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NITROGEN-CONTAINING PHORBOL DERIVATIVES OF *SAPIUM INDICUM*

STEPHEN E. TAYLOR, M. A. GAFUR,* A. K. CHOUDHURY* and FRED J. EVANS

Department of Pharmacognosy, The School of Pharmacy (University of London), 29–39, Brunswick Square, London WC1N 1AX, U.K.; * B.C.S.I.R. Laboratories, P.O. Bayezied Bostami, Chittagong, Bangladesh

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Abstract—From the ether-soluble fraction of an extract of *Sapium indicum* two new nitrogen-containing esters of deoxyphorbol, sapintoxins B and C, were isolated. Both were characterized by the bright blue fluorescence which they exhibited in UV light. Sapintoxin B was identified as 12-(*N*-methylaminobenzoyl)-4-deoxy-5-hydroxyphorbol-13-acetate and sapintoxin C as 12-(*N*-methylaminobenzoyl)-4,20-dideoxy-5-hydroxyphorbol-13-acetate.

INTRODUCTION

Esters of phorbol are currently of interest as pharmacological tools for the investigation of the mechanisms of the promotion stage of carcinogenesis [1] as well as being useful instruments for the investigation of the processes of inflammation in mammalian systems [2]. New biologically active nitrogen-containing esters of the tigliane nucleus have been predicted as occurring in plants of the family Euphorbiaceae [5]. Such compounds are required for pharmacological structure–activity studies [3].

Sapium indicum of the family Euphorbiaceae is a well-known poisonous plant and piscicidal agent [4] which has been previously investigated [5]. Only the non-biologically active 4α-tigliane ester, α-sapinine was isolated. Recently from the fruits the AB *trans*-isomer, sapintoxin A, was obtained [6]. Our further investigations of the fruit extract of this plant have resulted in the isolation of the biologically active compounds sapintoxins B and C, both of which are esters of new deoxyphorbol alcohols.

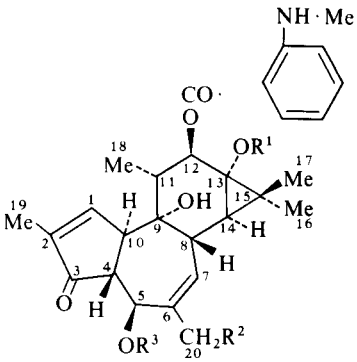
RESULTS AND DISCUSSION

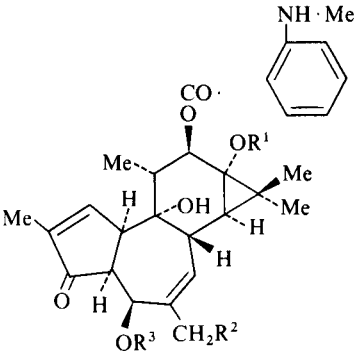
By the application of biological assays in conjunction with analytical TLC several esters were detected in the ether extracts of *S. indicum*. Two of these, sapintoxins B and C, **1** and **6** (Fig. 1), produced a pronounced blue fluorescence in UV light. Transesterification of **1** and **6** afforded a blue UV fluorescent Me ester which was identical to the Me ester synthesized from commercially available *N*-methylaminobenzoic acid. From the electron-impact mass spectrum of **1** and **6** it was evident that both compounds were diesters of new 4-deoxyphorbol derivatives, but no information was obtained from the spectra alone concerning the positions of the *N*-methylaminobenzoate and acetate moieties. The assignment of the *N*-methylaminobenzoyl group to C-12 of the nucleus and the acetate to C-13 in **1** and **6** was facilitated by hydrolysis reactions. In the ^{1}H NMR spectra of **3** and **7**, produced from **1** and **6** by methanolic KOH, the shift of the H-12 signal from 5.62 and 5.65 ppm to 5.25 and 5.17 ppm, respectively, together with the disappearance of the 3 H acetyl signal is characteristic of phorbol esters when the C-13 reactive tertiary OH group is hydrolysed. This reaction has previously been confirmed by synthesis combined with X-ray techniques [9]. The signal at 5.65 ppm in **6** was shown to belong to the H-12 by decoupling experiments. **3** was acetylated to give the acetate **5** and in the ^{1}H NMR spectrum of this product the signal for H-12 had moved down-field to 5.69 ppm together with the appearance of a 3 H acetyl signal, thereby confirming that the acetate group was introduced at C-13. The *trans* AB configuration of **1** and **6**, suspected from biological data, was confirmed by the ^{1}H NMR and circular dichroism (CD) spectra. The chemical shifts in the ^{1}H NMR spectra of **1** and **6** for H-1, H-10 and H-4 are diagnostic of *trans*-tigliane derivatives [10]. The characteristic Cotton effects produced in the CD spectra of **3**, **5**, **6** and **7** are similar to those exhibited by known ring AB *trans* and *cis*-isomers [5, 6, 10].

Compound **6** was shown to be the C-20 deoxy derivative of **1** because in its ^{1}H NMR spectrum an extra 3 H signal was present at 1.87 ppm and the 2 H signal for the C-20 protons was absent. Sapintoxin B, **1** was therefore confirmed as 12-(*N*-methylaminobenzoyl)-4-deoxy-5-hydroxyphorbol-13-acetate and sapintoxin C, **6** as 12-(*N*-methylaminobenzoyl)-4,20-dideoxy-5-hydroxyphorbol-13-acetate, both of which are new parent phorbol derivatives.

EXPERIMENTAL

Powdered fruits of *S. indicum* (*ca* 2 kg) were macerated with Me_2CO for 2 weeks at room temp. The oily residue left after the removal of Me_2CO was dissolved in 40% MeOH and partitioned with hexane to remove fats, steroids and triterpenoids. The MeOH phase was then re-extracted with Et_2O. The Et_2O phase was partitioned with 0.5% Na_2CO_3 soln and then with H_2O





1 R^1 = OC·Me; R^2 = OH; R^3 = H
2 R^1 = OC·Me; R^2 = OOC·Me; R^3 = OC·Me
6 R^1 = OC·Me; R^2 = H; R^3 = H
8 R^1 = H; R^2 = H; R^3 = H

3 R^1 = H; R^2 = OH; R^3 = H
4 R^1 = H; R^2 = OOC·Me; R^3 = H
5 R^1 = OC·Me; R^2 = OOC·Me; R^3 = OC·Me
7 R^1 = H; R^2 = H; R^3 = H

Fig. 1. The nitrogen-containing tigliane derivatives of *Sapium indicum*.

before evaporating down to a brown-yellow resinous solid (10 g). This residue induced pronounced erythema of mammalian skin [7] as well as inducing two-stage aggregation of human and rabbit blood platelets [8].

The Et_2O-soluble residue (*ca* 8 g) was separated by means of centrifugal liquid chromatography (CLC) using a 4-mm Si gel disc at a solvent flow of 4 ml/min, with the following gradient: toluene–hexane (3:1, 40 ml), toluene (100 ml), toluene–EtOAc 9:1, 6:1, 4:1, 3:1, 2:1, 1:1, 1:3, 1:4, 1:6, 1:9 (10 × 100 ml), EtOAc (200 ml). Fractions were automatically collected at 2-min intervals and monitored by a UV flow cell, analytical TLC and biological tests. The EtOAc and toluene–EtOAc (1:9) fractions were bulked as fraction 1 whilst the toluene–EtOAc 1:2, 1:3 and 1:4 fractions were bulked as fraction 2.

Fraction 1 (250 mg of an orange-brown solid) was further purified by prep. TLC on Si gel G (0.5-mm layers) developing × 3 with cyclohexane–toluene–EtOAc–Et_2O (4:3:8:6). The blue UV fluorescent zone (R_f 0.2) was recovered and finally purified by prep. TLC using kieselguhr G (0.5-mm layers) coated with 20% diethylene glycol and developing ×2 with cyclohexane–butanone (7:3).

Fraction 2 (150 mg of a yellow-brown solid) was purified by TLC on Si gel G (0.5-mm layers) developing ×2 with EtOAc–cyclohexane (7:3). A blue UV fluorescent band (R_f 0.41) was recovered and finally purified on kieselguhr G (0.5-mm layers) coated with 20% diethylene glycol using cyclohexane–butanone (4:1).

12-(N-*Methylaminobenzoyl*)-4-*deoxy*-5-*hydroxyphorbol*-13-*acetate* (**1**). (75 mg of a colourless resin.) **1** exhibited a single blue UV fluorescent spot in several analytical TLC systems. Crystallization of **1** was not attempted because of the danger of rings AB conversion to the biologically inactive 4α-series. EIMS (200°, 70 eV measured values were within 10 ppm of calculated values). Significant ions were exhibited at *m/z* (rel. int.) 539 ($M^{+\cdot}$, 5, $C_{30}O_8H_{37}N$), 521 (20), 480 (8), 389 (13), 371 (22), 353 (20), 335 (17), 329 (13), 310 (26), 292 (19), 151 (100), 105 (78), UV λ_{max}^{MeOH} (log ε) nm: 207 (sh) (4.24), 222 (4.38), 252 (3.99), 357 (3.73). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1720, 1685, 1580, 1520. ^1H NMR (90 MHz, $CDCl_3$, TMS): δ 7.81 (1 H, *dd*, *J* = 7.9 Hz, 1.4 Hz, aromatic), 7.69 (*s*, H-1), 7.69 (*s*, exchangeable D_2O, superimposed on H-1), 7.41 (1 H, *t*, *J* = 7.04 Hz, aromatic), 6.68 (1 H, *d*, *J* = 8.8 Hz, aromatic), 6.58 (1 H, *t*, *J* = 7.9 Hz, aromatic), 5.63 (*br s*, H-7), 5.62 (*d*, *J* = 9.68 Hz, H-12), 5.62 (1 H, exchangeable D_2O, superimposed on H-12), 5.14 (*br s*, H-5), 4.23 (*br s*, 2 H-20), 3.55 (*m*, H-10), 2.93 (*d*, *J* = 4.98 Hz, C$\underline{H}_3$N—), 2.63 (*t*, *J* = 4.4 Hz, H-4), 2.36 (*m*, H-8), 2.13 (*s*, C$\underline{H}_3$CO), 1.75 (*s*, 3 H-19), 1.74 (*m*, H-11), 1.29 (*s*, 3 H-17), 1.20 (*s*, 3 H-16), 1.10 (*d*, H-14), 0.96 (*d*, *J* = 6.16 Hz, 3 H-18) ppm. After reaction with Ac_2O–pyridine (2:1) **1** afforded an acetate **2**. This acetate like **1** was biologically active in the test systems described above.

12-(N-*Methylaminobenzoyl*)-4-*deoxy*-5-*hydroxyphorbol*-5,13,20-*triacetate* (**2**). MS *m/z* (rel. int.) 623 ($M^{+\cdot}$, 4, $C_{34}H_{41}O_{10}N$), 563 (3), 503 (6), 413 (7), 353 (21), 316 (18), 310 (50), 292 (25), 151 (100), 105 (54). ^1H NMR (60 MHz, $CDCl_3$): δ 7.85 (1 H, *dd*), 7.65 (*s*, H-1), 7.65 (*s*, exchangeable with D_2O, superimposed on H-1), 7.60 (1 H, *t*), 6.70 (1 H, *d*), 6.61 (1 H, *t*, superimposed on 6.70), 6.40 (*br s*, H-5), 5.82 (*br s*, H-7), 5.66 (*d*, H-12), 5.72 (1 H, exchangeable with D_2O), 4.51 (AB*q*, 2 H-20), 3.62 (*m*, H-10), 2.92 (*d*, C$\underline{H}_3$N—), 2.71 (*t*, H-4), 2.42 (*m*, H-8), 2.14, 2.08, 1.90 (3 × C$\underline{H}_3$CO), 1.74 (*s*, 3 H-19), 1.69 (*m*, H-11), 1.30 (*s*, 3 H-17), 1.21 (*s*, 3 H-16), 1.16 (*d*, H-14), 0.99 (*d*, 3 H-18) ppm. CD (MeOH) Cotton effects were evident at 355 ([θ] = −5610), 235 ([θ] = +33 264), 225 ([θ] = +41 580), 203 ([θ] = −47 520) nm. When treated with 0.1 M KOH in dry MeOH for 20 min **1** was converted to the blue UV fluorescent monoester **3**.

12-(N-*Methylaminobenzoyl*)-4α-*deoxy*-5-*hydroxyphorbol* (**3**). MS (rel. int.) *m/z* 497 ($M^{+\cdot}$, 1, $C_{28}H_{35}O_7N$), 479 (2), 454 (4), 346 (1), 328 (11), 310 (24), 292 (10), 151 (85), 105 (100). ^1H NMR (250 MHz, $CDCl_3$): δ 7.856 (*dd*, *J* = 7.80, 1.61 Hz, aromatic), 7.699 (1 H, exchangeable with D_2O), 7.428 (*t*, *J* = 8.49 Hz, aromatic), 7.194 (*s*, H-1), 6.710 (*d*, *J* = 8.49 Hz, aromatic), 6.599 (*t*, *J* = 7.80 Hz, aromatic), 5.371 (*d*, *J* = 3.20 Hz, H-7), 5.280 (1 H, exchangeable with D_2O), 5.253 (*d*, *J* = 11.87 Hz, H-12), 5.111 (*s*, exchangeable with D_2O), 4.797 (*d*, *J* = 3.67 Hz, H-5), 4.099 (AB*q*, *J* = 16.86 Hz, 2 H-20), 3.686 (*m*, H-10), 3.209 (*t*, *J* = 5.05 Hz, H-4), 2.935 (*d*, *J* = 3.44 Hz, C$\underline{H}_3$N—), 2.331 (*t*, *J* = 6.57 Hz, H-8), 1.806 (*s*, 3 H-19), 1.604 (*m*, H-11), 1.166 (*s*, 3 H-17), 1.089 (*s*, 3 H-16), 0.973 (*d*, *J* = 6.43 Hz, H-14), 0.841 (*d*, *J* = 5.51 Hz, 3 H-18) ppm. Acetylation of **3** with Ac_2O–7 pyridine (2:1) produced two products, **4** and **5**. Neither **3**, **4** nor **5** demonstrated biological activity *in vivo*.

12-(N-*Methylaminobenzoyl*)-4α-*deoxy*-5-*hydroxyphorbol*-20-*acetate* (**4**). MS (rel. int.) *m/z* 539 ($M^{+\cdot}$, 3, $C_{30}H_{37}O_8N$), 480 (5), 368 (10), 328 (7), 310 (20), 292 (9), 151 (75), 105 (100). ^1H NMR (250 MHz, $CDCl_3$–D_2O): δ 7.856 (*dd*, *J* = 7.80, 1.61 Hz, aromatic), 7.428 (*t*, *J* = 8.49 Hz, aromatic), 7.113 (*s*, H-1), 6.710 (*d*, *J* = 8.49 Hz, aromatic), 6.599 (*t*, *J* = 7.80 Hz, aromatic), 5.562 (*d*, *J* = 3.12 Hz, H-7), 5.253 (*d*, *J* = 11.87 Hz, H-12), 4.732 (*d*, *J*

= 3.67 Hz, H-5), 4.505 (*d*, *J* = 11.67 Hz, 2 H-20), 3.686 (*m*, H-10), 3.284 (*t*, *J* = 5.05 Hz, H-4), 2.935 (*s*, C$\underline{H}_3$N—), 2.331 (*t*, *J* = 6.57 Hz, H-8), 2.136 (*s*, C$\underline{H}_3$CO), 1.806 (*s*, 3 H-19), 1.604 (*m*, H-11), 1.166 (*s*, 3 H-17), 1.089 (*s*, 3 H-16), 0.973 (*d*, *J* = 6.43 Hz, H-14), 0.841 (*d*, *J* = 5.51 Hz, 3 H-18) ppm.

12-(N-*Methylaminobenzoyl*)-4α-*deoxy*-5-*hydroxyphorbol*-5,13,20-*triacetate* **5**. MS *m/z* (rel. int.) 623 ($M^{+\cdot}$, 6, $C_{34}H_{41}O_{10}N$), 563 (12), 520 (29), 503 (23), 472 (11), 353 (10), 328 (16), 310 (66), 292 (32), 151 (100), 105 (50). ^{1}H NMR (250 MHz, $CDCl_3$–D_2O). δ 7.856 (*dd*, *J* = 7.80, 1.61 Hz, aromatic), 7.428 (*t*, *J* = 8.49 Hz, aromatic), 7.049 (*s*, H-1), 6.710 (*d*, *J* = 8.49 Hz, aromatic), 6.599 (*t*, *J* = 7.80 Hz, aromatic), 6.043 (*d*, *J* = 3.67 Hz, H-5), 5.690 (*d*, *J* = 10.55 Hz, H-12), 5.562 (*d*, *J* = 3.21 Hz, H-7), 4.584 (AB*q*, *J* = 12.05 Hz, 2 H-20), 3.686 (*m*, H-10), 3.284 (*t*, *J* = 5.10 Hz, H-4), 2.935 (*s*, C$\underline{H}_3$N—), 2.331 (*t*, *J* = 6.57 Hz, H-8), 2.169, 2.163, 2.115 (3 × C$\underline{H}_3$CO.), 1.806 (*s*, 3 H-19), 1.604 (*m*, H-11), 1.166 (*s*, 3 H-17), 1.089 (*s*, 3 H-16), 0.973 (*d*, *J* = 6.43 Hz, H-14), 0.841 (*d*, *J* = 5.51 Hz, 3 H-18) ppm. Irradiation of the signal at 3.28 ppm (H-4) induced the multiplet at 3.69 ppm (H-10) to become a *br s* and the doublet at 6.04 ppm (H-5) to form a sharp *s*. CD (MeOH) Cotton effects were observed at 375 ([θ] = +264). 228 ([θ] = −7425 nm).

12-(N-*Methylaminobenzoyl*)-4,20-*dideoxy*-5-*hydroxyphorbol*-13-*acetate* (**6**). (60 mg of a colourless resin.) This product was isolated from fraction 2 of the CLC separation. **6** produced a single blue UV fluorescent spot in several TLC systems but like **1** no attempt was made to crystallize it. MS *m/z* (rel. int.) 523 ($M^{+\cdot}$, 2, $C_{30}O_7H_{37}N$), 373 (4), 313 (5), 296 (4), 280 (3), 151 (100), 105 (40). UV λ_{max}^{MeOH} (log ε) nm: 207 (sh) (4.39), 222 (4.47), 252 (4.10), 357 (3.82). IR ν_{max}^{KBr} cm^{-1}: 3500 (sh), 3400, 1725, 1685, 1630, 1605, 1580, 1520 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.872 (*dd*, *J* = 8.09, 2.04 Hz, aromatic), 7.698 (*s*, exchangeable with D_2O), 7.698 (*s*, H-1), 7.433 (*t*, *J* = 6.98 Hz, aromatic), 6.690 (*d*, *J* = 8.09 Hz, aromatic), 6.587 (*t*, *J* = 8.09 Hz, aromatic), 5.645 (*d*, *J* = 9.19 Hz, H-12), 5.608 (*s*, exchangeable with D_2O), 5.315 (*d*, *J* = 5.15 Hz, H-7), 4.866 (*d*, *J* = 3.67 Hz, H-5), 3.530 (*m*, H-10), 2.928 (*d*, *J* = 4.41 Hz, C$\underline{H}_3$N—), 2.630 (*t*, *J* = 3.67 Hz, H-4), 2.339 (*m*, H-8), 2.127 (*s*, C$\underline{H}_3$CO), 1.873 (*s*, 3 H-20), 1.734 (*s*, 3 H-19), 1.660 (*dd*, *J* = 6.25, 9.56 Hz, H-11), 1.291 (*s*, 3 H-17), 1.201 (*s*, 3 H-16), 1.083 (*d*, *J* = 5.52 Hz, H-14), 0.964 (*d*, *J* = 6.25 Hz, 3 H-18) ppm. Irradiation of the signal at 2.63 ppm (H-4) induced the *d* at 4.87 ppm (H-5) to collapse to a sharp *s* and the *m* at 3.53 ppm (H-10) to form a *br s*, whilst irradiation at 5.32 ppm (H-7) induced the *m* at 2.34 ppm (H-8) to form a *d* (*J* = 5.52 Hz). Furthermore, irradiation of the signal at 2.34 ppm induced the *d* at 1.08 (H-14) and 5.32 ppm to form sharp *s*. Finally, irradiation at 1.660 ppm (H-11) induced the *d* at 5.65 and 0.84 ppm to collapse to *s*. CD (MeOH) Cotton effects were observed at 350 ([θ] = −3432), 233 ([θ] = +29 205), 222 ([θ] = +44 220), 202 ([θ] = −54 120) nm. Exposure of **6** to 0.1 M KOH in MeOH for 15 min produced two products, **7** and **8**.

12-(N-*Methylaminobenzoyl*)-4α-20-*dideoxy*-5-*hydroxyphorbol* (**7**). MS *m/z* (rel. int.) 481 ($M^{+\cdot}$, 7, $C_{28}O_6H_{35}N$), 463 (5), 445 (6), 351 (3), 330 (4), 312 (11), 294 (9), 151 (100), 105 (60). ^{1}H NMR (250 MHz, $CDCl_3$–D_2O): δ 7.872 (*dd*, *J* = 8.09, 1.66 Hz, aromatic), 7.433 (*t*, *J* = 6.98 Hz, aromatic), 7.175 (*s*, H-1), 6.717 (*d*, *J* = 7.91 Hz, aromatic), 6.605 (*t*, *J* = 8.09 Hz, aromatic), 5.171 (*d*, 9.74 Hz, H-12), 5.054 (*br s*, H-7), 4.603 (*d*, *J* = 4.60 Hz, H-5), 3.643 (*m*, H-10), 3.127 (*dd*, *J* = 4.60, 6.43 Hz, H-4), 2.949 (*s*, C$\underline{H}_3$N—), 2.317 (*m*, H-8), 1.862 (*s*, 3 H-20), 1.826 (*s*, 3 H-19), 1.633 (*m*, H-11), 1.162 (*s*, 3 H-17), 1.107 (*s*, 3 H-16), 0.970 (*d*, H-14), 0.84 (*d*, 3 H-18) ppm. CD (MeOH) Cotton effects were observed at 365 ([θ] = +1056), 230 ([θ] = −12 507), 213 ([θ] = +16 962) nm.

12-(N-*Methylaminobenzoyl*)-4,20-*dideoxy*-5-*hydroxyphorbol* **8**. MS *m/z* (rel. int.) 481 ($M^{+\cdot}$, 8, $C_{28}O_6H_{35}N$), 463 (6), 445 (3), 351 (2), 330 (7), 312 (36), 294 (4), 151 (100), 105 (80). ^{1}H NMR (250 MHz, $CDCl_3$–D_2O): δ 7.872 (*dd*, *J* = 8.09, 1.66 Hz, aromatic), 7.698 (*s*, H-1), 7.433 (*t*, *J* = 6.98 Hz, aromatic), 6.690 (*d*, *J* = 8.09 Hz, aromatic), 6.587 (*t*, *J* = 8.09 Hz, aromatic), 5.298 (*d*, *J* = 2.57 Hz, H-7), 5.018 (*d*, *J* = 8.82 Hz, H-12), 4.846 (*br s*, H-5), 3.424 (*m*, H-10), 2.928 (*s*, C$\underline{H}_3$N—), 2.630 (*t*, *J* = 3.67 Hz, H-4), 2.340 (*m*, H-8), 1.879 (*s*, 3 H-20), 1.789 (3 H-19), 1.660 (*m*, H-11), 1.290 (*s*, 3 H-17), 1.200 (*s*, 3 H-16), 1.083 (*d*, H-14), 0.963 (*d*, 3 H-18) ppm.

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