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STRUCTURE AND SYNTHESIS OF CHLOROPHENOL DERIVATIVES FROM *HELICHRYSUM* SPECIES

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Abstract—The isolation of a further chlorophenol acetylene from *Helichrysum coriaceum* as well as the synthesis of three naturally occurring chlorophenols are described.

Some time ago we have isolated from *Helichrysum tenuifolium* two unusual chlorophenols, helitenuin (**6**) and helitenuone (**7**).[1] The possible biogenesis of these phenols has been discussed. The chloro compound **1**, present in many *Helichrysum* species,[2] could be transformed via **2** and **3** to the triyne **4**, which itself should be the precursor of **6** and **7**. We now have isolated in addition to known compounds (see Experimental) from the roots of *H. coriaceum* Harv. the methyl ether of the proposed intermediate **4**. The structure easily could be deduced from the molecular formula and the spectroscopic data. While the UV spectrum indicated the presence of a phenyl triyne,[2] the ^{1}H-NMR spectrum (Experimental) clearly showed the typical pattern of the aromatic protons for a 1,2,4-trisubstituted benzene derivative, which were close to that of **6** and **7**.[1] Though all data were in agreement with the relative position of the substituents a definite proof by synthesis of **5**–**7** was desirable. Starting with 5-chloro-2-methoxybenzaldehyde (**9**) the corresponding phenyl acetylene **13** could be easily prepared via the dibromide **11** by using the Corey-method.[3] Cadiot–Chodkiewicz-coupling[4] of **13** with 1-bromo-penta-1,3-diyne gave the triyne **5**. The ^{1}H-NMR spectrum of **5** was completely identical with that of the natural compound.

For the synthesis of **6** and **7** with a free phenolic OH the corresponding desmethyl derivative of **13** could not be prepared as by elimination of hydrogen bromide the dibromide **10** always gave 2-bromo-5-chloro-benzofuran. We therefore have transformed the dibromophenol **10**, obtained by reaction of **8** with carbon tetrabromide-triphenyl phosphine to the tetrahydropyranyl ether **12**. Partial elimination of hydrogen bromide afforded **14** which could be coupled with but-3-yn-2-ol leading to **15**. Addition of hydrogen sulfide[5] in the presence of base afforded **16** which after manganese dioxide oxidation gave **17**. Hydrolysis yielded the ketone **7** which was identical with the natural occurring thiophene.

For the preparation of **6** we have coupled **14** with propargyl alcohol. The obtained carbinol **18** could be transformed to the thiophene **19** by addition of hydrogen sulfide. Manganese dioxide-oxidation gave **20** which by Corey-reaction[3] could be transformed via **21** to the acetylene **6** which was identical with the natural compound. Thus the proposed relative position of chloro and O-function in all three compounds was established.

EXPERIMENTAL

^{1}H-NMR spectra: $CDCl_3$, TMS as internal standard, 400 MHz; IR spectra: CCl_4; MS: 70 eV, direct inlet; Column chromatography (CC): SiO_2; TLC: SiO_2 PF 254.

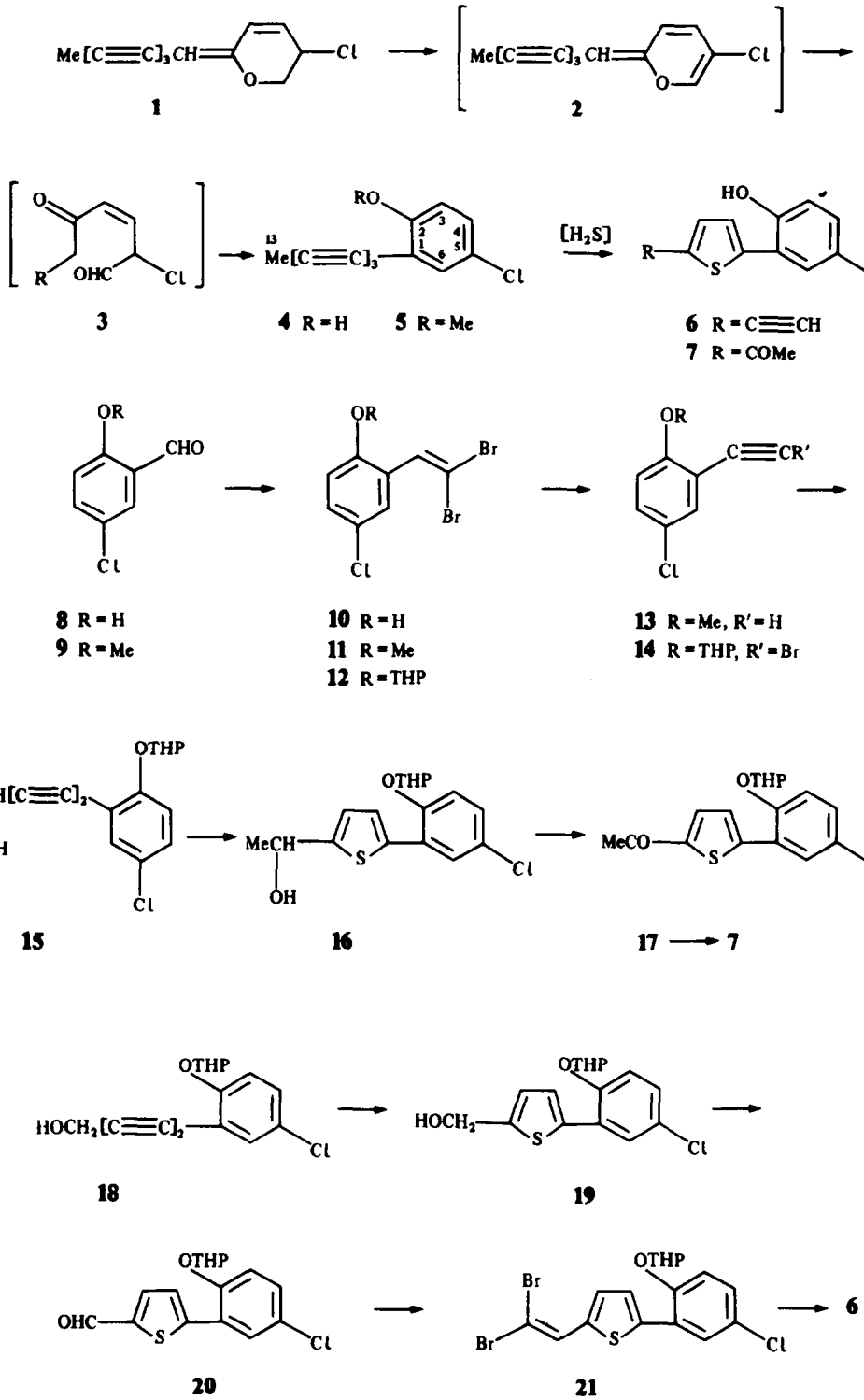
Isolation of the natural compounds. 410 g air dried roots (voucher 81/135, collected in February 1981 in Transvaal) were extracted at room temp with Et_2O–petrol, 1:2, and the extract obtained was separated first by CC affording three fractions: 1 (petrol), 2 (Et_2O–petrol, 1:9), 3 (Et_2O). TLC of fraction 1 (petrol) gave 10 mg isocomene and 2 mg α-bergamotene. TLC of fraction 2 (Et_2O–petrol, 1:9) afforded 5 mg **5**, colourless crystals, m.p. 85–90° (dec.), IR: 2220 (C≡C); ^{1}H-NMR: 6.77 d (J = 9, H-3), 7.27 dd (J = 9, 2, H-4), 7.40 d (J = 2, H-6), 3.86 s (OMe), 2.00 s (H-13); UV (Et_2O) λ_{max} = 344, 325, 307, 287, 276, 254, 241, 233 nm; MS *m/z* (rel. int.): 230.031 (31) and 228.034 (100) $[M]^+$ (calc for $C_{14}H_9O^{37}Cl$: 230.031 and for $C_{14}H_9O^{35}Cl$: 228.034), 227 $[M-H]^+$ (42), 192 $[227-Cl]^+$ (18), 165 $[M-C_5H_3]^+$ (54).

TLC of fraction 3 (Et_2O–petrol, 1:2) gave 10 mg abienol and 7 mg isoabienol (identical with authentic samples by 400 MHz ^{1}H-NMR).

Synthesis of 4-*chloro*-2-[*hepta*-1,3,5-*tryin*-1-*yl*]-*phenol* (**5**). To 11.7 g CBr_4 and 18.3 g triphenyl phosphine in 300 ml CH_2Cl_2 1.5 g **9** (8.8 mmol) was added. Usual work-up and CC (petrol) afforded 2.5 g (84%) 4-chloro-2-[2',2'-dibromo-ethenyl]-anisol (**11**), colourless crystals, m.p. 97°; MS: *m/z* = 330 (6), 328 (24), 324 (12) $[M]^+$, 247 (20), 245 (17) $[M-Br]^+$, 168 (33), 167 (40), 166 (83), 165 (65) $[M-2Br]^+$; ^{1}-NMR: 6.75 d (J = 9, H-3), 7.20 dd (J = 9, 2, H-4), 7.65 d (J = 2, H-6), 7.50 s (H-7), 3.80 s (OMe). At −78° 2.3 g **11** (7.0 mmol) in 75 ml Et_2O was stirred with 16 ml 1.6 molar n-BuLi soln in hexane. After addition of water the residue of the organic layer was filtered over SiO_2 (petrol) affording 730 mg 4-chloro-2-ethynyl anisol (**13**) (63%), colourless crystals, m.p. 75°, IR: 3310, 2120 (C≡CH); MS: *m/z* = 166 $[M]^+$ (100), 151 $[M-Me]^+$ (19), 123 $[151-CO]^+$ (48); ^{1}H-NMR: 6.75 d (J = 9, H-3), 7.22 dd (J = 9, 2, H-4), 7.38 d (J = 2, H-6), 3.32 s (H-8).

To 1.1 g **13** (6.6 mmol) in 15 ml MeOH 2.5 ml $EtNH_2$ (30%), 250 mg $NH_2OH \cdot HCl$ and 10 mg Cu_2Cl_2 was added. During 2 hr at −5–0° 0.9 g 1-bromo-penta-1,3-diyne in 10 mg THF was added. After stirring for 30 min at room temp Et_2O was added. The organic layer was washed with NH_4Cl aq and the residue was purified by CC (Et_2O–petrol, 1:20) affording 840 mg of a 2:1 mixture of **5** (39%) and **13**. TLC with $AgNO_3$-coated SiO_2 (petrol) afforded pure **5**, colourless, very unstable crystals, m.p. 85–90° (dec.); MS: *m/z* = 228.034 $[M]^+$ (100) (calc for $C_{14}H_9OCl$: 228.034); ^{1}H-NMR, UV and IR spectra identical with those of the natural compound.

Synthesis of helitenuone (2-[5-*acetyl thien*-2-*yl*]-4-*chloro phenol* (**7**). To 13.2 g CBr_4 and 21.0 g triphenyl phosphine in 400 ml CH_2Cl_2 2.3 g **8** (14.7 mmol) was added. Usual work-up and CC (Et_2O–petrol, 1:3) gave 2.5 g (80%) 4-chloro-2-[2',2'-dibromo ethenyl]-phenol (**10**), colourless crystals, m.p. 67°; ^{1}H-NMR: 6.75 d (J = 9, H-3), 7.17 dd (J = 9, 2, H-4), 7.54 d (J = 2, H-6), 7.49 s (H-7). 12.5 g **10** (40 mmol) in 13.5 g dihydropyran were heated with 50 mg pTs for 30 min at 40°. After addition of Et_2O the organic phase was washed with dil NaOH and water. The residue (**12**, 15.0 g (95%)) was used directly for the next step; MS: *m/z* = 396 $[M]^+$ (2), 312 $[M-C_5H_8O]^+$ (14), 152 $[312-2Br]^+$ (13), 85 $[C_5H_9O]^+$ (100); 40.0 g **12** (100 mmol) in 500 ml MeOH was stirred for 1 hr with 56 g KOH. After addition of water the product was extracted with Et_2O and the residue was purified by CC (petrol)



affording 23.0 g (76%) 4-chloro-2-ethynyl phenol tetrahydropyranyl ether (**14**), colourless oil, IR: 2210 (C≡C); MS: *m/z* = 316 $[M]^+$ (0.5), 232 $[M-C_5H_8O]^+$ (5), 85 $[C_5H_9O]^+$ (100); ^{1}H-NMR: 7.04 d (J = 9, H-3), 7.22 dd (J = 9, 2, H-4), 7.37 d (J = 2, H-6), 5.48 br dd (J = 3, 3, H-2'), 3.88 ddd (J = 11, 11, 3, H-6'$_1$), 3.60 ddd (J = 11, 4, 4, H-6'$_2$).

To 2.6 g (37 mmol) but-3-yn-2-ol in 80 ml MeOH 15 ml 30% $EtNH_2$ soln, 1.5 g $NH_2OH \cdot HCl$ and 70 mg Cu_2Cl_2 was added. At −5–0° during 3 hr 11.5 g **14** (37 mmol) in 50 ml THF were added. Usual work-up and purification by CC (Et_2O–petrol, 9:1) gave 6.8 g 4-chloro-2-[5'-hydroxy hexa-1,3-diyn-1-yl]-phenol tetrahydropyranyl ether (**15**) (61%), colourless oil, UV (Et_2O) 320, 313, 282, 265, 250, 236 nm; IR: 3600 (OH), 2240 (C≡C); ^{1}H-NMR: 7.04 d (J = 9, H-3), 7.22 dd (J = 9, 2, H-4), 7.36 d (J = 2, H-6), 4.65 q (J = 6.5, H-11), 1.54 d (J = 6.5, H-12) (THP signals s.a.); MS: *m/z* = 304 $[M]^+$ (1), 286 $[M-H_2O]^+$ (2), 220 $[M-C_5H_8O]^+$ (12), 85 $[C_5H_9O]^+$ (100).

To a soln of 75 g $Na_2S \cdot H_2O$ in 250 ml MeOH–acetone, 1:1,

adjusted by addition of HCl to P_H 9, 10.0 g **15** (33 mmol) was added. After boiling for 30 min ice was added and the organic layer was washed with NaCl aq. After CC (Et_2O–petrol, 1:9) 5.8 g (52%) 2-[5-(hydroxyethyl)thien-2-yl]-4-chloro phenol tetrahydropyranyl ether (**16**) was obtained, colourless oil, UV (Et_2O) 316, 293, 283, 232, 220 nm; IR: 3600 (OH); ^{1}H-NMR: 7.20 d (J = 9, H-3), 7.14 dd (J = 9, 2, H-4), 7.58 d (J = 2, H-6), 7.34 d (J = 4, H-8), 6.95 br d (J = 4, H-9), 5.12 br q (J = 7, H-11), 1.63 d (J = 7, H-12) (THP signals s.a.). 4.75 g **16** (14 mmol) in 75 ml Et_2O were boiled for 3 hr with 13 g MnO_2. After CC (CH_2Cl_2) 4.2 g 2-[5-acetyl thien-2-yl]-4-chloro phenol tetrahydropyranyl ether (**17**) (88%) yellow crystals, m.p. 109°, were obtained; UV (Et_2O): 334, 242, 237, 208 nm; IR: 1670 (C=O); ^{1}H-NMR: 7.24 br s (H-3, H-4), 7.64 br s (H-6), 7.47 d (J = 4, H-8), 7.67 d (J = 4, H-9), 2.57 s (H-12) (THF signals s.a.); MS: *m/z* = 336 $[M]^+$ (0.2), 252 $[M-C_5H_8O]^+$ (26), 85 $[C_5H_9O]^+$ (100). 4.0 g **17** (12 mmol) were stirred 30 min in 50 ml MeOH and 10 ml conc HCl at room temp. Usual work-up afforded 1.3 g **7**, yellow crystals, m.p. 218°; UV, IR and ^{1}H-NMR spectra identical with those of the natural compound; MS: *m/z* = 252.001 $[M]^+$ (54). (Found: C, 56.79; H, 3.59. Calc for $C_{12}H_9O_2ClS$: 252.001. $C_{12}H_9O_2ClS$ (252.7): C, 57.03; H, 3.59%).

Synthesis of helitenuin (2-[*5-ethynyl thien-2-yl*]-*4-chloro phenol*) (**6**). To 2.7 (48 mmol) propargylalcohol in 100 ml MeOH 20 ml 30% $EtNH_2$ soln, 2.0 g NH_2OH HCl and 90 mg Cu_2Cl_2 were added. At −5–0° during 3 hr 15.0 g **14** (48 mmol) in 65 ml THF were added. After 30 min stirring at room temp usual work-up and CC (Et_2O–petrol, 1:9) gave 6.8 g (49%) [5-hydroxy penta-1,3-diyn-1-yl]-4-chloro phenol tetrahydropyranyl ether (**18**), colourless oil, IR: 3600 (OH), 2250 (C≡C); MS: *m/z* = 290 $[M]^+$ (3), 206 $[M-C_5H_8O]^+$ (24), 85 $[C_5H_9O]^+$ (100); ^{1}H-NMR: 7.05 d (J = 9, H-3), 7.23 dd (J = 9, 2, H-4), 7.39 d (J = 2, H-6), 4.43 br s (H-11) (THF signal s.a.). 5.9 g **18** (20 mmol) was boiled for 30 min with 36 g $Na_2S \cdot H_2O$ in 150 ml MeOH–acetone, 1:1 (adjusted at P_H 9). Usual work-up and CC (Et_2O–petrol, 1:9) gave 3.3 g (50%) 2-[5-hydroxy methyl thien-2-yl]-4-chloro phenol tetrahydropyranyl ether (**19**), yellow oil, UV (Et_2O): 317, 293, 283, 210 nm; MS: *m/z* = 324 $[M]^+$ (5), 240 $[M-C_5H_8O]^+$ (22), 222 $(240-H_2O]^+$ (34), 85 $[C_5H_9O]^+$ (100); ^{1}H-NMR: 7.20 d (J = 9, H-3), 7.15 dd (J = 9, 2, H-4), 7.59 d (J = 2, H-6), 7.35 d (J = 4, H-8), 6.99 dt (J = 4, 1.5, H-9), 4.85 br s (H-11) (THP signals s.a.). 2.6 g **19** (8 mmol) in 50 ml Et_2O were boiled 3 hr with 7 g MnO_2. With further 3 g MnO_2 again the suspension was boiled for 1 hr. Usual work-up gave 1.8 g (70%) 2-[5-formyl thien-2-yl]-4-chloro phenol tetrahydropyranyl ether (**20**), yellow crystals, m.p. 119°; UV (Et_2O): 340, 315, 237, 210 nm; IR: 1680 (CHO); MS: *m/z* = 322 $[M]^+$ (0.5), 238 $[M-C_5H_8O]^+$ (18), 85 $[C_5H_9O]^+$ (100); MS: *m/z* = 322 $[M]^+$ (0.5), 238 $[M-C_5H_8O]^+$ (18), 85 $[C_5H_9O]^+$ (100). To 6.6 g CBr_4 and 10.5 g triphenyl phosphine in 200 ml CH_2Cl_2 1.5 g **20** (4.6 mmol) was added. After 5 min usual work-up and acid hydrolysis (s.a.) followed by CC (Et_2O–petrol, 1:3) gave 1.5 g 2-[5-(2',2'-dibromo ethenyl)-thien-2-yl]-4-dibromo phenol tetrahydropyranyl ether (**21**) (82%), yellow crystals, m.p. 121° (dec.); UV (Et_2O) (365 sh), 349, 316, 236, 213 nm; MS: *m/z* = 394 $[M]^+$ (71), 234 $[M-2Br]^+$ (100), 199 $[234-Cl]^+$ (17), 171 $(199-CO]^+$ (68); ^{1}H-NMR: 6.88 d (J = 9, H-3), 7.19 dd (J = 9, 2, H-4), 7.46 d (J = 2, H-6), 7.30 d (J = 4, H-8), 7.25 dd (J = 4, 0.5, H-9), 7.65 d (J = 0.5, H-11). (Found: C, 36.57; H, 1.41. Calc for $C_{12}H_7Br_2OClS$ (394.5): C, 36.53; H, 1.79%). To 790 mg **21** (2 mmol) in 25 ml Et_2O at −78° 4.5 ml of a 1.6 molar n-BuLi soln in hexane was added. After 1 hr stirring at −78° the soln was stirred 1 hr at room temp. The mixture was purified by CC (Et_2O–petrol, 1:3) affording 350 mg **6**, yellow oil, which rapidly decomposed; UV, IR and ^{1}H-NMR spectra identical with those of the natural compound. MS: *m/z* = 235.988 (38) and 233.991 (100) $[M]^+$ (calc for $C_{12}H_7ClOS$: 235.988 and 233.991), 205 $[M-CHO]^+$ (9), 199 $[M-Cl]^+$ (9), 171 $[199-CO]^+$ (57).

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