0.050 N sodium acetate in acetic acid and, for 2,2,2-trifluoroethanolysis, 0..020 N sodium methoxide in anhydrous methanol.[37] The indicators used were Bromphenol Blue (in acetic acid) and Bromphenol Blue (in 20% aqueous alcohol), respectively.

Treatment of Kinetic Data. The thermodynamic activation parameters were obtained by IBM 1620 computer regression analysis. The correlation coefficients, R, and also the Hammett ρ value were obtained by IBM 1620 computer regression analysis.

Acknowledgment. Appreciation is expressed to Mr. Richard Chang for experimental assistance.

Registry No.—1-Phenylcyclobutanecarbonitrile, 14377-68-5; benzyl cyanide, 140-29-4; 1,3-dibromopropane, 109-64-8; 1-*p*-methoxyphenylcyclobutanecarbonitrile, 29786-45-6; *p*-methoxybenzyl cyanide, 104-47-2; 1-*p*-methylphenylcyclobutanecarbonitrile, 29786-41-2; *p*-methylbenzyl cyanide, 2947-16-7; 1-*p*-nitrophenylcyclobutylcarbinol, 50921-42-1; 1-phenylcyclobutylcarbinyl acetate, 50921-43-2.

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Crystal and Molecular Structure of Cephalotaxine *p*-Bromobenzoate

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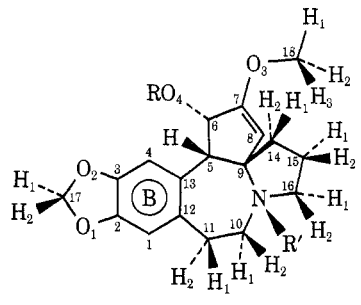
An X-ray study on the title compound verifies the constitution and relative configurations proposed for cephalotaxine and its esters, and shows for the first time the absolute configuration (5*S*). The conformation of the cephalotaxine portion of the molecule closely resembles that of the racemic methiodide, and is probably favored as well in the natural antileukemic cephalotaxine esters.

Several natural esters of cephalotaxine (I) have been found to be potent antileukemic agents, *e.g.*, homoharringtonine (II), which is undergoing preclinical testing.[1] An X-ray study has been carried out on the methiodide III, formed by reacting cephalotaxine (I, optically active) with methyl iodide at room temperature and recrystallizing from warm methanol.[2] Unexpectedly, the methiodide III was found to be racemic, indicating that the configurations at *all four* chiral centers are subject to change during the warming (no doubt *via* intermediates in which the C-9–N bond has cleaved), and thus no firm conclusions regarding the stereochemistry of cephalotaxine (I) could be drawn from the methiodide X-ray study. Two recent syntheses of racemic cephalotaxine (I), however, have lent some support to the view that its *relative* configurations are the same as those found in the racemic methiodide III.[3] We wish to report the results of an X-ray study on the title compound (IV), undertaken to check the proposed constitution and relative configurations and to establish the absolute configuration.

Experimental Section

Cephalotaxine *p*-Bromobenzoate (IV). A 2.05-g sample of *p*-bromobenzoyl chloride was added to a solution of 1.065 g of ce-



	R	R′
I	H	··
II	$C_9H_{17}O_4$—C(=O)—	··
III (racemic)	H	Me (+ on N, I^-)
IV	Br-F-O_5	··

phalotaxine (I), mp 136–137°, $[\alpha]_D$ −188° ($CHCl_3$), in 15 ml of dry pyridine. The reaction mixture was allowed to stand overnight and then evaporated to a red-brown syrup. This was taken up in a mixture of $CHCl_3$ and H_2O, NH_4OH was added, and the solution was extracted repeatedly with $CHCl_3$. The combined $CHCl_3$ extracts yielded 2.2 g of crude product. Chromatography on 50 g of Brockmann Grade III neutral alumina, eluting with ether and collecting 30-ml fractions, gave *p*-bromobenzoylcephalotaxine (IV, 1.35 g, 80%), concentrated in fractions 2–5. After recrystallization from ether, IV had mp 220–221° and $[\alpha]_D$ −289° ($CHCl_3$).

A sample of this derivative was saponified and gave back cephalotaxine (I), mp 134–136°, $[\alpha]_D$ −187° ($CHCl_3$).

Collection and Reduction of the Data. Oscillation and Weissenberg photographs of a needle of dimensions 0.2 × 0.3 × 0.5 mm indicated space group $P2_12_12_1$. The cell parameters were found by least squares to fit the settings for the four angles of eight reflections on a Picker-FACS-1 diffractometer (Cu Kα, λ 1.54178 Å, graphite monochromator) to be a = 7.055 (3), b = 17.494 (8), c = 18.192 (8) Å, ρ_c = 1.47, ρ_{obsd} = 1.44 g/ml, and Z = 4. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded 10^4 counts/sec, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1964 independent reflections measured, 1859 > $3\sigma(F)$ were considered observed. Three standard reflections were monitored every 50 measurements to check the crystal alignment and the stability; no decrease in the intensity of the standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Solution and Refinement. The bromine coordinates were found both from an E map obtained using the MULTAN[4] program and from Patterson peaks. The calculation of structure factors with phases from the bromine atom gave an R value ($R = \sum||F_o| - |F_c||/\sum|F_o|$) of 0.41. All the nonhydrogen atoms were located from the Fourier map computed with bromine phases only. Four cycles of isotropic least-squares refinement of nonhydrogen atoms reduced R to 0.128, and then two anisotropic cycles to 0.076. A difference Fourier map gave all of the hydrogen positions. One more cycle of least-squares refinement in which nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically reduced R to 0.046. Refinement was terminated at this stage, since the variations in parameters were less than the standard deviations. The scattering factors used throughout were those of Hanson, Herman, Lea, and Skillman.[5] No correction was applied for extinction.

Absolute Configuration. Using anomalous dispersion corrections of −0.9 for $\Delta f'$ and 1.5 for $\Delta f''$ for scattering of Cu X-rays by Br, structure factors were calculated for each enantiomer for all reflections. The reflections were sorted on D values.[6] Nine of the more intense reflections with $D \gtrsim 10$ were measured along with their negatives in 2θ. All nine showed differences in the direction expected if the absolute configuration depicted in IV is correct.

Table I
Fractional Coordinates and Estimated Standard Deviations

Atom	x/a	y/b	z/c
Br	0.3357 (2)	−0.1817 (1)	0.5582 (1)
O-1	0.5995 (9)	−0.0881 (3)	0.1306 (4)
O-2	0.9112 (8)	−0.0667 (3)	0.1270 (3)
O-3	0.8487 (8)	0.2497 (3)	0.4607 (2)
O-4	0.8022 (7)	0.1053 (2)	0.3938 (3)
O-5	1.0603 (8)	0.0337 (4)	0.4105 (4)
N	0.6188 (9)	0.2457 (3)	0.2137 (3)
C-1	0.5208 (11)	0.0225 (5)	0.2091 (5)
C-2	0.6398 (11)	−0.0238 (4)	0.1715 (4)
C-3	0.8372 (11)	−0.0101 (4)	0.1686 (4)
C-4	0.9132 (10)	0.0511 (4)	0.2016 (4)
C-5	0.8834 (9)	0.1704 (4)	0.2756 (4)
C-6	0.9072 (9)	0.1655 (4)	0.3599 (4)
C-7	0.8319 (10)	0.2394 (4)	0.3872 (4)
C-8	0.7637 (10)	0.2839 (4)	0.3360 (4)
C-9	0.7914 (10)	0.2505 (4)	0.2606 (4)
C-10	0.4449 (11)	0.2175 (5)	0.2465 (5)
C-11	0.4707 (11)	0.1416 (5)	0.2837 (5)
C-12	0.5989 (10)	0.0864 (4)	0.2430 (4)
C-13	0.7985 (10)	0.1022 (4)	0.2399 (4)
C-14	0.9186 (11)	0.3015 (4)	0.2128 (4)
C-15	0.7867 (18)	0.3515 (7)	0.1671 (7)
C-16	0.5921 (13)	0.3207 (6)	0.1783 (6)
C-17	0.7773 (13)	−0.1185 (5)	0.1055 (5)
C-18	0.7822 (12)	0.3222 (5)	0.4888 (4)
C-19	0.8894 (11)	0.0417 (4)	0.4163 (4)
C-20	0.7600 (11)	−0.0120 (4)	0.4506 (5)
C-21	0.5620 (10)	−0.0022 (4)	0.4427 (5)
C-22	0.4378 (11)	−0.0532 (5)	0.4763 (5)
C-23	0.5096 (13)	−0.1123 (5)	0.5152 (4)
C-24	0.7036 (13)	−0.1233 (5)	0.5240 (5)
C-25	0.8240 (13)	−0.0735 (5)	0.4902 (5)
H–C-1	0.391 (8)	0.015 (3)	0.195 (3)
H–C-4	1.046 (8)	0.057 (3)	0.195 (3)
H–C-5	0.997 (8)	0.177 (3)	0.253 (3)
H–C-6	1.050 (8)	0.162 (3)	0.371 (3)
H–C-8	0.719 (8)	0.338 (3)	0.343 (3)
H-1–C-10	0.381 (9)	0.257 (3)	0.293 (3)
H-2–C-10	0.365 (9)	0.224 (3)	0.204 (3)
H-1–C-11	0.358 (9)	0.112 (3)	0.286 (3)
H-2–C-11	0.515 (8)	0.153 (3)	0.331 (3)
H-1–C-14	0.980 (9)	0.271 (3)	0.179 (3)
H-2–C-14	1.017 (9)	0.339 (3)	0.247 (3)
H-1–C-15	0.809 (10)	0.395 (4)	0.206 (4)
H-2–C-15	0.820 (10)	0.374 (4)	0.116 (4)
H-1–C-16	0.527 (9)	0.352 (4)	0.215 (4)
H-2–C-16	0.523 (10)	0.313 (4)	0.130 (4)
H-1–C-17	0.796 (9)	−0.179 (3)	0.130 (3)
H-2–C-17	0.761 (9)	−0.145 (3)	0.048 (3)
H-1–C-18	0.816 (9)	0.318 (3)	0.545 (3)
H-2–C-18	0.675 (9)	0.323 (3)	0.476 (3)
H-3–C-18	0.819 (9)	0.369 (3)	0.458 (3)
H–C-21	0.523 (8)	0.042 (3)	0.418 (3)
H–C-22	0.299 (9)	−0.041 (3)	0.467 (3)
H–C-24	0.773 (8)	−0.167 (3)	0.557 (3)
H–C-25	0.950 (9)	−0.073 (3)	0.503 (3)

Results and Discussion

Table I shows the observed atomic coordinates. As can be seen by comparing the ORTEP[7] drawing in Figure 1 with formula III, cephalotaxine *p*-bromobenzoate (IV) has the same relative configurations (5*S*,6*S*,9*R*) as racemic cephalotaxine methiodide (III).[2] Even the spatial arrangement of groups about nitrogen is similar (*R* configuration in III), leading to essentially the same conformation for III and IV, the only cephalotaxine derivatives for which the conformation has been determined. In view of this finding, of the structural closeness between IV and the natural cephalotaxine esters (*e.g.*, II), and the observation that this conformation provides ample space for the variety of carboxylate portions of the natural esters, *it is very likely*

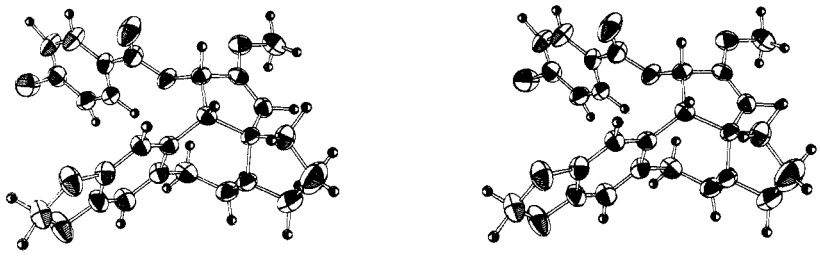


Figure 1. Stereoscopic view of a cephalotaxine *p*-bromobenzoate molecule. Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

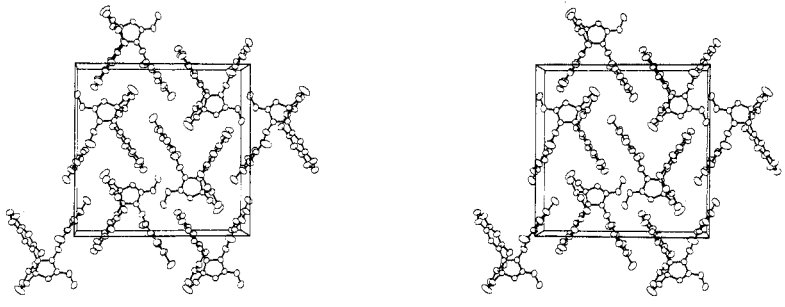


Figure 2. Stereoscopic view of a unit cell, *a* axis projection, with the *b* axis vertical and the *c* axis horizontal.

that the cephalotaxine portions of the natural antileukemic esters (e.g., II) also prefer this conformation. In this conformation, the seven-membered ring approximates a boat shape with the nitrogen at the prow. The methoxyl group lies essentially in the plane of the olefinic bond and bent toward C-8, with the rotation about the O-3–C-18 bond providing staggering between the methyl hydrogens and C-7. In the ester grouping, rotation about the bonds to O-4 puts the carbonyl oxygen (O-5) close to the hydrogen at C-6; the attached aromatic ring (F) is twisted 15° from the C-19–O-4–O-5 plane.

The absolute configuration from anomalous dispersion by bromine is as shown in IV; from chemical interconversions mentioned earlier, cephalotaxine (I) and its antileukemic esters (*e.g.*, II) share this configuration.

Figure 2 shows the packing diagram. The shortest intermolecular distances between nonhydrogen atoms are C-22–O-5 (3.292 Å), C-18–O-3 (3.432 Å), C-8–O-1 (3.456 Å), and C-18–O-5 (3.489 Å).

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Registry No.—I, 24316-19-6; IV, 50921-69-2.

Supplementary Material Available. Tables of temperature factors, bond distances, bond angles, least-squares planes, absolute configuration results from pair measurements, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1269.

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