

Synthesis and Transformations of New Spiro-4-piperidines. Acetyl Migration in 1-Acetyl-1'-Benzyl-4-Methyl-3,4-Dihydrospiro[(1*H*)quinoline-2,4'-piperidines] Under Debenzylation Conditions

Vladimir V. Kouznetsov^{*a}, Basilio Díaz P.^a, Clara Marcela Sanabria M.^a, Leonor Y. Vargas M.^a, Juan Carlos Poveda^a, Elena E. Stashenko^a, Alí Bahsas^b and Juan Amaro-Luis^b

^aLaboratorio de Síntesis Orgánica Fina, Centro de Investigación en Biomoléculas. Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia

^bLaboratorio de RMN, Grupo de Productos Naturales, Departamento de Química, Universidad de los Andes, Mérida 5101, Venezuela

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Abstract. Synthesis of new dihydrospiro[quinoline-2,4'-piperidines] by a two-step synthetic route based on 4-piperidone imine reactivity is reported. An acetyl migration in 1-acetyl-1'-benzyl-4-methyl-3,4-dihydrospiro[quinoline-2,4'-piperidines] under debenzylation conditions (HCOONH₄/Pd/C/MeOH) is found.

Keywords: Spiropiperidines, intramolecular alkene Friedel-Crafts alkylation, debenzylation, acetyl migration.

Spiropiperidinyl compounds have attracted an increasing interest as the synthetic targets due to their important activity as pharmacophores in several biologically active compounds [1-3]. The azaspirocyclic structure of some alkaloids has been discovered from various natural sources and their biological activities are presumably associated with this spiro structure [4]. The synthetic compounds with a 4-

“Fig.(1)”. In addition, the utility of 2,2-disubstituted 3,4-dihydroquinolines as pharmaceuticals and as feed additives is well documented [8]. However, little attention has been paid to the heteroaromatic system, where the piperidine and quinoline rings are linked through a spiro atom at their C-4 and C-2 positions respectively. This spiro system (3,4-dihydro-spiro[(1*H*)quinoline-2,4'-piperidine]), where the

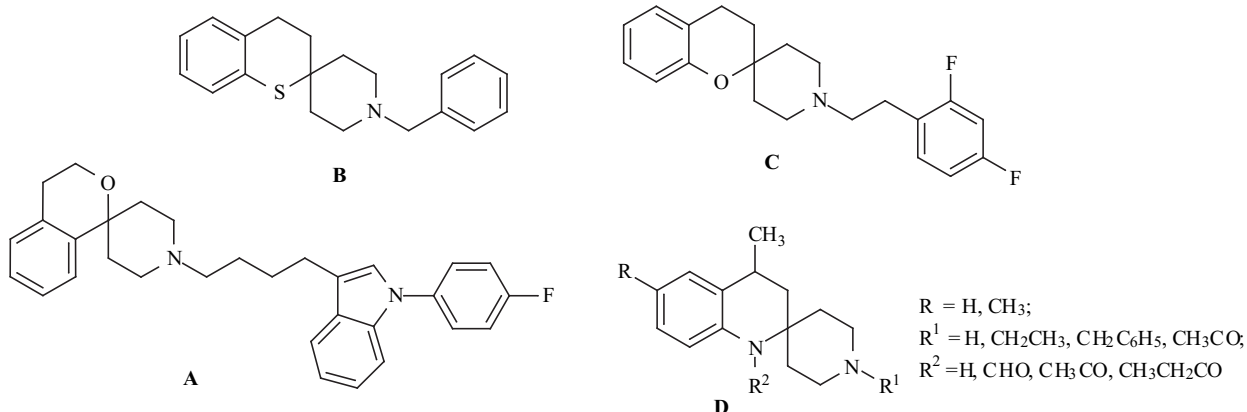


Fig. (1). Compounds with 4-spiro piperidine skeleton as pharmaceuticals.

spiropiperidine motif possess interesting activities as well. For instance, spiro[[2]benzopyran-1,4'-piperidine] **A** and spiro[[1]benzothiopyran-2,4'-piperidine] **B** belong to the most potent and σ_2 - and σ_1 -selective ligands respectively [5,6], and spiro[[1]benzopyran-2,4'-piperidine] **C** is used as a lead compound to identify a series of acyclic sulfones as the selective high-affinity 5-HT_{2A} receptor antagonist [7]

spiranic center is the carbon adjacent to the phenylamine nitrogen, shows interesting features that make them attractive for synthetic and pharmacological use. We have been engaged in systematic study of spiroannulated quinolines [9] including some spiro[(1*H*)quinoline-2,4'-piperidines] [10]. To the best of our knowledge, little has so far been published on the synthesis and chemistry of related spiropiperidinoquinolines [11,12].

In a continuation of our efforts to exploit the synthetic potential of 1-allyl-1-*N*-arylamino-cyclanes (homoallylamines) in the preparation of a wide variety of nitrogen heterocycles with various biological activities, we

*Address correspondence to this author at the Laboratorio de Síntesis Orgánica Fina, Centro de Investigación en Biomoléculas. Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia; Fax: 57-76-349069 (358210); E-mail:kouznet@uis.edu.co

Table 1. ¹H NMR Spectra [400 MHz, CDCl₃/TMS, δ, J (Hz)] of Compounds (3b,c-5b,c)

Comp.	Tetrahydroquinoline protons									Piperidine protons			
	N-R ²	3-Ha	3-He	4-H	5-H	6-R	7-H	8-H	4-CH ₃	N-R ¹	3'(5')-H	2'(6')-Ha	2'(6')-He
3b	3.98 (s, NH)	1.38 (t, J = 12.6)	1.84 (dd, J = 13.0, 5.4)	2.58 (ddc, J = 9.0, 4.6, 1.5)	6.48 (dd, J = 7.4, 1.0)	6.63 (dt, J = 7.4, 1.0)	6.95 (dt, J = 7.4, 1.0)	7.12 (d, J = 7.6)	1.31 (d, J = 6.7)	3.52 (s, CH ₂), 7.20-7.30 (m, Ph)	1.55-1.77 (m)	2.30-2.39 (m)	2.52-2.64 (m)
3c	3.85 (s, NH)	1.40 (t, J = 12.6)	1.85 (dd, J = 13.0, 5.5)	2.89 (heptet, J = 6.7)	6.96 (dd, J = 2.3, 1.0)	2.24 (s, Me)	6.80 (dd, J = 8.0, 2.3)	6.4 (d, J = 8.0)	1.32 (d, J = 6.7)	3.54 (s, CH ₂); 7.28-7.33 (m, Ph)	1.62-1.74 (m)	2.31-2.35 (m)	2.35-2.64 (m)
4b	2.00 (s, Ac)	1.53 (br. d, J = 14.0)	2.04-2.12 (m)	2.42 (dd, J = 10.6, 6.0)	7.02-7.36 (m)				1.34 (d, J = 6.9)	3.53 (s, CH ₂); 7.17-7.36 (m, Ph)	1.20-1.51 (m)	2.23-2.35 (m)	2.53-2.82 (m)
4c	1.99 (s, Ac)	2.02 (d, J = 13.8)	2.10 (d, J = 10.6)	2.58 (dd, J = 12.6, 6.0)	6.99 (s)	2.34 (s, Me)	6.89 (d, J = 8.1)	6.97 (d, J = 8.1)	1.31 (d, J = 6.5)	3.52 (s, CH ₂); 7.21-7.35 (m, Ph)	1.12-1.51 (m)	2.19-2.42 (m)	2.69-2.75 (m)
5b	3.85 (s, NH)	1.93 (ddd, J = 12.0, 10.0, 5.2)	1.46 (t, J = 12.8)	2.58 (sextet, J = 6.4)	7.19 (d, J = 7.6)	7.02 (s)	6.72 (d, J = 7.6)	7.19 (d, J = 7.6)	1.37 (d, J = 6.4)	2.13; 2.14 (s, Ac)	1.56-1.71 (m)	3.42-3.63 (m)	3.77-4.00 (m)
5c	3.80 (s, NH)	1.89 (ddd, J = 12.0, 10.0, 6.0)	1.42 (t, J = 12.6)	2.88 (sextet, J = 6.5)	6.89 (s)	2.24 (s, Me)	6.45 (dd, J = 8.0, 2.0)	6.82 (d, J = 8.0)	1.34 (d, J = 6.5)	2.10; 2.11 (s, Ac)	1.52-1.72 (m)	3.38-3.50; 3.55-3.60 (m)	3.79 (dt, J = 13.6, 5.5); 3.95 (dt, J = 14.0, 5.0)

boat-like conformation of the debenzylated piperidine ring (compounds **6b,c**).

In conclusion, the synthesis described herein provides an effective route in two steps to the substituted 3,4-dihydrospiro[(1*H*)quinoline-2,4'-piperidines] and in excellent yields from commercial piperidinones and anilines. The obtained products can be used as potential starting synthons for the subsequent preparation of drug-like molecules based on the spiro[quinoline-2,4'-piperidine] system. During this study we found the possibility of acetyl group migration from tetrahydroquinoline nitrogen atom to piperidinic nitrogen of the same molecule. This interesting fact is further being studied in our laboratory.

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- Data for compound **4c**: This compound was isolated (86%) as yellow very viscous liquid; IR (KBr) $\nu_{C=O}$ 1666 cm^{-1} ; ^{13}C NMR (100 MHz, CDCl_3): δ 21.2 (+), 26.68 (+), 29.2 (+), 29.7 (+), 31.8 (-), 36.7 (-), 44.7 (-), 50.3 (-), 50.8 (+), 61.2 (spiro), 62.7 (-), 126.4 (+), 126.5 (+), 126.9 (+), 128.0 (+), 128.1 (+), 128.2 (+), 129.0 (+), 129.1 (+), 135.6, 137.8, 138.6, 140.1, 172.2; GC-MS: t_R 44.39 min.; Mass spectrum (EI): m/z (%) 362 (M^+ , 7), 319 ($[\text{M}-\text{C}_2\text{H}_3\text{O}]^+$, 26), 271 ($[\text{M}-\text{C}_7\text{H}_7]^+$, 7), 230 ($[\text{M}-\text{C}_9\text{H}_{10}\text{N}]^+$, 9), 186 ($[\text{M}-\text{C}_{11}\text{H}_{14}\text{NO}]^+$, 31), 146 ($[\text{M}-\text{C}_{14}\text{H}_{18}\text{NO}]^+$, 53), 91 ($[\text{M}-\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}]^+$, 100). Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}$: C, 79.52; H, 8.34; N, 7.73%. Found: C, 79.33; H, 8.56; N, 7.58%.
- Data for compound **5c**: This compound was isolated (58%) as beige crystals; mp 143-144°C (from heptane and ethyl acetate, 1:1); IR (KBr) ν_{NH} 3233 cm^{-1} , $\nu_{\text{C-N}}$ 2914 cm^{-1} , $\nu_{\text{C=O}}$ 1655 cm^{-1} , $\nu_{\text{C=C}}$ 1500 cm^{-1} ; ^{13}C NMR (100 MHz, CDCl_3): δ 20.4/20.5, 20.6, 21.4/21.5, 26.6/26.7, 35.4, 37.4/37.6, 38.5, 42.0/42.2, 42.4/42.5, 49.2/49.3, 114.7/114.8, 125.6/125.7, 126.7/128.8, 127.5, 127.6/127.7, 140.2, 168.9/169.0; GC-MS: t_R 32.90 min.; Mass spectrum (EI): m/z (%) 272 (M^+ , 71), 257 ($[\text{M}-\text{CH}_3]^+$, 26), 243 ($[\text{M}-\text{C}_2\text{H}_5]^+$, 3), 229 ($[\text{M}-\text{C}_2\text{H}_3\text{O}]^+$, 14), 185 ($[\text{M}-\text{C}_4\text{H}_8\text{O}]^+$, 97), 170 ($[\text{M}-\text{C}_5\text{H}_{12}\text{NO}]^+$, 100), 158 ($[\text{M}-\text{C}_6\text{H}_{11}\text{NO}]^+$, 49). Calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}$: C, 74.96; H, 8.88; N, 10.28%. Found: C, 74.71; H, 9.06; N, 10.05%.
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