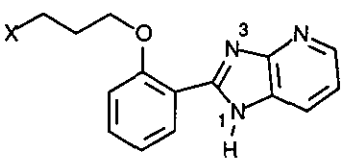
SYNTHESIS OF NOVEL, FUSED BENZOXAZOCINES BY AN UNEXPECTED INTRAMOLECULAR CYCLISATION

William J. Coates and Dashyant Dhanak*

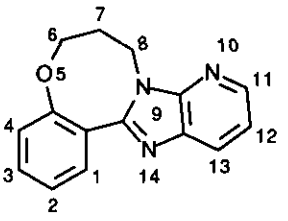
SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire, AL6 9AR, United Kingdom

Abstract - Novel, fused benzoxazocines are obtained from the treatment of 2-(2-(3-hydroxypropoxy)phenyl)benzimidazole and imidazopyridine derivatives with trifluoroacetic anhydride followed by heating in HMPA.

Recently, Camps *et al.* reported[1] a simple one-pot synthesis of primary nitriles from the corresponding primary alcohols. This involved activation of the alcohol, by reaction with trifluoroacetic anhydride in dichloromethane solution, followed by nucleophilic displacement of the derived trifluoroacetate with cyanide ion in a 1:1 mixture of boiling THF:HMPA. In connection with other work, we had need to transform the hydroxyl group in the 2-(2-alkoxyphenyl)imidazo[4,5-*b*]-pyridine (**1**) into the corresponding nitrile (**2**).



1: X = OH
2: X = CN



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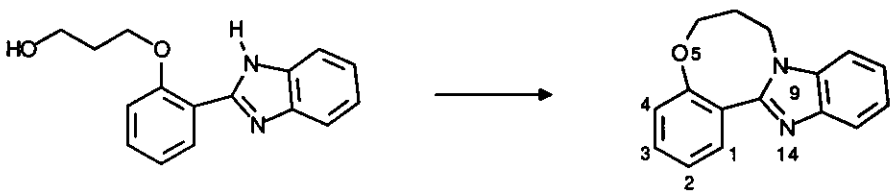
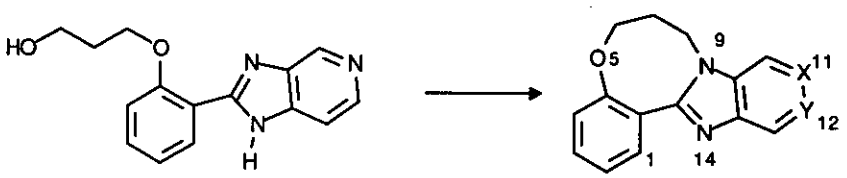
Application of the Camps methodology, however, failed to produce **2**. Instead a novel tetracyclic compound incorporating an oxazocine moiety was obtained in 52% yield. The structure (**3**) was

assigned on the basis of microanalytical and spectroscopic data (see below). The desired product (**2**) was not observed.

Results from a limited further investigation have shown that the reaction proceeds even in the absence of cyanide ion and the mixed solvent system can be replaced with neat HMPA. Thus, trifluroacetylation of **1** in HMPA followed by the addition of triethylamine and heating at 150°C for 5 hours gave **3** in 80% yield. Other dipolar aprotic solvents such as DMF and 1,3 -dimethyl -2-imidazolidinone can be used but the reactions are slower and the yields of oxazocines are reduced.[2] The reaction has also been extended to other 2-alkoxyphenylimidazole derivatives. Thus, trifluoroacetylation of the benzimidazole (**4**) and subsequent heating in HMPA gave the fused oxazocine (**6**) in 59% yield, while the imidazo[4,5-*c*]pyridine (**5**) gave a 35% yield of a mixture of the isomeric fused oxazocines (**7**) and (**8**) in approximately equal proportions.



4 **6**



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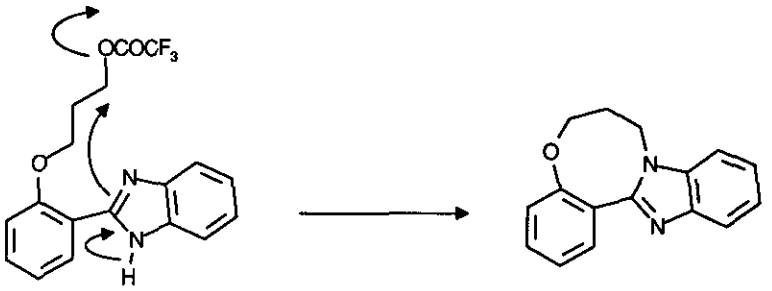
7: X = N, Y = CH
8: X = CH, Y = N

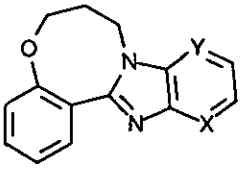
A possible mechanism for the transformation is outlined in Scheme 1. Intramolecular S_N2 displacement of trifluoroacetate ion by one of the nucleophilic imidazole nitrogens results in the formation of the oxazocine system. Since cyanide ion is not required for the formation of the oxazocine, it is unlikely that the reaction proceeds *via* displacement of the nitrile group in **2**. The

facile formation of an eight membered ring is likely to be due to the presence of the two aromatic rings which both bring the reacting centres closer together and reduce the flexibility of the chain between them.



Scheme 1

In order to distinguish between the isomers (**3**) and (**9**) that could arise from the intramolecular cyclisation of **1**, a combination of ^{13}C nmr and ^{1}H-^{1}H NOE difference measurements were carried out.



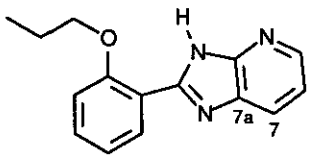
3: X = CH, Y = N
9: X = N, Y = CH

Lindon *et al.*[3] in a study of tautomerism in related imidazo[4,5-*c*]pyridines reported that, in ^{13}C nmr spectra, upfield shifts occur for carbon atoms α- and β- to an imidazole nitrogen bearing a proton or methyl group.

	10	**11**		**3**
C-7	125.7	119.4	C-13	126.6
C-7a	134.3	126.3	C-13a	134.7

Table 1. Selected ^{13}C nmr chemical shifts for compounds (**10**, **11** and **3**)

We have found that similar changes also occur in the ^{13}C nmr spectra of imidazo[4,5-*b*]pyridines. Chemical shift values for C-7 and C-7a in **10** and **11**, which exist as a mixture of tautomers in DMSO solution at room temperature, are shown in Table 1.[4] The assignment of these resonances is supported by $^{1}H/^{13}C$ correlation. The carbon atoms α- and β- to the proton bearing nitrogen atom both show upfield shifts whose magnitude is similar to those reported by Lindon *et al.* Comparison of the shifts for C-13 and C-13a in **3** with those of the corresponding carbons in **10** and **11** (Table 1) shows good agreement with tautomer (**10**). In addition, ^{1}H-^{1}H NOE difference measurements in which the N-CH_2 resonance of **3** was irradiated did not show enhancement of the signal due to H-**13**. Taken together these results clearly indicate that the single product from the cyclisation of **1** is the compound **3** and not the isomer (**9**).



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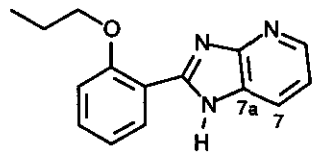

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In contrast with the formation of the single isomer (**3**), the reaction of the imidazo[4,5-*c*]pyridine (**5**) gave ≈ a 3:2 mixture of isomeric oxazocines (**7**) and (**8**) which were readily distinguished by ^{1}H-^{1}H NOE. Thus, irradiation of the N-CH_2 signals caused enhancement of the 10-H signal (at δ 8.83) of **7** and the 10-H signal (at δ 7.32) of **8** (in addition to enhancement of both adjacent CH_2 signals). While the difference in product formation observed with the imidazo[4,5-*b* and 4,5-*c*]pyridines might be a reflection of the ratio of tautomers present in the reaction, we do not have any evidence to support this[5] and it may be that the relative reactivities of the tautomers are more important. The formation of isomeric products is in qualitative agreement with that found on alkylation of 2-butylimidazo[4,5-*b* and 4,5-*c*]pyridines.[6] In addition, methylation of imidazo[4,5-*b*]pyridine with dimethyl sulphate[7] occurs at N-3 but not N-1, which is entirely consistent with the intramolecular alkylation of **1** to give **3** as the sole product.

Conclusion

Treatment of 2-(2-(3-hydroxypropoxy)phenyl)imidazo[4,5-*b*]pyridine with trifluroacetic anhydride followed by heating in a dipolar aprotic solvent, particularly HMPA, leads to the formation of a fused 1,5-oxazocine. Additionally, the isomeric imidazo[4,5-*c*]pyridine and the benzimidazole systems have both been shown to undergo analogous reactions. The unusually facile formation of an eight membered ring probably occurs *via* an intramolecular S_N2 process in which the normally disfavourable entropy factors are overridden by the presence of two aromatic rings.

EXPERIMENTAL SECTION

Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. All analytical data were obtained by the Analytical Sciences Department at SmithKline Beecham. Nmr spectra were obtained for all compounds as $CDCl_3$ or d_6-DMSO solutions on a Bruker AM250 spectrometer and chemical shifts are quoted in parts per million (δ) relative to tetramethylsilane. Mass spectral determinations were carried out on a VG analytical 7070F mass spectrometer. All final compounds were analysed for C, H and N and gave results within ± 0.4% of the theoretical value. Analytical and preparative chromatography was carried out on Merck Kieselgel 60 grade silica. All starting materials were obtained from commercial sources and were used as received unless otherwise stated.

2-[2-(3-Hydroxypropoxy)phenyl]-1*H*-imidazo[4,5-*c*]pyridine (5)

An intimate mixture of 2-(3-hydroxypropoxy)benzaldehyde[8] (9.0 g, 50 mmol), 3,4-diaminopyridine (5.5 g, 50 mmol) and sulfur (3.5 g, 110 mmol) was heated at 130°C for 6 h. After cooling to room temperature, EtOH (30 ml) was added and insoluble materials removed by filtration. Treatment of the filtrate with concentrated HCl (10 ml) gave a hydrochloride salt which was dissolved in water and the solution treated with concentrated ammonium hydroxide solution. The resulting solid was recrystallised from MeCN to give the title compound (7.2 g, 53%), mp 183-184.5 °C. Anal. Calcd for

$C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 67.00; H, 5.65; N, 15.62. ^{1}H Nmr (DMSO-d_6): δ 2.08 (m, 2H, $CH_2CH_2CH_2$); 3.80 (t, J = 5.1 Hz, 2H, CH_2CH_2OH); 4.36 (t, J = 5.7 Hz, 2H, OCH_2CH_2); 7.15 (t, J = 7.2 Hz, 1H, *Ph-4H*); 7.30 (d, J = 8.1 Hz, 1H, *Ph-6H*); 7.52 (m, 2H, *Ph-3,5-H*); 8.31 (d, J = 5.5 Hz, 1H, *7-H*); 8.37 (dd, J = 6.0, 1.7 Hz, 1H, *6-H*); 8.93 (s, 1H,*5-H*). Ms m/z 270 $(M + H)^+$, 212 (50).

The following compounds were prepared in an analogous manner:

2-(2-[3-Hydroxypropoxy]phenyl)-1*H*-benzimidazole (**4**)

2-(3-Hydroxypropoxy)benzaldehyde and 1,2-phenylenediamine were converted into the title compound in 39% yield after recrystallisation from MeCN, mp 183-184 °C. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. *Found*: C, 71.42; H, 5.95; N, 10.41. ^{1}H Nmr (DMSO-d_6): δ 2.07 (m, 2H, $CH_2CH_2CH_2$); 3.79 (t, J = 5.2 Hz, 2H, CH_2OH); 4.34 (t, J = 5.7 Hz, 2H, CH_2CH_2OPh); 5.58 (br, 1H, *OH*); 7.19 (m, 4H, *5,6-H, Ph-3,5-H*); 7.44 (m, 1H, *Ph-4-H*); 7.59 (br, 2H, *4,7-H*); 8.36 (dd, J = 7.7, 1.6 Hz, 1H, *Ph-6-H*). Ms m/z 268 (M^+), 237, 223.

2-(2-[3-Hydroxypropoxy]phenyl)-1*H*-imidazo[4,5-*b*]pyridine (**1**)

2-(3-Hydroxypropoxy)benzaldehyde and 2,3-diaminopyridine were converted into the title compound in 36% yield after recrystallisation from CH_2Cl_2/Et_2O, mp 148 °C. Anal. Calcd for $C_{15}H_{15}N_3O_2.0.1H_2O$: C, 66.45; H, 5.57; N, 15.50. Found: C, 66.14; H, 5.56; N, 15.53. In DMSO solution this compound exists as a 1:1 mixture of tautomers. ^{1}H Nmr (DMSO-d_6) δ 2.07 (br, 2H, $CH_2CH_2CH_2$); 3.78 (br, 2H, CH_2CH_2OH); 4.35 (br, 2H, OCH_2CH_2); 5.35 and 5.60 (br, 1H, CH_2OH); 7.12-7.27 (m, 3H, *6-H*, Ph-*3,5-H*); 7.49-7.54 (m, 1H, Ph-*4-H*); 7.80-8.10 (br, 1H, Ph-*6-H*); 8.20-8.38 (br, 2H, *5-H, 7-H*); 12.85 (br d, <1H, *NH*). Ms m/z 269 (M^+), 224 (100)

7,8-Dihydro-6*H*-pyrido[3,2-*b*]imidazo[1,2-*e*][1,5]benzoxazocine (**3**)

Method A

A stirred suspension of 2-(2-(3-hydroxypropoxy)phenyl)imidazo[4,5-b]pyridine (1) (2.7 g, 10 mmol) in dry CH_2Cl_2 (15 ml) was treated with trifluoroacetic anhydride (3.1 g, 15 mmol). The mixture was stirred for 1h and evaporated to dryness. The residue, in HMPA:THF (1:1, 40 ml), was treated with dry sodium cyanide (1.9 g, 39mmol) at 100°C for 1 h. The cooled mixture was added to ether (100 ml) and washed with water and brine. The organic layer was dried ($MgSO_4$) and the residue after evaporation was purified by flash chromatography using ether as the eluting solvent. Evaporation of the appropriate fractions gave the product as a pale yellow solid (1.3 g, 52%), mp 102°C. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.65; H, 5.07; N, 16.78. ^{1}H Nmr (DMSO-d_6): δ 2.02 (m, 2H, *7-CH*$_2$); 4.22 (t, *J* = 5.3 Hz, 2H, *6-CH*$_2$); 4.35 (m, 2H, *8-CH*$_2$); 7.27 (m, 2H, *2,4-H*); 7.34 (m, 1H, *12-H*); 7.58 (dt, *J* = 8.0, 1.8 Hz, 1H, *3-H*); 7.78 (dd, *J* = 8.2, 1.9 Hz, 1H, *1-H*); 8.15 (dd, *J* = 7.9, 1.4 Hz, 1H, *13-H*); 8.41 (dd, *J* = 4.7, 1.4 Hz, 1H, *11-H*). Irradiation of the 8-CH_2 resonance did not give any enhancement of the resonance due to H-13 at δ 8.15. ^{13}C Nmr (DMSO-d_6) δ 158.55 (*4a-C*); 152.65 (*14a-C*); 147.43 (*9a-C*); 143.38 (*11-C*); 134.67 (*13a-C*); 132.35 (*3-C*); 131.98 (*1-C*); 126.57 (*13-C*); 123.14 (*2-C*); 121.82 (*4-C*); 120.35 (*14b-C*); 118.24 (*12-C*); 71.45 (*6-C*); 39.72 (*8-C*); 28.26 (*7-C*). Ms m/z 251 (M^+,100), 222 (60)

Method B

Trifluoroacetic anhydride (0.23 g, 1.1 mmol) was added to a solution of 2-(2-(3-hydroxypropoxy)-phenyl)imidazo[4,5-*b*]pyridine(**1**)(0.25 g, 1 mmol) in dry HMPA (1 ml). Triethylamine (0.10 g, 1.1 mmol) was added and after stirring for 10 min the reaction was heated at 130°C for 5h. The cooled mixture was partitioned between ether and saturated aqueous Na_2CO_3 solution, the organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography using CH_2Cl_2:MeOH (99:1) as the eluting solvent to give a product which was identical to that obtained from method A above (0.19 g, 80%).

7,8-Dihydro-6*H*-benzimidazo[1,2-*e*][1,5]benzoxazocine (**6**)

Using the procedure described in Method B above, 2-(2-(3-hydroxypropoxy)phenyl)benzimidazole (**4**) was converted into the title compound which was transformed into the hydrochloride salt in 59% overall yield after recrystallisation from ethanol/ether, mp 258°C. Anal. Calcd for $C_{16}H_{14}N_2O$·HCl:

C, 67.02; H, 5.27; N, 9.77; Cl, 12.36. Found: C, 66.71; H, 5.40; N, 9.63; Cl, 12.37. ^{1}H Nmr (DMSO-d_6): δ 2.09 (m, 2H, *7-CH_2*); 4.29 (t, *J* = 5.3 Hz, 2H, *6-CH_2*); 4.50 (m, 2H, *8-CH_2*); 7.40 (m, 2H, *2,3-H*); 7.61 (m, 2H, *11,12-H*); 7.75 (m, 1H, *1-H*); 7.80 (m, 1H, *4-H*); 7.90 (m, 1H, *13-H*); 8.10 (m, 1H, *10-H*). Ms m/z 250 (M^+, 100), 221 (45).

7,8-Dihydro-6*H*-pyrido[3,4-*b*]imidazo[1,2-*e*][1,5]benzoxazocine (**7**) and 7,8-Dihydro-6*H*-pyrido[4,3-*b*]imidazo[1,2-*e*][1,5]benzoxazocine (**8**)

Using the procedure described in Method B above, 2-(2-(3-hydroxypropoxy)phenyl)imidazo-[4,5-*c*]pyridine (**5**) (3.0 g, 11 mmol) gave 1.2 g (35%) of an approximately equimolar mixture of **7** and **8**. These were separated by careful flash chromatography using a gradient of MeOH in CH_2Cl_2 (0 - 4%) as the eluting solvent. Recrystallisation from isopropylacetate gave, in order of elution:

(i) 7,8-Dihydro-6*H*-pyrido[3,4-*b*]imidazo[1,2-*e*][1,5]benzoxazocine (**7**, 0.41 g, 15%), mp 184.5 - 185.5 °C. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.79; H, 5.20; N, 16.80. ^{1}H Nmr ($CDCl_3$): δ 2.14 (m, 2H, *7-CH_2);* 4.17 (t, 2H, *6-CH_2*); 4.58 (m, 2H, *8-CH_2*); 7.14 (d, *J* = 8.2 Hz, 1H, *4-H*); 7.19 (m, 1H, *2-H*); 7.48 (m, 1H, *3-H*); 7.72 (dd, *J* = 5.6, 0.8 Hz, 1H, *13-H*); 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H, *1-H*); 8.48 (d, *J* = 5.7 Hz, 1H, *12-H*); 8.83 (d, *J* = 0.8 Hz, 1H, *10-H*). Irradiation of the *8-CH_2* resonance gave enhancement of the *7-CH_2* multiplet at δ 2.14 (3.1%) and the *10-H* doublet at δ 8.83 (9.3%). Ms m/z 251 (M^+), 222 (55); and

(ii) 7,8-Dihydro-6*H*-pyrido[4,3-*b*]imidazo[1,2-*e*][1,5]benzoxazocine (**8**, 0.32 g, 11%), mp 165.5 - 166.5°C. Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.42; H, 5.15; N, 16.75. ^{1}H Nmr ($CDCl_3$): δ 2.10 (m, 2H, *7-CH_2*); 4.18 (t, *J* = 5.5 Hz, 2H, *6-CH_2*); 4.30 (m, 2H, *8-CH_2*); 7.13 (dd, *J* = 8.3, 1.0 Hz, 1H, *4-H*); 7.19 (m, 1H, *H-2*); 7.32 (dd, *J* = 5.6, 0.9 Hz, 1H, *10-H*); 7.47 (m, 1H, *3-H*); 7.87 (dd, *J* = 7.8, 1.8 Hz, 1H, *1-H*); 8.45 (d, *J* = 5.6 Hz, 1H, *11-H*); 9.14 (d, *J* = 0.9 Hz, 1H, *13-H*). Irradiation of the *8-CH_2* resonance gave enhancement of the *7-CH_2* multiplet at δ 2.1 (3.5%) and the *10-H* signal at δ 7.32 (7.5%). Ms m/z 251 (M^+), 222 (50).

REFERENCES

1. F. Camps, V. Gasol and A. Guerrero, *Synth. Commun.*, 1988, **18**, 453.

2. In DMF solution, the isolated yield of **3** was 20% after 8 h and in 1,3-dimethyl-2-imidazolidinone the reaction was incomplete, as judged by tlc, after 40 h at 130°C.

3. P. Barraclough, J. C. Lindon, M. S. Nobbs and J. M. Williams, *Mag. Res. Chem.*, 1989, **27**, 992.

4. The preparation of this compound has been described previously: W. J. Coates, B. Connolly, D. Dhanak, S. A. Flynn and A. Worby, *J. Med. Chem.*, 1993, in press. Mp 152 -153°C. Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.76. Found: C, 71.51; H, 5.99; N, 16.76. ^{1}H Nmr (DMSO-d_6): δ 1.12 (t, J = 7.5 Hz, 3H, CH_3CH_2); 1.99 (m, 2H, $CH_3CH_2CH_2$); 4.20 (t, J = 6.7 Hz, 2H, OCH_2); 7.21 - 7.03 (m, 3H, *6-H,* Ph-*3,5-H*); 7.44 (dt, J = 1.7, 7.0 Hz, 1H, Ph-*4-H*); 8.06 (dd, J = 1.4, 8.0 Hz, 1H, *7-H*); 8.37 (dd, J = <1, 3.7 Hz, 1H, Ph-*6-H*); 8.56 (dd, J = 1.8, 7.9 Hz, 1H, *5-H*); 9.45 (br, 1H, *NH).* ^{13}C Nmr (DMSO-d_6): δ 10.1, 21.4, 68.9, 113.0, 118.1, 119.4, 121.1, 125.7, 126.3, 130.7, 131.8, 134.3, 143.2, 143.8, 150.4, 151.2, 156.2. Ms m/z 253 (M^+).

5. In DMSO solution at room temperature both ^{1}H and ^{13}C Nmr spectra of **1** show an approximately 1:1 mixture of tautomers. However the possibility that under the reaction conditions one of the tautomers may predominate cannot be excluded. The Nmr spectra of **5** show no evidence of tautomerism.

6. W. W. K. R. Mederski and K. G. R. Pachler, *Tetrahedron,* 1992, **48**, 10549.

7. J. Elguero, A. Fruchier and S. Mondon-Mignonac, *Bull. Soc. Chim. France*, 1972, 2916.

8. J. Almog, J. E. Baldwin, M. J. Crossley, J. F. Debernardis, R. L. Dyer, J. R. Huff and M. K. Peters, *Tetrahedron,* 1981, **37**, 3589.

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