SYNTHESIS OF 5,6,9,10,11,11a-HEXAHYDRO-8H-NAPHTHO[2,1-a]QUINOLIZINE

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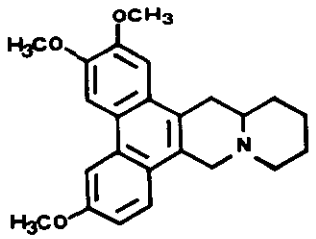
Abstract——Naphtho[2,1-a]quinolizidine was synthesized by the reaction of 1,2-dihydrobenz[f]isoquinoline with methyl vinyl ketone. The heterolytic fragmentation of 10-p-tosyl-5,6,9,10,11,11a-hexahydro-8H-naphtho[2,1-a]quinolizine (11) is described.

Biochemical studies of protein synthesis inhibitors in eukaryotic cells strongly indicate that the mechanism of action of cryptopleurine (1) is very similar to that of emetine (2) and related compounds[1,2] although these alkaloids belong to two different chemical families. These observations have led us to investigate the possible common structural determinants shared by the two different groups of alkaloids, which may be responsible for their biological activity.[3,4] In this outline we considered the synthesis of 5,6,9,10,11,11a-hexahydro-8H-naphtho[2,1-a]quinolizine (3) as a structural approach to both families of alkaloids.



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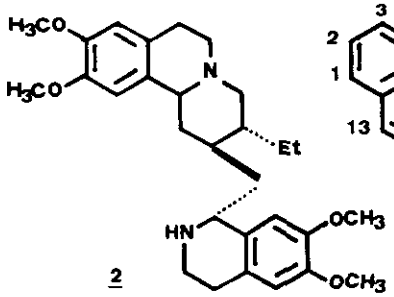

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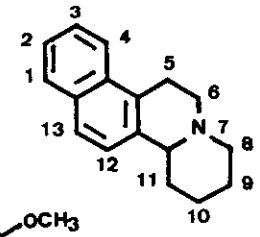

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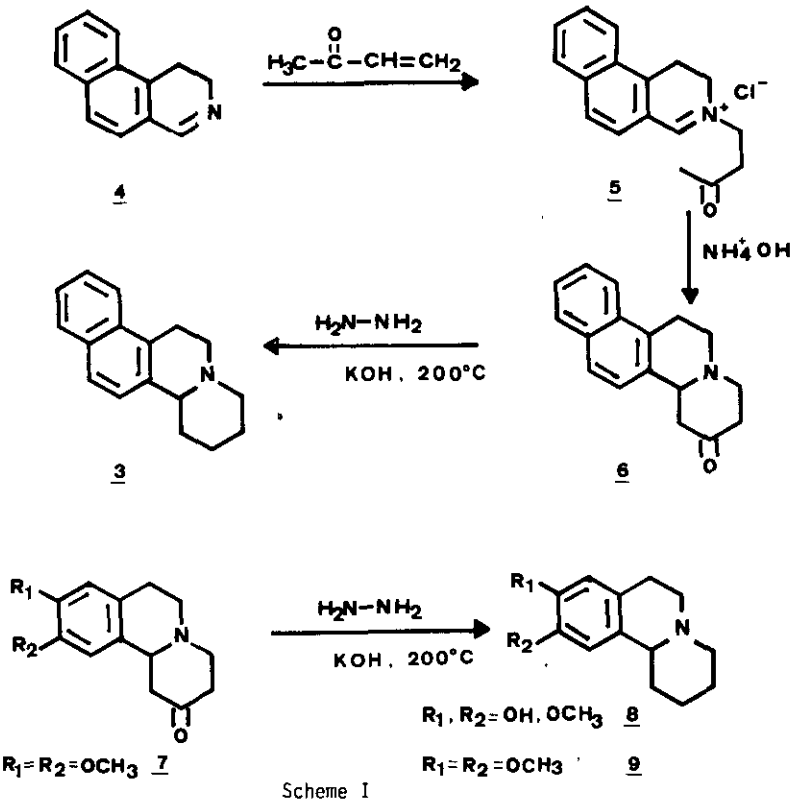
The fact that this compound is a 13-aza-D-homo analogue of equilenin has led to two different synthetic schemes of naphto[2,1-a]quinolizidines.[5,6] In view of the current interest in this nucleus, we achieved a short synthesis of (3) taking essentially advantage of some previous synthesis *reported* [7,8] *for benzo[a]quinolizidin-2-ones, which involve a condensation of* 3,4-dihydroisoquinoline with methyl vinyl ketone or its synthetic precursors (Scheme 1).



Scheme I

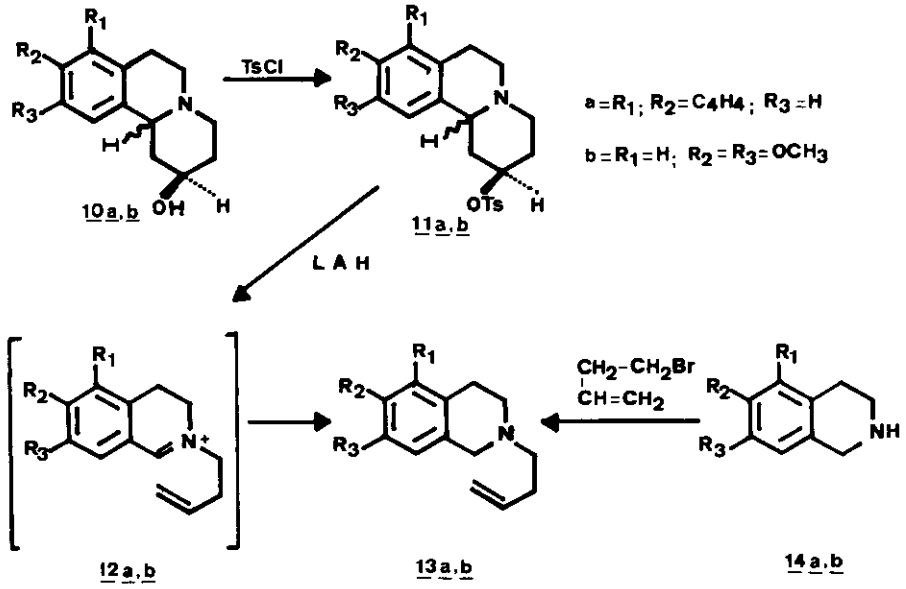
The starting 1,2-dihydrobenz[f]isoquinoline (4) was easily obtained in high yield from N-[2-(α-naphthyl)ethyl] formamide through Bischler-Napieralski cyclization as described by Kessar et al.[9]

The condensation of (4) to afford the tetracyclic aminoketone (6) was achieved by a two-step reaction as described by Beke et al.[7] Namely, refluxing of 1,2-dihydrobenz[f]isoquinoline hydrochloride in methyl vinyl ketone for 1 h gave 1,2-dihydro-3(3-oxobutyl)benz[f]isoquinolinium chloride (5) as a solid, which was washed with acetone, dissolved in water, and without further purification, basified with concentrated NH_4OH, affording the aminoketone (6) in 64 % overall yield, mp 128-130°C (ethanol/H_2O).[10] Attempts to condense (4) with 4-dimethylamino-2-butanone, as described by Whittaker[8] for benzo[a]quinolizidines, resulted in a tarry gum, which could not be purified.

Transformation of the aminoketone (6) into the naphtho[2,1-a]quinolizidine (3) was carried out smoothly through Huang-Minlon reduction. Thus, after refluxing (6) in a mixture of potassium hydroxide, hydrazine hydrate, and ethylene glycol for 1 h, water was distilled off and the residue was heated to 200°C for 6 h. Usual work-up afforded an oil, which was extracted with light petrol to yield (3) (90 %).[11]

Attemps to apply the same Huang-Minlon reduction to 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-one (7) led, as expected, to a monodemethylated benzo[a]quinolizidine (8) in 48 % yield, mp 185-187°C (isopropanol).[12] Treatment of (8) with diazomethane gave the dimethoxy

derivative (9),[13] which was characterised as the hydrochloride, mp 232-234°C (isopropanol). Application of a more gentle reduction process to convert the aminoketone (6) or (7) into (3) or (9) failed to give the expected amines. Thus, the reduction of (6) with sodium borohydride or lithium aluminium hydride led almost exclusively[14] to 5,6,9,10,11,11a-hexahydro-8H-naphtho[2,1-a]quinolizin-10β(eq)-ol (10)[15] which was converted to the tosylate (11a)[16] by usual methods. Further reduction of (11a) or (11b) with an excess of lithium aluminium hydride in dry ether afforded the unexpected ring-cleaved compound (13a)[17] or (13b).[18]



It is known[19] that amines with nucleofugal substituents in the β-position can react in several ways. The aminotosylates (11a) and (11b) probably underwent in the reduction process a heterolytic fragmentation into an immonium salt and an olefin since the structural and electronic requirements of the compounds allow both a two-step carbocation mechanism and a synchronous fragmentation mechanism.

The intermediates (12a) and (12b) so formed suffered a further reduction to (13a) and (13b) with an excess of lithium aluminium hydride. Support to the latter structures was secured as in the sequel. The tetrahydroisoquinolines (14a)[20] and (14b) were condensed with 4-bromo-1-butene in dry toluene for 4 h, affording after usual work-up compounds (13a) and (13b), respectively.[21]

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10. 6: Ir (KBr): 2810, 2760, and 1715 cm^{-1}. ^1H-nmr ($CDCl_3$, 90 MHz): δ 8-7.3 (5H, m, Ar), 7.1 (1H, d, H-12), 3.67 (1H, dd, H-11a), 3.35-2.2 (10H, m); ms, m/z (%): 251(M^+, 60), 250(100), 208(29), 181(35), 180(30), 165(11), 152(12); ^{13}C-nmr ($CDCl_3$, 80 MHz): δ (ppm) 208.39 (C-10, s), 131.97* and 131.87* (C-4a and C-13a, s), 129.59 (C-11b, s), 129.38 (C-4b, s), 128.26 (C-1, d, J = 159 Hz), 126.55 (C-13, d, J = 161 Hz), 126.28* and 125.54* (C-2 and C-3, d, J = 161 Hz), 122.95 (C-4, d), 122.82 (C-12, d, J = 158 Hz), 61.90 (C-11a, d, J = 131 Hz), 54.43 (C-8, t, J = 134 Hz), 49.96 (C-6, t, J = 133 Hz), 47.17 (C-11, t, J = 130 Hz), 40.81 (C-9, t, J = 130 Hz), 26.49 (C- 5, t, J = 128 Hz). Carbon signals marked in the table with * could not be assigned with certainty.
11. 3: Mp 87-89°C; ir (KBr): 2860, 2800, 2760, 2742 cm^{-1}. ^1H-nmr ($CDCl_3$, 90 MHz): δ 7.9-7.3 (4H, m, ArH), 7.65 (1H, d, H-13), 7.25 (1H, d, H-12), 3.55 (1H, m, H-11a), 3.3-1.4 (12H, m); ms, m/z (%): 237(M^+, 57), 236(100), 208(46), 195(11), 181(32), 180(42), 165(18), 152(21); 3: HCl salt: mp 315°C (nitromethane); ^{13}C-nmr ($CDCl_3$, 80 MHz): δ (ppm) 135.56 (C-11b, s), 132.22* and 131.92* (C-4a and C-13a, s), 129.71 (C-4b, s), 128.16 (C-1, d, J = 160 Hz), 125.94 (C-13, d, J = 162 Hz), 125.94 (C-2, d, J = 160 Hz), 125.09 (C-3, d, J = 161 Hz), 123.30 (C-12, d, J = 159 Hz), 123 (C-4, d), 63.80 (C-11a, d, J = 131 Hz), 56.70 (C-8, t, J = 134 Hz), 52.15 (C-6, t, J = 131 Hz), 31.42 (C-11, t, J = 127 Hz), 26.48 (C-5, t, J = 128 Hz), 25.27 (C-9 and C-10, t, J = 128 Hz).
12. 8: Ir (KBr): 2930, 2810, 2750, 2580, 1615, 1535, 1445, 1335, 1265, 1225, 1170 cm^{-1}. ^1H-nmr ($CDCl_3$, 60 MHz): δ 8.5 (1H, ws, ArOH), 6.55 and 6.5 (2H, 2s, 8H and 11H), 3.68 (3H, s, OCH_3), 3-1.3 (13H, m); ms, m/z (%): 233(M^+, 23), 232(53), 218(7), 204(53), 191(28), 189(12), 177(100),

176(43), 162(55), 133(25), 116(27), 103(33), 91(55), 77(67).

13. J. Gootjes and W. T. Nauta, Rec. Trav. Chim. Pays Bais., 1965, 84, 1183, lit. mp: 234-235°C, (HCl salt).
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15. 10: Yield 95 %; mp 201-202°C (ethanol); ir (KBr): 3150, 2810, 2760, 2710 and 1080 cm^{-1}. ^{1}H-nmr (DMSO-d_6, 60 MHz): δ 8-7.5 (5H, m, ArH), 7.4 (1H, d, H-12), 4.82 (1H, m, H-10), 3.75-1.3 (11H, m), 3.45 (1H, s, OH); ms, m/z (%): 253(M^+, 68), 252(100), 236(34), 208(45), 195(33), 181(38), 180(26), 165(11), 152(10).
16. 11a: Yield 50 % for analytically pure product; ir (KBr): 1800, 1750, 1595, 1355, 1175, 945 cm^{-1}.
17. 13a: HCl salt: yield 76 %; mp 220-223°C (isopropanol); ir (KBr): 3060, 2920, 2680, 2480, 1645, 1605, 1520, 1445, 1430, 1100 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 60 MHz): δ 7.9-7.3 (5H, m, ArH), 7.2 (1H, d, 5-H), 5.75 (1H, m, 3'-H'), 5.05 (1H, dd, J = 16.5 Hz, 4'-H), 4.95 (1H, dd, J = 11 Hz, 4'-H), 3.8 (2H, s, 4-H), 3.1 (2H, t, J = 6 Hz, 2H), 2.78 (2H, t, J = 6 Hz, 1H), 2.35 (4H, m, 1'-H and 2'-H).
18. 13b: HCl salt: yield 68 %; mp 220-222°C (ethanol); ir (KBr): 3060, 2920, 2835, 2560, 1645, 1612, 1520, 1465, 1365, 1260, 1230, 1120 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 90 MHz): δ 6.65 (2H, s, 5-H and 8-H), 5.67 (1H, m, 3'-H), 5.18 (1H, J = 14.5 Hz dd, 4'-H), 5.12 (1H, J = 8.5 Hz, dd, 4'-H), 4.3 (2H, bs, 1-H), 3.84 (6H, s, 2-OCH_3), 3.45 (2H, bm, 3-H), 3.18 (4H, m, 4H and 1'-H), 2.78 (2H, m, 2'-H); ^{13}C-nmr ($CDCl_3$, 80 MHz): δ (ppm) 132.22 (C-3', d), 118.45 (C-4', t), 111.50 (C-5, d), 109.76 (C-8, d), 56.02 and 55.91 (C-6 and C-7, s), 53.76 (C-1, t), 51.81 (C-3, t), 48.94 (C-1', t), 28.19 (C-4, t), 23.83 (C-2', t); ms, m/z (%): 247(M^+, 4), 246(3), 207(14), 206(100), 191(3), 190(5), 174(7), 165(9), 164(9), 149(11), 121(11), 97(15), 91(11), 83(20), 81(30), 77(9).
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20. 14a: bp 155°C (0.1 mm, Kugelrohr); 14a HCl: mp 219-220°C (water); ir (KBr): 3260, 2880, 2830, 1605, 1510, 1395 cm^{-1}. ^{1}H-nmr ($CDCl_3$, 60 MHz): δ 7.7-7.2 (5H, m, Ar-H), 6.7 (1H, d, 5-H), 3.7 (2H, s, 4-H), 2.9-2.4 (4H, m, 1-H and 2-H), 1.25 (1H, s, N-H).
21. 13a: HCl salt: yield 47 %; mp and mixed mp 220-223°C. 13b: HCl salt: yield 45 %; mp and mixed mp 220°C.

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