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Synthesis of Amides from *Glycosmis* Species: Methylthiopropenoic Acid, Methylsulfonylpropenoic Acid, Thiocarbamic Acid *S*-Methyl Ester, and Senecioic Acid Amides

Sabine Hinterberger[a], **Otmar Hofer**[a*], and **Harald Greger**[b]

[a] Institute of Organic Chemistry, University of Vienna, A-1090 Wien, Austria
[b] Comparative Phytochemistry Department, Institute of Botany, University of Vienna, A-1030 Wien, Austria

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Abstract: Representative samples of several types of naturally occurring amides from south and southeast Asian *Glycosmis* species were synthesized for proof of structures and for bioactivity testing. With one exception (senecioic acid) all these amides were characterized by sulfur containing acid components (methylthiopropenoic acid, methylsulfonylpropenoic acid, and thiocarbamic acid) in combination with phenethylamine derived amino moieties.

In the course of our search for new bioactive compounds from Asian Rutaceae, we have reported on a series of sulfur containing amides isolated from the leaf extracts of different species of the genus *Glycosmis* collected in Sri Lanka, Thailand, and Malaysia[1-8]. Since some of these compounds showed strong antifungal and insect-toxic properties[8], the synthesis of the structures was of interest for extensive biotesting and proof of structures. During the synthesis of compounds described in Refs.[1-3] it turned out that the originally published structures had to be revised: the suggested basic type of cinnamic acid methylthioethyl amides had to be changed to the isomeric methylthiopropenoic acid phenethyl amides by exchanging the phenyl and the methylthio groups in the proposed structures[4]. Two further papers on the synthesis of (*E*)-3-(methylthio)-propenoic acid phenethyl amide (sinharine) have been published[9,10]. Later it became apparent that the sulfur containing acid moieties (which are probably derived from the amino acid cysteine) represent a unique chemical character of the genus *Glycosmis*, whereas cinnamic acid derivatives are rather common in the plant kingdom. In papers[5-8] we have described further sulfur containing amides characterized by acid components where the methylthiopropenoic acid moiety was either oxidized to methylsulfonylpropenoic acid (**11**, **12**)[5] or chain shortened to thiocarbamic acid (e.g. **16**)[6,8]. In all sulfonyl-amides the aromatic ring of the amino moiety is *para*-substituted by a prenyloxy or a sometimes further oxidized geranyloxy side chain[5,7]. A non-sulfur amide related to this series of compounds is represented by the simple senecioic amide **18**, which was isolated from a Thai *Glycosmis* species[8]. In the present paper, the syntheses of the biogenic amides methyl-illukumbin-A (**4**)[3], dambullin (**11**)[5], gerambullin (**12**)[5], niranin (**16**)[8], and dehydrothalebanin-A (**18**)[8] are reported and some closely related compounds are described as well. Some of the latter, e.g. the 2-hydroxy-phenethylamide **2** or the sulfoxide-amides **8** or **9** are of interest with regard to other naturally occurring compounds isolated from *Glycosmis* species or for the identification of minor constituents in some leaf extracts (**14**).

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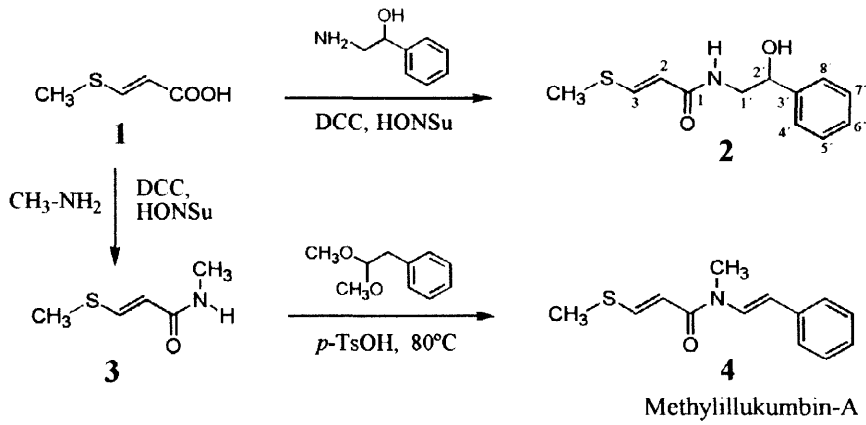
The synthesis of methylillukumbin-A (**4**) with an unsaturated (*E*)-phenylethenylamide moiety attached to (*E*)-phenylthiopropenoic acid (**1**) succeded via (*E*)-3methylthiopropenoic methylamide (**3**, penangin[3,4]) by the reaction of the latter with phenylacetaldehyde dimethyl acetal[11] (Scheme 1). Attempts to obtain enamide **4** via the easily accessible 2-hydroxyphenethylamide **2** by means of direct or indirect water elimination after transformation into derivatives like halogenide or tosylate failed. However, since we have isolated a related natural 2-hydroxyphenethylamide from *Glycosmis* (e.g. *G. chlorosperma* from Penang, Malaysia[12]), the chemical and biological data for amide **2** were also of interest. Methylillukumbin-A (**4**) showed a remarkable antifungal activity in the germtube inhibition test using *Cladosporium herbarum*[8], whereas compound **2** did not show any effect. The synthesis of the amides followed the general method using N-hydroxysuccinimide (HONSu) and dicyclohexylcarbodiimide (DCC) for the activation of the acid component (compare Ref.[4] for other methylthiopropenamides).

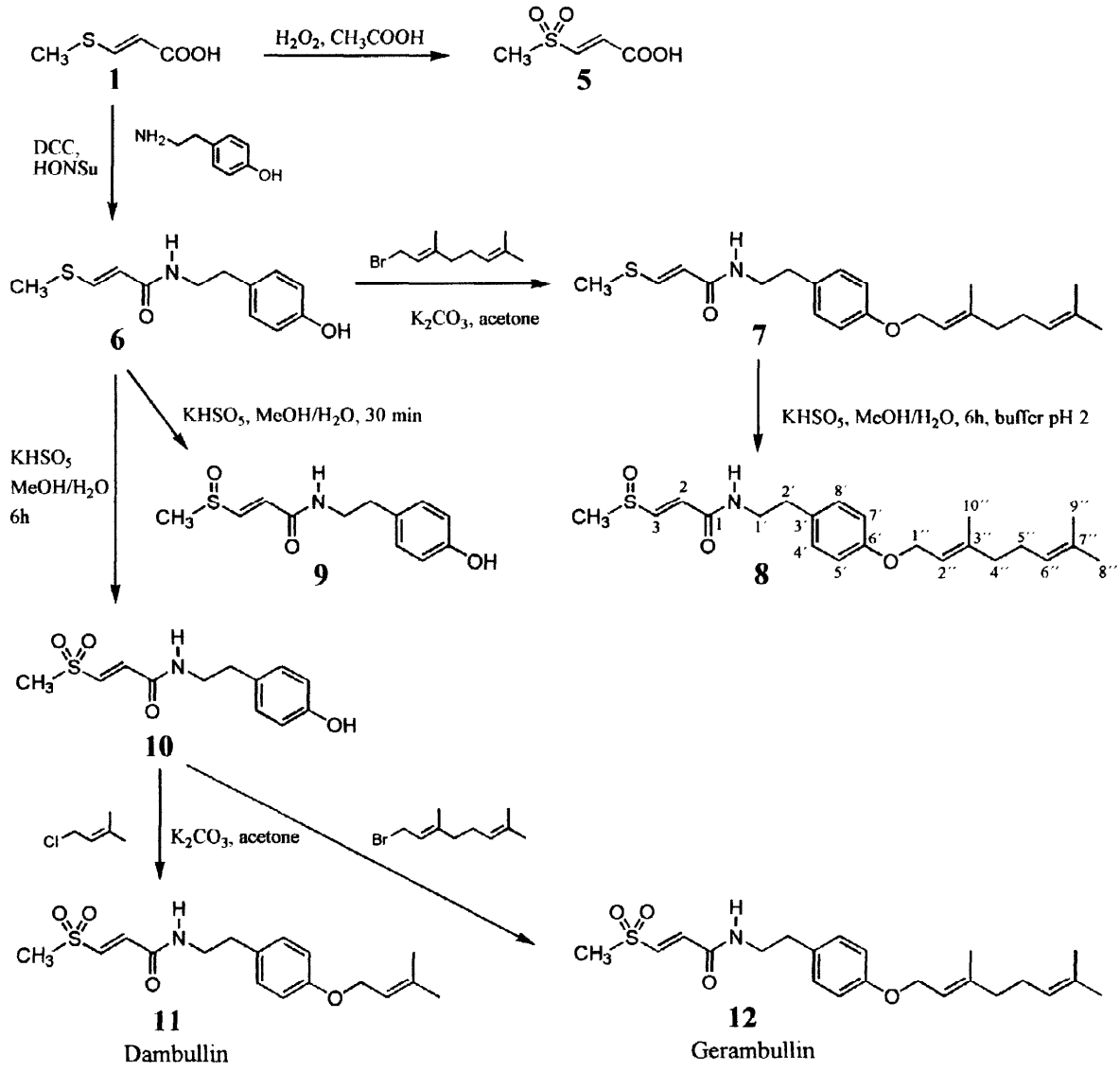


Scheme 1

The ^{1}H NMR data of methylillukumbin-A are already listed in Ref.[4], however, the consequences of the restricted rotation about the amide C—N bond deserve some additional comments. At room temperature (300 K) only the 1′-H resonances appear separately for both rotational isomers (ca. 8.2 and 7.4 ppm, $\Delta\nu$ = 188 Hz !), for all other protons a temperature of 300 K is already high enough for a fast exchange on the NMR time scale. However, the two resonances for 1′-H are very broad and hardly detectable at 300 K, because this temperature is only little below the coalescence temperature for this signal. At 310 K, even in concentrated samples, no 1′-H resonance is detectable at all. At 320 K a new very broad d emerges at δ = 7.72 ppm. The coalescence temperature of 310 K and a $\Delta\nu$ of 188 Hz allows an estimation of ΔG^* = 60.4 ± 1 kJ/mol. A clear slow exchange spectrum with two complete sets of resonances for both rotamers (*s-cis and s-trans*) was obtained at 253 K (see Exp. Part).

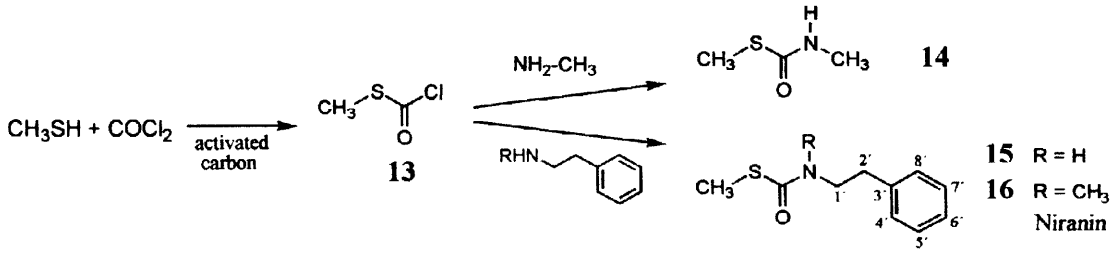
Scheme 2 shows the synthetic steps towards the methylsulfonyl-amides dambullin (**11**) and gerambullin (**12**), which are characterized by an additional prenyloxy or geranyloxy substituent in the *para*-position of the phenethylamide moiety. A key step is the oxidation of the methylthiopropenoic acid (**1**) or derivatives (**6**, **7**) to methylsulfonylpropenoic acid or to proper derivatives. The oxidation of **1** to the sulfonyl analog **5** is easily achieved with hydrogenperoxide in refluxing acetic acid[13]. However, all attempts to obtain methylsulfonyl-propenoic acid *p*-hydroxyphenethyl amide (**10**) by reaction of **5** with *p*-hydroxyphenethylamine failed. Therefore we synthesized the easily accessible methylthiopropenoic analog (**1**→ **6**) and tested different

oxidation methods for **6**. H_2O_2 led to decomposition, a milder method using a mixture of 2 mol $KHSO_5$, 1 mol K_2SO_4 and 1 mol $KHSO_4$ (commercial „oxone“)[14] was successful. After a short reaction time (30 min) the preponderant product was the sulfoxide **9**, after 6 h the only oxidation product was sulfone **10**. The phenolic prenyl or geranyl ethers of *p*-hydroxyphenethylamide **10** could be obtained easily with prenyl chloride or geranyl bromide after deprotonation of the phenolic hydroxyl group with K_2CO_3 in acetone as a mild base[15,16]. The oxidation of prenyloxy or geranyloxy phenethylamides of methylthiopropenoic acid (e.g. **7**) to the corresponding sulfonyl-amides failed. At the normal pH conditions of the „oxone“ reagent (pH = 2) many unidentified products were formed, after addition of acetic acid / sodium acetate buffer (pH = 6) no decomposition products were observed, however, the oxidation stopped at the sulfoxide level (**7** → **8**, yield 76 %). The optimal route to the biogenic compounds **11** and **12** starting from methylthio-acid **1** was therefore the amide formation to **6** followed by oxidation to the methylsulfonyl derivative **10** and final etherification to dambullin (**11**) or gerambullin (**12**).



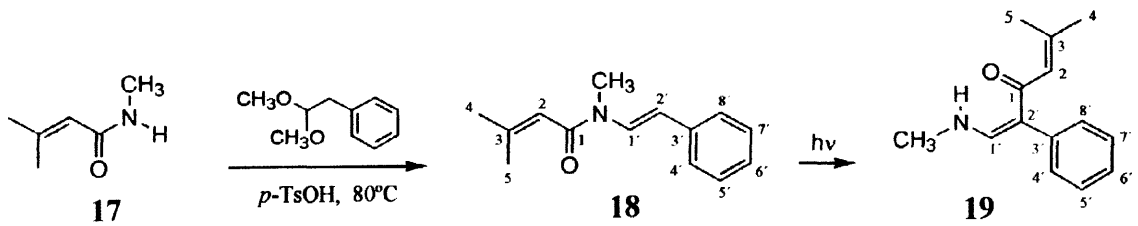
Scheme 2

The synthesis of the chain shortened sulfur containing derivatives like niranin (**16**) started from methylthiocarbonylchloride **13** which could be obtained from methanethiol and phosgene over activated carbon[17,18] (Scheme 3). Compound **13** is the acid chloride of methylthiocarbonic acid and reacts readily with primary or secondary amines under formation of the thiocarbamic acid S-methyl esters **14-16**[19]. The simple *S*-methyl-*N*-methylthiocarbamate (**14**) was of interest for the identification of **14** as a minor constituent which was detected in the HPLC-UV chromatograms of several leaf extracts of *Glycosmis* species (*G. mauritiana, G. parviflora*)[12]. Niranin (**16**) was recently isolated from *G. cf. mauritiana* (Thailand) and exhibited a pronounced toxicity against the test insect *Spodoptera littoralis*[8]. For the restricted rotation about the amide C—N bond of **16** a ΔG^* value of 62.3 ± 1 kJ/mol was determined (see Exp. Part).



Scheme 3

Some of the naturally occurring amides from *Glycosmis* species do not possess sulfur containing acid components. One of these amides is the senecioic acid derived dehydrothalebanin-A (**18**) which was isolated from *G. crassifolia* together with several other related compounds. In preliminary tests, these „thalebanins" showed also a high insect toxicity[8]. Chemically they are characterized by either a senecioic or isovaleric acid component and a penylethenyl (styryl) amide component either in *E* or *Z* configuration[8]. The synthesis of dehydrothalebanin-A was straightforward. For the formation of the unsaturated amide moiety, the easily accessible methylamide of senecioic acid (**17**) was reacted with phenylacetaldehyde dimethyl acetal[11]. The only product obtained was the *E* configurated styrylamide **18**. All attempts to transform the *E*-configurated dehydrothalebanin-A photochemically into the *Z*-configurated dehydrothalebanin-B failed. The only compound obtained was the aminoketone **19** as a rearrangement product. According to the literature this acyl shift should only occur as a side reaction using unfiltered UV[19,20]. In the present case, even with a filter absorbing wave lengths below 300 nm, the rearrangement product **19** was formed almost quantitatively.



Scheme 4

EXPERIMENTAL PART

General. – NMR: Bruker AM 400 WB and AC 250 (TMS, δ/ppm, *J* in Hz); MS: Finnigan MAT 900 S; HPLC: Hewlett-Packard HP 1090 II, UV diode array detection at 230 nm, column 290 × 4 mm (Spherisorb ODS, 5μm), mobile phase MeOH (gradient 60-100%) in aqueous buffer (0.015 M phosphoric acid, 0.0015 M tetrabutylammonium hydroxide, pH 3), flow rate 1 ml/min; all synthetic steps and the purity of the final products were examined by HPLC.

rac. N-(2-Hydroxyphenethyl)-(*E*)-3-(methylthio)-propenamide (**2**)

885 mg (7.5 mmol) of (*E*)-3-(methylthio)-2-propenoic acid (**1**)[4] was reacted with 1.7 g (12.4 mmol) racemic 2-hydroxyphenethylamine in the presence of N-hydroxysuccinimide (HONSu) and dicyclohexylcarbodiimide (DCC) in DMF at 5 °C following the general procedure outlined in Ref.[4]. The crude reaction product (after filtration of dicyclohexylurea) was recrystallized from ethyl acetate (no chromatography necessary). Yield 853 mg (48%) of amide **2**. Colourless crystals from ethyl acetate, m.p. 186-188°C. ^{1}H NMR (DMSO-d_6) δ = 7.89 (br. dd, 1H, J = 6 and 7.5 Hz, NH), 7.39 (d, 1H, *J* = 14.8 Hz, 3-H), 7.15-7.35 (m, 5H, 4′-H – 8′-H), 5.91 (d, 1H, *J* = 14.8 Hz, 2-H), 5.48 (d, 1H, *J* = 4.5 Hz, OH), 4.61 (ddd, 1H, *J* = 4.5, 5.1, and 5.5 Hz, 2′-H), 3.38 (ddd, 1H, *J* = 5.1, 6.0, and 13 Hz, 1′-H), 3.16 (ddd, 1H, *J* = 5.5, 7.5, and 13 Hz, 1′-H), 2.28 (s, 3H, S-Me). ^{1}H NMR ($CDCl_3$) δ = 7.68 (d, 1H, *J* = 14.6 Hz, 3-H), 7.20-7.40 (m, 5H, 4′-H – 8′-H), 5.79 (br. dd, 1H, J = 5.2 and 7.0 Hz, NH), 5.62 (d, 1H, *J* = 14.6 Hz, 2-H), 4.89 (dd, 1H, *J* = 3.3 and 7.8 Hz, 2′-H), 3.78 (ddd, 1H, *J* = 3.3, 7.0, and 14.0 Hz, 1′-H), 3.41 (ddd, 1H, *J* = 5.2, 7.8, and 14.0 Hz, 1′-H), 2.32 (s, 3H, S-Me). ^{13}C NMR (DMSO-d_6) δ = 163.9 (s, C-1), 143.7 (s, C-3′), 139.8 (d, C-3), 128.0 (d, C-4′/8′ or C5′/7′), 127.0 (d, C-6′), 126.0 (d, C-4′/8′ or C5′/7′), 117.3 (d, C-2), 71.5 (d, C-2′), 46.9 (t, C-1′), 13.8 (q, S-Me). MS (70 eV, 170 °C) *m/z* (rel. int.) = 237 (1%, M^+), 131 (86, $[MeSCH{=}CHCONHMe]^+$), 116 (57, $[MeSCH{=}CHCONH]^+$), 101 (100, $[MeSCH{=}CHCO]^+$), 84 (44, $[CH{=}CHCONMe]^+$), 73 (23, $[MeSCH{=}CH]^+$).

(*E*)-*N*-Methyl-*N*-(2-phenylethenyl)-(*E*)-3-(methylthio)-propenamide (**4**, methylillukumbin-A)

(*E*)-*N*-Methyl-3-(methylthio)-propenamide (**3**, penangin) was prepared analogously to amide **2** (see Ref.[4]). For the synthesis of the unsaturated tertiary amide **4** 1.65 g (12.6 mmol) of **3** were stirred together with 2.7 g (16.3 mmol) phenylacetaldehyde dimethyl acetal and 25 mg (0.15 mmol) *p*-toluenesulfonic acid at 80 °C without solvent[11]. The reaction mixture was directly chromatographed on a silica column (3 × 60 cm) with petrol ether : ether = 7.5 : 2.5). The yellow fraction containing amide **4** (TLC comparison with an authentic sample[3]) was evaporated to dryness and the remaining material was recrystallized from ether (661 mg, 22.5%). By elution of the column with ethyl acetate, 650 mg (5 mmol) of the non reacted compound **3** could be recovered and again reacted with the acetal and *p*-TsOH. The second run gave always better yields (538 mg **4** from 650 mg **3**, 46%). This amounts to a total yield of 1.2 g (41%) of amide **4**. Light yellow crystals from diethyl ether, m.p. 84-85 °C (Ref.[3] 83-84 °C). For UV, IR, and MS compare Ref.[3]. The ^{1}H NMR data for 300 K ($CDCl_3$) are listed in Ref.[4], however, for proton 1′-H the correct values are δ = 8.2 and 7.4 (very broad and hardly detectable humps in the base line, due to the close coalescence temperature). This assignment is supported by the spectrum at 310 K (T_c for the 1′-H resonance, no signal detectable) and at 320 K with an averaged fast exchange resonance for 1′-H appearing as a broad d at δ = 7.72. The ^{1}H NMR spectrum at 253 K ($CDCl_3$, slow exchange region) shows two data sets for the amide conformers in the ratio 55/45 %: 8.17 and 7.42 (2 × d, 1H, *J* = 14.9 and 14.0 Hz, 1′-H), 7.84 and 7.79 (2 × d,1H, *J* = 14.3 Hz, 3-H),

ca. 7.3 (m, 2H, 4′ and 8′-H), ca. 7.25 (m, 2H, 5′ and 7′-H), ca. 7.12 (m, 1H, 6′-H), 6.02 and 6.18 (2 × d, 1H, J = 14.3 Hz, 2-H), 5.86 and 5.89 (2 × d, 1H, J = 14.9 and 14.0 Hz, 2′-H), 3.09 and 3.17 (2 × s, N-Me), 2.24 and 2.27 (2 × s, S-Me); J(1′,2′) is different for the *s-cis* and *s-trans* form; the assignments were confirmed by decoupling experiments, the first mentioned values correspond to the 55% conformer; ΔG^{*} = 60.4 ±1 kJ/mol for T_c = 310 K and $\Delta\nu$ = 188 Hz (1′-H). ^{13}C NMR at 300 K ($CDCl_3$) δ = 147.4 (d, C-3), 136.8 (s, C-3′), 128.7 (d, C-5′/7′), 128.3 (v.br.d, C-1′), 126.4 (d, C-6′), 125.5 (d, C4′/8′), 111.9 (d, C-2), 111.6 (br.d, C-2′), 15.0 (q, S-Me); assignments based on C,H-COSY shift correlation; the carbonyl C-1 and the N-Me resonances were not detectable at 300 K, however, at 320 K (fast exchange region) additional signals at 163.5 (br.s, C-1) and 31.0 (br.q, N-Me) emerged. At 253 K (slow exchange) all resonances for two conformers were detectable: δ = 163.4 and 162.6 (2 × s, carbonyl C-1), 146.6 and 146.4 (2 × d, C-3), 136.1 and 135.7 (2 × s, C-3′), 128.1 and 127.9 (2 × d, C-5′/7′), 127.4 and 126.7 (2 × d, C-1′), 125.7 and 125.5 (2 × d, C-6′), 124.8 and 124.7 (2 × d, C4′/8′), 110.7 / 110.6 / 110.5 / 110.2 (4 × d, C-2 and C-2′), 31.6 and 29.6 (2 × q, N-Me), 14.1 and 14.0 (2 × q, S-Me).

(*E*)-3-(Methylsulfonyl)-propenoic acid (**5**)

189 mg (1.6 mmol) of methylthio-acid **1**[4] was dissolved in 2 ml acetic acid and 1.5 ml of H_2O_2 in water (30%) was added dropwise[13]. After refluxing 30 min the cooled reaction mixture was diluted with 5 ml water and extracted with ethyl acetate. Yield 156 mg (65 %) of white crystals from ethyl acetate, m.p. 111-113 °C. ^{1}H NMR ($CDCl_3$) δ = 8.96 (v.br.s, 1H, COOH), 7.48 (d, 1H, J = 15.2 Hz, 3-H), 6.88 (d, 1H, J = 15.2 Hz, 2-H), 3.06 (s, 3H, S-Me). ^{13}C NMR ($CDCl_3$) δ = 166.3 (s, C-1), 143.8 (d, C-3), 131.7 (d, C-2), 43.6 (q, S-Me). MS (70 eV, 90 °C) *m/z* (rel. int.) = 151 (2%, M^+), 88 (16), 81 (33), 71 (100, $[CH{=}CH{-}COOH]^+$), 70 (21), 65 (34), 63 (97), 53 (17), 45 (53), 43 (17).

N-(*p*-Hydroxyphenethyl)- (*E*)-3-(methylthio)-propenamide (**6**)

0.88 g (7.5 mmol) of **1**[4] was reacted with 1.71 g (12.5 mmol) *p*-hydroxyphenethylamine in the presence of N-hydroxysuccinimide (HONSu) and dicyclohexylcarbodiimide (DCC) in DMF at 5°C following the general procedure outlined in Ref.[4]. After chromatography with SiO_2 / ethyl acetate the product was recrystallized from $CHCl_3$. Yield 995 mg (56 %) of white crystals from $CHCl_3$, m.p. 155-156 °C. Moderate solubility in $CDCl_3$. ^{1}H NMR (CD_3OD) δ = 7.56 (d, 1H, J = 14.7 Hz, 3-H), 7.04 (d, 2H, J = 8.5 Hz, 4′/8′-H), 6.73 (d, 2H, J = 8.5 Hz, 5′/7′-H), 5.80 (d, 1H, J = 14.7 Hz, 2-H), 3.43 (t, 2H, J = 7.3 Hz, 1′-H), 2.73 (t, 2H, J = 7.3 Hz, 2′-H), 2.32 (s, 3H, S-Me). ^{1}H NMR ($CDCl_3$) δ = 7.63 (d, 1H, J = 14.5 Hz, 3-H), 7.05 (d, 2H, J = 7.9 Hz, 4′/8′-H), 6.78 (d, 2H, J = 7.9 Hz, 5′/7′-H), 5.54 (d, 1H, J = 14.5 Hz, 2-H), 5.36 (br.t, 1H, J = 6.8 Hz, NH), 3.55 (dt, 2H, J = 6.8 and 6.8 Hz, 1′-H), 2.77 (t, 2H, J = 6.8 Hz, 2′-H), 2.30 (s, 3H, S-Me). ^{13}C NMR (CD_3OD) δ = 167.2 (s, C-1), 156.8 (s, C-6′), 143.4 (d, C-3), 131.2 (s, C-3′), 130.7 (d, C-4′/8′), 116.6 (d, C-2), 116.2 (d, C-5′/7′), 42.3 (t, C-1′), 35.7 (t, C-2′), 14.3 (q, S-Me). MS (70 eV, 190 °C) *m/z* (rel. int.) = 237 (21%, M^+), 190 (9), 121 (35), 120 (97), 119 (25), 118 (74), 107 (32), 101 (100, $[MeSCH{=}CHCO]^+$), 77 (18), 73 (32), 45 (16).

(*E*)-*N*-(*p*-Geranyloxyphenethyl)-3-(methylthio)-propenamide (**7**)

95 mg (0.4 mmol) of **6** and 61 mg K_2CO_3 were dissolved/suspended in 6 ml acetone p.a. and refluxed for 30 min[15,16]. Then 250 mg (1.15 mmol) of geranyl bromide in 3 ml acetone was added dropwise. After stirring 2 h at room temperature all precipitates were filtered off and the solvent evaporated. The remaining material was subjected to column chromatography (SiO_2, column 3 × 50, ethyl acetate) yielding 90 mg (60%) of pure **7**

as a white crystalline powder with a m.p. of 70-72 °C. ^{1}H NMR ($CDCl_3$) δ = 7.60 (d, 1H, *J* = 14.5 Hz, 3-H), 7.09 (d, 2H, *J* = 8.4 Hz, 4′/8′-H), 6.86 (d, 2H, *J* = 8.4 Hz, 5′/7′-H), 5.53 (d, 1H, *J* = 14.5 Hz, 2-H), 5.48 (t, 1H, *J* = 6.5 Hz, 2″-H), 5.32 (br.t, 1H, *J* = 6.8 Hz, NH), 5.09 (tm, 1H, *J* = 6.0 Hz, 6″-H), 4.51 (d, 2H, *J* = 6.5, 1″-H), 3.55 (dt, 2H, *J* = 6.8 and 6.8 Hz, 1′-H), 2.77 (t, 2H, *J* = 6.8 Hz, 2′-H), 2.29 (s, 3H, S-Me), 2.08–2.11 (m, 4H, 4″-H and 5″-H), 1.72 (s, 3H, 10″-H), 1.67 (s, 3H, 8″-H), 1.60 (s, 3H, 9″-H). ^{13}C NMR ($CDCl_3$) δ = 164.4 (s, C-1), 157.6 (s, 6′-H), 142.8 (d, C-3), 141.1 (s, C-3″), 131.8 (s, C-7″), 129.6 (d, C-4′/8′), 125.5 (s, C-3′), 123.7 (d, C-6″), 119.5 (d, C-2″), 115.7 (d, C-2), 114.8 (d, C-5′/7′), 64.9 (t, C-1″), 40.8 (t, C-1′), 39.5 (t, C-4″), 34.8 (t, C-2′), 26.3 (t,C-5″), 24.7 (q, C-8″), 17.7 (q, C-9″), 16.6 (q, C-10″), 14.6 (q, S-Me). MS (70 eV, 230 °C) *m/z* (rel. int.) = 373 (3%, M^+), 238 (59), 237 (53), 120 (100), 118 (91), 101 (94, $[MeSCH{=}CHCO]^+$), 81 (55), 69 (93).

(*E*)-*N*-(*p*-Geranyloxyphenethyl)-3-(methylsulfoxyl)-propenamide (**8**)

To a solution of 90 mg (0.24 mmol) of **7** in 1 ml MeOH, 228 mg of commercial „oxone" dissolved in 2 ml of a AcOH/NaOAc-buffer (pH 6) were added dropwise under cooling[14]. After stirring at room temperature for 3 h, 10 ml of H_2O was added and the resulting mixture was extracted five times with 10 ml portions of ethyl acetate. The dried extracts ($MgSO_4$) were crystallized from ethyl acetate to give 75 mg (80%) of white crystals with a m.p. 158-160 °C. ^{1}H NMR ($CDCl_3$) δ = 7.50 (d, 1H, *J* = 14.5 Hz, 3-H), 7.08 (d, 2H, *J* = 8.5 Hz, 4′/8′-H), 6.84 (d, 2H, *J* = 8.5 Hz, 5′/7′-H), 6.66 (d, 1H, *J* = 14.5 Hz, 2-H), 6.60 (br.t, 1H, *J* = 6.8 Hz, NH), 5.46 (t, 1H, *J* = 6.6 Hz, 2″-H), 5.07 (tm, 1H, *J* = ca. 5.5 Hz, 6″-H), 4.49 (d, 2H, *J* = 6.6, 1″-H), 3.55 (dt, 2H, *J* = 6.8 and 6.8 Hz, 1′-H), 2.78 (t, 2H, *J* = 6.8 Hz, 2′-H), 2.61 (s, 3H, S-Me), 2.01–2.19 (m, 4H, 4″-H and 5″-H), 1.71 (s, 3H, 10″-H), 1.65 (s, 3H, 8″-H), 1.58 (s, 3H, 9″-H). ^{13}C NMR ($CDCl_3$) δ = 162.4 (s, C-1), 157.7 (s, 6′-H), 146.1 (d, C-3),141.1 (s, C-3″), 131.7 (s, C-7″), 130.5 (s, C-3′), 129.6 (d, C-4′/8′), 128.5 (d, C-2), 123.8 (d, C-6″), 119.5 (d, C-2″), 114.9 (d, C-5′/7′), 64.9 (t, C-1″), 41.1 (t, C-1′), 39.8 (q, S-Me), 39.5 (t, C-4″), 34.5 (t, C-2′), 26.3 (t, C-5″), 25.6 (q, C-8″), 17.7 (q, C-9″), 16.6 (q, C-10″). MS (70 eV, 220 °C) *m/z* (rel. int.) = 373 (1%, M^+), 254 (10), 136 (20), 121 (40), 120 (100), 107 (32), 101 (34, $[MeSCH{=}CHCO]^+$), 93 (35), 81 (41), 69 (85).

(*E*)-*N*-(*p*-Hydroxyphenethyl)-3-(methylsulfoxyl)-propenamide (**9**)

To a solution of 88 mg (0.37 mmol) of **6** in 2 ml MeOH, 230 mg of commercial „oxone" dissolved in 2 ml water were added dropwise under cooling[14]. After stirring 30 min at room temperature, the methanol was evaporated *in vacuo*. Extraction with five 10 ml portions of ethyl acetate, drying over $MgSO_4$ and evaporation of the solvent yielded a white solid which was chromatographed with ethyl acetate : methanol = 9 : 1 on silica gel (column 3 × 50 cm). 25 mg (27%) of sulfoxide **9** were obtained together with 21 mg (21%) of sulfone **10**. Sulfoxide **9**: m.p. 170-172 °C. ^{1}H NMR (CD_3OD) δ = 7.58 (d, 1H, *J* = 14.8 Hz, 3-H), 7.03 (d, 2H, *J* = 8.5 Hz, 4′/8′-H), 6.70 (d, 2H, *J* = 8.5 Hz, 5′/7′-H), 6.63 (d, 1H, *J* = 14.8 Hz, 2-H), 3.45 (t, 2H, *J* = 7.3 Hz, 1′-H), 2.73 (t, 2H, *J* = 7.3 Hz, 2′-H), 2.73 (s, 3H, S-Me). ^{13}C NMR (CD_3OD) δ = 164.9 (s, C-1), 157.0 (s, C-6′), 147.4 (d, C-3), 131.0 (s, C-3′), 130.7 (d, C-4′/8′), 129.3 (d, C-2), 116.3 (d, C-5′/7′), 42.6 (t, C-1′), 39.9 (q, S-Me), 35.5 (t, C-2′). MS (70 eV, 160 °C) *m/z* (rel. int.) = 253 (7%, M^+), 134 (11), 121 (49), 120 (100), 117 (32), 107 (71), 101 (56, $[MeSCH{=}CHCO]^+$), 91 (13), 77 (25), 45 (11).

(*E*)-*N*-(*p*-Hydroxyphenethyl)-3-(methylsulfonyl)-propenamide (**10**)

To a solution of 88 mg (0.37 mmol) of sulfide **6** in 2 ml MeOH, 230 mg of commercial „oxone" dissolved in 2 ml water were added dropwise under cooling[14]. After stirring 6 h at room temperature, the

methanol was evaporated in vacuo. Extraction with five 10 ml portions of ethyl acetate, drying over $MgSO_4$ and evaporation of the solvent yielded a white solid which was recrystallized from methanol: yield 58 mg (58%) of white crystals with m.p. 167-169 °C. ^{1}H NMR (CD_3OD) δ = 7.40 (d, 1H, J = 15.0 Hz, 3-H), 7.03 (d, 2H, J = 7.5 Hz, 4′/8′-H), 6.93 (d, 1H, J = 15.0 Hz, 2-H), 6.71 (d, 2H, J = 7.5 Hz, 5′/7′-H), 3.46 (t, 2H, J = 7.3 Hz, 1′-H), 3.06 (s, 3H, S-Me), 2.74 (t, 2H, J = 7.3 Hz, 2′-H). ^{13}C NMR (CD_3OD) δ = 164.3 (s, C-1), 157.0 (s, C-6′), 140.1 (d, C-3), 136.2 (d, C-2), 130.9 (s, C-3′), 130.7 (d, C-4′/8′), 116.3 (d, C-5′/7′), 42.8 (t, C-1′), 42.4 (q, S-Me), 35.3 (t, C-2′). MS (70 eV, 150 °C) *m/z* (rel. int.) = 224 (31%), 143 (39), 99 (63), 98 (33), 70 (44), 61 (66), 56 (100), 55 (28), 43 (26).

(*E*)-*N*-(*p*-Prenyloxyphenethyl)-3-(methylsulfonyl)-propenamide (**11**, dambullin)

108 mg (0.4 mmol) of **10** and 61 mg K_2CO_3 were dissolved/suspended in 6 ml acetone p.a. and refluxed for 30 min [15,16]. Then 120 mg (1.15 mmol) of prenyl chloride in 3 ml acetone were added dropwise. After stirring 8 h at room temperature the precipitates were filtered off, the solvent evaporated, and the remaining material chromatographed (SiO_2, column 3 × 50, ethyl acetate). The resulting crude product was recrystallized from petrol ether : ethyl acetate = 3 : 1, finally yielding 38 mg (28%) of pure **11** as white crystals with a m.p. of 146-147 °C. All spectral data (^{1}H NMR, ^{13}C NMR, UV, IR, and MS) were identical with an authentic sample isolated from a Sri Lankan *G. angustifolia*[5].

(*E*)-*N*-(*p*-Geranyloxyphenethyl)-3-(methylsulfonyl)-propenamide (**12**, gerambullin)

108 mg (0.4 mmol) of **10** and 61 mg K_2CO_3 were dissolved/suspended in 6 ml acetone p.a. and refluxed for 30 min [15,16]. Then 250 mg (1.15 mmol) of geranyl bromide in 3 ml acetone were added dropwise. After stirring 3 h at room temperature all precipitates were filtered off and the solvent evaporated. The remaining material was subjected to column chromatography (SiO_2, column 3 × 50, ethyl acetate) yielding 106 mg (65%) of pure **12** as a white crystalline powder with a m.p. of 130-133 °C. ^{1}H NMR, UV, IR, and MS data were in full agreement with the corresponding data of an authentic sample[5]. ^{13}C NMR ($CHCl_3$) δ = 161.5 (s, C-1), 157.8 (s, 6′-H), 141.3 (s, C-3′′), 138.8 (d, C-3), 135.5 (d, C-2), 131.8 (s, C-7′′), 129.9 (s, C-3′), 129.6 (d, C-4′/8′), 123.8 (d, C-6′′), 119.4 (d, C-2′′), 115.0 (d, C-5′/7′), 64.9 (t, C-1′′), 42.5 (q, S-Me), 41.3 (t, C-1′), 39.5 (t, C-4′′), 34.3 (t, C-2′), 26.3 (t, C-5′′), 25.7 (q, C-8′′), 17.7 (q, C-9′′), 16.6 (q, C-10′′).

Methylthiocarbonylchloride (**13**)

A Liebig condensor (l = 40 cm) was filled with granulated activated carbon (held on place with fiberglass stoppers). Simultaneously two streams of gas, methyl mercaptane and phosgene, were conducted through the Liebig condensor. The gas stream of phosgene should be about twice as fast as that of methyl mercaptane (gas bubble counter, phosgene 2 bubbles/sec, methylmercaptane 1 bubble/sec). The liquid product was collected in a cooled flask (ice/sodium chloride). Since no heating of the carbon catalyst was observed, contrary to the literature[17,18] no cooling of the reaction tube was necessary (nevertheless, for the sake of security, the reaction was always carried out in a Liebig condensor with connected water tubing). After 6 h 5 g of the product was collected. Volatile contaminations were evaporated by leaving the crude material at water jet vacuum for 3 h, afterwards the material was distilled in vacuum (54 °C / 100 mm Hg) to yield 4.5 g of a colourless liquid with n_D^{20} = 1.4872 (Ref.[17] 1.4865).

N-Methyl-thiocarbamic acid *S*-methyl ester (**14**)

Methyl amine gas (dried by passing through a KOH filled drying flask) was bubbled into a solution of 241 mg (2.2 mmol) of **13** in 10 ml absolute ether until no further precipitation of NH_4Cl was observed. The precipitates were filtered of and the clear solution was put on a rotatory evaporator at room temperature. According to HPLC and NMR the remaining 224 mg (97%) colourless liqid material was very pure compound **14**. ^{1}H NMR ($CDCl_3$) δ = 5.54 (v.br.q, 1H, J = 4.9 Hz, NH), 2.86 (d, 2H, J = 4.9 Hz, N-Me), 2.34 (s, 3H, S-Me). ^{13}C NMR ($CDCl_3$) δ = 160.1 (C=O), 26.1 (N-Me), 11.4 (S-Me).

N-Phenethyl-thiocarbamic acid *S*-methyl ester (**15**)

A solution of 363 mg (3.00 mmol) phenethyl amine in 2 ml of absolute ether was dropped to a solution of 170 mg (1.54 mmol) of chloride **13** in 2 ml ether. After 30 min of stirring at room temperature, the white precipitate was filtered of and the solvent was removed on a rotatory evaporater. The remaining material was chromatographed (silica gel, column 3 × 30 cm, petrol ether : acetyl acetate = 8.5 : 1.5) to yield 242 mg (81%) of colourless crystalline product mith m.p. 49-49.5 °C. ^{1}H NMR ($CDCl_3$) δ = 7.25-7.08 (m, 5 H, 4′-H – 8′-H), 5.49 (br.t, 1H, J = ca. 7.1 Hz, NH), 3.44 (dt, 2H, J = 7.1 and 7.1 Hz, 1′-H), 2.74 (t, 2H, J = 7.1 Hz, 2′-H), 2.25 (s, 3H, S-Me). ^{13}C NMR ($CDCl_3$) δ = 167.7 (s, C-1), 138.4 (s, C-3′), 128.6 and 128.5 (2 × d, C-4′/8′ and C-5′/7′), 126.5 (d, C-6′), 42.5 (t, C-1′), 35.8 (t, C-2′), 12.2 (q, S-Me). MS (70 eV, 60 °C) *m/z* (rel. int.) = 195 (50%, M^+), 248 (19), 147 (84), 105 (77), 104 (94), 91 (100), 75 (49), 65 (37), 47 (22).

N-Methyl-*N*-phenethyl-thiocarbamic acid *S*-methyl ester (**16**, niranin)

In analogy to amide **15**, 363 mg (2.69 mmol) of N-methyl-phenethyl amine (synthesized from phenethyl amine via LAH reduction of its formamide[21]) and 308 mg (2.8 mmol) of chloride **13** yielded after chromatography 432 mg (77%) of liquid product **16** which was identical with the natural niranin isolated from *G. mauritiana*[8] (spectral data Ref.[8]). Slow exchange ^{1}H NMR ($CDCl_3$, 253 K, two rotamers in the ratio 0.55 : 0.45) δ = 7.38-7.20 (m, 5 H, 4′-H –8′-H), 3.61 and 3.51 (t, 2H, J = 7.8 and 8.0 Hz, 1′-H), 2.91 and 3.00 (s, 3H, N-Me), 2.85 and 2.90 (t, 2H, J = 7.8 and 8.0 Hz, 2′-H), 2.34 and 2.35 (s, 3H, S-Me); the coupling constants for 1′-H and 2′-H are slightly different in the rotamers (7.8 and 8.0 Hz); T_c = 295 K for 1′-H ($\delta\nu$ = 25 Hz), ΔG^* = 62.3 ± 1 kJ/mol.

N-Methyl-3-methyl-2-butenamide (**17**)

3.3 g (33 mmol) senecioic acid were transformed to the acid chloride by means of $SOCl_2$. The distilled acid chloride (148 °C, 2.5 g, 64%) was obtained as a colourless liquid which changes even under exclusion of air rapidly to brownish colour. 704 mg (5.94 mmol) of this chloride were dissolved in 10 ml absolute ether and treated with methyl amine according to the procedure described for the synthesis of methylamide **14**. Yield 600 mg (89%) white crystals, m.p. 76-76.5 °C.

(*E*)-*N*-Methyl-*N*-(2-phenylethenyl)-3-methyl-2-butenamide (**18**, dehydrothalebanin-A)

431 mg (3.81 mmol) of methylamide **17**, 816 mg (4.92 mmol) phenylacetaldehyde dimethyl acetal, and 14 mg (0.08 mmol) *p*-toluenesulfonic acid were stirred for 12 h at 60 °C[11]. After chromatography (silica gel, column 3 × 30 cm, petrol ether : acetyl acetate = 7.5 : 2.5) 355 mg (43%) of lemon yellow crystals with a

m.p. of 56-58 °C were obtained. The spectral data were in full agreement with the corresponding data for natural dehydrothalebanin-A[8].

5-Methyl-1-methylamino-2-phenyl-1,4-hexadien-3-one (**19**)

60 mg (0.28 mmol) dehydrothalebanin-A (**18**) were dissolved in 300 ml cyclohexane and irradiated with UV light with wave lengths above 300 nm (Hg-lamp, DURAN filter). After 15 min a total transformation of **18** into **19** was observed, no (*E*)-(*Z*) isomerization to dehydrothalebanin-B[8] was observed. The crude product was purified by chromatography (silica gel, column 3 × 30 cm, petrol ether : acetyl acetate = 1 : 1) yielding 53 mg (88%) of aminoketone **19** as a colourless liquid. ^{1}H NMR ($CDCl_3$) δ = 10.42 (v.br.m, 1H, NH), 7.33-7.16 (m, 5H, 4′-H – 8′-H), 6.84 (d, 1H, *J* = 12.6, 1′-H), 5.89 (s, 1H, 2-H), 3.05 (d, *J* = 5.1 Hz, N-Me), 2.17 (s, 3H, 4-H), 1.74 (s, 3H, 5-H). ^{13}C NMR ($CDCl_3$) δ = 190.2 (s, C-1), 155.9 (d, C-1′), 149.0 (s, C-3), 140.3 (s, C-3′), 130.2 (d, C-5′/7′), 128.0 (d, C-4′/8′),125.6 and 125.0 (2 × d, C-2 and C-6′), 111.5 (s, C-2′), 35.3 (q, N-Me), 27.5 (q, C-4), 20.4 (q, C-5).

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