Cephalotaxine Chemistry: Unusual Addition Reactions of seco-Cephalotaxine Derivatives

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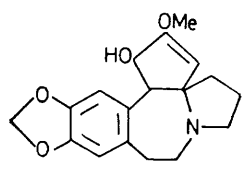
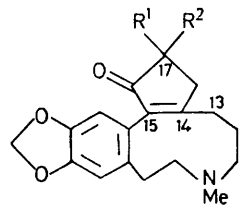
Summary Addition reactions of two seco-cephalotaxine derivatives are described which appear to proceed *via* 1,6-additions to cyclopentadienone intermediates; the structure of one of these addition products has been verified by *X*-ray analysis.

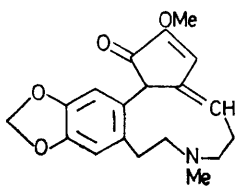
PLANTS of the genus *Cephalotaxus* (*Cephalotaxaceae*) produce a group of unique alkaloids, the most abundant of which is cephalotaxine (**1**) whose structure and absolute stereochemistry have been determined by *X*-ray analysis.[1] Two syntheses of (**1**) have been reported.[2] In *C. harringtonia*, cephalotaxine is accompanied by related alkaloids which are of particular importance owing to their promising anti-leukaemic activity.[3] As part of an investigation of *Cephalotaxus* alkaloid biosynthesis,[4] we developed methods for the degradation of (**1**) which have yielded a number of novel cephalotaxine derivatives; some unusual addition reactions exhibited by two of these derivatives are described here.



(1)



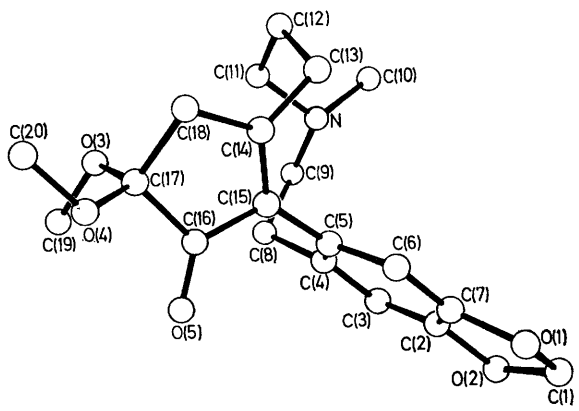
(3) $R^1 = R^2 = OMe$
(4) $R^1 = R^2 = H$, $\Delta^{14,15}$ reduced
(5) $R^1 = OMe$, $R^2 = H$
(6) $R^1 = R^2 = H$
(7) $R^1 = Me$, $R^2 = H$



(2)

Oppenauer oxidation of (**1**) to cephalotaxinone,[5] followed by quaternization with MeI and Hofmann elimination, gives the seco-dienone (**2**), 30%, ν_{max} 1711 and 1600 cm^{-1}, δ 1·60 (2H, m, allylic-H), 2·02 (3H, s, NMe), 3·82 (3H, s, OMe), 5·34 (1H, s, benzylic-H), 5·76 (1H, t, J 8 Hz, vinyl-H coupled to allylic-H at δ 1·60), and 6·05 (1H, s, vinyl-H). Treatment of (**2**) with NaOMe in aqueous MeOH gives a new crystalline compound (*ca.* 60%) tentatively assigned structure (**3**) on the basis of spectral data, ν_{max} 1717 cm^{-1}, *m/e* 359 (M^+), δ 2·01 (3H, s, NMe) and 3·39 (6H, s, OMe). Because the formation of (**3**) requires the addition of MeO^- to (**2**) in an unexpected direction, its structure was investigated by *X*-ray analysis.

Crystal data: $C_{20}H_{25}NO_5$, monoclinic, space group $P2_1/c$, $a = 9{\cdot}516$, $b = 16{\cdot}372$, $c = 12{\cdot}590$ Å; $\beta = 110{\cdot}89°$, $Z = 4$. The 1266 independent reflexions, for which $I/\sigma(I) > 3{\cdot}0$, were measured on a Syntex $P2_1$ diffractometer (crystal-monochromated Mo-K_α radiation). The structure was solved using direct methods, and full-matrix least-squares refinement of positional and isotropic thermal parameters for



FIGURE

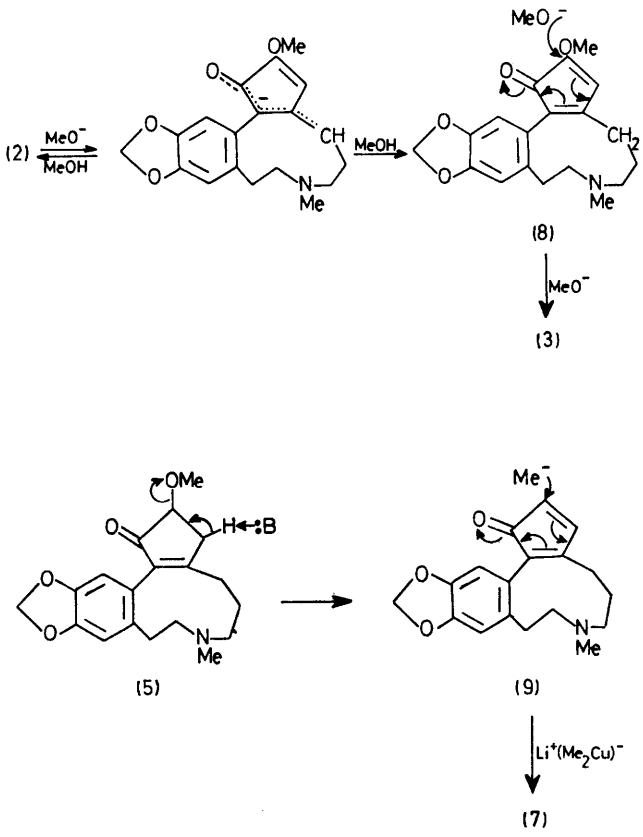
all nonhydrogen atoms has converged to a conventional *R*-factor of 0·11. The overall geometry of the molecule is shown in the Figure. The proposed structure is confirmed, including location of a double bond (1·35 Å) between C(14) and C(15).

The ring systems of this molecule have two striking features. First, the dihedral angle between the cyclopentenone and benzene ring systems is 78·2°. Inspection of models suggests that this near orthogonal arrangement is a consequence of the severe steric interactions which develop in the ten-membered ring when the benzene and cyclopentenone rings approach co-planarity. Secondly, the ten-membered ring is in nearly a *'chaise longue'* conformation, the dihedral angles between least-squares planes containing atoms C(5)–C(4)–C(8)–C(15), C(8)–C(15)–C(9)–C(14), C(9)–C(14)–N–C(13), and C(13)–N–C(11)–C(12) being 70·7, 27·4, and 82·7°, respectively.

The mechanism of methoxide addition to (**2**) appears to be related to an unusual addition reaction exhibited by another seco-cephalotaxine derivative, the methoxyenone (**5**). This enone is obtained by Emde reduction of cephalotaxine methiodide with sodium amalgam. The major product[4] is the saturated ketone (**4**) (50%), (**5**) being a minor product (20%). The structure of (**5**) follows from spectral data, ν_{max} 1709 cm^{-1}, δ 2·01 (3H, s, NMe), 3·55 (3H, s, OMe), and 4·00 (1H, m, C*H*OMe), and from correlation with the acetal (**3**). Reduction of (**5**) with Zn and H_2SO_4 yields the enone (**6**) (70%), ν_{max} 1688 cm^{-1}, δ 2·04 (3H, s, NMe), which is also formed (55%) by reduction (Zn–H_2SO_4) of (**3**).

The methoxyenone (**5**) exhibits anomalous behaviour on treatment with lithium dimethylcuprate. Instead of the expected[6] 1,4-addition to the αβ-unsaturated ketone, addition of a methyl group takes place at C(17) with loss of OMe to give the methylated enone (**7**) (20%), ν_{max} 1690 cm^{-1}, δ 1·59 (3H, d, *J* 2·5 Hz, CHMe), 1·99 (3H, s, NMe), 3·39 (1H, m, COC*H*Me, disappearing with MeO^- in MeOD).

A possible mechanism for the unusual reactions leading to compounds (**3**) and (**7**) is outlined in the Scheme. We suggest that both reactions could proceed *via* 1,6-addition of nucleophiles to a cyclopentadienone intermediate. Thus, (**3**) could result from the methoxide-catalysed isomerization of (**2**) to the cyclopentadienone (**8**) followed by 1,6-addition of MeO^-.† The *C*-methyl derivative (**7**) could be formed in analogous fashion: base catalysed elimination of methoxide ion from (**5**) to generate the cyclopentadienone (**9**) could be followed by 1,6-addition of lithium dimethylcuprate. The 1,6-addition of lithium dimethylcuprate to αβγδ-dienones is known,[7] but there appears to be no experimental evidence bearing on the mode of addition of nucleophiles to cyclopentadienones. However, calculations[8] predict that 1,6-additions of nucleophiles to cyclopentadienones should be



SCHEME

favoured over 1,4-additions. This prediction is indirectly supported by the propensity of cycloheptatrienones toward 1,8-additions of nucleophiles.[9]

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† When the transformation of (**2**) into (**3**) was carried out with MeO^- in MeOD–D_2O and the reaction interrupted before it was complete, the n.m.r. spectrum of the recovered methine showed that no exchange of the vinyl proton at C(13) had taken place. Therefore, if the cyclopentadienone (**8**) is an intermediate in this conversion, it undergoes 1,6-addition of MeO^- at C(17) much more readily than methoxide-catalysed deprotonation at C(13).

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