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Synthesis of the New (Cyclopenta [b]pyrrolo[1,2-d])azepino[4,5-b]indole Ring System

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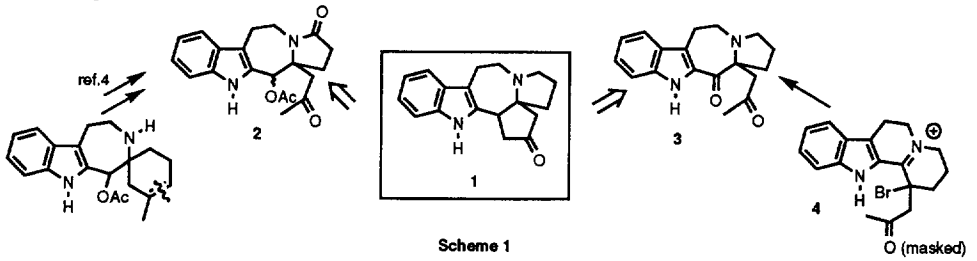
Abstract : *The 2-oxo functionalized title compound 1 was synthesised in 7 steps from tryptamine via rearrangement of the bromoiminium ion 13 in alkaline medium to azepinone 14 with concomitant formation of ketone 15. The ratio 14:15 was shown to depend on the nature of the hydroxide counter-ion.* Copyright © 1996 Published by Elsevier Science Ltd

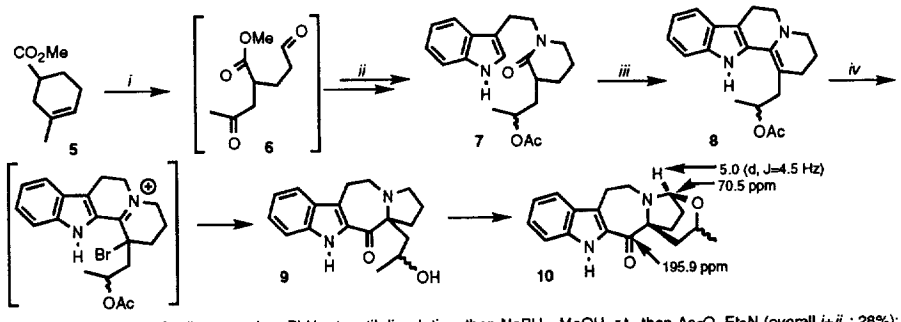
As part of our work on indole analogues of the derivatives of cephalotaxine, we recently reported[4] the synthesis of **2**, as a possible intermediate towards the hitherto unknown indole pentacycle **1** (Scheme 1). Unfortunately we were unable to improve the yield of the last stage of our synthesis and so we decided to follow a more conventional route to the pyrroloazepinoindole ring system of the target compound **3**, *i.e.* Duhamel's[5] oxidative rearrangement of α-bromoiminium ion **4** that was also used by Buzas[6] and Husson[7] to transform indoloquinolizidines into pyrroloazepinoindoles. This route requires protection of the side chain carbonyl group.



Scheme 1

The non-tryptamine carbons of the molecules were first derived from ester **5**,[8] (Scheme 2) which was transformed in 3 steps into enamine **8**, *via* oxidation to the tricarbonyl derivative **6**, regioselective reductive cyclisation to **7**, and finally Bischler-Napieralski ring closure. Under Buzas' conditions, (Br_2, then KOH-H_2O), **8** smoothly gave the rearranged hydroxyketones **9**,[9] which, unfortunately, could not be oxidised to the target ketone **3**. It appears that the position α to nitrogen in the pyrrolidine ring is extremely prone to oxidation and we observed formation of the amino-ether **10** in 81% yield (catalytic tetra-*n*-propylammonium tetraoxoruthenate, 4-methylmorpholine-N-oxide, 1 eq., CH_2Cl_2, 20°C, 16 h).

To avoid the problem of oxidation we chose to introduce the acetonyl side-chain in the protected form of a halogeno-propenyl substituent (Scheme 3). The yellow bromo-iminium ion **13a** was prepared in 3 steps



i : O_3, -70°C, then Me_2S; *ii*: tryptamine, PhH, r.t. until dissolution, then $NaBH_4$, MeOH, r.t., then Ac_2O, Et_3N (overall *i+ii* : 28%); *iii* : $POCl_3$, 60°C then 30% aqueous NH_3 (94%); *iv* : Br_2 1 eq., THF, -70°C, then KOH 2 eq. in H_2O.

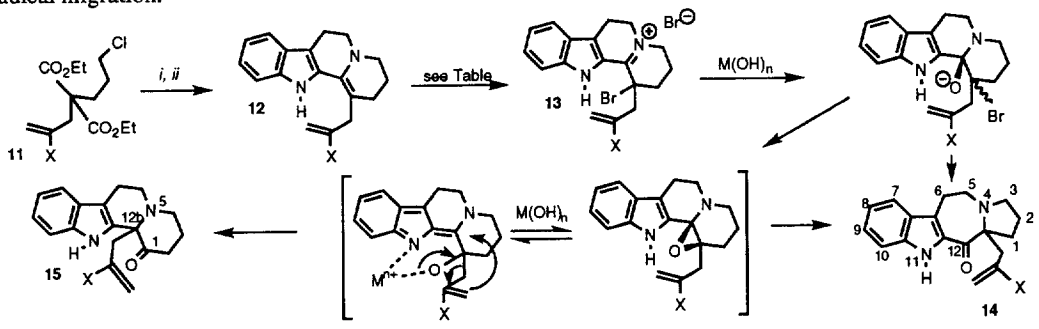
Scheme 2

from tryptamine and chloro-diester **11a**[10] in 59% overall yield, *via* enamine **12a**[11], following a similar strategy as above; the yield was slightly higher (67%) in the **b** bromo-series. Unfortunately, the rearrangement step did not proceed cleanly as before. The expected azepinone **14a**[12] (25%) was accompanied by a new rearrangement product **15a**[13] (30%). Such a rearrangement has not been previously observed by us or others (for a range of substituents : H, Et, 2-alkoxypropyl...) and we suppose that it is due to the nature of the side chain giving rise to a [2,3] allylic transposition instead of a classical [1,2] Wagner-Meerwein radical migration.

Table : Rearrangement of bromoiminium ion **13**

Entry	X	M^{n+}	**14**§	**15**§
1	Cl	K	25	30
2	Cl	K(*)	18	1
3	Cl	Cs	9	37
4	Cl	Li	62	12
5	Cl	Mg	31	1
6	Cl	Ba	37	16
7	Br	Li	46	10
8	Br	Ba	23	26

§ : isolated yield from **12**, (*) : 1 eq. 18-C-6



a : x=Cl **b** : x=Br *i* : tryptamine, K_2CO_3 1.1 eq., *iso*-amylalcohol, reflux, 72 h (75%); *ii* : $POCl_3$ 1.5 eq., toluene, reflux, 5 h (85%).

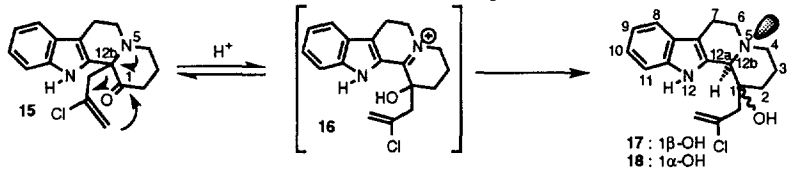
Scheme 3

It was soon apparent that the hydroxide counter-ion plays an important role in the course of the rearrangement : the addition of a selective cryptand for K^+ (entry 2) considerably reduced the formation of **15a**, in favour of the desired ketone **14a**. CsOH favored **15a** (entry 3), but LiOH finally gave quite good selectivity for **14a**.[14] The same result was obtained with the divalent cations Mg^{++} and Ba^{++}, (entries 5 and 6) but the overall yields were lower, relative to Li^+. It is noteworthy that, in contrast to **14**, **15** was never isolated in more than 50% yield. All these facts can be explained as follows : under the action of the metal hydroxide $M(OH)_n$, both *cis* and *trans* bromohydrins are formed, whose oxyanionic forms can rearrange to **14**. Only the *trans* one (C1-αBr) can give rise to an epoxyamine which either rearranges (Stevens *et al*[15]) to

ketone **14** or equilibrates with a metal-chelated form. In these intermediates, hard cations (Li^+, Mg^{++}) strongly interact with the oxygen site and increase its stability.

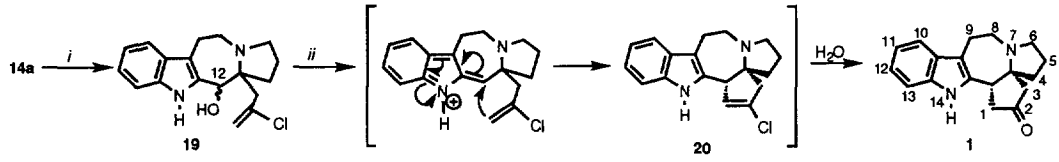
In contrast, larger cations like Cs^+ allow the alkoxide to induce the allylic rearrangement to **15**. As the Br-series (entries 7 and 8) did not give any improvement in yield or selectivity, the following work was carried out with the cheaper chloro-compounds.

Whatever the cation, we were unable to avoid completely the formation of **15**, and we speculated that it could be further rearranged to an indolopyrroloazepine system by reductive N5-C12b bond cleavage of the α-aminoketone and N5-C1 bond formation in Zn-AcOH.[16] Under these conditions (Zn powder 12 eq., AcOH, reflux 2 h), we found that **15a** gave rise only to a mixture of the alcohols **17** (less polar, 69%) and **18** (more polar, 11%).[17] Obviously, nitrogen did not directly attack C1=O. First, an allylic rearrangement of the side chain occurred to iminium ion **16**, which was further reduced to **17**+**18** whose structures were established by extensive COSY, HMBC and HMQC NMR measurements. Bohlman's bands[18] between 2780 and 2750 cm^{-1} in their IR spectra showed that both isomers **17**and **18** are *trans*-quinolizidines.



Scheme 4

As ketone **15a** was not useful for our purpose, we concentrated our attention on azepinone **14a**, which was cleanly converted to ketone **3** in 84% yield (mercuric acetate 1.1 eq., 88% formic acid, 0°C, 15 min then r.t., 3 h, H_2S gas). Unfortunately all attempts at ring-closure to the target pentacycle failed, probably on account of the low reactivity of the indole-deactived C12=O, and the sensitivity of β-aminoketones to acid or alkaline conditions (*retro*-Mannich). However reduction of **14a** gave a mixture of alcohols **19** which underwent rapid intramolecular cyclisation in acidic medium. The reaction was conveniently carried out in a degassed 95% solution of H_2SO_4, leading directly to the pentacyclic ketone **1**[19] (75-80%), sometimes accompanied by the intermediate chloro-olefin **20** (0-5%).



i : $NaBH_4$ 2eq., MeOH, r.t., 24h (98%); *ii* : 95% H_2SO_4, 0°C (15 min) then r.t. (4h).

Scheme 5

Work is currently in progress on the oxidation of the 1-position, and on the extension of this work to the cephalotaxane skeleton.

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2. Present adress : Université d'Angers (France).
3. Present adress : Medical University of Shanghaï (People's Republic of China).
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8. Obtained by chromic oxidation of 3-methyl-1-formylcyclohex-3-ene (ref.4) and esterification by MeOH-HCl.
9. All new compounds were characterized by UV, IR, ^{1}H and ^{13}C NMR, HRMS or elemental analysis.
10. Prepared in two steps as follows : *i* : Na 1 eq., EtOH, diethyl malonate 1 eq., r.t. 30 min then 2,3-dichloropropene 1.1 eq., r.t., 96 h; *ii* : NaH 1 eq., 1-bromo-3-chloropropane 1 eq., THF, reflux, 48 h; overall yield 64 %.
11. **12a**: mp 77°C; UV (MeOH) 229, 308, 318 nm
12. **14a**: mp 142°C; UV (MeOH) 208, 238, 314 nm; IR (KBr) 3325, 1610 cm^{-1};^{1}H NMR ($CDCl_3$) δ 9.25 (br s, NH), 7.65 (d, J = 7, C7-H), 7.45-7.30 (m, C9-H, C10-H), 7.12 (m, C8-H), 5.32 and 5.25 (s, CH_2=), 3.60-3.40 (m, C5-H_2, C6-H), 3.15-2.95 (m, C3-H_2, C6-H', CH_2CCl), 2.30-2.20 (m, C1-H'), 2.15-2.00 (m, C1-H), 2.00-1.80 (m, C2-H), 1.70-1.60 (m, C2-H'); ^{13}C NMR ($CDCl_3$) δ 201.0 (C12), 138.9 (CCl), 136.9 (C10a), 132.0 (C11a), 127.7 (C6b), 126.7 (C9), 123.6 (C6a), 121.7 (C8), 120.1 (C7), 116.5 (CH_2=), 111.9 (C10), 75.0 (C12b), 48.9 (C3), 45.8 ($\underline{C}H_2$-CCl), 44.7 (C5), 37.5 (C1), 25.0 (C2), 22.4 (C6).
13. **15a**: mp 153°C; UV (MeOH) 224, 284, 293 nm; IR (KBr) 3370, 1700 cm^{-1};^{1}H NMR ($CDCl_3$) δ 8.22 (br s, NH), 7.50 (d, J=7, C8-H), 7.30 (d, J=7, C11-H), 7.15 (t, J=7, C10-H), 7.10 (t, J=7, C9-H), 5.30 and 5.20 (s, CH_2=), 3.65 (d, J=14, C2-H), 3.45 -3.30 (ddd, J=14, J=12, J=4.5, C2-H'), 3.30 -3.15 (dd, J=14, J=5, C3-H), 3.15 -2.90 (m, C4-H_2, C6-H_2), 2.80 - 2.65 (m, C7-H), 2.65 - 2.50 (dd, J=14, J=4.5, C3-H'), 2.45 - 2.15 (m, CH_2-CCl), 2.00 -1.80 (m, C7-H'); ^{13}C NMR ($CDCl_3$) δ 210.3 (C1), 138.2 (CCl), 135.8 (C11a), 130.4 (C12a), 127.3 (C7b), 122.2 (C10), 119.5 (C9), 118.3 (C8), 115.6 (CH_2=), 111.1 (C11), 107.9 (C7a), 69.7 (C12b), 47.8 (C4), 47.0 (C6), 46.5 (C2), 37.9 ($\underline{C}H_2$-CCl), 21.8 (C7), 16.5 (C3).
14 Reaction performed in 2 steps : *i* : Br_2 1 eq., THF, -70°, 1 h; *ii* : LiOH 2eq., H_2O, r.t., 2 h then reflux 4 h .
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17 We assume that the major product **17** has the chloropropenyl chain equatorial. This is supported by the NMR shielding (approx. 0.8 ppm) of C12b-H in **17** relative to **18**, due to the influence of the allylic π system. **17**: mp 188°C; UV (MeOH) 225, 281, 290 nm; IR (KBr) 3431, 3275, 2942, 2820, 2754 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10 (br s, NH), 7.50 (d, J=7, C8-H), 7.35 (d, J=7, C11-H), 7.0 (t, J=7, C10-H), 6.95 (t, J=7, C9-H), 5.30 (m, C=CH_2), 3.25 (s, C12b-H), 3.05 -2.90 (m, C4-H, C6-H), 2.81 and 2.15 (d, J=14, CH_2-C1), 2.80-2.70 (m, C7-H), 2.65-2.45 (m, C7-H', C6-H'), 2.40-2.25 (m, C4-H'), 2.25-2.15 (m, C2-H), 1.80-1.65 (m, C3-H), 1.65-1.45 (m, C3-H', C2-H'); ^{13}C NMR (DMSO-d_6) δ 138.7 (CCl), 135.9 (C11a), 132.2 (C12a), 126.6 (C7b), 121.3 (C10), 118.9 (C9), 117.9 (C8), 116.6 ($\underline{C}H_2$=C), 110.9 (C11), 110.0 (C7a), 74.6 (C1), 68.1 (C12b), 55.7 (C4), 53.1 (C6), 41.9 (C13), 36.5 (C2), 23.3 (C3), 21.6 (C7). **18**: mp 189°C; UV (MeOH) 225, 281, 290 nm; IR (KBr) 3362, 2932, 2820, 2787 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.05 (br s, NH), 7.45 (d, J=7, C8-H), 7.30 (d, J=7, C11-H), 7.15 (t, J=7, C10-H), 7.05(t, J=7, C9-H), 5.45 and 5.35 (s, C=CH_2), 4.05 (s, C12b–H), 3.25 (d, J=14, CCl-CH), 3.25-3.15 (m, C6-H), 3.15-2.95 (m, C6-H', C7-H), 2.90 (d, J=14, CCl-CH'), 2.85-2.70 (m, C4-H), 2.65-2.50 (m, C4-H', C7-H'), 1.80-1.70 (m, C2-H, C3-H), 1.70-1.50 (m, C2-H', C3-H'); ^{13}C NMR (DMSO-d_6) δ 137.7 (CCl), 135.3 (C11a), 131.6 (C12a), 126.8 (C7b), 121.3 (C10), 119.0 (C9), 117.8 (C8), 117.5 ($\underline{C}H_2$=C), 110.9 (C11), 74.5 (C1), 66.7 (C12b), 51.8 (C6), 46.9 (C4, CCl-$\underline{C}H_2$), 31.9 (C2), 22.5 (C3), 17.9 (C7).
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19. **1**: oil; UV (MeOH) 225, 283, 291 nm; IR (film) 3400, 2930, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.12 (br s , NH), 7.47 (d, J=7, C10-H), 7.25 (d, J=7, C13-H), 7.15 (dd, J=7, J=1.5, C12-H), 7.08 (dd, J=7, J=1.5, C11-H), 3.65 (t, J=7, C14b-H), 3.35 - 2.85 (m, C1-H_2, C6-H_2, C9-H_2), 2.70 (d, J=17, C3-H), 2.17 (d, J=17, C3-H'), 2.05 - 1.70 (m, C4-H_2, C5-H_2); ^{13}C NMR ($CDCl_3$) δ 216.1 (C2), 135.2 (C13a), 133.1 (C14a), 129.0 (C9b), 121.6 (C12), 119.2 (C11), 118.0 (C10), 111.1 (C9a), 110.4 (C13), 69.8 (C-3a), 53.2 (C6), 46.1 (C8), 45.9 (C14b), 45.8 (C3), 45.7 (C1), 40.8 (C4), 23.7 (C5), 21.7 (C9).

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