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

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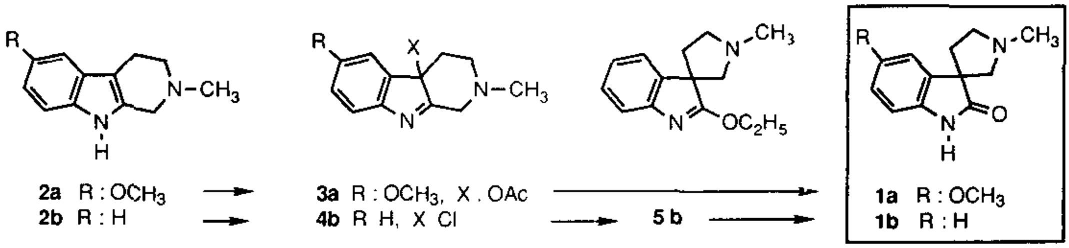
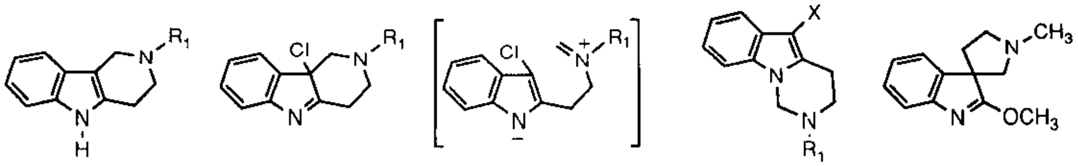
*Abstract-Two syntheses of the title compound [(±)-**1a**] have been described: the first one is based upon the oxidative rearrangement of 7-methoxy-N-methyltetrahydro-γ-carboline (**6a**), while the second path involves a spiro-cyclization between 2-oxo-5-methoxytryptamine (**18a**) and formaldehyde.*

(-)-Horsfiline (**1a**) is a simple oxindole alkaloid, isolated from *Horsfieldia superba*.[2] 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[3] Demethoxyhorsfiline (**1b**) had been obtained from **4b** chloroindolenine by thallium ethoxide assisted rearrangement and subsequent hydrolysis.[4]



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.[5] 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[6] 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.[7]



6b R_1 : CH_3
7b R_1 : Bn

8b R_1 CH_3
9b R_1 Bn

10b R_1 CH_3
11b R_1 Bn

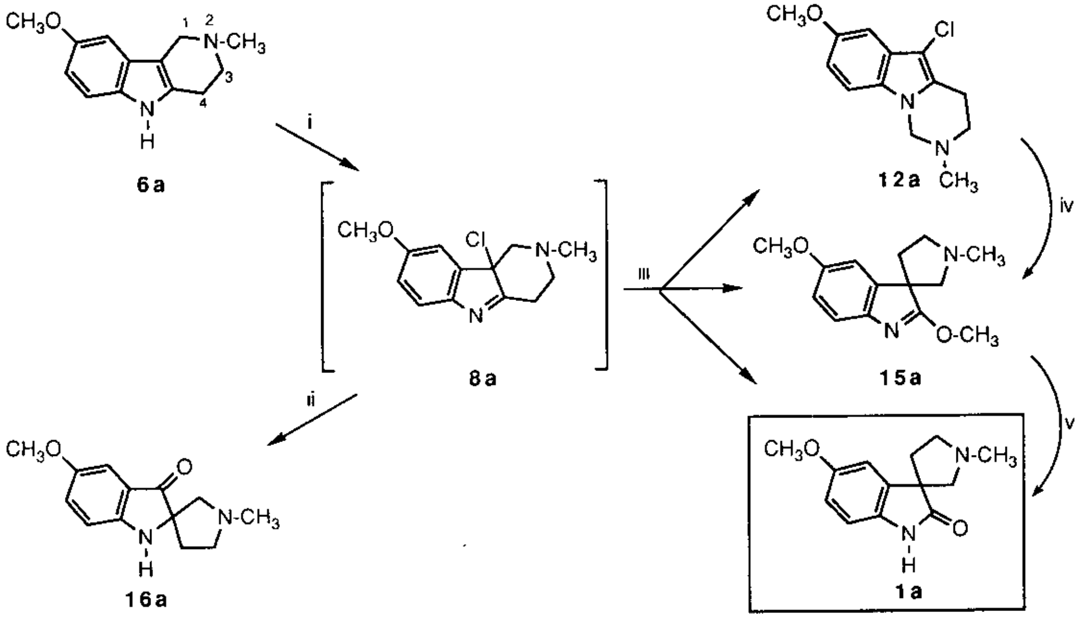
12b R_1 · CH_3, X = Cl
13b R_1 · CH_3, X = OCH_3
14b R_1 Bn, X = Cl

15b

Scheme 2.

Here we report two alternative routes, using a) oxidative rearrangement of tetrahydro-γ-carboline (**6a**) and b) spirocyclization,[8] starting from the appropriate 2-oxotryptamine.

Chlorination of **6a**[9,10] with *t*-BuOCl smoothly led to the non-isolable chloroindolenine (**8a**), which was then rearranged to indoxyle (**16a**)[11] in aqueous acetic acid Treatment of **8a** with aqueous methanolic NaOH resulted in the formation of (±)-horsfiline (**1a**)[12] (13%), its corresponding imidoether (**15a**)[13] (9%) and the chloropyrimido[1,6-*a*]indole (**12a**)[14] (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**).[5] 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).

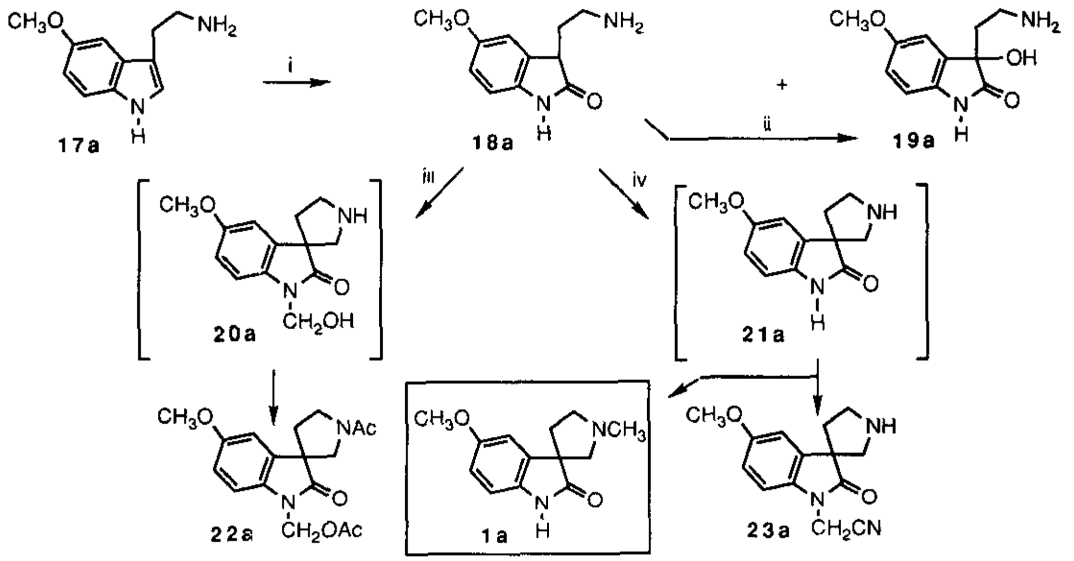


i. *t*-BuOCl, Et_3N, CH_2Cl_2, -78°C; ii: AcOH, MeOH-H_2O, room temperature, iii: NaOH, MeOH-H_2O, 70°C, 2 h; iv: NaOMe, MeOH, reflux, 48 h, v. *p*-TsOH H_2O, toluene, reflux, 3 h

Scheme 3.

In continuation with previous studies[15] on the synthesis of indole alkaloids starting from 2-oxo-tryptamine, we turned to the straightforward cyclization with formaldehyde (Scheme 4).

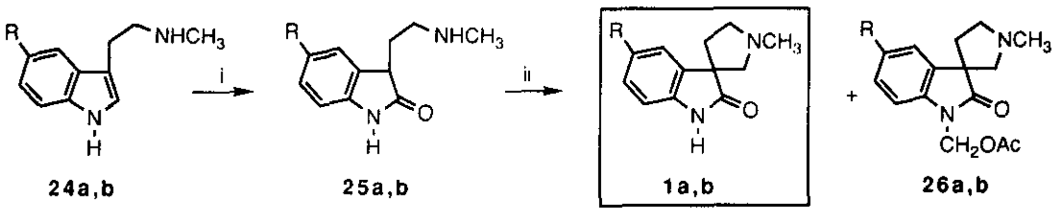
2-Oxo-5-methoxytryptamine (**18a**)[16] was obtained (64%) from **17a** by the DMSO-HCl oxidation method,[17] along with some 3-hydroxy derivative (**19a**).[18] Otherwise, this latter could quantitatively be prepared from **18a** with *t*-BuOOH. Cyclization of **18a** with paraformaldehyde in refluxing acetic acid afforded a water soluble product (**20a**), which was isolated and characterized in diacetylated form **22a**.[19] N_a-Hydroxymethylation could apparently be suppressed with slight excess of aqueous formaldehyde in alkali solution but the non-isolated intermediate (**21a**) suffered partial N_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%).[20]



i: DMSO (2.6 eq), 37% HCl (2 eq.), 80°C, ii: *t*-BuOOH, H_2O, room temperature; iii: $(CH_2O)_x$ (3 eq), AcOH, reflux 60 h then AcCl, Et_3N, MeCN, iv: CH_2O aq (1.25 eq), NaOH (1 25 eq.), MeOH-H_2O then AcOH, CH_2O aq. (15 eq.), $NaCNBH_3$ (4 eq).

Scheme 4.

In order to avoid this impediment, the N_b-methyl group was introduced prior to oxidation and cyclization (Scheme 5). By this way (±)-horsfiline (**1a**) could be obtained in 35% overall yield from **24a** *via* **25a**.[21] (±)-Demethoxyhorsfiline (**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]



a R OCH$_3$, **b** R H

i: DMSO (3 eq.), 37% HCl (3 eq.), 80°C; ii: $(CH_2O)_x$ (1 2 eq.), AcOH, reflux, 3 h.

Scheme 5.

REFERENCES AND NOTES

1. On leave from Central Research Institute for Chemistry, Budapest, Hungary
2. A. Jossang, P. Jossang, H.A. Hadi, T. Sévenet, and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527.
3. K. Jones and J. Wilkinson, *J. Chem. Soc., Chem. Commun.*, 1992, 1767.
4. M.E. Kuehne, D.M. Roland, and R. Hafter, *J. Org. Chem.*, 1978, **43**, 3705.
5. F.M. Hershenson, L. Swenton, and K.A. Prodan, *Tetrahedron Lett.*, 1980, 2617.
6. For this kind of rearrangement see also:
   A. Ebnother, P. Niklaus, and S. Suess, *Helv. Chim. Acta*, 1969, **52**, 629
   V. Snieckus and K.S. Bhandari, *Synthesis*, 1971, 327
   C.J. Cattanach, A. Cohen, and B.H Brown, *J. Chem. Soc. (C)*, 1971, 359
   Y. Nagai, A. Irie, H. Uno, and S. Minami, *Chem. Pharm. Bull.*, 1979, **27**, 1922.
7. M.E. Kuehne, J.C. Bohnert, W.G. Bornmann, C.L. Kirkemo, S.E. Kuehne, P.J. Seaton, and T.C. Zebovitz, *J. Org. Chem.*, 1985, **50**, 919.
8. J. Harley-Mason and R.F.J. Ingleby, *J. Chem. Soc.*, 1958, 3639.
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) ν 3410(NH); ^{1}H-nmr (300 MHz, CDCl$_3$) δ 2.55(3H, s, N-CH$_3$), 2.65, 2.77(4H, t, J=6 Hz, H-3, H-4), 3.65(2H, s, H-1), 3.82(3H, s, CH$_3$O), 6.70(1H, dd, J=9, 2 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); ^{13}C-nmr (CDCl$_3$) δ 23.5(C-4), 45.6(N-CH$_3$), 51.7(C-3), 52.3(C-1), 55.8(CH$_3$O), 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:
    C.J. Cattanach, A. Cohen, and B.H. Brown, *J. Chem. Soc. (C)*, 1968, 1235
    C.A. Harbert, J.J. Plattner, W.M. Welch, A. Weissman, and B.K. Koe, *J. Med. Chem.*, 1980, **23**, 635, and references cited therein.
11. **16a**: mp 147-148°C (MeOH-ether); uv (MeOH) 255, 227, 420; ir (KBr) ν 3420(NH), 1680(CO);

^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.01(1H, m, $C\underline{H}_2$-CH_2-N), 2.37(1H, dt, J=9, 3 Hz, CH_2-$C\underline{H}_2$-N), 2.41(3H, s, N-CH_3), 2.43(1H, m, $C\underline{H}_2$-CH_2-N), 2.59, 2.80(2H, d, J=10 Hz, C-CH_2-N), 3.13(1H, dt, J=9, 3 Hz, CH_2-$C\underline{H}_2$-N), 3.77(3H, s, CH_3O), 5.23(1H, s, NH), 6.80(1H, d, J=9 Hz, H-7), 7.04 (1H, d, J=2 Hz, H-4) 7.30(1H, dd, J=9, 2 Hz, H-6); ^{13}C-nmr ($CDCl_3$) δ 37.0($\underline{C}H_2$-CH_2-N), 41.6 (N-CH_3), 55.6(CH_2-$\underline{C}H_2$-N), 55.7(CH_3O), 67.4(C-$\underline{C}H_2$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 $C_{13}H_{16}N_2O_2$ 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); ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.08 (1H, m, $C\underline{H}_2$-CH_2-N), 2.33(1H, m, $C\underline{H}_2$-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-$C\underline{H}_2$-N), 2.89(1H, d, J=9 Hz, H-1'), 3.80(3H, s, CH_3-O-C), 4.04(3H, s, CH_3O-C=N), 6.76(1H, dd, J=9, 2 Hz, H-6), 6.97(1H, d, J=2 Hz, H-7), 7.21(1H, d, J=9 Hz, H-4); ^{13}C-nmr ($CDCl_3$) δ 35.8($\underline{C}H_2$-CH_2-N), 41.9(NCH_3), 55.7($\underline{C}H_3O$-C), 56.4(N=C-O$\underline{C}H_3$), 56.6(C-3), 56.8(CH_2-$\underline{C}H_2$-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; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.51(3H, s, N-CH_3), 2.94(4H, m, $C\underline{H}_2$-$C\underline{H}_2$-N), 3.84(3H, s, CH_3O), 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); ^{13}C-nmr ($CDCl_3$) δ 19.3($\underline{C}H_2$-CH_2-N), 40 9(N-CH_3), 49.2(CH_2-$\underline{C}H_2$-N), 55.7(CH_3O), 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 $C_{13}H_{15}N_2OCl$ 250.0872 and 252.0842).

15. see the first and the latest paper:

J.-Y. Laronze, J. Laronze-Fontaine, J Lévy, and J. Le Men, *Tetrahedron Lett.*, 1974, 491.
D. Cartier, M. Ouahrani, G. Hugel, and J. Lévy, *Heterocycles*, 1988, **27**, 657.

16. **18a·HCl** : mp 231°C (EtOH); uv (MeOH) 303, 258, 208; ir (KBr) ν 3140(NH), 1675(CO); ^{1}H-nmr (300 MHz, DMSO-d_6+CD_3OD) δ 2.17(2H, m, C$\underline{H}_2$-CH_2-NH_2), 2.97(2H, m, CH_2-C$\underline{H}_2$-NH_2), 3.58(1H, t, J=6 Hz, H-3), 3.73(3H, s, CH_3O), 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); ^{13}C-nmr (DMSO-d_6+CD_3OD) δ 25.8($\underline{C}H_2$-CH_2-NH_2), 34.3($\underline{C}H_2$-NH_2), 41.3(C-3), 53.4(CH_3O), 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 $C_{11}H_{14}N_2O_2$ 206.1053).

17. K. Szabo-Pusztay, and L. Szabo, *Synthesis*, 1979, 276.

18. **19a·HCl**: mp 206°C(decomp., MeOH); uv (MeOH) 309, 263, 210; ir (KBr) ν 3220(NH,OH), 1705(CO); ^{1}H-nmr (300 MHz, DMSO-d_6) δ 2.07(2H, m, C$\underline{H}_2$-CH_2-NH_2), 2.87(2H, m, C$\underline{H}_2$-NH_2), 3.74(3H, s, CH_3O), 6.25(1H, br, OH), 6.78(1H, d, J=9 Hz, H-4), 6.82(1H, dd, J=9, 2 Hz, H-6), 6.94(1H, d, J=2 Hz, H-7), 8.15(2H, br, NH_2), 10.35(1H, s, NH); ^{13}C-nmr (DMSO-d_6) δ 34.2($\underline{C}H_2$-CH_2-N), 35.1(CH_2-NH_2), 55.8(CH_3O), 74.4(C-OH), 110.6(C-7), 111.0(C-6), 114.1 (C-4), 133.0(C-3a), 134.6(C-7a), 155.3(C-5), 178.6(CO); ms m/z 222(M$^+$,100), 204(17), 192 (10), 189(10), 179(88); high resolution ms 222.1000 (calcd for $C_{11}H_{14}N_2O_3$ 222.1003).

19. **22a**: uv (MeOH) 301,258, 203; ir ($CHCl_3$) ν 1740, 1720, 1695(CO); ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.09(3H, s, $OCOCH_3$), 2.41(2H, m, C$\underline{H}_2$$CH_2$-N-Ac), 2.71(3H, s, $NCOCH_3$), 3.06(2H, m, H-1'), 3.45(2H, m, C$\underline{H}_2$-NAc), 3.82(3H, s, CH_3O), 5.74(2H, s, N-C$\underline{H}_2$-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); ^{1}H-nmr (300 MHz, $CDCl_3$) δ 2.12, 2.46(2H, m, C$\underline{H}_2$-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-C$\underline{H}_2$-NH), 3.76(2H, s, N-CH_2-CN),

3.80(3H, s, CH_3O), 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 ($CDCl_3$) δ 36.9($\underline{C}H_2$-CH_2-N), 41.2(N-$\underline{C}H_2$-CN), 52.5(CH_2-$\underline{C}H_2$-N), 53.5(C-3), 55.7(CH_3O), 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 $C_{14}H_{15}N_3O_2$ 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, $CDCl_3$) δ 2.08(3H, s, $OCOCH_3$) , 2.11, 2.40(2H, m, $C\underline{H}_2$-CH_2-N), 2.46(3H, s, N-CH_3), 2.75, 3.10(2H, m, CH_2-$C\underline{H}_2$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 ($CDCl_3$) δ 20.8($CO\underline{C}H_3$), 38.4($C\underline{H}_2$-CH_2-N), 41.6(N-CH_3), 53.6(C-3), 55.9(CH_3O), 56.5(CH_2-$C\underline{H}_2$-N), 63.4(N-CH_2O), 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($\underline{C}OCH_3$), 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, $CDCl_3$) δ 2.09(3H, s, $OCOCH_3$), 2.20, 2.41(2H, m, $C\underline{H}_2$-CH_2-N), 2.57(3H, s, N-CH_3), 2.93, 3.21(2H, m, CH_2-$C\underline{H}_2$-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).

24. A.B.A. Jansen and C.G. Richards, *Tetrahedron*, 1965, **21**, 1327.

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