Phytochemistry, Vol. 23, No. 2, pp. 399–401, 1984.
Printed in Great Britain.

0031–9422/84 $3.00 + 0.00

VOLATILE CONSTITUENTS OF *CLAUSENA WILLDENOVII*: STRUCTURES OF THE FURANOTERPENES α-CLAUSENAN, DICLAUSENAN A AND DICLAUSENAN B

G. S. R. SUBBA RAO, BHAGAVATULA RAVINDRANATH and V. P. SASHI KUMAR

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

(*Received* 4 *April* 1983)

Key Word Index—*Clausena willdenovii*; Rutaceae; furanoterpenes; α-clausenan; γ-clausenan (rosefuran); diclausenans A and B.

Abstract—Four furanoid terpenic compounds, α-clausenan, rosefuran (γ-clausenan) and diclausenans A and B, were isolated from the essential oil of the leaves of *Clausena willdenovii*. Their structures were determined by chemical and spectral data. The occurrence of a high concentration of rosefuran is noteworthy. Selenium dioxide oxidation of diclausenan gave an unusual product, identified as an epoxy-dicarbonyl compound.

INTRODUCTION

Clausena willdenovii is a large shrub, found in the Sikkim, Himalayas and some elevated parts of southern and western peninsular India and Sri Lanka. The leaves are aromatic and the essential oil has an agreeable fruity odour. Rao and Subramanian reported [1] the isolation of four furanoid constituents, α-, β-, γ-clausenans and diclausenan, from the essential oil of the leaves of *C. willdenovii*. The structure of α-clausenan was tentatively established [2] as 5-(3′-furanyl)-2-methylpenta-1,4-diene (**1**) based on chemical degradation. Re-investigation of this essential oil revealed [3] the presence of α- and γ-clausenans and diclausenan—the latter being a mixture of two isomeric compounds, designated as diclausenans A and B. γ-Clausenan was shown to be identical with rosefuran, 2-(3′,3′-dimethylallyl)-3-methylfuran (**2**). The bark and root of *C. willdenovii* afforded [4] 3-(1,1-dimethylallyl)-xanthyletin (**3**).

We now report detailed investigations leading to the structures of α-clausenan, γ-clausenan, diclausenans A and B based on spectroscopic data.

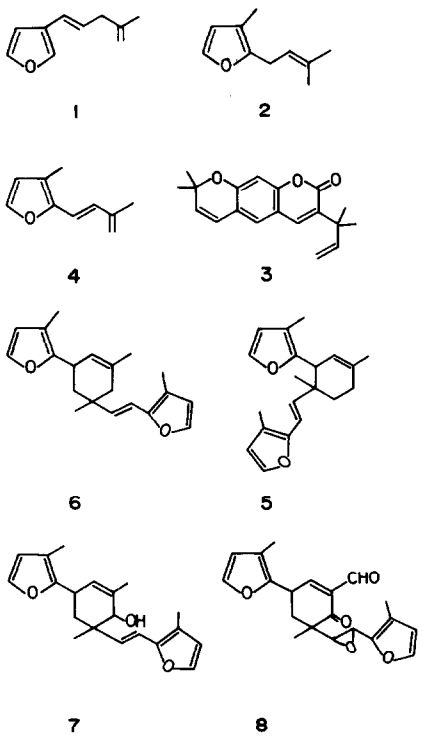
RESULTS AND DISCUSSION

The essential oil (0.69%) of the leaves of *C. willdenovii*, obtained by steam distillation, was separated into three fractions by fractional distillation under reduced pressure.

Fraction 1 (bp 103–105°/50 mm; 17% of the oil) was very labile and prone to oxidative resinification in air. Its physical and chemical properties were identical to those recorded for γ-clausenan, $C_{10}H_{14}O$. It formed a dihydro derivative ($C_{10}H_{16}O$, $[M]^+$ 152) and an adduct with dimethyl acetylenedicarboxylate, $C_{16}H_{20}O_5$. The IR spectrum indicated the presence of a disubstituted furan ring (ν_{max} 1668, 1620, and 1505 cm^{-1}) and a trisubstituted double bond (895 and 850 cm^{-1}). The ^1H NMR spectrum of the freshly distilled sample showed the presence of two vinylic methyl groups (δ 1.75, *s*, 6H), a methyl (δ 1.9, *s*, 3H) and an allylic methylene (δ 3.2, *br d*, J = 6 Hz), both attached to the furan ring. The two doublets at δ 6.05 and 7.10 (1H each, J = 2 Hz) were attributed to the α- and β-protons of the furan nucleus and the broad triplet at δ 5.2 was ascribed to the vinylic proton adjacent to the allylic methylene. The compound was thus identified as the furanoid monoterpene, rosefuran (**2**) [5], first isolated in minute quantities from Bulgarian rose oil. In view of its importance in perfumery, several syntheses have been reported for rosefuran [5–7]. The ^{13}C NMR spectrum of rosefuran has now been recorded and the spetcral data are given in the Experimental. The assignments are based on correlation with the spectra of compounds having similar structural features [7–9] and SFORD experiments [10].

Fraction 2 (bp 105°/50 mm; 3%) was found by GC and TLC to be a mixture of two compounds in the ratio 4:1, the major component being rosefuran. The minor constituent, presumably α-clausenan (for which Rao suggested [2] a tentative structure **1**, which, however, is unlikely on biogenetic considerations), could not be isolated in a pure form owing to its very labile nature and tendency to resinify in air. The ^1H NMR spectrum of α-clausenan could, however, be obtained by recording the spectrum of the total fraction 2 and subtracting the signals due to rosefuran. This revealed the structure of α-clausenan as **4** and not **1**. Thus, it showed two methyl signals at δ 1.9 and 2.2, the vinylic methylene as a broad doublet at δ 6.05 and the protons on the furan ring as doublets at δ 6.15 and 7.20 (J = 2 Hz). The two protons on the *trans*-disubstituted double bond formed an AB quartet centered at δ 6.50 (J = 15 Hz). The ^{13}C NMR spectrum of fraction 2 also supported this conclusion. After eliminating the peaks due to rosefuran, the following peaks were observed: δ 9.7 (*q*), 24.6 (*q*), 112.9 (*d*), 114.9 (*t*), 117.0 (*d*), 129.0 (*s*), 132.9 (*s*), 138.8 (*d*), 141.0 (*d*) and 150.2 (*s*); structure (**1**) would require one of the saturated carbons to appear as a triplet.

Fraction 3 (bp 140°/0.5 mm; 4%, named diclausenan by earlier workers) was found to be a mixture of two compounds, diclausenans A and B, separated by preparative GC. As recorded earlier, the two compounds have



been found to be diastereoisomers and in view of the difficulty in obtaining large quantities of the individual compounds, structural investigation was carried out on the diclausenan fraction, which was a mixture of diclausenans A and B (45:55).

Diclausenan, $C_{20}H_{24}O_2$ ($[M]^+$ *m/z* 296, base peak *m/z* 148) was considered to be a dimeric monoterpene on the basis of its spectral data. The disubstituted furanoid nature of the compound was revealed by the UV (λ_{max} 225 nm) and IR (ν_{max} 1665, 1620 and 1505 cm^{-1}) spectra which were similar to those for rosefuran. The ^1H NMR spectrum of diclausenan A showed the presence of a tertiary methyl group at δ 1.2, a vinylic methyl at δ 1.74, two α- and two β-protons of the furan rings at δ 6.15 and 7.15, respectively (overlapped doublets), two *trans*-related olefinic protons (AB pattern centred at δ 6.2, J = 16 Hz), a vinylic proton (δ 5.35, *m*) and a doubly allylic methine proton (δ 3.30, *m*). Assuming that diclausenan was formed by dimerization of the diene α-clausenan, two structures were possible, **5** and **6**. Structure **6** was favoured as the doubly allylic proton on C-5 appeared as a multiplet and not as a doublet. Furthermore, irradiation of the vinylic proton at C-6 (δ 5.35) collapsed this signal into a doublet of doublets thus confirming the presence of a methylene adjacent to C-5.

The ^1H NMR spectrum of diclausenan B was very similar to that of diclausenan A, the main difference being that the tertiary methyl in this case appeared at δ 0.9 compared to δ 1.2 in the case of the latter. The two compounds were therefore considered to be diastereoisomers. The low field resonance of the tertiary methyl in diclausenan A could be explained as due to the deshielding effect of the furan ring in a *cis*-diaxial relationship to the methyl. The above conclusions were supported by chemical evidence.

Oxidation of diclausenan with osmium tetroxide–periodic acid followed by esterification of the product gave methyl 3-methyl-2-furoate indicating the presence of a 3-methyl-2-furyl moiety conjugated to a double bond. The presence of a double bond conjugated to an aromatic ring was also supported by reduction of diclausenan by sodium in liquid ammonia, yielding dihydrodiclausenan, $C_{20}H_{26}O_2$, $[M]^+$ 298. Dihydroclausenan was also a mixture of two compounds, the tertiary methyl groups appearing at δ 1.00 and 0.85. Hydroboration followed by oxidation of the dihydro derivative gave a six-membered cyclic ketone (IR ν_{max}^{NaCl} 1710 cm^{-1}) confirming the presence of a second double bond in the carbocyclic ring.

Selenium dioxide oxidation of diclausenan gave an interesting result. One of the two products was the expected secondary alcohol **7**, which showed a singlet at δ 4.02 for the proton α to the hydroxyl confirming that there were no protons on the adjacent carbons. The second compound was found to be the epoxy-ketoaldehyde **8** from its spectral data. The ^1H NMR spectrum showed two doublets for one proton each at δ 2.55 and 3.40 (J = 2 Hz) for the protons on the epoxide ring. The doubly allylic proton (C_5-H) appeared at δ 3.68 as a triplet of doublets (J = 6 Hz, 2 Hz), additional evidence supporting structure **6** rather than **5**. The two α- and two β-protons appeared as doublets at δ 5.90, 6.10, 6.82 and 6.92 (J = 2 Hz). The doublet at δ 7.15 (J = 2 Hz) was assigned to the vinylic proton, conjugated to the carbonyl groups; the aldehyde proton appeared at δ 9.0. The tertiary methyl in this case appeared as single peak at δ 1.1, indicating that equilibration at the activated allylic carbon occurred during the reaction, confirming that diclausenans A and B were diastereoisomers. This appears to be the first report of the formation of an epoxide from selenium dioxide oxidation.

The ^{13}C NMR spectrum of diclausenan (see Experimental) was in complete agreement with the structure proposed. Thus, C-10 appeared at δ 27.7 as a triplet. As the material was a mixture of diastereoisomers at C-5 and C-9, the C-5 appeared as a pair of peaks at δ 43.5 and 45.0 (both doublets) and the C-18 methyl appeared as a pair of quartets at δ 23.3 and 21.8.

Structure **6** for diclausenan represents a novel type of dimerization of isoprenyl units; the other two naturally occurring dimeric isoprenoids, phebalin [11] and thannosin [12], are coumarins with structures analogous to **5**. However, the occurrence of α-clausenan in the plant and the fact that diclausenan is optically inactive suggest that diclausenan could be an artefact, formed by dimerization of the former. Oxidation of γ-clausenan (rosefuran) afforded a 3:2 mixture of diclausenans A and B in 30% yield.

EXPERIMENTAL

Mps and bps are uncorr. ^1H NMR spectra were recorded at 100 MHz and ^{13}C NMR spectra at 270 MHz with FT in $CDCl_3$ or CCl_4 using TMS as int. standard.

Isolation of α-, β- and di-clausenans. Dried leaves of *C. willdenovii* Weight and Arn. (syn. *C. dentata* (Willd.) Roem.), collected in Nandi Hills near Bangalore, India, were steam-distilled yielding a yellow oil (0.69%). The oil was redistilled under red. pres. using a Vigreux column and the following fractions were collected: fraction 1 (rosefuran, bp 103–105°/50 mm, 17% of oil), fraction 2 (4:1 mixture of rosefuran and α-clausenan, bp 105°/50 mm, 3%) and fraction 3 (diclausenan, bp 104°/0.5 mm, 4%); the remainder was involatile,

probably due to resinification. Each of the fractions was passed through a short column of Al_2O_3 using pentane as eluant, prior to spectral or chemical examination. Rosefuran was obtained as a colourless liquid, darkening on standing. IR ν_{max}^{NaCl} cm^{-1}: 1668, 1620, 1550, 1505, 895, 850, 805; ^1H NMR (CCl_4): δ 1.75 (6H, *s*), 1.9 (3H, *s*), 3.2 (2H, *d*, J = 6 Hz), 5.2 (1H, *br t*), 6.05 (1H, *d*, J = 2 Hz) and 7.10 (1H, *d*, J = 2 Hz); ^{13}C NMR (CCl_4): δ 9.7 (*q*, C-10), 17.7 (*t*, C-5), 25.3 (*q*, C-9), 25.5 (*q*, C-8), 112.9 (*d*, C-2), 12.0 (*d*, C-6), 132.9 (*s*, C-7), 133.0 (*s*, C-3), 138.8 (*d*, C-1) and 150.2 (*s*, C-4). (Found: C, 80.31; H, 9.31. $C_{10}H_{14}O$ requires: C, 80.00; H, 9.33%.)

Reaction of rosefuran with dimethyl acetylenedicarboxylate. A mixture of rosefuran (5 g) and dimethyl acetylenedicarboxylate (5 ml) in C_6H_6 (10 ml) was left to stand at room temp. for 8 hr, the solvent removed and the residue chromatographed on silica gel yielding a pale yellow solid, recrystallized from Me_2CO–hexane (5 g); mp 115°. IR ν_{max}^{KBr} cm^{-1}: 1720, 1620; ^1H NMR ($CDCl_3$): δ 1.7 (6H, *s*), 1.95 (3H, *s*), 2.75 (2H, *m*), 3.75 (3H, *s*), 3.8 (3H, *s*), 5.2 (1H, *br t*), 5.55 (1H, *d*, J = 1 Hz) and 5.65 (1H, *d*, J = 1 Hz). (Found: C, 62.92; H, 7.31. $C_{16}H_{20}O$ requires: C, 63.24; H, 7.34%.)

Dihydrorosefuran. Rosefuran (1 g) in EtOH (10 ml) was hydrogenated over Pd–C (5%, 20 mg) yielding, after chromatography over neutral Al_2O_3, a colourless liquid, bp 65–66°/20 mm. IR ν_{max}^{NaCl} cm^{-1}: 1668, 1620, 1550; ^1H NMR (CCl_4): δ 0.95 (6H, *d*, J = 6 Hz), 1.9 (3H, *s*), 1.2–1.8 (3H, *m*), 2.45 (2H, *t*), 6.0 (1H, *d*, J = 2 Hz) and 7.0 (1H, *d*, J = 2 Hz); $[M]^+$ 152. (Found: C, 78.92; H, 10.50. $C_{10}H_{16}O$ requires: C, 78.95; H, 10.53%.)

Diclausenan. Fraction 3 (above) was purified by redistillation under vaccum, yielding a pale yellow liquid, bp 104°/0.5 mm. IR ν_{max}^{KBr} cm^{-1}: 1665, 1620, 1505; $[M]^+$ 296. (Found: C, 79.92; H, 10.00. $C_{20}H_{24}O_2$ requires: C, 80.00; H, 10.00%.) ^{13}C NMR (CCl_4): δ 9.90 (*q*, C-17), 10.5 (*q*, C-20), 21.8 (*q*, C-18A), 23.3 (*q*, C-18B), 25.5 (*q*, C-19), 27.7 (*t*, C-10), 33.7 (*t*, C-8), 39.2 (*s*, C-9), 43.5 (*d*, C-5A), 45.0 (*d*, C-5B), 112.9 (*d*, C-2, 15), 113.7 (*s*, C-7), 113.8 (*d*, C-11), 120.7 (*d*, C-6), 134.3 (*s*, C-3), 134.8 (*s*, C-14), 137.5 (*d*, C-1, 16), 140.0 (*d*, C-12) and 151.2 (*s*, C-4, 13). It was separated into diclausenans A and B by prep. GC on Carbowax 20M at 225°. Diclausenan A: ^1H NMR (CCl_4): δ 1.20 (3H, *s*), 1.74 (5H, *br s*), 1.95 (8H, *br s*), 3.30 (1H, *m*), 5.35 (1H, *m*), 6.20 (4H, *m*) and 7.15 (2H, *m*). Diclausenan B: ^1H NMR (CCl_4): δ 0.90 (3H, *s*), 1.75 (5H, *br s*), 1.95 (2H, *s*), 1.95–2.0 (8H, *br*), 3.30 (1H, *m*), 5.35 (1H, *m*), 6.20 (4H, *m*) and 7.15 (2H, *m*).

Osmium tetroxide–periodic acid oxidation of diclausenan. A soln of diclausenan (1.58 g) in dioxan (20 ml) was treated with OsO_4 (1 g). After 17 hr at room temp. the soln was saturated with H_2S and filtered. The filtrate was evapd to dryness under red. pres. and the residue dissolved in dry Et_2O (50 ml). HIO_4 (570 mg) in dry Et_2O (30 ml) was added and the mixture stirred for 1 hr after which it was decanted from the precipitated iodic acid, washed with H_2O and treated with CH_2N_2. The resulting product after evapn of Et_2O was chromatographed on neutral Al_2O_3, yielding methyl 3-methyl-2-furoate (30 mg), bp 73–74°/8 mm. (lit. [13] bp 72–78°/8 mm). ^1H NMR ($CDCl_3$): δ 2.40 (3H, *s*), 4.00 (3H, *s*), 6.42 (1H, *d*, J = 2 Hz) and 7.60 (1H, *d*, J = 2 Hz). (Found: C, 59.95; H, 5.70. $C_7H_8O_3$ requires: C, 60.00; H, 5.72%.)

Dihydrodiclausenan. Diclausenan (6 g) in dry Et_2O (50 ml) was added to liquid NH_3 (200 ml, distilled over Na), followed by Na (1.8 g). After stirring the mixture for 1 hr, excess Na was destroyed by NH_4Cl, treated with H_2O and the product extracted into Et_2O (4 × 50 ml). The product, after evapn of solvent, was chromatographed over silica gel (hexane), yielding a colourless, viscous oil (2.4 g). IR ν_{max}^{NaCl} cm^{-1}: 1510, 1450, 1380; ^1H NMR (CCl_4): δ 0.80, 0.97 (3H, *s*), 1.70 (3H, *s*), 1.82 (2H, *s*), 1.96 (3H, *s*), 1.98 (3H, *s*), 2.25 (2H, *m*), 2.30 (2H, *m*), 3.20 (1H, *m*), 5.20 (1H, *m*), 6.00 (2H, *m*) and 7.10 (2H, *m*); $[M]^+$ 298. (Found: C, 80.4; H, 8.69. $C_{20}H_{26}O_2$ requires: C, 80.5; H, 8.73%.)

Hydroboration–oxidation of dihydrodiclausenan. Diborane in THF (1 ml, 1 M soln) at −5° was treated with dihydrodiclausenan (200 mg) in THF (5 ml) under N_2 for 30 min. After 3 hr at 25°, the solvent was removed under red. pres., the residue dissolved in Et_2O (5 ml) and stirred overnight with a soln of CrO_3 (0.1 g) in H_2O (5 ml). The Et_2O layer was separated, washed (saturated $NaHCO_3$), dried and evapd. The residue was chromatographed on silica gel (hexane–C_6H_6, 1:1), yielding a yellow syrup. IR ν_{max}^{NaCl} cm^{-1}: 1710.

Selenium dioxide oxidation of diclausenan. Diclausenan (0.6 g) in dioxan (25 ml) was treated with SeO_2 (0.5 g) and a few drops of H_2O. The mixture was heated at 100° for 2 hr, diluted with H_2O and extracted with Et_2O. The Et_2O layer was washed with aq. KCN to remove Se, then with H_2O, dried and evapd. The product was chromatographed on silica gel, yielding two fractions: product 1 (hexane–C_6H_6, 1:1) and product 2 (C_6H_6). Product 1 (**7**) was a colourless oil (25 mg). IR ν_{max}^{NaCl} cm^{-1}: 3500; ^1H NMR (CCl_4): δ 0.90 (3H, *s*), 1.20 (3H, *s*), 1.90 (3H, *s*), 1.98 (3H, *s*), 2.02 (3H, *s*), 3.42 (1H, *m*), 4.02 (1H, *s*), 5.40 (1H, *m*), 6.15 (4H, *m*), and 7.15 (2H, *m*). (Found: C, 76.80; H, 7.62. $C_{20}H_{24}O_3$ requires: C, 76.90; H, 7.69%.) Product 2 (**8**) was a yellow syrup (100 mg). IR ν_{max}^{KBr} cm^{-1}: 1680; ^1H NMR ($CDCl_3$): δ 1.1 (3H, *s*), 1.92 (3H, *s*), 2.05 (3H, *s*), 2.55 (1H, *d*, J = 2 Hz), 3.40 (1H, *br*), 3.65 (1H, *sextet*), 5.90, 6.10, 6.82, 6.92 (1H each, *d*, J = 2 Hz), 7.15 (1H, *d*, J = 2 Hz) and 9.0 (1H, *s*). (Found: C, 70.51; H, 5.94. $C_{20}H_{20}O_5$ requires: C, 70.58; H, 5.88%.)

Acknowledgements—We thank Dr. P. Schudel of Givaudan-Esrolko AG, Givaudan, Zurich, for the GC separation of the diclausenans using capillary columns and for helpful discussions. One of us (B.R.) thanks the CSIR for financial assistance.

REFERENCES

1. Rao, B. S. and Subramanian, K. S. (1934, 1935, 1936) *Proc. Indian Acad. Sci.* **1A**, 189; **2A**, 574; **3A**, 31.
2. Rao, P. L. N. (1948) *J. Sci. Ind. Res.* **7B**, 11.
3. Subba Rao, G. S. R., Rao, K. S. and Ravindranath, B. (1976) *Tetrahedron Letters* 1019.
4. Subba Rao, G. S. R., Raj, K. and Shashikumar, V. P. (1981) *Indian J. Chem. Sect. B* **20**, 88.
5. Buchi, G., Kovats, E. Sz., Enggist, P. and Uhde, G. (1968) *J. Org. Chem.* **33**, 1227.
6. Ly, N. D. and Schlossen, M. (1977) *Helv. Chim. Acta* **60**, 2085.
7. Birch, A. J. and Slobbe, J. (1976) *Tetrahedron Letters* 2079.
8. Page T. F., Jr., Alger, T. and Grant, D. M. (1965) *J. Am. Chem. Soc.* **87**, 5335.
9. Stothers, J. B. (1972) *Carbon-13 NMR Spectroscopy.* Academic Press, New York.
10. Levy, G. C. and Nelson, G. (1972) *Carbon-13 NMR for Organic Chemists.* Wiley-Interscience, New York.
11. Brown, K., Cambie, R. C. and Hall, D. (1971) *Chem. Ind.* 1020.
12. Kutney, J. P., Inaba, T. and Dreyer, D. L. (1970) *Tetrahedron* **26**, 3171.
13. Burns, D. H. (1963) *Organic Synthesis*, Coll. Vol. **4**, p. 649.