

## A Synthetic Entry into the 2- and 3-Substituted-Methyl 2,3-Dihydro-1,4-benzoxazine Series

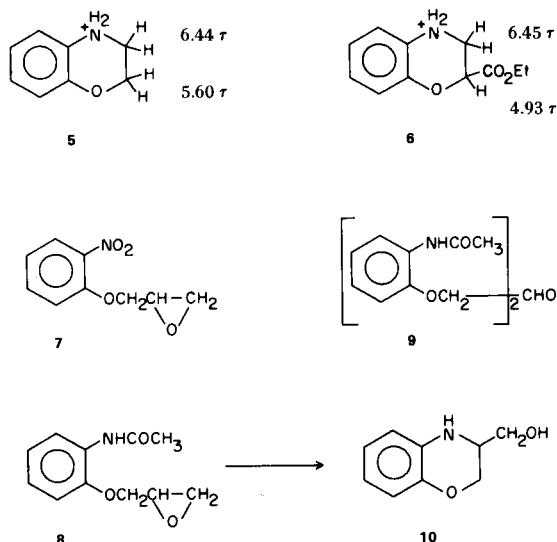
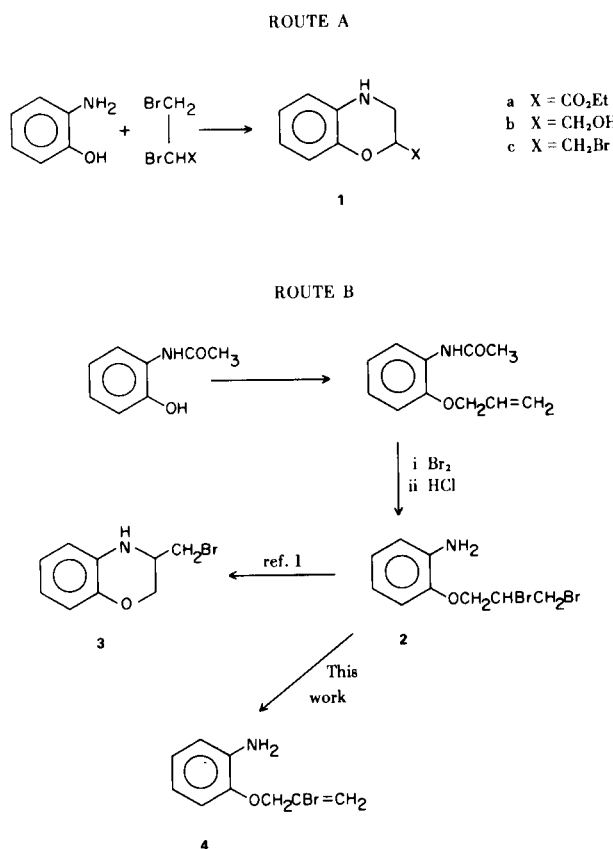
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Nmr spectroscopy has been used to demonstrate that the reported preparation of supposed 3-bromomethyl-2,3-dihydro-1,4-benzoxazine (**3**) is in error, the product of the reaction being in reality a monocyclic compound, **4**. An alternative entry to the 3-substituted series is described in the synthesis of the 3-hydroxymethyl derivative, **10**, the structure of which was established by nmr and mass spectroscopy. The previous assignment of structure to 2-carbethoxy-2,3-dihydro-1,4-benzoxazine, prepared by an ambiguous route, and to compounds derived from this ester, is shown to be correct.

We wished to obtain a synthetic access to the 2- and 3-methyl-substituted derivatives of 2,3-dihydro-1,4-benzoxazine. The synthesis of the 2-bromomethyl derivative **1c** via the ambiguous route A has been reported (2,3). The course of the reaction was considered (2) to be as shown,



resulting in 2-substitution, because the compound **1c** was different from the supposed 3-bromomethyl derivative **3** prepared by the unambiguous route B. In repeating this work we found that the final cyclisation in route B does not occur under the reported conditions: instead, the product is the isomeric 2-bromoallyl derivative **4**. In this paper we present spectral evidence to show that the structural assignment of the 2-substituted derivatives is correct, and we describe an unambiguous route into the 3-substituted series.

The ester **1a** was prepared by the described method (4) and the nmr spectrum of its protonated form (**6**) compared with that of the unsubstituted parent 2,3-dihydrobenzoxazine **5** (5). Upon introduction of the substituent, the 2-proton signal at 5.60 τ is replaced by a

1-proton signal showing the expected (6) downfield shift of 0.67 ppm while the signal for the protons at C<sub>3</sub> is unchanged in position. This confirms the 2-substitution for this compound and also for the corresponding amide and aminomethyl derivatives (4) and for **1b** and **1c**, all of which were derived from it.

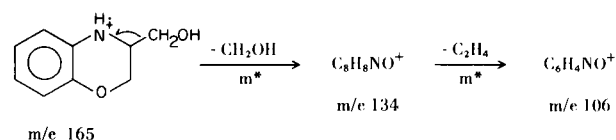
In attempting to repeat the sequence of reactions in Route B, the dibromo derivative **2** was isolated as reported (2), but on refluxing with potassium carbonate in acetone (3) it was recovered unchanged. However, treatment with ethanolic potash yielded a product, the hydrochloride of which had a m.p. some 20° lower (7) than that reported (2) for the supposed **3**, but with an infrared spectrum almost identical with that published. The nmr spectrum of this product indicated clearly that it had structure **4**. The absence of signals above 5  $\tau$  was incompatible with structure **3**, because all five aliphatic protons would be expected to resonate at field strengths higher than this (*cf.* **5**). Instead the spectrum showed only four aliphatic protons to be present, with the OCH<sub>2</sub> signal being 0.7 ppm downfield from that in **5**. This is consistent with the deshielding effect from an adjacent olefinic linkage, and the absence of any coupling of greater than 3 Hz indicated that a C=CH<sub>2</sub> rather than a CH=CH group was present. The product also reacted rapidly with bromine, and could be diazotised and coupled with 2-naphthol.

Treatment of **2** with triethylamine in dichloroethane according to the Russian workers gave in our hands a mixture of **2** and **4**. Thus it appears that treatment of **2** with basic reagents leads to an 1,2-elimination of hydrogen bromide rather than the cyclisation claimed.

As alternative routes to the 3-functionally substituted derivatives, several reactions starting from 2-nitrophenol were investigated. Attempted reaction with ethyl bromopyruvate was unsuccessful, and reaction with epichlorohydrin gave only low yields of the desired epoxide 1,2-epoxy-3-(2-nitrophenoxy)propane (**7**), which unfortunately proved unsuitable for further cyclisation experiments (8). Similarly reactions of 2-aminophenol with epichlorohydrin under a variety of conditions all ended in failure.

A successful synthesis was achieved by treating 2-acetamidophenol with epichlorohydrin under basic conditions to give **8**. Despite an excess of the epoxide the major product was the disubstituted propan-2-ol, **9**. Cyclisation of **8** with sodium hydride in dimethylformamide followed by hydrolysis of the amide function with hydrochloric acid gave **10** in good yield. The nmr spectrum (see Experimental) of compound **10**, when compared with that of **5**, was compatible with a 2,3-dihydro-1,4-benzoxazine structure assignment. Further evidence in support of this assignment was obtained from the mass spectrum. The major fragmentation followed the predicted  $\beta$ -elimination

pathway (scheme) with loss of  $\cdot\text{CH}_2\text{OH}$  (metastable) to give a base peak of  $m/e$  134, which underwent a further loss of C<sub>2</sub>H<sub>4</sub> (metastable) to give an ion of  $m/e$  106. This is in excellent accord with mass spectrum reported by Coulson *et al.* (9) for the 2 (or 3)-chloromethyl derivative.



As a synthetic intermediate for 3-substituted 2,3-dihydro-1,4-benzoxazine derivatives, the hydroxymethyl compound **10** is of obvious potential value. Acetylation with acetyl chloride yielded the *O*-acetate, whereas tosylation yielded the *N*-tosylate as the main product along with some of the *O,N*-bis derivative.

## EXPERIMENTAL

Melting points were taken on a Koffler block and are uncorrected. Nmr spectra were obtained on a Varian A60 instrument and ir spectra on a Perkin-Elmer 137 or 237 instrument. The mass spectrum was obtained on an A.E.I. MS 12 instrument, using the direct insertion probe.

### Attempted Cyclisation of 2-(2,3-Dibromopropoxy)aniline.

The dibromo compound **2** (10 g.) was heated under reflux with potassium hydroxide (3.3 g.) in ethanol (150 ml.) for 11 hours. The mixture was cooled, filtered, and evaporated. The residue was taken up in ether, filtered and treated with hydrogen chloride gas to give the hydrochloride salt (7.5 g., 97%) of 2-bromo-3-(2-aminophenoxy)propene (**4**). This was recrystallized from 1-butanol to give m.p. 181-187°;  $\nu$  max (nujol) 1640 cm<sup>-1</sup>, nmr (deuterium oxide)  $\tau$  2.42 (4H, m, Ar-H), 3.68 (1H, m) and 3.96 (1H, m, =CH<sub>2</sub>), 4.90 (2H, m, OCH<sub>2</sub>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>BrNO·HCl: C, 40.9; H, 4.2; N, 5.3. Found: C, 40.8; H, 4.3; N, 5.5.

Treatment of **2** with triethylamine-1,2-dichloroethane according to ref. 2, gave a product with m.p. 140-142°, the spectral properties of which indicated it to be a mixture of **2** and 4-2-(2,3-Epoxypropoxy)acetanilide (**8**).

2-Acetamidophenol (5 g., 33 mmoles) was added to a solution of sodium ethoxide (from 0.9 g. of sodium, 39 mmoles) in ethanol (100 ml.) under nitrogen. The resulting solution was added slowly to a refluxing solution of epichlorohydrin (17.7 g., 190 mmoles) in ethanol (100 ml.) under nitrogen by means of a pressure-equalizing dropping funnel. Refluxing was continued for 3 hours, and when cool, the mixture was treated with iced water (200 ml.) and brought to pH 7 with 2*N* hydrochloric acid. The mixture was extracted with methylene chloride and, after being washed with 2*N* sodium hydroxide and dried (magnesium sulfate), the organic layer was evaporated down. The residue was extracted with portions of boiling petrol (80-100°) (4 x 50 ml.) which, on cooling, yielded 2-(2,3-epoxypropoxy)acetanilide (**8**) (1.85 g., 18%), m.p. 103-105° (from ethanol or by sublimation); nmr (deuteriochloroform)  $\tau$  1.66 (1H, m, ArH<sub>6</sub>), 2.2 (1H, broad, NH), 3.05 (3H, m, remaining Ar-H), 5.5-6.3 (2H, AB part of ABX

pattern ArOCH<sub>2</sub>), 6.6 (1H, m,  $-\text{CH} \begin{array}{l} \text{CH}_2 \\ | \\ \text{O} \end{array}$ ), 7.0-7.3 (2H, m,  $-\text{CH} \begin{array}{l} \text{CH}_2 \\ | \\ \text{O} \end{array}$ ), 7.81 (3H, s, COCH<sub>3</sub>).

*Anal.* Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub>: C, 63.7; H, 6.3; N, 6.7. Found: C, 63.9; H, 6.6; N, 6.4.

The material which was insoluble in petrol was recrystallized from water-ethanol. This was 1,3-bis(2-acetamidophenoxy)propan-2-ol (**9**) (ca. 1.5 g., 25%), obtained in two forms, m.p. 110-112° and 160-165°, which were identical in ir, nmr, and chromatographic properties; nmr (DMSO-d<sub>6</sub>)  $\tau$  -0.08 (2H, s, 2NH), 1.95, (2H, m, 2 x Ar-H<sub>6</sub>), 2.9 (6H, m, remaining Ar-H), 4.29 (1H, d, OH), 5.78 (5H, broad, CH<sub>2</sub>CH(O)CH<sub>2</sub>), 7.90 (6H, s, 2 x COCH<sub>3</sub>).

*Anal.* Calcd. for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>: C, 63.7; H, 6.2; N, 7.8. Found: C, 63.4; H, 6.0; N, 7.6.

### 3-Hydroxymethyl-2,3-dihydro-1,4-benzoxazine (**10**).

The epoxide (**8**) (9.8 g., 47 mmoles) in DMF (150 ml.) was added to a vigorously stirred suspension of sodium hydride (20 g., 50% in oil, 410 mmoles) in the same solvent (150 ml.) under nitrogen at room temperature during 2 hours. After a further 1 hour stirring the mixture was poured cautiously onto ice, and acetic acid was added to pH 5. The mixture was washed with petrol to remove the oil, and then extracted with methylene chloride. The organic layer was evaporated down, and the residue refluxed with 5*N* hydrochloric acid for 1 hour. The mixture was cooled, basified, and extracted with ether to give the benzoxazine (**10**), 5.0 g., 65%, b.p. 142-150°/0.8 mm. The toluene-*p*-sulphonate salt had m.p. 117-120° (from acetone-ether) and m.p. 143-146° (from ethanol-ether): nmr (DMSO-d<sub>6</sub>)  $\tau$  1.40 (3H, s, NH<sub>2</sub>, OH), 2.48 and 2.86 (2 x 2H, d, ArH of tosylate), 3.07 (4H, m, ArH), ~5.76 (2H, m, OCH<sub>2</sub>) 6.35 (3H, s, NHCHCH<sub>2</sub>OH), (3H, s, CH<sub>3</sub> of tosylate).

*Anal.* Calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub>·C<sub>7</sub>H<sub>8</sub>SO<sub>3</sub>: C, 57.0; H, 5.7; N, 4.1. Found: C, 56.8; H, 5.5; N, 3.9.

### 3-Acetoxyethyl-2,3-dihydro-1,4-benzoxazine.

The carbinol **10** was treated at room temperature with equivalent quantities of acetyl chloride and of triethylamine in benzene to give the *O*-acetate, isolated as the hydrochloride salt, m.p. 125-133° (from 2-propanol); ir  $\nu$  max (nujol) 1760 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub>·HCl: C, 54.2; H, 5.8; N, 5.8. Found: C, 54.6; H, 5.9; N, 5.3.

### Reaction of Carbinol **10** with Tosyl Chloride.

The carbinol **10** (3.4 g., 21 mmoles) in dry pyridine (5 ml.) was treated at 0° with powdered tosyl chloride (3.95 g., 21 mmoles).

After 3 hours stirring, the mixture was diluted with dry benzene, filtered, and evaporated to leave an oil. Trituration with ethanol yielded the *N,O*-bis(toluene-*p*-sulphonyl)-3-hydroxymethyl-2,3-dihydro-1,4-benzoxazine, (1.5 g., 15%), m.p. 136-137.5° (from ethanol).

*Anal.* Calcd. for C<sub>23</sub>H<sub>23</sub>NO<sub>6</sub>S<sub>2</sub>: C, 58.4; H, 4.9; N, 3.0; S, 13.5. Found: C, 58.6; H, 4.8; N, 2.7; S, 13.7.

The ethanol liquors from the trituration were evaporated to give an oil, insoluble in mineral acid, which was crystallized from 2-propanol to give *N*-(toluene-*p*-sulphonyl)-3-hydroxymethyl-2,3-dihydro-1,4-benzoxazine (2.2 g.), 33%, m.p. 55-61°, ir  $\nu$  max (carbon tetrachloride) 3620 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub>S: C, 60.2; H, 5.4; N, 4.4; S, 10.0. Found: C, 60.2; H, 5.5; N, 4.4; S, 10.4.

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