structures **1a** and **2a**, respectively. Close proximity of the two hydroxyl functions of **1a** leads to some unusual reaction products. Nearly quantitative conversion of **1a** to ketal **2a** occurs under mild acidic conditions. Treatment of **1a** with tosyl chloride in pyridine affords cyclic ether **5**, and oxidation of **1a** under modified Oppenauer conditions results in formation of hemiketal **7**. The diacetate of **1a** is epimerized under extraordinarily mild conditions.

Initial investigations of the alkaloids of *Cephalotaxus drupacea* were carried out by Paudler, *et al.*,[2] and by McKay.[3] Although earlier listed as a member of the family Taxaceae,[4] the genus *Cephalotaxus* has now been assigned to a separate family, the Cephalotaxaceae, and the plant formerly referred to as *C. drupacea* is now considered to be *C. harringtonia* var. *drupacea*.[5] Two different structural types of *Cephalotaxus* alkaloids have been noted; the first group is based on the cephalotaxine ring system (**3**), and the second group embodies the homoerythrina ring system.[6,7] Several natural cephalotaxine esters have recently gained attention as potential tumor inhibitors.[8] This paper gives details of the structural determinations of two oxygenated cephalotaxine derivatives first noted in a seed extract of *C. harringtonia* var. *drupacea* and describes some unusual reactions of hydroxycephalotaxine. Portions of this work were described in a preliminary communication.[9]

Alkaloids **1a**, **2a**, and **3** were isolated by preparative tlc of an alkaloid concentrate from *C. harringtonia* var. *drupacea* twigs. The first of these (**1a**, $C_{18}H_{21}NO_5$, $[\alpha]^{26}D$ −139°) had a broad hydroxyl band in its ir spectrum (3500 cm^{-1}) indicative of strong intramolecular hydrogen bonding. An nmr spectrum of **1a** contained signals (Table I) that allowed assignment of the cephalotaxine (**3**) ring system to **1a** and, in addition, exhibited a signal at δ 4.78 which was assigned to a proton on a carbon bearing both hydroxyl and aryl groups (C_{11}). Preparation of a di-*O*-acetyl derivative (**1b**, $C_{22}H_{25}NO_7$) demonstrated that **1a** contained two hydroxyl groups. Signals attributed to protons on the two hydroxyl-bearing carbons (C_3 and C_{11}) were shifted markedly downfield, as expected, upon acetylation of **1a**. These observations led to the conclusion that **1a** was an 11-hydroxycephalotaxine.[9]



The second alkaloid was isomeric with **1a** (**2a**, $C_{18}H_{21}NO_5$, $[\alpha]^{26}D$ −137°), and its ir spectrum demonstrated the presence of at least one hydroxyl group (3600

Table I
Nmr Data for Hydroxycephalotaxine (1) and Some Reaction Products[a]

Protons and assignments	Alkaloid 1a	1b	2a	2b	4	5	7	9
H-1	4.68 s	4.74 s	1.49 d	1.55 d		4.56 s	4.60 s	5.33 s
H-1′			2.65 d	2.70 d				
$J_{1,1'}$			14.0	14.0				
H-3	4.48 d	5.71 d	3.99 d	4.78 d	4.12 t	4.05 d		5.72 d
H-4	3.48 d	3.57 d	3.45 d	3.75 d	3.16 m	3.17 d	3.24 s	3.58 d
$J_{3,4}$	8.0	8.0	9.0	9.0		5.0		8.0
H-10	3.21 m	3.26 m	3.05 m	3.07 m	3.16 m	2.77 d	2.79 m	4.25 q[b]
H-11	4.78 t	6.17 t	4.87 q	4.90 q	4.71 q	4.74 t	4.76 m	6.34 q
H-14	6.62 s	6.58 s	6.65 s	6.51 s	6.56 s	6.64 s	6.67 s	6.59 s
H-17	6.88 s	6.70 s	6.65 s	6.63 s	6.81 s	6.67 s	6.73 s	6.69 s
$-OCH_3$	3.71 s	3.68 s	3.47 s	3.45 s	3.39 s	3.68 s	3.72 s	3.80 s
$-OCH_2O$	5.91 s	5.90 s	5.82 s	5.87 m	5.87 s	5.89 s	5.89 s	5.97 s
$-OC(=O)CH_3$		1.85 s		1.66 s				1.88 s
		2.06 s						2.09 s

[a] Measured in $CDCl_3$ with a Varian HA-100 spectrometer. Chemical shifts (δ) are expressed in ppm from tetramethylsilane and coupling constants (J) are expressed in Hz. [b] This signal is due to only one of the H-10 protons.

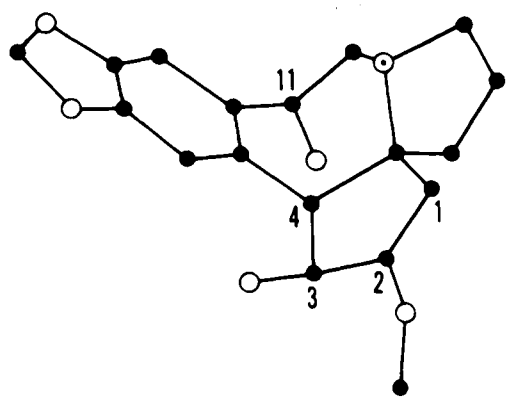


Figure 1. Stereoformula of 11-hydroxycephalotaxine (**1a**): O, carbon; ⊙, nitrogen; O, oxygen.

cm^{-1}); no carbonyl band was present. As in the case of **1a**, there were signals in the nmr spectrum of **2a** associated with a methylenedioxy group (δ 5.82), two para aromatic protons (δ 6.65), a methoxyl group (δ 3.47), and a proton on an oxygen-bearing carbon (δ 3.99) which was coupled to a benzylic proton (δ 3.45). The signal at δ 3.99 appeared as a broad triplet in $CDCl_3$ but collapsed to a sharp doublet when D_2O was added. Absence of any vinyl proton signals argued against the presence of a double bond in **2a**. A quartet appeared at δ 4.87 which was the X portion of an ABX system. Assuming that **2a** also had the cephalotaxine ring system, this signal was assigned to a proton on a carbon bearing both oxygen and aryl functions (C_{11}). An outstanding feature in the nmr spectrum of **2a** was the presence of two coupled (J = 14.0 Hz) one-proton doublets at δ 1.49 and 2.65. This coupling suggested that these were geminal protons in an isolated methylene group (C_1); no similar pair of doublets appeared in the spectrum of **1a**. Acetylation of **2a** gave a mono-*O*-acetyl derivative (**2b**, $C_{20}H_{23}NO_6$) demonstrating that **2a** contained only one hydroxyl group. The doublet at δ 3.99 in the nmr spectrum of **2a** shifted downfield to δ 4.78 in **2b**; however, the quartet at δ 4.87 was essentially unaffected. Thus the oxygen function assigned to C_{11} was necessarily involved in an ether-type linkage, and we concluded that the structure of **2a** could only be as shown. An alternative structure with an oxygen bridge between C_{10} and C_2 was considered unlikely from the nmr data and from inspection of molecular models.

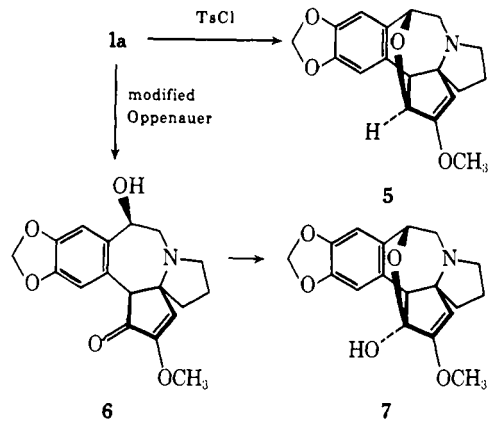
Alkaloid **2a**, for which we propose the name drupacine, can be regarded as a ketal formed by intramolecular addition of the C_{11} hydroxy group of **1a** to the double bond. McKay[3] reported an alkaloid (*Cephalotaxus* alkaloid G) with an nmr spectrum similar to that of **2a** although he did not assign a structure to it. In a recent paper, Asada[10a] reported an extensive reinvestigation of *Cephalotaxus* alkaloids including isolation of a compound (alkaloid IV) which he considers to be identical with McKay's alkaloid G.[10b] Neither of these workers appears to have encountered 11-hydroxycephalotaxine.

The structural relationship between **1a** and **2a** was confirmed by converting **1a** to **2a** under mildly acidic conditions; this conversion was essentially complete after 6 hr in 1.0 *N* hydrochloric acid at ambient temperature. In 5% tartaric acid, the reaction was approximately 5% complete in 1 hr and 50% complete in 24 hr. These observations suggest that a portion of **2a** from *Cephalotaxus* may be an artifact of isolation. However, it is unlikely that all of **2a** is formed in this manner since the time in contact with 5% tartaric acid was less than 2 hr during our isolation procedure. In order for such a reaction to occur, the configuration at C_{11} must be as shown in the accompanying stereoformula for **1a** (Figure 1). Molecular models reveal that a hydroxyl group at C_{11} is easily within bonding distance of C_2 and that the cage-like structure of **2a** is rigid but relatively unstrained. Models also demonstrate the close proximity of the C_3 and C_{11} hydroxyl groups of **1a** and explain the strongly hydrogen-bonded hydroxyl absorption noted in the ir spectrum.

We have confirmed the earlier observation that cephalotaxine (**3**) is resistant to catalytic hydrogenation.[3] In contrast, alkaloid **1a** was reduced to 11-hydroxy-1,2-dihydrocephalotaxine (**4**) in good yield with Adams catalyst in acetic acid. Under identical conditions, **1b**, **2a**, and **3** all gave no reaction. It is not apparent why the 11-hydroxyl group of **1a** should have such an accelerating effect on reduction. The configuration of the methoxyl group in **4** is uncertain although the nmr spectrum indicates that only one epimer is formed.

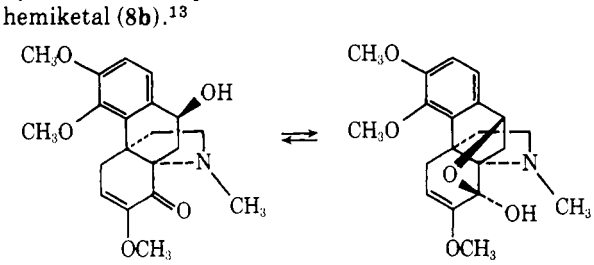
Previous experimentation had shown that the C_3 hydroxyl in cephalotaxine (**3**) is resistant to tosylation despite the fact that it is readily acetylated. We anticipated that the C_{11} hydroxyl in **1a** might be tosylated, leaving the C_3 hydroxyl unaffected and thus allowing removal of the C_{11} oxygen function by reduction with lithium aluminum hydride. However, when **1a** was treated with *p*-toluenesulfonyl chloride in pyridine, the only identifiable product was a cylic ether (**5**, $C_{18}H_{19}NO_4$). The structure of **5** was deduced from inspection of its ir (no hydroxyl or carbonyl), nmr, and mass spectra. Formation of **5** could be explained if an intermediate C_{11} tosylate or chloride

were the initial product. The chloride intermediate would most likely be inverted at C_{11} and consequently would be in a favorable position for back-side attack by the C_3 oxygen function to give the observed product. Similar chlorination reactions accompanied by inversion have been observed with methanesulfonyl chloride.[11,11a]

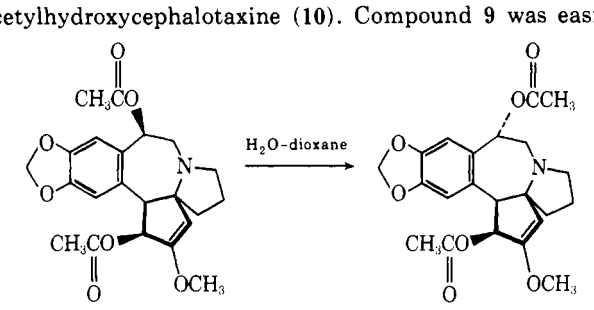


Oxidative approaches were also considered as a possible means of interconverting **1a** and **3**. Previous work had demonstrated that cephalotaxine is oxidized to cephalotaxinone by a modified Oppenauer procedure.[3,12] We applied this method to **1a** and obtained neither a dione nor **6** but instead isolated an abnormal product which was identified as 11-hydroxycephalotaxinone hemiketal (**7**). Although the nmr spectra of **5** and **7** were quite similar, the signal due to the proton on C_3 (d, δ 4.05) in **5** was absent in the spectrum of **7**, and the signal assigned to the proton on C_4 appeared as a singlet (rather than a doublet). Molecular models again demonstrated the rigid, but not highly strained, character of both **5** and **7**.

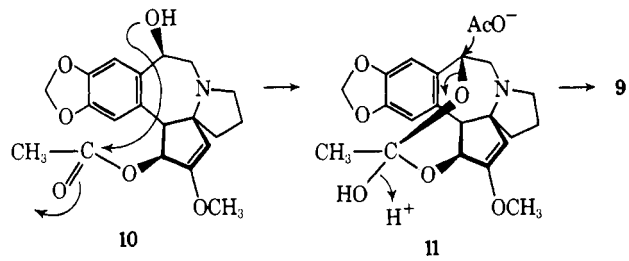
The relationship between compounds **6** and **7** is similar to that encountered with prometaphanine, which reportedly exists as an equilibrium mixture of a ketone (**8a**) and a hemiketal (**8b**).[13]



Slabaugh and Wildman[14] have reported the removal of a benzylic hydroxyl function in a successful conversion of 6-hydroxypowelline to powelline. The first step of their sequence involved a selective hydrolysis of 3,6-*O*,*O*-diacetylhydroxypowelline to 3-*O*-acetylhydroxypowelline at ambient temperature in dioxane-water. Following their procedure, we attempted selective hydrolysis of **1b** which gave an isomer (**9**) rather than the desired product, 3-*O*-acetylhydroxycephalotaxine (**10**). Compound **9** was easily



separated from the remaining **1b** by preparative tlc, and ir indicated that it contained no free hydroxyl groups. Mass spectra of **1b** and **9** were nearly identical. An nmr spectrum of **9** was similar to the spectrum of **1b** in that there were signals which could be attributed to two acetyl groups, a methoxyl group, a vinyl proton, a methylenedioxy group, and two aromatic protons. Also present was the characteristic pair of one-proton doublets due to the C_3 and C_4 protons (δ 5.72 and 3.58, J = 8.0 Hz). The chemical shift and coupling constant of the C_3 proton were nearly the same in both **1b** and **9** indicating that the configuration at C_3 had not changed. The vinyl proton signal had shifted downfield to δ 5.33 in the spectrum of **9**. A one-proton quartet at δ 6.34 was assigned to the C_{11} proton, and another quartet at δ 4.25 was assigned to one of the two C_{10} protons. These two protons were coupled, J = 11.0 Hz. Thus alkaloid **9** could only be the C_{11} epimer of **1b**. An acetate at C_3 is situated in an ideal position for transannular interaction with a C_{11} hydroxyl group formed in the hydrolysis. Although the mechanism of the epimerization is not known, S_N2 attack by the acetate ion on an ortho acid intermediate (**11**) could explain the results.



Other approaches to the interconversion of **1a** and **3** involved attempts to functionalize **3** at C_{11}. Oxidation of **3** under Étard conditions[15] gave a low yield of cephalotaxinone as the only recognized product. Reaction of **3** with *N*-bromosuccinimide,[16] in an attempt to brominate **3** selectively at C_{11}, again gave only cephalotaxinone; oxidation of alcohols is a well-known alternative reaction of *N*-bromosuccinimide.[17] Future attempts to functionalize **3** at C_{11} should be carried out on suitably blocked derivatives because the C_3 hydroxyl is quite sensitive to oxidation.

Conversion of **1a** to **2a** and to **5** and **7** leads us to conclude that the two hydroxyl groups can only be at C_3 and C_{11} with stereochemistry as shown. Examination of spectral data, molecular models, and considerations of possible mechanisms of formation of these products and of **9** all reinforce our structural assignment for **1a** which, incidentally, occurs as the most hindered of four possible geometric isomers. *C. harringtonia* var. *drupacea* is unique in containing these two alkaloids (**1a** and **2a**) not yet found elsewhere.[6,18]

Experimental Section

Melting points were determined on a Fisher-Johns[19] block and are uncorrected. A Beckman DK-2A spectrophotometer was used to record uv spectra, and ir analyses were done on 1% solutions in $CHCl_3$ with a Perkin-Elmer Model 137 instrument. Optical rotations were determined with a Cary Model 60 recording spectropolarimeter in 0.5-dm cells. Low-resolution mass spectra were obtained on a Du Pont (CEC) 21-492-1 spectrometer, and high resolution data with a Nuclide 12-90G spectrometer. Proton nmr spectra were measured with a Varian HA-100 instrument in $CDCl_3$ solution, and extensive spin decoupling was used to verify assignments.

All compounds and reaction mixtures were analyzed by tlc with appropriate solvent systems, normally $CHCl_3$–MeOH (9:1), on Brinkmann precoated 0.25-mm Silica Gel F-254 plates. Spots were visualized by staining the plates with iodine vapor. Preparative tlc separations were made on 1-mm Silica Gel G layers and

visualized with Bromothymol Blue. Samples were recovered from silica gel by washing with $CHCl_3$–MeOH (3:1), and all $CHCl_3$ extracts were routinely dried over anhydrous Na_2SO_4.

Isolation of Alkaloids. The general method for isolating crude alkaloid mixtures from *Cephalotaxus* plant material has previously been described in detail.[6] *Cephalotaxus harringtonia* var. *drupacea* (Sieb. + Zucc.) Koidzumi plants parts examined in this study included leaves, green twigs, woody stems, and seed.[20] Yields of crude alkaloid, expressed as percentages of total plant material, were as follows: leaf (0.15), twig (0.13), stem (0.12), and seed (0.81). Preliminary tlc of the leaf, twig, and stem samples indicated similar compositions with major amounts of alkaloids **1a** and **2a** along with lesser amounts of **3** and three minor unidentified materials. The seed sample contained several additional alkaloids.

A 1.0-g sample of crude alkaloid from twigs was separated on ten preparative tlc plates, which were developed with 15% MeOH in $CHCl_3$. This procedure gave alkaloids **1a** (280 mg), **2a** (290 mg), **3** (167 mg), and a mixture of unidentified materials (75 mg).

Preliminary separation of a 12.2-g sample of seed alkaloid was done by countercurrent distribution, and final separation of the individual alkaloids was carried out by a combination of column chromatography and preparative tlc. The entire procedure was described earlier.[6] Final alkaloid yields were as follows: **1a** (1.2 g), **2a** (1.9 g), and **3** (3.8 g). Two other alkaloids were positively identified by their mass and nmr spectra: harringtonine (0.8 g) and isoharringtonine (0.4 g).[8] A 3.3-g loss was encountered, most of which occurred during the column chromatographic step and left 0.9 g of unidentified material.

11-Hydroxycephalotaxine (1a). Alkaloid **1a** afforded colorless crystals from MeOH: mp 235–242° dec; $[\alpha]^{26}D$ −139° (*c* 0.56, $CHCl_3$); ir ($CHCl_3$) 3500 cm^{-1} (broad hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 331 (100), 314 (61), 313 (39), 300 (24), 298 (39), 295 (36), 287 (24), 270 (59), 255 (25), 253 (21), 244 (22), 214 (24), 138 (24), 110 (22).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.38; N, 4.22. Found: C, 65.41; H, 6.41; N, 4.23.

3,11-*O,O*-Diacetylhydroxycephalotaxine (1b). A 430-mg sample of **1a** was acetylated in 6 ml of acetic anhydride–pyridine (1:1) 18 hr at 26° and was then evaporated to a red-brown syrup on a rotary evaporator. The residue was dissolved in dilute NH_4OH, and products were recovered by $CHCl_3$ extraction. Crude product (443 mg) gave 265 mg of **1b** after preparative tlc on three plates (5% MeOH in $CHCl_3$). Alkaloid **1b** was obtained as a white amorphous solid: $[\alpha]^{26}D$ −168° (*c* 0.42, $CHCl_3$); uv max (C_2H_5OH) 289 nm (ϵ 3520), 237 (5830); ir ($CHCl_3$) 1740 cm^{-1} (ester carbonyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 415 (10), 372 (7), 356 (30), 342 (100), 329 (4), 324 (3), 312 (5), 296 (11), 282 (5), 268 (6), 264 (5), 253 (5), 252 (5), 227 (5), 214 (9).

Drupacine (2a). Alkaloid **2a** afforded colorless crystals from a minimum solution of MeOH–$CHCl_3$ (1:1) to which a large excess of hexane had been added: mp 70–72°; $[\alpha]^{26}D$ −137° (*c* 0.79, $CHCl_3$); uv max (C_2H_5OH) 291 nm (ϵ 4090), 242 (3110); ir ($CHCl_3$) 3600 cm^{-1} (hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 331 (88), 314 (10), 300 (26), 272 (10), 242 (14), 228 (23), 214 (14), 190 (84), 173 (14), 161 (73), 160 (14), 159 (20), 154 (41), 142 (100), 141 (48), 138 (38), 131 (16), 124 (28), 110 (31), 96 (18), 83 (36), 70 (18).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.38; N, 4.22. Found: C, 65.55; H, 6.49; N, 4.13.

3-*O*-Acetyldrupacine (2b). A 53-mg sample of **2a** was converted to **2b** (47 mg) by the procedure cited for the preparation of **1b**. Acetate **2b** was obtained as an amorphous white solid upon evaporation of an ether solution under vacuum: mp 75–90°; $[\alpha]^{26}D$ +26° (*c* 0.23, $CHCl_3$); ir ($CHCl_3$) 1740 cm^{-1} (ester carbonyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 373 (77), 356 (12), 330 (10), 314 (100), 254 (10), 242 (13), 228 (12), 214 (11), 190 (13), 189 (11), 173 (18), 172 (33), 161 (36), 154 (20).

Conversion of Hydroxycephalotaxine (1a) to Drupacine (2a). An 88-mg sample of **1a** in 10 ml of 1.0 *N* HCl was allowed to react at 26° for 6 hr. The reaction mixture was basified with Na_2CO_3 and then extracted repeatedly with $CHCl_3$. Preparative tlc of the crude product (91 mg) yielded 86 mg of **2a**: $[\alpha]^{26}D$ −62° (*c* 0.70, $CHCl_3$). The nmr, ir, uv, and mass spectra of **2a** produced in this manner were all indistinguishable from the corresponding spectra of naturally occurring **2a**.

In order to approximate acidic conditions encountered during isolation of the crude alkaloid mixture, 35-mg samples of **1a** were allowed to stand in 5% tartaric acid solution (26°) for periods of 1 and 24 hr, respectively. Products were recovered, after basification with ammonia, by extraction into $CHCl_3$. Under these conditions, conversion of **1a** to **2a** was approximately 5% complete in 1 hr and 50% complete in 24 hr, as judged by tlc.

Hydrogenation of Hydroxycephalotaxine (1a). A 53-mg sample of **1a** was hydrogenated at 26° and atmospheric pressure using Adams platinum catalyst in glacial HOAc (4 hr). Compound **4** (26 mg) was obtained by preparative tlc: ir ($CHCl_3$) 3400 cm^{-1} (broad hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 333 (100), 318 (28), 302 (18), 274 (65), 245 (64), 244 (35), 228 (46), 227 (21), 214 (18), 188 (20), 140 (26), 128 (19), 126 (39), 112 (27), 96 (37). Under identical conditions, **1b**, **2a**, and **3** all gave no reaction.

Anal. Calcd for $C_{18}H_{23}NO_5$: M^+, *m/e* 333.158. Found: M^+, *m/e* 333.156.

Compound 5 from Attempted Tosylation of 1a. To a solution of 120 mg of 1a in 5 ml of pyridine was added 177 mg of *p*-toluenesulfonyl chloride, and the resulting solution was allowed to react at 26° for 18 hr. Solvent was then evaporated under reduced pressure, the residue was dissolved in dilute NH_4OH, and 103 mg of crude product was recovered by ether extraction. Preparative tlc of the crude product yielded 19 mg of **5** along with 60 mg of a complex mixture of ill-defined materials. Compound **5** was an amorphous solid: $[\alpha]^{26}D$ +23° (*c* 0.18, $CHCl_3$), ir ($CHCl_3$) no hydroxyl or carbonyl bands; uv max (C_2H_5OH) 291 nm (ϵ 4460); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 313 (100), 298 (26), 282 (8), 270 (9), 255 (10), 243 (10), 188 (14), 175 (25), 150 (16), 110 (22).

Anal. Calcd for $C_{18}H_{19}NO_4$: M^+, *m/e* 313.131. Found: M^+, *m/e* 313.129.

Oppenauer Oxidation of 1a and Recovery of 11-Hydroxycephalotaxinone Hemiketal (7). Alkaloid **1a** (129 mg), benzophenone (540 mg), and potassium *tert*-butoxide (86 mg) were dissolved in 25 ml of *tert*-butyl alcohol, and the solution was refluxed for 6 hr. Solvent was removed on a steam bath under a stream of N_2, the residue was dissolved in 5% HOAc, and the resulting solution was extracted with $CHCl_3$ to remove neutral or acidic materials. The remaining aqueous solution was basified with NH_4OH and extracted again with $CHCl_3$. Preparative tlc of the crude product (86 mg) gave 49 mg of **7** and 24 mg of unreacted **1a**. Compound **7** was an amorphous material: ir ($CHCl_3$) 3600 cm^{-1} (hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 329 (100), 314 (18), 312 (22), 311 (13), 298 (17), 296 (22), 286 (25), 268 (19), 241 (15), 166 (15), 150 (45), 139 (77).

Anal. Calcd for $C_{18}H_{19}NO_5$: M^+, *m/e* 329.126. Found: M^+, *m/e* 329.126.

Attempted Selective Hydrolysis of 1b. A solution of 60 mg of **1b** in 10 ml of dioxane–water (1:1) was allowed to stand at room temperature for 72 hr. The solution was evaporated under reduced pressure, and chromatography of the crude product on a silica gel plate yielded 16 mg of unreacted **1b** and 21 mg of a new compound (**9**). The amorphous compound **9** gave no hydroxyl bands in the ir; nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 415 (5), 414 (6), 356 (11), 355 (6), 343 (19), 342 (100), 328 (8), 310 (6), 298 (5), 296 (6), 284 (6), 282 (5), 280 (5), 214 (6).

Anal. Calcd for $C_{22}H_{25}NO_7$: M^+, *m/e* 415.163. Found: M^+, *m/e* 415.164.

Oxidation of 3 with Chromyl Chloride. To a solution of 1.0 g of **3** in CCl_4 was added a solution of 0.3 ml of chromyl chloride in 5 ml of CCl_4. Considerable precipitate was formed immediately upon addition, and the mixture was allowed to stand for 3 hr. The precipitate was filtered and washed with CCl_4, yielding 285 mg of product. The precipitate was then dissolved in dilute aqueous NH_4OH, and the resulting solution was extracted repeatedly with $CHCl_3$ to yield an additional 500 mg of product. The recovered fractions appeared to be identical by analytical tlc and so they were combined; 400 mg of this mixture was separated by preparative tlc. This procedure yielded 21 mg of cephalotaxinone and 286 mg of unreacted **3**. These products were identical with known samples of the alkaloids as judged by ir, nmr, and mass spectra.

Reaction of 3 with *N*-Bromosuccinimide. To a solution of 200 mg of **3** in 6 ml of CCl_4 was added 115 mg of *N*-bromosuccinimide, and the resulting mixture was refluxed for 2 hr. Solids were then filtered and washed with $CHCl_3$. The filtrates yielded 237 mg of crude product which was then separated by preparative tlc. This procedure gave 68 mg of cephalotaxinone and 48 mg of unreacted **3**.

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(10) (a) S. Asada, *Yakugaku Zasshi*, **93**, 916 (1973). (b) The nmr spectra of McKay's alkaloid G, Asada's alkaloid IV, and our alkaloid **2a** show most of the same major peaks with only minor differences in some of the reported chemical shifts. Strikingly similar are the two doublets (δ 1.44 and 2.64, J = 14.0 Hz) attributed to an isolated methylene group. However, there are considerable differences in the melting points of our sample of **2a** (70–72°), Asada's alkaloid IV (80–82°), and McKay's alkaloid G (131–131.5°). The nmr spectra of the acetate derivatives of all three samples are also nearly identical.
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Oxymercuration–Demercuration of Limonene

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The oxymercuration–demercuration procedure, in aqueous THF, was applied to limonene (**1**) to investigate the behavior of its two double bonds. It was shown that *cis*-1,8-terpin (*cis*-**7**) and 1,8-cineole (**9**) were produced when a 1:2 limonene-$Hg(OAc)_2$ mole ratio was used. Production of α-terpineol (**5**) together with *cis*-**7** and **9** was observed when the limonene-$Hg(OAc)_2$ mole ratio was reduced (1:1 and 1:0.5). The reactions were very fast and no oxidative side process was evident. Further information on the reactivity of the endocyclic limonene double bond was given by comparison of the behavior of **5** and 1-*p*-menthene under the same reaction conditions. The results indicate that the first hydroxyl group that adds onto the external limonene double bond enhances the reactivity of the internal double bond, promoting a high overall reaction rate. Moreover, the unexpected production of both *cis*-**7** and **9** indicates that, although the first hydroxyl group is in an ideal position to react, *via* a six-membered ring, to give the corresponding cyclic ether **9**, the latter only partially forms, the major product being the corresponding diol *cis*-**7**.

We undertook the present study in order to investigate the relative reactivity of the two differently hindered unconjugated double bonds of limonene, with respect to the mercuric acetate addition, as part of a program which involves the combined use of mercuric acetate addition and tlc as a qualitative analytical tool for the monoterpene hydrocarbon class.[1] The isolation for identification purposes of the hydroxymercurials obtained carrying out the addition reactions in aqueous medium, appeared to be a matter of considerable difficulty. We then monitored the reactions *via* the isolation and identification of the products obtained by reduction of the mercuric adducts with $NaBH_4$, according to Brown's procedure.[2] This consists of an oxymercuration–demercuration sequence which provides, in this case, a convenient method of obtaining known monoterpene alcohols, easily detectable by glpc.

Results and Discussion

The following oxymercuration–demercuration scheme might result if account is taken of both reaction sites on the limonene molecule (Scheme I).

The reaction carried out in a 1:2 limonene–mercuric acetate molecular ratio was very fast,[3] coming to completion in a matter of seconds. Analysis for alcohols, after reduction, showed an almost quantitative yield of *cis*-1,8-terpin (*cis*-**7**) (hydrate) and 1,8-cineole (**9**). This implies that the endo- and exocyclic double bonds, despite the different steric hindrance, show a similar high reactivity. On the other hand, a considerable difference in reactivity should have promoted a sequence in the mercuration stage, most likely initially involving the external double bond and then the internal one after the first attack arrived at completion. Accordingly, running a reaction in a 1:1 limonene–mercuric acetate molecular ratio, would give rise to the adduct **4** as the major product which, on reduction, leads to α-terpineol (**5**), while β-terpineol (**3**), *cis*- or *trans*-**7** and **9**, which originate respectively from **2**, **6**, and **8** adducts, should be absent or present in only very small amounts. On the contrary, a high yield of *cis*-**7** (hydrate) and **9**, together with the expected **5**, was observed carrying out this 1:1 reaction, which was complete in the same time as the 1:2 ratio reaction. Obviously a corresponding amount of unreacted limonene was also found. The same situation concerning both products and rate was also observed running a 1:0.5 limonene–mercuric acetate reaction. It should be emphasized that the reactions were ex-