Limonoids from *Trichilia heudelottii*. Part II.[1]

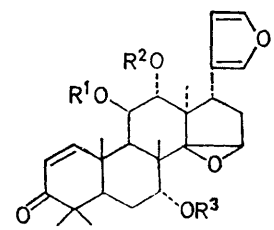
By **D. A. Okorie** and **D. A. H. Taylor,*** Department of Chemistry, University of Obadan, Nigeria

It is shown that heudelottin E is 14β,15β-epoxy-11β-formyl-7α-(2-hydroxy-3-methylbutyryl)-12α-(2-hydroxy-3-methylvaleryl)-3-oxomeliac-1-ene (1b), and the other heudelottins are related to this.

In Part I [1] it was shown that the timber of *Trichilia heudelottii* contains a group of limonoid esters. We called these heudelottins, and described four of them: C, $C_{39}H_{54}O_4$; D, not obtained pure; E, $C_{38}H_{52}O_{11}$; and F. Since then, D has been found to be a mixture of C and F, and the formula of F has been revised to $C_{40}H_{54}O_{12}$. We showed that the heudelottins were esters of the general formula (1), where the nature of the acyl groups remained unknown.

We have now investigated the nature and mode of attachment of the esterifying acids. We describe first our work with heudelottin E. Hydrolysis of this [1] gave a non-volatile acid and two volatile acids identified as formic acid and 2-methylbutyric acid from the n.m.r. spectrum of the sodium salts of the steam volatile fraction.[2] We have now shown that the identification of 2-methylbutyric acid was wrong.

The n.m.r. spectrum of heudelottin E (see Table) is generally similar to that of the hydrolysis product triacetate (1a), in particular the resonances due to



(1)

(a) $R^1 = R^2 = R^3 = Ac$
(b) $R^1 = CHO$, $R^2 = Bu^sCH(OH)\cdot CO\cdot$, $R^3 = Pr^iCH(OH)\cdot CO\cdot$
(c) $R^1 = H$, $R^2 = Bu^sCH(OAc)\cdot CO\cdot$, $R^3 = Pr^iCH(OH)\cdot CO\cdot$
(d) $R^1 = CHO$, $R^2 = Bu^sCH(OAc)\cdot CO\cdot$, $R^3 = Pr^iCH(OH)\cdot CO\cdot$
(e) $R^1 = H$, $R^2 = Bu^sCH(OH)\cdot CO\cdot$, $R^3 = Pr^iCH(OH)\cdot CO\cdot$
(f) $R^1 = R^2 = H$, $R^3 = Pr^iCH(OH)\cdot CO\cdot$

7-, 11-, and 12-H appear at similar chemical shifts. This shows that the three esterifying acids are attached

[1] Part I, D. A. Okorie and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1968, 1828.

[2] D. H. Calam and D. A. H. Taylor, *J. Chem. Soc.* (*C*), 1966, 949.

at C-7, C-11, and C-12. Heudelottin E has also two hydroxy-groups and gives a diacetate.

Chemical shifts (δ/p.p.m.) and coupling constants (*J*/Hz) (in parentheses) for protons adjacent to hydroxy- or acyloxy-groups in heudelottin derivatives

Compound	H-11 [a]	H-12 [b]	H-7 [a]	Hydroxy-acid I	Hydroxy-acid II
Triacetate (1a)	5·74 (8)	5·39 (3·5)	4·76 (4)		
Heudelottin E (1b)	5·88 (7)	5·48 (3)	4·85 (4)	4·01 (4·5)	3·68 (3·5)
Heudelottin C (1c)	4·3 (7·5)	4·98 (2·5)	4·75 (4)	3·95 (4·5)	4·80 (3·5)
Heudelottin F (1d)	5·78 (7)	5·30 (3·5)	4·08 [c]	3·95 (4·5)	4·75 [c]
Compound I [d] (1e)	4·31 (7·5)	4·98 (3)	4·76 (4)	4·05 [c]	3·95 [c]
Compound II [d] (1f)	4·33 (8)	3·91 (3·5)	4·68 (4·5)	4·08 (4·5)	
C Acetate	5·71 (7·5)	5·31 (3·5)	4·78 (4)	4·96 (4)	4·81 (3·5)
E Acetate	5·81 (7)	5·31 (2·5)	4·78 (4)	4·96 (4)	4·78 (3·5)

[a] $J_{AX} + J_{BX}$ for an ABX multiplet. [b] *J* Values for alcohols in the presence of D_2O. [c] Not resolved. [d] From hydrogen carbonate hydrolysis of heudelottin E.

In the hope of removing the formate group, we investigated the partial hydrolysis of heudelottin E. Treatment with sodium hydrogen carbonate in cold methanol gave two products. The first was readily identified as the expected deformylheudelottin E (1e). The n.m.r. spectrum showed the absence of the characteristic formate band; the mass spectrum gave a molecular weight of 656·3651, corresponding to the expected formula $C_{37}H_{52}O_{10}$. The n.m.r. spectrum had lost the signal at δ 5·98 p.p.m. (C*H*O) and gained an extra resonance at δ 4·31 p.p.m. (CH·O*H*), while the signal attributed to 12-H in heudelottin E (δ 5·48 p.p.m.) moved upfield to δ 4·98 p.p.m. in the deformyl derivative. This showed clearly that the formate was attached to C-11. The triacetate of deformylheudelottin E showed five resonances attributable to protons adjacent to acyloxy-groups.

The second hydrolysis product had an n.m.r spectrum lacking the resonances attributed in the spectrum of E to both 11- and 12-H, although the 7-H resonance was still present, the formate resonance was also absent. There were also three C*H*·OH resonances. The compound had clearly lost the formate and one of the other two esters. The mass spectrum did not give the expected result; the molecular ion was at 542·2872, corresponding to $C_{31}H_{42}O_8$. This indicates the loss of a saturated hydroxy-acid, $C_6H_{12}O_3$, and the remaining acid must be also a saturated hydroxy-acid $C_5H_{10}O_3$. Thus it appears that heudelottin E is esterified at C-11 with formic acid, at C-12 with the acid $C_6H_{12}O_3$, and at C-7 with the acid $C_5H_{10}O_3$.

Since these results exclude a 2-methylbutyric acid residue, we re-examined the spectrum of the steam-volatile acids. This was a rather weak spectrum; close examination showed however that although it was very similar to that of 2-methylbutyric acid, the spectrum lacked the resonance due to the methine proton α to the carboxy-group. There is absorption at δ *ca.* 3·5 p.p.m. consistent with the presence of a C*H*·OH group. It now appeared that the spectrum was due to the steam-distillation of small amounts of the two hydroxy-acids revealed in the mass spectral studies. This view was supported by separation of the acid fraction of the non steam-volatile residue from the hydrolysis of heudelottin E, which gave an identical spectrum.

The spectrum of heudelottin E shows that both the hydroxy-groups are secondary, and that the protons adjacent to each resonate as doublets, indicating two ·CH(OH)·CH· systems. Examination of the methyl region of the spectrum of heudelottin E at 100 MHz shows five tertiary methyl groups (belonging to the nucleus), an ethyl group, and three secondary methyl groups, all with slightly different chemical shifts. These data can only be accommodated if the acids are 2-hydroxy-3-methylbutyric acid and 2-hydroxy-3-methylvaleric acid, analogous to the more usual isobutyric and α-methylbutyric acids. Heudelottin E is therefore represented by the structure (1b), and the hydrolysis products by (1e) and (1f).

We now consider heudelottin C, $C_{39}H_{54}O_{11}$, which yields acetic acid on hydrolysis, and in the n.m.r. spectrum shows an acetate band instead of the formate band present in E. It is not however the acetate analogue of E, for the n.m.r. spectrum is not closely similar, resembling rather that of deformyl E. In particular, instead of two doublet C*H*·OH signals, the spectrum of C shows an additional doublet at δ 4·8 p.p.m. (*J* 4 Hz), as in heudelottin E acetate (attributable to a proton adjacent to an acyl group) and a multiplet at δ 4·35 p.p.m. ($J_{AX} + J_{BX}$ 8·5 Hz in presence of D_2O) due to a proton adjacent to a hydroxy-group, which can be ascribed to 11-H. There is also a doublet at δ 4·0 p.p.m. (*J* 4·5 Hz, C*H*·OH). Heudelottin C is therefore deformylheudelottin E, in which one of the two hydroxy-acids is acetylated. This is confirmed by the observation that the diacetate of heudelottin C is the same as the triacetate of deformylheudelottin E (1e).

Heudelottin F has a higher molecular weight (726, $C_{40}H_{54}O_{12}$), and contains both an acetate and a formate. There is only one CH·OH group, the proton adjacent to which resonates as a doublet (δ 4·02 p.p.m., *J* 4·5 Hz), and which is therefore present in one of the esterifying acids. It would appear to be a monoacetate of heudelottin E, and this is confirmed by acetylation to heudelottin E diacetate.

As expected, the spectrum of heudelottin F acetate is very similar to that of heudelottin C diacetate, the only difference being the substitution of a formyl group for one of the acetate groups, and the consequent slight shift in the resonance of 11-H.

The protons on the two α-carbon atoms in the hydroxy-acids have slightly, but characteristically, different resonances; δ 3·95—4·10 p.p.m. (*J* 4—4·5 Hz) (δ 4·96 p.p.m. for C*H*·OAc), and δ 3·68 p.p.m. (in heudolottin E) (*J* 3·5 Hz) (δ 4·75—4·8 p.p.m. for C*H*·OAc). This

higher field resonance is absent in the di-hydrolysis product of heudelottin E, and therefore belongs to hydroxymethylvaleric acid, the substituent at C-12 in heudelottin E. Its lower field resonance in the deformyl compound (δ 3·95 p.p.m.) is easily explained by the absence of the ester at C-11. In both heudelottin C and heudelottin F this proton appears as C*H*·OAc, resonating at about δ 4·8 p.p.m.

It follows that heudelottin C is the 11β-hydroxy-7α-(2-acetoxy-3-methylbutyryl)-12α-(2-hydroxy-3-methylvaleryl)-compound (1c), while heudelottin F is the 11β-formate of C (1d). These conclusions are supported by the fact that neither heudelottin C nor F is hydrolysed by sodium hydrogen carbonate under the same conditions as is heudelottin E, which shows there must be some difference in the C-11 and C-12 substituents in these compounds. The ready hydrolysis of heudelottin E presumably depends on a neighbouring group effect.

EXPERIMENTAL

Hydrolysis of Heudelottin E.—(a) Heudelottin E (152·5 mg) was dissolved in methanol (30 ml) and sodium hydroxide solution (30 ml, 0·1054N) added. After heating under reflux for 1 h, the solution was titrated with sulphuric acid (21·6 ml, 0·1147N; phenolphthalein). More acid (6·0 ml) was added, and the solution was evaporated under reduced pressure. The distillate was titrated with alkali (1·68 ml; phenolphthalein) and then evaporated to dryness. The residue was extracted with acetone and re-evaporated. The residue, in D_2O, showed a formate proton and resonances due to primary and secondary methyl groups, similar to those in α-methylbutyric acid.[2]

(b) Heudelottin E (200 mg) was dissolved in methanol (40 ml) and sodium hydrogen carbonate (40 ml, 0·5N-aqueous) was added. After 24 h the solution was diluted with water and extracted with ether. The residue was chromatographed over silica gel with ether–pentane. Two fractions were obtained; (1e) (80 mg), m.p. 146—148° (from ether–pentane) (Found: C, 67·7; H, 8·2%; M^+, 656·3651. $C_{37}H_{52}O_{10}$ requires C, 67·7; H, 8·0%; *M*, 656·3560), $[\alpha]_D^{20}$ 62°; the second fraction (1f) (70 mg) had m.p. 236—238° (from ether–pentane) (Found: C, 68·9; H, 7·8%; M^+, 542·2872. $C_{31}H_{42}O_8$ requires C, 68·6; H, 7·8%; *M*, 542·2854), $[\alpha]_D^{20}$ 33°.

Heudelottin E Acetate.—Heudelottin E (50 mg) was acetylated in the usual way. The acetate (43 mg) had m.p. 84—86° (from methanol) (Found: C, 65·6; H, 7·0. $C_{42}H_{56}O_{13}$ requires C, 65·6; H, 7·3%), $[\alpha]_D^{20}$ 60°. Acetylation of heudelottin F gave the same compound.

Acetate of Deformylheudelottin E.—The deformate (42 mg) was acetylated in the usual way. The acetate (34 mg) had m.p. 170—172° (from methanol) (Found: C, 65·7; H, 7·5. $C_{43}H_{58}O_{13}$ requires C, 66·0; H, 7·5%), $[\alpha]_D^{20}$ 51°. Acetylation of heudelottin C gave the same compound.

We thank Dr. A. G. Loudon of University College, London, for the mass measurements.

[1/2361 *Received*, 9*th December*, 1971]