Unfortunately, these problems will always plague stereochemical studies of the pinacol rearrangement.

Experimental Section

The compounds discussed in this paper, **1–5**, have been reported elsewhere: **1** and **2**,[4] **3**,[5] **4**,[6] **5**.[3] Comparison of physical constants with those reported as well as the agreement of infrared and nmr spectra with the assigned structures confirmed the identity of the products.

General Procedure for Pinacol Rearrangement.—The glycol (0.1 g) was stirred with 5 ml of concentrated sulfuric acid. After 10 min the reaction mixture was poured into ice and water. The resulting aqueous solution was immediately extracted with methylene chloride, and the extracts were washed with 10% bicarbonate solution. The crude product was analyzed by analytical glc (6 ft × 6 mm glass column, packed with 16% hyprose SP 80 on 60–68 mesh Chromosorb W).

The spiranone **3** and the epoxide **5** were subjected to the same reaction conditions and work-up.

Registry No.—**1**, 39837-98-4; **2**, 39837-53-1; **4**, 14727-58-3.

Acknowledgments.—We are happy to acknowledge the financial support of the Endowment and Research Foundation of Montana State University, and the support of R. D. O. by a NDEA Predoctoral Fellowship, 1968–1971.

The Structures of Some of the Minor Alkaloids of *Cephalotaxus Fortunei*

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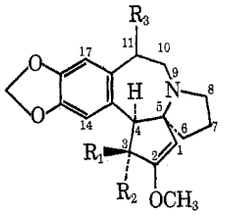
Received January 26, 1973

Some time ago[1] we reported on the isolation and partial structure elucidation of the major alkaloid of *Cephalotaxus fortunei* and *C. drupacea*, and named it cephalotaxine. Since this publication, the complete structure of cephalotaxine (**1**), as its methiodide, has been determined by X-ray crystallography,[2] and the alkaloid has been synthesized.[3,4]

Powell and coworkers[5] have also isolated, along with cephalotaxine, an ester of cephalotaxine, named harringtonine, which has shown significant inhibitory activity against experimental lymphoid leukemia systems L1210 and P388. Two minor alkaloids containing an oxygen function at R_3 in structure **1** have also been described.[5a]

We now wish to report on the isolation and structure

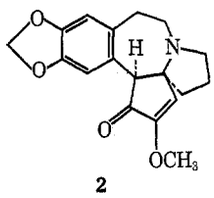


1, R_1 = OH; R_2 = H; R_3 = H
4, R_1 = H; R_2 = OH; R_3 = H

determination of some of the minor alkaloids of *Cephalotaxus fortunei*.

These minor alkaloids were obtained pure by careful column chromatography of the crude alkaloid mixture on neutral grade III alumina.

Alkaloid B.—This alkaloid was obtained in 1.08% yield of the crude alkaloid mixture. Its formula, as established by its mass spectrometric molecular weight and elemental analyses, is $C_{18}H_{19}NO_4$. Thus, it differs from cephalotaxine by having two fewer hydrogens. The infrared spectrum of this alkaloid, which is devoid of the hydroxyl absorption (3500 cm^{-1}) present in cephalotaxine, shows the presence of a carbonyl group (1720 cm^{-1}). Furthermore, the absorption due to the olefinic function in cephalotaxine (1665 cm^{-1}) is shifted to 1625 cm^{-1}. This bathochromic shift of the olefin absorption, in conjunction with the other observations (see Table I), suggests that alkaloid B is cephalotaxinone (**2**). It has now been shown that



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this alkaloid is also found in *C. harringtonia*.[5d] Furthermore, (±)-cephalotaxinone has recently been prepared as a key intermediate in the synthesis of racemic cephalotaxine,[3,4] and we have prepared it by Oppenauer oxidation of cephalotaxine (see Experimental Section).

Alkaloid C.—This minor alkaloid constitutes 5.4% of the crude alkaloidal mixture and is identical in every respect (infrared, ultraviolet, proton magnetic resonance spectrum, as well as by a mixture melting point determination) with an authentic sample of acetylcephalotaxine.[1] This alkaloid has also been isolated from *C. wilsoniana*.[1d]

Alkaloid D.—This compound is identical in every respect with demethylcephalotaxine (**3**), the product obtained by mild acid hydrolysis of cephalotaxine.[1]

Since cephalotaxine is stable to the conditions of isolation (as shown by subjecting it to the isolation procedure and recovering it without any loss), this alkaloid cannot be an artifact of isolation but is indeed present in the plant.

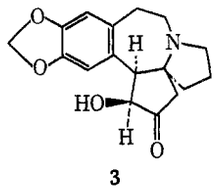

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TABLE I

PMR DATA FOR SOME MINOR ALKALOIDS OF *Cephalotaxus drupacea*

Positions[a]	Alkaloid B (2) cephalotaxinone	Alkaloid C acetylcephalotaxine	Alkaloid D (3) demethylcephalotaxine	Alkaloid E (4) epicephalotaxine	Cephalotaxine[1] (1, R = H)
1	6.42	5.76	2.51 (2 H)	4.76 (s)	4.85
3		5.02 (d)	3.48	4.59 (d)	4.71 (d)
4	3.51	3.75 (d)	3.70	3.04 (d)	3.62 (d)
14	6.69	6.56	6.92	6.59	6.63
17	6.61	6.53	6.65	6.64	6.60
$-OCH_2O-$	5.88	5.82	5.92	5.79 (s)	5.83
$-OCH_3$	3.78	3.68		3.66 (s)	3.67
$-OCOCH_3$		2.20			
J_{34}		9.0	4.6	5.3	9.0

[a] The numbering of this ring system is delineated in structure 1. The pmr spectra were obtained as dilute solutions in $CDCl_3$ with a Varian HA-100 spectrometer. Chemical shifts are given in δ (parts per million).

Alkaloid E.—This minor alkaloid was obtained in 0.001% yield from the crude alkaloidal mixture. Its infrared spectrum is almost superimposable on that of cephalotaxine. It is, however, not cephalotaxine, since its melting point is depressed upon admixture with cephalotaxine. The physical properties of this alkaloid are identical with those of the minor product obtained from the lithium aluminum hydride reduction of cephalotaxinone.[6] Thus, it is reasonable to assign to this alkaloid the epicephalotaxine structure **4.**

Experimental Section

All infrared spectra were obtained on either a Perkin-Elmer Model 21 or Model 237 infrared spectrophotometer. The optical rotations were measured on a Rudolph polarimeter. Mass spectra on all of the compounds were obtained with a Hitachi Perkin-Elmer RMU-6D instrument and gave the correct molecular weights. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn., and by the Analytical Services Laboratory of Ohio University. Chromatographic purity of all compounds was established by thin layer chromatography on silica gel G plates. The developing reagent was an aqueous potassium hexaiodoplatinate solution.

Isolation of Some of the Minor Alkaloids of *C. drupacea* (Table II).—A 31.1-g sample of the crude alkaloidal mixture of *Cephalotaxus drupacea* obtained as described in ref 1 was chromatographed on 1800 g of neutral grade III (Brockmann scale) alumina.

TABLE II

Fraction (12 ml/fraction)	Eluent	Weight, mg	Alkaloid
1–480	Benzene	0	
481–590	Benzene–ether (4:1)	0	
591–600	Benzene–ether	350	B
601–639	Benzene–ether	150	E + 3 compounds
640–1110	Benzene–ether	9910	cephalotaxine
1111–1120	Ether	400	F
1121–1169	Ether	0	
1170–1360	Ether–ethyl acetate (95:5)	841	G
1361–1612	Ethyl acetate	0	
1613–1622	Methyl alcohol	3730	C + other alkaloids
1623–1910	Methyl alcohol	9000	D + complex mixture

Alkaloid B.—The 350 mg (fractions 591–600) (1.08% of the crude alkaloidal mixture) of the crude alkaloid obtained from column chromatography was dissolved in ether and the hot suspension was filtered through 5.0 g of Brockmann grade V neutral alumina. The eluent was evaporated to a volume of 5 ml and allowed to stand at room temperature overnight. The white, crystalline solid which separated (75 mg) was recrystallized from ether (mp 198–200° dec, vacuum cap), $[\alpha]^{24}D$ −146° (*c* 0.63, $CHCl_3$). An additional 160 mg of this compound was obtained from further concentration of the ether solution. *Anal.* Calcd for $C_{18}H_{19}NO_4$: C, 68.97; H, 6.11; N, 4.5; O, 20.42. Found: C, 69.05; H, 6.37; N, 4.76. The infrared spectrum of this alkaloid as well as its pmr spectrum and chromatographic behavior are identical with those of cephalotaxinone.

Cephalotaxinone (2).—A solution of potassium *tert*-butoxide was prepared by dissolving 66 mg of potassium in 15 ml of *tert*-butyl alcohol. To this solution was then added 49 mg of cephalotaxine and 61 mg of benzophenone. The resulting solution was then refluxed for 10 hr and evaporated to near dryness under a stream of nitrogen. The residual material was partitioned between 20 ml of water and 20 ml of $CHCl_3$. The basic, aqueous layer was extracted with four 10-ml portions of 5% aqueous hydrochloric acid and the combined extracts were made basic with saturated aqueous Na_2CO_3. This solution was then extracted with two 20-ml portions of $CHCl_3$ and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to yield 27 mg of a white solid which was recrystallized from ether to afford 18 mg of cephalotaxinone [mp 199.5–200.6° dec, vacuum cap; $[\alpha]^{24}D$ −155° (*c* 0.35, $CHCl_3$)]. This compound is identical in every respect with alkaloid B (infrared and pmr spectra, mixture melting point).

Alkaloid C.—The material obtained from the combined fractions 1613–1622 was dissolved in 50 ml of 5% aqueous HCl. The solution was filtered and the filtrate was made basic with solid Na_2CO_3. The precipitate which formed (678 mg) was filtered and dried (silica gel G). Tlc of this dark brown, amorphous material with 10:1 cyclohexane–diethylamine as solvent showed at least six components. The aqueous basic filtrate was extracted with four 50-ml portions of $CHCl_3$, the combined extracts were dried over anhydrous Na_2SO_4, and the filtrate was evaporated to dryness. The light yellow, amorphous solid (1.69 g) was found to be fairly basic ($pK_A' = 7.1$) and was obtained crystalline by recrystallization from ether. The resulting compound (mp 141–143°) is identical in every respect (infrared, pmr spectra, and mixture melting point) with acetylcephalotaxine as described in ref 1.

Alkaloid D.—The combined fractions 1623–1910 (9.00 g) were rechromatographed on neutral grade IV alumina. Elution with ether afforded 600 mg of a white, amorphous solid whose infrared spectrum shows absorption at 1705 cm^{-1}. The spectrum lacks the strong 1665-cm^{-1} absorption of the C=C function present in cephalotaxine. The compound gives a positive test with periodic acid.

The compound could, finally, be obtained crystalline by recrystallization from a small amount of ethanol to afford a solid, mp 109–111°, $[\alpha]^{25}D$ −110° (*c* 0.28, $CHCl_3$). This alkaloid is identical (nmr, infrared, tlc) in every respect with the acid hydrolysis product of cephalotaxine, identified as demethylcephalotaxine.

Demethylcephalotaxine.—This compound was described by us in an earlier paper, but had not been obtained in crystalline form at the time.[1] The amorphous material (100 mg) obtained by the procedure described in this paper was finally obtained crystalline by dissolving it in a minimum amount of absolute ethanol and allowing it to stand undisturbed in the refrigerator for 2 days.

The crystalline compound (70 mg) melted at 110–112.5°, $[\alpha]^{25}D$ −125° (*c* 0.60, $CHCl_3$). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 59.45; H, 5.58; N, 16.32. Found: C, 59.20; H, 5.79; N, 16.58.

(6) It is of interest to note that reduction of cephalotaxinone with $NaBH_4$ or with diisobutylaluminum hydride has been reported to yield cephalotaxine exclusively.[4,5]

Alkaloid E.—The combined fractions 601–639 (150 mg) were rechromatographed on 500 g of neutral grade IV alumina; elution with benzene (200 ml) afforded 50 mg of a readily crystallizable alkaloid, mp 136–137°, $[\alpha]^{25}D$ −150° (*c* 0.8, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.72; N, 4.44. Found: C, 68.46; H, 6.49; N, 4.60. This alkaloid is identical in every respect (infrared, pmr, tlc) with the minor reduction product, epicephalotaxine, obtained from the reduction of cephalotaxinone.

Epicephalotaxine.—In a 50-ml flask of a micro Soxhlet extractor was placed 150 mg of cephalotaxinone and 40 ml of dry tetrahydrofuran. The solution was refluxed for 4 hr, and the condensing vapors were passed over 500 mg of lithium aluminum hydride contained in the extraction cup of the apparatus. The excess lithium aluminum hydride was then decomposed with saturated aqueous Na_2SO_4. The mixture was filtered and to the filtrate was added 200 ml of ether. The organic layer was then collected, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The remaining amorphous material (120 mg) was chromatographed on 200 g of neutral grade IV alumina. Slow chromatographic elution with benzene (75 ml) afforded 15 mg of epicephalotaxine, mp 135–137°. *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.5; H, 6.72; N, 4.44. Found: C, 68.38; H, 6.90; N, 4.60.

Further elution with benzene (300 ml) afforded a mixture (105 mg) of mainly cephalotaxine with only a trace of epicephalotaxine, as determined by tlc [R_f (epicephalotaxine)/R_f (cephalotaxine) 1.0–1.35, tlc silica gel plates, benzene].

Registry No.—**1**, 24316-19-6; **2**, 38750-57-1; **3**, 39707-71-6; **4**, 39707-72-7; acetylcephalotaxine, 24274-60-0; benzophenone, 119-61-9; tetrahydrofuran, 109-99-9.

Acknowledgment.—The partial financial support of this work by the National Science Foundation in the form of Grant G-25071 is gratefully acknowledged.

Thermal Decomposition of a Phenanthroxyl Quinol Ether. A Kinetic Study Using Laser Raman Spectroscopy

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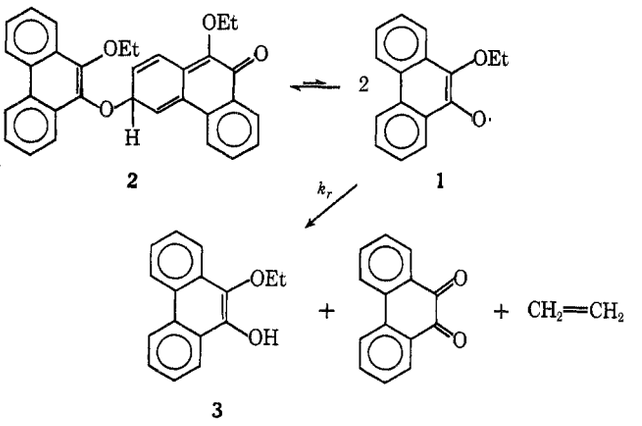
Received December 15, 1972

We have recently shown that the 10-ethoxy-9-phenanthroxyl radical **1** exists in equilibrium with its dimer **2** both in solution[2] and in the solid state,[3] and that the thermolysis of degassed samples of **2**, either in solution or as neat melts, leads to the slow formation of equimolar amounts of 10-ethoxy-9-phenanthrol (**3**), phenanthrenequinone, and ethylene.[2,3] This is thought to occur *via* disproportionation of **1**, as indicated in Scheme I, although unimolecular decomposition of **2** cannot be rigorously excluded. It is characteristic of this system and of other quinol ethers[4,5] that the ir, uv, and nmr spectra of the dimers and of the decomposition products are sufficiently complex and overlapped as to be useless for kinetic analysis of the decomposition; the usual recourse has been to monitor the concentration of radicals by esr.[2,5] We now wish to report that the thermolysis of **2** in degassed solution may be conveniently followed by laser Raman spectroscopy, which makes possible the direct monitoring of both **2** and **3**.

SCHEME I



In the course of routine laser Raman studies, it was noticed that spectra of *ca.* 0.1 *M* solutions of **2** in CCl_4 contained a peak at 1354 cm^{-1} attributable to **3** in addition to a peak at 1292 cm^{-1} characteristic of **2** (Figure 1). The frequency of the peak at 1292 cm^{-1} suggests that it is associated with the aryl ether C–O linkage in **2**; since the peak at 1354 cm^{-1} is also present in spectra of 10-chloro-9-phenanthrol, we infer that it is associated with the phenanthrol C–O bond. It should be noted that the positions of both peaks are insensitive to concentration and are, in fact, the same in solution as in the solid phase.

Since the amplitudes of the two peaks are proportional to the concentrations of **2** and **3**, it should in principle be possible to use the measured amplitudes directly for kinetic analysis. That turned out not to be true in this case; the high concentration of **2** required for the laser Raman spectra resulted in gradual precipitation of phenanthrenequinone as the decomposition progressed, causing excessive noise and base-line drift at reaction times longer than about 55 hr. As Table I shows, the observed amplitudes were unsuitable for direct analysis because of light scatter and base-line drift induced by the precipitate. However, since both peaks appear to arise from a vibrational mode of the aryl C–O group, it is not unreasonable to assume that the molar intensities of the two peaks are similar, if not equal. Given the known[2] 1:1 re-

TABLE I

NORMALIZATION OF LASER RAMAN KINETIC DATA[a]

Time, hr	Observed amplitudes, mm 1292 cm^{-1}	1354 cm^{-1}	Sum	N^b	Normalized amplitudes, mm 1292 cm^{-1}	1354 cm^{-1}
0.0	47	24	71	1.41	66	34
5.0	48	43	91	1.10	53	47
18.0	40	47	87	1.15	46	54
30.0	38	58	96	1.04	40	60
42.3	25	47	72	1.39	35	65
54.5	19	44	63	1.59	30	70

[a] Degassed 0.10 *M* solution in CCl_4 at 67°. [b] Normalization factor = 100/sum.

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