ON THE SYNTHESIS OF THE OXINDOLE ALKALOID: 
(±)-HORSFILINE

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Abstract—Two syntheses of the title compound [(±)-1a] have been described: the first one is based upon the oxidatively rearrangement of 7-methoxy-N-methyltetrahydro-γ-carboline (6a), while the second path involves a spirocyclization between 2-oxo-5-methoxytryptamine (18a) and formaldehyde.

(-)-Horsfiline (1a) is a simple oxindole alkaloid, isolated from Horsfieldia superba. Its structure has been proved by synthesis of the racemate through oxidation of 2a, followed by acidic rearrangement of the acetoxyindolenine intermediate (3a). A new synthesis of (±)-1a along a radical cyclization strategy has also been reported. Demethoxyhorsfiline (1b) had been obtained from 4b chloroindolenine by thallium ethoxide assisted rearrangement and subsequent hydrolysis.

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\begin{align*}
2a & \quad R : \text{OCH}_3 & & 3a & \quad R : \text{OCH}_3, X : \text{OAc} \\
2b & \quad R : \text{H} & & 4b & \quad R, X : \text{Cl} & \quad 5b & \quad R : \text{OCH}_3 \\
1a & \quad R : \text{OCH}_3 & & 1b & \quad R : \text{H}
\end{align*}
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Scheme 1.
The spiroindolenine ring system in 5b is accessible by oxidative rearrangement of tetrahydro-γ-carboline (6b), as well (Scheme 2). Indeed, Hershenson prepared 13b and 15b from chloroindolenine (8b) upon basic treatment. Prolonged reaction of 6b with t-BuOCl alone furnished chloroindole derivative (12b), which could subsequently be transformed into 13b and 15b by sodium methoxide in refluxing methanol. Mechanistic explanation for the formation of the chloropyrimido[1,6-a]indole core would involve a retro-Mannich reaction via the intermediacy of 10b. Similarly, 14b has been obtained along the attempted purification of chloroindolenine (9b) on silica gel.

Here we report two alternative routes, using a) oxidative rearrangement of tetrahydro-γ-carboline (6a) and b) spirocyclization, starting from the appropriate 2-oxotryptamine.

Chlorination of 6a with t-BuOCl smoothly led to the non-isolable chloroindolenine (8a), which was then rearranged to indoxyl (15a) in aqueous acetic acid. Treatment of 8a with aqueous methanolic NaOH resulted in the formation of (±)-horsfiline (1a) (13%), its corresponding imidoether (15a) (9%) and the chloropyrimido[1,6-a]indole (12a) (41%). It is worth noting that the chloro substituent survived the basic treatment in methoxy series (12a), while it had suffered nucleophilic displacement in demethoxy series (13b). Compound (12a) could be transformed into (±)-1a in sodium methoxide-methanol, followed by acid hydrolysis. These transformations allowed the preparation of (±)-horsfiline (1a) from 6a with 52% overall yield (Scheme 3).
In continuation with previous studies\(^\text{15}\) on the synthesis of indole alkaloids starting from 2-oxo-tryptamine, we turned to the straightforward cyclization with formaldehyde (Scheme 4).

2-Oxo-5-methoxytryptamine (18a)\(^\text{16}\) was obtained (64\%) from 17a by the DMSO-HCl oxidation method,\(^\text{17}\) along with some 3-hydroxy derivative (19a).\(^\text{18}\) Otherwise, this latter could quantitatively be prepared from 18a with t-BuOOH. Cyclization of 18a with paraformaldehyde in refluxing acetic acid afforded a water soluble product (20a), which was isolated and characterized in diacetylated form 22a.\(^\text{19}\) \(N_\text{a}\)-Hydroxymethylation could apparently be suppressed with slight excess of aqueous formaldehyde in alkali solution but the non-isolated intermediate (21a) suffered partial \(N_\text{a}\)-alkylation again in the course of the reductive methylation. Treatment of 21a with a large excess of formaldehyde in acetic acid in the presence of NaCNBH\(_3\) gave (±)-1a as major derivative (40\%) along with 23a (29\%).\(^\text{20}\)
In order to avoid this impediment, the \( N_b \)-methyl group was introduced prior to oxidation and cyclization (Scheme 5). By this way (±)-horstiline (1a) could be obtained in 35% overall yield from 24a via 25a.\(^{21}\) (±)-Demethoxyhorstiline (1b)\(^{4}\) was also prepared from 24b under similar conditions. As the cyclizations were conducted in acetic acid, in both cases concomitant formation of \( N_a \)-substituted derivatives (26a)\(^{22}\) and (26b)\(^{23}\) were observed, in agreement with former results.\(^{24}\)

\[\text{Scheme 5.}\]
REFERENCES AND NOTES

1. On leave from Central Research Institute for Chemistry, Budapest, Hungary
6. For this kind of rearrangement see also:
   V. Snieckus and K.S. Bhandari, Synthesis, 1971, 327
7. M.E. Kuehne, J.C. Bohnert, W.G. Bornmann, C.L. Kirkemo, S.E. Kuehne, P.J. Seaton, and
9. 6a·HCl: prepared from p-methoxyphenylhydrazine and 1-methyl-4-piperidone (1.2 eq.) in
   MeOH-HCl, yield: 75%; mp 130°C (decomp., ether); uv (MeOH) 295, 278, 222; ir (KBr) v
   3410(NH); 1H-nmr (300 MHz, CDCl3) δ 2.55(3H, s, N-CH3), 2.65, 2.77(4H, t, J=6 Hz, H-3,
   H-4), 3.65(2H, s, H-1), 3.82(3H, s. CH3O), 6.70(1H, dd, J=9 Hz, H-7), 6.83(1H, d, J=2 Hz,
   H-9), 7.01(1H, d, J=9 Hz, H-6), 8.70(1H, s, NH); 13C-nmr (CDCl3) δ 23.5(C-4), 45.6(N-CH3),
   51.7(C-3), 52.3(C-1), 55.8(CH3O), 99.8(C-9), 107.8(C-9b), 110.5(C-6), 111.3(C-7), 126.2(C-9a),
   131.3(C-4a), 132.7(C-5a), 153.7(C-8); ms m/z 216(M+, 25), 173(100), 158(55).
10. For some related compounds see:
    23, 635, and references cited therein.
11. 16a: mp 147-148°C (MeOH-ether); uv (MeOH) 255, 227, 420; ir (KBr) v 3420(NH), 1680(CO);
1H-nmr (300 MHz, CDCl$_3$) δ 2.01 (1H, m, CH$_2$-CH$_2$-N), 2.37 (1H, dt, J=9 Hz, CH$_2$-CH$_2$-N), 2.41 (3H, s, N-CH$_3$), 2.43 (1H, m, CH$_2$-CH$_2$-N), 2.59, 2.80 (2H, d, J=10 Hz, C-CH$_2$-N), 3.13 (1H, dt, J=9 Hz, CH$_2$-CH$_2$-N), 3.77 (3H, s, CH$_3$O), 5.23 (1H, s, NH), 6.80 (1H, d, J=9 Hz, H-7). 7.04 (1H, d, J=2 Hz, H-4); 13C-nmr (CDCl$_3$) δ 37.0 (CH$_2$-CH$_2$-N), 41.6 (N-CH$_3$), 55.6 (CH$_2$-CH$_2$-N), 55.7 (CH$_3$O), 67.4 (C-CH$_2$-N), 74.2 (C-2), 104.4 (C-7), 113.7 (C-4), 120.3 (C-3a), 127.8 (C-6), 153.2 (C-7a), 156.2 (C-5), 202.6 (CO); ms m/z 232 (M$^+$, 10), 215 (13), 189 (10), 175 (100); high resolution ms 232.1182 (calcd for C$_{13}$H$_{16}$N$_2$O$_2$ 232.1200).

12. (±)-1a: mp 153-154°C (acetone); mp 156-157°C$^2$; All other physical data were identical in all respects with the published ones.

13. 15a: uv (MeOH) 294, 265, 212; ir (CHCl$_3$) ν 1605 (C=N); 1H-nmr (300 MHz, CDCl$_3$) δ 2.08 (1H, m, CH$_2$-CH$_2$-N), 2.33 (1H, m, CH$_2$-CH$_2$-N), 2.44 (3H, s, N-CH$_3$), 2.73 (1H, d, J=9 Hz, H-1'), 2.8-2.9 (2H, m, CH$_2$-CH$_2$-N), 2.89 (1H, d, J=9 Hz, H-1'), 3.80 (3H, s, CH$_3$-O-C), 4.04 (3H, s, CH$_3$O-C=N), 6.76 (1H, dd, J=9 Hz, H-6), 6.97 (1H, d, J=2 Hz, H-7), 7.21 (1H, d, J=9 Hz, H-4); 13C-nmr (CDCl$_3$) δ 35.8 (CH$_2$-CH$_2$-N), 41.9 (NCH$_3$), 55.7 (CH$_3$O-C), 56.4 (N=C-OCH$_3$), 56.6 (C-3), 56.8 (CH$_2$-CH$_2$-N), 64.4 (C-1'), 108.7 (C-4), 112.1 (C-6), 118.1 (C-7), 144.2 (C-3a), 145.2 (C-7a), 156.9 (C-5), 182.4 (C=N); ms m/z 246 (M$^+$, 18), 203 (20), 188 (20), 174 (8). For numeration of the spirocyclic system see ref. 2.

14. 12a: mp 78°C (ether); uv (MeOH) 309, 298, 283, 223, 209; ir (KBr) ν 1625; 1H-nmr (300 MHz, CDCl$_3$) δ 2.51 (3H, s, N-CH$_3$), 2.94 (4H, m, CH$_2$-CH$_2$-N), 3.84 (3H, s, CH$_3$O), 4.59 (2H, s, N-CH$_2$-N), 6.80 (1H, dd, J=9, 2 Hz, H-6), 6.99 (1H, d, J=2 Hz, H-4), 7.04 (1H, d, J=9 Hz, H-7); 13C-nmr (CDCl$_3$) δ 19.3 (CH$_2$-CH$_2$-N), 40.9 (N-CH$_3$), 49.2 (CH$_2$-CH$_2$-N), 55.7 (CH$_3$O), 65.8 (N-CH$_2$-N), 99.0 (C-4), 100.7 (C-3), 109.5 (C-7), 111.6 (C-6), 125.9 (C-3a), 128.7 (C-2), 130.2 (C-7a), 154.7 (C-5); ms m/z 252 (M$^+$, 35), 250 (M$^+$, 12), 209 (33), 207 (100); high resolution ms 250.0852 and 252.0802 (calcd for C$_{13}$H$_{15}$N$_2$OCl 250.0872 and 252.0842).

15. see the first and the latest paper:
**18a·HCl** : mp 231°C (EtOH); uv (MeOH) 303, 258, 208; ir (KBr) ν 3140(NH), 1675(CO); 1H-nmr (300 MHz, DMSO-d$_6$+CD$_3$OD) δ 2.17(2H, m, CH$_2$-CH$_2$-NH$_2$), 2.97(2H, m, CH$_2$-CH$_2$-NH$_2$), 3.58(1H, t, J=6 Hz, H-3), 3.73(3H, s, CH$_3$O), 6.75(1H, d, J=9 Hz, H-7), 6.81(1H, d, J=9 Hz, H-6), 6.91(1H, s, H-4), 8.29(2H, br, NH$_2$), 10.40(1H, s, NH); 13C-nmr (DMSO-d$_6$+CD$_3$OD) δ 25.8(CH$_2$-CH$_2$-NH$_2$), 34.3(CH$_2$-NH$_2$), 41.3(C-3), 53.4(CH$_3$O), 107.8(C-7), 109.1(C-6), 110.4(C-4), 127.9(C-3a), 133.8(C-7a), 152.8(C-5), 176.2(CO); ms m/z 206(M+, 43), 189(42), 176(100); high resolution ms 206.1046 (calcd for C$_{11}$H$_{14}$N$_2$O$_2$ 206.1053).

19. 22a: uv (MeOH) 301, 258, 203; ir (CHCl$_3$) ν 1740, 1720, 1695(CO); 1H-nmr (300 MHz, CDCl$_3$) δ 2.09(3H, s, OCOCH$_3$), 2.41(2H, m, CH$_2$CH$_2$-N-Ac), 2.71(3H, s, NCOCH$_3$), 3.06(2H, m, H-1'), 3.45(2H, m, CH$_2$-N-Ac), 3.82(3H, s, CH$_3$O), 5.74(2H, s, N-CH$_2$-OAc), 6.83(1H, dd, J=9, 2 Hz, H-6), 6.94(1H, d, J=9 Hz, H-4), 7.37(1H, d, J=2 Hz, H-7); ms m/z 332(M$^+$,2), 304(43), 247(97), 245(35).

20. 23a: mp 168-171°C (MeOH-ether); uv (MeOH) 303, 260, 228; ir (KBr) ν 3450(NH), 2235(CN), 1705 (CO); 1H-nmr (300 MHz, CDCl$_3$) δ 2.12, 2.46(2H, m, CH$_2$-CH$_2$-NH), 2.79(1H, br, NH), 2.93, 3.10(2H, d, J=11 Hz, H-1'), 3.00-3.17(2H, m, CH$_2$-CH$_2$-NH), 3.76(2H, s, N-CH$_2$-CN),
3.80(3H, s, CH$_3$O), 6.75(1H, dd, J=9, 2 Hz, H-6), 6.83(1H, d, J=9 Hz, H-7), 6.98(1H, d, J=2 Hz, H-4); $^{13}$C-nmr ([CDCl$_3$] $\delta$ 36.9(CH$_2$-CH$_2$-N), 41.2(N-$\text{CH}_2$-CN), 52.5(CH$_2$-CH$_2$-N), 53.5(C-3), 55.7(CH$_3$O), 62.0(C-1'), 110.1(C-4), 110.2(C-7), 112.6(C-6), 114.8(CN), 133.5(C-7a), 136.9(C-3a), 156.1(C-5), 181.7(CO): ms m/z 257(M$^+$, 26), 232(9), 230(9), 217(13); high resolution ms 257.1167 (calcd for C$_{14}$H$_{15}$N$_3$O$_2$ 257.1164).

21. **25a**: (crude product, reacted without purification) uv (MeOH) 304, 258, 211; ir (CHCl$_3$) ν 3310(NH), 1705(CO); **25b**: (crude product) uv (MeOH) 280, 251, 215; ir (CHCl$_3$) ν 3460(NH), 1715(CO); ms m/z 190(M$^+$, 28), 173(13), 159(10), 147(24), 146(28).

22. **26a**: uv (MeOH) 301, 258, 209; ir (CHCl$_3$) ν 1725, 1595(CO); $^1$H-nmr (300 MHz, CDCl$_3$) $\delta$

2.08(3H, s, OCOCH$_3$), 2.11, 2.40(2H, m, CH$_2$-CH$_2$-N), 2.46(3H, s, N-CH$_3$), 2.75, 3.10(2H, m, CH$_2$-CH$_2$N), 2.80, 2.90(2H, d, J=9 Hz, H-1'), 3.80(3H, s, OCH$_3$), 5.74(2H, s, N-CH$_2$-O), 6.79(1H, dd, J=9, 2 Hz, H-6), 6.92(1H, d, J=9 Hz, H-7), 7.10(1H, d, J=2 Hz, H-4); $^{13}$C-nmr (CDCl$_3$) $\delta$ 20.8(COCH$_3$), 38.4(CH$_2$-CH$_2$-N), 41.6(N-CH$_3$), 53.6(C-3), 55.9(CH$_3$O), 56.5(CH$_2$-CH$_2$-N), 63.4(N-CH$_2$O), 66.2(C-1'), 109.2(C-4), 110.3(C-7), 112.7(C-6), 133.6(C-3a), 136.1(C-7a), 156.9(C-5), 170.5(COCH$_3$), 180.4(NCO); ms m/z 304(M$^+$, 16), 248(52), 216(18), 202(10), 189(17).

23. **26b**: uv (MeOH) 290, 250, 215; ir (CHCl$_3$) ν 1720, 1680, 1610(CO); $^1$H-nmr (300 MHz, CDCl$_3$) $\delta$

2.09(3H, s, OCOCH$_3$), 2.20, 2.41(2H, m, CH$_2$-CH$_2$-N), 2.57(3H, s, N-CH$_3$), 2.93, 3.21(2H, m, CH$_2$-CH$_2$-N), 5.76(2H, s, N-CH$_2$-O), 6.97-7.50(4H, m, aromatic); ms m/z 274(M$^+$, 4), 217(7), 186(6).


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