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BENZODIAZEPINE ANALOGUES. PART 14.[1] SYNTHESIS OF 2-PHENYL-1,4-BENZOXAZEPIN-5(4*H*)-ONE

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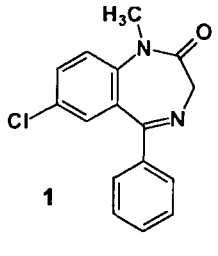
ABSTRACT: The preparation of 2-phenyl-1,4-benzoxazepin-5(4*H*)-one **11** *via* stepwise cyclisation of bromoacetal and salicylamide precursors is described.

Diazepam **1**, widely used as a minor tranquiliser, and midazolam **2** [2] both exhibit unsaturation in the 7-membered ring — a structural feature typical of potent benzodiazepine receptor ligands. As part of an ongoing study of related systems, we have explored several approaches to somewhat analogous Δ^2- or Δ^3-unsaturated derivatives of 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **3** and its tetrazolo[1,5-*d*] analogue **4**.



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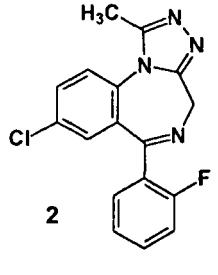

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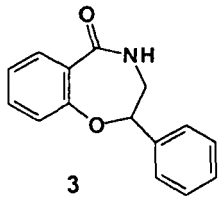
Compounds **3** and **4**, obtained *via* azidotrimethylsilane-mediated ring expansion of flavanone,[3,4] appeared to be logical precursors to their unsaturated derivatives, but attempts to effect dehydrogenation, either directly† or by means of a halogenation-dehydrohalogenation sequence,‡ proved unsuccessful.



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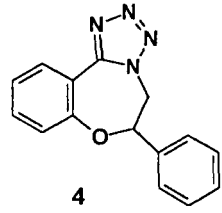

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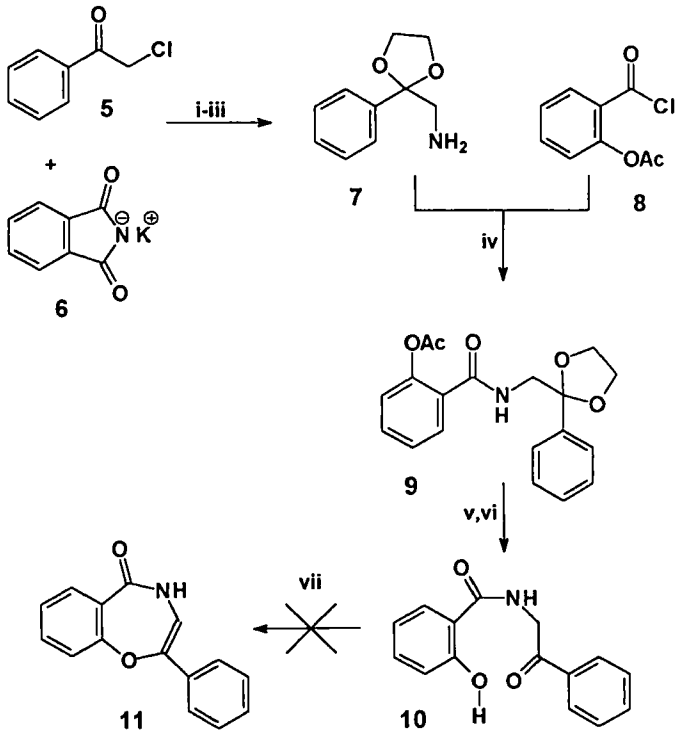
Attention was consequently given to a stepwise strategy involving cyclisation of salicylamide derivatives. In the first such approach (Scheme 1), the protected amine **7**[10] was acylated with *O*-acetylsalicyloyl chloride **8**, but the deprotected amide **10** resisted various attempts at cyclisation.[9] Successful synthesis of the title compound was finally achieved using a variation (outlined in Scheme 2) of Schenker's[11,12] method for preparing the 3-phenyl analogue. Reaction of the bromo acetal **14** with salicylamide **15**, under basic conditions, afforded the intermediate acetal **16** which, in the presence of a trace of water,

† The tetrazolo derivative **4** was treated with DDQ in refluxing toluene [5] and with 5% Pd/C in refluxing decalin.[6]

‡ Treatment of the 1,4-benzoxazepin-5(4*H*)-one **3** with *t*-BuOCl led to an A-ring chlorinated product[7] instead of the expected *N*-chloro amide,[8] while no change was detected when the tetrazolo derivative **4** was treated with LDA followed by Br_2 or NBS.[9]

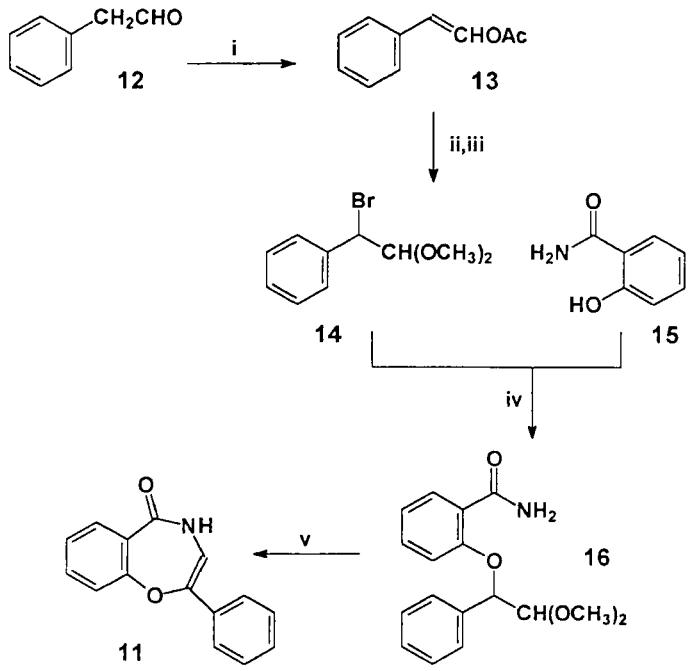


Reagents: i, DMF, heat, 4h; ii, $HO(CH_2)_2OH$, *p*-TsOH, toluene, heat; iii, 30% NaOH, heat; iv, pyridine, THF, v, KOH, H_2O; vi, 10% HCℓ; and vii, *p*-TsOH, toluene, heat.

SCHEME 1

underwent acid-catalysed cyclisation and dehydration to afford the desired 2-phenyl-1,4-benzoxazepin-5(4*H*)-one **11** in reasonable yield.

The isomeric 3-phenyl derivative, required for comparative purposes, was prepared using Schenker's method,[11,12] which commences with



Reagents: i, KOAc, Ac_2O, heat; ii, Br_2, $CC\ell_4$; iii, CH_3OH, 24-25°C, 72h; iv, K_2CO_3, KI, $(CH_3)_2CO$, heat; and v, *p*-TsOH, H_2O (2 drops), toluene, heat, 12h.

SCHEME 2

α-bromoacetophenone rather than the bromo acetal **14**, in which the bromo and (masked) carbonyl functions are transposed.

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).

The synthesis of 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **3** and its tetrazolo[1,5-*d*] derivative **4** [3,4] as well as the intermediates **7**,[10] **13** and **14**[13] have been described previously. The experimental procedures for the preparation of new compounds are as follows.

O-*Acetyl*-N-*(2,2-ethylenedioxy-2-phenylethyl)salicylamide* **9**.— A stirred solution of the aminoketal **7** (5.0 g, 28 mmol) and triethylamine (2.8 g, 28 mmol) in THF (25 ml) was treated dropwise with a solution of 2-acetylsalicyloyl chloride **8** [5.5g, 28 mmol) prepared[14] from acetylsalicylic acid] in THF (20 ml) at room temperature. The resulting mixture was stirred for 1.5 h at room temperature and then filtered. Ethyl acetate (50 ml) was added to the filtrate and the organic solution was washed with water (3 x 30 ml) and dried (anhyd. Na_2SO_4). The solvent was evaporated to afford O-*acetyl*-N-*(2,2-ethylenedioxy-2-phenylethyl)salicylamide* **9** (9.1 g, 96%), m.p. 140-142 °C (from EtOH); δ_H 2.28 (3H, s, CH_3), 3.77 (4H, m, OCH_2CH_2O), 3.98 (2H, m, CH_2), 6.62 (1H, br s, NH) and 7.02-7.73 (9H, m, ArH); υ_{max} (KBr/cm^{-1}) 3440, 1760 and 1650.

N-*(Benzoylmethyl)salicylamide* **10**.— A stirred solution of *O*-acetyl-*N*-(2,2-ethylenedioxy-2-phenylethyl)salicylamide **9** (9.0 g, 26 mmol) and 10% aq. NaOH

(30 ml) was stirred at room temperature for 18h and then acidified with 10% HCℓ. The product was extracted with ethyl acetate (3 x 30 ml), and the combined organic extracts were washed with water (2 x 30 ml) and dried (anhyd. Na_2SO_4). The solvent was evaporated and the residue was taken up in glacial acetic acid (75 ml) and then treated with conc. H_2SO_4 (1.5 ml). The resulting solution was stirred for 6 h and the precipitated material was filtered off to afford N-*(benzoylmethyl)salicylamide* **10** (5.7 g, 85%), m.p. 176-178 °C (from EtOH) (Found: M^+, 255.0901. $C_{15}H_{13}NO_3$ requires *M*, 255.0895); δ_H, 4.93 (2H, d, CH_2), 6.91-8.05 (10H, m, NH and ArH) and 12.1 (1H, s, OH); υ_{max} (KBr/cm^{-1}), 3400, 1700 and 1635.

*2-Phenyl-1,4-benzoxazepin-5(4*H*)-one* **11**.— A stirred mixture of *O*-(2,2-dimethoxy-1-phenylethyl)salicylamide **16** (2.0 g, 6.6 mmol) and *p*-toluenesulphonic acid (0.06 g, 0.3 mmol; containing 2 drops of water) in toluene (100 ml) was boiled under reflux using a Dean-Stark trap for 12 h. The mixture was allowed to cool to afford *2-phenyl-1,4-benzoxazepin-5(4*H*)-one* **11** (0.88 g, 56%), m.p. 208°C (from toluene) (Found: M^+, 237.0782. $C_{15}H_{11}NO_2$ requires *M*, 237.0790); δ_H (DMSO-d_6), 6.67 (1H, d, 3-H), 7.13-7.79 (9H, m, ArH) 8.83 (1H, s, NH); δ_C (DMSO-d_6) 110.4 (C-3), 119.6 (C-9), 122.7 (C-2′ and C-6′), 123.8 (C-7), 125.7 (C-5a), 126.9 (C-4′), 127.6 (C-3′ and C-5′), 130.7 (C-6), 132.5 (C-1′), 133.0 (C-8), 144.6 (C-9a), 158.0 (C-2) and 166.5 (C-5); υ_{max} (KBr/cm^{-1}) 3200 and 1650; *m/z* 237 (M^+, 92.2%) and 105 (100%).

O-(2,2-dimethoxy-1-phenylethyl)salicylamide **16**.— A stirred mixture of salicylamide (3.0 g, 22 mmol), α-bromophenylacetaldehyde dimethyl acetal **14** (5.4 g, 22 mmol), K_2CO_3 (6.3 g, 46 mmol) and KI (0.06 g, 0.4 mmol) in dry acetone (55 ml) was boiled under reflux for 12 h. The mixture was filtered and the solvent was evaporated *in vacuo*. The residue was taken up in chloroform (50 ml) and the resulting solution was washed with water (2 x 20 ml) and dried (anhyd. $MgSO_4$). The solvent was evaporated to afford *O-(2,2-dimethoxy-1-phenylethyl)salicylamide* **16** (2.6 g, 54%), m.p. 84-86°C (Found: M^+, 301.1300. $C_{17}H_{19}NO_4$ requires *M*, 301.1314); δ_H 3.30 and 3.38 (6H, 2 x s, 2 x OCH_3), 4.61 (1H, d, 1'-H), 5.20 (1H, d, 2'-H), 5.98 (1H, br s, NH), 6.66 (1H, d, 3-H), 6.99 (1H, t, 5-H), 7.22 (1H, ddd, 4-H), 7.30-7.45 (5H, m, C_6H_5), 8.16 (1H, dd, 6-H) and 8.40 (1H, br s, NH); *m/z* 301 (M^+, 2.5%) and 75 (100%).

Acknowledgements

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