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SYNTHESIS and STRUCTURE of 3,4-DIHYDRO-4-PHENYL-1,5-BENZODIOXEPIN-2-ONES

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ABSTRACT: Baeyer-Villiger rearrangement of substituted flavanones using MCPBA affords ring-expanded products, shown by NMR spectroscopy to be the corresponding 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-ones.

We have been investigating methods of expanding the C-ring in flavanone systems and have recently reported mass fragmentation studies of 1,4-benzoxazepin-5(4*H*)-ones **3**[1] and 4*H*-tetrazolo[1,5-d]-1,4-benzoxazepines **4**[2] obtained by Schmidt rearrangement[3] of the corresponding flavanones **1** (Scheme 1). Baeyer-Villiger rearrangement of chromanone precursors has recently been shown to afford ring expanded 3,4-dihydro-1,5-benzodioxepin-2-ones[4] and, in this communication, we discuss :- (i) extension of the Baeyer-Villiger rearrangement to substituted flavanones; (ii) spectroscopic confirmation of the structures of the resulting 3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-ones; and (iii) solvolytic transesterification of ring expanded systems.

m-Chloroperbenzoic acid (MCPBA) oxidation of specially prepared flavanone precursors **1a-1f** afforded the corresponding ring-expanded lactones **2a-2f** - the change in carbonyl functionality from ketone to lactone being reflected in a significant shift (*ca.* 50 cm^{-1}) of

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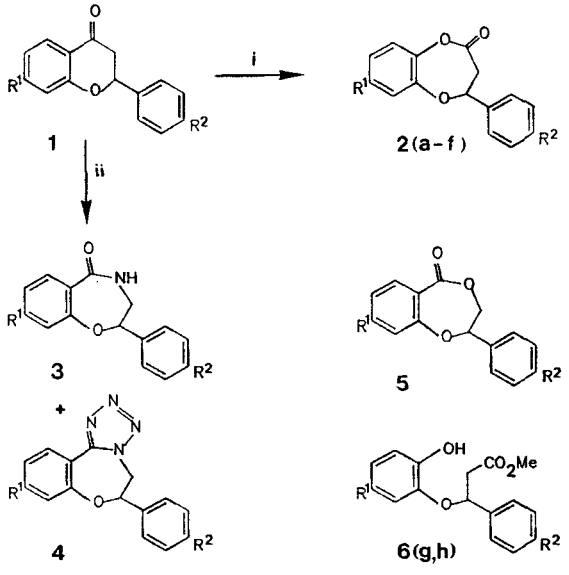
the IR carbonyl absorption band to higher frequencies. Reaction conditions have not been optimised, but it is apparent that yields can be improved dramatically by increasing reaction times (as illustrated for compounds **2b**, **2c** and **2e**; Table 1).

The ring-expanded products were shown, by ^{1}H and ^{13}C NMR spectroscopy, to be the corresponding 1,5-benzodioxepin-2-ones **2a-2f** rather than the isomeric 1,4-benzodioxepin-5-ones **5** (Scheme 1). Thus, the ^{1}H chemical shifts (*ca.* δ 3.1 ppm) observed for the diastereotopic 3-H nuclei in these products (and illustrated for compound **2d** in Figure 1) are significantly upfield of the values (*ca.* δ 4.5 ppm) calculated[5] for the 1,4-benzodioxepin-5-ones **5**; significant differences are also apparent between the observed ^{13}C chemical shifts for the C-3 nuclei and the shift calculated[5] for the corresponding nuclei in compounds **5**. In contrast, the close correspondence between the observed and calculated ^{1}H and ^{13}C NMR shift data[6] detailed in Table 1 permits unequivocal identification of the MCPBA oxidation products as the 3,4-dihydro-1,5-benzodioxepin-2-ones **2**.



SCHEME 1

	R^1	R^2
a	H	H
b	MeO	H
c	H	Br
d	H	Cl
e	H	F
f	H	MeO
g	Br	H
h	F	H

Reagents: (i) MCPBA-CH_2Cl_2; (ii) $TMSN_3$-CF_3CO_2H.

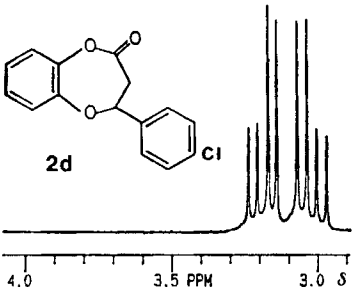


FIGURE 1
Partial 200 MHz ^{1}H NMR spectrum of 2-(4-chlorophenyl)-3,4-dihydro-1,5-benzodioxepin-4-one (2d).

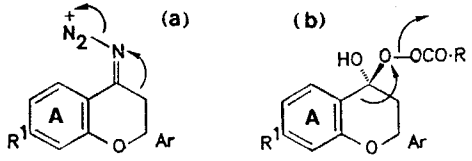


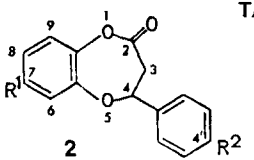
FIGURE 2
Rearrangement of the migrating group in : (a) Schmidt and (b) Baeyer-Villiger reactions.[9]

In some cases, attempted recrystallisation of the crude products from methanol resulted in opening of the expanded C-ring, *via* solvolytic transesterification, to afford the corresponding methyl esters (*e.g.* the bromo and fluoro analogues, **6g** and **6h** respectively).[7] The apparently regioselective migration of the aryl substituent (ring A) in all of the systems examined, while consistent with the trend reported for chromanones,[4] is opposite to that observed for Schmidt rearrangement of the series of flavanones **1a-1c, 1e-1f**.[8] Considering the similarity of the mechanisms which have been proposed[9] for the Schmidt and Baeyer-Villiger reactions (Figure 2), the complete reversal of regioselectivity in these rearrangements is quite remarkable. Elucidation of the stereoelectronic effects operating in these reactions is to be the subject of further investigation.

EXPERIMENTAL

Synthesis of the title compounds **2** from specially prepared flavanone precursors **1** is illustrated by the following example.

TABLE 1 ANALYTICAL DATA FOR 3,4-DIHYDRO-4-PHENYL-1,5-BENZODIOXEPIN-2-ONES (2)



2

Compd.	R^1	R^2	m.p./°c	Elemental analysis: Found	Molecular formula	Requires	$\nu_{max.}$[a] /cm^{-1}	^1H and ^{13}C NMR Chemical shift data[b]/ppm: 3-H[c] (2.93)	C-3 (41.1)	Yield/%	Rn.time /h
2a	H	H	85-86[d]	C,75.0; H,5.0%	$C_{15}H_{12}O_3$	C,75.0; H,5.0%	1770	3.12	38.4	69	24
2b	MeO	H	72-74[d]	*m/z* 270.089	$C_{16}H_{14}O_4$	M^+, 270.089	1760	3.13	38.6	78 17	96 16
2c	H	Br	115-117[d]	*m/z* 319.987	$C_{15}H_{11}O_3Br$	M^+, 319.987[e]	1745	3.11	38.4	78 48	72 48
2d	H	Cl	113-114[d]	C,66.2; H,3.8%	$C_{15}H_{11}O_3Cl$	C,65.6; H,4.0%	1745	3.10	38.4	78	48
2e	H	F	125-127[d]	*m/z* 215.051	$C_{13}H_8O_2F$	M-C_2H_3O,[f] 215.051	1750	3.10	38.6	60 25	60 16
2f	H	MeO	121-122[d]	*m/z* 270.089	$C_{16}H_{14}O_4$	M^+, 270.089	1760	3.10	38.5	22	23

[a]Infrared CO absorption maximum (KBr disc); the corresponding band in the flavanone precursors appears at *ca.* 1700 $cm.^{-1}$ [b]Calculated[5] values in parentheses [values calculated for the corresponding nuclei in the isomeric 1,4-benzodioxepin-5-one are :- 4.48 (3-H) and 75.0 (C-3)]. [c]The quoted chemical shift corresponds to the centre of the *pair* of double doublets (see Fig. 1). [d]New compound which gave satisfactory spectroscopic (^1H and ^{13}C NMR, IR, and MS) analyses. [e]For ^{81}Br. [f]Corresponds to a common fragment in the mass spectra of compounds **2**.

A mixture of flavanone **1a** (1 g, 5mmol) and MCPBA (85%; 1.73 g, 10mmol) in dry CH_2Cl_2 (20 ml) was boiled under reflux for 24 h. After evaporating the solvent, the residue was dissolved in EtOAc (50 ml), washed sequentially with aqueous $NaHCO_3$ and H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the solvent afforded a brown residue which was purified[10] by sublimation and recrystallisation from MeOH to give *3,4-dihydro-4-phenyl-1,5-benzodioxepin-2-one* **2a** (0.83 g, 69%).

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5. Using correlation tables by Brown, D.W., Floyd, A.J., and Sainsbury, M., in 'Organic Spectroscopy', Wiley, Chichester, 1988, p.97ff.
6. ^{13}C Spectra were edited by APT (50 MHz) or ORD (125 MHz) techniques. In the case of the parent system **2a**, signal assignments are supported by 2-dimensional (HETCOR and COSY) analyses.
7. Analytical data for these methyl esters are as follows :- *Methyl 3-(5-bromo-2-hydroxyphenoxy)-3-phenylpropanoate* **6g**, m.p. 90-91°C (Found : *m/z* 350.015. $C_{16}H_{15}O_4{}^{79}Br$ Requires : M^+, 350.015); δ_H (200 MHz; $CDCl_3$) 2.78 and 3.17 (2H, 2 x dd, 2-H), 3.77 (3H, s, Me), 5.27 (1H, dd, 3-H), and 6.59 and 6.81 (2H, 2xd, ArH), 6.91 (1H; dd, ArH) and 7.36 (5H, m, ArH); δ_C (50 MHz; $CDCl_3$) 42.09 (C-2), 52.66 (Me), 80.16 (C-3), 110.80, 112.64, 117.74, 123.17, 126.97, 127.47, 129.35, 139.12, 145.43 and 148.39 (ArC), and 173.11 (CO); ν_{max} (KBr disc) 3295 (OH) and 1715 cm^{-1} (CO).

Methyl 3-(5-fluoro-2-hydroxyphenoxy)-3-phenylpropanoate **6h**, m.p. 70-71°C (Found : *m/z* 290.095. $C_{16}H_{15}O_4F$ Requires : M^+, 290.095); δ_H (60 MHz; $CDCl_3$) 2.9 and 3.1 (2xH, 2xd, 2-H), 3.7 (3H, s, Me), 5.35 (1H, dd, 3-H), 6.2 - 7.0 (3H, m, ArH) and 7.45 (5H, s, ArH); ν_{max} (KBr disc) 3410 (OH) and 1710 cm^{-1} (CO).

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9. March, J., in 'Advanced Organic Chemistry : Reactions, Mechanisms, and Structure', 3rd Edn., McGraw-Hill, New York, 1985, pp 986 and 990.

10. In other cases purification was typically effected by flash chromatography on silica (elution with ethyl acetate-hexane) and/or recrystallisation from MeOH. (The possibility of lactone methanolysis should, however, be noted).

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