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NEW HIGHLY IRRITANT 1-ALKYLDAPHNANE DERIVATIVES FROM SEVERAL SPECIES OF THYMELAEACEAE

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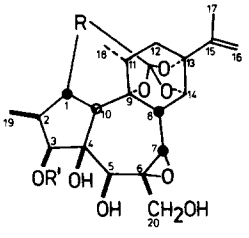
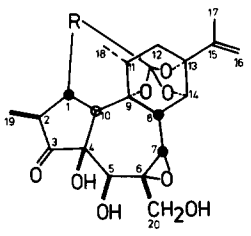
We report herein the isolation of new highly irritant diterpene esters from the genera Pimelea, Daphnopsis and Synaptolepis (Thymelaeaceae), which are structurally related to gnidimacrin[1] recently isolated from Gnidia subcordata (Meissn.) Engl. (Thymelaeaceae).





I a) (C-1)-R=(C=1)-CH(CH$_3$)-(CH$_2$)$_7$; R'=COC$_6$H$_5$
b) (C-1)-R=(C-1)-CH(CH$_3$)-(CH$_2$)$_7$; R'=H

II a) (C-1)-R=(C-1)-CH(CH$_3$)-(CH$_2$)$_7$
b) (C-1)-R=(C-1)-C$_{13}$H$_{26}$-CH=CH
c) (C-1)-R=(C-1)-CH(CH$_3$)-(CH$_2$)$_6$-CH(OCOC$_6$H$_5$)

Pimelea factor P$_2$ and Daphnopsis factor R$_1$ (Ia). Both factors are identical according to their spectral data. (P$_2$ 0.005 and 0.4% of methanol extract from leaves and roots or stems, respectively; R$_1$ 0.08%; ID$_{50}$ 0.003 nmoles/ear) ms: 638; ir (CH$_2$Cl$_2$): 3470 (OH), 1700 (CO), 1640 cm^{-1} (C=C); uv (MeOH): λ_{max} 195, 229 and 279 nm (ε_{max} 45200, 14800 and 1570); nmr (CDCl$_3$,δ): 5 arom. H: 8.05 (m) and 7.57 (m); 3-H: 5.06 (d, J=5Hz); 16-H$_2$: 4.95 (s) and 4.85 (s); 14-H: 4.24 (d, J=3Hz); 5-H: 4.1 (s); 20-H$_2$: 3.76±0.12 (J$_{AB}$= 12Hz); 7-H: 3.32 (s); 10-H: 3.1 (d, J=13Hz); 8-H: 2.88 (d, J=3Hz); 17-H$_3$: 1.75 (s); 19-H$_3$: 1.04 (d, J=7Hz); 18-H$_3$: 0.82 (d, J=7Hz); a further methyl group (1.44 ppm, d, J=6Hz) is decoupled upon irradiation at 2.6 ppm. - The spectral data suggest the presence of a 9α,13α,14α-orthoester and a 6α,7α-oxide group. The data indicate the absence of a 1,2-double bond and the presence of a saturated C$_{10}$-orthoester moiety including a methyl group and a double bond equivalent. The latter suggests a cyclic structure for the orthoester rest. The assignment of the signal at 3.1 ppm for 10-H lends support from the finding that in a hydrogenation product of the Hippomane factor group M$_x$[2] the signal of this proton appears as dd (J=13 and 5 Hz) at 2.95 ppm. The chemical shift of 10-H indicates its α-position (vicinity of the 6α,7α-oxide), multiplicity and coupling constant are consistent with configuration of a 1-alkyl side chain.

P$_2$ gives a 5,20-acetonide with acetone and p-toluene-sulfonic acid. Alkaline transesterification of P$_2$ leads to Ib which yields a 3,5,20-triacetate upon acetylation (Ac$_2$O/pyridine). The β-position of the 3-acyl group could be established, since upon reaction with acetone and p-toluene-sulfonic acid Ib affords a 3,4:5,20-diacetonide, which contains no free OH group. Moreover, Ib can be cleaved with sodium periodate in aqueous dioxan solution[3] to give a 3-aldehyde-4-ketone (10-H: 4.45 ppm). The latter affords, upon acetylation, a 5,20-diacetate which contains no free

OH-group. From these reactions, structure Ia is suggested for Pimelea factor P_2. The secondary methyl group of the 1-alkyl residue was located by analogy to gnidimacrin, at C-21. - Another Gnidia factor, gnilatimacrin, reportedly[4] is identical with P_2; chemical data are not available, yet it has been assayed for its capacity to induce plasminogen activator[4].

Pimelea factor S_7 (IIa, 0.008%, ID_{50}= 0.009): ms: 532; ir (CH_2Cl_2): 3510 (OH), 1730 (CO), 1640 cm^{-1} (C=C); uv (MeOH): λ_{max} 193, 306 nm (ε_{max} 10020, 105); nmr ($CDCl_3$,δ): 16-H_2: 5.05 (s) and 4.94 (s,br.); 14-H: 4.24 (d,J=3Hz); 5-H: 4.05 (s); 20-H_2: 3.80±0.03 (J_{AB}= 12Hz); 7-H: 3.34 (s); 10-H: 3.1 (d, J=12Hz); 8-H: 2.93 (d, J=3Hz); 17-H_3: 1.71 (s); 19-H_3 and 18-H_3: 1.13 (d, J=6Hz) and 0.95 ppm (d, J=7Hz).

Synaptolepis factor K_1 (IIb, 0.1%, ID_{50} = 0.003): ms: 614; ir (CH_2Cl_2): 3520 (OH) 1735 cm^{-1} (CO); nmr ($CDCl_3$): 16-H_2: 5.05 (s) and 4.92 (s,br.); 14-H: 4.35 (s, J=3Hz); 5-H: 4.05 (s); 20-H_2: 3.80±0.02 (J_{AB}=12Hz); 7-H: 3.42 (s); 10-H: 3.0 (d, J=12Hz); 8-H: 2.94 (d, J=3Hz); 17-H_3: 1.8 (s); 19-H_3 and 18-H_3: 1.14 (d, J=7Hz) and 0.9 (d, J=6Hz); signals of olefinic protons in the alkyl chain 6.25 (dd), 5.6 (d), appr. 22-24 H: 1.28-1.30 ppm (s). Decoupling experiments support the presence of an α,ß-unsaturated orthoester group.

Pimelea factor P_6 (IIc, 0.006%, ID_{50} = 0.08): ir (CH_2Cl_2): 3460 (OH), 1740, 1710 (C=O), 1640 cm^{-1} (C=C); uv (MeOH): λ_{max} 195, 229, 265, 273, 280 nm (ε_{max} 43030, 13960, 1150, 1270, 1080); nmr ($CDCl_3$,δ): 16-H_2: 5 arom. H: 8.0 (m), 7.5 (m); 16-H_2: 5.0 (s) and 4.9 (s,br.); 14-H: 4.32 (d,J 5-H: 4.12 (s); 20-H_2: 3.82 (s); 7-H: 3.42 (s); 10-H: 3.35 (d, J=10Hz); 8-H: 2.9 (d, J=3Hz); 17-H_3: 1.76 (s); 19-H_3: 1.08 (d, J=7Hz); 18-H_3: 0.92 (d, J=6Hz); a further CH_3-group (1.46 ppm, d, J=7Hz) is decoupled upon irradiation at 2.55 ppm. The signal of a geminal ester proton (5.05 ppm, m) appears as a singlet upon irradiation at 1.66 ppm. In contrast to P_2 the factors S_7, K_1 and P_6 contain a 3-keto group.

As in Ia, acid hydrolysis of S_7, K_1 and P_6 did not afford free acids. Analysis of the mass spectral data of the three factors suggest that, as in P_2 (Ia), the acid moieties of S_7, K_1 and P_6 are associated with one double bond equivalent indicating a cyclic structure for the ortho-ester residue. Hence, by analogy, for factors S_7, K_1 and P_6 the structures IIa, IIb and IIc are proposed, respectively. For K_1, a possible branching of the side chain remains to be clarified. The position of the benzoyl group in P_6 (IIc) lends support from decoupling experiments and the multiplicity of the geminal ester proton signal in P_6 and its derivatives.

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References

1) S.M. Kupchan, Y. Shizuri, T. Murae, J.G. Sweeny, H.R. Haynes, Ming-Shing Shen, J.C. Barrick, R.F. Bryan, J.Amer.Chem.Soc., 98, 5719 (1976).
2) W. Adolf, E. Hecker, Tetrahedron Lett., 19, 1587 (1975).
3) E. Hecker, R. Schmidt, Progr. Chem.Org.Nat.Prod., 31, 377 (1974).
4) B. Weinstein, M. Wigler, C. Pietropaolo, Cold Spring Harbor Symposium on the Origin of Human Cancer, Sept. 1976, in press.