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A SYNTHESIS OF AAPTAMINE FROM 6,7-DIMETHOXY-1-METHYLISOQUINOLINE

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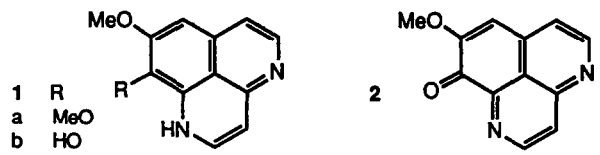
Summary : A five-step total synthesis of aaptamine, **1a**, is described starting from 6,7-dimethoxy-1-methylisoquinoline

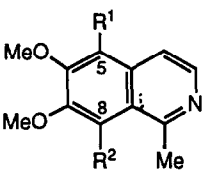
Yellow aaptamine, **1a**, was isolated[1] as its protonic salt from the sea sponge *Aaptos aaptos*. It was reported[1,2] to have powerful α-adrenoceptor blocking activity. Later, demethylated (**1b**) and oxidised (**2**) variations were isolated[3] from the same natural source. Six syntheses[4] of aaptamine have been previously reported.



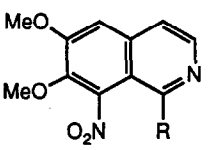
The use of 6,7-dimethoxy-1-methylisoquinoline[5], **3a**, as a starting substance for a synthesis of aaptamine demanded the introduction of nitrogen at C-8. It was anticipated that electrophilic substitution would proceed most readily at the less hindered C-5 rather than C-8[6] and accordingly we began by blocking C-5 by brominating (Br_2/$CHCl_3$/reflux/24 h), to give (mainly) the 5-bromo-derivative **3b**[7], and were than able to nitrate (fuming HNO_3/ -45°C/30 min)(->**3c**) at C-8, hydrogenation/hydrogenolysis (H_2/Pd-C/RT/60psi/K_2CO_3/16 h) of **3c**[7] producing the desired 8-amino-6,7-dimethoxy-1-methylisoquinoline, **3d**[7]. Subsequently, we found that direct nitration (fuming HNO_3/-40°C/45 min) of **3a** gives the 8-mono-nitro-derivative, **3e**[7,8,9] which could be reduced (Pd-C/$NH_4^+HCO_2^-$) to **3d**.

Our strategy for the introduction of the C_1-unit required between 8-nitrogen and C-1-carbon substituents rested on the predicted acidity of hydrogens on the isoquinoline-1-methyl. We converted the amine **3d** into isonitrile **3f**[7] ($CHCl_3$/50% aqNaOH/CH_2Cl_2) in the hope that cyclisation could be effected[10] with lithium diisopropylamide[10a] (LDA) or copper (I) oxide[10b], however the former gave only a multi-component mixture and the latter, even in refluxing xylene, brought no change to **3f.**

Conversion of amine **3d** to formamide **3g**[7] (HCO_2H/Ac_2O/RT) allowed attempts to follow a seemingly excellent precedent[11], involving the cyclising condensation of a 5-formamide with a quinoline 4-methyl group, to be pursued, however treatment of the formamide with $POCl_3$, P_4O_{10} or TsOH led only to recovery of starting amide. Arguing that the employment of base-catalysed conditions to achieve cyclising condensation would require prior removal of the acidic amide-N-hydrogen, the formamide **3g** was N-benzylated ($NaH/PhCH_2Br$), giving **3h**[7], but even then no cyclisation[12] could be achieved with a variety of strong bases, from NaH to $NaN(SiMe_3)_2$.



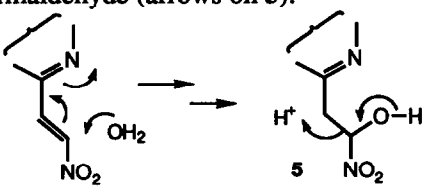
3	R^1	R^2		R^1	R^2
a:	H	H	f:	H	NC
b:	Br	H	g:	H	NHCHO
c:	Br	NO2	h:	H	$N(CH_2Ph)CHO$
d:	H	NH2			
e:	H	NO2			



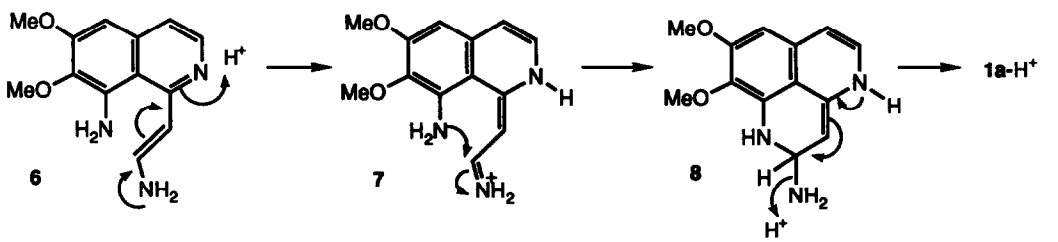
4	R
a:	CHO
b:	$CH(OH)CH_2NO_2$
c:	$CH(CH_2NO_2)_2$
d:	$CH{:}CHNO_2$

These failures to capitalise on 1-methyl acidity led to a changed tactic - the conversion ($1.5xSeO_2$/dioxan(dry)/reflux/2.5h) of **3e** to aldehyde **4a**[7]. Condensation of aldehyde **4a** and nitromethane could be effected with BuLi/N,N'-dimethylpropyleneurea (DMPU) and did produce some of the desired alcohol **4b**, but it took a great deal of experimentation to improve on the 15% yield. Attempts to use MeONa, *t*-BuOK, Et_3N, *n*-Pr_2NH in varying quantities, solvents, hot and cold were all unsuccessful. The key observation came from an examination of the use of basic Al_2O_3 which in 50 fold excess and in nitromethane as solvent (3.5h/reflux) gave trinitro-compound **4c**[7]. This was taken to mean that the required condensation had indeed taken place, that dehydration had followed to generate the target nitroalkene, **4d**, which, under the conditions of reaction had undergone the Michael addition of a second mol equivalent of nitromethane anion. Further experimentation allowed efficient and clean synthesis of the alcohol **4b**[7] ($8xAl_2O_3$ (activated; basic)/ $MeNO_2$(solvent)/RT/3.5h).

Dehydration of the alcohol also proved to be more difficult than we had anticipated, a variety of acidic conditions failed, probably because of interaction of the isoquinoline nitrogen with proton/acid. The production of adduct **4c** (above) prompted an investigation into the use of base-catalysed dehydration; many conditions were assessed, including florisil and molecular sieves; the best found ($10xAl_2O_3$(activated; basic)/PhH/reflux1h) gave the desired nitroalkene **4d**[7], together with aldehyde, **4a** (19%) and original nitro-methyl-isoquinoline **3e** (22%). This latter must derive from the nitro-alkene *via* hydration to a species (part structure **5**) which then loses the elements of nitroformaldehyde (arrows on **5**).



The final ring closure was modelled on the frequently used cyclisation of 2-(2-nitrophenyl)-1-nitroethenes to give indoles[13]. Such indole ring syntheses might have been thought to derive benefit from the final formation of the aromatic system however in the present context no such benefit acrues. One may view the desired process as needing reduction of both nitro-groups to generate **5**, or its equivalent, for enamine protonation, cyclisation and loss of ammonia, generating the aaptamine system. Mildly acidic conditions in the reduction/cyclisation would facilitate the step proceeding from conjugated enamine **5** to **6**, and, in the final elimination (arrows on **7**), by protonating the amino-group thus giving rise to aaptamine, as a protonic salt.



Attempts to utilise catalytic hydrogen transfer conditions[14] , $TiCl_3$ or Fe in HCl were unsuccessful, however the use of Fe powder in AcOH[15] allowed conversion of nitroalkene **4d** into aaptamine[16] in 83% yield.

Acknowledgements

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References and Footnotes

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6 Nitration of isoquinoline itself occurs (*via* the isoquinolinium cation (R. D. Brown and R. D. Harcourt, *Tetrahedron*, 1960, **8**, 23)) at the 5- and 8-positions, with the former predominating to the extent of 9:1 (M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 1957, 2521).

7 Satisfactory analytical data were obtained for all new compounds. M.ps., yields, and key spectroscopic data are : **3b**, 109-110°C, 63%, $\delta_H(CDCl_3)$ 2.92 (3H, s, 1-CH_3), 7.33 (1H, s, H-8), 7.84, 8.44 (2x1H, 2xd, J 6 Hz, H-4, H-3), 22% n.O.e. between signal at δ 7.33 and C-methyl signal at δ 2.92; **3c**, 128-31°C, 68%, $\delta_H(CDCl_3)$ 8.01, 8.56 (2x1H, 2xs, H-4, H-3); **3d**, 149-51°C, 83%, $\delta_H(CDCl_3)$ 2.28 (2H, bs, NH_2), 6.56 (1H, s, H-5), 7.18, 8.12 (2x1H, 2xd, J 6Hz, H-4, H-3); **3e**, 185-86°C, 41%, δ_H ($CDCl_3$) 7.07 (1H, s, H-5), 7.29, 8.22 (2x1H, 2xd, J 6Hz, H-4, H-3); **3f**, 180-84°C, 31%, δ_H ($CDCl_3$) 7.63 (1H, s, 5-H), 7.66, 8.38 (2x1H, 2xd, J 6 Hz, H-4, H-3); **3g**, 200-04°C, 89%, $\nu_{max.}$ 1700 cm^{-1}; $\delta_H((CD_3)_2SO)$ 2.84 (2/3x3H, s, 1-CH_3), 2.89 (1/3x3H, s, 1-CH_3), 3.72 (1/3x3H, s, 7-OCH_3), 3.74 (2/3x3H, s, 7-OCH_3), 3.93 (3H, s, 6-OCH_3), 7.44 (1H, s, 5-H), 7.57, 8.20 (2x1H, 2xd, J 6 Hz, H-4, H-3), 8.09 (1/3x1H, d, J 12Hz, CH:O), 8.44 (2/3x1H, s, NCH:O), 9.63 (1/3x1H, d, J 12 Hz, NH), 9.94 (2/3x1H, s, NH); **3h**, 135-38°C, 55%, $\nu_{max.}$ 1670 cm^{-1}; δ_H ($CDCl_3$) 2.86 (3H, s, 1-CH_3), 3.12 (3H, s, 7-OCH_3), 4.08, 5.54 (2H, 2xd, J 11 Hz, $PhCH_2$), 7.42, 8.40 (2x1H, 2xd, J 6Hz, H-4, H-3), 8.36 (1H, s, NCH:O); **4a**, 209-10°C, 75%, $\nu_{max.}$ 1700 cm^{-1}; δ_H ($CDCl_3$) 7.30 (1H, s, H-5), 7.75, 8.66 (2x1H, 2xd, J 6Hz, H-4, H-3), 10.12 (1H, s, CH:O); **4b**, 158-60°C, 84%, δ_H ($CDCl_3$) 1.75 (1H, brs, OH), 4.52 (1H, dd, J 13, 8 Hz, $CHNO_2$), 4.73 (1H, dd, J 13, 3 Hz, $CHNO_2$), 5.64 (1H, dd, J 8, 3 Hz, *C*HOH), 7.30 (1H, s, H-5), 7.65, 8.43 (2x1H, 2xd, J 6 Hz, H-4, H-3); **4c**, 153°C, 51%, δ_H ($CDCl_3$) 4.56 (1H, pentet, J 7, CH_2CHCH_2), 4.75 (2H, dd, J 14, 7 Hz, CH_2NO_2), 5.15 (2H, dd, J 14, 7 Hz, CH_2NO_2), 7.25 (1H, s, H-5), 7.54, 8.42 (2x1H, 2xd, J 6 Hz, H-4, H-3); **4d**, 188-90°C, 36%, 7.26 (1H, s, H-5), 7.67, 8.57 (2x1H, 2xd, J 6 Hz, H-4, H-3), 7.93, 8.14 (2x1H, 2xd, J 13Hz, CH:$CHNO_2$).

8 Even nitration at -45°C always produced some 5,8-dinitro-derivative[9]. Traces of the 5-nitro-isomer were present in the mother liquor from crystallising **3e**.

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16 The synthetic material, isolated as its hydrochloride, m.p.110-115°C (lit[1] 110-113°C), had spectroscopic properties identical with published[1] data.

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