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SYNTHESIS, STRUCTURE, AND PROPERTIES OF NEW LUPININE *O*-ACYL DERIVATIVES

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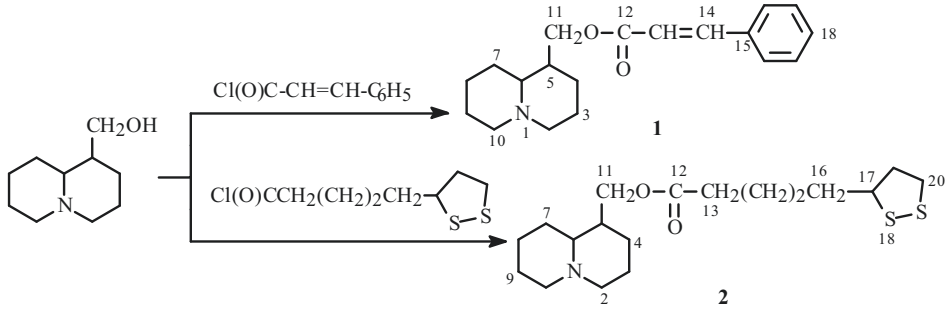
Acylation of the alkaloid lupinine produced O-*cinnamoyllupinine and* O-*lipoyllupinine. The structure of* O-*cinnamoyllupinine was established by an X-ray crystal structure analysis.*

Keywords: alkaloid lupinine, cinnamoyl chloride, lipoic acid, *O*-cinnamoyllupinine, *O*-lipoyllupinine.

The possibility of discovering highly efficacious, selective, and stereospecific biologically active compounds can be greatly improved by modifying quinolizidine alkaloids. The simple quinolizidine alkaloid lupinine is a convenient and available synthetic starting material with a tertiary base and primary alcohol. Lupinine has a *trans*-quinolizidine ring and an axial hydroxymethyl group and changes configuration from *trans*- to *cis*-fusion of the quinolizidine ring with conversion of the axial hydroxymethyl to equatorial with a change of sign of the torsion angle after protonation (iodomethylation) [1, 2]. Reactions of fatty-acid and benzoic-acid chlorides with lupinine produced esters with steric structures that might not correspond to the conformation of lupinine because of the lability of the quinolizidine fragment in solution [3]. These features of lupinine are very important for studying the structure–bioactivity relationship.

In continuation of research on lupinine transformations, new acyl derivatives were synthesized by us using reactions with 3-phenylacrylic (cinnamoyl) and 5-[(3*R*)-dithiolan-3-yl]pentanoic (lipoic) acid chlorides. Many cinnamoyl derivatives are recommended as promising drugs for treating and/or preventing arterial and/or venous thrombosis, acute coronary syndrome, restenosis, stable angina, arrhythmia, myocardial infarct, hypertension, cardiac failure, and stroke [4]. Lipoic acid (lipoate, vitamin N) is a very important antioxidant and acts as a coenzyme in oxygen metabolism, especially in the pyruvate dehydrogenase complex. The *R*-enantiomer has biological significance [5].

Lupinine was acylated by the aforementioned acid chlorides in anhydrous C_6H_6 in the presence of Et_3N. The reaction occurred smoothly and produced *O*-acyl lupinines in 82.3% (**1**) and 82.0% yields (**2**), respectively.



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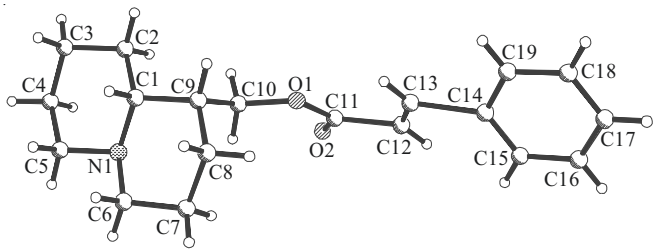

Fig. 1. Molecular structure of *O*-cinnamoyllupinine (**1**).

Synthesized compounds **1** and **2** were a crystalline solid and oil, respectively, that were very soluble in most organic solvents. The structures of **1** and **2** were confirmed using PMR spectra and two-dimensional HMQC (^1H–^{13}C) NMR spectroscopy.

The molecular structure of **1** was established by an X-ray crystal structure analysis and is shown in Fig. 1. The configurations of chiral centers C1 and C9 were the same as in the crystal structure of lupinine hydrochloride [6].

The geometry of **1** was analyzed and showed that the phenyl bond lengths were slightly less than the standard value (1.384 Å) [7] because of large thermal vibrations of the ring atoms. The adjusted isotropic thermal vibration constants U_{eq} were 0.096–0.125 Å^2. The large thermal vibrations of O1, O2, and C11–C13 (U_{eq} 0.123–0.156 Å^2), which linked the lupinine framework and the phenyl ring, caused the bond lengths to deviate significantly from the standard values (given in parentheses): O1–C11 1.363 (1.332), C11–C12 1.642 (1.340), C12–C13 1.063 (1.340), and C13–C14 1.759 (1.488 Å). The disordering of the atoms was dynamic rather than static. The electron-density peaks of these atoms were slightly broadened in space but did not separate into individual peaks. The low melting point even for molecular crystals (77–78°C) indicated that the binding energy between molecules in the crystal of **1** was rather low.

The conformations of six-membered rings C1–C2…N1(A) and C1…C9(B) were similar to the corresponding ones in the crystal structure of lupinine [8] and formed an almost ideal chair (ΔC_S^2 = 0.9° and $\Delta C_2^{3,4}$ = 0.7° for the former and ΔC_S^8 = 0.3° and $\Delta C_2^{7,8}$ = 1.5° for the latter).

EXPERIMENTAL

PMR spectra of **1** and **2** were recorded in DMSO-d_6 on a JNM-ECA 400 spectrometer (JEOL) at frequencies 400 and 100 MHz for ^1H and ^{13}C, respectively. Chemical shifts were measured relative to resonances of residual protons and ^{13}C atoms in DMSO-d_6. Melting points were determined on a Boetius apparatus. TLC used Silufol UV-254 plates and solvent systems *i*-PrOH–NH_4OH–H_2O (7:2:1) and EtOH–$CHCl_3$ (1:4) with detection by I_2 vapor. Reaction products were isolated by column chromatography over Al_2O_3.

Synthesis of *O*-Cinnamoyllupinine (1). A solution of lupinine (3 g, 17.75 mmol) in C_6H_6 (50 mL) was stirred, treated with Et_3N (2.47 mL, 17.75 mmol) and a solution of 3-phenylacrylic acid chloride (2.95 g, 17.75 mmol) in C_6H_6 (20 mL), and stirred for 4 h at room temperature as a precipitate formed. The precipitate of Et_3NHCl was filtered off. The filtrate was evaporated. The residue was chromatographed over Al_2O_3 (petroleum ether–C_6H_6 eluent) to afford **1** (2.47 g, 82.3%) as yellow crystals with mp 77–78°C. The elemental analysis agreed with that calculated for $C_{19}H_{25}NO_2$. ^1H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.09–1.15 (1H, m, H-8ax), 1.31–1.35 (5H, m, H-3ax, 4ax, 7, 9ax), 1.43–1.46 (1H, m, H-9eq), 1.52–1.55 (1H, m, H-3eq), 1.61–1.64 (1H, m, H-8eq), 1.74–1.89 (5H, m, H-4eq, 5, 6, 2ax, 10ax), 2.66–2.69 (2H, m, H-2eq, 10eq), 4.22–4.35 (2H, m, H-11), 6.58 (1H, d, J = 16.0, H-13), 7.60 (1H, d, J = 18.3, H-14), 7.37–7.38 (3H, m, H-16, 18, 20), 7.66 (2H, br.s, H-17, 19). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 21.12 (C-3), 25.14 (C-8), 25.74 (C-9), 27.23 (C-4), 29.81 (C-7), 37.81 (C-5), 57.42 (C-2, 10), 63.57 (C-11), 64.34 (C-6), 118.67 (C-13), 128.88 (C-17, 19), 129.43 (C-16, 20), 130.96 (C-18), 134.54 (C-15), 144.92 (C-14), 166.80 (C-12). HMQC NMR spectrum (^1H–^{13}C): H^{4ax}–C^4 (1.30, 27.26), H^{4eq}–C^4 (1.78, 27.20), H^{3ax}–C^3 (1.20, 27.26), H^{3eq}–C^3 (1.52, 27.26), H^7–C^7 (1.40, 29.65), H^5–C^5 (1.87, 37.78), $H^{2ax,10ax}$–$C^{2,10}$ (1.77, 57.13), $H^{2eq,10eq}$–$C^{2,10}$ (2.66, 57.17), H^{13}–C^{13} (6.60, 118.64), H^{18}–C^{18} (7.36, 130.98), H^{16}–C^{16} (7.37, 129.42), H^{17}–C^{17} (7.67, 128.92) and H^{14}–C^{14} (7.62, 144.93).

Synthesis of *O*-Lipoyllupinine (2). Lipoic acid (1.5 g, 7.317 mmol) was dissolved in C_6H_6 (25 mL), stirred, treated dropwise with thionylchloride (0.64 mL, 4.387 mmol), and stirred for 3 h at room temperature to afford lipoylchloride (1.46 g). A solution of lupinine (1.5 g, 8.862 mmol) in C_6H_6 (50 mL) was stirred, treated with Et_3N (1.22 mL, 8.783 mmol)

and lipoylchloride (1.46 g, 6.465 mmol) dissolved in C_6H_6 (25 mL), and stirred for 5 h at room temperature as a precipitate formed. The precipitate was filtered off. The filtrate was evaporated. The residue was chromatographed over Al_2O_3 (C_6H_6–$CHCl_3$ eluent) to afford **2** (1.23 g, 82.0%) as a yellowish-green thick oil. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm): 1.13–1.25 (2H, m, H-15), 1.31–1.96 (14H, m, 2H-14, 3, 4, 8, 9, H-5, 6, 21ax, 7ax), 2.25–2.29 (3H, m, H-13, 13, 7eq), 2.40–2.44 (1H, m, H-21eq), 2.72–2.79 (4H, m, H-2, 10), 3.04–3.16 (2H, m, H-20), 3.49–3.56 (1H, m, H-17), 4.14–4.19 (1H, m, H-11ax), 4.31–4.35 (1H, m, H-11eq). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 21.22 (C-2), 24.80 (C-9), 25.07 (C-8), 27.05 (C-14), 28.88 (C-4), 29.69 (C-15), 34.28 (C-13, 7), 34.70 (C-16), 37.96 (C-5), 38.58 (C-20), 40.29 (C-21), 56.43 (C-17), 57.39 (C-2, 10), 63.64 (C-11), 64.43 (C-6), 173.56 (C-12). HMQC NMR spectrum (^{1}H–^{13}C): H^8–C^8 (1.23, 24.89), H^{15}–C^{15} (1.21, 29.81), H^{14ax}–C^{14}(1.36, 27.06), H^4–C^4 (1.43, 29.15), H^{3eq}–C^3 (1.67, 21.36), H^8–C^8 (1.71, 25.06), H^{14eq}–C^{14} (1.78, 26.96), H^{16}–C^{16} (1.66, 34.57), H^5–C^5 (1.84, 37.98), H^{21ax}–C^{21} (1.90, 40.12), H^{21eq}–C^{21} (2.41, 40.42), $H^{2ax,10ax}$–$C^{2,10}$ (1.92, 57.05), $H^{2eq,10eq}$–$C^{2,10}$ (2.78, 57.42), H^6–C^6 (1.98, 64.33), $H^{13,7}$–$C^{13,7}$ (2.27, 34.30), H^{17}–C^{17} (3.55, 56.40), H^{11ax}–C^{11} (4.16, 63.64), H^{11eq}–C^{11} (4.30, 63.76).

X-ray Crystal Structure Analysis (XSA) of 1. Cell constants and intensities of 3296 reflections (2509 independent, R_{int} = 0.0309) were measured on an Xcalibur Ruby diffractometer (Oxford Diffraction) (Cu Kα-radiation, graphite monochromator, ω-scanning, 3.86° ≤ θ ≤ 76.02°) at 293 K. The crystals were monoclinic, a = 8.4783(5), b = 8.7702(6), c = 11.9317(7) Å , β = 106.471(6)°, V = 850.80(9) Å^3, Z = 2 ($C_{19}H_{25}NO_2$), space group $P2_1$, d_{calcd} = 1.557 g/cm^3, μ = 0.124 mm^{-1}.

The structure of **1** was solved by direct methods. Positions of nonhydrogen atoms were refined using anisotropic full-matrix least-squares methods. H atoms were positioned geometrically and refined isotropically with fixed positional and thermal parameters (rider model). The calculations used 1477 independent reflections with $I \geq 2\sigma(I)$. The number of refined parameters was 200. The final agreement parameters were R_1 = 0.0673, wR_2 = 0.1606 ([reflections with $I \geq 2\sigma(I)$], and R_1 = 0.1100, wR_2 = 0.1950 (all reflections), GooF = 1.057. The structure was solved and refined using SHELXS-97 [9] and SHELXL-97 programs [10]. XSA data were deposited as a CIF file in the Cambridge Crystallographic Data Centre (CCDC 1869785).

REFERENCES

1. R. T. Tlegenov, D. N. Dalimov, Kh. Kh. Khaitbaev, A. A. Abduvakhabov, and K. U. Uteniyazov, *Chem. Nat. Compd.*, **26**, 434 (1990).
2. A. A. Abduvakhabov, R. Tlegenov, Kh. Kh. Khaitbaev, G. I. Vaizburg, D. N. Dalimov, and K. U. Uteniyazov, *Chem. Nat. Compd.*, **26**, 60 (1990).
3. A. A. Abduvakhabov, K. Toremuratov, Kh. A. Aslanov, V. B. Leont′ev, S. I. Mukhamedkhanova, and A. S. Sadykov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1**, 219 (1973).
4. M. Peres, M. Lamot, et al., RU Pat. No. 2,440,997, "Cinnamoyl-piperazine derivatives and their application as PAR-1 antagonists," Jul. 27, 2012; *Byull.*, No. 3.
5. A. A. Savchenko, E. N. Anisimova, A. G. Borisov, and A. E. Kondakov, *Vitamins as a Basis for Immunometabolic Therapy* [in Russian], KrasGMU, Krasnoyarsk, 2011, 213 pp.
6. A. E. Koziol, M. Gdaniec, and Z. Kosturkiewicz, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, **36**, 980 (1980).
7. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 19 (1987).
8. A. E. Koziol, Z. Kosturkiewicz, and H. Podkowinska, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, **34**, 3491 (1978).
9. G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr. (Suppl.)*, **64**, 112 (2008).
10. G. M. Sheldrick, *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Goettingen, Germany, 1997.