SESQUITERPENIC LACTONES FROM *Grossheimia macrocephala*. STRUCTURE OF GROSHEIMINOL*

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From the leaves of *Grossheimia macrocephala* (MUSS.-PUSCHK.) D. SOSN. et TAKHT. cynaropicrin (*II*), isolipidiol (*III*) and the so far undescribed lactone grosheiminol (*IV*) were isolated in addition to grosheimin (*I*), detected in this species earlier. For grosheiminol the structure *IV* was derived, including relative and absolute configuration, on the basis of chemical correlation.

Several years ago, we isolated[1] from the leaves of *Grossheimia macrocephala* (MUSS.-PUSCHK). D. SOSN. et TAKHT. grosheimin (*I*), for which we derived structure *I*, including relative and absolute configuration. The so-called lactone fraction contained, according to thin-layer chromatography, further substances which we were unable – at that time – to separate by current chromatographic methods. Now we have succeeded in separating this mixture by means of high-performance liquid chromatography. We obtained non-crystalline cynaropicrin (*II*) the structure of which was elucidated earlier[2] and the identification of which we carried out on the basis of physical constants, IR and ^{1}H NMR spectra, further isolipidiol[2] (*III*) which we identified in a similar manner, and finally a non-crystalline substance *IV* of $[\alpha]_D$ +56·4° and the composition $C_{15}H_{20}O_4$. Its IR spectrum showed the presence of a hydroxyl group (3 500 cm^{-1}), a γ-lactone group (1 750 cm^{-1}) and a double bond (1 660 and 1 600 cm^{-1}). Determination of active hydrogen demonstrated the presence of two free hydroxyl groups. The mass spectrum contained the molecular peak at 264 and characteristic fragments at 246 (M−18) and 228 (M−18−18) mass units, which were in agreement with the presence of two free hydroxyl groups in its molecule. We checked this fact by the preparation of non-crystalline diacetate *V* the IR spectrum of which indicated the presence of a γ-lactone group (1 770 cm^{-1}), an acetate

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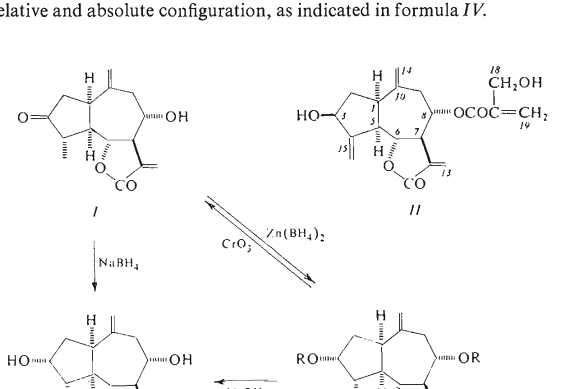
group (1 240 and 1 730 cm^{-1}) and a double bond (1 660 and 1 640 cm^{-1}). The mass spectrum of diacetate *V* had molecular peak value 348 and characteristic fragments 306 (M−42), 288 (M−60) and 228 (M−60−60). A comparison of the ^1H NMR spectra of compound *IV* and its diacetate *V* suggested a chemical structural relation with grosheimin[1] (*I*).

Careful oxidation of compound *IV* with chromium trioxide gave grosheimin (*I*), which, when reduced with zinc borohydride[4] gave the native compound *IV* studied. Its reduction with sodium borohydride afforded isolipidiol (*III*) which we also prepared on reduction of grosheimin with sodium borohydride. The set of reactions mentioned proved the structure of the newly isolated lactone unambiguously, including its relative and absolute configuration, as indicated in formula *IV*.



EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. The IR spectra were measured on a Unicam SP 200 spectrophotometer. The ^1H NMR spectra were measured with a JEOL JNM 100 instrument, in deuteriopyridine, unless stated otherwise. The mass spectra were measured on a LKB instrument. Optical rotation was determined on an objective polarimeter Perkin–Elmer.

Isolation of Cynaropicrin (*II*), Isolipidiol (*III*) and Grosheiminol (*IV*)

The lactonic fraction (9·8 g) from which grosheimin[1] (*I*) was separated by column chromatography on silica gel, was submitted to liquid-column chromatography on silica gel (100 g;

40—60 μ; Merck), using a mixture of chloroform, hexane and methanol (9 : 9 : 1) for elution. From the first fraction non-crystalline cynaropicrin (*II*) was obtained, with the composition $C_{19}H_{22}O_6$ and $[\alpha]_D^{25}$ +100·7° (*c* 0·1; chloroform). IR spectrum (nujol; cm^{-1}): 3 450 (hydroxyl), 1 760 (γ-lactone), 1 720 (α,β-unsaturated ester), 1 660 and 1 640 (double bond). Mass spectrum, (*m/e*): 346 (M), 262 (M—84). ^1H NMR spectrum (in $CDCl_3$; in ppm; *J* in Hz): 6·44 s (1 H) (H_{19}); 6·10 s (1 H) ($H_{19'}$); 6·28 d, $J \approx 3$ (1 H) (H_{13}); 5·72 d, $J \approx 3$ (1 H) ($H_{13'}$); 5·55 s (1 H) (H_{15}); 5·46 s (1 H) ($H_{15'}$); 5·24 bs (1 H) (H_{14}); 5·20—5·60 m (1 H) (H_8); 5·02 s (1 H) ($H_{14'}$) 4·70—4·30 m (H_3, H_6 and others). The IR and ^1H NMR spectra of this substance were identical with those of authentic cynaropicrin[2]. Further fractions were combined (0·5 g) and separated by preparative liquid chromatography on 4 columns 30 cm long, 8 mm I.D. and 20 000 theoretical plates, using a mixture of chloroform, hexane and methanol (9 : 9 : 1) for elution. From the first fraction non-crystalline grosheminol (*IV*), $C_{15}H_{20}O_4$ and $[\alpha]_D^{25}$ +56·4° (*c* 0·1; pyridine), was obtained. IR spectrum (nujol; cm^{-1}): 3 500 (hydroxyl), 1 750 (γ-lactone) 1 660, 1 600, (double bond). Mass spectrum (*m/e*): 264 (M), 246 (M—18), 228 (M—18—18). ^1H NMR spectrum (ppm): 6·50 d (H_{13}); 6·35 d ($H_{13'}$); 5·70 s (H_{14}); 5·00 s ($H_{14'}$); 4·15—3·80 m (H_3, H_6, H_8); 3·00—2·80 m (H_7 and others); 1·35 d (H_{15}). For $C_{15}H_{20}O_4$ (264·3) calculated: 68·16% C, 7·63% H, 0·38% H act. (1); found: 68·57% C, 7·37% H, 0·42% H act. From a further fraction isolipidiol (*III*) was obtained, m.p. 158—161°C, composition $C_{15}H_{22}O_4$, $[\alpha]_D^{25}$ +43·8° (*c* 0·1; ethanol). IR spectrum (nujol; cm^{-1}): 3 450 (hydroxyl), 1 750 (γ-lactone), 1 640 (double bond). Mass spectrum (*m/e*): 266 (M), 248 (M—18), 230 (M—18—18). ^1H NMR spectrum (ppm): 6·68 d, $J \approx 5·5$ (C_3—OH); 6·46 d, $J \approx 5·5$ (C_8—OH); 5·11 s (H_{14}); 5·02 s ($H_{14'}$); 4·09—3·76 m (H_3, H_6, H_8); 3·10—2·70 m (H_7 and others); 1·71 d, $J \approx 6·5$ (H_{13}); 1·46 d, $J \approx 6$ (H_{15}). IR spectrum and ^1H NMR spectrum of this substance were identical with the spectra of a standard of isolipidiol[3]. Mixture melting point with a standard sample of isolipidiol was undepressed. The starting mixture and individual fractions were checked by HPLC using a column 30 cm long and 4 mm I. D., packed with Partisil 10. Flow rate 1 ml per minute, elution with a mixture of chloroform–hexane and methanol (9 : 9 : 1).

Diacetate of Grosheminol (*V*)

Grosheminol (*IV*; 50 mg) was dissolved in pyridine (1 ml) and acetic anhydride (0·5 ml) and allowed to stand at room temperature for 24 h. After working up non-crystalline diacetate *V* (60 mg) was obtained. IR spectrum (nujol; cm^{-1}): 1 770 (γ-lactone), 1 730, 1 240 (acetate), 1 660, 1 640 (double bond). Mass spectrum (*m/e*): 348 (M), 306 (M—42), 288 (M—60), 228 (M—60—60). ^1H NMR spectrum ($CDCl_3$; ppm; *J* in Hz): 6·28 d, $J \approx 3$ (1 H) (H_{13}); 5·68 d, $J \approx 3$ (1 H) ($H_{13'}$); 5·11 s (2 H) (H_{14}, $H_{14'}$); 5·10—4·67 m (2 H) (H_3, H_8); 4·12 t, $J \approx 10$ (1 H) (H_6); 3·20—2·80 m (3 H) (H_7, H_9, $H_{9'}$); 2·18 s (3 H), (CH_3CO); 2·10 s (3 H) (CH_3CO); 1.21 d, $J \approx 6·5$ (3 H) (H_{15}). For $C_{19}H_{24}O_6$ (348·4) calculated: 65·49% C, 6·94% H; found: 65·20% C, 7·05% H.

Grosheimin (*I*) from Grosheiminol (*IV*)

Grosheiminol (*IV*; 50 mg) was dissolved in acetic acid (2 ml), mixed with a solution of 50 mg of CrO_3 in 1 ml of water under cooling with ice and water, and the mixture was allowed to stand at 0°C for 2 days. The mixture was diluted with water and extracted with chloroform. The combined chloroform extracts were washed with a saturated $NaHCO_3$ solution and water, dried over anhydrous Na_2SO_4 and the solvent evaporated. The residue (43 mg) was chromatographed on silica gel to give grosheimin (*I*; 30 mg), m.p. 199—200°C (ethyl acetate). The IR spectrum and the ^1H NMR spectrum were identical with those of a standard. The mixture melting point with a standard was undepressed.

Grosheiminol (*IV*) from Grosheimin (*I*)

An ethereal solution (5 ml) of zinc borohydride[4] was added to a solution of grosheimin (*I*; 100 mg) in 20 ml of ether, cooled with ice, and the mixture was allowed to stand at room temperature for 1 h. Water was added and the mixture acidified with acetic acid. The ethereal phase was separated and the aqueous phase extracted with ether. The combined ethereal extracts were worked up and grosheiminol (*IV*; 99 mg) was thus obtained. The IR and the ^{1}H NMR spectra of the product were identical with those of a standard.

Isolipidiol (*III*) from Grosheiminol (*IV*)

A solution of sodium borohydride (3 mg) in ethylene glycol dimethyl ether (1 ml) was added to a solution of grosheiminol (*IV*; 5·3 mg) in the same solvent (2 ml) and the mixture was allowed to stand for 30 min. Water and then acetone were added and the solution was extracted with ethyl acetate. The extract was worked up and isolipidiol (*III*; 5 mg) was obtained, m.p. 158 to 161°C. The IR and the ^{1}H NMR spectra of the product were identical with the spectra of an authentic sample. The melting point with a standard was undepressed.

Isolipidiol (*III*) from Grosheimin (*I*)

A solution of sodium borohydride (10 mg) in ethylene glycol dimethyl ether (5 ml) was added to a solution of grosheimin (*I*; 30 mg) in the same solvent (10 ml) and the mixture was allowed to stand at room temperature for 1 h. A working up as in the preceding experiment gave isolipidiol (*III*), m.p. 159—161°C, $[\alpha]_D^{25}$ +25·5° (*c* 0·1; methanol). The IR and the ^{1}H NMR spectra were the same as those of a standard. The mixture melting point with an authentic sample of isolipidol was undepressed.

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