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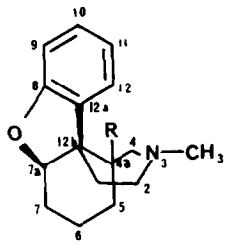
METHYLENE-INDOLINES, INDOLENINES AND INDOLENINIUMS, XXI[1]
AN INDOLENINE APPROACH TO MORPHINE RELATED COMPOUNDS

J.Y.LARONZE, J.LARONZE, D.PATIGNY and J.LEVY*
Centre d'Etude des Substances Naturelles à Activité Thérapeutique, Université de Reims
U.A. n°492 au C.N.R.S., Faculté de Pharmacie, 51 rue Cognacq-Jay
51096 REIMS CEDEX, FRANCE

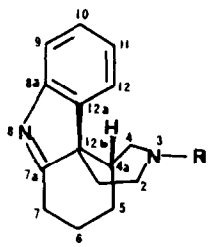
Summary : Nitrous acid deamination of indolenine 15 was used as the key reaction in a new strategy for preparing the morphine analogue 1b.

The morphine fragments 1a,b have recently received notable attention[2-5]. The preparation of the "*cis*" isomer 1b is presented hereafter as a further illustration of the synthesis of substituted dihydrobenzofurans through nitrous acid deamination of indolenines[6].

Indolenine 2 appeared as a suitable intermediate for this purpose. The closely related indolenine 3 was prepared several years ago by Georgian[7] as a morphine analogue, through the Fischer rearrangement of the appropriate phenylhydrazone and, very recently, Bird[8] showed it to possess the depicted "*cis*" configuration.



1a R=α-H "*trans*"
1b R=β-H "*cis*"

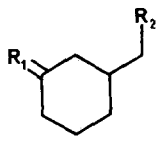


2 R= $-CH_3$
3 R= $-COCH_3$

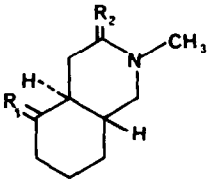
The required perhydroisoquinolone 14 (table 1) was synthesized in 19% yield from 2-cyclohexenone : addition of nitromethane (THF, tetrabutylammonium fluoride on silica[9], 80°C,1h) gave 4 (75%), which was protected as the dioxolane 5 (100%) and reduced ($LiAlH_4$,THF) to amine 6(71%).

Monomethylation was effected by $LiAlH_4$ reduction (96%) of urethane 7 (88% *ex* 6). The resulting secondary amine 8 was N-acylated with $ClCOCH_2Cl$ to 9 (mp 78°C), then O-deprotected with 10% HCl (Δ,1h) to 10 (59% from 8). Cyclisation (K^tBuO/PhH - ^tBuOH 90:10, reflux 3h, 84%) afforded 11 as unique compound. The lactam group was then selectively reduced after protection of the ketone : 11 → 12 (98%) ; 12 → 13 ($LiAlH_4$, Et_2O, reflux 3h, 96%) ; 13 → 14 (10% HCl, reflux 0.5h, 97%). The oily ketone 14, $M^{+\cdot}$ 167, ν_{CO} 1710 cm^{-1}, appeared to be unique (tlc ;

no splitting of the N-Me ^1H NMR signal at 2.65 ppm).



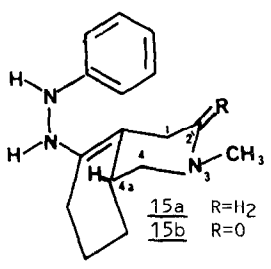
	R_1	R_2
4	= O	NO_2
5	$-O(CH_2)_2O-$	NO_2
6	$-O(CH_2)_2O-$	NH_2
7	$-O(CH_2)_2O-$	$NHCO_2CH_3$
8	$-O(CH_2)_2O-$	$NHCH_3$
9	$-O(CH_2)_2O-$	$N(CH_3)COCH_2Cl$
10	= O	$N(CH_3)COCH_2Cl$



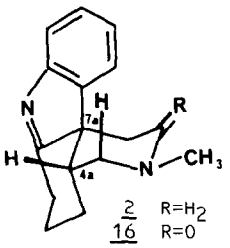
	R_1	R_2
11	=O	=O
12	$-O(CH_2)_2O-$	=O
13	$-O(CH_2)_2O-$	H_2
14	=O	H_2

Table 1

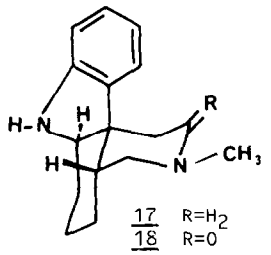
Unexpectedly 14 gave the derived phenylhydrazone in only poor yield (17%) and, moreover, the expected indolenine 2 could not be isolated after acetic acid treatment. It is likely that it decomposes during the work up, since indoline 17 ($M^{+\cdot}$ 242, λmax 208, 225, 285 nm δ_{NMe} 2.3 ppm) was isolated as the sole product when $NaBH_3CN$ was further added to the reaction mixture (table 2). We turned then to the synthesis of indolenine 16 : the nicely crystalline phenylhydrazone (mp 250°C) obtained from keto lactam 11 ($PhNHNH_2$, EtOH, reflux 16h, 85%) was refluxed for 1h in AcOH and partitioned from acidic, then alkaline medium to allow separation of the basic indolenine 16 (72%) as a single stereoisomer (16 signals on the ^{13}C NMR spectrum). Indolenine 16, mp 160°C, $M^{+\cdot}$ 254, λmax 215,252 nm, $\nu_{CO+C=N}$ 1635 cm^{-1}, showed no NH proton (IR, NMR) and could be reduced ($NaBH_3CN$, AcOH, RT) to indoline 18, $M^{+\cdot}$ 256 ; λmax 210,230,278 nm ; ν_{CO} 1635 cm^{-1} ; ν_{NH} 3280 cm^{-1} ; δ_{NH} 3.75 ppm[10].



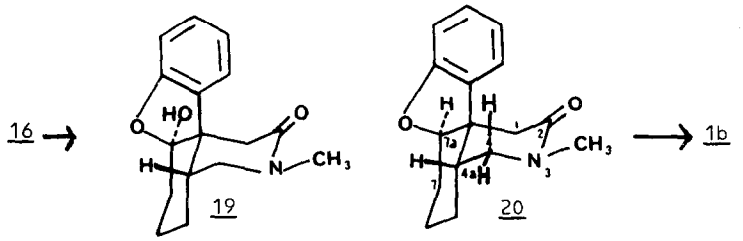
15a R=H_2
15b R=O



2 R=H_2
16 R=O



17 R=H_2
18 R=O



19

20

Table 2

Examination of the reacting tautomeric forms 15a,b of the phenylhydrazones led to the prediction that the Fischer rearrangement would imply approach of the benzene ring from the side of the angular hydrogen, so that indolenines 2 and 16 would have the "*cis*" relative configuration. In agreement with this hypothesis, the 90MHz NMR spectrum of indolenine 16 exhibited a double doublet centered at 3.96 ppm (J=13Hz,J'=5Hz). These signals were attributed to the *axial* H(4), and were consistant with the geometry depicted in the scheme, in full agreement with Bird's findings concerning indolenine 3.

Although these results precluded access to the naturel "*trans*" configuration of morphine analogues, deamination of indolenine 15 was nevertheless performed through careful nitrosation (10% aqueous HCl, 0°C, slow addition of a molar soln. of $NaNO_2$ monitored with external KI and starch impregnated paper strip) followed by decomposition of the diazo compound (50% HCl, 60°C, 1h). Hemiketal 18 was purified by centrifuge chromatography over silica (61%, m/z (rel.int.) 273($M^{+\cdot}$ 45%), 245(80%), 244(65%), 216(4%), 202(100%), 181(25%) ; λmax 210,273,280 nm ; ν_{OH} 3300 cm^{-1}, ν_{CO} 1630 cm^{-1} ; δ_{OH} 5.18 ppm, δ_{NMe} 2.97 ppm). Reduction (Et_3SiH/TFA-RT 10 min) gave lactam 19 (48%) ; mp 226°C ; m/z 257 ($M^{+\cdot}$,100%), 184(68%), 144(40%), 97(80%) ; ν_{CO} 1650 cm^{-1}. The 400MHz ^1H NMR spectrum was fully consistent with the structure and configuration : the N-Me group and the equivalent C(1)-methylene protons gave rise to sharp signals at 3.04 and 2.57 ppm, respectively. The methylene protons on C(4) coupled together with a constant of 13Hz. The axial proton was deshielded to 3.55 ppm by the lactam anisotropy, and it further coupled with H(4a) (d.d,J=13Hz,J'=5Hz). The equatorial proton gave a d.d. (J=13Hz,J'=1Hz) centered at 2.9 ppm. Proton H(7a) gave a signal at 4.12 ppm and exhibited couplings with the vicinal H(7)-protons (J=5Hz,J'=1Hz). The values of the coupling constants supported the equatorial orientations of H(4a) on the piperidinone ring and of H(7a) on the cyclohexane ring.

Finally, lactam 19 was quantitatively reduced ($LiAlH_4$,THF) to 1b, (mp=66°C, $M^{+\cdot}$ 243). The C(4)-methylene gave rise to signals centered at 2.67 ppm (d.d,J=8.3Hz,J'=1.7Hz) and 1.42 ppm (dd,J=8.3Hz,J'=3Hz), partly masked by the signals of the C(2)-methylene (broad singlets at 2.60 and 2.68 ppm). The position of the N-Me signal at 2.33 ppm still confirmed the "*cis*" configuration[4,5a].

This indolenine strategy somewhat parallels the photochemical rearrangements developed in the field by Schultz and coworkers[2], and moreover both approaches appear to follow similar stereochemical courses.

Introduction of the oxygen substituents onto the two carbocycles was further envisioned by using a methoxyphenylhydrazone, and through oxidative functionalization of the intermediate

indolenine. However, the Fischer indolization of the o-methoxyphenylhydrazone of 10 gave only poor yields of the indolenine, which in turn appeared to give minute amounts of the methoxy derivative of 18 upon HNO_2 treatment. Nevertheless, nitrous acid deamination of indolenines, when combined with Fischer's rearrangement, is thought to be a simple and powerful method for building various angularly arylated compounds.

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References and notes

1. Methylene indolines, indolenines and indoleniniums, XX, Hugel, G. ; Lévy, J. *J.Org.Chem.*, in press.
2. (a) Schultz, A.G. ; Lucci, R.D. *J.C.S. Chem.Comm.*, 1976, 925.
   (b) Schultz, A.G. ; Lucci, R.D. ; Fu, W.Y. ; Berger, N.H. ; Erhardt, J. ; Hagmann, W.Y. *J.Am.Chem.Soc.*, 1978, 100, 2150.
   (c) Schultz, A.G. ; Lucci, R.D. ; Napier, J.J. ; Kinoshita, H. ; Ravichandran, R. ; Shannon, P. ; Yee, Y.K. *J.Org.Chem.*, 1985, 50, 217.
3. Ciganek, E. *J.Am.Chem.Soc.*, 1981, 103, 6261.
4. (a) Weller, D.D. ; Weller, D.L. *Tetrahedron Lett.*, 1982, 23, 5239.
   (b) Weller, D.D. ; Stirchak, E.P. ; Weller, D.L. *J.Org.Chem.*, 1983, 48, 4597.
5. (a) Moss, W.H. ; Gless, R.D. ; Rapoport, H. *J.Org.Chem.*, 1981, 46, 5064.
   (b) Moss, W.H. ; Gless, R.D. ; Rapoport, H. *J.Org.Chem.*, 1983, 48, 227.
6. (a) Lévy, J. ; Sigaut, F. *Tetrahedron Lett.*, 1983, 24, 4983.
   (b) Lévy, J. ; Sigaut, F. *Tetrahedron Lett.*, 1983, 24, 4987.
7. Georgian, V. *Chem. and Ind.*, 1957, 1124.
8. Bird, C.W. ; Wee, A.G.H. *Tetrahedron*, 1985, 41, 2019.
9. Clark, J.H. *J.Chem.Soc., Chem.Comm.*, 1978, 789.
10. In agreement with Bird's work, we found that hydrogenation of the azomethine double bond in 2 was stereoselective, and that gave only one isomer 17. The 90MHz NMR spectrum of the N-deuteriated derivative of 17, showed a double doublet at 3.68 ppm (J=6.5Hz,J'=3.5Hz). It was indicative that H(7a) was *equatorial* on the cyclohexane ring.

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