Athrotaxin, a C_{17}-Phenolic Constituent from *Athrotaxis selaginoides* Don.

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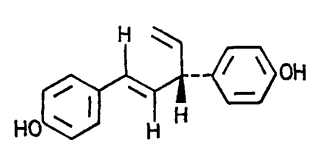
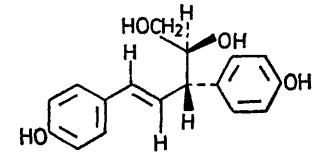
Summary The heartwood of *Athrotaxis selaginoides* Don. (Cupressales, Taxodiaceae) contains hinokiresinol (**1**), agatharesinol (**2**), and a novel C_{17}-phenol, athrotaxin, the structure, (**5**), of which has been derived from chemical results, spectroscopic data, and *X*-ray crystallography.

IN 1960 Erdtman and Vorbrüggen[1] briefly described a phenolic product, $C_{17}H_{18}O_7$, from the heartwood of the Tasmanian conifer *Athrotaxis selaginoides* Don. (Cupressales, Taxodiaceae), obtained in small and varying amounts from different samples, but it was not pure. Re-isolations afforded the pure phenol, $C_{17}H_{16}O_6$, $[\alpha]_D$ −225° (DMF–H_2O, 1:1; *c* 0·23), now called (*cf.* ref. 2) athrotaxin. From dilute alcohol it forms plates containing 1 mol. equiv. of water, but has no characteristic m.p. It turns brown and sometimes partly melts at *ca.* 183—185°, then resolidifies and remains solid up to 300°.

Athrotaxin is accompanied by several other C_{17}-phenols including hinokiresinol (**1**) and agatharesinol (**2**). The latter has now been obtained in a crystalline state, m.p. 105—109° (*cf.* ref. 3). T.l.c. analyses of small-scale extracts gave several spots none of which corresponded to sugiresinol (**3**). This compound, however, was present in large-scale extracts. After boiling a solution of pure agatharesinol in methanol containing a trace of sulphuric acid it gave a strong spot corresponding to sugiresinol. Moreover, agatharesinol and sugiresinol gave identical phenylurethanes (m.p. 179—180°). Thus the sugiresinol from large-scale extracts is probably an artefact.



(1)



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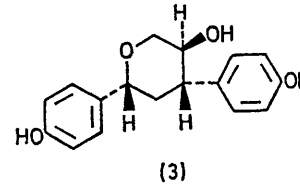

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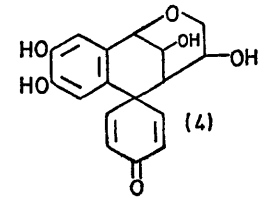

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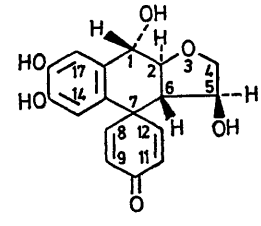

(5)

Athrotaxin gave a dimethyl ether $C_{17}H_{12}O_2(OH)_2(OMe)_2$, m.p. 120—122°, $[\alpha]_D$ −257° (MeOH; *c* 0·12), which gave metahemipinic acid on oxidation with permanganate, and the dimethyl ether diacetate $C_{17}H_{12}O_2(OAc)_2(OMe)_2$, m.p. 216—217°, $[\alpha]_D$ −158° ($CHCl_3$; *c* 0·36), on acetylation. Alkaline hydrolysis of the diacetate gave athrotaxin dimethyl ether.

The presence of a dienone group in athrotaxin was clearly demonstrated by its n.m.r. (see Table), u.v. [λ_{max} (EtOH) 217·5, 241, and 283 nm; log ϵ 4·49, 4·25 and 3·40, respectively] and i.r. (ν_{KBr} 1659 and 1615 cm^{-1}) spectra.

A difference curve[4] of athrotaxin dimethyl ether diacetate and its hexahydro-derivative (compound A, see below) showed λ_{max} (EtOH) 245 nm (log $\Delta\epsilon$ 4·20), characteristic of *para*-blocked cyclohexadienones.

Since athrotaxin occurs together with the C_{17}-phenols hinokiresinol and agatharesinol it was natural to assume a structural relation between these compounds. The dienone athrotaxin could have been formed by intramolecular phenol coupling.

On catalytic hydrogenation (PtO_2–HOAc) athrotaxin dimethyl ether diacetate gave a mixture of products from which a compound A (m.p. 179–180°; $[\alpha]_D$ −46°, MeOH; *c* 0·52) was isolated. Analytical results indicated the composition $C_{17}H_{17}O(OH)(OMe)_2(OAc)_2$. It contained an oxo-group (i.r.) and one free hydroxy-group (i.r., active H). Contrary to athrotaxin dimethyl ether, compound A on hydrolysis yielded a product which on oxidation with periodate gave formaldehyde (80% yield calc. for one 1,2-glycol group).

Structure (**4**) has been advanced for athrotaxin (ref. 5, *cf.* ref. 2). The formation of the HO–CH_2–CH(OAc) group in compound A was assumed to proceed *via* a hydrogenolysis of the benzyl ether linkage. However, athrotaxin exhibits an n.m.r. signal at δ 4·64 p.p.m. (corresponding signal of its dimethyl ether diacetate δ 6·21 p.p.m.) at low field indicating that it arises from an Ar-C*H*(OH) group as in structure (**5**). This structure is compatible with all the observed coupling constants. The formation of the HO–CH_2–CH(OAc) group in compound A might involve solvolytic elimination of the C(1)-(OAc) group with formation of a cyclic ether which undergoes hydrolytic cleavage.

Since only small amounts of athrotaxin were available it was decided to submit the compound to a direct *X*-ray phase structure determination. The compound crystallized in space group $P2_12_12_1$; $Z = 4$; $a = 15{\cdot}263$, $b = 6{\cdot}960$, $c = 14{\cdot}529$ Å. *X*-Ray intensity data were collected on a Siemen's automatic diffractometer.

The phase determinations were carried out by application of the Σ_1, Σ_2 and 'weighed sum' formulae.[6] An *E*-map based on the correct set of phases (for reflections with $|E| > 1{\cdot}5$) revealed the positions of 15 atoms. The remainder of the structure was obtained by a combination of difference syntheses and least-squares refinements. Anisotropic refinement of the non-hydrogen atoms resulted in an *R*-index of 0·07, which was reduced to 0·044 after introduction of the hydrogen atoms into the least-squares analysis with fixed isotropic temperature factors. The molecular structure of athrotaxin [identical with structure (**5**)] is shown in the Figure. The absolute configuration has not been determined but considering the probable biosynthetic relation between athrotaxin and the compounds (**1**) and (**2**) that indicated in formula (**5**) appears to be the most likely one.

TABLE

N.m.r. data[a] *for athrotaxin and derivatives*

	Athrotaxin in $(CD_3)_2SO$	Athrotaxin dimethyl ether in $(CD_3)_2CO/(CD_3)_2SO$ (10 : 1)	Athrotaxin dimethyl ether diacetate in $CDCl_3$
1-H	4·64(d); $J_{1,2}$ 8·5	4·76(d); $J_{1,2}$ 8·5	6·21(d); $J_{1,2}$ 8·5
2-H	3·8[b]	4·0[b]	4·00(q); $J_{2,1}$ 8·5; $J_{2,6}$ 12·5
6-H	2·25(q); $J_{6,2}$ 11; $J_{6,5}$ 6	2·25(q); $J_{6,2}$ 12·5; $J_{6,5}$ 8	2·60(q); $J_{6,2}$ 12·5; $J_{6,5}$ 8
5-H	3·8[b]	4·0[b]	4·97(s); $J_{5,6}$ 8; $J_{5,4}$ 7 and 4
4-H	3·8[b]	4·0[b]	3·9(m)
8-H, 12-H	6·32(m);[b] $J_{8,9(12,11)}$ *ca.* 10	6·27 (m)[b]	6·25(m)[b]
9-H, 11-H	7·00(bd); $J_{9,8(11,12)}$ *ca.* 10	6·88(bd); $J_{9,3(11,12)}$ *ca.* 10	6·80(m)[b]
14-H, 17-H	6·36(s); 7·13(s)	6·29(s); 7·22(s)	6·35(s); 6·64(s)

[a] p.p.m. from Me_4Si, internal standard; *J*, observed coupling constants, Hz. [b] Unresolved.

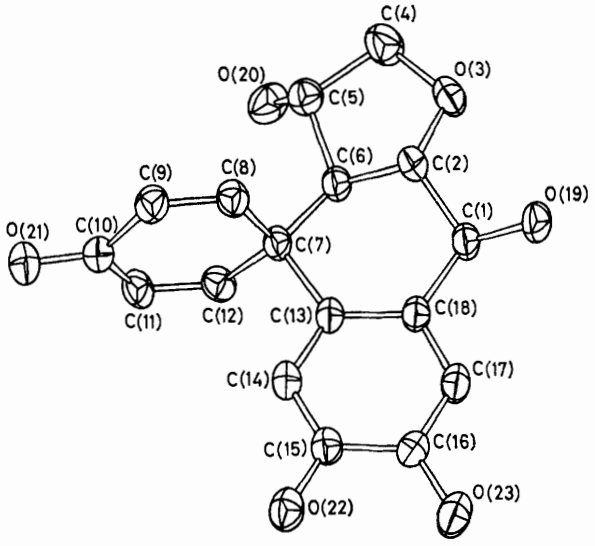

FIGURE. *Molecular structure of athrotaxin*

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