SYNTHESIS AND CONFORMATIONAL ANALYSIS OF 9,10,11,12,12a,13-HEXAHYDRO-7H-NAPHTHO[1,2-b]-QUINOLIZIDINE

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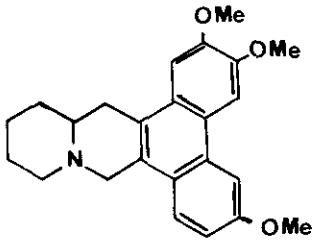
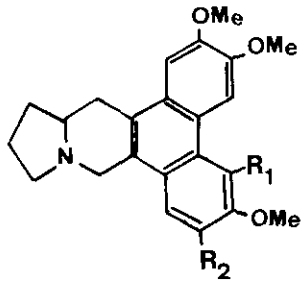
Abstract —— The synthesis of 9,10,11,12,12a,13-hexahydro-7H-naphtho[1,2-b]quinolizine, which has structural similarity to antitumor alkaloid cryptopleurine (1), has been accomplished by a sequence involving as a key step the Friedel-Crafts acylation of 1-(2-naphthylmethyl)pipecolinic acid (9). Ir, ^{1}H, and ^{13}C nmr data indicate a trans-fused quinolizidine conformer for naphtho[1,2-b]quinolizidine (14).

Cryptopleurine (1), first isolated from Cryptocarya pleurosperma (Lauraceae), is known not only by means of its noxious vesicant action[1], but also by its various interesting pharmacological properties, like antiviral[2] and antitumoral[3] activities. This alkaloid along with the structural related tylophorine (2) and tylocrebrine (3) inhibit protein synthesis in eukaryotic cells affecting the EF-2 dependant translocation step by a common mechanism of action[4].

Our previous studies[5] followed the synthesis of cryptopleurine related compounds with a simplier structure, which may allow to recognize a pattern of relationship between the chemical structure of these alkaloids and their inhibitory effect on protein synthesis. One of the criteria used for simplification of the alkaloidal structure in this series was the elimination of either the A or the C benzene ring of the phenenthrene nucleus in ring system 4 with retention of the quinolizidine moiety.

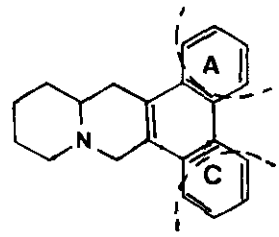


1 cryptopleurine



2 R_1= H, R_2= OMe tylophorine

3 R_1= OMe, R_2= H tylocrebrine



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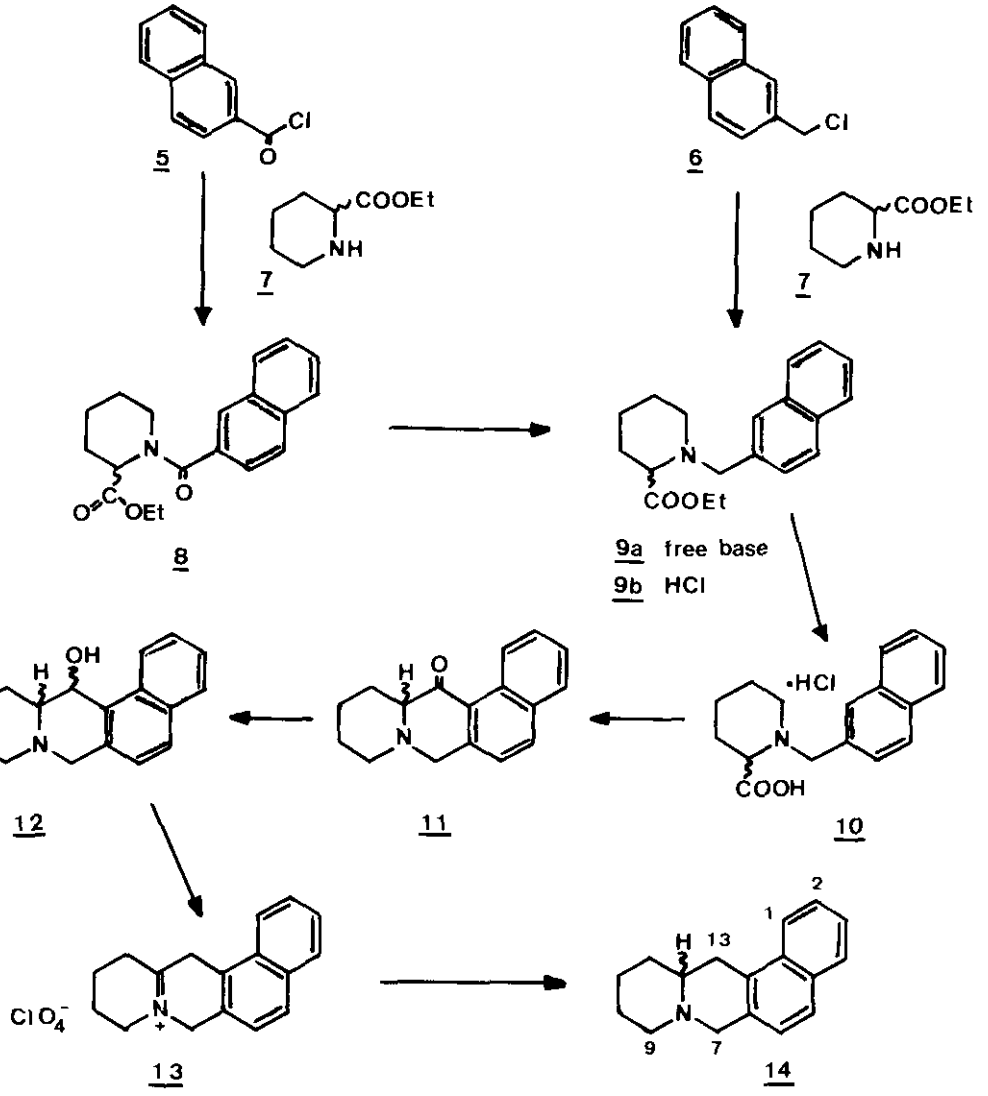
In this outline we considered of interest the preparation of 9,10,11,12,12a,13-hexahydro-7H-naphtho[1,2-b]-quinolizine (14). Only one reduced form of naphtho[1,2-b]quinolizine nucleus, obtained from reduction of the corresponding naphthoquinolizinium salt, has to our knowledge been described[6]. The synthesis of the target compound 14 is depicted in Scheme 1, and was accomplished in accordance with a former synthesis of cryptopleurine[7].

The preparation of ethyl N-(2-naphthylmethyl)-2-piperidinecarboxylate (9) was attempted by two different ways. Thus, condensing the suitable acid chloride 5 with one equivalent of ethyl pipecolinate (7) and 2 equivalents of pyridine in dry toluene at room temperature afforded the amide 8 in 96.5% yield[8], mp 55-57ºC (ether - light petrol). By selective Borch reduction[9] this amide was converted to amino



Scheme 1

ester 9. Namely, O-ethylation with triethyloxonium fluoroborate in dry CH_2Cl_2, followed by sodium borohydride reduction in absolute ethanol at room temperature, gave in our hands the amino ester 9[10] in a surprisingly poor overall yield (53%). Better results were achieved by the alternative method. Thus, the reflux of 2-chloromethylnaphthalene, either with 2 equivalents of 7 in dry benzene for 3 h, or with 1.1 equivalent of 7 hydrochloride in absolute ethanol in the presence of 1.1 equivalent of anhydrous sodium carbonate for 6 h, yielded in both cases 83% of the amino ester 9, which was purified as the hydrochloride 9b, mp 164-166ºC (acetone). Hydrolisis of 9b with concentrated hydrochloric acid afforded the amino acid 10 in 77% yield[11], mp 192-194ºC (hydrochloride).

Cyclization to naphtho[1,2-b]quinolizidin-13-one (11) was brought about through an intramolecular Friedel-Crafts acylation. Thus, stirring the amino acid 10 in polyphosphoric acid under nitrogen atmosphere at 105ºC during 6 h, followed by careful work-up at 20ºC, afforded the unstable solid ketone 11 in 89% yield. As 11 was very sensitive to aerial oxidation, it was characterized only by spectroscopic means[12] and was immediately reduced by sodium borohydride in ethanol to yield 81.4% of a diastereomeric mixture of 12 in a ratio 7/3[13]. The bad solubility of these compounds did not allow a further characterization. Dehydration of 12 proceeded smoothly on reflux with 70% perchloric acid in glacial acetic acid during 1.5 h. The iminium perchlorate 13, whose structure was confirmed by spectroscopical data[14], precipitated from the cold reaction mixture in 90% yield, mp 195ºC (acetic acid). Sodium borohydride reduction of this derivative in ethanol at 0ºC during 0.5 h afforded the naphtho[1,2-b]quinolizidine 14[15] as white needles (85.2%), mp 105-106ºC (ethanol/H_2O).

The most significant feature of nmr spectra of these compounds is the non equivalence of methylene protons between the naphthalene nucleus and the nitrogen atom observed in amino ester 9 and in the tetracyclic bases. The non equivalence of the C-7 axial (ax) and equatorial (eq) protons observed in the benzo[1,2-b]quinolizidine systems[12,15] 11 and 14, whose coupling constants are J = 16 and 15.5 Hz, respectively, has before been described by Johns et al.,[16] at cryptopleurine, and is in accordance with the observations made by Fitzgerald et al.[17], and Hamlow et al.[18], that the ax and eq protons of methylene groups α to the nitrogen in quinolizidines have a marked difference in chemical shift. In accordance with the study carried out by Földéak et al.[19], at phenanthro[9,10-b]quinolizidines, this non equivalence of C-7 protons allows to assign to compound 14 a trans-fused quinolizidine conformer. This is confirmed by means of the strong Bohlmann bands[20] observed in the ir spectra of these compounds.

The ^{13}C chemical shift assignment of 14 was made by coupling constants and from analogy with that of cryptopleurine[21], as well as by comparing chemical shifts of trans-quinolizidine[22] and derivatives[23]. The chemical shifts observed for C-7, C-9, and C-13 are in agreement with a trans-quinolizidine conformation.

For amino ester 9, we can suggest, as it is the case in analogous phenanthrene derivatives[7], that a

preferred orientation of the two methylenic protons concerned relative to the naphthalene ring and the nitrogen lone pair is due to conformational rigidity, probably caused by restricted rotation about naphthalene C-7 bond.

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8. Ir (KBr): 1738 and 1642 cm^{-1}; ^1H-nmr ($CDCl_3$, 60 MHz): δ 7.9 - 7.4 (7H, m, Ar-H), 5.5 (1H, broad s, 2-H), 3.9 - 3 (2H, m, 6-H), 4.25 (2H, q, O-CH_2-), 2.5 - 1.5 (6H, m), 1.3 (3H, t, CH_3).
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10. 9a: Bp 180ºC (0.8 mm, Kugelrohr); ir (NaCl): 1745 sh and 1730 cm^{-1}; ^1H-nmr ($CDCl_3$, 60 MHz): δ 7.85 - 7.25 (7H, m, Ar-H), 4.2 (2H, q, -OCH_2-), 3.94 (1H, d (J = 13 Hz), N-CH_2-Ar), 3.5 (1H, d (J = 13 Hz), N-CH_2-Ar), 3.2 (1H, t, H-2), 2.9 (1H, m, 6-H eq), 2.35 (1H, q, 6-H ax), 2.1 - 1.3 (6H, m), 1.25 (3H, t, -CH_3). 9b: Ir (KBr): 1740 cm^{-1}; ^1H-nmr ($CDCl_3$, 60 MHz): 8.1 - 7.4 (7H, m, Ar-H), 4.75 (1H, d (J = 13 Hz), N-CH_2-Ar), 4.45 (1H, d (J = 13 Hz), N-CH_2-Ar), 4.25 (2H, q, -O-CH_2-), 3.9 - 3.2 (3H, m, 2-H and 6-H), 2.6 - 1.4 (6H, m), 1.25 (3H, t, -CH_3).
11. Ir (KBr): 1725 cm^{-1}; ^1H-nmr (DMSO - d_6, 60 MHz): 8.2 - 7.5 (7H, m, Ar-H); 4.75 (1H, d (J = 13 Hz), N-CH_2-Ar), 4.45 (1H, d (J = 13 Hz), N-CH_2-Ar), 4.1 (1H, m, 2-H), 3.35 (2H, m, 6-H), 2.5 - 1.5 (6H, m).
12. Ir (NaCl): 2802, 2760, and 1670 cm^{-1}; ^1H-nmr ($CDCl_3$, 60 MHz):δ9.45 (1H, dd, 1-H), 7.62 (1H, d, 5-H), 7.15 (1H, d, 6-H), 8 - 7.4 (3H, m, Ar-H), 3.98 (1H, d (J = 16 Hz), 7-H eq), 3.47 (1H, d, (J = 16 Hz), 7-H ax), 3.04 (1H, d (J = 10.5 Hz), 9-H eq), 2.25 (1H, m, 9-H ax), 3.04 (1H, m, 12a-H), 2.8 -1.4 (6H,m).
13. Mp 240-243ºC (DMF); ir (KBr): 3150, 2810, 2760, and 1095 cm^{-1}; t.l.c. (elution with benzene -methanol- - ethanol (20 : 1: 1)) Rf_1 = 0.03 (30 %); Rf_2 = 0.19 (70 %); ms: 253(M^+, 17), 170(14), 169(17),

142(12), 141(27), 115(13), 84(100).

14. Ir (KBr): 1710 and 1080 cm^{-1}; ^{1}H-nmr (DMSO-d_6, 60 MHz):δ7.39 (1H, d, 6-H), 8.1 -7.3 (5H, m, Ar-H), 5.1 (2H, m, 7-H), 4.45 (2H, m, 13-H), 3.9(2H, m, 9-H), 3.05 (2H, m, 12-H), 1.92 (4H, m).

15. Ir (KBr): 2808, 2745, and 1610 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 80 MHz):δ6.85 (1H, d, 6-H), 7.7 - 7 (5H, m, Ar-H), 3.86 (1H, d (J = 15.5 Hz), 7-H eq), 3.38 (1H, d (J = 15.5 Hz), 7-H ax), 3.15 (1H, d (J = 11 Hz), 9-H eq), 3 - 2.75 (2H, m, 12a-H and 13-H eq), 2.37 - 2.05 (2H, m, 9-H ax and 13-H ax), 2 - 1.3 (6H, m); ^{13}C-nmr ($CDCl_3$, 80 MHz): δ(ppm) 122.64 (C-1, d, J = 157 Hz), 125.85 (C-2 and C-3, d, J = 160 Hz), 128.36 (C-4, d, J = 158 Hz), 131.4* (C-4a, s), 124.83 (C-5, d, J = 161 Hz), 124.71 (C-6, d, J = 160 Hz), 128.6 (C-6a, s), 58.73 (C-7, t, J = 132 Hz), 55.94 (C-9, t, J = 131 Hz), 25.80 (C-10, t, J = 129 Hz), 24.24 (C-11, t, J = 128 Hz), 33.72 (C-12 and C-13, t, J = 126 Hz), 57.98 (C-12a, d, J = 131 Hz), 132.2* and 131.6* (C-13a and C-13b, s); ms: 237(M^+, 56), 236(76), 180(10), 165 (7), 155(21), 154(100), 153(25), 152(16), 139(4), 115(4), 82(6).

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