221. Terpenoids Derived from Linalyl Oxide. Part 2. The Isolation and Synthesis of Nordavanone, A C_{11}-Terpenoid from *Artemisia pallens*

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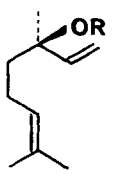
Summary. The isolation, absolute stereochemistry, and synthesis of a new C_{11}-terpenoid, 3*S*,4*S*,7*R*-3,7-dimethyl-4,7-oxido-non-8-en-2-one, related to davanone, are described.

From the fraction of the oil of *Artemisia pallens* that immediately follows davanone [1] [2] in polarity (as measured by the retention on a column of silica gel), there was isolated by distillation about 1% of a mixture made up of four main components. These were separated by gas chromatography into (–)-linalool (**1**, R = H), dehydro-α-linalool (**2**), (+)-menth-1-en-4-ol, and a new compound that was readily identified from its NMR.-spectrum (see experimental section) and molecular formula, $C_{11}H_{18}O_2$, as a lower homologue (**3**) of davanone. Only one isomer was present, and this had a rotation $[\alpha]_D^{20}$ of +54°.



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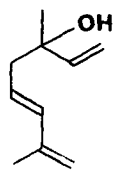

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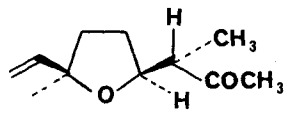

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Synthessis of the mixture of isomers of the new compound which we name nordavanone (**3**) was achieved from (–)-linalyl acetate (**1**, R = $COCH_3$) by selenium oxide oxidation [3] and base-catalyzed cyclization to the mixture of isomeric aldehydes (**4**) [4]. Reaction of methylmagnesium iodide on the latter gave the isomeric mixture of alcohols (**5**), from which the ketones (**3**, mixture of stereoisomers) were made by chromic acid oxidation. Gas chromatography on a Carbowax column separated the mixture into two pure isomers and a mixture of the other two isomers. The latter were partially separated by collecting each side of the gas chromatographic peak, and the proportions of the two isomers found by rechromatographing on a UCON capillary column. Using the two concentrated fractions of the two isomers thus obtained, it was possible to measure two different optical rotations and compute the rotation for each one of the pure isomers. The rotations $[\alpha]_D^{20}$ of the four isomers were found to be (in order of elution from the Carbowax column): i) +13.9°, ii) –20.0°, iii)[1]) –51.0°, iv) +42.9°. The latter had identical spectra and retention times to the natural product.

[1]) Peak ii is observed as a shoulder on peak iii.

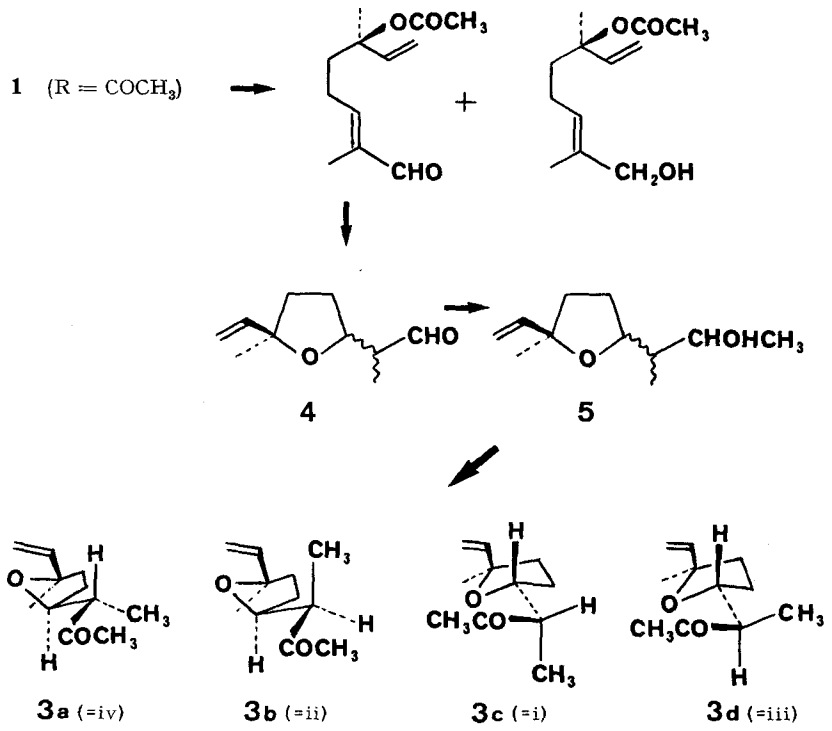
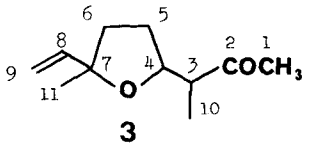


Table. *NMR.-data for the nordavanones* (**3**), chemical shifts in ppm, with respect to tetramethylsilane 0.00 ppm



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	Order of elution from a Carbowax column			
Attribution	i (*trans, erythro*)	ii (*cis, erythro*)	iii (*trans, threo*)	iv (*cis, threo*)
1-CH_3	2.10	2.09	2.11	2.11
3-CH	2.65	2.65 ?	2.55 ?	2.52
4-CH	4.05	3.95[a])		3.93
5,6-CH_2CH_2	1.5–2.0	1.5–2.0[a])		1.5–2.0
8-CH	5.83	5.88	5.82	5.88
9-CH_2	4.90	4.90[a])		4.88
	5.09	5.09		5.11
10-CH_3	1.07	1.11	0.96	0.94
11-CH_3	1.23	1.24[a])		1.24
$J_{3,4}$	7.5 Hz	5 Hz ?	9 Hz ?	8 Hz

[a]) In the case of these signals, the two isomers could not be distinguished.

Equilibration of any of the pure isomers of nordavanone (**3**) in the presence of base (sodium hydroxide in methanol or potassium *t*-butoxide in *t*-butyl alcohol) led rapidly (*ca.* 15 min) to a mixture of all four isomers in the approximate proportions (again in order of elution) 4:2:6:5.

The table lists some of the NMR.-signals we have observed for the nordavanone isomers, and, using the earlier arguments [1] [4] [5] concerning the double doublet of the vinyl group, we assign the pair with this signal at lower field (ii, iv) to the *cis*-isomers, i and iii having *trans*-substitution.

The higher coupling constants are attributed, as in the davanone case, [1] to the isomers (*threo*) having antiparallel protons, which are also the isomers having the methyl groups further removed from the oxygen of the tetrahydrofuran ring; *i.e.* at higher field. All the evidence thus points to the natural isomer of nordavanone having similar stereochemistry to davanone, *i.e.* it is 3*S*,4*S*,7*R*-3,7-dimethyl-4,7-oxidonon-8-en-2-one, the *cis,threo*-isomer. This is the same absolute configuration as davanone, and corresponds to the absolute configuration of (–)-linalool [6] which we isolated from the same fraction of the crude oil as nordavanone.

Experimental Part

NMR. spectra were recorded on a *Varian* A-60 instrument, and chemical shifts are given in ppm with tetramethylsilane as 0.00 ppm. Other spectral measurements were carried out as described in part 1 [1]. Rotations were measured using 10% solutions in chloroform.

Isolation of nordavanone from Artemisia pallens (carried out with the aid of Mrs. *G. Pitton*). Commercial Davana oil[2]) was chromatographed on ten times its weight of silica gel using toluene containing 3% of ethyl acetate. Following the elution of 300 g oil by thin-layer chromatography (TLC.) enabled the identification of a fraction (*ca.* 70 g) consisting of almost pure davanone, followed immediately by 17 g of a fraction that still contained davanone, but with some less polar substances. Distillation of this material gave a head fraction (b.p. 30–32°/0.01 Torr) weighing 0.95 g, which was purified by gas chromatography on Carbowax. Each of the four main substances thus separated was purified by re-chromatographing on a column of silicone oil. By comparison of the spectra with those of authentic materials, there were identified (in order of elution from Carbowax):

1. (–)-Linalool, $[\alpha]_D^{20}$ –18°.

2. 3,7-Dimethylocta-1,5,7-trien-3-ol.

3. (+)-Menth-1-en-4-ol, $[\alpha]_D^{20}$ +17°.

4. Nordavanone, $[\alpha]_D^{20}$ +54°. – NMR.-spectrum: 0.94 (3H, *d*, J = 6.5 Hz, $CH_3CH<$); 1.23 (3H, *s*, CH_3–C<); 1.5–2.0 (4H, CH_2CH_2); 2.11 (3H, *s*, CH_3CO); 2.52 1H, $d \times q$, J = 6.5 and 8 Hz, CH–CH(CH$_3$)–CO); 3.95 (1H, *m*, O–CH(CH=CH$_2$)–CH$_2$); 4.75–5.2 (2H, *m*, CH=CH$_2$); 5.88 (1H, $d \times d$, J = 10 and 17, CH=CH$_2$). – MS.: 43 (100), 55 (55), 93 (34), 111 (32), 41 (23), 125 (22), 69 (21), 72 (19), 67 (17), 68 and 110 (16)... 167 (M-15$^+$) (10). – IR.: 1710 cm^{-1} (ν (C=O)).

Cyclization of 2,6-dimethyl-6-acetoxyocta-2,7-dienal (*cf.* [4]). We were unable to reproduce regularly the yields of *Naegeli & Weber*, [4] but the following procedure gave 25–30% yields of an isomeric mixture of 2,6-dimethyl-3,6-oxido-oct-7-enals (**4**). A mixture of 50 g of 2,6-dimethyl-6-acetoxyocta-2,7-dienal, 15 g of sodium carbonate monohydrate, and 250 ml of 75% aqueous methanol is stirred at RT. Overnight, the pH of the mixture falls from 12.0 initially to 11.5, and 5 ml of 10% aqueous sodium hydroxide solution are added to bring the pH to 12.3. After a further 6 h, another 3 ml of 10% sodium hydroxide are added, bringing the pH (now again at 11.5) back

[2]) Purchased from the East Indian Sandaloil Distilleries (Provate) Ltd.

to 12.1. The pH is similarly adjusted morning and night for 3 days, when the product is isolated in ether, washed, dried and distilled, b.p. 33–35°/0.01 Torr. The individual isomers are incompletely separated by gas-chromatography on Carbowax; nevertheless, the following were characterized, stereochemical attributions being based on the NMR. evidence quoted in the theoretical part.

Peak 1, *ca.* 20% of total, presumably the *trans,erythro*-isomer, although the quality of the NMR.-spectrum was poor: 1.07 (*d*, J = 7 Hz, CH_3–CH); 1.26, (*s*, CH_3–C); 5.79 (*d*×*d*, J = 10 and 17 Hz); 9.68 (*d*, J = 2 Hz, CH–C*H*O).

Peak 2, 55% of total, composed of two substances in the ratio of 33:66. (i) The major isomer in this peak was the *trans,threo*-isomer; NMR. spectrum: 1.00 (*d*, J = 6.5 Hz, CH_3CH); 1.26 (*s*, CH_3–C); 2.38 (*m*, CH–C*H*(CH$_3$)–CHO); 5.82 (*d*×*d*, J = 10 and 17 Hz, C*H*=CH_2); 9.73 (*d*, J = 2 Hz, CH–C*H*O). (ii) The minor isomer was presumably the *cis,erythro*-isomer; NMR.-spectrum: 1.08 (*d*, J = 6.5 Hz); 5.93 (*d*×*d*, J = 10 and 17 Hz); 9.70 (*d*×*d*).

Peak 3, 25% of the total, was the *cis,threo*-isomer; NMR.-spectrum: 0.97 (3H, *d*, J = 6.5 Hz, CH_3–CH<; 1.26 (3H, *s*, CH_3–C<; *ca.* 2.35 (1H, *m*, but one J at least 8 Hz, CH–C*H*(CH$_3$)–CHO); *ca.* 4.08 (1H, *m*, O–C*H*(CH)–CH_2); 5.87 (1H, *d*×*d*, J = 10 and 17 Hz, C*H*=CH_2); 9.69 (1H, *d*, J = 2 Hz, CH–C*H*O). – The mass spectra of all isomers are fairly similar: 55 (100), 43 (67), 71 (49), 41 (45), 93 (41), 111 (35), 67 (32), 69 (31), 68 (25), 27, 81, and 153 (M-15$^+$) (23).

3,7-Dimethyl-4,7-oxidonon-8-en-2-ol. A *Grignard* reagent is prepared in dry ether from 6.2 g of methyl iodide and 1.0 g of magnesium. A solution of 6.0 g of the stereoisomeric mixture of 2,6-dimethyl-3,6-oxidooct-7-enals in 30 ml of dry ether was added dropwise over 30 min. After stirring for 30 min longer at RT., the mixture was poured onto ice, and the products isolated in ether. The mixture of stereoisomers was distilled, b.p. 42°/0.01 Torr, and characterized by the spectra: NMR. spectrum: 0.7–0.95 (3H, *m*, CH_3CH<); 0.95–1.20 (3H, *m*, CH_3CH<); 1.27 (3H, *s*, CH_3–C<), the ratio of *cis*:*trans*-isomers present was *ca.* 4:6, as estimated from the intensity of the signals (*d*×*d*, J = 10 and 17 Hz) centred on 5.83 and 5.90 respectively. – MS.: 111 (100), 55 (95), 43 and 93 (86), 71 (70), 41 (40), 67 (37), 81 (35), 69 (28), 43 (26)... 169 (M-15$^+$) (7).

Nordavanones. A solution of 4.0 g of 3,7-dimethyl-4,7-oxidonon-8-en-2-ol in 50 ml of acetone at 0° was stirred while a solution of 2.5 g chromic oxide in 2.25 ml of conc. sulfuric acid and 7.5 ml of water was added dropwise over 30 min. After a further 10 min, the solution was neutralized with sodium carbonate solution and the products isolated in ether. Distillation (b.p. 33°/0.01 Torr), yielded 2,1 g of a mixture of isomers which were purified by gas chromatography, and, in order of elution, were assigned the following configuration (see theoretical section): *trans, erythro* (**3c**), *cis,erythro* (**3b**), *trans,threo* (**3d**), *cis,threo* (**3a**). The mass spectra were all very similar, and that of the *cis,threo* isomer (**3a**) was identical with the MS. of natural nordavanone, as were the NMR.- and IR.-spectra.

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