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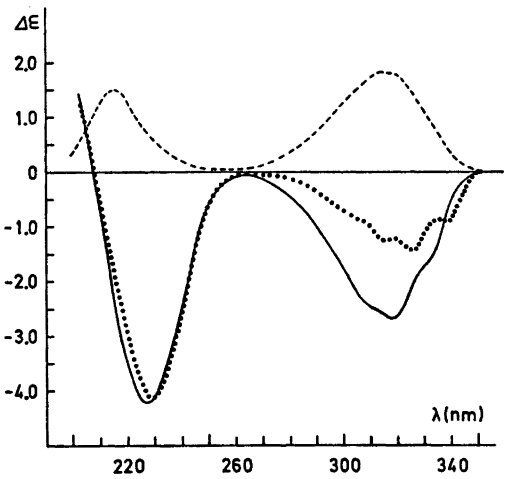

Fig. 1. CD curves of methyl dihydroketo-picrotoxinate (*3*, ——), methyl keto-β-picrotoxinate (*4*, · · ·) and methyl dihydroketo-β-picrotoxinate (*5*, - - -) in methanol.

Studies on Orchidaceae Alkaloids. 41.* The Configuration at C-4 in δ-Nobilonine and Dihydroketopicrotoxinic Acid

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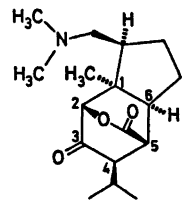
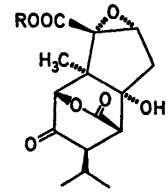
In a previous communication [1] we reported on a determination of the absolute configuration of the dendrobine alkaloids. The assignment was based on a comparison of the circular dichroism (CD) curve of δ-nobilonine (*1*) with that of dihydroketopicrotoxinic acid (*2*), derived from picrotoxinin for which the absolute configuration was known. As the two CD curves show negative Cotton effects at ~315 nm, a 4*R* configuration in *1* was suggested.

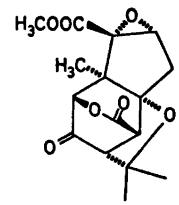
To gain further evidence concerning the configuration at C-4 in *1* and *2*, the picrotoxinin derivatives *3*, *4*, and *5* have now been synthesised and their CD curves recorded. In *4* and *5* an epimerisation at C-4 is impossible due to the ether linkage between C-6 and



1



2:R=H
3:R=CH_3



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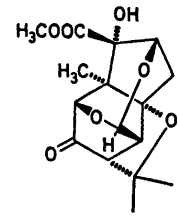

5

C-12. Compounds *1*, *2* and *3*, which have the same chromophore as *4*, exhibit negative Cotton effects at ~315 nm which are almost twice that of *4*. This large difference in amplitude indicates that the isopropyl groups in *1*, *2* and *3* make a significant negative contribution to the Cotton effect associated with the $n \rightarrow \pi^*$ transitions of the C-3 carbonyl group. Hence *1* and *2* have the 4*R* configuration.

The CD curves of *4* and *5* show Cotton effects at ~315 nm of about the same magnitude

* For Paper 40 in this series, see Ref. 1.

but of opposite sign. It has been shown that oxygen-containing substituents, such as hydroxyl or acetoxyl, in the α-position to a carbonyl group give a contribution to the Cotton effect opposite to that predicted by the octant rule.[3] Little is known, however, about the amplitude contributions of these substituents and great care should be exercised in applying the octant rule to compounds containing such systems, *e.g.* *1* – *5*.

The proposed configuration (*R*) at C-4 was further supported by NMR studies on *3* using tris(dipivalomethanato)europium [Eu(DPM)$_3$] as shift reagent. It has been shown that complex formation preferentially occurs at hydroxyl groups, rather than at ester, lactone, ketone or epoxide groups.[4] In sterically hindered alcohols, however, complex formation at other sites may compete.

The magnitudes of the induced chemical shifts were investigated and found to vary linearly with the molar ratio of *3* to Eu(DPM)$_3$, when this ratio was varied between 0.20 – 0.45. The largest shifts were observed for those hydrogen atoms which are located closest to the hydroxyl group, with the exception of H-8. It thus seems probable that the shift reagent forms a complex mainly with the hydroxyl group. The large induced chemical shift for H-8 is probably due to competing complex formation with the ester group, which also explains why the changes in shifts for the two hydrogen atoms at C-7 are the same.

The small induced chemical shifts for the hydrogen atoms of the isopropyl group indicate that these atoms are located at a longer distance from the europium complex than H-4, H-5 and the methyl group at C-1. This is only possible if *3* has the 4*R* configuration.

Experimental. Melting points are corrected. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, IR spectra on a Perkin-Elmer 257 instrument, NMR spectra on a Varian XL-100 spectrometer and CD spectra on a Jasco J-40 spectropolarimeter. Concentrations were performed under reduced pressure, at bath temperatures not exceeding 40 °C. Elemental analyses were carried out at Lantbrukshögskolan, Uppsala, Sweden.

Methyl dihydroketopicrotoxinate (3). Dihydroketopicrotoxinic acid[2] (*2*, 35 mg) was dissolved in methanol and esterified with diazomethane. Evaporation of the solvent and crystallisation of the residue from ethyl acetate – hexane (1:2) gave *3* (19 mg), m.p. 85 – 86 °C. $[\alpha]_{578}^{22}$ – 93° (*c* 0.48, methanol). Anal. $C_{16}H_{20}O_7$: C,H. IR (KBr): 3420(s), 1755(s), 1740(s), 1725(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.98 (d, 3 H, *J* 7 Hz), 1.05 (d, 3 H, *J* 7 Hz), 1.45 (s, 3 H) 2.22 (m, H-12, J_1 6.5 Hz, J_2 7 Hz), 2.57 (d, H-7′, *J* 16 Hz) and 2.74 (dd, H-7, J_1 16 Hz, J_2 2 Hz) AB part of an ABX system, 3.05 (dd, H-4, J_1 2 Hz, J_2 6.5 Hz), 3.36 (d, H-5, *J* 2 Hz), 3.60 (s, 3 H), 4.08 (d, H-8, *J* 2 Hz), 5.55 (s, H-2). The following induced chemical shifts, in ppm, were observed at the molar ratio 0.45 of *3* to Eu(DPM)$_3$: H-2 +1.4, H-4 +2.9, H-5 +2.7, H-7α +1.5, H-7β +1.5, H-8 +2.0, H-12 +0.4, CH_3-1 +1.8, CH_3-12 +0.2 and −0.2.

Methyl keto-β-picrotoxinate (4). Methyl-β-picrotoxinate[5] (256 mg) was dissolved in acetone (25 ml) and an excess of Jones reagent[6] was added. After stirring the solution at room temperature for 45 min, sodium hydrogen sulfite was added to destroy the excess of chromic acid. The reaction mixture was filtered and evaporated to dryness. The residue was crystallised from ethyl acetate – hexane (1:2) giving *4* (182 mg), m.p. 170 – 171 °C. $[\alpha]_{578}^{22}$ – 93° (*c* 0.96, methanol). Anal. $C_{16}H_{18}O_7$: C, H. IR (KBr): 1777(s), 1750(s), 1729(s) cm^{-1}. ^{1}H NMR (pyridine-d_5): δ 1.23 (s, 3 H), 1.33 (s, 6 H), 2.37 (d, H-7, *J* 15 Hz) and 2.59 (dd, H-7′, J_1 15 Hz, J_2 3 Hz) AB part of an ABX system, 3.12 (d, H-4, *J* 3.5 Hz), 3.60 (s, 3 H), 4.02 (d, H-5, *J* 3.5 Hz), 4.11 (d, H-8, *J* 3 Hz), 5.17 (s, H-2).

Methyl dihydroketo-β-picrotoxinate (5). Methyl dihydro-β-picrotoxinate[5] (375 mg) was oxidised in the same way as described above for methyl-β-picrotoxinate. Crystallisation from ethyl acetate-hexane (1:1) gave *5* (301 mg), m.p. 243 – 245 °C. $[\alpha]_{578}^{22}$ – 3.0° (*c* 0.60, methanol). Anal. $C_{16}H_{20}O_7$: C,H. IR (KBr): 3400(s), 1735(s) cm^{-1}. ^{1}H NMR (pyridine-d_5): δ 1.32 (s, 3 H), 1.33 (s, 3 H), 1.36 (s, 3 H), 1.94 (dd, H-7, J_1 11 Hz, J_2 1.4 Hz), 2.63 (d, H-4, *J* 3.8 Hz), 2.94 – 3.18 (m, 2 H), 3.62 (s, 3 H), 4.34 (s, H-2), 4.72 (dd, H-8, J_1 2.4 Hz, J_2 1.4 Hz), 5.72 (d, H-15, *J* 3.5 Hz), 8.44 (broad, −OH).

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