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Synthesis of new derivatives of 11-thiolupinine

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A set of 11-thiofunctionalized derivatives of natural (−)-lupinine have been synthesized using phosphine-based redox type methods such as Hata and Mitsunobu reactions.

Keywords: thioalkaloids; thiolupinine; thiofunctionalization; Hata reaction; Mitsunobu reaction

1. Introduction

Sulfur-containing alkaloidic structures constitute an important niche as a remarkable sub-class among alkaloids, usually exhibiting interesting biological properties (*1*). The most frequently reported activities for thioalkaloids involve, in particular, cytotoxicity, antifungal, antiviral and immunosuppressive activity (*2*). Some thioalkaloids found in Nuphar species can act as antimicrobial and antiherbivore compounds (*3*).

In alkaloids, the simple quinolizidinic frame is mainly encountered within a few vegetable genera (*Lupinus*, *Thermopsis*, *Anabasis*, etc.) in which (−)-lupinine (**1**) and its derivatives constitute a major class of biologically relevant compounds (*4*, *5*).

Some sulfur-containing lupinine analogs have been synthesized in the frame of a pharmacomodulation approach by Sparatore *et al*. (*6*), with a view to building up new ligands for diverse receptors. All those thiolupinine-derived sulfides were generally prepared by reacting 11-thiolupinine (**2**) (*7*) with diverse electrophilic partners. The strongly oxidizable character of primary thiol **2** makes it a very inconvenient reagent to access thio-functionalized derivatives of lupinine in good conditions. Therefore, taking advantage of previous findings (*8*) related to direct conversion of alcohols into miscellaneous hetero-functionalized derivatives using PPh_3-based redox methods (*9*, *10*), we explored the introduction of a thiofunction on natural (−)-lupinine (**1**). This quinolizidine alkaloid can be obtained in enantiomerically pure form either from several *Lupinus* species (*Leguminosae*) or *Anabasis aphylla* L. (*Chenopodiaceae*) (*5*). With a view to

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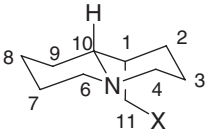
Table 1. Comparison of ^{1}H and ^{13}C NMR data of lupinine (**1**) and thiolupinine (**2**).



X = OH lupinine (**1**)
SH thiolupinine (**2**)

	δH_n (ppm)		δC_n (ppm)	
n	**1**	**2**	**1**	**2**
1	1.41	1.82	38.1	38.1
2	1.40, 1.73	1.36, 1.96	30.4	27.6
3	1.38, 1.97	1.41, 1.68	22.3	20.6
4	1.70, 2.68	1.91, 2.79	56.7	57.2
6	1.70, 2.68	1.91, 2.79	56.7	57.2
7	1.42	1.48, 1.54	25.1	25.4
8	1.12, 1.64	1.22, 1.73	24.3	24.7
9	1.34, 1.58	1.38, 1.44	29.2	29.7
10	1.97	1.96	64.7	65.3
11	3.56, 3.95	2.78, 2.97	64.7	37.1

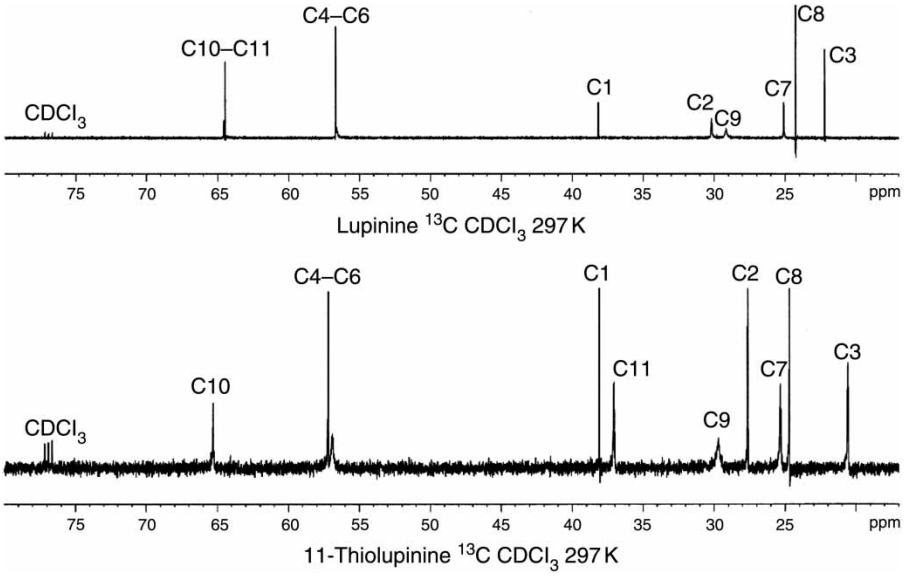
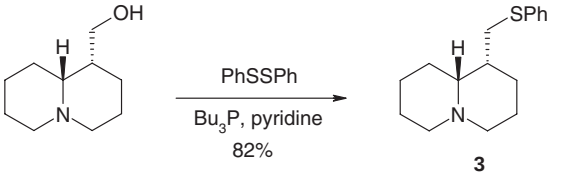


Figure 1. ^{13}C NMR spectra of lupinine (**1**) and thiolupinine (**2**).

explore the bioactivity modulation of this alkaloid through heterofunctional modifications, we here report the introduction of miscellaneous sulfur-centered functions in place of the hydroxyl group of lupinine.

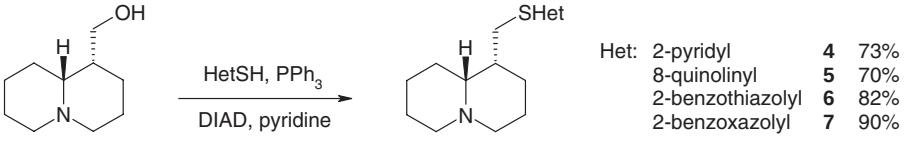
In a first attempt to introduce a sulfur function on the primary position, we produced 11-thiolupinine (**2**) from (−)-lupinine using Sparatore's three-step sequence (*7*). Full assignment of 11-thiolupinine (**2**) was performed using an adapted set of dedicated NMR experiments, and ^{1}H and ^{13}C data of lupinine and thiolupinine were compared (Table 1, Figure 1).

Conversion of **1** into the phenylsulfanyl derivative **3** was readily effected by reacting the primary alcohol with diphenyl disulfide and tri-*n*-butylphosphine under Hata's conditions (Scheme 1) (*10*, *11*).



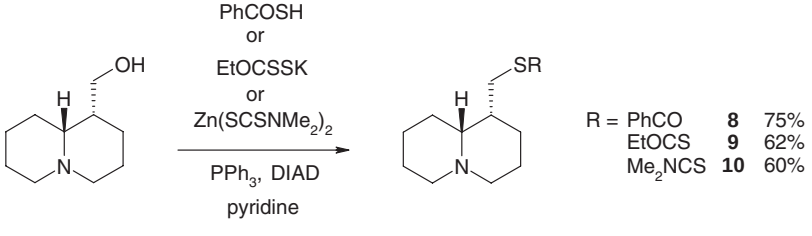
Scheme 1. Direct conversion of **1** into the phenylsulfanyl derivative.

However, in connection with methodological studies previously developed in the laboratory (*8b*, *8d*, *12*), the Mitsunobu reaction appeared as an optimal tool to synthesize aza-heterocyclic hybrid compounds based on the lupinine frame. A range of heteroarylsulfanyl derivatives were thus obtained in 70–90% yields using a single-step Mitsunobu approach involving commercially available and easy-to-handle heteroaryl mercaptans (Scheme 2).



Scheme 2. Single-step synthesis from lupinine of aza-heterocyclic hybrid compounds.

Likewise, a similar methodology allowed transformation of lupinine into thioesters: 11-thiolupinine *S*-benzoate (**8**) was prepared from thiobenzoic acid in 75% yield (*13*), whereas the corresponding *S*-xanthate (**9**) and *S*-dithiocarbamate (**10**) were obtained in ca. 60% yield by using inexpensive potassium *O*-ethylxanthate and ziram (Scheme 3) (*14*).



Scheme 3. Single-step synthesis of thioesters derived from lupinine.

In conclusion, we have introduced a convenient one-pot procedure to convert natural (−)-lupinine into diverse sulfur-functionalized derivatives, including aryl and heteroaryl sulfides and thioesters, by using phosphine-based redox-type methods such as Hata and Mitsunobu reactions. Current efforts focus on broadening the scope of the method and evaluate the biological activity of such thioalkaloidic compounds.

2. Experimental

2.1. *General*

Anhydrous reactions were performed in pre-dried flasks, using anhydrous solvents (which were distilled when necessary according to D.D. Perrin, W.L.F. Armarego and D.R. Perrin, *Purification*

of Laboratory Chemicals; Pergamon: Oxford, 1986) and under argon atmosphere. (−)-Lupinine was extracted from *A. aphylla* (*15*), and a sample of 11-thiolupinine was synthesized according to Novelli and Sparatore (*7*). All other chemicals obtained from commercial suppliers were used without further purification. TLC using pre-coated aluminum-back plates (Merck Kieselgel 60F254) were visualized by ultraviolet light (254 nm) and by charring after exposure to a 5% H_2SO_4 solution in ethanol. Flash column chromatography was performed using silica gel (36–63 mesh, E. Merck). Melting points (°C) were determined with a Köfler hot-stage apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a Bruker AMX 500 (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from TMS. Coupling patterns for ^{1}H NMR are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and coupling constants are given in Hertz (Hz). NMR peak assignments have been established using NOESY, COSY, HSQC and HMBC methods on all reported compounds. Mass spectra were recorded on an API-300 spectrometer [Ionspray® (IS) or heated nebulizer (HN) ionization mode]. HRMS were measured on a MicrOTOF-QII (ESI mode).

2.2. *11-Phenylsulfanyllupinane (3)*

A solution of (−)-lupinine (0.2 g, 1.18 mmol), diphenyl disulfide (515 mg, 2 equiv.) and tri-*n*-butylphosphine (0.6 ml, 2 equiv.) in pyridine (4 ml) was stirred at 80°C for 24 h. The solvent was evaporated under reduced pressure, and then co-evaporation with toluene was effected. Chromatographic purification (eluent EtOAc/MeOH/H_2O, 95:4:1) of the residue provided the 11-phenylsulfanyllupinane (**3**; 253 mg, 82% yield) as a yellow syrup, $[\alpha]_D$ −23 (ca. 1.0, $CHCl_3$) (*6c*). ^{1}H NMR ($CDCl_3$) δ 1.70–1.80 (m, 2H, H-3$_{eq}$, H-8$_{eq}$), 1.95–2.10 (m, 5H), 2.86 (m, 2H, H-4$_{eq}$, H-6$_{eq}$), 3.07 (dd, 1H, J_{gem} = 12.7, J_{vic} = 4.2, H-11b), 3.24 (dd, 1H, J_{gem} = 12.7, J_{vic} = 10.0, H-11a), 7.14 (brt, 1H, J_{vic} = 7.0, *para*-H-Ar), 7.25 (brt, 2H, J_{vic} = 7.2, *meta*-H-Ar), 7.32 (brd, 2H, J_{vic} = 7.5, *ortho*-H-Ar). ^{13}C NMR δ 20.3 (C-3), 24.7 (C-8), 25.3 (C-7), 27.8 (C-2), 29.6 (C-9), 32.1 (C-11), 37.9 (C-1), 57.2 (C-4, C-6), 65.2 (C-10), 125.4 (*para*-*C*-Ar), 128.6 (*C*-Ar), 137.2 (*ipso*-*C*-Ar). ESI-HRMS Calcd for $C_{16}H_{24}NS$: 262.1629. Found: 262.1612 $[M+H]^+$.

2.3. *General procedure for the Mitsunobu conversion of (−)-lupinine into 11-thiofunctionalized derivatives (4–10)*

To a stirred solution of (−)-lupinine (0.2 g, 1.18 mmol), the thio-nucleophile (1.1–1.5 equiv.) and triphenylphosphine (0.37 g, 1.2 equiv.) in pyridine (4 ml), diisopropylazodicarboxylate (0.28 ml, 1.2 equiv.) was added dropwise at 0°C, then stirring was continued at rt until complete consumption of the alcohol (TLC). The solvent was evaporated under reduced pressure, then co-evaporation with toluene was effected. Chromatographic purification of the residue provided the 11-thiofunctionalized derivatives.

2.4. *11-(2-Pyridylsulfanyl)lupinane (4)*

Compound **4** was isolated (after 30 min stirring; eluent CH_2Cl_2/MeOH, 19:1) in 73% yield as a yellow syrup. $[\alpha]_D$ −7 (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.97 (m, 2H, H-4$_{eq}$, H-6$_{eq}$), 3.23 (dd, 1H, J_{gem} = 13.3, J_{vic} = 9.7, H-11b), 3.53 (brdd, 1H, J_{vic} = 4.0, H-11a), 6.94 (dd, 1H, $J_{5,6}$ = 4.9, $J_{4,5}$ = 7.7, H-5$_{Pyr}$), 7.16 (brd, 1H, $J_{3,4}$ = 7.9, H-3$_{Pyr}$), 7.45 (brt, 1H, $J_{4,5}$ = 7.7, H-4$_{Pyr}$), 8.38 (brd, 1H, $J_{5,6}$ = 4.9, H-6$_{Pyr}$). ^{13}C NMR δ 20.6 (C-3), 24.2 (C-7, C-8), 27.2 (C-11), 28.8 (C-2), 29.6

(C-9), 37.9 (C-1), 56.8 (C-4, C-6), 65.1 (C-10), 119.1 (C-5_{Pyr}), 122.0 (C-3_{Pyr}), 135.7 (C-4_{Pyr}), 149.3 (C-6_{Pyr}), 158.5 (C-2_{Pyr}). ESI-HRMS Calcd for $C_{15}H_{23}N_2S$: 263.1582. Found: 263.1573 $[M+H]^+$.

2.5. *11-(8-Quinolinylsulfanyl)lupinane (5)*

Compound **5** was isolated (after 30 min stirring; eluent CH_2Cl_2/MeOH, 19:1) in 70% yield as a crystalline white solid, m.p. 110°C (m.p. 111–112°C) (*16*), $[\alpha]_D$ −19 (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.57 (m, 2H, H-4_{eq}, H-6_{eq}), 2.93 (dd, 1H, J_{gem} = 12.6, J_{vic} = 4.3, H-11b), 3.06 (brdd, 1H, J_{gem} = 12.6, J_{vic} = 10.1, H-11a), 7.09 (dd, 1H, $J_{3,4}$ = 8.2, $J_{2,3}$ = 4.2, H-3_{Qui}), 7.16 (dd, 1H, $J_{5,6}$=8.2, $J_{6,7}$=7.3, H-6_{Qui}), 7.22 (brd, 1H, $J_{5,6}$ = 8.2, H-5_{Qui}), 7.25 (brd, 1H, $J_{6,7}$ = 7.3, H-7_{Qui}), 7.78 (dd, 1H, $J_{3,4}$ = 8.2, $J_{2,4}$ = 1.8, H-4_{Qui}), 8.66 (dd, 1H, $J_{2,4}$ = 1.8, $J_{2,3}$ = 4.2, H-2_{Qui}). ^{13}C NMR δ 20.2 (C-3), 24.2 (C-8), 24.9 (C-7), 28.2 (C-2), 28.9 (C-11), 29.3 (C-9), 36.9 (C-1), 56.4 (C-6), 56.7 (C-4), 64.9 (C-10), 120.9 (C-3_{Qui}), 122.8 (C-5_{Qui}), 123.1 (C-7_{Qui}), 125.9 (C-6_{Qui}), 127.5 (C-$4a_{Qui}$), 135.7 (C-4_{Qui}), 138.9 (C-8_{Qui}), 144.7 (C-$8a_{Qui}$), 148.4 (C-2_{Qui}). ESI-HRMS Calcd for $C_{19}H_{25}N_2S$: 313.1738. Found: 313.1727 $[M+H]^+$.

2.6. *11-(Benzothiazol-2-ylsulfanyl)lupinane (6)*

Compound **6** was isolated (after 30 min stirring; eluent CH_2Cl_2/MeOH, 19:1) in 82% yield as a yellow syrup. $[\alpha]_D$ −28 (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.80–1.90 (m, 2H, H-3_{eq}, H-8_{eq}), 1.95–2.10 (m, 4H, H-1, H-2_{eq}, H-4_{ax}, H-6_{ax}), 2.12 (brs, 1H, H-10), 2.88 (m, 2H, H-4_{eq}, H-6_{eq}), 3.42 (dd, 1H, J_{gem} = 13.2, J_{vic} = 9.6, H-11b), 3.72 (dd, 1H, J_{gem} = 13.2, J_{vic} = 4.2, H-11a), 7.27 (brt, 1H, J_{vic} = 8.0, H-6_{Btz}), 7.39 (brt, 1H, J_{vic} = 8.1, H-5_{Btz}), 7.73 (brd, 1H, J_{vic} = 8.0, H-7_{Btz}), 7.84 (brd, 1H, J_{vic} = 8.1, H-4_{Btz}). ^{13}C NMR δ 20.5 (C-3), 24.6 (C-8), 25.1 (C-7), 27.9 (C-2), 29.4 (C-9), 33.4 (C-11), 38.1 (C-1), 56.6 (C-6), 57.1 (C-4), 65.3 (C-10), 120.8 (C-7_{Btz}), 121.3 (C-4_{Btz}), 123.9 (C-6_{Btz}), 125.8 (C-5_{Btz}), 135.0 (C-$7a_{Btz}$), 153.2 (C-$3a_{Btz}$), 167.5 (C-2_{Btz}). ESI-HRMS Calcd for $C_{17}H_{23}N_2S_2$: 319.1303. Found: 319.1295 $[M+H]^+$.

2.7. *11-(Benzoxazol-2-ylsulfanyl)lupinane (7)*

Compound **7** was isolated (after 30 min stirring; eluent CH_2Cl_2/MeOH, 19:1 and then 9:1) in 90% yield as a yellow syrup. $[\alpha]_D$ −23 (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.80–1.90 (m, 2H, H-3_{eq}, H-8_{eq}), 1.95–2.10 (m, 4H, H-1, H-2_{eq}, H-4_{ax}, H-6_{ax}), 2.12 (brs, 1H, H-10), 2.87 (m, 2H, H-4_{eq}, H-6_{eq}), 3.41 (dd, 1H, J_{gem} = 13.1, J_{vic} = 9.5, H-11b), 3.71 (dd, 1H, J_{gem} = 13.1, J_{vic} = 4.7, H-11a), 7.22 (brt, 1H, J_{vic} = 7.7, H-6_{Box}), 7.27 (brt, 1H, J_{vic} = 7.4, H-5_{Box}), 7.42 (brd, 1H, J_{vic} = 7.7, H-7_{Box}), 7.58 (brd, 1H, J_{vic} = 7.4, H-4_{Box}). ^{13}C NMR δ 20.4 (C-3), 24.7 (C-8), 25.1 (C-7), 28.0 (C-2), 29.6 (C-9), 31.2 (C-11), 38.1 (C-1), 56.6 (C-6), 57.0 (C-4), 65.2 (C-10), 109.5 (C-7_{Box}), 118.0 (C-4_{Box}), 123.5 (C-6_{Box}), 124.0 (C-5_{Box}), 142.5 (C-$3a_{Box}$), 152.5 (C-$7a_{Box}$), 165.0 (C-2_{Box}). ESI-HRMS Calcd for $C_{17}H_{23}N_2OS$: 303.1531. Found: 303.1520 $[M+H]^+$.

2.8. *11-Thiolupinine S-benzoate (8)*

Compound **8** was isolated (after 3 h stirring; eluent EtOAc/MeOH/H_2O, 90:8:2) in 75% yield as a white solid, m.p. 98–100°C, $[\alpha]_D$+3 (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 3.02 (m, 2H, H-4_{eq}, H-6_{eq}), 3.18 (dd, 1H, J_{gem} = 13.5, J_{vic} = 9.7, H-11b), 3.48 (dd, 1H, J_{gem} = 13.5, J_{vic} = 4.0, H-11a), 7.65 (m, 3H, H-Ar), 7.95 (m, 2H, H-Ar).^{13}C NMR δ 20.6 (C-3), 24.8 (C-7, C-8), 27.8 (C-2), 29.5 (C-9), 31.0 (C-11), 37.7 (C-1), 56.9 (C-4, C-6), 65.2 (C-10), 126.5, 127.6 (CH-Ar),

128.5 (C_{IV}-Ar), 133.3 (CH-*para*-Ar), 193.0 (C=O). ESI-HRMS Calcd for $C_{17}H_{24}NOS$: 290.1579. Found: 290.1573 $[M+H]^+$.

2.9. *11-Thiolupinine S-ethylxanthate (9)*

Compound **9** was isolated (after 3 h stirring; eluent EtOAc/MeOH/H_2O, 95:4:1) in 62% yield as a beige gum, $[\alpha]_D -20$ (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, $J_{vic} = 7.1$, CH_3), 2.87 (m, 2H, H-4_{eq}, H-6_{eq}), 3.21 (dd, 1H, $J_{gem} = 13.6$, $J_{vic} = 9.6$, H-11b), 3.53 (dd, 1H, $J_{gem} = 13.6$, $J_{vic} = 4.1$, H-11a), 4.64 (q, 2H, $J_{vic} = 7.1$, OCH_2).^{13}C NMR δ 13.7 (CH_3), 20.7 (C-3), 24.7 (C-8), 25.0 (C-7), 28.2 (C-2), 29.6 (C-9), 34.5 (C-11), 37.5 (C-1), 56.5, 57.0 (C-4, C-6), 65.0 (C-10), 69.7 (OCH_2), 215.0 (C=S). ESI-HRMS Calcd for $C_{13}H_{24}NOS_2$: 274.1299. Found: 274.1286 $[M+H]^+$.

2.10. *11-Thiolupinine S-(N,N-dimethyl)dithiocarbamate (10)*

Compound **10** was isolated (after 3 h stirring; eluent EtOAc/MeOH/H_2O, 90:8:2) in 60% yield as a beige gum, $[\alpha]_D -11$ (ca. 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.96 (m, 2H, H-4_{eq}, H-6_{eq}), 3.36 and 3.53 (2s, Me_2N), 3.40 (dd, 1H, $J_{gem} = 13.8$, $J_{vic} = 9.5$, H-11b), 3.76 (dd, 1H, $J_{gem} = 13.8$, $J_{vic} = 4.2$, H-11a). ^{13}C NMR δ 20.4 (C-3), 24.7 (C-8), 25.0 (C-7), 27.1 (C-2), 29.2 (C-9), 36.2 (C-1), 37.1 (C-11), 41.6 and 45.1 (Me_2N), 57.0 (C-4, C-6), 65.4 (C-10), 197.5 (C=S). ESI-HRMS Calcd for $C_{13}H_{25}N_2S_2$: 273.1459. Found: 273.1441 $[M+H]^+$.

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