Reinvestigation of the Epichlorohydrin Synthesis of 2-Aminomethylnaphthodioxanyl Derivatives

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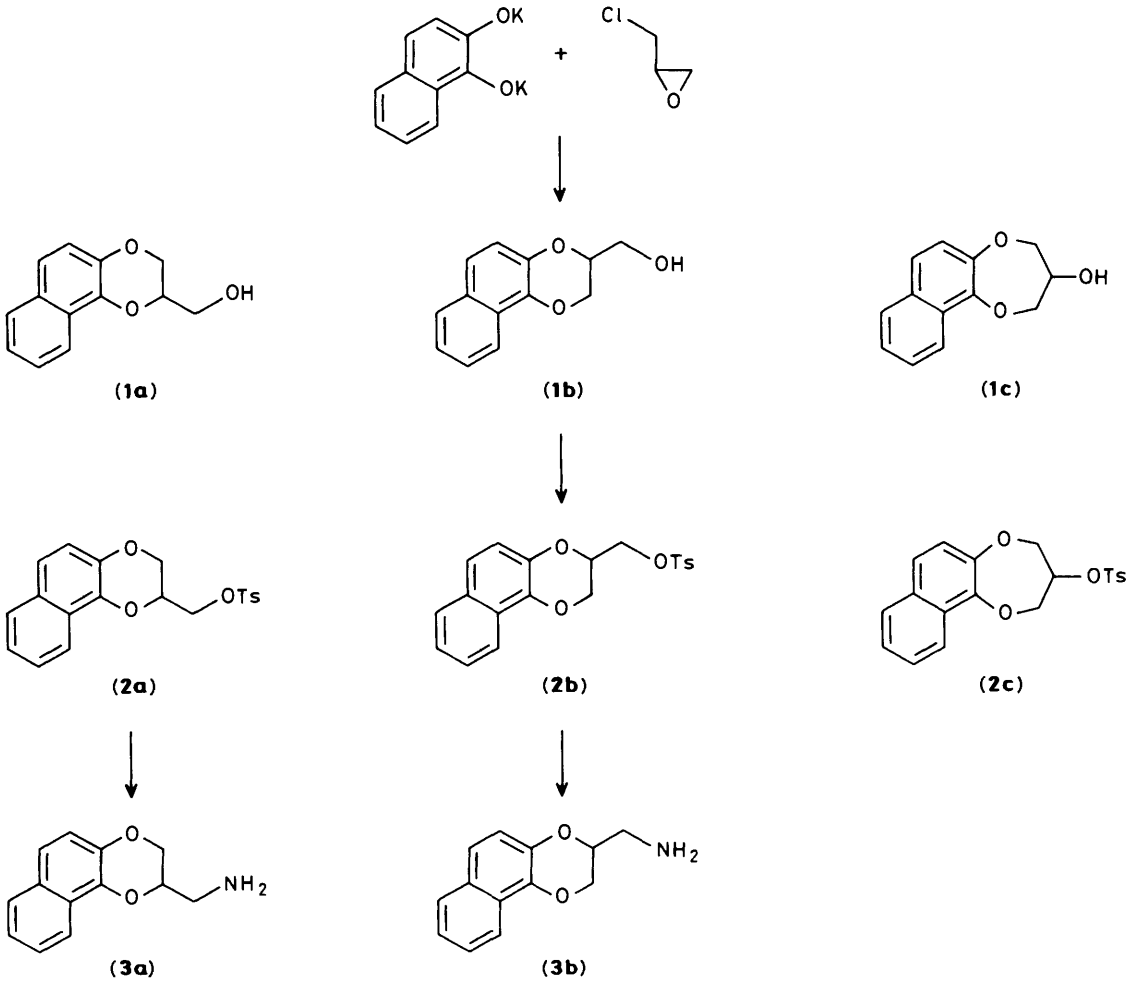
The synthesis of putative pharmacologically active 2-substituted naphthodioxanyl derivatives has been reinvestigated and the structures of key intermediates have been unambiguously reassigned.

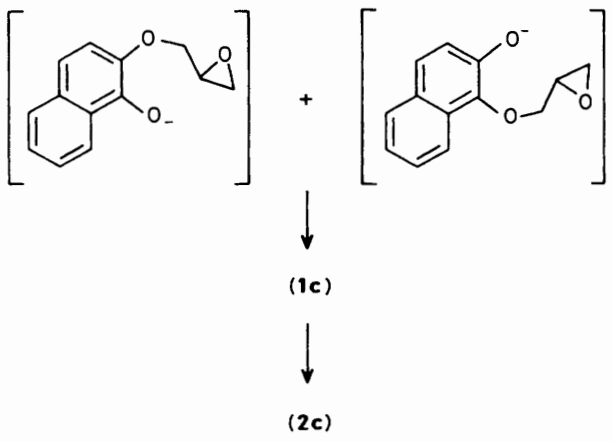
In recent years, structures containing the benzodioxanyl radical and its derivatives have become pharmacologically important mainly because of their α- and β-adrenoreceptor antagonist properties.[1,2] Our interest in naphthodioxanyl analogues led us to reinvestigate the reported syntheses of the isomeric 2- and 3-tosyloxymethylnaphthodioxanes (tosyl = *p*-$MeC_6H_4SO_2$) which are the key intermediates in the preparation of several important compounds.[3,4] These intermediates (**2a**) and (**2b**) were described by Brasili *et al.*[3] but on attempting to reproduce their results, we discovered discrepancies in their data which indicate that the reaction is more complicated and produces more products than those reported.

Brasili *et al.*[3] followed the synthetic pathway in Scheme 1. Condensation between the dipotassium salt of 1,2-dihydroxynaphthalene and epichlorohydrin was claimed to lead to the two isomeric alcohols (**1a**) and (**1b**) which would afford the mixture of tosylates (**2a**) and (**2b**) after treatment with tosyl chloride in pyridine. At that stage, they separated and purified by column chromatography (eluant: 10% Et_2O in hexane) two compounds to which structures (**2a**) (more polar) and (**2b**) (less polar) were assigned on the basis of n.m.r. data. The structure of (**2a**) after crystallisation, m.p. 111 °C, was confirmed by *X*-ray analysis. Using the same experimental conditions we obtained three compounds, whose n.m.r. spectra appeared to be too different to be explained by isomerism.

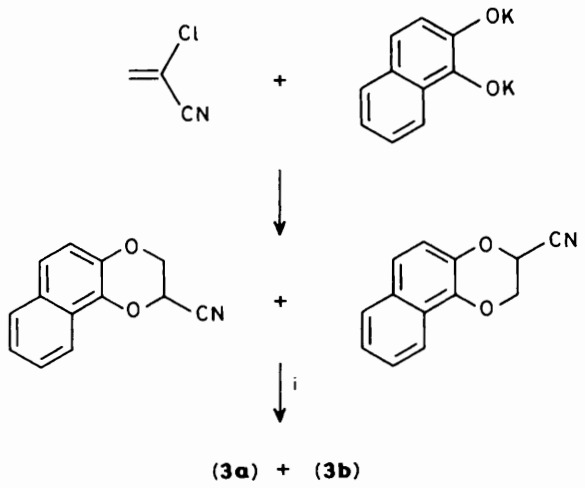
T.l.c. revealed that the more polar component was actually a mixture of two compounds (R_f 0.47 and 0.53, AcOEt–toluene, 10:90). Flash chromatography (eluant: Et_2O–hexane, 15:85) or recrystallisation from Et_2O–EtOAc gave these two products as solids: m.p. 76.5 °C (less polar) and m.p. 111 °C (more polar). N.m.r. studies (^1H at 200 MHz, ^{13}C with



Scheme 1. Ts = *p*-$MeC_6H_4SO_2$.



Scheme 2



Scheme 3. i, $LiAlH_4$–tetrahydrofuran.

total and partial proton coupling at 100 MHz) gave results consistent with the isomeric structures (**2a**) and (**2b**). An unequivocal assignment of the two structures was, however, not possible by n.m.r. spectroscopy.

N.m.r. (200 MHz ^1H, ^{13}C) examination of the less polar product, to which Brasili *et al.* assigned structure (**2b**), and which we obtained as an oil, revealed that it had structure (**2c**). The likely possibility that the three isomers were already present at the alcohol stage was confirmed by g.c.–mass spectroscopy. Three peaks were observed (ratio 6.7 : 53.8 : 39.5). When performed on the tosylates (**2**), g.c.–mass spectroscopy gave the same ratio of the three peaks. Thus, we conclude that the condensation with epichlorohydrin gives not only (**1a**) and (**1b**) but also (**1c**). To the best of our knowledge, the formation of such a seven-membered ring has not been reported in the synthesis of benzodioxane analogues. Nevertheless, the formation of (**1c**) could easily be explained by the attack of phenoxide ion on the less substituted carbon atom of the epoxide in the intermediates of Scheme 2. These results were reproducible in our hands using the reported experimental conditions.

Finally, the two solid tosylates (**2a**) and (**2b**) were separately converted into the primary amines (**3a**) and (**3b**), which appeared to be identical with the amines prepared by another method (Scheme 3) where formation of a seven-membered ring was not possible. This supports the structural assignment of (**2a**) and (**2b**) as indicated.

We suspect that when crystallizing their compound '(**2a**),' which we have demonstrated is actually a mixture of (**2a**) and (**2b**), Brasili *et al.* separated and obtained pure (**2a**). Since the m.p. of our fraction 3 (110 °C) is almost identical to that given by these authors (111 °C), structural assignment is now unambiguous: fraction 1 = (**2c**); fraction 2 = (**2b**); fraction 3 = (**2a**). The synthesis and biological evaluation of compounds derived from (**2a**) and (**2b**) will be published elsewhere.

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