Phytochemistry, 1980, Vol. 19, pp. 2713–2715. © Pergamon Press Ltd. Printed in England. 0031 9422/80/1201-2713 $02.00/0

STRUCTURE OF ACARANOIC AND ACARENOIC ACIDS*

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(*Received* 5 *March* 1980)

Key Word Index *Acarospora chlorophana*; Acarosporaceae; acaranoic acid; acarenoic acid; δ-lactones.

Abstract For acaranoic and acarenoic acids from the lichen *Acarospora chlorophana*, the revised structures of (−)-2*S*-methyl-3*R*-carboxypentadecyl-1→5*S*-olide and (−)-2-methylene-3*R*-carboxypentadecyl-1→5*S*-olide respectively have been established.

INTRODUCTION

In 1895, Zopf [1] isolated from the lichen *Acarospora chlorophana* a compound, pleopsidic acid, mp 131–132° and $[\alpha]_D^{18}$ − 55 to −60°. Later, Santesson [2] recognized pleopsidic acid as a mixture of two components which he named acaranoic and acarenoic acids and for which he put forward the γ-lactone structures **1** and **2**. To support **1**, Santesson [2] reacted Me β-ketotetradecanoate with di Me bromosuccinate and received, after hydrolysis and subsequent reduction with $NaBH_4$, a mixture, mp 112–116°, which he assumed to be identical with racemic **1** by comparison of IR and mass spectra. We have reexamined acaranoic and acarenoic acids and now propose the δ-lactone structures **3** and **4** for the two compounds.

RESULTS AND DISCUSSION

Acaranoic acid has two carbonyl bands in the IR spectrum; in KBr, 1678 (CO_2H) and 1716 cm^{-1} (δ-lactone-CO), in $CHCl_3$, 1708 ($-CO_2H$) and 1720 cm^{-1} (δ-lactone-CO–). Me acaranoate (**5**), easily accessible from **3** by reaction with CH_2N_2, shows only one CO band at 1710 cm^{-1} (in KBr) (1740 cm^{-1} in CCl_4). Contrary to these data, similar γ-lactones such as roccellaric acid and its Me ester [3] absorb at 1740 and 1782 cm^{-1} (in KBr) (1713 and 1772 cm^{-1} in $CHCl_3$), respectively. The correct carbon skeleton was given from the ^1H NMR spectrum (270 MHz, $CDCl_3$, δ values in ppm) of **5**: 0.88 (3 H, *t*, 15-Me), 1.26 (14 H, *br. s*, 7-CH_2--14-CH_2-), 1.32 (3 H, *d*, J = 7 Hz, 16-Me), 1.55 (2 H, *m*, 6-CH_2-), 1.76 (1 H, *dt*, $J_{4a,5}$ = 12, $J_{4a,4e}$ = 14 Hz, C-4H_a), 2.13 (1 H, *dt*, $J_{4e,5}$ = 3.5, $J_{4e,4a}$ = 14 Hz, C-4H_e), 2.62 (1 H, *td*, $J_{3,4a}$ = 12, $J_{3,4e}$ = 3.5 Hz, C-3H), 2.78 (1 H, *dq*, $J_{2,16}$ = 7, $J_{2,3}$ = 11 Hz, C-2H), 3.75 (3 H, *s*, CO_2Me), 4.29 (1 H, *m*, C-5H). A key to the δ-lactone structure as well as the relative stereochemistry is the vicinal coupling of four protons at C-2, C-3, C-4 and C-5. With coupling constants of 11 and 12 Hz these protons must occupy coplanar positions to each other, which can only be achieved in a 6-membered ring with the protons axially arranged as depicted in **3a**.

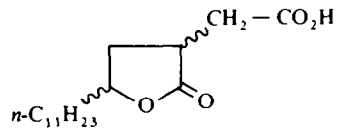
The ^{13}C NMR spectrum (25.05 MHz, $CDCl_3$) of acaranoic acid is in good agreement with structure **3** although the γ-lactone isomer (**6**) also fits the observed chemical shifts: C-1: 177.0 (*s*), C-2: 45.3 (*d*), C-3: 37.7 (*d*), C-4: 36.1 (*t*), C-5: 79.6 (*d*), C-6: 32.7 (*t*), C-7: 24.8 (*t*), C-8–C-12: 29.4–29.6 (*t*), C-13: 32.0 (*t*), C-14: 22.4 (*t*), C-15: 14.2 (*q*), C-16: 16.6 (*q*), C-17: 172.3 (*s*).

The sign of the Cotton effect of saturated δ-lactones depends on the chirality of the conformation with a planar lactone group (–C–O–CO–C–) [4]. (−)-Acaranoic acid (**3**) and its Me ester (**5**) show positive Cotton effects in the CD curves: **3**: $\Delta\varepsilon_{222}$ + 2.23, **5**: $\Delta\varepsilon_{221}$ + 1.83. This means (−)-acaranoic acid has the chirality shown in **3a** and the absolute configuration (−)-2*S*-methyl-3*R*-carboxy-pentadecyl-1 → 5*S*-olide.

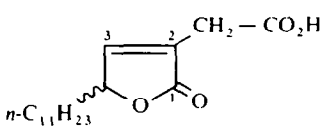
The hydroxy acid **7** resulting from hydrolysis of **3** theoretically can relactonize either to γ-lactone acid **6** (path *a*) or to acaranoic acid (path *b*). Alkaline hydrolysis of **3** and **5** and subsequent acidification yielded (−)-acaranoic acid; so relactonization follows path *b* to the more stable δ-lactone acid.

Santesson's structure **2** of acarenoic acid [2] can be eliminated from the ^1H NMR spectrum (270 MHz, $CDCl_3$), which shows no signal corresponding to a vinylic proton (**2**, C-3H): 0.88 (3 H, *t*, J = 7 Hz, 15-Me), 1.26 (14 H, *br. s*, 7-CH_2--14-CH_2-), 1.3 1.8 (2 H, *m*, 6-CH_2-), 2.03 (1 H, *dt*, $J_{4a,5}$ = 12, $J_{4a,4e}$ = 14 Hz, C-4H_a), 2.21 (1 H, *ddd*, $J_{4e,5}$ = 2, $J_{4e,3}$ = 6, $J_{4e,4a}$ = 14 Hz, C-4H_e), 3.69 (1 H, *m*, C-3H), 4.23 (1 H, *m*, C-5H), 5.93 (1 H, *d*, $J_{3,11b}$ = 2.5 Hz, C-16H_b), 6.64 (1 H, *d*, $J_{3,11c}$ = 2.5 Hz, C-16H_c). The doublets at 5.93 and 6.64 confirm the presence of an exo-methylene group α to the lactone carbonyl. Structure **4** was finally proved by catalytic hydrogenation of (−)-acarenoic acid which gives as the main product a compound identical with (−)-acaranoic acid (**3**) in all respects. Hence the absolute configuratin of **4** is (−)-2-methylene-3*R*-carboxypentadecyl-1→5*S*-olide. The CD spectrum of **4** shows a positive band at 268 nm ($\Delta\varepsilon$ +0.20) and a negative one at 216 nm ($\Delta\varepsilon$ −5.23). (−)-Acarenoic

* Part 124 in the series "Lichen Substances". For Part 123 see Huneck, S. (1980) *Lichenologist* (in press).



1



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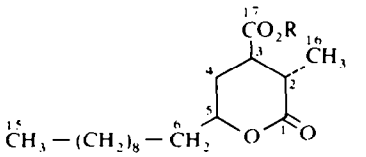
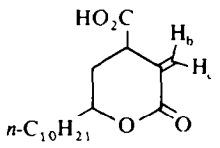


3 R = H
5 R = Me



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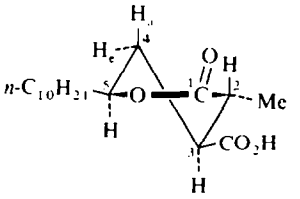
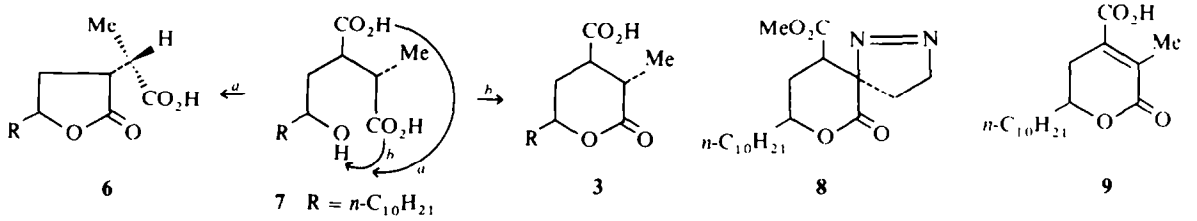


3a



6

7 R = n-$C_{10}H_{21}$

3

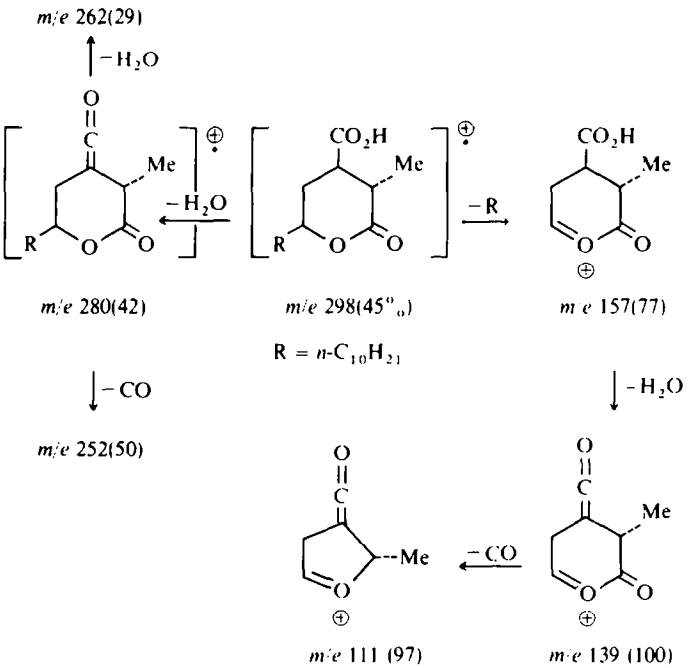
8

9

acid reacts with CH_2N_2 to give the pyrazoline Me ester **8**, whose configuration at C-2 was deduced from the positive CD bands at 327 nm ($\Delta\varepsilon$ +10.0) and 233 nm ($\Delta\varepsilon$ +4.28) according to the rule of Snatzke [5]. This means CH_2N_2 attacks the C=C double bond from the re-side. On heating with Ac_2O, **4** is isomerized to *iso*-acarenoic acid (**9**). The main fragments in the mass spectrum of (−)-acaranoic acid are given in Scheme 1.

EXPERIMENTAL

Extraction. A. chlorophana (Wahlenb. ex Ach.) Mass. (India, Himalayas, Distr. Pithoragarh, May 1978, voucher specimen in the herbarium of S.H.: 162 g) was extracted with Et_2O (200 ml) for 20 hr and the extract evapd to dryness. The resulting residue was dissolved in C_6H_6 (300 ml) and chromatographed on Si gel (80 g, with 5% H_2O). C_6H_6 (3000 ml) eluted (+)-rhizocarpic acid



Scheme 1. MS fragmentation of (−)-acaranoic acid (**3**) at 40 kV.

(2.05 g, 1.2%), mp 174–175° ($CHCl_3$–MeOH) and $[\alpha]_D^{24}$ +104° ($CHCl_3$, *c* 1.095). Further elution with C_6H_6–Et_2O (1:1) (2 l.) yielded a mixture of (−)-acaranoic and (−)-acarenoic acids (1.77 g, 1.09%), mp 135–145° (MeOH). Part of this mixture (1 g) was rechromatographed on Si gel (60 g, with 5% H_2O); elution with C_6H_6–Et_2O (9:1) (400 ml) gave pure (−)-acaranoic acid (**3**, 0.32 g) as plates, mp 150–151° ($CHCl_3$–MeOH) and $[\alpha]_D^{25}$ −38.9° ($CHCl_3$–MeOH 1:1, *c* 1.36). $C_{17}H_{30}O_4$ (298.41). UV λ_{max}^{MeOH} nm (log ε): 210 (2.85). IR, ν_{max}^{KBr} cm^{-1}: 688, 722, 748, 814, 850, 920, 960, 990, 1000, 1050, 1102, 1140, 1150, 1178, 1196, 1228, 1250, 1270, 1304, 1330, 1362, 1384, 1398, 1428, 1448, 1470, 1678, 1716, 2800, 2900, 3500. ^{1}H NMR (270 MHz, $CDCl_3$–CD_3OD, 4:1, 60°): 0.89 (3 H, *t*, 15-Me), 1.26 (14 H, *br. s*, 7-CH_2–14 CH_2-), 1.35 (3 H, *d*, 16-Me), 1.40–1.60 (2 H, *m*, 6-CH_2-), 1.75 (1 H, *dt*, C-4H_a), 2.20 (1 H, *dt*, C-4H_e), 2.58 (1 H, *td*, C-3H), 2.76 (1 H, *dq*, C-2H), 4.31 (1 H, *m*, C-5H).

The other part of the mixture of **3** and **4** (50 mg) was separated by prep.-TLC (Si gel Merck PF 254 + 366, 20 × 20 × 1 mm, C_6H_6–dioxane–HOAc (90:25:4), 10 mg mixture/plate, detection UV). The band of highest R_f value yielded after extraction with Et_2O (−)-acaranoic acid (5 mg), mp 148–150° and the band of lower R_f value (−)-acarenoic acid (**4**, 25 mg), plates, mp 130–132° (C_6H_6) and $[\alpha]_D^{24}$ −84.3° ($CHCl_3$, *c* 0.265). $C_{17}H_{28}O_4$ (296.40). UV λ_{max}^{MeOH} nm (log ε): 219 (3.42). IR ν_{max}^{KBr} cm^{-1}: 684, 718, 810, 928, 954, 1000, 1048, 1080, 1102, 1136, 1178, 1196, 1276, 1310, 1360, 1398, 1422, 1442, 1470, 1614 (C=CH_2), 1670 (-CO_2H), 1720 (lactone-CO-), 2900, 2960, 3500 (-CO_2H).

Me *acaranoate* (**5**). Prepared from **3** (0.1 g) in MeOH (10 ml) with CH_2N_2 in Et_2O for 5 min at 20°. Chromatography of the reaction product on Al_2O_3 (6 g, activity II, neutral) in hexane afforded needles, mp 58–59° (pentane or MeOH–H_2O) and $[\alpha]_D^{25}$ −31.1° ($CDCl_3$, *c* 1.595). $C_{18}H_{32}O_4$ (312.44). IR ν_{max}^{KBr} cm^{-1}: 678, 712, 722, 734, 768, 810, 850, 882, 910, 922, 940, 960, 990, 1008, 1020, 1030, 1050, 1064, 1078, 1100, 1114, 1130, 1138, 1160, 1170, 1190, 1210, 1222, 1238, 1270, 1280, 1300, 1328, 1340, 1362, 1380, 1440, 1462, 1472, 1710, 2850, 2940; $\nu_{max}^{CCl_4}$ cm^{-1}: 938, 1029, 1072, 1098, 1113, 1172, 1193, 1226, 1270, 1300, 1767, 1380, 1440, 1462, 1740, 2940. MS *m/e* (rel. int.): 312 (M^+, 30), 294 (19), 281 (21), 267 (24), 253 (30), 239 (38), 171 (73), 155 (26), 146 (77), 143 (42), 142 (73), 139 (49), 128 (42), 127 (46), 114 (48), 102 (54), 101 (100).

Hydrolysis and relactonization of acaranoic acid. (−)-Acaranoic acid (0.1 g) was dissolved in an aq. soln (2 ml) of KOH (50 mg) and kept at room temp. for 20 hr. After acidification with 10% H_2SO_4, extraction with Et_2O and crystallization ($CHCl_3$–MeOH), plates, mp 151–152°, were obtained which were identical with (−)-acaranoic acid.

Hydrolysis of Me *acaranoate.* Me acaranoate (**5**, 80 mg) was refluxed in a soln of KOH (50 mg) in MeOH (2 ml) and H_2O (1 ml) for 2 hr. After removing the solvents, acidification with 10% H_2SO_4, extraction with Et_2O and crystallization ($CHCl_3$–MeOH), plates, mp 149–150° and $[\alpha]_D^{25}$ −39.6° ($CHCl_3$–MeOH, 1:1, *c* 0.9) were obtained. These were identical with (−)-acaranoic acid.

Hydrogenation of (−)*-acarenoic acid.* (−)-Acarenoic acid (**4**, 20 mg) was hydrogenated with Adams catalyst (10 mg) in EtOH under normal conditions for 2 hr. After usual work-up, plates, mp 142–144° (MeOH–H_2O) and $[\alpha]_D^{24}$ −39.5° ($CHCl_3$, *c* 0.27) were obtained, identical with (−)-acaranoic acid.

Addition product of CH_2N_2 *with* (−)*-acarenoic acid* (**8**). (−)-Acarenoic acid (0.1 g) was treated with CH_2N_2 in Et_2O for 4 hr. The residue after evapn of Et_2O was chromatographed in C_6H_6 on Si gel (10 g, with 5% H_2O). After elution with C_6H_6 (300 ml), further C_6H_6 (100 ml) eluted the pyrazoline Me ester as plates, mp 48–48.5° (MeOH–H_2O) and $[\alpha]_D^{25}$ +238.5° ($CHCl_3$, *c* 0.35). $C_{20}H_{32}N_2O_4$ (340.46).

Iso-*acarenoic acid* (**9**). (−)-Acarenoic acid (10 mg) was heated with Ac_2O (2 ml) to 100° for 2 hr. After usual work-up and crystallization from MeOH–H_2O, plates mp 123–125° were obtained. $C_{17}H_{28}O_4$ (296.40). UV λ_{max}^{MeOH} nm (log ε): 232 (3.56). IR ν_{max}^{KBr} cm^{-1}: 702, 760, 780, 920, 940, 960, 1000, 1100, 1116, 1156, 1180, 1198, 1232, 1250, 1310, 1370, 1398, 1430, 1470, 1670, 1700, 2960, 3500. MS *m/e* (rel. int.): 296 (M^+, 75), 278 (62), 260 (29), 252 (47), 233 (64), 225 (48), 207 (48), 193 (38), 179 (53), 165 (53), 155 (100), 139 (98), 126 (100), 111 (93), 97 (93), 87 (96).

Acknowledgements—We are grateful to Dr. K. G. Sarma, Secunderabad, India, for providing us with *A. chlorophana*. We are also indebted to Prof. G. Snatzke, Bochum, FRG and Dr. G. Sundholm, Uppsala, Sweden, for CD and ^{13}C NMR data.

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