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THERMAL REARRANGEMENTS OF SOME NEO-CLERODANE DITERPENOIDS

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Abstract – Some neo-clerodane diterpenoids isolated from plants belonging to the *Teucrium* genus and possessing different functionalities at the C-6, C-7 and C-19 positions were heated above their melting points without any solvent. This treatment produced good yields of different rearranged products, which are useful intermediates for the synthesis of other natural neo-clerodane derivatives.

A large number of diterpenoids with the neo-clerodane skeleton have been isolated from plants in the last few years. Interest in these compounds has been stimulated by their biological activity as insect antifeedants and as antifungal, antitumor, antimicrobial and molluscicidal agents. The *Teucrium* species (family Labiatae) have afforded a great number of these compounds.[1]

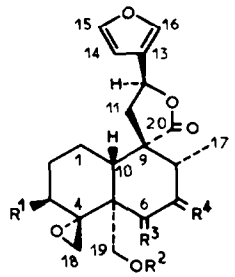
In continuation of our studies on neo-clerodane diterpenoids from *Teucrium* species[1], we were interested in establishing chemical correlations between some of these compounds and also in obtaining synthetic derivatives in order to test biological activities. This communication reports the results achieved by thermal treatment of a series of natural neo-clerodanes having a 4α,18 oxirane ring and different functions at the C-6 (ketone, α-hydroxyl or acetoxyl groups), C-7 (α- or β-hydroxyl or acetoxyl functions) and C-19 (hydroxyl or acetoxyl substituents) positions. In general, each compound undergoes different thermal rearrangement depending on its functionality, giving good yields of suitable intermediates for the synthesis of other natural neo-clerodane diterpenoids and, in some cases, substances previously found as natural products. Moreover, assays of the biological activity of these intermediates are now in progress.

RESULTS AND DISCUSSION

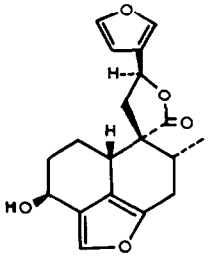
When the neo-clerodane teulepicin[2] (**1**, mp 174-176°C), with C-19 hydroxyl and C-6 keto functions, was heated at 185°C for 5 minutes without any solvent, the furanoid 19-nor-neo-clerodane derivative **2**[2] was obtained in almost quantitative yield. This transformation, which takes place *via* a retroaldol reaction and subsequent opening of the oxirane ring[3,4], has been achieved previously starting from 19-hydroxy- and 19-acetoxy-4α,18-epoxy-6-keto-neo-clerodane derivatives by using basic catalysis[2-4].

Since it is known that air oxidation of compounds such as **2** produces 19-nor-neo-clerodan-18,6-olide derivatives[3-5], thermal fragmentation of substances of type **1** can be an alternative route for obtaining these widespread natural nor-diterpenoids.[1]

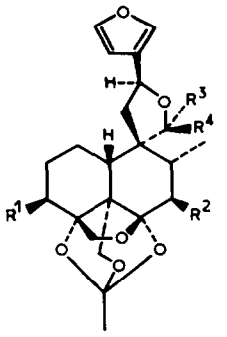
Thermal treatment of 19-acetylgnaphalin[3,4] (**3**, mp 227-229°C) at 240°C for 10 minutes and in the absence of solvent gave a mixture of compounds from which, after column chromatography, the ortho-acetate **4** was isolated as the major constituent (49% from **3**), besides minor quantities of an inseparable mixture of the epimeric aldehydes **5** and **6** (4 : 1 ratio, 15%, see Experimental) and the starting material (**3**, 11%). This result could be rationalized by considering that 19-acetylgnaphalin **3** undergoes thermal



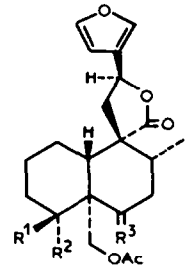
	R^1	R^2	R^3	R^4
1	OH	H	O	H_2
3	H	Ac	O	H_2
8	H	Ac	αOAc, βH	H_2
11	H	Ac	αOH, βH	H_2
12	H	Ac	O	αOH, βH
13	H	Ac	O	αOAc, βH
14	H	Ac	O	αH, βOAc
15	H	Ac	αOH, βH	O
16	H	Ac	αOAc, βH	O



2



	R^1	R^2	R^3	R^4
4	H	H	O	
7	OAc	H	OAc	H
17	H	OAc	O	



	R^1	R^2	R^3
5	H	CHO	O
6	CHO	H	O
9	H	CHO	αOAc, βH
10	CHO	H	αOAc, βH

cleavage of the C-4 - oxygen bond of its oxirane ring followed by hydride migration reaction[6], thus yielding compounds **5** and **6**. Furthermore, the hydride migration is in unfavourable competition with a concerted rearrangement which leads to the formation of the C-6β - C-18 tetrahydrofuran ring and the 4α,6α,19-orthoacetate moiety of compound **4**. This hypothesis is consistent with the fact that compound **4** was the major product of the reaction and the β aldehyde **6** was less abundant than its α epimer **5**. These results may also be interpreted on the basis of other mechanistic pathways.[6]

It is noteworthy that teulanigeridin **7**, a neo-clerodane diterpenoid recently isolated by us from *Teucrium lanigerum*,[7] possesses an orthoacetate group and a C-6β - C-18 tetrahydrofuran ring identical to those of compound **4**. Thus, thermal rearrangement of 19-acetoxy-4α,18-epoxy-6-keto-neo-clerodane derivatives such as 19-acetylgnaphalin **3** is a convenient method for obtaining the unusual functionalities found in teulanigeridin **7**.

Pyrolysis of acetylteucjaponin B[4,8,9] **8** gave the epimeric aldehydes **9** and **10** in poor yield (12% and 14%, respectively), besides major quantities (60%) of the starting material **8**. Attempts to improve this transformation were unsuccessful (see Experimental).

The configuration at C-4 of compounds **9** and **10**, and hence that of **5** and **6** (see above and Experimental), were firmly established from their ^{1}H NMR spectra. In compound **9** (aldehydic proton at δ 9.75, *d*, $J_{18,4\beta}$ = 3.7 Hz) the signal of the C-4β proton appeared as a doublet of triplets at δ 2.05 with coupling values ($J_{4\beta,18} = J_{4\beta,3\beta}$ = 3.7 Hz, $J_{4\beta,3\alpha}$ = 12.5 Hz) in complete agreement with an axial configura-

tion, whereas in compound **10** (H-18 at δ 9.78, *d*, $J_{18,4\alpha}$ = 1.2 Hz) the equatorial C-4α proton showed a double doublet of doublets ($J_{4\alpha,18}$ = 1.2 Hz, $J_{4\alpha,3\alpha}$ = 1.8 Hz, $J_{4\alpha,3\beta}$ = 5.4 Hz) at δ 3.09. In addition, the larger chemical shift value of the C-4α proton in compound **10**, as compared with that of the same proton in compound **9** (Δδ + 1.04), also supported these assignments, since in compound **10** the C-4α proton and the C-6α acetoxyl group are coplanar.[10]

In contrast with acetylteucjaponin B **8**, thermal treatment of its 6-deacetyl derivative **11** (teucjaponin B[4,8,10]) was unfruitful, because complete decomposition of the starting diterpenoid was always observed (see Experimental).

Finally, we have also studied the thermal behaviour of the diterpenoids **12** (7-deacetylcapitatin[11]), **13** (capitatin[11,12]) and **14** (19-acetylteupolin IV[13]). Compounds **12** and **13** gave the natural neo-clerodane picropolin[11,14] **15** (≃ 100% yield) and its acetate[14] **16** (30%), respectively, through thermal α-ketol rearrangement, whilst 19-acetylteupolin IV **14** yielded the orthoacetate **17** (34%), besides unreacted material (50%). These results may be rationalized by arguing that in compounds **12** and **13** the driving force for ketol isomerization is the relief of the 1,3-diaxial interaction[12] between the C-7α substituent and the C-20 lactone ring, whereas compound **14**, in which this interaction is not present, reacts as 19-acetylgnaphalin **3** (see above).

EXPERIMENTAL SECTION

Melting points are uncorrected. Starting materials (compounds **1, 3, 8, 11-14**) have been previously isolated by us from *Teucrium* species.[1-4,8,11,13] Although each of these diterpenoids has been found in several *Teucrium* species,[1] the most readily available natural source of each compound is *T. lepicephalum*[2] for **1**, *T. gnaphalodes*[3] for **3**, *T. scordium*[9] for **8**, *T. japonicum*[10] for **11**, *T. polium* subsp. *capitatum*[11,12] for **12** and **13**, and *T. polium* subsp. *pilosum*[13] for **14**.

Small scale pyrolysis tests. The best conditions (temperature and time of reaction) for the pyrolysis of the substances were determined by heating a small sample (≃ 1-2 mg) of the diterpenoid on a Kofler melting point apparatus and monitoring the result of each assay by tlc. Table 1 shows some results of these tests.

General procedure for large scale reactions. The diterpenoid (30-400 mg) in a round-bottom flask was heated under argon in a silicone oil bath preheated to the temperature selected for each compound during the time established in the assays (see Table 1). The reaction mixture was allowed to cool to room temperature and separation was carried out on silica gel columns [Merck, No. 7734, deactivated with 15% (w/v) H_2O] eluted with a different solvent mixture in each case.

***Thermal decomposition of teulepicin* 1 : *Compound* 2.** Teulepicin **1** (400 mg) yielded a crude of reaction from which compound **2** (330 mg) was isolated by crystallization from EtOAc - *n*-hexane. Compound **2** was identical (mp, $[\alpha]_D$, IR, ^{1}H NMR, MS) with the previously described substance.[2] Comparison (mmp, tlc) with an authentic sample[2] confirmed its identity.

***Compounds* 4,5 *and* 6 *from 19-acetylnaphalin* 3.** Diterpenoid **3** (300 mg) gave a reaction mixture from which an inseparable mixture of compounds **5** and **6** (45 mg), the orthoacetate **4** (146 mg) and the starting material **3** (33 mg) were successively isolated by column chromatography (EtOAc - *n*-hexane 1:1 as eluent).

Compound **4.** Mp 208-211°C (EtOAc - *n*-hexane); $[\alpha]_D^{19}$ -2.9° ($CHCl_3$, c 0.343); IR ν_{max}^{KBr} cm^{-1}: 3150, 3120, 2970, 2860, 1760, 1508, 1415, 1330, 1290, 1225, 1205, 1175, 1155, 1125, 1020, 990, 965, 875, 810; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (1H, *m*, H-16), 7.44 (1H, *t*, *J* = 1.7 Hz, H-15), 6.38 (1H, *dd*, J_1 = 1.7 Hz, J_2 = 0.8 Hz, H-14), 5.33 (1H, *dd*, J_1 = 9.6 Hz, J_2 = 7.4 Hz, H-12), 4.97 (1H, *d*, *J* = 10.2 Hz, H_B-19), 4.19 (1H, *d*, *J* = 9.7 Hz, H_B-18), 3.98 (1H, *d*, *J* = 10.2 Hz, H_A-19), 3.93 (1H, *d*, *J* = 9.7 Hz, H_A-18), 2.43 (1H, *dd*, J_1 = 14.3 Hz, J_2 = 12.8 Hz, H-7α), 2.47 (1H, *dd*, J_1 = 13.8 Hz, J_2 = 9.6 Hz, H_B-11), 2.28 (1H, *dd*, J_1 = 13.8 Hz,

Table 1. Pyrolytic conditions

Compound	Mp (°C)	Temperature (°C)	Time of reaction (min)	Result (tlc analysis)	
1	174-176	180	5	1 (≃ 50 %) + 2 (≃ 50 %)	
		185	5	2 (≃ 100 %)	*
		200	3	Total decomposition	
3	227-229	230	10	3 (no reaction)	
		240	10	3 + 4 + 5 + 6	*
		240	20	Total decomposition	
8	163-164	170-200	5-30	8 (no reaction)	
		210	15	8 + 9 + 10	*
		220	5	Total decomposition	
11	256-259	256-260	15	11 (no reaction)	
		260-262	1	Total decomposition	
12	197-200	200	5	15 (≃100 %)	*
13	164-166	170	30	13 (≃ 70 %) + 16 (≃ 30 %)	*
		180	5	Total decomposition	
14	230-234	240	10	14 (≃ 60 %) + 17 (≃ 40 %)	*
		240	20	Partial decomposition	

(*) *Conditions used in large scale reactions.*

J_2 = 7.4 Hz, H_A-11), 2.13 (1H, *dd*, J_1 = 14.3 Hz, J_2 = 4.4 Hz, H-7β), 1.94 (1H, *ddq*, J_1 = 12.8 Hz, J_2 = 6.8 Hz, J_3 = 4.4 Hz, H-8β), 1.49 (3H, *s*, orthoacetate), 1.09 (3H, *d*, J = 6.8 Hz, Me-17); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.8 *t* (C-1), 24.3 *t* (C-2), 25.8 *t* (C-3), 82.7 *s* (C-4), 41.8 *s* (C-5), 106.5 *s* (C-6)*, 34.1 *t* (C-7), 36.6 *d* (C-8), 49.8 *s* (C-9), 46.9 *d* (C-10), 42.7 *t* (C-11), 71.6 *d* (C-12), 124.8 *s* (C-13), 107.9 *d* (C-14), 144.3 *d* (C-15), 139.7 *d* (C-16), 15.7 *q* (C-17), 74.7 *t* (C-18), 56.7 *t* (C-19), 176.8 *s* (C-20), 106.0 *s* (orthoacetate)*, 23.5 *q* (orthoacetate) (* these assignments may be reversed); EIMS (direct inlet) 70eV, *m/z* (rel. int.): 402 $[M]^+$(18), 360 (7), 342 (7), 321 (89), 313 (47), 301 (21), 285 (6), 238 (9), 220 (11), 218 (13), 134 (24), 105 (20), 95 (38), 91 (28), 81 (30), 79 (22), 69 (23), 53 (17), 43 (100). (Found: C, 65.42; H, 6.57. $C_{22}H_{26}O_7$ requires: C, 65.66; H, 6.51 %).

***Mixture of aldehydes* 5 *and* 6.** Thick oil; IR ν_{max}^{NaCl} cm^{-1}: 3140, 3130, 3110, 2950, 2880, 1760 (br), 1720, 1710, 1505, 1450, 1385, 1235, 1190, 1175, 1155, 1145, 1030, 1020, 990, 965, 875, 810, 720; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.02 (broad *s*) and 9.78 (*d*, J = 3 Hz) in a 4:1 integral ratio (H-18 of **5** and **6**, respectively), signals of the major epimer **5**: δ 7.45 (2H, *m*, H-15 and H-16), 6.39 (1H, *dd*, J_1 = 1.7 Hz, J_2 = 0.9 Hz, H-14), 5.57 and 4.52 (an AB system, J = 12.3 Hz, 2H-19), 5.43 (1H, *t*, J = 8.5 Hz, H-12), 3.50 (1H, *t*, J = 13.1 Hz, H-7α), 2.68 (1H, *br dd*, J_1 = 12.2 Hz, J_2 = 3.7 Hz, $J_{4\beta,18}$ < 0.3 Hz, H-4β), 2.43 (2H, *d*, J = 8.5 Hz, 2H-11), 1.93 (3H, *s*, OAc), 1.15 (3H, *d*, J = 6.8 Hz, Me-17), EIMS (direct inlet) 70eV: $[M]^+$ at *m/z* 402, M_r for $C_{22}H_{26}O_7$ 402.

***Compounds* 9 *and* 10 *from acetylteucjaponin* 8 8.** Diterpenoid **8** (250 mg) yielded a reaction mixture which was subjected to column chromatography (*n*-hexane - EtOAc 4:1 as eluent), giving compounds **10** (40 mg), **9** (30 mg) and the starting material **8** (150 mg) in order of elution.

***Compound* 9.** Mp 195-197°C (EtOAc - *n*-hexane); $[\alpha]_D^{21}$ + 32.0° ($CHCl_3$, c 0.394); IR ν_{max}^{KBr} cm^{-1}: 3140, 3120, 3050, 2970, 2870, 1775, 1745, 1735, 1703, 1505, 1445, 1380, 1365, 1250, 1230, 1175, 1035, 1025, 980, 875; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (1H, *d*, J = 3.7 Hz, H-18), 7.45 (1H, *m*, H-16), 7.44 (1H, *t*, J = 1.6 H-15), 6.38 (1H, *dd*, J_1 = 1.6 Hz, J_2 = 1.1 Hz, H-14), 5.38 (1H, *d*, J = 13.1 Hz, H_B-19), 5.36 (1H, *t*, J =

8.6 Hz, H-12), 4.79 (1H, *br dd*, J_1 = 11.8 Hz, J_2 = 4.0 Hz, J_3 < 0.3 Hz, H-6β), 4.48 (1H, *br d*, J_1 = 13.1 Hz, J_2 < 0.3 Hz, H_A-19), 2.39 (2H, *d*, *J* = 8.6 Hz, 2H-11), 2.18 (1H, *dd*, J_{gem} = 13.9 Hz, $J_{7\alpha,6\beta} = J_{7\alpha,8\beta}$ = 11.8 Hz, H-7α), 2.05 (1H, *dt*, J_1 = 12.5 Hz, J_2 = 3.7 Hz, H-4β), 2.06 (3H, *s*, OAc), 1.97 (3H, *s*, OAc), 1.03 (3H, *d*, *J* = 6.5 Hz, Me-17); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.7 *t* (C-1)*, 22.1 *t* (C-2)*, 25.3 *t* (C-3), 62.3 *d* (C-4), 46.2 *s* (C-5), 78.8 *d* (C-6), 31.9 *t* (C-7), 38.3 *d* (C-8), 51.0 *s* (C-9), 54.4 *d* (C-10), 43.7 *t* (C-11), 71.6 *d* (C-12), 125.1 *s* (C-13), 108.0 *d* (C-14), 144.2 *d* (C-15), 139.5 *d* (C-16), 16.3 *q* (C-17), 202.6 *d* (C-18), 60.8 *t* (C-19), 176.1 *s* (C-20), OAc: 170.0 *s*, 169.8 *s*, 21.2 *q*, 21.1 *q* (*these assignments may be reversed); EIMS (direct inlet) 70eV, *m/z* (rel. int.): 446 $[M]^+$ (0.4), 403 (6), 387 (2), 386 (2), 361 (52), 358 (24), 298 (48), 253 (29), 204 (46), 179 (32), 171 (40), 159 (71), 145 (33), 133 (25), 131 (25), 119 (28), 107 (25), 105 (57), 96 (97), 95 (95), 94 (68), 91 (57), 81 (91), 79 (49), 67 (38), 55 (33), 43 (100). (Found: C, 64.41; H, 6.68. $C_{24}H_{30}O_8$ requires: C, 64.56; H, 6.77 %).

***Compound* 10.** Thick oil; $[\alpha]_D^{19}$ + 8.3° ($CHCl_3$, c 0.228); IR ν_{max}^{NaCl} cm^{-1}: 3140, 2970, 2940, 2880, 1765, 1745, 1720, 1505, 1465, 1375, 1260, 1180, 1020, 875; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (1H, *d*, *J* = 1.2 Hz, H-18), 7.44 (1H, *m*, H-16), 7.43 (1H, *t*, *J* = 1.7 Hz, H-15), 6.37 (1H, *dd* J_1 = 1.7 Hz, J_2 = 0.9 Hz, H-14), 5.40 (1H, *ddd*, J_1 = 11.7 Hz, J_2 = 3.3 Hz, J_3 = 1.4 Hz, H-6β), 5.34 (1H, *d*, *J* = 13.2 Hz, H_B-19), 5.32 (1H, *t*, *J* = 8.7 Hz, H-12), 4.25 (1H, *dd*, J_1 = 13.2 Hz, J_2 = 1.4 Hz, H_A-19), 3.09 (1H, *ddd*, J_1 = 5.4 Hz, J_2 = 1.8 Hz, J_3 = 1.2 Hz, H-4α), 2.07 (3H, *s*, OAc), 2.03 (3H, *s*, OAc), 1.03 (3H, *d*, *J* = 6.5 Hz, Me-17); EIMS (direct inlet) 70eV, *m/z* (rel. int.): 446 $[M]^+$ (3), 428 (1), 418 (2), 403 (3), 386 (8), 358 (28), 326 (20), 298 (44), 253 (24), 204 (38), 159 (50), 145 (34), 131 (32), 119 (32), 105 (62), 96 (100), 95 (96), 81 (78), 79 (46), 67 (44), 57 (70), 43 (99); M_r for $C_{24}H_{30}O_8$ 446.

***Picropolin* 15 *from 7-deacetylcapitatin* 12.** Compound **12** (200 mg) yielded a crude of reaction from which a pure substance **15** (191 mg) was obtained by crystallization from EtOAc - *n*-hexane. Compound **15** was identical (mp, mmp, $[\alpha]_D$, IR, ^{1}H NMR, MS, tlc) with an authentic sample of picropolin.[11,14]

***Acetylpicropolin* 16 *from capitatin* 13.** Capitatin **13** (300 mg) yielded a reaction mixture which, after chromatography (*n*-hexane - EtOAc 1 : 1 as eluent), gave a compound (82 mg) identical (mp, mmp, $[\alpha]_D$, IR, ^{1}H NMR, MS, tlc) with an authentic sample of acetylpicropolin[14] **16** as well as major quantities of the starting material **13** (190 mg).

***Thermal rearrangement of 19-acetylteupolin IV* 14 *to give compound* 17.** Diterpenoid **14** (30 mg) yielded a reaction mixture from which compound **17** (10 mg) and unreacted **14** (15 mg) were isolated by chromatography (eluent *n*-hexane - EtOAc 3 : 1).

***Compound* 17.** Mp 214-216°C (EtOAc - *n*-hexane); $[\alpha]_D^{18}$ + 10.2° ($CHCl_3$, c 0.108); IR ν_{max}^{KBr} cm^{-1}: 3150, 2960, 2920, 2880, 1750, 1735, 1505, 1410, 1370, 1310, 1270, 1235, 1180, 1160, 1125, 1030, 990, 925, 880, 815, 790; ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.35 (2H, *m*, H-15 and H-16), 6.40, (1H, *dd*, J_1 = 1.8 Hz, J_2 = 0.9 Hz, H-14), 5.96 (1H, *d*, *J* = 10.8 Hz, H-7α); 5.37 (1H, *t*, *J* = 8.7 Hz, H-12), 5.02 (1H, *d*, *J* = 10.2 Hz, H_B-19), 4.25 (1H, *d*, *J* = 9.6 Hz, H_B-18), 4.00 (1H, *d*, *J* = 9.6 Hz, H_A-18), 3.98 (1H, *d*, *J* = 10.2 Hz, H_A-19), 2.18 (3H, *s*, OAc), 1.47 (3H, *s*, orthoacetate), 1.05 (3H, *d*, *J* = 6.6 Hz, Me-17); EIMS (direct inlet), 70eV, *m/z* (rel. int.): 460 $[M]^+$ (2.6), 400 (1.6), 387 (7), 371 (19), 328 (12), 312 (10), 173 (7), 121 (10), 105 (8), 95 (21), 94 (13), 91 (11), 81 (18), 77 (7), 69 (9), 55 (10), 43 (100). (Found: C, 62.39; H, 6.21. $C_{24}H_{28}O_9$ requires: C, 62.60; H, 6.13 %).

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