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TETRANORTRITERPENOIDS—IX[1, 2]

THE CONSTITUTION AND STEREOCHEMISTRY OF SALANNIN

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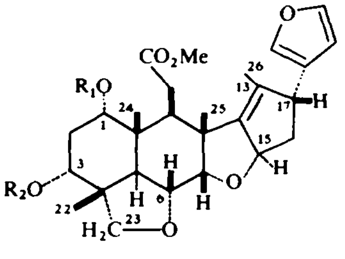
Abstract—Formulation of salannin as I is based largely on analysis of the PMR spectrum of the diacetate II and on its evident relationship with nimbin.

During the isolation of nimbin[2] from the seed oil of *Melia azadirachta*, we obtained a new related tetranortriterpenoid which we name salannin and formulate as I on the evidence which follows.

Salannin, m.p. 167–170°, $[\alpha]_D$ + 167°, analysed for $C_{34}H_{44}O_9$. Its PMR spectrum showed the presence of three tertiary Me's (τ 9·0, 8·77 and 8·67; 3H each, singlets) and one vinyl Me (τ 8·31; 3H, doublet, $J = 1 \cdot 5$ Hz), one carbomethoxyl (τ 6·72; 3H singlet), one acetate (τ 8·05, 3H, singlet) and one tiglate ester (τ 3·0, 1H, multiplet and τ 8·0–8·25; 6H, characteristic multiplets at 100 Mc/s), one β-substituted furan ring (τ 2·65, 2H, multiplet and τ 3·67, 1H, diffuse singlet). In the IR salannin showed ν_{max} (CCl_4) 1710 (tiglate ester), 1743 (acetate and methyl esters), 1653 (olefinic linkage) cm^{-1}. Salannin does not contain a OH group (absence of IR bands above 3000 cm^{-1}) or a ketone or aldehyde function (quantitative evaluation of CO absorption in the IR), so that the two remaining oxygen atoms are probably present as ethers.



I: $R_1 = CO.C_4H_7; R_2 = CO.CH_3$
II: $R_1 = R_2 = CO \cdot CH_3$
III: $R_1 = CO \cdot C_4H_7; R_2 = H$
IV: $R_1 = R_2 = H$
V: $R_1 = H; C_3$ carbonyl

The common botanical source and the similarity of several functional groups, as indicated by the spectroscopic data, suggested a close structural relationship between salannin and nimbin. This became indeed apparent when the PMR spectrum (Fig. 1) of the diacetate (II), $C_{31}H_{40}O_9$, m.p. 232–234°, $[\alpha]_D$ + 126°, obtained from salannin by hydrolysis and acetylation, was scrutinized. Two features in particular stood out: (1) There is in salannin an isolated 3-proton system, reminiscent of the H-5, H-6, H-7 system in nimbin. Thus H-6 (τ 6·0) is, as in nimbin,[2] coupled to two neighbours, namely H-5 (τ 7·22; $J = 13$ Hz) and H-7 (τ 5·82; $J = 3$ Hz), neither of which is otherwise coupled. Application of first-order treatment is here justified, since for each pair of protons $\Delta\delta > 5 \times J$. The observed coupling constants, as in nimbin,

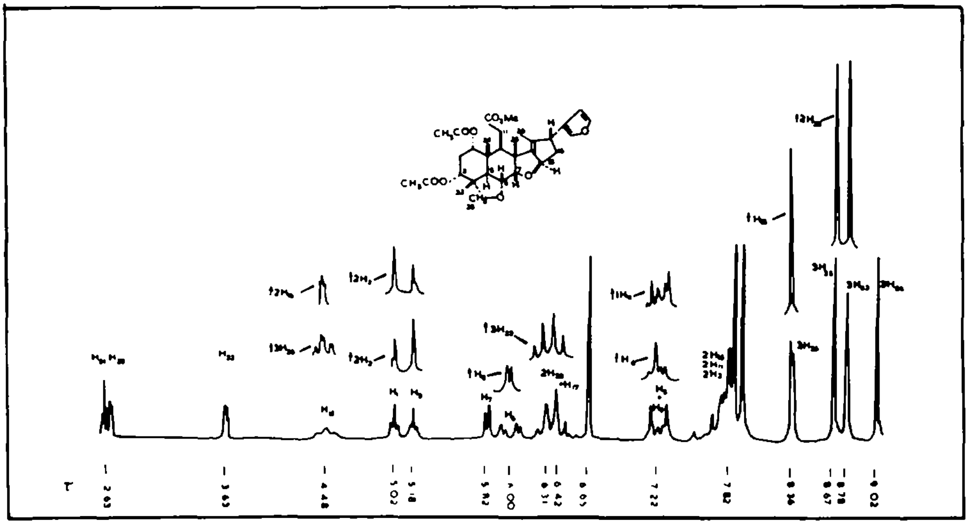


FIG. 1. NMR single and double resonance spectra at 100 MHz of the diacetate (II).

define the configurations of the protons in question as H-5 (α, axial), H-6 (β, axial) and H-7 (β, equatorial). (2) The moiety representing rings C and D, that had proved so perplexing in nimbin, is here well defined by the PMR spectrum: H-15 (τ 4·48) is coupled with both protons at C-16 (τ 7·82; $J = 7$ Hz), with the vinyl methyl group (τ 8·36; $J = 2$ Hz) and with H-17 (τ 6·30; $J = 2·5$ Hz). This follows from the observations (Fig. 1) that H-15, a diffuse multiplet (τ 4·48; τ 4·46 in nimbin), collapses to a triplet of doublets upon irradiation at the C-26 vinyl Me group (τ 8·36; τ 8·35 in nimbin). The reverse experiment sharpens the vinyl Me group to a singlet. Irradiation at the C-16 methylene group (τ 7·82), removes the major (7 Hz) coupling from H-15 ($\theta H_{15}H_{\alpha 16} = 20°$, $\theta H_{15}H_{\beta 16} = 140°$) and leaves it as a triplet. Comment has been made[3] on the abnormally low chemical shift value of H-15.

The methyl ester function in salannin is accommodated as in nimbin, on the assumption that it represents C-12 of a ring-C cleaved apoeuphol structure. Attachment of an acetic acid chain at C-9 is indeed supported when the quartet (τ 7·30) assignable to H-9, collapses to a doublet on irradiation at τ 7·82 (1H-11). The other two ester functions in salannin, one acetate and one tiglate, must be located between C-1 and C-3. They cannot be vicinal, since the two protons (τ 5·05 and 5·20), attached to the same carbon atoms as the ester functions, are not mutually coupled. They are however individually coupled with the intermediate methylene group at C-2 (τ 7·56, $J_{AX_2} = J_{BX_2} = 3$ Hz), as demonstrated by double irradiation. The tiglate must be attached at C-1 and the acetate at C-3, rather than the reverse, for the following reasons. Alkaline hydrolysis of salannin affords, after methylation, a mixture of two compounds, the hydroxytiglate (III), $C_{32}H_{42}O_8$, m.p. 213–215°, $[\alpha]_D$ +137°, which has lost the acetate, and the diol IV, $C_{27}H_{36}O_7$, m.p. 201–205°, $[\alpha]_D$ +135° which has lost both the acetate and tiglate esters. The methyl ester —CH_3 resonances are abnormally high in the NMR spectrum of salannin (τ 6·72) and the hydroxytiglate (III) (τ 6·78), suggesting that the tiglate shields the methyl ester protons and must therefore be at C-1. This suggestion accords with the observations that (i) in the IR, the methyl ester CO group is unbonded in dilute solution of the hydroxytiglate (III) [ν_{max} (CCl_4) 1742 cm^{-1}], but is intramolecularly hydrogen bonded in dilute solution of the diol (IV) [ν_{max} (CCl_4) 1718 cm^{-1}]; and (ii) the less hindered acetate at C-3 can be hydrolyzed in preference to the tiglate at C-1.

The ninth oxygen atom in salannin remains to be assigned. The preceding discussion limits this to a primary-secondary oxide spanning C-22 (or C-23) and C-6. In fact the C-22 (or C-23) methylene group in the diacetate (II) gives rise to an AB quartet (τ 6·25, 6·42; 2H; J = 8·5 Hz) at the expected position. Double irradiation (Fig. 1) shows that the A branch (τ 6·25) has a small (<1 Hz) ^4J coupling with the C-22 (or C-23) Me group (τ 8·78).

TABLE 1. RESONANCES (τ) OF ANGULAR Me GROUPS IN THE PMR SPECTRA OF SALANNIN AND ITS DERIVATIVES

Compound	I	II	III	IV	V
C_{25}	8·67	8·70	8·70	8·72	8·62
C_{22}	8·77	8·78	8·85	8·89	8·70
C_{24}	9·01	9·06	9·05	9·11	8·88

The configurations at C-4, C-1, C-3, C-15 and C-17 remain for discussion. The C-4 configuration can be such as to produce a *cis*- or a *trans*-fused ether ring with the α-(equatorial)-oxygen at C-6, depending on whether the C-4 equatorial or axial Me group, respectively, is oxidized. The *cis*-fusion appears more probable for the following reasons. Oxidation of diol IV by the Sarett reagent leads to a ketol V, $C_{27}H_{34}O_7$, m.p. 253–255°, $[\alpha]_D$ +160°. The IR dilute solution spectrum ($CHCl_3$) shows one broad carbonyl band at 1719 cm^{-1}, assignable to superimposed cyclohexanone and bonded methyl ester functions (*v. supra*). The newly introduced CO group must therefore be at C-3 and not at C-1. Comparison of the Me group resonances in the hydroxy-ketone V and the diol IV, shows (Table 1) that the new CO group exerts a marked deshielding effect on the resonances of the C-22 and C-24 groups. Dreiding models show that a trans-fused C-6(α)→C-22 oxide ring would impose a quasi-boat conformation on ring A. In what from models appears to be the most stable conformation, the C-3 CO function should strongly shield[4] the C-24 Me group, contrary to observation. If, on the other hand, the oxide ring is cis-fused, C-6(α)→C-23, the C-24 Me group is in the deshielding region of the CO group at C-3. Ring A should then be in the chair conformation and consequently the ester groups at C-1 and C-3 must be axially (α)-oriented to account for the relatively small (ca. 5 Hz) band widths at half height ($W^{\frac{1}{2}}$)[5] observed for the H-1 and H-3 resonances in the PMR spectrum of the diacetate II.

The C-15 configuration can be inferred from the chemical shift of the C-25 Me group in salannin and its derivatives. This, as the Table shows, is consistently the most deshielded of the tertiary Me's and must owe its appreciable paramagnetic shift to the isolated double bond. The necessary favourable geometry exists if H-15 is α since the C-25 Me group is then situated in the deshielding region of the olefinic double bond.† The H-17 configuration is assigned on the assumption that no inversion occurs at this centre during the derivation of salannin from euphol.

Salannin and nimbin both isolated from the same plant, are at present unique, being the only tetranortriterpenoids in which ring C of apoeuphol is cleaved.

EXPERIMENTAL

For general experimental see Part I.[7] Salannin was isolated as described in the preceding paper.[2]

Hydrolysis of salannin

The hydroxytiglate (III) *and diol* (IV). Salannin (400 mg) was dissolved in 5% methanolic KOH and left at 20° for 2 hr. The soln was diluted with water, acidified and extracted with EtOAc. Removal of solvent gave a gum (390 mg) which on methylation with diazomethane showed (TLC) as a mixture of starting material and two more polar compounds. The mixture of methyl esters was chromatographed on Grade IV acid alumina (20 g). Benzene eluted salannin (165 mg), m.p. 165–168°. $CHCl_3$–benzene (3:17) eluted *hydroxy-tiglate* (III; 130 mg) m.p. 213–215° (from EtOAc–light petroleum), $[\alpha]_D$ +137° (*c*, 0·94), ν_{max} (CCl_4) 3600 (free OH), 1742 (methyl ester) and 1717 (tiglate ester) cm^{-1}. [Found: C, 69·3; H, 7·7. $C_{32}H_{42}O_8$ requires: C, 69·3; H, 7·6%]. $CHCl_3$–benzene (1:1) eluted the *diol* IV (80 mg), m.p. 201–205° (from EtOAc–light petroleum). $[\alpha]_D$ +135° (*c*, 1·13), ν_{max} (CCl_4) 3465 (bonded OH), 1718 (bonded methyl ester) cm^{-1}. (Found: C, 68·7; H, 7·5. $C_{27}H_{36}O_7$ requires: C, 68·6; H, 7·7%.)

Destigloylsalannin diacetate (II). Diol IV (230 mg) was dissolved in AnalaR pyridine (2 ml) and AnalaR Ac_2O (2 ml) and left at 20° for 3 days. Water was added and the soln extracted with EtOAc. The usual work-up gave a gum (225 mg) which was chromatographed on Grade III acid alumina (8 g). Ether–benzene (3:17) eluted *destigloylsalannin diacetate* (II; 180 mg), m.p. 230–234° (from EtOAc-light petroleum), $[\alpha]_D$ +126° (*c*, 1·1), ν_{max} (CCl_4) 1743 (acetates and methyl ester) cm^{-1}. (Found: C, 66·8; H, 7·3. $C_{31}H_{40}O_9$ requires: C, 66·9; H, 7·2%.)

Oxidation of the diol (IV)

The ketol (V). Diol (IV) (110 mg) was dissolved in AnalaR pyridine (6 ml), CrO_3 (400 mg) added and the soln left at 20° for 18 hr. The usual work-up gave a red gum which was chromatographed on Grade IV acid alumina (10 g). $CHCl_3$ eluted the *ketol* (V; 40 mg), m.p. (from EtOAc) 253–255°, $[\alpha]_D$ +160° (*c*, 0·5), ν_{max} ($CHCl_3$) 3450 (bonded OH), 1719 (bonded methyl ester) cm^{-1}. (Found: C, 67·8; H, 7·1. $C_{27}H_{34}O_7$ requires: C, 68·9; H, 7·3%.)

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† A recent re-evaluation of the McConnell Equation[6] throws some doubt on the validity of these arguments.