FISCHER INDOLE SYNTHESIS WITH ALKYL GROUP ELIMINATION: A THREE-STEP PREPARATION OF A PYRIDO[2,3-c]CARBAZOLE DERIVATIVE

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Abstract
An angular tetrahydropyridocarbazole derivative was synthesized in a three-step reaction sequence involving the Fischer Indole cyclization with elimination of a methyl group.

Introduction

Ellipticine and 9-methoxyellipticine are important alkaloids isolated from various plants of the Apocynacea family[1]. The ellipticine derivatives have in common a pyrido[4,3-b]carbazole moiety which is very important for their activities. Since these alkaloids and some of their derivatives exhibit antitumor activity many efforts have been devoted for synthesizing these compounds[1-8].

Continuing our work towards the synthesis of new derivatives of pyridocarbazole having a similar structure to ellipiticine with higher biological properties, we wish to report the preparation of the angular 1,3,5-trimethyl-8,9,10,11-tetrahydro-7H-pyrido[2,3-c]carbazole 7 starting from 2,4,5,8-tetramethylquinoline 4 in a three-step reaction sequence involving an unusual Fischer Indole cyclization with elimination of a methyl group as the key step[9].

Experimental

The infrared spectra were recorded in a Perkin Elmer model 1420 instrument. The nuclear magnetic resonance spectra, ^{1}H and ^{13}C, were obtained from a Varian-Unity Plus instrument with frequency of 300 MHz for ^{1}H and 75,0 MHz for ^{13}C. Elemental analyses were obtained using a Carlo Erba instrument. Low-resolution EIMS were recorded on a Finnigan MAT 711A instrument. The ionization energy used was 70 eV with the source at 200 °C and the accelerating voltage of 8 kV. Samples were introduced by the standard direct insertion probe. FAB positive-ion mass spectra were recorded on a Finnigan MAT-TSQ 70, triple quadrupole mass spectrometer. For FAB analysis, the samples were dissolved in the matrix *m*-nitrobenzyl alcohol (NBA) and were bombarded with energetic fast atom gun. Xenon was used to generate the bombarding atoms and the gun was operated at 2 mA emission, providing fast atoms with

an energy of 10 kV. 2,4,5,8-Tetramethylquinoline **4** was synthesized according to a previous method described in the literature[10].

***6-Nitro-2,4,5,8-tetramethylquinoline* 5.** The compound was recrystallized from ethanol giving 75 % yield; mp 110 °C; IV (KBr) cm^{-1} 2910, 1510, 1330; ^1H NMR ($CDCl_3$) δ 2.70 (s), 2.78 (s), 2.80 (s), 2.86 (s), 7.17 (s), 7.70 (s); ^{13}C NMR ($CDCl_3$) δ 18.61, 19.19, 24.75, 25.45, 122.28, 126.22, 126.77, 127.25, 137.23, 146.46, 148.66, 149.03, 158.96; EILRMS (70 eV) *m/z* (%) M^+ 230 (92), 213 (23), 184 (100), 182 (23), 168 (24), 128 (15), 115 (13). *Anal. Calcd.* for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.08; N, 12.17. Found: C, 67.87; H, 6.03; N, 12.11.

***6-Amino-2,4,5,8-tetramethylquinoline* 6.** The compound was recrystallized from ethanol giving 75 % yield; mp 145 °C; IV (KBr) cm^{-1} 3410-3320, 2900, 2920; ^1H NMR ($CDCl_3$) δ 2.52 (s), 2.60 (s), 2.68 (s), 2.80 (s), 3.70 (sl), 6.99 (sl), 6.96 (sl); ^{13}C NMR ($CDCl_3$) δ 16.22, 18.56, 24.32, 25.42, 111.28, 121.24, 124.84, 127.95, 135.43, 141.35, 142.73, 143.60, 152.56; EILRMS *m/z* (%) M^+ 200 (100), 185 (57), 182 (10), 172 (30), 158 (14), 100 (14). *Anal. Calcd.* for $C_{13}H_{16}N_2$: C, 78.00; H, 8.00; N, 14.00. Found: C, 77.92; H, 8.03; N, 13.87.

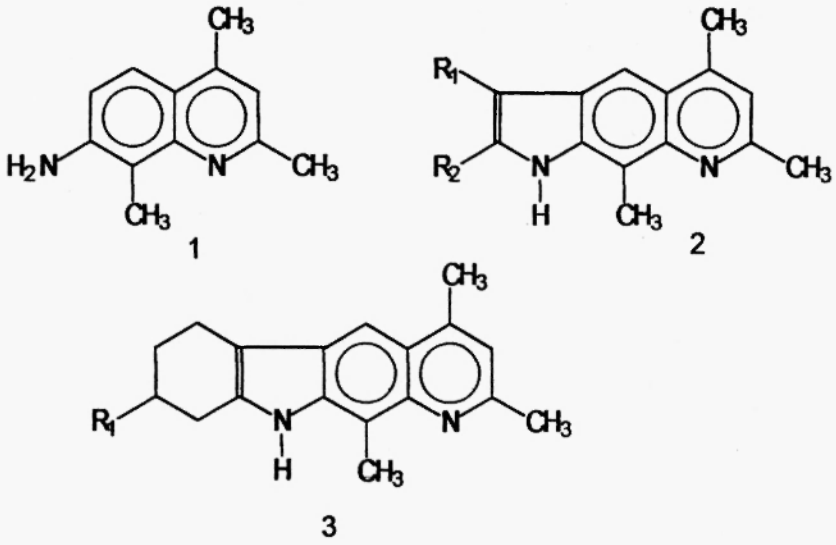
***1,3,5-Trimethyl-8,9,10,11-tetrahydro-7H-pyrido[2,3-c]carbazole* 7.** Compound **7** was isolated and recrystallized from ethanol giving 25% yield; mp 199 °C; IR (KBr) cm^{-1} 3140 (NH), 1590, 1580; ^1H NMR ($CDCl_3$) δ 1.70-2.20 (m, 4H, $2CH_2$), 2.47 (s, 3H, CH_3), 2.67-2.74 (2s, 10H, $2CH_3$, $2CH_2$)), 6.83 (s, 1H, Ar), 7.52 (s, 1H, Ar), 8.40 (l, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ 0.72, 0.85, 1.17, 1.22, 2.36, 19.37, 20.80, 21.95, 22.45, 24.41, 25.40, 25.65, 112.43, 121.05, 122.17, 127.82, 133.01, 139.80 ppm; EILRMS *m/z* (%) 264 (M^+, 100), 265 (18), 266 (2), 263 (21), 236 (85), 205 (3), 186 (10), 185 (12), 132 (18), 118 (30); FABMS *m/z* (%) M^+ 264 (100), $[M + 1]^+$ 265 (87), 263 (50), 236 (40). *Anal. Calcd.* for $C_{19}H_{22}N_2$: C, 82.01; H, 7.91; N, 10.07. Found: C, 81.09; H, 7.85; N, 10.02.

Results and discussion

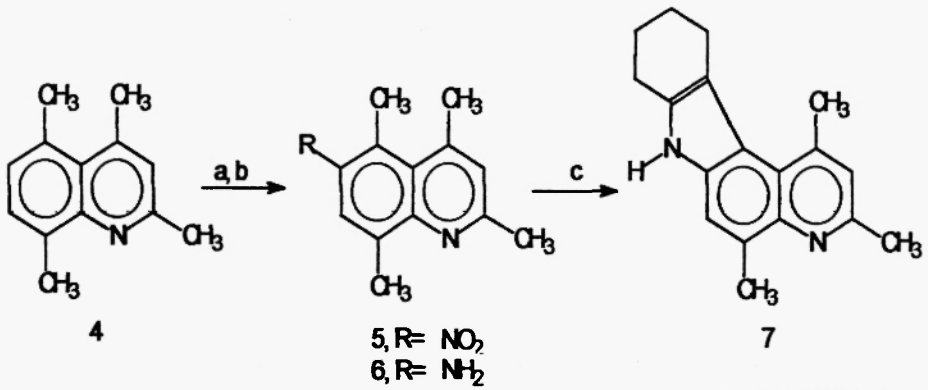
The usual preparations of ellipticine derivatives are based on the well-know Fischer Indole cyclization[11] between an acyclic or cyclic ketone and an appropriated hydrazine derivative of quinoline.

We described in an earlier work[12] a cyclization of the quinoline derivative **1** with acylic ketones giving the pyrroloquinoline **2** while with cyclic ketones afford to the linear ellipticine-like, tetrahydropyridocarbazole **3**.

Since we needed an angular pyrido[2,3-c]carbazole having an extra methyl group at position five we attempted to extend the scope of this reaction using 2,4,5,8-tetramethylquinoline **4**. Initially the quinoline **4** was nitrated to give the nitro derivative **5** which was reduced to the corresponding amino **6**. The later compound was diazotized with $NaNO_2$ and reduced *in situ* with $SnCl_2$ to give the corresponding hydrazine which was reacted with cyclohexanone producing only the angular tetrahydropyrido[2,3-c]carbazole **7**, Scheme **1**.



The cyclization occurred preferentially at position 5 eliminating the methyl group. Although this is an unusual result, similar observation had been already reported in the literature[9]. A probable explanation for this unusual eletrophilic aromatic substitution is the electron-donating effect of the methyl group at position 8.



Scheme 1: Reaction sequence for preparing 7. a- HNO_3/H_2SO_4 ; b- H_2/Pd-C and $NaNO_2/SnCl_2$/cyclohexanone.

Several spectroscopy methods were used to prove the correct structure of 7. The mass spectra data were proven to be very useful and gave the final arguments for this structure. Compound 7 showed high intensity relative abundance in EI spectra for $[M]^{+\cdot}$ 264 (100), consistent with the expulsion of methyl group. The FAB spectra data showed the molecular ion $[M]^{+\cdot}$ 264 (100), the protonated molecule $[M + 1]^+$ 265 (87) and the $[M - 1]^+$ 263 (50) fragment, also in agreement with the structure 7. FAB and EI indicated the presence of a Retro Diels Alder

(RDA) fragmentation *m/z* 236 $[M - 28]^+$ consistent with $[M - C_2H_4]^+$ or $[M - H - HCN]^+$. The ^1H RMN data showed only three signals correspondent to the methyl groups in accordance with the substitution of one methyl in the position 5 of the precursor quinoline. Two protons in the aromatic region were also in agreement with the structure 7.

Conclusion

Only few cases of alkyl elimination during Fischer Indole synthesis have been reported. This Fischer Indole cyclization of 6 with elimination of a methyl group offers an inexpensive and convenient method to obtain 7 as a new angular derivative of pyrido[2,3-c]carbazole system.

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