# An Investigation of Some Base Induced Transformations of The 1,4-Benzodioxan Ring System

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The reaction between benzodioxan-2-carboxylic acid and ethylenediamine has been examined and related base induced transformations investigated.

Recently we reported [1] a new synthesis of 2-[2-(1,4-benzodioxanyl)]-2-imidazoline (1) and showed that the previously claimed route [2] to this compound gave the formula isomer 2-[2-methyl-2-(1,3-benzodioxolyl)]-2-imidazoline (2).
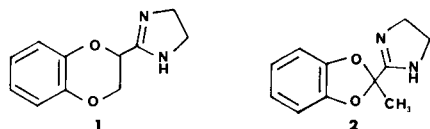


We report here an investigation of the original patent procedure [2] together with our results on some related ring transformations within the 1,4 benzodioxan system.
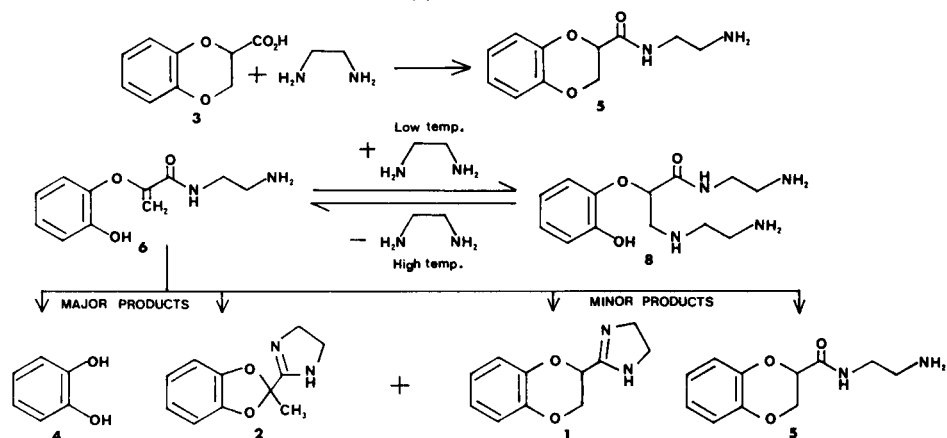
The reaction between ethylenediamine and 1,4-benzodioxan-2-carboxylic acid (3) under conditions quoted in [2] yielded four detectable products (see scheme I). The two major products were shown to be the dioxole 2 (45%) and catechol (4) (29%) with amide 5 (2%) and the dioxan 1 (6%) as minor components. An analytical investigation of this process has revealed that prior to the final distillation the reaction gave a major product which was different from the four mentioned above. Clearly therefore the distillation step is an integral part of the reaction process and it is assumed that an intermediate is produced which is thermally unstable forming catechol (4) and the dioxole 2 in the high temperature (160-170°) of the distillation. The reaction mixture, prior to the distillation step, was chromatographed and a sample of the intermediate was obtained. Specific tlc spray reagents gave results which were characteristic of a phenol and an amine. The uv spectrum showed a λ max of 275 nm with a reversible shift to 293 nm in alkali typical of a phenolic compound. The ir spectrum showed a carbonyl band at 1660 cms⁻¹ indicative of an amide.
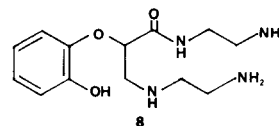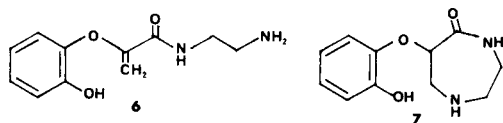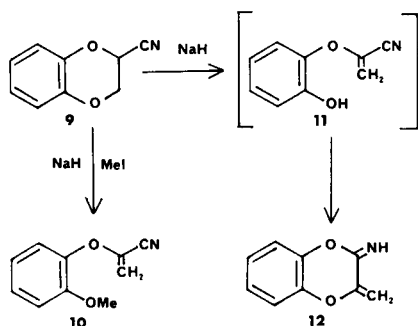




Initially it was assumed that the intermediate possessed structure 6 (see later) but the nmr spectrum showed no evidence of olefinic protons. A broad triplet at 4.59 ppm (1 proton) was shown to be coupled to a doublet at 3.08 ppm and this could be accommodated by structures 7 and 8. However the mass spectrum revealed a molecular ion of 282 which indicated structure 8 as the intermediate and this was finally confirmed by characterisation of its triphenylisothiocyanate derivative. The proposed structure 8 is a feasible intermediate for the products of the distillation as the base induced ring opening of the dioxan ring of 5 to give a phenol provides a route for conversion to the dioxole ring, which is thermodynamically more stable under the conditions of the final distillation (see [1] and compare [3]). Formation of an imidazoline ring from the amide grouping is also likely under these conditions. Further support for the above conclusions is given by the fact that 8 is also obtained by reaction of amide 5 with ethylenediamine under similar conditions to those used with acid 3, but is absent on reaction of 5 with tetramethyl-ethylenediamine. Thus amide 5 is proposed as a precursor of 8 and the overall sequence of events can be summarised as shown in Scheme I. In addition the phenol 6 has been obtained by treating amide 5 with sodium hydride and upon distillation 6 was shown to give a mixture of the four products depicted in scheme I.

Similar ring openings have also been observed with 2-cyanobenzodioxan (9) but subsequent ring closures were of a different nature. In the presence of sodium hydride and methyliodide the unsaturated nitrile 10 was isolated (Scheme II). In the absence of alkylating agent however the unstable phenol 11 was obtained which quickly recyclised to give the imino structure 12. Support for this type
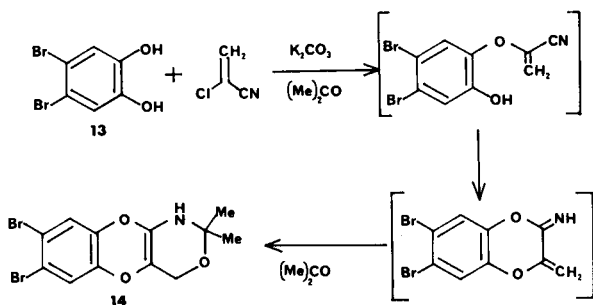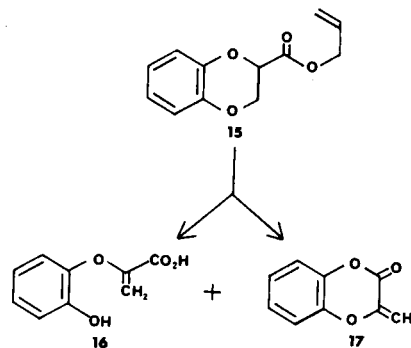
Scheme I



Scheme II



formed from an alternative ring closure of the phenol **16** in an analogous fashion to that described in scheme II.



of ring closure was obtained when 4,5-dibromocatechol (**13**) and chloroacrylonitrile were reacted together in the presence of potassium carbonate with acetone as solvent. The only isolable product was the 1,3-oxazine **14**. The likely sequence of events is shown in scheme III and involves the formation of an imine which then undergoes a 1,3 dipolar cyclo-addition with acetone to give the final product.

Scheme III



Finally in some related work it was observed that the allyl ester **15** on treatment with sodium hydride gave a complex mixture of products from which two unstable compounds were isolated and partially characterised. Spectroscopic data suggests these to be the phenol **16** and the lactone **17**

### EXPERIMENTAL

Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 700 or 397 spectrophotometer. Mass spectra were obtained from a Kratos MS 25 (DS 55 data system) or LKB -2091 instrument. Ultraviolet spectra were recorded on a Pye Unicam SP 800 spectrometer. Nuclear magnetic resonance spectra were taken at 60 MHz or 220 MHz (Varian Associates T-60 and Perkin Elmer R34 spectrophotometers) and chemical shifts are given relative to internal tetramethylsilane. Elemental analysis was performed on a Carlo Erba 1106 elemental analyser. Liquid chromatography was carried out with a system containing a Milton-Roy high pressure pump, Pye Unicam LC3 variable wavelength ultra-violet detector set at 275 nm and Rheodyne 7010A loop injector.

Reaction Between Ethylenediamine and 1,4-Benzodioxan-2-carboxylic acid (**3**).

a) The distilled reaction mixture was obtained following the literature procedure [2]. Analysis of this mixture was carried out, prior to hydrochloride salt formation, in the following way:

Catechol was separated in the reaction distillation product by reversed phase partition chromatography, using a 200 mm × 4.6 mm stainless steel column packed with Spherisorb 5 ODS and a mobile phase of 20% v/v methanol in water, containing 0.2 g/litre of citric acid. The presence of an acid modifier in this mobile phase prevented elution of the imidazoline products **1** and **2** and the amide **5** but allowed separation and determination of benzodioxan-2-carboxylic acid (**3**) as well as catechol (**4**).

The imidazoline products **1** and **2** and the amide **5** were separated and determined in the reaction distillation product by partition chromatogra-

phy on a 200 mm × 4.6 mm stainless steel column packed with Spherisorb S 5W silica and a mobile phase of 50% v/v methanol in water, containing 0.5 g/litre of ammonium carbonate. Catechol (4) and benzodioxan-2-carboxylic acid (3) were completely retained in this system.

Samples (20 μl) dissolved in methanol (0.5 mg/ml) were injected and comparison of peak heights with external standards were used for quantitation.

Of the total distillate 82% was accounted for by the above assays including 29% catechol (4), 45% dioxole 2, 6% dioxan 1 and 2% amide 5. The identities of these products were confirmed by nmr [1] and tlc.

b) *N*-(2-Aminoethyl)-3-(2-aminoethylamino)-2-(2-hydroxyphenoxy)propanamide (8).

Analysis of this reaction was also carried out prior to the final distillation and tlc indicated the reaction mixture contained two major components, the intermediate 8 and ethylenediamine. A Merck Kieselgel 60 F254 tlc plate with developing solvent chloroform/methanol/ammonia/water (80/54/6/10 by volume) and detection by iodine vapour was used. The intermediate 8 also gave a positive reaction with the following specific spray reagents: Ninhydrin spray reagent for amines and ferric chloride/ferricyanide reagent for phenols.

A portion of the reaction mixture was chromatographed on silica to give a sample of the intermediate 8 for spectroscopic analysis: ir (potassium bromide): 1660 cm$^{-1}$ (amide); uv (methanol): λ max 275 nm reversible shift to 293 nm in alkali (0.1 *N* sodium hydroxide); ms: (M)$^+$ m/e 282, (M-NH$_3$) m/e 265, (M-CH$_2$NH$_2$) m/e 252, (M-CH$_2$NH$_2$-H$_2$O) m/e 234, (M-NH$_2$CH$_2$CH$_2$NH$_2$) m/e 222, (M-NH$_2$CH$_2$CH$_2$NH$_2$-CH$_2$NH$_2$) m/e 192; nmr (methanol-d$_4$): δ 2.80 (m, 8, N-CH$_2$'s), 3.08 (d, 2, CH-CH$_2$), 4.59 (t, 1, CH$_2$-CH), 6.7-7.1 (m, 4, aromatic H).

Triphenylisothiocyanate Derivative of Propanamide 8.

To a solution of a mixture of 8 and ethylene diamine (see above) (0.15 g, 0.00053 mole) in 2 ml of methanol was added dropwise phenylisothiocyanate (0.38 g, 0.0028 mole). After 2 hours the solvent was removed *in vacuo* and the residue chromatographed on silica with 20% m e t h a n o l / -
chloroform to give 0.05 g (14%) of an amorphous white solid.

*Anal.* Calcd. for C$_{34}$H$_{37}$N$_7$O$_3$S$_3$: C, 56.09; H, 5.74; N, 13.47. Found: C, 56.17; H, 5.51; N, 13.04.

*N*-(2-Aminoethyl)-1,4-benzodioxan-2-carboxamide (5).

To a stirred solution of ethylenediamine (37.5 g, 0.62 mole) in 100 ml of ethanol was added dropwise ethyl 1,4-benzodioxan-2-carboxylate (25 g, 0.12 mole) [4]. After 2 hours at room temperature solvent was removed *in vacuo* and the residue partitioned between dichloromethane and water. The organic phase was collected, washed with water, aqueous sodium chloride, dried (sodium sulphate) and evaporated to leave 21 g of a white solid.

Recrystallisation from ethanol/ethereal hydrochloric acid gave 20.4 g (66%) of a white solid, mp 217-218°.

*Anal.* Calcd. for C$_{11}$H$_{15}$ClN$_2$O$_3$: C, 51.07; H, 5.84; N, 10.83. Found: C, 50.87; H, 5.91; N, 10.47.

Reaction of Amide 5 with Ethylene Diamine.

A mixture of amide 5 (0.23 g, 0.001 mole) and ethylenediamine (0.23 g, 0.0038 mole) was heated at 140° for 16 hours. The intermediate 8 was obtained from this reaction using the same procedure described above in the preparation of 8. When the reaction was repeated using tetramethylethylenediamine as the reagent tlc indicated that no reaction occurred.

*N*-(2-Aminoethyl)-2-(2-hydroxyphenoxy)-2-propenamide (6).

To a solution of amide 5 (1.11 g, 0.005 mole) in 10 ml of anhydrous dimethylformamide was added sodium hydride (50% dispersion in oil 0.24 g, 0.005 mole) and the mixture was stirred and heated at 70° for 1 hour. On cooling saturated aqueous ammonium chloride was added and the product was extracted with dichloromethane. The combined extracts were dried (sodium sulphate) and evaporated to leave a wet solid which

on trituration with ether gave 0.65 g (59%) of a cream solid. A portion of this hygroscopic material was recrystallised from ethanol to give an analytically pure sample, mp 147-149°; δ nmr (DMSO-d$_6$): 2.70 (t, 2, NCH$_2$), 3.25 (t, 2, NCH$_2$), 4.20 (d, 1, =CH), 5.26 (d, 1, =CH), 6.6-7.2 (4, m, aromatic H).

*Anal.* Calcd. for C$_{11}$H$_{14}$N$_2$O$_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.14; H, 6.22; N, 12.08. The analysis figures indicate that this hygroscopic material contains 1% water (w/w).

Distillation of Propenamide 6.

Distillation of 6 at 250°/0.5 mm gave a mixture of products which by tlc and hplc were shown to be catechol (4) and dioxole 2 as the major products and dioxan 1 and amide 5 as the minor products.

2-(2-Methoxyphenoxy)-2-propenonitrile (10).

To a solution of 2-cyano-1,4-benzodioxan (9) (1.61 g, 0.01 mole) [5] in 10 ml of dimethyl sulphoxide was added sodium hydride (50% dispersion in oil, 0.5 g, 0.011 mole) over 5 minutes at room temperature. After hydrogen evolution had ceased, methyl iodide (14.2 g, 0.1 mole) was added in one portion and slight evolution of heat was noted. After stirring for 2 hours at room temperature the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed successively with water, 2*N* sodium hydroxide solution and water, dried (magnesium sulphate) and evaporated to give a brown oil which was distilled to yield 1.1 g (63%) of a colourless oil; ms: (M$^+$) m/e 175; nmr (deuteriochloroform): δ 3.90 (s, 3, OCH$_3$), 5.02 (d, 1, =CH), 5.20 (d, 1, =CH), 6.7-7.4 (m, 4, aromatic H).

Reaction of 2-Cyano-1,4-benzodioxan (9) With Sodium Hydride.

Sodium hydride (0.75 g, 0.03 mole) was added to a solution of 9 (5.0 g, 0.03 mole) in 35 ml of anhydrous tetrahydrofuran and the mixture was stirred at room temperature for 5 hours. The reaction mixture was poured into excess water and acidified (2*N* hydrochloric acid). The inorganic phase was washed with dichloromethane and ethyl acetate. The combined extracts were washed with saturated sodium chloride, dried (sodium sulphate) and the solvent removed *in vacuo* to give 3.9 g of a brown oil. Although this oil was shown by tlc to be a mixture the nmr spectrum revealed signals consistent with 2-(2-hydroxyphenoxy)-2-propenonitrile (11); nmr (DMSO-d$_6$): δ 5.12 (d, 1, =CH), 5.54 (d, 1, =CH), 6.7-7.3 (m, 4, aromatic H). This oil on standing changed to a red solid which was purified chromatographically on silica with chloroform initially followed by 5% methanol/chloroform for later fractions. A solid was obtained which was recrystallised from ethyl acetate/light petroleum (bp 40-60°) to give 0.93 g (19%) of 2-imino-3-methylene-1,4-benzodioxan (12), as a white solid, mp 178-180°; ir (nujol): 3475, 1630, 1600 cm$^{-1}$; ms: (M)$^+$ m/e 161; nmr (DMSO-d$_6$): δ 4.78 (d, 1, =CH), 6.10 (d, 1, =CH), 6.6-7.3 (m, 4, aromatic H), 10.10 (s, 1, NH).

*Anal.* Calcd. for C$_9$H$_7$NO$_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.86; H, 4.40; N, 8.52.

A second compound was obtained from the chromatographic purification as a solid and recrystallised from ethylacetate/light petroleum (bp 40-60°) gave 0.15 g (3%) of a white solid, mp 129-131°. The following data found for this compound is consistent with 2-(2-hydroxyphenoxy)-2-propenamide; ir (nujol): 1670 cm$^{-1}$ (amide); ms: (M)$^+$ m/e 179; nmr (DMSO-d$_6$): δ 4.25 (d, 1, =CH), 5.30 (d, 1, =CH), 7.00 (s, 4, aromatic H), 7.3-7.8 (broad s, 2, NH$_2$).

*Anal.* Calcd. for C$_9$H$_9$NO$_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 59.93; H, 5.14; N, 7.60.

7,8-Dibromo-2,4-dihydro-2,2-dimethyl-1*H*-1,3-oxazino[4,5-*b*]1,4-benzodioxin (14).

A mixture of 4,5-dibromocatechol (13) [6] (57 g, 0.26 mole), chloroacrylonitrile (18 g, 0.21 mole), anhydrous potassium carbonate (84 g, 0.61 mole) and 400 ml of acetone was heated under reflux conditions for 18 hours with stirring. On cooling water was added and the product extracted with dichloromethane. The combined extracts were washed with 2*N* sodium hydroxide, 2*N* hydrochloric acid and saturated sodium chloride,

dried (sodium sulphate) and evaporated to leave 10 g of a brown solid which was shown by tlc to be a mixture. An attempt was made to convert the intermediate cyano compound to an imidazoline ring by heating a mixture of the crude product (10 g) and ethylenediamine (1.9 g, 0.03 mole) at 100° for 4 hours. The mixture was then chromatographed on silica with 5% methanol/chloroform to give 0.45 g (1%) of an off-white solid (pure by tlc). A portion was recrystallised from chloroform/light petroleum (bp 40-60°) to give an analytically pure sample, mp 171-173°; ir (nujol): 3520 (NH) cm⁻¹; ms: (M)⁺ m/e 379/377/375; nmr (DMSO-d₆/methanol-d₄): δ 1.28 (s, 3, CH₃), 1.38 (s, 3, CH₃), 3.98 (s, 1, NH), 4.18 and 4.76 (both d, together 2, CH₂), 7.42 (s, 2, aromatic H).

*Anal.* Calcd. for $C_{12}H_{11}Br_2NO_3$: C, 38.23; H, 2.94; N, 3.71. Found: C, 37.93; H, 2.90; N, 3.61.

Allyl-1,4-benzodioxan-2-carboxylate (**15**).

1,4-Benzodioxan-2-carbonyl chloride (7.4 g, 0.037 mole), allyl alcohol (2.2 g, 0.037 mole) and pyridine (2.96 g, 0.037 mole) were dissolved in 125 ml of anhydrous dichloromethane and the mixture was stirred at room temperature for 24 hours. The solution was washed with water, saturated sodium chloride and then dried (sodium sulphate). Removal of the solvent gave 6.7 g (82%) of a brown oil; ir (film): 1780, 1750, 1660 cm⁻¹; nmr (deuteriochloroform): δ 4.40 (d, 2, CH₂), 4.6-5.0 (m, 3, OCH + OCH₂), 5.26 ( d × m, 2, = CH₂), 5.6-6.2 (m, 1, =CH), 6.86 (s, 4, aromatic H).

Reaction of **15** With Sodium Hydride.

The ester **15** (1.5 g, 0.007 mole) was added to a stirred suspension of sodium hydride (0.17 g, 0.007 mole) in 20 ml of anhydrous dimethyl formamide at room temperature under an atmosphere of nitrogen. An exothermic reaction occurred and the mixture was cooled (ice-water bath) for 10 minutes. The suspension was stirred at room temperature for 24 hours and then poured into an excess of water. This solution was acidified (2*N* hydrochloric acid) and extracted with dichloromethane. The combined extracts were washed with saturated sodium chloride, dried (sodium sulphate) and evaporated to leave 1.7 g of a brown oil which was chromatographed on silica with chloroform initially and then with 0.20%

methanol/chloroform in 5% increments. Two slightly impure compounds were isolated and only partially characterised because of stability problems [7]. One component consisted of 0.2 g (18%) of a brown solid mp 142-144°. The spectroscopic data of this solid is consistent with 3-methylene-1,4-benzodioxan-2-one (**17**); ir (nujol): 1720 (C=O), 1600 (=CH₂) cm⁻¹; ms: (M)⁺ 162 m/e; nmr (DMSO-d₆): δ 4.70 (s, 1, =CH), 5.44 (s, 1, =CH) 6.6-7.2 (m, 4, aromatic H).

The second compound isolated was 0.3 g (24%) of a yellow oil and the following spectroscipic data is consistent with 2-(2-hydroxyphenoxy)-2-propenoic acid (**16**); ir (film): 3700-3200 (OH + CO₂H), 1690 (CO₂H), 1650 (=CH₂) cm⁻¹; ms: (M)⁺ 180 m/e; nmr (deuteriochloroform): δ 5.15 (s, 2, CO₂H + OH), 6.84 (pseudo s, 2, =CH₂), 8.00 (s, 4, aromatic H).

Acknowledgement.

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