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SYNTHETIC STUDIES ON 1,4-BENZODIOXIN: THE PREPARATION OF ANALOGUES OF BIOLOGICALLY IMPORTANT INDOLES

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Summary:- The expectation that some benzodioxin derivatives are potentially pharmacologically valuable has led to the development of new chemistry for the construction and functionalisation of the benzodioxin moiety. This includes the preparation of 2-bromo-1,4-benzodioxin and its use in the synthesis of 2-alkenyl, alkyl and aryl-1,4-benzodioxins, plus studies on the novel cycloaddition of dienophiles and 2-ethenyl-benzodioxin. Additionally the reaction of 2-lithio-benzodioxin with epoxides has given access to benzodioxin analogues of biologically important indoles.

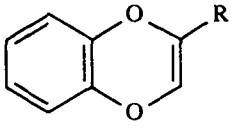
Introduction

Molecules containing the indole group display a wide range of biological activity as shown by a consideration of the pharmacology of natural products such as the indole alkaloids e.g. yohimbine. However this class of compounds often possess a complex pharmacological profile which limits their utility as medicinal agents e.g. yohimbine is known to possess both 5-HT and α_2-antagonist properties[1]. It is reasonable to suggest that the former activity arises through an interaction at the indole nucleus and that replacement of this nucleus with another moiety could decrease this mode of bioactivity.

Certain "indole mimics" related to yohimbine, have already been reported[2], with the structural modifications being shown to change its receptor selectivity, thus adding support to the above expectation. Molecular graphics studies[3] of benzodioxin analogues of indoles indicate that replacing the indole nucleus does not radically alter the conformational bias of the molecule. This suggests that the preparation of benzodioxin "indole mimics" could be of value since we would predict that they may retain just part of the pharmacological profile of the indole derivatives, leading to compounds with enhanced bioselectivity[2].

To achieve the synthesis of these analogues we required access to benzodioxin derivatives of a type which, despite an increasing interest in the chemistry of this heterocyclic system[4-9], were not readily available. In particular we needed a ready synthesis of 2-alkenyl and 2-aryl substituted benzodioxins.

The alkylation with sp^3-centred electrophilic species of 2-lithiobenzodioxin **1** has been established[10], as has its addition to aldehydes and ketones. Therefore anions of this type, especially bromomagnesium derivatives **2**, could be used in a nickel-phosphine catalysed coupling reaction[11] with aryl and alkenyl halides to give access to the required 2-alkenyl and 2-aryl benzodioxins. Alternatively the bromide **3** could be used in a coupling reaction with alkenyl and aryl Grignard reagents to arrive at the same valuable substrates. Having obtained ready access to 2-alkenyl benzodioxins we would be able to study their use in Diels-Alder reactions to give tricyclic products that were of interest, both as potential medicinal agents, and as precursors to "indole mimics".



(1) R = Li

(2) R = MgBr

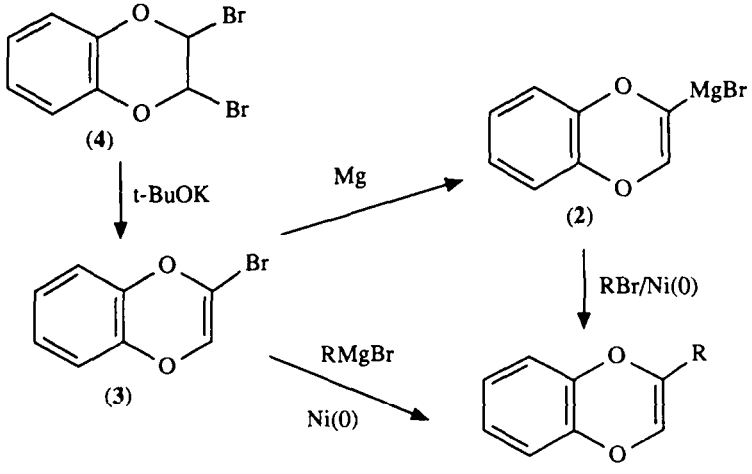
(3) R = Br

Results and Discussion

1. Preparation And Coupling Reactions of 2-Bromo-1,4-Benzodioxin

The initial starting point for these studies was the bromide **3** which can be readily obtained by base treatment of the known dibromide **4**[6], using potassium *tert*-butoxide in diethyl ether to give an 83% yield of **3**[9] (Scheme 1).

Scheme 1



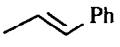
Two complementary methods were used for the synthesis of 2-substituted benzodioxins from the bromide **3**. The first method (**A**), involves the reaction of alkenyl Grignard reagents in the presence of a catalytic amount (1 mol%) of dichloro[1,3-bis(diphenylphosphino)propane] nickel (II) $NiCl_2$(dppp) resulting in the

formation of the coupled products **5b** and **5c** (**Table 1**). In a similar way the aryl coupled products **5d-f** are obtained by reaction with the corresponding aryl Grignard reagents. Alternatively, the second method (**B**) reverses the nature of the reagents by coupling the Grignard reagent **2** derived from the bromide **3** with the necessary alkenyl halides, using the same catalysts as above. With the exception of *trans* 2-bromostyrene or its derived Grignard reagent the yields are uniformly good. Furthermore there is little to choose between the use of $NiCl_2$(dppp) or the ethane equivalent $NiCl_2$(dppe) (Method **C**) as catalyst except in the case of the coupling of ethylmagnesium bromide and **3** whereby the former catalyst gives, in addition to the alkylated product **5a**, some 15% of 1,4-benzodioxin. In agreement with the original account of these reactions[11] we were unable to achieve any coupling via the second method using aryl halides, or with 3-halopyridines using either of the methods.

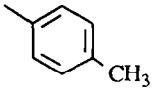
Table 1 2-Substituted Benzodioxins (**5**)

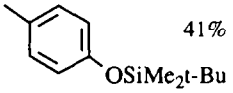
a) R = $-CH_2CH_3$ 67%

b) R =  80%

c) R =  39%

d) R =  75%

e) R =  81%

f) R =  41%

2. Diels-Alder Reaction of 2-Alkenyl-Benzodioxins[12]

In order to construct tricyclic systems containing the benzodioxin group the cycloaddition reactions of the diene **5b** were studied[13]. Reaction of **5b** with reactive dienophiles gave, in good yields, a range of tricyclic adducts **6** and **7a-e** (**Table 2**). The stereochemical outcome of the reaction follows the conventional pattern, giving the *endo* adduct in each case. For instance the adduct **7a**, formed from **5b** and maleic anhydride, shows, in its high field nmr spectra, a coupling of 8.8Hz between H_a and its vicinal proton, indicating a dihedral angle of ca.15° between them, which can only correspond to the *endo* adduct.

Other dienophiles that work in this process are dimethyl acetylenedicarboxylate (to give **6**), tetracyanoethene (giving **7b**) and diester azodicarboxylates (leading to **7c-e**). Attempts to use less reactive dienophiles, such as methylene diurethane[14], with this unsymmetrical diene failed however.

The synthetic transformations of these adducts are also interesting. For instance although it is not possible to hydrolyse the cycloadduct **7e** without decomposition, it is possible to hydrogenate **7c** and then hydrolyse and decarboxylate the t-butyl ester groups with trifluoroacetic acid to form, as the hydrochloride salt, the hydrazinoaminal **8** in 57% overall yield.

Of more value however is that due to their possessing the combination of a dihydroaromatic moiety with

a phenoxide leaving group, these cyclic adducts should undergo a ring opening sequence, driven by a favourable aromatisation process, to form 2-hydroxy substituted bisaryl ethers (Scheme 2). Precedent for this exists in a reaction of simple benzodioxans[15] for which the present compounds should display an enhanced propensity.

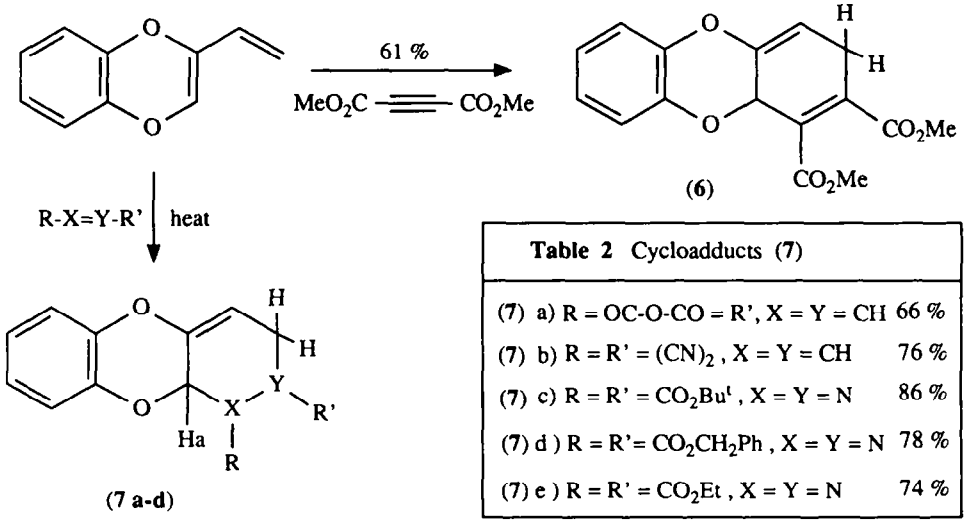
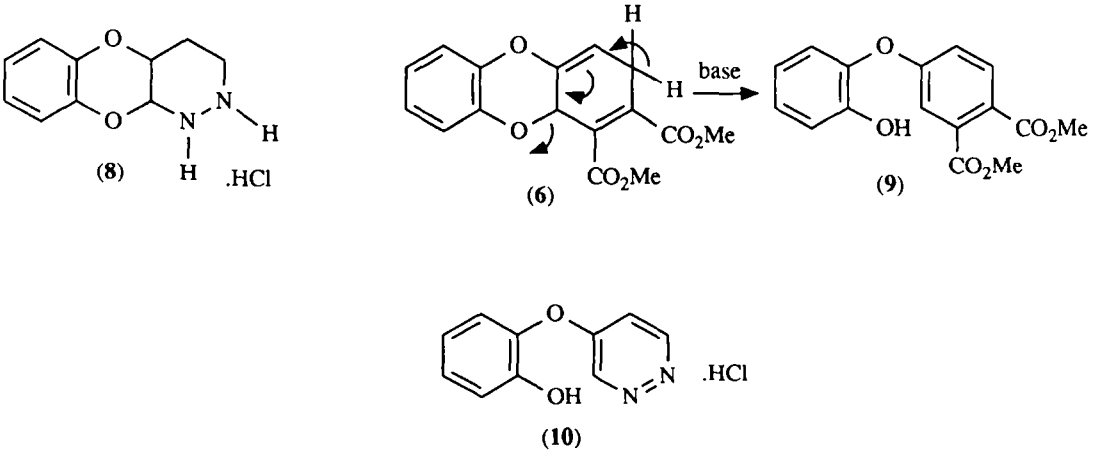


Table 2 Cycloadducts (7)

(7) a) R = OC-O-CO = R', X = Y = CH	66 %
(7) b) R = R' = $(CN)_2$, X = Y = CH	76 %
(7) c) R = R' = CO_2Bu^t, X = Y = N	86 %
(7) d) R = R'= CO_2CH_2Ph, X = Y = N	78 %
(7) e) R = R' = CO_2Et, X = Y = N	74 %

That this does happen was established by treatment of **6** with potassium *tert*-butoxide to give 70% of the bisaryl ether **9**. In addition upon hydrogenation of **7d** removal of the benzyl groups resulted in spontaneous ring opening, with concurrent aromatisation, to give cleanly **10**, as its mono hydrochloride salt in 43% yield.

Scheme 2

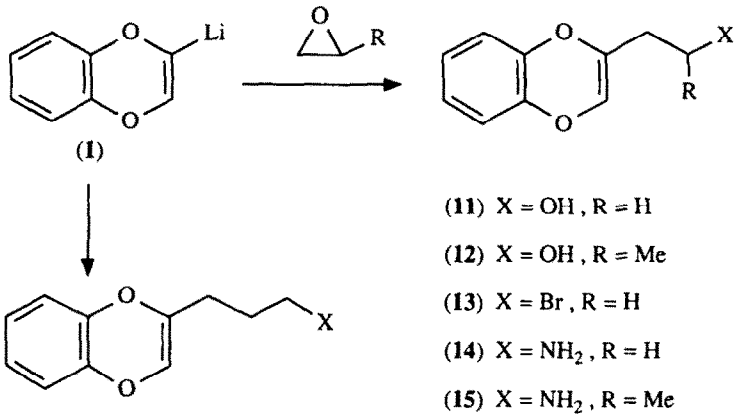


Since 2-hydroxy substituted bisaryl ethers occur as a key structural feature in many of the complex water soluble glycopeptide antibiotics, such as vancomycin[16] any new route to them is of interest and value. This is especially so since they are difficult to synthesise, and are also currently of some potential due to the pharmacological activity of certain derivatives. Therefore the advantages of this route are worth emphasising. These include the ease of preparation of 2-ethenyl-1,4-benzodioxin and its ready reaction with reactive dienophiles, so ensuring an efficient route to the tricyclic precursors of these molecules. The simple ring opening process, driven by aromatisation, is clean and relatively efficient and the new method should easily be adaptable to the preparation of the more useful unsymmetrical bisaryl ethers. This can be achieved via the use of correctly substituted benzodioxin derivatives, whose substituent directing effects will control which of the two benzodioxin oxygens acts as a leaving group. These studies emphasise the value of being able to efficiently prepare the benzodioxin nucleus, due to its properties as a pharmacophore, but also due to its value as a synthetic precursor to other interesting molecules.

3. The Preparation of Analogues of Simple Biologically Important Indoles

A recent synthetic report[17] further highlighted the pharmacological value of the benzodioxin nucleus[1] by describing a method for preparing 2-aminomethyl substituted benzodioxins related to the α_2-blocking agents, *Piperoxan* and *Prosympal*. This present paper describes a new reaction at the benzodioxin nucleus which gives ready access to 2-aminoethyl and propyl substituted compounds similarly related to known β-blocking agents[18].

Scheme 3



To prepare the 2-aminoethyl substituted compounds 2-lithiobenzodioxin **1** has been reacted with epoxides (Scheme 3), so that with ethylene oxide we formed the alcohol **11** (the benzodioxin analogue of tryptophol) in 84 % yield, and with propylene oxide, **12** in 61%. For an efficient transformation both of

these reactions require activation of the epoxide with Lewis acid, giving in the latter case the product derived from epoxide opening at the least hindered position only. The alcohol **11** was readily converted to the tryptophyl bromide analogue **13** by treatment with TsCl and LiBr (61% overall) whereas **11** and **12** can be converted to the analogue of tryptamine **14**, or the amine **15**, via the phthalimides, in 69% and 46% yield respectively.

Similarly reaction of **1** with 1,3-dibromopropane gives **17**, the propyl homologue of **13**, in 53% yield which acts as a precursor to the homologous 3-propylamine **18**. Additionally the halides **13** and **17** have been shown to serve as a precursor to a wide range of compounds of therapeutic interest. For instance reaction with secondary amine such as piperidine gave a 71% and 64% yield of the tertiary amines **16** and **19** respectively. The high yields in these processes and the simple nature of the reactions makes these routes ideal for the synthesis of benzodioxin based "indole-mimics" whose chemistry and biological profile we are currently studying.

The studies described above constitute a significant addition to the synthetic chemistry of the benzodioxin nucleus, which until recently had been relatively poorly investigated, but is now sufficiently well developed to allow the preparation of a wide range of novel derivatives.

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Experimental

All organic solvents were distilled immediately prior to use as listed, (tetrahydrofuran and ether, which refers to diethyl ether, from sodium/benzophenone; dichloromethane and triethylamine from calcium hydride; methanol from dimethoxy magnesium; carbon tetrachloride from potassium hydroxide). Infra-red spectra were recorded on a Perkin-Elmer 1420 or 881 spectrophotometer, nmr on JEOL PMX 60, GX 270 and GX 400 spectrometers using TMS or CH_2Cl_2 as an internal standard, and mass spectra were obtained on a VG9090 mass spectrometer. Reactions involving air and/or moisture sensitive intermediates were performed under a nitrogen atmosphere and magnesium sulphate was used for drying solutions of organic compounds.

2-BROMO-1,4-BENZODIOXIN.

To a stirred suspension of potassium *tert*-butoxide (9.16g, 81.6mmol) in anhydrous diethyl ether (50ml) was added via a cannula a solution of 2,3-dibromo-2,3-dihydro-1,4-benzodioxin (20.0g, 68mmol) in anhydrous diethyl ether (50ml), and the mixture was stirred for 8 hours. The solid was filtered off to afford a residue which was purified by column chromatography (hexane as eluent) to yield a clear oil (12.0g,83%), b.p.118°C/20mmHg. Found; C,45.43; H,2.59%. $C_8H_5BrO_2$ requires C,45.10; H,2.36%. $\nu_{max}(CCl_4)$, 3 054, 2 970, 1 677, 1 601, 1 320, 1 095 cm^{-1}; δ_H ($CDCl_3$), 5.92 (1H, s), 6.50-6.85 (4H, m); $\delta_C(CDCl_3)$, 142.48, 141.49, 125.13, 124.62, 124.37, 118.02, 116.38, 116.26; m/z, 214,212 (M^+,100,98%), 133 (M^+-Br,30.9), 77(39.9).

FORMATION OF 2-SUBSTITUTED-1,4-BENZODIOXINS VIA NICKEL(0) CATALYSIS.

GENERAL METHOD A: To a stirred suspension of dichloro [1,3-bis(diphenylphosphino)propane] nickel(II) (0.020g, 0.04mmol) and 2-bromo-1,4-benzodioxin (0.80g, 3.75mmol) stirred in anhydrous diethyl ether (10ml) was added a Grignard reagent (5.6mmol) at 0°C, and the mixture was stirred for 2 hours. The reaction was quenched with saturated ammonium chloride solution (20ml) and extracted with diethyl ether (2x20ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a residue which was purified by column chromatography, using hexane as eluent. The following compounds were prepared by this method:-

2-Ethyl-1,4-benzodioxin (5a) as a colourless oil (62%). Found; C,74.00; H,6.48% $C_{10}H_{10}O_2$ requires C,74.05; H,6.21%. $\nu_{max}(CCl_4)$ 2 970, 2 935, 1 700, 1 595 cm^{-1}; $\delta_H(CDCl_3)$ 1.06 (3H, t, J=7.3Hz), 1.99 (2H, q, J=7.3Hz), 5.70 (1H,s), 6.57-6.83 (4H,m); $\delta_C(CDCl_3)$ 142.93, 142.61, 139.32, 123.75, 123.58,120.86, 116.02, 115.83, 22.60, 10.71; m/z, 162 (M^+,100%), 147 (M^+-Me,83.8), 133 (M^+-Et,31.1).

2-Vinyl-1,4-benzodioxin (5b) as a colourless oil (80%). Found; C,75.08; H,5.40% $C_{10}H_8O_2$ requires C,74.98; H,5.04%. ν_{max} (CCl_4) 3 100, 3 040, 1 668, 1 592, 1 485, 1 343, 1 250, 1 100 cm^{-1}; $\delta_H(CDCl_3)$ 5.07 (1H, dd, J=1.5,11.2Hz), 5.47 (1H, dd, J=1.5,17.0Hz), 5.86-5.97 (1H, m), 6.00 (1H, s), 6.53-6.86 (4H, m). δ_C ($CDCl_3$) 142.50, 141.97, 136.09, 126.47, 125.77, 124.21, 123.91, 116.42, 116.01, 111.67; m/z, 160 (M^+,100%), 131 (32.1), 80 (16.4), 55 (29.0).

2-(2-Phenyl-1-ethenyl)-1,4-benzodioxin (5c) as a white solid (39%), m.p.103°C. Found; C,81.06; H 5.34% $C_{16}H_{12}O_2$ requires C,81.33; H,5.12%. $\nu_{max}(CCl_4)$ 3 040, 3 020, 1 660, 1 590 cm^{-1}; $\delta_H(CDCl_3)$ 6.11 (1H, s), 6.27 (1H, d, J=15.9Hz), 6.67-6.73 (1H, m), 6.78-6.88 (4H, m), 7.20-7.42 (5H, m); $\delta_C(CDCl_3)$ 142.44, 141.99, 136.81, 136.40, 128.67, 127.51, 126.73, 126.34, 126.18, 124.28, 123.96, 117.29, 116.44, 116.17; m/z, 236 (M^+,100%), 128 (40.9), 77 (10.9).

2-Phenyl-1,4-benzodioxin (5d) as a white solid (75%), m.p.72°C. Found; C,79.71; H,4.98% $C_{14}H_{10}O_2$ requires C,79.98; H,4.79%. $\nu_{max}(CCl_4)$ 3 050, 1 675, 1 595, 1 490, 1 330, 1 240 cm^{-1}; $\delta_H(CDCl_3)$ 6.46 (1H, s), 6.70-6.90 (4H, m), 7.25-7.50 (5H, m); $\delta_C(CDCl_3)$ 142.75, 142.16, 136.65, 131.22, 128.42, 128.10, 124.04, 123.34 , 123.01, 116.35, 115.91; m/z, 210 (M^+,100%), 181 (65.4), 105 (53.6).

2-Tolyl-1,4-benzodioxin (5e) as a white solid (81%), m.p.66°C. Found; C,80.32; H,5.50% $C_{15}H_{12}O_2$ requires C,80.33; H,5.39%. $\nu_{max}(CCl_4)$ 3 040, 2 930, 1 680, 1 601, 1 532, 1 515, 1 463, 1 301, 1 035 cm^{-1}; $\delta_H(CDCl_3)$ 2.34 (3H, s), 6.41 (1H, s), 6.77-6.88 (4H, m), 7.14 (2H, d, J=8.2Hz), 7.33 (2H, d, J=8.2Hz); $\delta_C(CDCl_3)$ 142.78, 142.24, 138.00, 136.73, 129.10, 128.37, 123.97, 123.05, 122.71, 116.33, 115.86, 21.22; m/z, 224 (M^+,100%), 119 (34.5), 115 (20.8).

(*p*-^{t}Butyldimethylsilyloxyphenyl)-1,4-benzodioxin (5f) as a white solid (41%), m.p.64°C. Found; C,70.24; H,7.46% $C_{20}H_{24}O_3Si$ requires C,70.55; H,7.10%. $\nu_{max}(CCl_4)$ 3 047, 2 959, 2 932, 2 860, 1 680, 1 600, 1 512, 1 495, 1 334 cm^{-1}; $\delta_H(CDCl_3)$ 0.23 (6H, s), 1.01 (9H, s), 6.38 (1H, s), 6.84 (2H, d, J=8.6Hz), 6.70-6.91 (4H, m), 7.36 (2H, d, J=8.6Hz); $\delta_C(CDCl_3)$ 155.79, 142.75, 142.27, 136.67, 124.58, 124.37, 123.95, 123.90, 122.11, 120.08, 116.30, 115.84, 25.63, 8.20, -4.45; m/z, 340 (M^+,100%), 283 (M^+-^{t}Bu,72.6).

GENERAL METHOD B: A solution of 2-bromo-1,4-benzodioxin (0.80g, 3.75mmol) in anhydrous THF (10ml) was added slowly to magnesium turnings (0.20g, 8.2mmol) containing a crystal of iodine in anhydrous THF (5ml) at room temperature and stirred for 90 minutes. The solution was added via a cannula to a stirred suspension of dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (0.020g. 0.04mmol) and an

alkyl or alkenyl bromide (4.9mmol) in anhydrous diethyl ether (10ml) at 20°C. After 8 hours the mixture was quenched with saturated ammonium chloride solution (20ml) and extracted with diethyl ether (2*20ml). The combined extracts were dried ($MgSO_4$) and concentrated at reduced pressure to give a residue which was purified by column chromatography as in the above method. The following compounds were prepared by this method:-

2-Vinyl-1,4-benzodioxin (5b) as a colourless oil (63%), and **2-(2-Phenyl-1-ethenyl)-1,4-benzodioxin (5c)** as a white solid (39%), m.p. 103°C, both with identical spectra to the products described above.

GENERAL METHOD C: This was identical to GENERAL METHOD A except that dichloro [1,2-bis-(diphenylphosphino) ethane]nickel(II) was used instead of dichloro [1,3-bis(diphenylphosphino)propane] nickel(II). The following compounds were prepared by this method:-

2-Ethyl-1,4-benzodioxin 5a as a colourless oil (67%), **2-Vinyl-1,4-benzodioxin 5b** as a colourless oil (74%), and **2-(2-Phenyl-1-ethenyl)-1,4-benzodioxin 5c** as a white solid (35%), m.p. 103°C, all with identical spectra to the products described above.

DIELS-ALDER REACTIONS OF 2-VINYL-1,4-BENZODIOXIN.

a) Carbon Dienophiles:-

Dimethyl acetylenedicarboxylate. Dimethyl acetylenedicarboxylate (0.80g, 5.6mmol) was added to a solution of 2-vinyl-1,4-benzodioxin (0.9g, 5.6mmol) in dry benzene and refluxed for 16 hours under nitrogen. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane /ethyl acetate 9:1) to give a white solid and a clear oil.

Dimethyl acetylenedicarboxylate adduct (6) was recrystallised from ethanol to give white needles, (0.85g, 50%), m.p. 67°C. Found; C,63.37; H,4.72% $C_{16}H_{14}O_6$ requires C,63.57; H,4.67%. $\nu_{max}(CCl_4)$ 2 953, 1 737, 1 715, 1 599, 1 493, 1 277, 1 255, 1 172 cm^{-1}; $\delta_H(CDCl_3)$ 3.14 (1H, ddd, J=3.3,6.8,24.2Hz), 3.38 (1H, ddd, J=3.3,6.8,24.2Hz), 3.82 (3H, s), 3.88 (3H, s), 5.31 (1H, t, J=6.8Hz), 5.51 (1H, t, J=3.3Hz), 6.84-6.98 (4H, m); $\delta_C(CDCl_3)$ 166.86, 166.07, 144.05, 142.81, 142.70, 136.42, 130.65, 122.51, 122.07, 117.68, 116.24, 99.72, 66.08, 52.62, 52.55, 28.08; m/z, 302 (M^+,23.7%), 270 (100).

3,4-Dicarbomethoxyphenoxy-2'-hydroxybenzene (9) as a colourless oil (b.p. 250°C/0.01mmHg), (0.20g, 11%). Found; M^+ 302.0795 $C_{16}H_{14}O_6$ requires M^+ 302.0790. $\nu_{max}(CCl_4)$ 3567, 2 952, 1 733, 1 495, 1 435, 1 289, 1 210, 1 121 cm^{-1}; $\delta_H(CDCl_3)$ 3.87 (3H, s), 3.88 (3H, s) 5.73 (1H, br s), 6.89-7.17 (6H, m), 7.70 (1H, m); $\delta_C(CDCl_3)$ 168.08, 166.72, 159.81, 147.81, 141.70, 135.51, 131.64, 126.27, 124.92, 121.06, 120.38, 118.57, 117.06, 116.78, 52.84, 52.57; m/z, 302 (M^+, 16.1%), 270 (100%).

Maleic anhydride Adduct (7a). A solution of maleic anhydride (0.60g, 6.2mmol) in dry benzene (5ml) was added to a solution of 2-vinyl-1,4-benzodioxin (0.48g, 3.0mmol) in dry benzene (5ml) and refluxed for 7 hours. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/ethyl acetate 9:1) to give a white solid (0.51g, 66%), m.p. 164°C. Found; M^+ 258.0536 $C_{14}H_{10}O_5$ requires M^+ 238.0528. $\nu_{max}(CCl_4)$ 2 950, 2 930, 2 860, 1 870, 1 795, 1 700, 1 600, 1 490, 1 370, 1 275,1 265, 1 205, 1 160 cm^{-1}; $\delta_H(CDCl_3)$ 2.55 (1H, dddd, J=1.8,2.4,7.1,17.9Hz), 2.95 (1H, ddd, J=1.3,6.6,17.9Hz), 3.42 (1H, ddd, J=1.3,7.1,8.7Hz), 3.97 (1H, dd, J=8.7,8.8Hz), 4.67 (1H, d, J=8.8Hz), 5.59 (1H, dd, J=2.4,6.6Hz), 6.90-6.96 (4H, m); $\delta_C(CDCl_3)$ 171.74, 144.10, 142.73, 142.02, 123.06, 122.51, 117.78, 116.26, 102.68 , 62.67, 44.59, 38.05, 19.71; m/z, 258 (M^+, 100%), 186 (81.8) 134 (37.3).

Tetracyanoethene Adduct (7b). Tetracyanoethene (0.4g, 3.12mmol) was added to a solution of 2-vinyl-1,4-benzodioxin (0.5g, 3.12mmol) in dry benzene (5ml) and stirred under nitrogen for 16 hours to give a green solution. The solvent was removed *in vacuo* and the residue recrystallised from acetonitrile to give a white solid (0.68g, 76%), m.p. 209°C. Found; M^+ 288.0640 $C_{16}H_8N_4O_2$ requires M^+ 288.0647. ν_{max}(nujol) 2 258, 1 697, 1 608, 1 498, 1 306, 1 285, 1 268 cm^{-1}; $\delta_H(CD_3CN)$ 3.38 (1H, ddd, J=2.6,2.9,18.7Hz), 3.55 (1H, ddd, J=1.2,5.3,18.7Hz), 5.48 (1H,ddd, J=1.2,1.2,2.6Hz), 5.66 (1H, ddd, J=1.2,2.9,5.3Hz), 7.03-7.17 (4H, m); $\delta_C(CD_3CN)$ 142.04, 141.46, 140.86, 125.43, 124.64, 118.46, 117.56, 111.59, 111.00, 110.84, 108.78, 100.59, 69.21, 45.44, 39.30, 31.30 ; m/z, 288(M^+,59.7%), 160 (100).

b) Azo Dienophiles:-

GENERAL METHOD. To a solution of the 2-vinyl-1,4-benzodioxin (0.45g, 2.8mmol) in ethanol (6ml) was added a solution of the dienophile (2.8mmol) in ethanol (10ml) and the mixture ws stirred for 4 hours. The white precipitate was filtered and recrystallised from ethanol. The following compounds were prepared by this method:-

Di-*tert*-butyl azodicarboxylate adduct (7c) as white needles (86%), m.p.183°C. Found; C,61.56; H,6.70; N,7.06% $C_{20}H_{26}N_2O_6$ requires C,61.52; H,6.71; N,7.18%. ν_{max} (CCl_4) 2 982, 1 714, 1 492, 1 368, 1 258, 1 154 cm^{-1}; $\delta_H(CDCl_3)$ 1.49 (9H, s), 1.53 (9H, s), 3.75 (1H, d, J=15.0Hz), 4.69 (1H, d, J=15.0Hz), 5.64 (1H, s), 5.94 (1H, s), 6.90 (4H, br s); $\delta_C(CDCl_3)$ no ^{13}C=O, 142.65, 141.99, 122.60, 122.25, 117.99, 116.26, 103.05, 82.54, 81.59, 74.30, 41.82, 28.14, 28.07; m/z, 390 (M^+,2.7%), 261 (6), 234 (79), 189 (60), 57 (100).

Dibenzyl azodicarboxylate adduct (7d) as white needles (78%), m.p.103°C. Found; C,67.84; H,4.84; N,6.07% $C_{26}H_{22}N_2O_6$ requires C,68.11; H,4.84; N,6.11%. $\nu_{max}(CCl_4)$ 3 070, 3 035, 2 950, 2 900, 1 725, 1 695, 1 485, 1 410, 1 340, 1 320, 1 295, 1 275, 1 250, 1 230 cm^{-1}; $\delta_H(CDCl_3)$ 3.86, (1H, d, J=14.5Hz), 4.74 (1H, d, J=14.5Hz), 5.23 (4H, s), 5.64 (1H, s), 6.01 (1H, s), 6.93-7.00 (4H, s), 7.25-7.35 (10H, m); $\delta_C(CDCl_3)$ 155.25, 155.20, 142.21, 142.01, 141.79, 135.86, 128.49, 128.33, 127.92, 122.71, 122.62, 116.29, 102.68, 74.83, 68.73, 68.12, 42.51 ; m/z, 458 (M^+,10.0%), 414 (M^+-CO_2,5.8), 323 (M^+-CO_2Bz,33.3), 91 (100).

Diethyl azodicarboxylate adduct (7e) as white needles (74%) m.p. 152°C. Found; C,57.44, H,5.29; N,8.34% $C_{16}H_{18}N_2O_6$ requires C,57.48; H,5.43; N,8.38%. $\nu_{max}(CCl_4)$ 3050, 2 980, 2 935, 2 910, 2 860, 1 760, 1 740, 1 595 cm^{-1}; $\delta_H(CDCl_3)$ 1.29 (3H, t, J=7.1Hz), 1.33(3H, t, J=7.1Hz), 3.85 (1H, d, J=15.0Hz), 4.21-4.39 (4H, m), 4.73 (1H, d, J=15.0Hz), 5.66 (1H, s), 5.98 (1H, s), 6.91-6.98 (4H, m); $\delta_C(CDCl_3)$ no ^{13}C=O, 142.43, 141.91, 122.76, 122.61, 118.21, 116.32, 102.65, 75.03, 63.46, 62.83, 42.39, 14.77, 14.41; m/z, 334 (M^+,30.4%), 261 (M^+-CO_2Et,24), 189 (100).

Hydrogenation of 7e. A solution of the adduct (0.60g, 1.80mmol) in ethyl acetate (10ml) was stirred with 10% palladium on charcoal (0.050g) under hydrogen (1 atm) for 8 hours. The solution was filtered and concentrated under reduced pressure to give a white solid which was recrystallised from methanol (0.48g, 80%). m.p. 99°C. Found; C,57.12; H,5.94; N,8.27% $C_{16}H_{20}N_2O_6$ requires C,57.13; H,5.99; N,8.33%. $\nu_{max}(CCl_4)$ 2 983, 1 717, 1 598, 1 494, 1 380, 1 316, 1 250, 1 069 cm^{-1}; $\delta_H(CDCl_3)$ 1.31 (6H, m), 2.00 (2H, m), 3.13 (1H, m,), 4.16-4.22 (6H, m), 6.06 (1H, m), 6.83-6.87 (4H, m); $\delta_C(CDCl_3)$ no ^{13}C=O, 141.08 (C_9), 139.72 (C_{10}), 122.19 (C_7), 121.67 (C_6), 117.16 (C_8), 117.08 (C_5), 76.12 (C_2), 68.55 (C_3), 62.92 (C_{15}), 62.38 (C_{17}), 43.01 (C_{13}), 23.60 (C_{14}), 14.41 (C_{16}), 14.33 (C_{18}); m/z, 336 (M^+,100%), 263 (M^+-CO_2Et,74.9), 156 (58.8), 83 (52.7).

Hydrogenation of 7c. A solution of the adduct (0.60g, 1.54mmol) in ethyl acetate (10ml) was stirred with 10% palladium on charcoal (0.040g) under hydrogen (1 atm) for 8 hours. The solution was filtered and

concentrated under reduced pressure to give a white solid which was recrystallised from ethanol (0.54g, 91%). Found; C,60.98; H,7.25; N,6.91% $C_{20}H_{28}N_2O_6$ requires C,61.21; H,7.19; N,7.14%. $\nu_{max}(CCl_4)$ 2 981, 1 710, 1 495, 1 368, 1 251, 1 174 cm^{-1}; $\delta_H(CDCl_3)$ 1.46 (9H, s), 1.51 (9H, s), 1.60-2.00 (2H, m), 3.06 (1H, m), 4.30-4.39 (2H, m), 6.03 (1H, brs), 6.85 (4H, s); $\delta_C(CDCl_3)$ 155.13, 141.51, 140.00, 122.02, 121.70, 117.22, 117.16, 81.14, 68.90, 42.41, 28.22, 28.10, 23.87; m/z, 392 (M^+,13.6%), 236 (62.4), 57 (100).

Removal of *tert*-Butyl Ester Groups from Hydrogenated 7e. To a solution of the hydrogenated di-*tert*-butyl azodicarboxylate adduct (1.46g, 3.6mmol) in dry dichloromethane (5ml) under nitrogen was added trifluoroacetic acid (3ml) with stirring for 30 minutes. The volatile residues were removed *in vacuo*, and the resulting oil dissolved in chloroform (15ml) and extracted with sodium hydroxide solution (10ml, 0.1M). The organic fraction was dried ($MgSO_4$) and evaporated to give a clear oil. This liquid was dissolved in anhydrous THF (10ml) and hydrogen chloride in anhydrous diethyl ether (2ml, 2.2M soln, 4.5mmol) was added. The resultant white solid was filtered and washed with ethanol/ dichloromethane 1:1 (0.52g, 63%), m.p. 120°C (d). Found; C,52.34; H,5.87; N,12.02% $C_{10}H_{13}N_2O_2Cl$ requires C,52.52; H,5.73; N,12.25%. ν_{max}(nujol) 3 380, 1 597, 1 508, 1 274, 1 089, 1 048 cm^{-1}; $\delta_H(d_6\text{-DMSO})$ 1.80-2.10 (2H, m), 3.10-3.25 (2H, m), 4.54 (1H, ddd, J=2.5,4.8,10.5Hz), 5.23 (1H, d, J=2.5Hz), 6.90 (4H, s), 7.46 (1H, br s), 10.00 (1H, br s), 11.33 (1H, br s); $\delta_C(d_6\text{-DMSO})$ 140.91, 140.29, 122.36, 121.81, 117.40, 117.16, 78.04, 66.38, 42.37, 22.11; m/z, 192 (M^+-HCl,29.1%), 110 (81.1), 83 (100).

Hydrogenation of 7d. A solution of the adduct (0.90g, 1.96mmol) in ethyl acetate (10ml) was stirred with 10% palladium on charcoal (0.050g) under hydrogen (1 atm) for 8 hours. The suspension was filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in anhydrous THF (3ml) and hydrogen chloride in anhydrous diethyl ether (3.0ml, 0.8M soln, 2.4mmol) was added. More anhydrous diethyl ether was added until a white solid precipitated which was filtered and recrystallised from methanol (0.19g, 43.0%), m.p.170°C d. Found; C,53.46; H,3.90; N,12.60% $C_{10}H_9N_2O_2Cl$ requires C,53.46; H,4.04; N,12.47%. $\nu_{max}(CHBr_3)$ 3 250, 3 180, 1 610, 1 585, 1 490 cm^{-1}; $\delta_H(d_3\text{-MeOD})$ 7.10-7.40 (4H, m), 7.65 (1H, dd, J=2.6,6.8Hz), 9.22 (1H, d, J=2.6), 9.33 (1H, d, J=6.8Hz); $\delta_C(d_3\text{-MeOD})$ 164.15, 149.12, 147.74, 146.15, 139.75, 129.97, 122.87, 122.56, 118.97, 116.54; m/z, 188 (M^+-HCl,100%), 110 (36.6), 83 (75.4).

3,4-Dicarbomethoxyphenoxy-2'-hydroxybenzene (9). To a stirred suspension of potassium *tert*-butoxide (0.17g, 1.51mmol) in dry diethyl ether (5ml) under nitrogen was added a solution of the dimethyl acetylene dicarboxylate adduct (6) (0.30g, 1.0mmol) in diethyl ether (5ml) and the suspension was stirred for 2 hours. The solid was filtered off and the solvent removed under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane 85:15) to give 3,4-dicarbomethoxy-phenoxy-2'-hydroxybenzene (9) as a clear oil (0.21g, 70%) with identical spectra to the product described above.

THE PREPARATION OF ANALOGUES OF SIMPLE BIOLOGICALLY IMPORTANT INDOLES

GENERAL METHOD. To a solution of 1,4-benzodioxin (3.40g, 25.4mmol) in dry THF (150ml) at -78°C under a nitrogen atmosphere was added n-butyllithium (10.2ml, 2.75M soln in hexanes, 27.9mmol) and the mixture was stirred at -78°C for 2 hours to give a colourless solution. Boron trifluoride etherate (3.6g, 25.4mmol) and the epoxide (38.1mmol) were added and the reaction was stirred at -78°C for 30 minutes to give a yellow solution. Saturated ammonium chloride solution (50ml) and diethyl ether (50ml) were added and the aqueous layer was washed with diethyl ether (100ml). The combined organic extracts

were dried ($MgSO_4$) and concentrated under reduced pressure to give a residue which was purified by flash column chromatography. The following compounds were prepared by this method:-

2-(2-Hydroxy-1-ethyl)-1,4-benzodioxin (11) obtained after flash column chromatography (petrol/ethyl acetate 88:12) and distillation (b.p.135°C/0.1mmHg) as a colourless liquid (84%). Found; M^+ 178.0636 $C_{10}H_{10}O_3$ requires M^+ 178.0630. $\nu_{max}(CCl_4)$ 3 613, 2 960, 1 710, 1 601, 1 495, 1 257, 1 102 cm^{-1}; $\delta_H(CDCl_3)$ 2.05 (1H, br s), 2.20 (2H, dt, J=0.9,5.9Hz), 3.76 (2H, t, J=5.9Hz), 5.79 (1H, t, J=0.9Hz), 6.61-6.86 (4H,m); $\delta_C(CDCl_3)$ 142.14, 142.20, 134.55, 124.05, 123.77, 122.94, 116.03, 115.94, 59.06, 32.58; m/z, 178 (M^+,64.8%), 147 (M^+-CH_2OH,100).

2-(2-Hydroxy-1-propyl)-1,4-benzodioxin (12) obtained after flash column chromatography (petrol/ethyl acetate 9:1) as a colourless liquid (61%). Found; M^+ 192.0795 $C_{11}H_{12}O_3$ requires M^+ 192.0786. $\nu_{max}(CCl_4)$ 3 604, 2 934, 2 861, 1 709, 1 600, 1 583, 1 497, 1 255, 1 108 cm^{-1}; $\delta_H(CDCl_3)$ 1.23 (3H, d, J=6.2Hz), 2.02 (1H, ddd,J=0.9,7.7,14.7Hz), 2.08 (1H, ddd, J=0.9,4.6,14.7), 3.48 (1H, br s), 4.03 (1H, m), 5.77 (1H, t, J=0.9Hz), 6.60-6.83 (4H, m); $\delta_C(CDCl_3)$ 142.34, 142.15, 134.92, 124.00, 123.72, 123.12, 115.99, 115.89, 64.63, 26.31, 22.56; m/z 192 (M^+,100%), 148 (67.0), 147 (62.4), 45 (40.5).

2-(2-Toluenesulphonyl-1-ethyl)-1,4-benzodioxin. To a solution of 2-(2-hydroxy-1-ethyl)-1,4-benzodioxin (11) (2.0g, 11.2mmol) and tosyl chloride (2.46g, 12.9mmol) in dry dichloromethane (20ml) at 0°C under nitrogen was added triethylamine (1.30g, 12.9mmol). The mixture was stirred for 16 hours at 0°C when saturated sodium bicarbonate solution (20ml) was added, the organic layer separated and dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash column chromatography (petrol/ethyl acetate 19:1) to yield a white solid, (3.24g, 87%), m.p. 76°C. Found; C,61.35; H,5.09% $C_{17}H_{16}O_5S$ requires C,61.43; H,4.85%. $\nu_{max}(CCl_4)$ 2 967, 1 716, 1 600, 1 495, 1 258, 1 189, 1 179 cm^{-1}; $\delta_H(CDCl_3)$ 2.27 (2H, dt, J=0.9,6.2Hz), 2.33 (3H, s), 4.15 (2H, t, J=6.2Hz), 5.69 (1H, t, J=0.9Hz), 6.43-6.80 (4H, m), 7.50 (4H, dd, J=14.9Hz); $\delta_C(CDCl_3)$ 144.80, 142.16, 141.89, 132.75, 132.35, 129.72, 127.87, 124.05, 123.76, 123.45, 115.91, 65.79, 29.33, 21.58; m/z, 332 (M^+,2.9%), 172 (100), 91 (96.9).

2-(2-Bromo-1-ethyl)-1,4-benzodioxin (13). A solution of 2-(2-toluenesulphonyl-1-ethyl)-1,4-benzodioxin (2.0g, 6mmol) in dry THF (20ml) and lithium bromide (1.2g, 13.8mmol) was heated under reflux for 18 hours under nitrogen. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (hexane) to give a colourless oil (1.02g, 70%). Found; M^+ 239.9793 $C_{10}H_9O_2Br$ requires 239.9785. ν_{max} (CCl_4) 3 052, 2 975, 1 709, 1 601, 1 511, 1 490, 1 342, 1 251, 1 138, 1 092, 939; $\delta_H(CDCl_3)$ 2.50 (2H, t, J=7.0Hz), 3.50 (2H, dt, J=0.9,7.0Hz), 5.82 (1H, t, J=0.9Hz), 6.61-6.83 (4H, m); $\delta_C(CDCl_3)$ 142.46, 142.11, 134.51, 124.09, 123.87, 123.33, 116.06, 116.00, 32.96, 28.56 ; m/z, 240,242 (M^+,70.0%,68.1%), 161 (M^+-Br,12.3), 147 (M^+-CH_2Br,100).

2-(2-Phthalimido-1-ethyl)-1,4-benzodioxin. To a solution of 2-(2-hydroxy-1-ethyl)-1,4-benzodioxin (2.8g, 15.7mmol), triphenyl phosphine (4.4g, 16.7mmol) and phthalimide (2.4g, 16.7mmol) in dry THF (20ml) at 0°C under nitrogen was added diethyl azodicarboxylate (2.75mmol, 15.8mmol) dropwise over 10 minutes. After stirring for 16 hours saturated sodium chloride solution (10ml) was added and the mixture was washed with diethyl ether (2x20ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting solid was purified by column chromatography (hexane/ethyl acetate 9:1) to yield a white solid (3.72g, 77%), m.p. 123°C. Found; C,70.14; H,4.21; N,4.42% $C_{18}H_{13}NO_4$ requires C,70.35; H,4.26; N4.56%. $\nu_{max}(CCl_4)$ 2 948, 1 776, 1 722, 1 459, 1 257, 1 126, 1 083, 956cm^{-1}; $\delta_H(CDCl_3)$ 2.36 (2H, t, J=6.8Hz), 3.89 (2H, t, J=6.8Hz), 5.73 (1H, s), 6.55-6.80 (4H, m), 7.69-7.85 (4H, m); $\delta_C(CDCl_3)$ 168.08, 142.51, 142.08, 134.57, 133.94, 132.08, 123.91, 123.84, 123.28, 122.94, 116.23, 115.83,

35.26, 28.25; m/z 307 (M^+,50.4%), 160 (100).

2-(2-Amino-1-ethyl)-1,4-benzodioxin (14). To a solution of 2-(2-phthalimido-1-ethyl)-1,4-benzodioxin (1.67g, 5.4mmol) in anhydrous THF (10ml) was added anhydrous hydrazine (0.35g, 10.8mmol) with stirring under nitrogen for 30 minutes yielding a white suspension. The solid was filtered, washed with dry THF (2x5ml) and the filtrate was evaporated under reduced pressure. The residue was dissolved in THF (5ml) and hydrogen chloride in diethyl ether (2.9ml, 2.2M soln, 6.5mmol) was added and the mixture was stirred for 5 minutes. The volatile residues were removed *in vacuo* to give a white solid which was recrystallised from ethanol (1.00g, 87%), m.p. 154°C (d). Found; C,55.75; H,5.95; N,6.48% $C_{10}H_{12}NO_2Cl$ requires C,56.21; H,5.66; N,6.56%. ν_{max}(nujol) 2 449, 2 101, 1 712, 1 595, 1 243, 1 206, 1 122, 1 095 cm^{-1}; δ_H(d_3-MeOD) 2.35 (2H, dt, J=0.9,6.8Hz), 3.09 (2H, t, J=6.8Hz), 6.02 (1H, t, J=0.9Hz), 6.63-6.86 (4H, m); δ_C(d_3-MeOD) 143.58, 143.26, 134.31, 125.48, 125.19, 125.00, 117.20, 117.05, 37.70, 28.22; m/z, 177 (M^+-HCl,28.7%), 148 (100), 52 (19.3), 30 (97.4).

2-(2-Phthalimido-1-propyl)-1,4-benzodioxin. To a solution of 2-(2-hydroxy-1-propyl)-1,4-benzodioxin (3.0g, 15.7mmol), triphenyl phosphine (4.4g, 16.7mmol) and phthalimide (2.4g, 16.7mmol) in dry THF (20ml) at 0°C under nitrogen was added diethyl azodicarboxylate (2.75mmol, 15.8mmol) dropwise over 10 minutes. After stirring for 16 hours saturated sodium chloride solution (10ml) was added and the mixture was washed with diethyl ether (2x20ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting solid was purified by column chromatography (hexane/ethyl acetate 9:1) to yield a white solid (2.77g, 55%), m.p. 111°C. Found; C,71.06; H,4.73; N,4.41% $C_{19}H_{15}NO_4$ requires C,71.02; H,4.71; N,4.36%. ν_{max}(CCl_4) 2 980, 1 774, 1 714, 1 601, 1 492, 1 397, 1 378, 1 333, 1 263 cm^{-1}; δ_H($CDCl_3$) 1.50 (3H, d, J=7.0Hz), 2.41 (1H, dd, J=6.0,14.8Hz), 2.76 (1H, dd, J=9.4,14.8Hz), 4.68 (1H, ddq, J=6.0,7.0,9.4Hz), 5.72 (1H, s), 6.47-6.76 (4H, m), 7.63-7.82 (4H, m); δ_C($CDCl_3$) 168.31, 142.48, 142.10, 134.86, 133.86, 131.97, 123.86, 123.80, 123.27, 123.14, 116.11, 115.76, 44.27, 33.35, 18.20; m/z, 321 (M^+,34.5%), 174 (100).

2-(2-Amino-1-propyl)-1,4-benzodioxin (15). To a solution of 2-(2-phthalimido-1-propyl)-1,4-benzodioxin (1.30g, 4.0mmol) in anhydrous THF (10ml) was added anhydrous hydrazine (0.26g, 8.0mmol) with stirring under nitrogen for 30 minutes to yield a white suspension which was filtered, washed with dry THF (2x5ml) and the filtrate was evaporated under reduced pressure. The residue was dissolved in THF (5ml) and hydrogen chloride in diethyl ether (3.8ml, 2.2M soln, 8.4mmol) was added and the mixture was stirred for 5 minutes. The volatile residues were removed *in vacuo* to give a white solid which was recrystallised from ethanol (0.75g, 83%). Found; C,57.81; H,6.37; N,6.81% $C_{11}H_{14}NO_2Cl$ requires C,58.02; H,6.20; N,6.20%. ν_{max}(nujol) 2 057, 1 715, 1 601, 1 466, 1 261, 1 080 cm^{-1}; δ_H(d_3-MeOD) 1.37 (3H, d, J=6.6Hz), 2.35 (2H, ddd, J=0.9,6.8,15.0Hz), 3.52 (1H, dd, J=6.6,6.8Hz), 6.05 (1H, t, J=0.9Hz), 6.61-6.88 (4H, m); δ_C(d_3-MeOD) 143.52, 143.26, 134.15, 125.63, 125.51, 125.20, 117.22, 117.06, 46.45, 35.07, 18.44; m/z, 191 (M^+-HCl,5.8%), 148 (42.2), 44 (100).

2-(3-Bromo-1-propyl)-1-4-benzodioxin (17). To a solution of 1,4-benzodioxin (1.0g, 15mmol) in dry THF (40ml) at -78°C under a nitrogen atmosphere was added n-butyllithium (3.0ml, 2.70M soln in hexanes, 8.1mmol) and the mixture was stirred at -78°C for 2 hours to give a colourless solution. A solution of 1,3-dibromopropane (15mmol) in dry THF (5ml) was then added and stirred at -78°C for 2 hours and at 20°C for a further 8 hours. Saturated ammonium chloride solution (20ml) and diethyl ether (20ml) were added, the organic layer separated, and the aqueous layer was washed with diethyl ether (2x20ml). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a residue which was

purified by flash column chromatography (hexane) and kugelrohr distillation (b.p.135°C/ 0.05mmHg) to give a colourless oil (61%). $\delta_H(CDCl_3)$ 2.05-2.45 (4H, m), 3.40-3.60 (2H, m), 5.75 (1H, m), 6.50-6.95 (4H, m).

2-(3-Phthalimido-1-propyl)-1,4-benzodioxin. To a solution of 2-(3-bromo-1-propyl)-1,4-benzodioxin (1.40g, 5.50mmol) in dry DMF was added potassium phthalimide (1.40g, 7.56mmol) and stirred for 16 hours. The reaction was poured into water (10ml) and extracted with chloroform (3x15ml). The combined organic extracts were washed with 10% sodium hydroxide solution (20ml), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid which was recrystallised from methanol (1.53g, 86%). Found; C,71.02; H,5.00; N,4.29% $C_{19}H_{15}NO_4$ requires C,71.02; H,4.71; N,4.36%. $\nu_{max}(CCl_4)$ 2 935, 1 774, 1 721, 1 601, 1 495, 1 395, 1 257 cm^{-1}; $\delta_H(CDCl_3)$ 1.88-2.06 (4H, m), 3.75 (2H, t, J=6.8Hz), 5.77 (1H, s), 6.52-6.80 (4H, m), 7.67-7.85 (4H, m); $\delta_C(CDCl_3)$ 168.34, 142.54, 142.21, 139.32, 133.83, 132.00, 123.76, 123.59, 123.11, 121.86, 115.97, 115.73, 37.20, 26.66, 24.70; m/z, 322 (M^++1,22.5%), 321 (M^+,100), 174 (30.0).

2-(3-Amino-1-propyl)-1,4-benzodioxin (18). To a solution of 2-(3-phthalimido-1-propyl)-1,4-benzodioxin (1.50g, 4.67mmol) in anhydrous THF (10ml) was added anhydrous hydrazine (0.30g, 9.34mmol) with stirring under nitrogen for 30 minutes to yield a white suspension. The solid was filtered, washed with dry THF (2x5ml) and the filtrate was evaporated under reduced pressure. The residue was dissolved in THF (5ml) and hydrogen chloride in diethyl ether (2.3ml, 2.2M soln, 5.5mmol) was added and the mixture was stirred for 5 minutes. The volatile residues were removed *in vacuo* to give a white solid which was recrystallised from ethanol (0.66g, 74%), m.p. 146°C (d). Found; C,57.63; H,6.41; N,6.18% $C_{11}H_{14}NO_2Cl$ requires C,58.02; H,6.20; N,6.20%. ν_{max}(nujol) 2 056, 1 713, 1 600, 1 496, 1 260, 1 079.cm^{-1}; $\delta_H(d_3$-MeOD) 1.87 (2H, dt, J=7.3,7.7Hz), 2.15 (2H, t, J=7.3Hz), 3.00 (2H, t, J=7.7Hz), 5.96 (1H, s), 6.60-6.84 (4H, m); $\delta_C(d_3$-MeOD) 143.87, 143.61, 137.45, 125.31, 125.01, 123.68, 117.08, 116.99, 39.99, 26.82, 25.32; m/z, 191 (M^+,100%), 174 (90.8).

2-(2-Piperidyl-1-ethyl)-1,4-benzodioxin (16). To a solution of 2-(2-bromo-1-ethyl)-1,4-benzodioxin (0.85g, 3.3mmol) in dry dichloromethane was added piperidine (0.75ml, 6.9mmol) with stirring under nitrogen for 2 hours. Potassium hydroxide solution (10ml, 1M soln) was added, the organic layer separated and the aqueous phase washed with dichloromethane (2x10ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a pink oil. This was dissolved in dry THF (5ml) and hydrogen chloride in diethyl ether (1.8ml, 2.2M soln, 3.9mmol) was added dropwise and the mixture was stirred for 5 minutes. The volatile residues were removed *in vacuo* to yield a white solid which was recrystallised from dry ethanol (0.70g, 71%), m.p. 216°C (d). Found; C,63.33; H,7.38; N,4.93% $C_{15}H_{20}NO_2Cl$ requires C,63.94; H,7.15; N,4.97%. ν_{max}(nujol) 2 608, 2 515, 1 708, 1 599, 1 491, 1 096, 937 cm^{-1}; $\delta_H(CDCl_3)$ 1.50-1.98 (6H, m), 2.53 (2H, dt, J=0.9,7.6Hz), 3.02 (2H, m), 3.26 (2H, t, J=7.6Hz), 3.58 (2H, m), 6.09 (1H, t, J=0.9Hz), 6.63-6.89 (4H, m); $\delta_C(CDCl_3)$ 143.50, 143.22, 134.31, 125.60, 125.27, 125.01, 117.15, 117.12, 54.94, 54.44, 25.27, 24.20, 22.65; m/z, 245 (M^+-HCl,1.4%), 147 (3.1), 98 (100).

2-(3-Piperidyl-1-propyl)-1,4-benzodioxin (19). To a solution of 2-(3-bromo-1-propyl)-1,4-benzodioxin (0.96g, 4.0mmol) in dry dichloromethane was added piperidine (0.89ml, 8.2mmol) with stirring under nitrogen for 2 hours. Potassium hydroxide solution (10ml, 1M soln) was added, the organic layer separated and the aqueous phase washed with dichloromethane (2x10ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a clear oil. This was dissolved in dry THF (5ml) and hydrogen chloride in diethyl ether (1.8ml, 2.2M soln, 3.9mmol) was added dropwise and the mixture was

stirred for 5 minutes. The volatile residues were removed *in vacuo* to yield a white solid which was recrystallised from dry ethanol (0.76g, 64%), m.p. 179°C (d). Found; C,64.87; H,7.52; N,5.04% $C_{16}H_{22}NO_2Cl$ requires C,64.96; H,7.50; N,4.74%. ν_{max}(nujol) 2 480, 1 706, 1 601, 1 498, 1 259, 1 079 cm^{-1}; $\delta_H(CDCl_3)$ 1.48 (1H, m), 1.73-2.02 (7H, m), 2.10 (2H, t, J=6.7Hz), 2.89-2.99 (2H, m), 3.10-3.17 (2H, m), 3.51 (2H, m), 5.97 (1H, s), 6.60-6.86 (4H, m); $\delta_C(CDCl_3)$ 143.81, 143.54, 137.13, 125.32, 125.04, 123.77, 117.10, 116.99, 57.40, 54.32, 27.03, 24.27, 22.70, 21.78; m/z, 259 (M^+-HCl,32.9%), 147 (4.9), 111 (14.0), 98 (100).

References and Notes

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