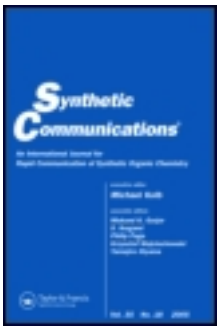

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Benzodiazepine Analogues. Part 15.[1] Synthesis of Benzoxathiepine Derivatives

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BENZODIAZEPINE ANALOGUES. PART 15.[1]

SYNTHESIS OF BENZOXATHIEPINE DERIVATIVES.

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ABSTRACT: Stepwise cyclisation sequences have provided access to a series of novel 4-phenyl-3,4-dihydro-1,5-benzoxathiepine-2-ones and 2- and 3-phenyl-4,1-benzoxathiepine analogues.

Various benzoheterothiepine systems exhibit interesting biological effects. For example, the 1,5-benzothiazepine derivative, diltiazem **1**, has found clinical use as a cardiac drug with calcium gating activity, and the synthesis of potent analogues has been reported.[2] Sugihara *et al.*[3] have prepared a number of aminoalkyl 3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols as oxygenated analogues, a piperazinyl derivative proving to be a potent and selective S_2-receptor blocker. 3*H*-1,5-Benzoxathiepine-2,4-dione, an active

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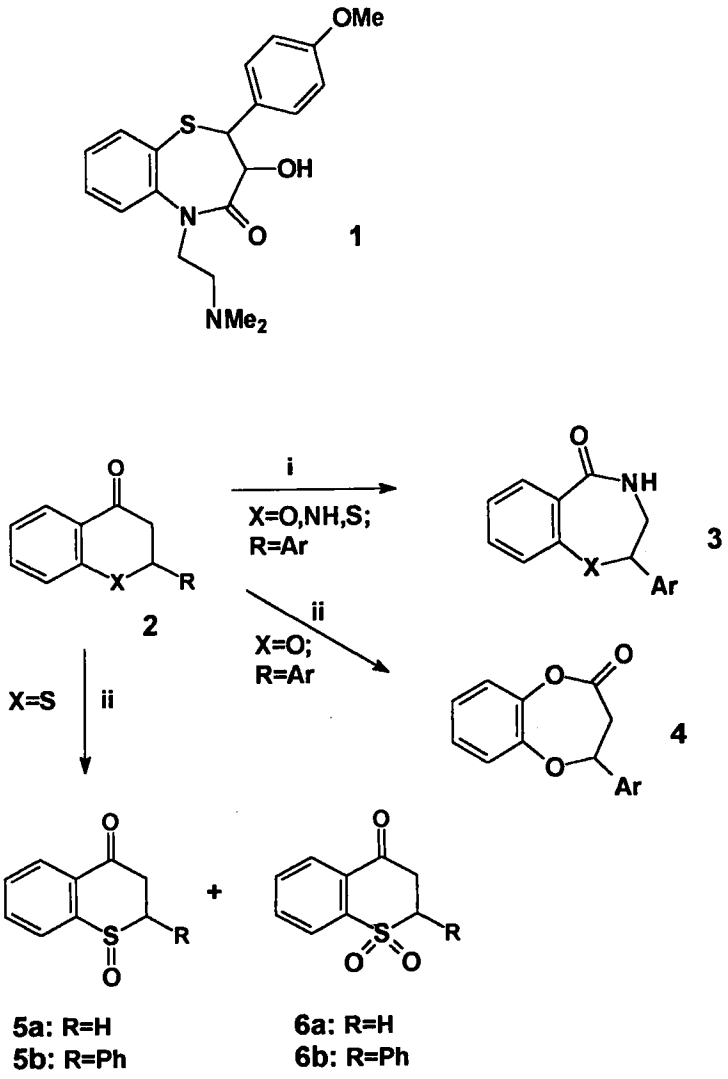
antimicrobial, has been obtained [4] by condensing carbon suboxide with 2-mercaptophenol - commonly used in the synthesis of 1,5-benzoxathiepines,[3,5] while 2-phenyl-1,5-benzothiazepinone derivatives have been reported to exhibit anti-depressant activity.[6]

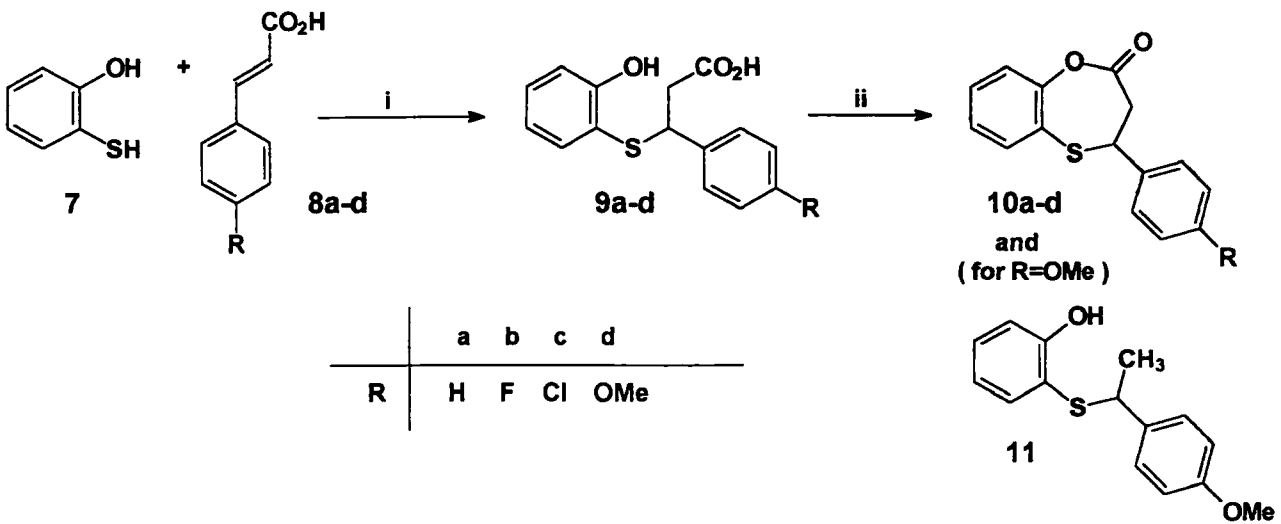
As part of an ongoing study of benzodiazepine analogues, we have prepared numerous oxygenated and thionated regioisomeric systems. Access to these compounds has typically been achieved *via* ring expansion of flavanone,[7] thioflavanone [8] and quinolone [9] precursors, using an azidotrimethylsilane-mediated Schmidt reaction for nitrogen insertion and an MCPBA-mediated Baeyer-Villiger reaction for oxygen insertion (Scheme 1). However, attempts to obtain benzoxathiepine derivatives by MCPBA oxidation of thioflavanone or thiochromanone precursors have been frustrated by competing oxidation of the ring sulfur to afford sulfones and sulfoxides which, in turn, resist Baeyer-Villiger oxidation.

Stepwise cyclisation strategies have therefore been adopted to prepare several series of benzoxathiepine derivatives. Scheme 2 outlines the synthesis of the 1,5-benzoxathiepin-2-ones **10a-d** from 2-mercaptophenol **7** and the corresponding cinnamic acids **8a - d**, following analogous condensations of 2-mercaptoaniline with cinnamic acid derivatives.[10] Formation of the intermediate acid **9a** *via* direct conjugate addition of 2-mercaptophenol **7** to



SCHEME 1

Reagents : i, TMS N_3 ,TFA ; ii, MCPBA , CH_2Cl_2 .



SCHEME 2

Reagents : i, 48% HBr in AcOH ; ii, TsOH, toluene, heat.

cinnamic acid **8a** was achieved simply by heating the neat reactants under nitrogen at 150°C; subsequent dissolution in toluene and cyclisation, in the presence of *p*-toluenesulfonic acid as catalyst, afforded the parent benzoxathiepinone **10a** in 24% yield. Use of this approach as a *general* method, however, was precluded by the high melting points of some of the substituted cinnamic acids **8**. Consequently, the intermediate acids **9** were generally obtained by heating the reactants in a 48% solution of hydrogen bromide in acetic acid (HBr-AcOH). Under these conditions, the initial coupling could involve acid-catalysed conjugate addition (path I; Fig. 1) and/or hydrobromination of the cinnamic acid **8** followed by nucleophilic substitution (path II). Lactonisation (**9** ⟶ **10**), however, still required the acids **9**† to be heated with toluene in the presence of *p*-toluenesulfonic acid - as evidenced by isolation of the intermediate acid **9d** in 69% yield even after boiling a mixture of 2-mercaptophenol **7** and cinnamic acid **8d** in 48% HBr-AcOH for 9 hours. Application of the two-step approach (Scheme 2) afforded the *p*-methoxy derivative **10d** in low yield together with a small quantity of 1-(2-hydroxyphenyl)thio-1-(4-methoxyphenyl)ethane **11**, formation of which requires decarboxylation of the intermediate acid **9d**.

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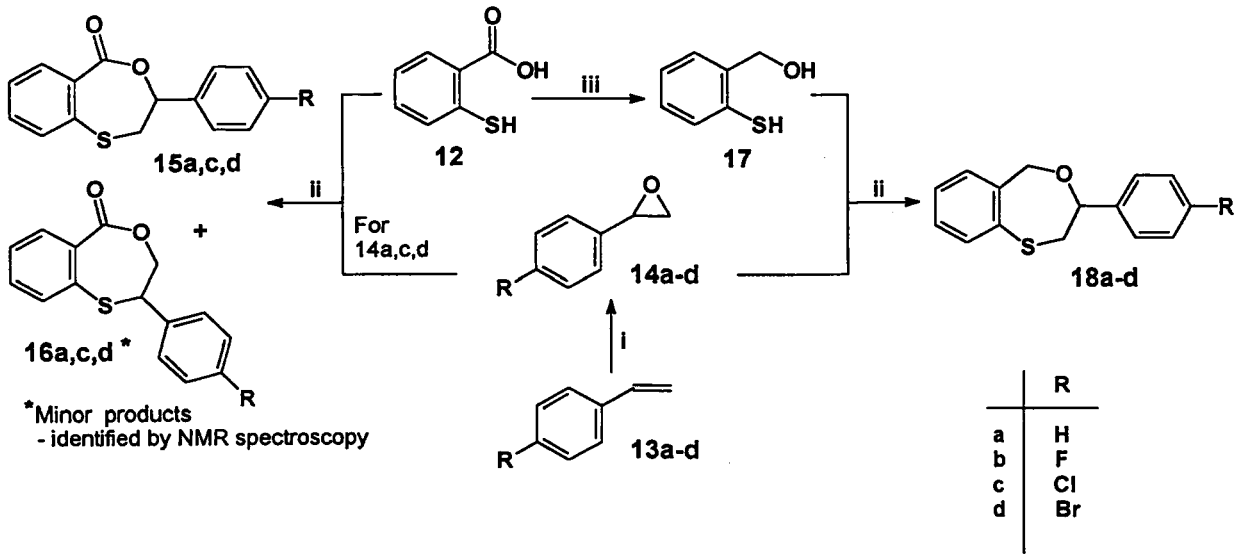
† After work-up, the crude acids **9** were typically cyclised without futher purification.

The 4,1-benzoxathiepin-5-one regioisomers (in which the lactone functionality is transposed) were obtained by condensing thiosalicylic acid **12** with the styrene oxides **14a,c** and **d**, which were prepared in turn by MCPBA oxidation of the corresponding styrene precursors **13** (Scheme 3). Nucleophilic ring-opening of the epoxides **14** by thiosalicylic acid **12** might be expected, *a priori*, to involve attack at either C-2′ or C-1′ (Fig. 2) to afford, after lactonisation, the 3-aryl-(**15**) or 2-aryl-4,1-benzoxathiepin-5-ones **16** respectively. In the substrates examined, attack at the less substituted centre, C-2′, was favoured affording the 3-aryl isomers **15** as the major products [albeit in relatively poor yield (8-26%)], the regioisomers being readily distinguished by ^{1}H and ^{13}C NMR spectroscopy. The 3-phenyl-4,1-benzoxathiepines **18a-d** were obtained similarly, but in somewhat better yield (43 - 53%), by condensing the styrene oxides **14a-d** with the reduced, bidentate nucleophile **17**; however, none of the 2-phenyl analogues was isolated.

The regiochemical bias observed in these reactions (Scheme 3) is, perhaps, a little surprising. Cleavage of epoxides in acidic medium generally favours nucleophilic attack at the *more substituted* carbon [11] and, with the styrene oxides **14**, the potential intermediacy of secondary benzylic carbocations might have been expected to favour a unimolecular (S_N1) process with nucleophilic attack at C-1′ rather than at the primary centre, C-2′



SCHEME 3

Reagents : i, MCPBA, CH_2Cl_2 ; ii, TsOH, C_6H_6, heat ; iii, $LiAlH_4$, THF.

(Figure 2). The observed regioselectivity could be attributed to preferential S_N2 displacement at the less hindered primary centre by the large and markedly nucleophilic sulfur atom. In their report on the synthesis of 1,5-benzoxathiepines from selected 2-mercaptophenols and epichlorohydrins, Cabiddu *et al.*[12] have also suggested that the relative size of the sulfur atom is responsible for the observed regiocontrol.

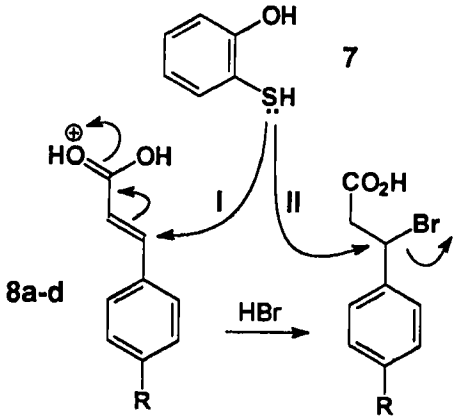


FIGURE 1

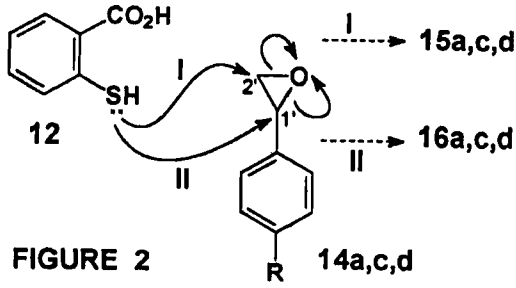


FIGURE 2

Experimental

^1H and ^{13}C NMR spectra were obtained for solutions in $CDC\ell_3$ on a Bruker AMX 400 spectrometer and were typically referenced using the solvent peaks (δ_H 7.25 and δ_C 77.0 ppm). Low resolution MS spectra were recorded on a Hewlett-Packard 5988A mass spectrometer and high resolution analyses were performed on a Kratos double focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit). Products were purified by flash chromatography prior to analysis.

Experimental procedures are illustrated by the following examples.

3,4-Dihydro-4-phenyl-1,5-benzoxathiepin-2-one **10a**.— A mixture of 2-mercaptophenol **7** (2.0g, 0.016mmol), cinnamic acid **8a** (2.3g, 0.016mmol) and 48% HBr - AcOH (10ml) was heated under reflux until most of the starting material had reacted (as determined by NMR spectroscopy). Ethyl acetate was added to the reaction mixture and the resulting solution was shaken with aqueous NaOH. The aqueous layer was acidified (dilute HCl), extracted with EtOAc (2 x 30 ml) and dried (anhydrous $MgSO_4$), and the solvent was evaporated *in vacuo* to give a residue which, together with a catalytic amount of *p*-toluenesulfonic acid in toluene (150ml), was boiled under reflux using a Dean-Stark apparatus for 12 hours. The solvent was evaporated

in vacuo and the residue dissolved in EtOAc. The resulting solution was washed with aqueous NaOH and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford two fractions:

(i) starting material; and

(ii) *3,4-dihydro-4-phenyl-1,5-benzoxathiepin-2-one* **10a** (0.35g, 9%),‡ m.p. 94-95°C (Found: M^+ 256.057. $C_{15}H_{12}O_2S$ requires *M*, 256.056); δ_H 2.93-3.02 (2H, m, 3-CH_2), 4.70 (1H, dd, 4-H), 7.17-7.56 (9H, series of multiplets, ArH); δ_C 40.0 (C-3), 50.3 (C-4), 120.3, 121.6, 126.3, 126.6, 128.2, 128.9, 131.4, 136.4, 141.8 and 154.1 (ArC) and 167.5 (C-2); *m/z* 256 (M^+, 10.1%) and 131 (100%).

2,3-Dihydro-3-phenyl-4,1-benzoxathiepin-5-one **15a** *and 2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-one* **16a**.— A mixture of thiosalicylic acid **12** (1.0g, 6.5mmol), epoxystyrene **14a** (0.77g, 6.5mmol) and *p*-toluenesulfonic acid (0.03g) in benzene (50ml) was boiled under a Dean-Stark trap for 12 h. After cooling, the solvent was evaporated *in vacuo* and the residue was dissolved in EtOAc (50ml). The resulting solution was washed with aqueous $NaHCO_3$ (2 x 30ml), dried (anhydrous $MgSO_4$), and the solvent was

‡ When the initial coupling was effected by heating the neat reactants (**7** and **8a**) in the absence of HBr-AcOH, the product **10a** was obtained in 24% yield.

evaporated *in vacuo*. The residue was purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford two fractions:

(i) *2,3-dihydro-3-phenyl-4,1-benzoxathiepin-5-one* **15a** (0.43g, 26%), m.p. 38-40°C (Found: M^+ 256.056. $C_{15}H_{12}O_2S$ requires *M*, 256.056); δ_H 3.29 and 3.46 (2H, 2 x dd, 2-CH_2), 5.74 (1H, dd, 3-H), 7.24-7.45 (8H, series of multiplets, ArH) and 8.14 (1H, dd, ArH); δ_C 40.6 (C-2), 83.3 (C-3), 124.1, 126.5, 127.4, 134.5, 127.6, 128.6, 129.5, 132.4, 133.5 and 138.1 (ArC) and 163.8 (C-5); *m/z* 256 (M^+, 21%) and 136 (100%); and

(ii) *2,3-dihydro-2-phenyl-4,1-benzoxathiepin-5-one* **16a** (0.12g, 7.2%);[§] δ_H 3.92 and 4.03 (2H, 2 x dd, 3-CH_2), 6.10 (1H, dd, 2-H), 7.19-7.45 (8H, m, ArH) and 8.13 (1H, m, ArH); δ_C 66.0 (C-3), 77.9 (C-2), 124.7, 125.9, 126.8, 128.6, 128.7, 131.0, 131.9, 132.7, 136.8 and 138.2 (ArC) and 166.0 (C-5).

2,3-Dihydro-3-phenyl-4,1-benzoxathiepine **18a**.— A mixture of 2-(hydroxymethyl)thiophenol **17** (1g, 7mmol), epoxystyrene **14a** (0.86g, 7.0mmol) and *p*-toluenesulfonic acid (0.03g) in benzene (50ml) was boiled under a Dean-Stark trap for 72 h. After cooling, the solvent was evaporated *in vacuo* and the oily residue was purified by flash chromatography [elution with EtOAc-hexane (3:7)] to afford *2,3-dihydro-3-phenyl-4,1-benzoxathiepine*

[§] Minor component characterised by NMR spectroscopy.

18a (0.81g, 48%) (Found: M^+ 242.076. $C_{15}H_{14}OS$ requires *M*, 242.077); δ_H 3.12 and 3.36 (2H, 2 x dd, 2-CH_2), 4.91 (2H, dd, 5-CH_2), 5.38 (1H, dd, 3-H), 6.95-7.48 (9H, series of multiplets, ArH); δ_C 42.3 (C-2), 70.0 (C-5), 82.4 (C-3), 124.5, 125.7, 127.0, 127.2, 127.4, 128.4, 129.4, 129.6, 131.9 and 136.2 (ArC); *m/z* 242 (M^+, 18.5%) and 151 (100%).

Analytical data for the remaining new compounds, described in this study, are as follows.

4-(4-Fluorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **10b** (0.44g, 10%), m.p. 77-80°C (Found: M^+ 274.046. $C_{15}H_{11}FO_2S$ requires *M*, 274.046); δ_H 2.95-3.04 (2H, m, 3-CH_2), 4.75 (1H, dd, 4-H), 7.00-7.60 (8H, series of multiplets, ArH); δ_C 40.1 (C-3), 49.5 (C-4), 115.8, 120.4, 121.4, 126.6, 128.1, 131.5, 136.3, 137.5, 154.1 and 162.4 (ArC) and 167.3 (C-2); *m/z* 274 (M^+, 12.5%) and 149 (100%).

4-(4-Chlorophenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **10c** (0.61g, 13%), m.p. 60-62°C (Found: M^+ 290.016. $C_{15}H_{11}{}^{35}C\ell O_2S$ requires *M*, 290.017); δ_H 2.95-3.04 (2H, m, 3-CH_2), 4.74 (1H, dd, 4-H), 7.18-7.59 (8H, series of multiplets, ArH); δ_C 39.8 (C-3), 49.5 (C-4), 120.4, 121.3, 126.7, 127.7, 129.1, 131.5, 134.0, 136.3, 140.1 and 154.0 (ArC) and 167.2 (C-2); *m/z* 290 [M^+(^{35}Cl), 8%) and 165 (100%).

4-(4-Methoxyphenyl)-3,4-dihydro-1,5-benzoxathiepin-2-one **10d** (0.2g, 4.4%) (Found: M^+ 286.030. $C_{15}H_{10}O_4S$ requires *M*, 286.030); δ_H 2.99 (2H, d, 3-CH_2), 3.78 (3H, s, OCH_3), 4.74 (1H, t, 4-H), 6.84 (2H, d, ArH), 7.16-7.58 (6H, series of multiplets, ArH); δ_C 40.1 (C-3), 49.8 (C-4), 55.2 (OCH_3), 114.2, 120.2, 121.7, 126.5, 127.5, 131.2, 133.8, 136.3, 154.0 and 159.3 (ArC) and 167.5 (C-2); *m/z* 286 (M^+, 11.1%) and 161 (100%).

1-(2-Hydroxyphenyl)thio-1-(4-methoxyphenyl)ethane **11** (0.24g, 5.2%) (Found: M^+ 260.086. $C_{15}H_{16}O_2S$ requires *M*, 260.087); ν_{max} (thin film)/cm^{-1} 3500-3300 (OH); δ_H 1.61 (3H, d, CH_3), 3.79 (3H, s, OCH_3), 4.09 (1H, q, 1-H), 6.68 (1H, s, OH) and 6.78-7.27 (8H, series of multiplets, ArH); δ_C 21.5 (CH_3), 48.7 (C-1), 55.2 (OCH_3), 113.8, 114.6, 118.0, 120.3, 128.1, 131.4, 134.4, 136.9, 157.4 and 158.9 (ArC); *m/z* 260 (M^+, 1.4%) and 135 (100%).

2,3-Dihydro-3-(4-chlorophenyl)-4,1-benzoxathiepin-5-one **15c** (0.5g, 8%), m.p. 30-32°C (Found: M^+ 290.018. $C_{15}H_{11}{}^{35}C\ell O_2S$ requires *M*, 290.017); δ_H 3.25 and 3.39 (2H, 2 x dd, 2-CH_2), 5.70 (1H, t, 3-H), 7.21-7.46 (7H, series of multiplets, ArH) and 8.12 (1H, dd, ArH); δ_C 39.7 (C-2), 82.8 (C-3), 123.9, 126.5, 127.5, 128.7, 130.8, 132.4, 132.9, 133.3, 133.5 and 137.8 (ArC) and 163.6 (C-5); *m/z* 290 [M^+(^{35}Cl),9%] and 165 (100%).

2,3-Dihydro-3-(4-bromophenyl)-4,1-benzoxathiepin-5-one **15d** (0.16g, 13%),

m.p. 50-52°C (Found: M^+, 333.967. $C_{15}H_{11}{}^{79}BrO_2S$ requires *M*, 333.966); δ_H 3.20 and 3.33 (2H, 2 x dd, 2-CH_2), 5.66 (1H, t, 3-H), 7.12-7.45 (7H, series of multiplets, ArH) and 8.08 (1H, d, 9-H); δ_C 40.0 (C-2), 82.9 (C-3), 121.6, 124.1, 126.7, 127.6, 131.3, 131.8, 132.6, 133.5, 133.6 and 137.9 (ArC) and 163.7 (C-5); *m/z* 336 [M^+(^{79}Br), 6%] and 165 (100%).

2,3-Dihydro-2-(4-chlorophenyl)-4,1-benzoxathiepin-5-one **16c** (0.1g, 2%);§ δ_H 3.84 and 3.94 (2H, 2 x dd, 3-CH_2), 5.98 (1H, dd, 2-H), 7.06-7.35 (7H, series of multiplets, ArH) and 8.02 (1H, dd, ArH); δ_C 65.7 (C-3), 77.1 (C-2), 124.8, 125.7, 128.1, 128.9, 131.1, 131.8, 132.8, 134.4, 135.4 and 138.3 (ArC) and 165.8 (C-5).

2,3-Dihydro-2-(4-bromophenyl)-4,1-benzoxathiepin-5-one **16d** (0.02g, 2%);§ δ_H 3.92 and 4.02 (2H, 2 x dd, 3-CH_2), 6.03 (1H, dd, 2-H), 7.16-7.55 (7H, series of multiplets, ArH) and 8.09 (1H, dd, ArH).

2,3-Dihydro-3-(4-fluorophenyl)-4,1-benzoxathiepine **18b** (0.96g, 53%) (Found: M^+ 260.069. $C_{15}H_{13}FOS$ requires *M*, 260.067); δ_H 3.06 and 3.27 (2H, 2 x dd, 2-CH_2), 4.89 (2H, dd, 5-CH_2), 5.31 (1H, dd, 3-H), 6.93-7.29 (8H, series of multiplets, ArH); δ_c 41.5 (C-2), 70.0 (C-5), 82.3 (C-3), 115.2, 115.3, 124.7, 125.7, 127.3, 127.5, 129.6, 130.95, 131.03 and 131.8 (ArC).

2,3-Dihydro-3-(4-chlorophenyl)-4,1-benzoxathiepine **18c** (0.83g, 43%) (Found: M^+ 276.037. $C_{15}H_{13}{}^{35}Cl OS$ requires *M*, 276.038); δ_H 3.08 and 3.28 (2H, 2 x dd, 2-CH_2), 4.89 (2H, dd, 5-CH_2), 5.33 (1H, dd, 3-H), 6.94-7.34 (8H, series of multiplets, ArH); δ_C 41.5 (C-2), 69.8 (C-5), 81.9 (C-3), 124.6, 125.6, 127.2, 127.3, 128.4, 129.5, 130.8, 131.6, 132.7 and 134.6 (ArC); *m/z* 276 [M^+(^{35}Cl), 8.4%] and 151 (100%).

2,3-Dihydro-3-(4-bromophenyl)-4,1-benzoxathiepine **18d** (1.05g, 47%), m.p. 42-44°C (Found: M^+ 319.988. $C_{15}H_{13}{}^{79}BrOS$ requires *M*, 319.987); δ_H 3.06 and 3.27 (2H, 2 x dd, 2-CH_2), 4.88 (2H, dd, 5-CH_2), 5.33 (1H, dd, 3-H), 6.94-7.49 (8H, series of multiplets, ArH); δ_C 41.4 (C-2), 69.7 (C-5), 81.7 (C-3), 120.8, 124.5, 125.6, 127.1, 127.2, 129.4, 131.1, 131.3, 131.5 and 135.1 (ArC); *m/z* 320 [M^+(^{79}Br), 5%] and 151 (100%).

Acknowledgements

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