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Synthesis of Vinca Alkaloids and Related Compounds 99[1]. A New Heterocyclic System

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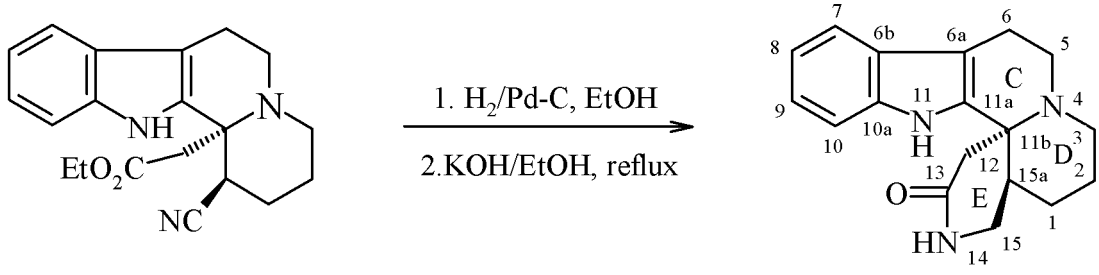
Abstract: Utilising our earlier intermediate obtained by the umpolung reactivity of quinolizidine enamines, a new heterocyclic system: (11bSR, 15aSR)-1,2,3,6,11,14,15,15a-Octahydro-5H-indolo[2',3':3,4]pyrido[2,1-j]-1,6-naphthyridin-13(12H)-one was synthesised and its biological effects evaluated. Although modest, significant and selective effects were detected.

Keywords: alkaloids, stereochemistry, cyclization; new ring system, indolo[2,3-a]quino-lizidines

1 Introduction

Recently we reported the formation of an unusually substituted indolo[2,3-a]-quinolizidine derivative (1) [2]. The compound was only possible to synthesize by using the umpolung reactivity newly discovered in this heterocyclic family.



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Taking advantage of two functionalities (ester and nitrile) being in favourable steric positions, we aimed at the synthesis of a new heterocyclic system.

The nitrile group was catalytically reduced in the presence of palladium/carbon (Pd/C) and the resulting amine, without isolation, was allowed to react intramolecularly with the ester function. After work-up, we isolated compound 2 in crystalline form (2) in 46% yield.

2 Structure elucidation

The formation of the heterocyclic ring E is verified by the presence of an amide unit (NH: 6.92 ppm; CO: 170.5 ppm) and from the appearance of the 15-methylene protons at 3.45 and 3.59 ppm in the proton spectrum. These protons showed vicinal couplings with the H15a methine proton. The cis C/D ring anellation, similarly to that of the starting material (1), follows from the chemical shifts of C3 and C5 carbons (45.7 and 47.8 ppm, respectively). The trans stereochemistry of the D/E ring junction is deduced from the C2 and C15 carbon resonances (20.7 and 43.2 ppm, respectively). These carbon signals are expected to be shifted upfield when D and E rings are in cis relation [3].

3 Biological data

Several pieces of biological data were established with compound 2. Its displacing effect was studied in binding assays on different subclasses of serotonin, adrenaline, dopamine, and benzodiazepine receptors in order to investigate its activity on the central nervous system (CNS). The preliminary results are summarised in Table 1. The effects are modest but significant, since they were detected at a concentration of 10^{-7} mol/L. The inhibitory effect observed here also appeared to be highly selective.

4 Methods and Materials

Melting points (Mp) were measured on a Boetius hot-stage apparatus and are uncorrected; IR spectra were recorded on a Nicolet 205FT spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with a Varian VXR-400 spectrometer. Chemical shifts (δ values) are reported relative to the internal standard Me_4Si, J values are recorded in Hz. Abbreviations s, d, t, m, and brs are used to designate singlet, doublet, triplet, multiplet and broad singlet, respectively. Mass spectrometry (MS) values were taken on a VG ZAB2-SEQ tandem MS using electron impact ionisation. For TLC analysis Kieselgel 60 F_{254} plastic sheets, for separation by column chromatography Kieselgel 60 (0.063-0.200) adsorbent (both provided by Merck) were used

Receptor	Conc.	Inhibition (%)
5-HT_{1A}	10^{-7} M	4
5-HT_{2A}	10^{-7} M	0
5-HT_{2C}	10^{-7} M	0
5-HT_6	10^{-7} M	15
5-HT_7	10^{-7} M	3
α_1 adrenaline	10^{-7} M	1
α_2 adrenaline	10^{-7} M	15
β adrenaline	10^{-7} M	2
D_1 dopamine	10^{-7} M	0
D_2 dopamine	10^{-7} M	2
$BZD_{1,4}$	10^{-7} M	5

Table 1.

5 Formation of (11bSR, 15aSR)-1,2,3,6,11,14,15,15a-Octahydro-5*H*-indolo[2′,3′:3,4]pyrido[2,1-*j*]-1,6-naphthyridin-13(12*H*)-one (2)

To a solution of disubstituted quinolizidine derivative 1 (230 mg, 0.68 mmol) in ethanol (20 ml), concentrated HCl solution (6 drops) and 10% Pd/C (40 mg) were added and the reaction mixture was stirred under hydrogen atmosphere at room temperature for 4 h. The solution was then filtered off, washed with ethanol (5 ml), and solid KOH (0.45 g, 8.0 mmol) was added to the filtrate. The reaction mixture was refluxed for 2 days, then the solvent was evaporated. The residue was purified by column chromatography on silica gel with chloroform-methanol 5:1 to give 2 as yellow crystals (92 mg, 46%). Mp: 247-250 °C. IR (KBr): ν 3300 (NH indole), 3200 (NH amide), 1660 cm^{-1} (C=O amide). ^{1}H NMR (DMSO-d_6 + $CDCl_3$), δ (ppm): 1.50-1.85 m, 4H (H1 + H2); 2.43 + 2.98 d, J=17.6 Hz, 2H (H12); 2.65 m, 1H (H15a); 2.60 + 2.95 m, 2H (H6); 2.83-3.37 m, 4H (H3 + H5); 3.45 m, J= 12.2 + 6.0 + 2.0 Hz, 1H (H_A15); 3.59 m, J= 12.2 + 7.8 + 2.0 Hz,1H (H_B15); 6.92 brs, 1H (CONH); 7.03 m, J= 7.8 + 7.1 + 1.2 Hz, 1H (H8); 7.09 m, J= 8.0 + 7.1 + 1.2 Hz, 1H (H9); 7.36 dd, J= 8.0 + 1.2 Hz, 1H (H10); 7.43 dd, J= 7.8 + 1.2 Hz, 1H (H7); 9.88 brs, 1H (NH). ^{13}C NMR (DMSO-d_6 + $CDCl_3$), δ (ppm): 18.1 (C6), 20.7 (C2), 25.0 (C1), 33.5 (C15a), 41.3 (C12), 43.2 (C15), 45.7 + 47.8 (C3 + C5), 56.6 (C11b), 106.5 (C6a), 111.3 (C10), 117.8 (C7), 118.7 (C8), 121.1 (C9), 127.1 (C6b), 136.2 + 136.8 (C10a + C11a), 170.5 (C13). Ms (m/z, %): 295 (M^+, 84), 294 (M^+-1, 41), 252 (M^+-43, 15), 237 (M^+-58, 61), 236 (M^+-59, 45), 223 (M^+-72, 100). Exact molecular weight measured: 295.167700; calcd. for $C_{18}H_{21}N_3O$: 295.168463. Analysis: calcd 73.19% C, 7.17% H, 14.23% N; found 73.10% C, 7.12% H, 14.32% N.

6 Conclusions

By the means of umpolung reactivity an unusual substitution of quinolizidine enamine skeleton was achieved [2]. Further modification (reduction) of the disubstituted intermediate 1 thus obtained led to intramolecular ring closure and resulted in a new pentacyclic ring system. Utilisation of this method can provide some more new derivatives with heteroatoms O, S in ring E.

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