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Synthesis of new 2-oxosparteine derivatives

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ABSTRACT

For the first time, substituents to the 3-position of 2-oxosparteine have been introduced. The synthesis of 3-phenylthiolupanine, 3,3-di(phenylthio)lupanine, 3-dehydrolupanine, 3-bromodehydro-lupanine and 2-thiono-3-dehydrosparteine has been described. The stereochemistry of these compounds has been determined and by NMR spectroscopy and X-ray crystallography.

1. Introduction

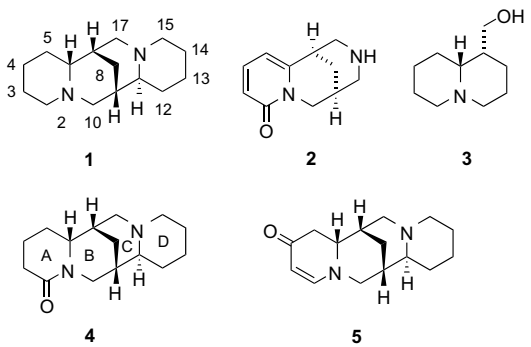
Quinolizidine alkaloids with sparteine (**1**), cytisine (**2**) or lupinine (**3**) skeletons (Scheme 1),[1] called lupin alkaloids, have been of great interest due to their chemical and biological significance. Lupin extracts obtained from the seeds of *Lupinus albus* have been used in traditional medicine for the treatment of diabetes, eczema and as anti-inflammatory agents. The pharmaceutical activity of these extracts is due to the presence of derivatives of sparteine with the oxo-enamine or enamide system in ring A.[2] It has been confirmed that some lupin alkaloids such as 2-oxosparteine (lupanine **4**) and multiflorine (**5**, Scheme 1) demonstrate a hypoglycemic effect.[3] Lupin alkaloids also play an important role in many chemical reactions, and (−)-sparteine (**1**) continues to be a popular chiral base.[4]

It has been found that chemical modifications of these lupin alkaloids can strongly influence their potential biological activity.[2,3] Lupanine (**4**) is the second most commonly occurring bisquinolizidine alkaloid after sparteine (**1**). In this paper, the first modification of the lupanine molecule at the 3-position in ring A is described.

2. Results and discussion

2.1. Synthesis

We synthesized the new derivatives by the transformation of lupanine **4** into its potentially more active 3-phenylthio analogues and their further modification via oxidation to dehydromolecules. There are a number of methods for transformation of ketones into enones,[5] but only a few enabling a transformation of amides into enamides. The method most often used for the latter transformation is based on selenoxide elimination. However, sulfoxide elimination has also been explored for the introduction of the unsaturated bond. For this purpose, we attempted to transform (±)-lupanine (**4**), the main alkaloid of *L. albus* (90%)[6] in the reaction which is well known for the compounds with carbonyl and amide group, but used for the first time for the modification of the quinolizidine alkaloids. This modification has been performed by introducing a phenylthio group into ring A, followed by oxidation of the product into the enamide analogue (Scheme 2).



Scheme 1. The quinolizidine alkaloids.

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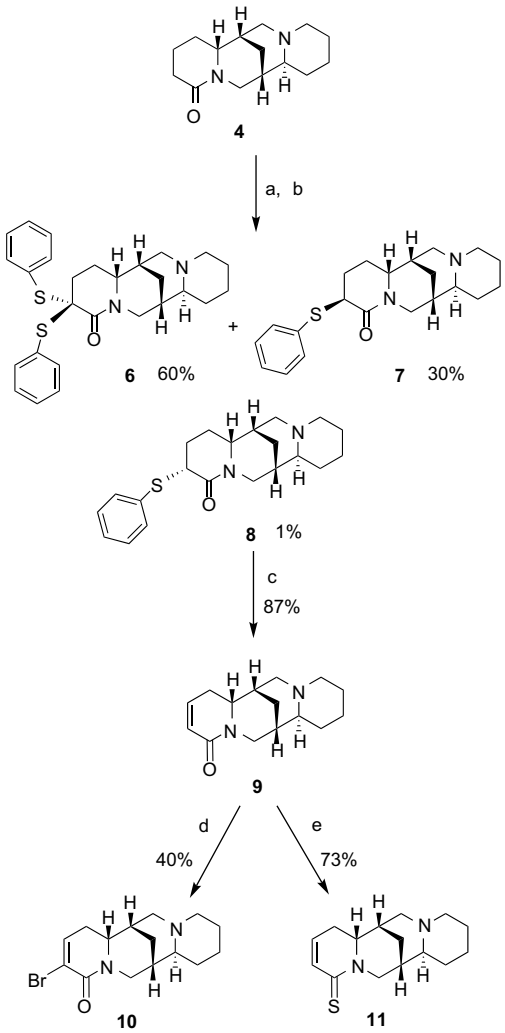

Scheme 2. Synthesis of lupanine derivatives. *Reagents and conditions*: (a) LDA, THF, −78 °C; (b) $(C_6H_5S)_2$, −78 °C; (c) $NaIO_4/NaHCO_3$ in MeOH; (d) NBS; (e) Lawesson's reagent.

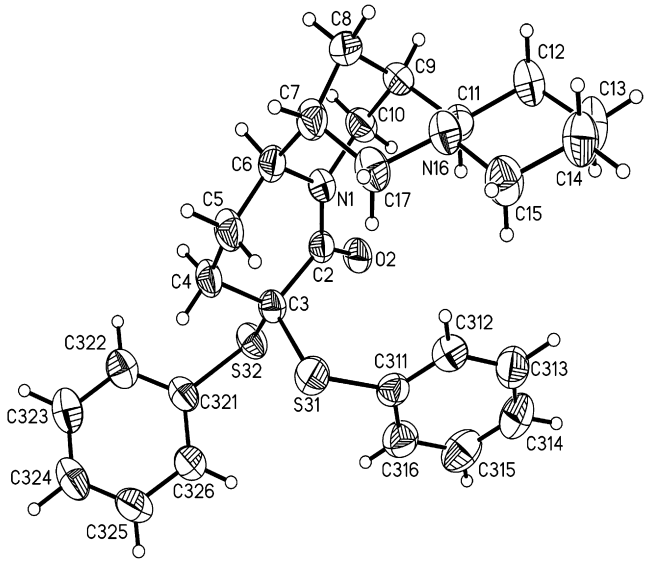

Figure 1. Anisotropic ellipsoid representation of **6**. Crystal data: $C_{27}H_{32}N_2OS_2$, colourless prismatic crystals, monoclinic, $P2_1/c$, a=10.6332(10) Å, b=19.4324(16) Å, c=11.5803(10) Å, β=94.420(7)°, V=2385.7(4) Å^3, Z=4, ρ_{calcd}=1.29 Mg m^{-3}. Final $R_1(I>2\sigma(I))$=0.036.

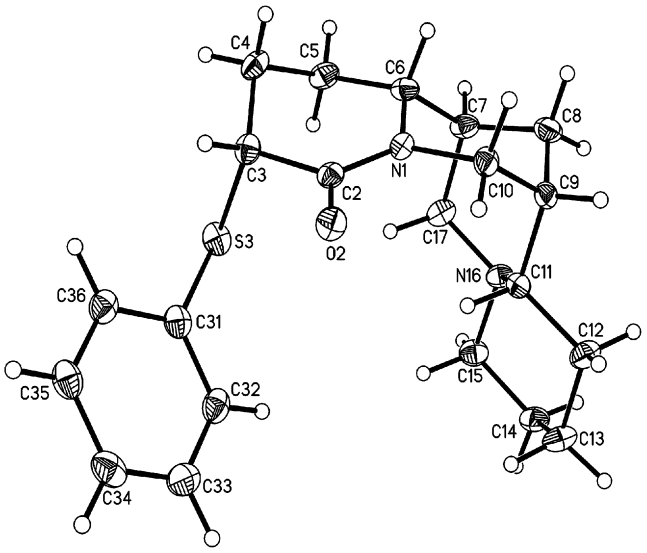

Figure 2. Anisotropic ellipsoid representation of **7**. Crystal data: $C_{21}H_{28}N_2OS$, colourless planar crystals, crystal size 0.05×0.2×0.3 mm, triclinic, $P\bar{1}$, a=9.0648(13) Å, b=10.2863(16) Å, c=11.3313(10) Å, α=96.686(10)°, β=96.489(9)°, γ=115.501(15)°, V=931.3(3) Å^3, Z=2, ρ_{calcd}=1.27 Mg m^{-3}. Final $R_1(I>2\sigma(I))$=0.036.

To start with, we prepared enolates by deprotonation of **4** using lithium diisopropylamide (LDA). Phenylthio lupanines were obtained in the direct reaction with diphenyl disulfide. The mixture of products **6** (60%) and **7** (30%) was separated on SiO_2 column with a satisfactory total yield (90%) and the products were identified. The GC–MS spectra indicated the presence of another isomer **8**. It occurred in a very low percentage (~1%) but was isolated from the reaction mixture and also analysed. For other compounds,[5] this reaction was usually carried out in one pot, but in our experiment, the products were isolated from the mixture in order to analyse the new alkaloids **6**, **7** and **8**.

The crude mixture of **6**, **7** and **8** was used for the next step of the synthesis of the unsaturated ring and this transformation proved to be a challenge. The oxidation of **6**, **7** and **8** was explored with sodium metaperiodate, hydrogen peroxide and to a lesser extent with *m*-chloroperbenzoic acid as oxidants, but only sodium metaperiodate gave the expected enamide **9** (87% yield). Subsequent bromination of 3-dehydrolupanine **9** with NBS provided 3-bromo-3-dehydrolupanine **10** in 40% yield. Another modification of 3-dehydrolupanine **9** was performed with Lawesson's reagent to obtain 2-thiono-3-dehydrosparteine **11** in 73% yield. The structures of the novel products were determined by IR and NMR spectroscopy and X-ray diffraction. The ^{1}H and ^{13}C NMR spectra of **4**[7] allowed tentative assignments of the signals in the spectra of the products **6**–**11**.

Table 1
Selected torsion angles with s.u.'s in parentheses (x=1,2)

	6	7
C2–N1–C6–C5	15.9(2)	9.9(2)
C7–C6–N1–C10	−54.1(2)	54.3(1)
C9–C11–N16–C17	54.2(2)	56.1(1)
C12–C11–N16–C15	−59.4(2)	−59.1(1)
C5–C4–C3–S3(1)	70.0(2)	68.3(1)
C5–C4–S3–C32	−166.7(2)	
N1–C4–C3–S3(1)	−93.5(2)	−95.9(2)
N1–C4–C3–SC32	145.6(2)	
C2–C3–S3x–C3x	−44.8(2)	−74.3(1)
	−167.6(2)	
C4–C3–S3x–C3x	−166.8(2)	161.5(1)
	−46.2(2)	

Table 2
^{13}C NMR chemical shifts in $CDCl_3$ (ppm, from TMS)

C atom	**4**[7]	**6**	**7**	**8**	**9**	**10**	**11**
2	171.4	168.1	169.5	169.4	166.2	161.4	206.3
3	33.1	66.4	49.0	50.0	124.1	118.3	141.2
4	19.7	32.9	25.7	25.0	138.2	138.5	136.0
5	26.8	23.7	22.5	23.2	27.7	29.8	27.9
6	61.0	61.2	61.1	61.9	57.8	57.9	64.5
7	32.4	32.4	32.3	32.7	32.4	32.2	33.3
8	27.5	26.3	26.7	25.7	26.0	25.9	26.7
9	34.9	34.7	34.9	34.8	34.1	34.5	34.8
10	46.8	47.9	47.2	47.0	47.6	49.5	51.6
11	64.2	64.1	63.8	66.6	64.3	63.8	57.6
12	33.5	33.4	33.7	32.9	32.1	31.0	31.0
13	24.5	24.7	24.4	24.1	24.6	24.9	25.5
14	25.2	25.1	25.3	25.0	24.4	23.6	24.8
15	55.6	55.6	55.4	56.9	55.3	55.1	55.5
17	52.9	52.4	52.7	53.2	52.0	51.1	46.7
1′		132.2	135.0	—			
2′/6′		136.9	132.0	—			
3′/5′		128.6	128.9	—			
4′		129.6	127.4	—			
1″		130.7	—	133.7			
2″/6″		136.3	—	133.4			
3″/5″		128.5	—	130.4			
4″		129.0	—	129.2			

2.2. X-ray structure

Lupanine (**4**) has trans configurations of the A/B and C/D ring systems. Its ring A has a semi-chair conformation as a consequence of a change in the hybridisation of the atoms N-1 and C-2 from sp^3 into sp^2 relative to sparteine (**1**). The other rings B, C and D assume the following conformations chair, boat and chair.[8]

Figures 1 and 2 show the perspective views of the molecules of **6** and **7**, as determined in the solid state by the X-ray crystallography.[9] The conformation and configuration of both compounds agree with the theoretical prediction as well as with a number of previously studied crystal structures of bisquinolizidine derivatives.

The ring junctions are quasi-trans/trans, as can be seen from the torsion angles along the junction bonds (cf. Table 1), the conformations of rings B, C and D are chair, boat and chair, while those of ring A might be in both cases described as intermediates between the half-chair and sofa. The conformation of ring A is closer to the half-chair in **6** while in **7** to sofa. Quantitatively, it might be shown by using Duax and Norton asymmetry parameters[10] describing the deviation of the ring from the ideal symmetry for a given conformation. The half-chair has C_2 symmetry and the appropriate asymmetry parameters ΔC_2^{1-2} are 8.8° for **6** and 16.5° for **7**. On the other hand, sofa is connected with the C_s symmetry; the asymmetry parameters ΔC_s^{N1} are 12.4° and 7.8° for **6** and **7**, respectively. Also, the deviations from the least-squares plane of the four atoms (C6, N1, C2, C3) differ more in **7** (C4: 0.561(2) Å and C5 −0.155(2) Å) than in **6** (0.474(3) Å and −0.243(3) Å).

The orientation of thiophenyl substituents in the solid state is described by the C–C–S–C torsion angles (Table 1); in **7** the thiophenyl ring is in the axial position, close to one of the rings in **6**.

2.3. ^{1}H and ^{13}C NMR spectra

The ^{1}H and ^{13}C NMR spectra of lupanine (**4**)[7] allowed tentative assignments of the signals in the spectra of the reaction products **6**–**11**. The ^{13}C NMR and ^{1}H NMR chemical shifts of the compounds studied are given in Tables 2 and 3.

Table 3
^{1}H NMR chemical shifts in $CDCl_3$ (ppm, from TMS)

At. H	**4**[7]	**6**	**7**	**8**	**9**	**10**	**11**
3α	2.33	—	3.92 br s	—	5.87 dd; *J*=9.8; 2.1	—	4.73 dd; *J*=9.5; 1.8
3β	2.47	—	—	3.97 br s		—	
4α	1.83	1.81–1.79 m	2.04–1.99 m (3H)[b]	1.92–1.81 m (3H)[b]	6.47 m; *J*=9.8	6.91 dd; *J*=6.1; 3.0	6.09 ddd; *J*=9.5; 6.2; 3.1
4β	1.62	1.57–1.50 m (3H)[b]	2.04–1.99 m (3H)[b]	1.92–1.81 m (3H)[b]	—	—	—
5α	~1.55	1.57–1.50 m (3H)[b]	1.70–1.62 m (4H)[b]	1.92–1.81 m (3H)[b]	2.44–2.38 m	2.47 ddd, *J*=18.2; 12.2; 3.0	2.47–2.44 m
5β	1.76	1.79–1.74 m (3H)[b]	2.12–2.08 m (2H)[b]	1.79–1.73 m (4H)[b]	2.27–2.23 m	2.28 ddd; *J*=18.2; 6.4; 6.1	2.41–2.26 m (2H)[b]
6	3.29	3.22–3.19 m	3.33–3.30 m	3.57–3.54 m	3.62–3.58 m	3.69–3.66 m	3.52–3.45 m
7	2.06	2.10–2.08 m	2.12–2.08 m (2H)[b]	2.38–2.36 m	2.07–2.05 m	2.08–2.06 m	2.15–2.01 m (2H)[b]
8α[a]	2.16	2.19–2.15 m	2.20–2.18 m	2.20–2.18 m	2.17–2.15 m	2.17 dd; *J*=12.4; 2.5	2.23–2.19 m
8β[a]	1.24	1.25–1.23 m	1.26–1.24 m	1.38–1.29 m (3H)[b]	1.28 ddd; *J*=12.4; 5.5; 3.0	1.35–1.29 m (2H)[b]	1.30–1.25 m (2H)[b]
9	~1.62	1.64 br s	1.70–1.62 m (4H)[b]	1.79–1.73 m (4H)[b]	1.68 br s	1.70 br s	1.89–1.76 m (2H)[b]
10α	4.50	4.35 ddd; *J*=13.4; 4.4; 2.2	4.46 d; *J*=13.2	4.45 d; *J*=13.0	4.17 ddd; *J*=13.4; 4.4; 2.2	4.24 ddd; *J*=13.6; 4.1; 2.0	5.87 ddd; *J*=13.4; 4.6; 2.2
10β	2.51	2.51 dd; *J*=13.4; 2.7	2.54 dd; *J*=13.2; 2.6	2.55 dd; *J*=13.0; 2.8	2.71 dd; *J*=13.4; 3.4	2.83 dd; *J*=13.6; 3.6	2.68 dd; *J*=13.4; 3.4
11	~1.62	1.79–1.74 m (3H)[b]	1.70–1.62 m (4H)[b]	1.79–1.73 m (4H)[b]	1.87 ddd; *J*=10.7; 5.7; 2.9	2.07–2.05 m	1.89–1.76 m (2H)[b]
12α	~1.54	1.57–1.51 m (3H)[b]	1.57–1.54 m (3H)[b]	1.59–157 m	1.55–1.39 m (4H)[b]	1.53–1.49 m	1.43–1.39 m (3H)[b]
12β	1.35	1.41–1.39 m	1.38–1.35 m	1.38–1.29 m (3H)[b]	1.55–1.39 m (4H)[b]	1.46–1.41 m (2H)[b]	1.43–1.39 m (3H)[b]
13α	1.26	1.34–1.29 m	1.31–1.29 m	1.38–1.29 m (3H)[b]	1.32–1.29 m	1.35–1.29 m (2H)[b]	1.30–1.25 m (2H)[b]
13β	1.69	1.79–1.74 m (3H)[b]	1.70–1.62 m (4H)[b]	1.79–1.73 m (4H)[b]	1.74–1.71 m	1.76–1.74 m	1.72–1.65 m
14α	~1.56	1.59 br s[b]	1.57–1.54 m (3H)[b]	1.45–1.41 m (2H)[b]	1.55–1.39 m (4H)[b]	1.61–1.58 m	1.54–1.52 m
14β	~1.53	1.59 br s[b]	1.57–1.54 m (3H)[b]	1.45–1.41 m (2H)[b]	1.55–1.39 m (4H)[b]	1.46–1.41 m (2H)[b]	1.43–1.39 m (3H)[b]
15α	1.90	2.15–2.12 m	2.04–1.99 m (3H)[b]	2.05–2.01 m	2.05 ddd; *J*=12.0; 11.8; 3.1	2.22–2.18 m	2.15–2.01 m (2H)[b]
15β	2.76	2.88–2.86 m	2.84–2.82 m	2.89–2.87 m	2.78–2.76 m	2.78–2.7 m	2.76–2.73 m
17α	1.86	2.42 dd; *J*=11.9; 3.5	2.24 dd; *J*=12.0; 3.4	2.28 dd; *J*=11.8; 3.0	2.30 dd; *J*=11.7; 3.8	2.35 dd; *J*=11.7; 3.4	2.41–2.26 m (2H)[b]
17β	2.84	2.92–2.88 m	2.93–2.89 m	2.94–2.90 m	2.88 dd; *J*=11.7; 9.5	2.95 dd; *J*=11.7; 8.5	2.86 dd; *J*=11.7; 9.5
2′/6′		7.62 d; *J*=6.5	7.59d; *J*=7.6	—			
3′/5′		7.33–7.35 m	7.28 d; J=7.6	—			
4′		7.33–7.29 m	7.33 dd; *J*=7.6;7.6	—			
2″/6″		7.81 d; *J*=6.8	—	7.71 d; *J*=6.7			
3″/5″		7.39–7.41 m	—	7.63 d; *J*=6.7			
4″		7.40–7.36 m	—	7.36 dd; *J*=6.7; 6.7			

[a] In the ring B.
[b] Assignment of the splitting pattern is uncertain because of the overlapping signals in the ^{1}H NMR and ^{1}H–^{1}H COSY spectrum; m multiplet, br s broad singlet, dd doublets of doublets; *J* coupling constant in hertz.

3. Conclusions

In conclusion, we have synthesized the new, unprecedented substituted at position 3 lupanine derivatives: 3,3-di(phenylthio)lupanine (**6**), 3β-phenylthiolupanine (**7**), 3α-phenylthiolupanine (**8**), 3-dehydro-lupanine (**9**), 3-bromodehydrolupanine (**10**) and 2-thiono-3-dehydrolupanine (**11**) and have shown a new and convenient route to modification of the bisquinolizidine alkaloids. It has been also shown that certain modifications of the lupanine structure is possible even if it is only in ring A and that the derivatives of sparteine are very reactive and can be easily modified.

4. Experimental

4.1. General techniques

Thin layer chromatography (TLC) was performed using aluminium sheets precoated with silica gel 60 F_{254} (Merck). Flash chromatography was carried out on silica gel 60 G F_{254} (Merck). Melting points were determined on a Boetius apparatus (PHMK 05 VEB Wagetechnik Rapido, Radebeul). Low- and high-resolution electron ionization (EI) mass spectra were recorded using an AMD Intectra GmbH (Harpsted, Germany) model 402 two-sector mass spectrometer (ionising voltage 70 eV, accelerating voltage 8 kV, resolution 1000 for low-resolution and 10,000 for high-resolution mass spectra).

IR spectra were obtained on a FT-IR Bruker IFS 113v spectrometer (KBr pellets technique).

4.2. NMR spectra

NMR spectra were measured on a Bruker AVANCE 600 (600.31 MHz for ^{1}H and 150.052 MHz for ^{13}C) spectrometer, with a 5 mm triple-resonance inverse probe head ($^{1}H/^{31}P/BB$) with actively shielded *z* gradient coil (90°, ^{1}H pulse width 90 μs, ^{13}C pulse width 13.3 μs). All 2D spectra were acquired and processed using standard Bruker software. Spectral width of 6313.13 and 25,000 Hz were used for ^{1}H and ^{13}C, respectively. All 2D spectra were collected with 2K points in F2 and 256 increments (F1) with 4 (g-COSY) and 64 (g-HSQC) transients each and zero filling in F2 to 2048×1024 data matrix.

4.3. Compounds

(±)-Lupanine (**4**), mp 98–99 °C (lit.[11] 99 °C). NMR data in Tables 1 and 2. IR (KBr): ν C=O 1632 cm^{-1}, trans-band[12] 2810–2760 cm^{-1} with maxima at 2756 cm^{-1} and weaker at 2820 cm^{-1}. $HClO_4$ salt, mp 251–252 °C (lit.[11] 249 °C). IR (KBr) ν C=O 1620 cm^{-1}, ν N^{+}–H 3140 cm^{-1}; ^{13}C NMR: 171, 63.9, 60.9, 55.4, 52.9, 46.7, 34.9, 33.7, 33.1, 32.4, 27.4, 26.8, 25.4, 24.5, 19.7, the same as in the literature.[7] (±)-Lupanine (**4**) was extracted from the lupin seeds of *L. albus* (*Leguminosae* plant, Gene Bank, Experimental Station of Plant, Wiatrowo, 62-100 Wągrowiec, Poland) according to the literature procedure.[6]

4.3.1. Synthesis of lupanine derivatives *6*, *7* and *8*

To a solution of (±)-lupanine (**4**, 0.248 g, 1 mmol) in dry THF (10 mL), a portion of 2.0 M LDA (1.2 mL, 2.4 mmol) was added dropwise at −78 °C under argon. Then the temperature of the reaction mixture was allowed to increase to 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then cooled to −78 °C and a solution of diphenyl disulfide (0.218 g, 1 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 2 h at −78 °C, allowed to warm up to rt and stirred overnight. Water (1 mL) was added dropwise to the reaction mixture and then THF was removed in vacuo. The residue was extracted with CH_2Cl_2. The organic layer was dried over and the solvent was removed to afford crude mixture. The crude mixture was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH 100:10:1) to afford **6** with 30% yield (0.107 g) and **7** in 60% yield (0.278 g). The residue also contained equatorial isomer of 3-phenylthiolupanine (**8**), which was observed by GC–MS in less than 1% of yield. After purification on SiO_2 preparative plate ~3 mg of **8** was obtained.

*4.3.1.1. 3,3-Di(phenylthio)lupanine (**6**).* White crystals, mp 191–192 °C. NMR data in $CDCl_3$ in Tables 2 and 3. IR (KBr): 2800–2700 cm^{-1} (*trans*-band with maxima at 2834 cm^{-1}), 1635 cm^{-1} (ν C=O), 710–570 cm^{-1} (ν C–S). EIMS *m/z*: 355 (15%), 354 (23%), 247 (35%), 245 (33%), 218 (73%), 185 (25%), 148 (49%), 109 (87%), 98 (100%). FABMS, M^{+}=465 (38%), *m/z*: 355 (100%), 247 (9%), 148 (56%). HRMS (EI) calcd for $C_{27}H_{32}N_2OS_2$ 464.1956, found 464.1952. Anal. Calcd for $C_{27}H_{32}N_2OS_2$: C, 69.79; H, 6.94; N, 6.03; S, 13.80. Found: C, 69.45; H, 6.69; N, 5.99; S, 13.70.

*4.3.1.2. 3β-Phenylthiolupanine (**7**).* White crystals, mp 126–127 °C. NMR data in $CDCl_3$ in Tables 2 and 3. IR (KBr): 2860–2700 cm^{-1} (trans-band, with maximum at 2857 cm^{-1}), 1632 cm^{-1} (ν C=O), 710–570 cm^{-1} (ν C–S). EIMS *m/z*: 356 (1%), 247 (100%), 148 (36%), 134 (11%), 109 (8%), 98 (12%). HRMS (EI) calcd for $C_{21}H_{28}N_2OS$ 356.1938, found 356.1922. Anal. Calcd for $C_{21}H_{28}N_2OS$: C, 70.75; H, 7.92; N, 7.86. Found: C, 70.62; H, 8.12; N, 7.83.

4.3.2. Synthesis of 3α-phenylthiolupanine (*8*)

Yellow oil. NMR data in $CDCl_3$ in Tables 2 and 3. EIMS *m/z*: 356 (1%), 247 (100%), 148 (26%), 98 (15%), 134 (8%), 109 (7%), 136 (7%). HRMS (EI) calcd for $C_{21}H_{28}N_2OS$ 356.1938, found 356.1927.

4.3.3. Synthesis of 3-dehydrolupanine (*9*)

To a mixture of **6** and **7** (0.1 g, ca. 0.2 mmol) in MeOH (10 mL), a solution of $NaHCO_3$ (22 mg, 0.25 mmol) and $NaIO_4$ (0.175 g, 0.5 mmol) in 7 mL H_2O at 0 °C was slowly added. The reaction mixture was removed from ice-bath and stirred vigorously for 2 h at rt, warmed up to 60 °C and stirred vigorously for additional 4 h. The reaction mixture was poured into satd aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was separated and washed with brine. Then solvent was removed. The residue was purified by Al_2O_3 and gave **9** with 87% yield (50 mg, 0.20 mmol) as light yellow oil.

$HClO_4$ salt, mp 230–231 °C. NMR data in Tables 2 and 3. IR (film of free base): 1612 and 1667 cm^{-1} (ν –C=C–C=O), 2800–2600 cm^{-1} (trans-band, with maxima at 2853 cm^{-1} and weak at 2770 cm^{-1}). EIMS *m/z*: 246 (68%), 150 (76%), 136 (100%), 110 (78%), 98 (63%), 148 (53%). HRMS (EI) calcd for $C_{15}H_{22}N_2O$ 246.1732, found 246.1732. Anal. Calcd for $C_{15}H_{22}N_2O\cdot 5HClO_4\cdot 0.3H_2O$: C, 51.15; H, 6.75; N, 7.95. Found: C, 51.28; H, 6.70; N, 7.70.

4.3.4. Synthesis of 3-bromo-3-dehydrolupanine (*10*)

To a solution of **9** (30 mg, 0.122 mmol) in CH_2Cl_2 (5 mL), NBS (20 mg, 0.122 mmol) was added. After 30 min the reaction was complete. The mixture was purified by Al_2O_3 and gave **10** with 40% yield (16 mg, 0.049 mmol) as a light yellow oil. NMR data in Tables 2 and 3. IR (film): 1615 and 1681 cm^{-1} (ν –C=C–C=O), 2800–2600 cm^{-1} (trans-band, with maximum at 2850 cm^{-1}). EIMS *m/z*: 326 (11%), 324 (12%), 244 (100%), 148 (50%), 134 (91%), 110 (30%), 98 (25%). HRMS (EI) calcd for $C_{15}H_{21}N_2O^{81}Br$ 326.0817, found 326.0806.

4.3.5. Synthesis of 2-thiono-3-dehydrolupanine (*11*)

A mixture of **9** (21 mg, 0.085 mmol) and Lawesson's reagent in toluene (1 mL) was heated in a closed tube for 5 h. The mixture was purified by Al_2O_3 and gave **11** with 73% yield (16 mg, 0.049 mmol, but it decomposes easily on the air) as a light yellow

oil, from hexane—yellowish powder, mp 149–151 °C (with decomposition). NMR data in $CDCl_3$ in Tables 2 and 3. IR (film): 1637 cm^{-1} (–C=C–), 1488 cm^{-1} (ν –N–C=S), 2800–2600 cm^{-1} (trans-band, with maximum at 2853 cm^{-1}). EIMS m/z: 262 (55%), 261 (100%), 134 (80%), 229 (64%), 136 (61%), 148 (57%), 94 (30%), 150 (27%), 67 (22%). HRMS (EI) calcd for $C_{15}H_{22}N_2S$ 262.1504, found 262.1506.

4.4. X-ray diffraction

Diffraction data were collected on a KUMA KM4CCD diffractometer,[13] using graphite-monochromated Mo Kα radiation (λ=0.71073 Å) at room temperature (**6**) and at 100(1) K (**7**). In the latter case, temperature was controlled with Oxford Cryosystem cooling device. The unit-cell parameters were determined by the least squares fit of the positions of the 8574 (**6**) and 5012 (**7**) most intense reflections chosen from the whole experiment. The Lorentz-polarization and absorption corrections were applied.[13] The structures were solved by direct methods with SHELXS-97 program,[14] and refined by full-matrix least-squares on F^2 using SHELXL-97.[14] Scattering factors incorporated in SHELXL-97 were used. Non-hydrogen atoms were refined anisotropically, hydrogen atoms were located in the difference Fourier maps and both their positional and isotropic displacement parameters were freely refined.

Crystallographic data (excluding structure factors) for the structural analyses has been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 677963 (**6**) and 677964 (**7**). Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk, or www.ccdc.cam.ac.uk.

4.4.1. Compound **6**

$C_{27}H_{32}N_2OS_2$, colourless prismatic crystals, crystal size 0.2×0.2×0.6 mm, monoclinic, $P2_1/c$, a=10.6332(10) Å, b=19.4324(16) Å, c=11.5803(10) Å, β=94.420(7)°, V=2385.7(4) $Å^3$, Z=4, ρ_{calcd}=1.29 Mg m^{-3}, $F(000)$=992, μ=0.25 mm^{-1}, 15,949 reflections measured ($2\theta_{max}$=58.2°), 5966 independent reflections (R_{int}=0.013). Final $R_1(I>2\sigma(I))$=0.036, wR_2(all reflections)=0.110, S=1.14, largest diff. peak and hole 0.18 and −0.36 e $Å^{-3}$.

4.4.2. Compound **7**

$C_{21}H_{28}N_2OS$, colourless planar crystals, crystal size 0.05×0.2×0.3 mm, triclinic, $P\bar{1}$, a=9.0648(13) Å, b=10.2863(16) Å, c=11.3313(10) Å, α=96.686(10)°, β=96.489(9)°, γ=115.501(15)°, V=931.3(3) $Å^3$, Z=2, ρ_{calcd}=1.27 Mg m^{-3}, $F(000)$=384, μ=0.19 mm^{-1}, 9631 reflections measured ($2\theta_{max}$=59.6°), 4721 independent reflections (R_{int}=0.027). Final $R_1(I>2\sigma(I))$=0.036, wR_2(all reflections)=0.090, S=1.00, largest diff. peak and hole 0.33 and −0.26 e $Å^{-3}$.

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