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SYNTHESIS OF 8-BENZODIOXANE AZOMETHINES OF THE ALKALOID LUPININ

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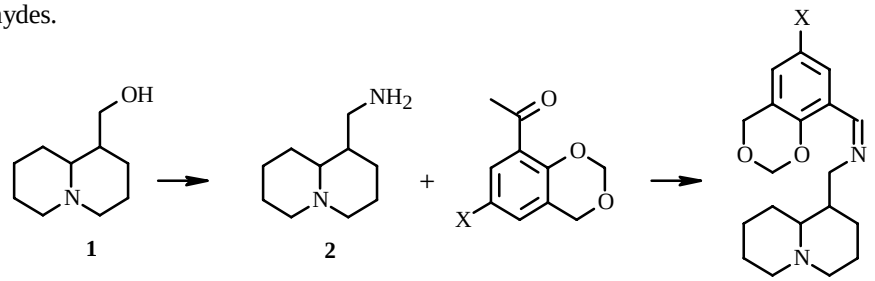
(-)-Lupinin (**1**) is a quinolizidine alkaloid that was isolated in an enantiomerically pure form from several species of *Lupinus* (Leguminosae) and *Anabasis aphylla* L. (Chenopodiaceae) [1] and can be used to prepare several biologically active derivatives.

In order to prepare the desired azomethines, we synthesized aminolupinin (**2**), which was condensed with 8-benzodioxane aldehydes.



1 **2** **3a, b, c**

The resulting azomethines of lupinin (**3**) were brightly colored crystalline compounds that were practically insoluble in water and poorly soluble in most organic solvents. The yields depended on the nature of the substituent in the aromatic ring of the azomethine. Electron-accepting substituents (NO_2, Cl) in the benzene ring increased the yields. The structures of the synthesized compounds were established using UV, IR, and PMR spectral methods.

IR spectra (Specord IR-75, KBr) of azomethines **3a-c** exhibited absorption bands at 2765-2840 cm^{-1} (*trans*-quinolizidine), 1635-1652 (HC=N), and 1576-1612 (Ar). The presence of NO_2 in the compounds (**3b**) was confirmed by characteristic absorption bands near 1545 cm^{-1}.

PMR spectra of **3a-c** showed resonances for aromatic protons of the azomethines situated at 7.7-8.15 ppm and of the azomethines (HC=N) as singlets at 8.50-8.53 ppm. This is characteristic of the (*E*)-isomers of lupinin azomethines. A broad doublet (J = 10.6 Hz) at 2.71-2.79 ppm belonged to equatorial protons of the quinolizidine moiety. The remaining protons of the quinolizidine ring were located at 1.0-2.1 ppm. The presence of other resonances was determined by the nature of the substituent. Mass spectra of the azomethines gave characteristic peaks with base peaks at *m*/*z* 152 and peaks for ions with *m*/*z* 196, 168, 138, 124, and 98, which are characteristic of *trans*-quinolizidine alkaloids [2]. The synthesized compounds were investigated *in vitro* for antituberculosis activity against *M. tuberculosis* $R_{37}Rv$ at the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), Southern Research Institute, USA, using literature methods [2].

Azomethines **3b** and **c** did not exhibit antimycobacterial activity at a concentration of 12.5 μg/mL. Only azomethine **3a** of the synthesized azomethines of lupinin showed weak (14%) antimycobacterial activity.

The purity of the synthesized compounds was monitored by TLC on Silufol UV-254 plates (Merck, Germany) with elution by benzene:ethanol (9:1). UV spectra were recorded on a SF-26 spectrophotometer using 10-mm cuvettes and 0.002% concentrations. PMR spectra were recorded on a Bruker AC-300 instrument (Germany, operating frequency 300 MHz) with Me_4Si internal standard. Mass spectra were obtained in a Varian MAT-311 instrument at ionization potential 70 eV, accelerating potential 3 kV, and vaporizer temperature 80-100°C. The experimental uncertainty was ±3-5%. Elemental analyses of compounds corresponded with those calculated. Starting 8-formyl-6-X-1,3-benzodioxanes were prepared according to the literature [3, 4]; starting lupinin and chlorolupinin [5] and aminolupinin were prepared by literature methods [6].

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[(6-Chloro-8-yl-1,3-benzylidenodioxane)-imino]lupinin (3a). The appropriate aldehyde (0.01 mol) was dissolved in absolute ethanol (propan-2-ol) (50 mL), treated dropwise with aminolupinin (0.01 mol), refluxed for 1.5-2 h, and left at 20-25°C for 20-30 h. The resulting azomethine precipitates were filtered off, washed with a small amount of alcohol, and dried in vacuo. The resulting compounds were rather pure and did not require recrystallization. Other azomethines **3b** and **c** were synthesized analogously. Yield 90%, mp 227-229°C, R_f 0.35, $C_{19}H_{25}N_2O_2Cl$. UV spectrum (DMF, λ_{max}, nm, log ε): 355 (3.20). IR spectrum (ν, cm^{-1}): 2810 (*trans*-quinolizidine), 1638 (HC=N), 1576 (Ar), 950 (C–Cl). PMR spectrum (DMSO-d_6 + CCl_4, δ, ppm, J/Hz): 1.1-2.1 (14H, m, CH_2), 2.77 (2H, d, H_{2e} and H_{10e}, J = 10.6), 5.1 (2H, s, CH_2), 5.4 (2H, s, CH_2), 7.8 (1H, s, Ar–H), 8.06 (1H, s, Ar–H), 8.5 (1H, s, HC=N). Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 349 (1.5), 348 (49) $[M]^+$, 347 (8), 345 (12), 343 (0.4), 330 (1), 329 (1), 327 (3), 310 (2), 308 (27), 307 (3), 304 (3), 303 (3), 302 (6), 301 (2), 279 (10), 265 (1), 255 (1), 228 (1), 210 (3), 197 (1), 196 (63), 168 (27), 152 (100), 151 (41), 150 (72), 138 (45), 136 (26), 124 (23), 98 (27).

[(6-Nitro-8-yl-1,3-benzylidenodioxane)-imino]lupinin (3b). Yield 88%, mp 253-255°C, R_f 0.49, $C_{19}H_{25}N_3O_4$. UV spectrum (DMF, λ_{max}, nm, log ε): 329 (3.85). IR spectrum (ν, cm^{-1}): 2765 (*trans*-quinolizidine), 1652 (HC=N), 1605 (Ar), 1545 (NO_2). PMR spectrum (DMSO-d_6 + CCl_4, δ, ppm, J/Hz): 1.1-2.1 (14H, m, CH_2), 2.71 (2H, d, H_{2e} and H_{10e}, J = 10.6), 5.0 (2H, s, CH_2), 5.4 (2H, s, CH_2), 7.7 (1H, s, Ar–H), 8.10 (1H, s, Ar–H), 8.5 (1H, s, HC=N). Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 360 (0.5), 359 (78) $[M]^+$, 358 (14), 356 (4), 353 (15), 349 (1.5), 345 (2.5), 343 (12), 341 (0.4), 340 (0.5), 329 (7), 327 (1), 310 (2), 285 (3), 283 (2), 279 (9), 264 (17), 263 (8), 249 (1.5), 245 (2.5), 236 (0.5), 235 (1), 222 (3), 221 (1), 216 (1), 208 (0.5), 202 (6), 196 (65), 168 (51), 152 (100), 151 (64), 150 (39), 138 (53), 136 (13), 124 (27), 98 (11).

[(6-Carboxy-8-yl-1,3-benzylidenodioxane)-imino]lupinin (3c). Yield 73%, mp >300°C, R_f 0.45, $C_{20}H_{26}H_2O_4$. UV spectrum (DMF, λ_{max}, nm, log ε): 360 (4.07). IR spectrum (ν, cm^{-1}): 2840 (*trans*-quinolizidine), 3320 (OH), 1710 (C=O), 1635 (HC=N), 1612 (Ar). PMR spectrum (DMSO-d_6 + CCl_4, δ, ppm, J/Hz): 1.0-2.1 (14H, m, CH_2), 2.79 (2H, d, H_{2e} and H_{10e}, J = 10.6), 5.1 (2H, s, CH_2), 5.3 (2H, s, CH_2), 7.9 (1H, s, Ar–H), 8.15 (1H, s, Ar–H), 8.53 (1H, s, HC=N), 10.3 (1H, s, COOH). Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 359 (0.5), 358 (52) $[M]^+$, 352 (10), 351 (0.5), 349 (25), 331 (7), 322 (3), 321 (3), 321 (1), 308 (16), 299 (12), 295 (4), 283 (3), 257 (5), 256 (15), 242 (2), 241 (20), 201 (3), 197 (17), 196 (47), 168 (71), 152 (100), 151 (31), 150 (62), 138 (19), 136 (27), 124 (3), 98 (12).

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