Tetrahedron Letters,Vol.23,No.28,pp 2913-2916,1982 0040-4039/82/282913-04$03.00/0
Printed in Great Britain 

# STUDIES AIMED AT THE SYNTHESIS OF MORPHINE V[1]
## AN ECONOMIC APPROACH TO (±)-RETICULINE FROM 3,4-DIHYDROPAPAVERINE

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*Regioselective demethylation of 3,4-dihydropapaveraldine (2a) at 7 and 3' positions affords a properly substituted diphenolic key intermediate (2d) for the synthesis of reticuline and N-norreticuline.*

The different reticuline and N-norreticuline derivatives are commonly known to play an important role in the biosynthesis[2,3] as well as in the total synthesis[4,5] of morphine alkaloids. Compounds of type 1 proved to be proper starting materials in the formation of morphinandienone structure *via* phenolic oxidative coupling[4,5].

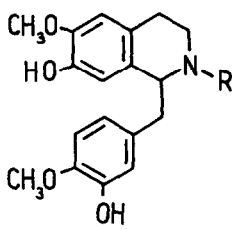
In spite of the fact, that the synthesis of N-norreticuline and its derivatives *via* Bischler-Napieralski cyclization has already been thoroughly investigated[6-9], our aim was to find an economic procedure to synthesize 1a and 1b starting from 3,4-dihydropapaverine, an inexpensive and advanced intermediate of the industrial papaverine production.

Earlier experimental data[10] as well as our investigations unanimously showed, that neither 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-isoquinolines, nor their 6'--halogenated derivatives can be cleaved regioselectively at 7 and 3' positions. The relative lability of the four methoxy functions in acidic media is the following: $3' \cong 4' > 7 > 6$.

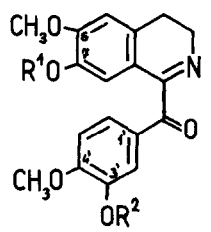
No investigation has been made, however, on the acidic ether cleavage of 3,4-dihydropapaveraldine (2a), which is easily obtained by air oxidation[11] of 3,4-dihydropapaverine. The formation of α-ketimine function, conjugated to both aromatic rings, was expected to level off the electron density in the two rings, moreover it ensures relatively greater basicity for C(7)- and C(3')-methoxyls.

It has been accordingly found, that strong mineral acids under controlled conditions (48% HBr, 120 °C, 1h; or 50% $H_2SO_4$, 120 °C, 72h) do cleave the desired 7 and 3' Me-O bonds regioselectively thus furnishing the key intermediate 2d

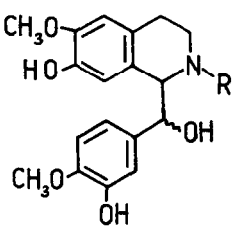
[mp: 227-228 °C (MeOH); $C_{18}H_{17}NO_5$ [12]; IR(KBr): 1660, 1630 and 1595 $cm^{-1}$ ( O=C-C=N- ); $^1$H-NMR(DMSO-$d_6$): δ 2.80 (2H,t,C(4)-$H_2$), 3.83 (2H,t,C(3)-$H_2$), 4.00 (6H,s,$OCH_3$), 6.75 (1H,s,C(8)-H), 7.10 (1H,s,C(5)-H), 7.30-7.70 (3H,m,C(2'), C(5') and C(6')-H), 9.50 ppm (2H,broad,OH)] in crystalline form (50-60%), in the mother liquor the two monophenolic derivatives (2b and 2c) could also be detected. Under milder conditions (24% HBr, 120 °C, 15h) these compounds become the main product and after removing the nonphenolic and diphenolic compounds[13] by subsequent extraction their mixture could be isolated in about 60% yield. The separation of the two monophenols was achieved by treating the crystal mixture with 0.5 N NaOH solution estimated upon the amount of the more acidic 3'-hydroxy isomer (2c). After recrystallization the insoluble residue proved to be pure 2b [mp: 186-188 °C (MeOH); $C_{19}H_{19}NO_5$ [12]; IR(KBr):1650 and 1610 $cm^{-1}$ (O=C-C=N-); $^1$H-NMR($CDCl_3$+DMSO-$d_6$): δ 2.77 (2H,t, C(4)-$H_2$), 3.80 (2H,m,C(3)-$H_2$), 3.83 (3H,s,$OCH_3$), 3.86 (6H,s,$OCH_3$), 6.73 (1H,s,C(8)-H), 6.85 (1H,s,C(5)-H), 6.90-7.60 (3H,m,C(2')-H,C(5')-H and C(6')-H),8.15 ppm (1H,broad,OH)]. From the alkaline solution 2c [mp: 171-172.5 °C (MeOH); lit. mp[14]: 167-168 °C; $C_{19}H_{19}NO_5$ [12]; IR(KBr): 1640 and 1590 $cm^{-1}$ (O=C-C=N-); $^1$H-NMR($CDCl_3$+DMSO-$d_6$): δ 2.83 (2H,m,C(4)-$H_2$), 3.85 (2H,m,C(3)-$H_2$), 3.70 (3H,s,C(7)-$OCH_3$), 3.88 (3H,s,$OCH_3$), 3.90 (3H,s, $OCH_3$), 6.80-7.50 (5H,m,aromatic protons), 8.76 ppm (1H, broad,OH)] could be obtained by acidification and recrystallization.



1a R=$CH_3$
b R=H
c R=CHO



2a $R^1$=$R^2$=$CH_3$
b $R^1$=H, $R^2$=$CH_3$
c $R^1$=$CH_3$, $R^2$=H
d $R^1$=$R^2$= H



3a R=H
b R=CHO

The $^1$H-NMR of the resulted monophenols (2b and 2c) are not characteristic, however their mass spectra (see Table 1) and the fact, that they are intermediates of 2d, prove the structure.

To obtain (±)-reticuline (1a) and (±)-N-norreticuline (1b) the carbonyl oxygen has to be removed. The sodium borohydride or catalytic reduction of 2d, however, provided us only with 3a [72% yield, mp: 217-218 °C (EtOH); $C_{18}H_{21}NO_5$ [12]; IR(KBr): 3410 and 3310 cm$^{-1}$ (OH and NH); $^1$H-NMR($CDCl_3$+DMSO-$d_6$): δ 2.50-2.80 (4H,C(3) and C(4)-$H_2$), 3.69 (6H,s,$OCH_3$), 3.86 (1H,d,J=5Hz,C(1)-H), 4.66 (1H,d,J=5Hz,(-CH-OH), 4.30-4.80 (4H,broad,OH and NH), 6.39, 6.62, 6.73 and 6.85 (5H, aromatic protons)] because of the stability of the ethanolamine structure[15]. The hydrogenolysis of the benzylalcohol function failed in any conditions.

To complete this new synthetic route to reticuline (1a) and N-norreticuline (1b) further steps were applied for removing the oxygen. Treating 3a with ethyl formate in DMF gave N-formyl-α-hydroxy-N-norreticuline (3b) [88% yield; mp: 187-188 °C (EtOAc); $C_{19}H_{21}NO_6$ [12]; IR(KBr): 1640 (C=O amide); 3380 cm$^{-1}$ (OH); $^1$H-NMR(DMSO-$d_6$): δ 3.78 (6H,s,$OCH_3$), 4.36 and 4.65 (1H,C(1)-H), 4.70 (1H,m, (CH-OH), 6.50-6.98 (5H,aromatic protons), 7.90 and 8.73 (1H,s,s,CHO), 8.95 and 8.99 ppm (1-1H,s,OH)]. Due to the N-acylation the benzylalcohol function has become reducible. Transfer hydrogenolysis of 3b in formic acid with Pd-C catalyst resulted in N-formyl-N-norreticuline (1c, 75%) identical in every respect with authentic sample prepared by formylating N-norreticuline (1b)[9].

The above identity, in addition to spectroscopic evidences unambiguously verifies the proper regioselectivity in the demethylation step.

N-Formyl-norreticuline (1c) can be easily reduced[9] to (±)-reticuline (1a) or hydrolized[9] into (±)-N-norreticuline (1b).

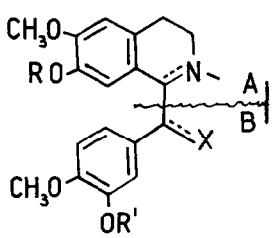
N-Formyl-norreticuline (1c) itself or preferentially its 6'-halogen derivatives have been found to be excellent starting materials for phenolic oxidative coupling into morphinandienones[4]. Further important key intermediates for this purpose could be synthesized from N-norreticuline (1b) by acylation[5] and subsequent selective halogenation[4].

Acknowledgements: The authors wish to thank the CHINOIN Pharmaceutical and Chemical Works (Budapest) for financial support, L.Radics and E.Baitz-Gács for the 100 MHz-NMR, S.Holly for the IR, and J.Tamás for the mass spectra measurements.

References and Notes


1. For part IV. see: Cs.Szántay, G.Dörnyei, G.Blaskó, M.Bárczai-Beke and P.Péchy: Arch.Pharm. 314, 983 (1981)
2. D.H.R.Barton, G.W.Kirby, W.Steglich, G.M.Thomas, A.R.Battersby, T.A.Dobson and H.Ramuz: J.Chem.Soc. 1965, 2423
3. D.H.R.Barton, D.S.Bhakuni, R.James and G.W.Kirby: J.Chem.Soc.C. 1967, 128
4. Cs.Szántay, G.Blaskó, M.Bárczai-Beke, P.Péchy and G.Dörnyei: Tetrahedron Lett. 21, 3509 (1980)
5. M.A.Schwartz and I.S.Mami: J.Am.Chem.Soc. 97, 1239 (1975)
6. M.Tomita and J.Kunimoto: J.Pharm.Soc. 80, 1238 (1980)
7. A.R.Battersby, R.Binks, R.J.Francis, D.J.McCaldin and H.Ramuz: J.Chem.Soc. C. 1964, 3600
8. S.Teitel and A.Brossi: J.Heterocycl.Chem. 5, 825 (1968)
9. K.C.Rice and A.Brossi: J.Org.Chem. 45, 592 (1980)
10. S.Teitel and A.Brossi: Heterocycles 1, 73 (1973)
11. a/ T.Kametani and K.Fukumoto: J.Pharm.Soc. Japan 83, 1031 (1963); *cf. also* b/ N.H.Martin, S.L.Champion and P.B.Belt: Tetrahedron Lett. 21, 2613 (1980)
12. Molecular formulas were determined by high resolution mass spectrometry. The characteristic low resolution ions of all compounds of the synthetic route are summarised in Table 1.


Table 1




| No | Characteristic ions [ m/z (%) ] | | |
|---|---|---|---|
| 2b | 341 (M;34) | 178 (A+2;14) | 165 (B;100) |
| 2c | 341 (M;74) | 192 (A+2;48) | 151 (B;100) |
| 2d | 327 (M;59) | 178 (A+2;27) | 151 (B;100) |
| 3a | 313 (M-18;0.5) | 178 (A;100) | 152 (B-1;9)<br>151 (B-2;9) |
| 3b | 359 (M;1) | 207 (A+1;100)<br>206 (A;76) | 153 (B;8)<br>152 (B-1;8)<br>151 (B-2;9) |


13. From the dichloromethane solution of the mixture of 2b, 2c and 2d the more acidic diphenol (2d) could be totally removed by extraction with 0.01 N NaOH.
14. T.Kametani, H.Matsumoto, Y.Satoh, H.Nemoto and K. Fukumoto: J.Chem.Soc.Perkin I. 1977, 376
15. R.Baltzly and J.S.Buck: J.Am.Chem.Soc. 65, 1984 (1943)


(Received in UK 30 April 1982)