Tetrahedron Letters, Vol.22, No.34, pp 3321 - 3324, 1981
Printed in Great Britain

0040-4039/81/343321-04$02.00/0

4-DEOXYPHORBOL AND 4α-DEOXYPHORBOL ALDEHYDES
NEW DITERPENES AND THEIR ESTERS

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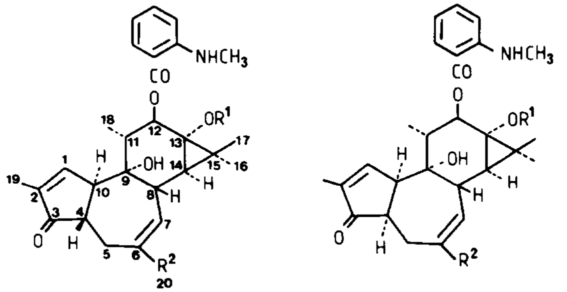
ABSTRACT. Two diterpenes were isolated from Sapium indicum L. The first was 12-[2-methylaminobenzoyl]-4-deoxyphorbaldehyde-13-acetate and the second its 4α-isomer. These compounds are the first natural tiglianes to exhibit a C-20 aldehyde.

Sapium indicum (Euphorbiaceae) is a natural drug which is used in Indian native medicine[2]. From the dried fruits two nitrogen containing derivatives of 4-deoxy and 4α-deoxyphorbol were isolated. These compounds are the first phorbol type diterpenes from natural sources which exhibit an aldehyde group at C-20 of the tigliane nucleus (Fig. 1). Accordingly they are of interest in studies involving the mechanism of action of the phorbol tumour-promoting and pro-inflammatory agents[3].

FIGURE 1



1 $R^1 = OC\,CH_3$, $R^2 = CHO$
3 $R^1 = OC\,CH_3$, $R^2 = CH_2OH$

2 $R^1 = OC\,CH_3$, $R^2 = CHO$
4 $R^1 = OC\,CH_3$, $R^2 = CH_2OH$
5 $R^1 = H$, $R^2 = CH_2OH$

The ether soluble portion of the fruit oil ~~was~~ fractionated[4, 5] by a neutral process involving high speed centrifugal liquid chromatography (CLC) followed by partition chromatography. Oxygen was excluded during the whole of the isolation procedure. 1 and 2 exhibited an intense blue fluorescence under u.v. light.

1. ($C_{30}H_{35}O_7N$, hr-MS), M.S. (C.I.), m/z 521 ($M^{+\cdot}$, 9%), 489 (5%), 371 ($M^{+\cdot}$-150, 11%), 311 ($M^{+\cdot}$-[150 + 60], 15%), 293 (5%), 151 (100%). i.r. (KBr), ν_{max}, cm.$^{-1}$, 3500, 3390, 1725, 1680, 1630, 1580, 1520, u.v., $\lambda^{MeOH}_{max.}$, n.m. (log ε), 224 (4.99), 252 (4.65), 356 (4.23). ^{1}H-NMR. See Fig. 2.

2. ($C_{30}H_{35}O_7N$, hr-MS), M.S. (C.I.), m/z 521 ($M^{+\cdot}$, 5%), 371 (12%), 311 (17%), 293 (3%), 151 (100%), i.r. (KBr), $\nu_{max.}$, cm.$^{-1}$, 3510, 3390, 1710, 1685, 1650, 1610, 1580, 1520. u.v., $\lambda^{MeOH}_{max.}$, n.m., (log ε), 224 (4.59), 252 (4.14), 356 (3.78). ^{1}H-NMR. See Figure 2. The 2H-20 signal which normally occurs at about 4.0 ppm[3] in the ^{1}H-NMR spectra of phorbol esters is absent in the spectra of 1 and 2. The 1H singlet at 9.45 ppm in 1 and 9.33 ppm in 2 indicates that in these compounds the C-20 oxygen function is an aldehyde group. Furthermore, the shift of H-1 from 7.51 ppm to 7.06 ppm, H-8 from 2.71 ppm to 2.02 ppm and the H-10 from 3.09 ppm to 3.59 ppm in the spectra of 1 and 2 respectively suggests[6] that 1 is a derivative of 4-deoxyphorbol and 2 of 4α-deoxyphorbol.

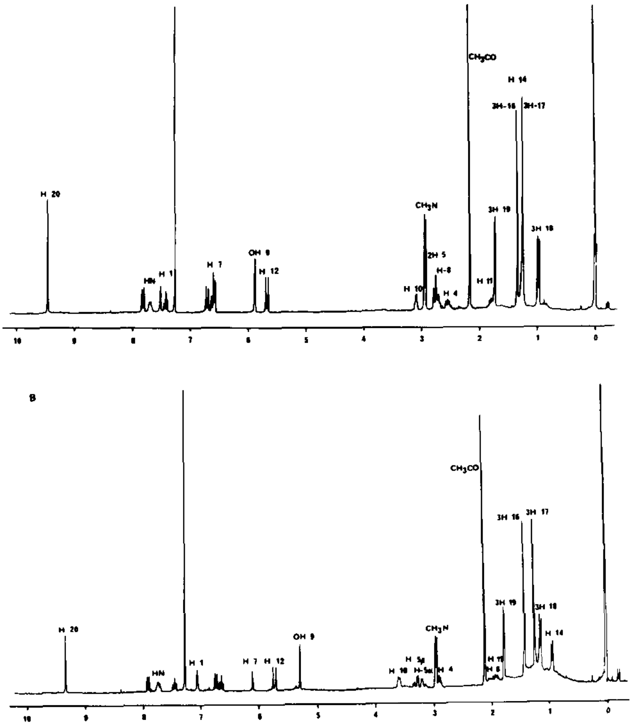


Figure 2.

^{1}H-NMR spectra, solvent $CDCl_3$. 250 MHz.

A. 12-[2-methylaminobenzoyl]-4-deoxyphorbaldehyde-13-acetate.

B. 12-[2-methylaminobenzoyl]-4α-deoxyphorbaldehyde-13-acetate.

1 was reduced with NaBH$_4$ under N$_2$ in MeOH to produce 3. M.S. (E.I.), m/z 523 ($M^{+\cdot}$, 4%), 373 (5%), 313 (6%), 295 (3%), 151 (100%). ^{1}H-NMR (CDCl$_3$), δ 7.82 (d.d., J = 1.8, 8.1 Hz, 1H), 7.69 (d, J = 5.1 Hz, HN-, exchangeable), 7.57 (s, H-1), 7.41 (t, J = 6.9 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.59 (t, J = 8.1 Hz, 1H), 5.69 (OH, exchangeable), 5.64 (d, J = 11.6 Hz, H-12), 5.59 (d, J = 3.68 Hz, H-7), 4.04 (s, 2H-20), 3.28 (m, H-10), 2.94 (d, J = 5.1 Hz, C$\underline{H}_3$N-), 2.85 (m, H-4), 2.54 (m, 2H-5), 2.45 (m, H-8), 2.18 (m, H-11), 2.13 (s, C$\underline{H}_3$CO.), 1.73 (s, 3H-19), 1.32 (s, 3H-16), 1.19 (s, 3H-17), 1.13 (d, J = 5.2 Hz, H-14), 0.96 (d, J = 6.3 Hz, 3H-18) ppm. C.D. (MeOH), n.m., (θ), 220 ($+5.05 \times 10^4$), 240 ($+3.56 \times 10^4$), 265 ($+0.49 \times 10^4$), 325 (-0.71×10^4). In an identical manner 2 was reduced with NaBH$_4$ to 4. M.S. (E.I.) m/z 523 ($M^{+\cdot}$, 5%), 481 (2%), 373 (13%), 313 (15%), 295 (8%), 151 (100%). ^{1}H-NMR (CDCl$_3$) δ 7.09 (s, H-1), 5.71 (d, J = 10.3 Hz, H-12), 5.15 (s, H-7), 3.97 (ABq, JA/B = 28.6 Hz, 2H-20), 3.54 (m, H-10), 3.46 (d.d., J = 3.1, 15.4 Hz, H-5α), 2.51 (d.d., J = 5.8, 15.4 Hz, H-5β), 2.03 (m, H-8), 1.87 (d.d., J = 3.7, 10.3 Hz, H-11), 1.12 (d, J = 6.3 Hz, 3H-18), 0.88 (d, J = 6.6 Hz, H-14) ppm, other signals were similar to the spectra for 3. C.D. (MeOH), n.m., (θ), 207 ($+ 2.67 \times 10^4$), 262 (-0.27×10^4), 321 ($+ 0.12 \times 10^4$), 355 ($- 0.12 \times 10^4$). 3 and 4 were hydrolysed with NaOMe in MeOH to a common polyol which after acetylation was identical to the previously known 4α-deoxyphorbol-12,13,20-triacetate[6]. The conversion of AB trans to AB cis analogues is known to occur[6,7] during base catalysed hydrolysis. A blue u.v. fluorescent methyl ester was also obtained which was identical to the methyl ester produced from 2-methylamino benzoic acid (Aldrich Chemicals Ltd.). By means of mild base hydrolysis (0.1 M KOH in MeOH) 3 and 4 were converted to the mono-ester 5. M.S. (E.I.), m/z 481 ($M^{+\cdot}$, 7%), 330 (10%), 312 (20%), 151 (100%). ^{1}H-NMR (CDCl$_3$) was similar to that of 4. However the 3H acetyl signal was absent in the spectrum of 5, and the H-12 had moved from 5.71 ppm in 4 to 5.21 ppm in 5. The shift in the signal for the H-12 due to removal of the C-13 acetyl group has previously been confirmed using synthetic methods[8]. On this basis 3 was 12-[2-methylaminobenzoyl]-4- deoxyphorbol-13-acetate and 4 was α-sapinine[9]. Compounds 1 and 2 are the naturally occurring C-20 aldehydes of 4-deoxy and 4α-deoxyphorbol esters respectively.

ACKNOWLEDGEMENTS. S.E. Taylor is grateful to the Science Research Council for a maintenance grant.

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(Received in UK 24 June 1981)