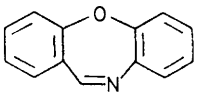
Preparation of the Eight Monohydroxydibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones

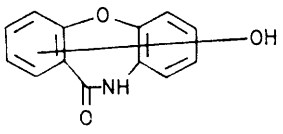
By **Keith Brewster, Raymond J. Clarke, John M. Harrison, Thomas D. Inch,* and David Utley,** Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire SP4 0JQ

The eight possible isomeric monohydroxydibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones have been prepared and their mass spectra determined. With the exception of the 7-hydroxy-derivative the fragmentation patterns of the isomers were similar, although the relative line intensities allowed distinctions between the isomers to be made. The syntheses of several irritant monomethoxydibenz[*b,f*][1,4]oxazepines are also described.

METABOLIC studies [1] of dibenz[*b,f*][1,4]oxazepine (1) in rats have indicated that some of the metabolites are monohydroxydibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones (2). To confirm this observation and to establish the positions of ring hydroxylation, all eight isomeric monohydroxy-



(1)

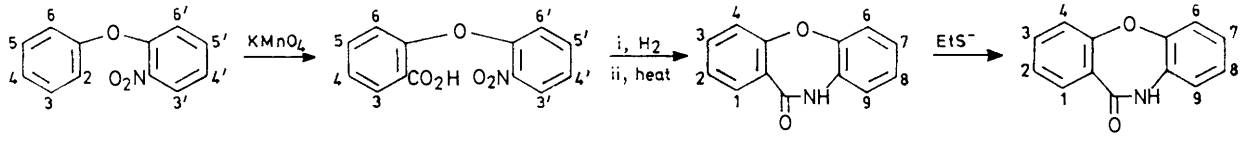


(2)

derivatives (2) have been synthesised. The corresponding methoxy-derivatives and the eight isomeric monomethoxydibenz[*b,f*][1,4]oxazepines have also been prepared.

thiolate in dimethylformamide afforded the monohydroxy-derivatives (27)—(34) in good yields. Other attempted demethylation procedures which involved use of hydrogen bromide or boron tribromide were unsuccessful. The convenience or otherwise of the sequences outlined in the Scheme depended on the ease with which the diphenyl ethers (3)—(10) could be prepared. In most cases convenient starting materials were available commercially. In other cases, where intermediates were prepared, details and references are given in the Experimental section. Attempts to make the 2-formyl analogues of (7) and (9) were unsuccessful.

The aromatic patterns in the n.m.r. spectra [solvent $(CD_3)_2SO$] of the hydroxy-derivatives (27)—(34) were similar to those in the spectra of the corresponding methoxy-derivatives (19)—(26). Only for the 6-, 7-,



(3) 2-Me; 3-OMe
(4) 2-CHO; 4-OMe
(5) 2-CHO; 5-OMe
(6) 2-CHO; 6-OMe
(7) 2-Me; 6'-OMe
(8) 2-Me; 5'-OMe
(8a) 2-Me; 5'-OMe
(9) 2-Me; 4'-OMe
(10) 2-Me; 3'-OMe

(11) 3-OMe
(12) 4-OMe
(13) 5-OMe
(14) 6-OMe
(15) 6'-OMe
(16) 5'-OMe
(17) 4'-OMe
(18) 3'-OMe

(19) 1-OMe
(20) 2-OMe
(21) 3-OMe
(22) 4-OMe
(23) 6-OMe
(24) 7-OMe
(25) 8-OMe
(26) 9-OMe

(27) 1-OH
(28) 2-OH
(29) 3-OH
(30) 4-OH
(31) 6-OH
(32) 7-OH
(33) 8-OH
(34) 9-OH

SCHEME

In essence, the syntheses of the eight monohydroxydibenzoxazepinones (27)—(34) followed the sequence outlined in the Scheme. The appropriately substituted diphenyl ethers (3)—(10) were oxidised to the corresponding nitro-carboxylic acids (11)—(18) with potassium permanganate in pyridine (at room temperature for aldehydes and at *ca.* 100 °C for methyl derivatives). Catalytic hydrogenation afforded the corresponding amino-acids; in some cases (see Experimental section) these could be isolated conveniently whereas in others some spontaneous amide formation occurred. In any event the reduced products were all converted into the corresponding methoxy-lactams (19)—(26) when heated under nitrogen to *ca.* 200 °C. Demethylation of the methoxy-derivatives (19) to (26) with sodium ethane-

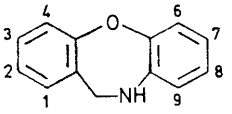
and 8-monohydroxy-derivatives (31)—(33) and the corresponding methoxy-derivatives was it possible to confirm the position of aromatic substitution by essentially complete first-order analysis of the aromatic proton region. The 1-, 2-, 3-, and 4-monohydroxy-derivatives (27)—(30) gave compact, complex spectra with no distinctive features. However in deuteriochloroform the 2-methoxy-derivative (20) showed the H-1 signal as a distinctive low-field doublet with only 1,3-coupling, and the 3-methoxy-derivative (21) showed the H-1 signal as a distinctive low-field doublet with only 1,2-coupling. The i.r. spectra (KBr discs) of the eight monohydroxy-isomers (27)—(34) showed differences in

[1] D. B. Cooper, J. M. Harrison, T. D. Inch, J. Newman, and D. G. Upshall, in preparation.

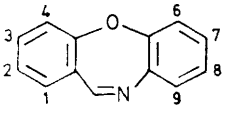
fine structure rather than any distinctive features. However, for purposes of metabolite identification where only microgram quantities of material might be available it is differences in the mass spectra of the isomers which are most important. Accordingly detailed mass spectrometric comparisons of the isomers were made and the results are discussed below.

The monomethoxydibenzoxazepinones (19), (23), and (25) were converted by lithium aluminium hydride into the dihydro-derivatives (35)—(37). These derivatives were dehydrogenated over 10% palladium–charcoal in hot mesitylene, to afford the corresponding monomethoxydibenzoxazepines (38), (42), and (44). Dehydrogenation with sulphur was less successful than with the dibenz[*b*,*e*]azepine derivatives described previously.[2]

The 2-, 3-, 4-, and 7-methoxydibenzoxazepines were prepared more conveniently by reduction of the nitroaldehydes (4)—(6) and (8a) with iron(II) sulphate in ammonia. The intermediate amino-aldehyde underwent spontaneous Schiff's base formation to give the dibenzoxazepines (39)—(41) and (43). The irritant over 10% palladium–charcoal in mesitylene to afford 3-hydroxydibenz[*b*,*f*][1,4]oxazepine (46). This hydroxy-derivative showed none of the irritant properties of its methoxy-analogue.



(35) 1—OMe
(36) 6—OMe
(37) 8—OMe
(45) 3—OH



(38) 1—OMe
(39) 2—OMe
(40) 3—OMe
(41) 4—OMe
(42) 6—OMe
(43) 7—OMe
(44) 8—OMe
(46) 3—OH

The low-resolution mass spectra of all eight monohydroxy-lactams (27)—(34) have been recorded with a view to the routine identification of individual isomers

TABLE 1

Significant peaks in the mass spectra of the hydroxy-lactams (27)—(34)

		Relative intensity (%)							
m/e	Fragment	(27) (1-OH)	(28) (2-OH)	(29) (3-OH)	(30) (4-OH)	(31) (6-OH)	(32) (7-OH)	(33) (8-OH)	(34) (9-OH)
228	$(M + 1)^+$	17	16	26	16	16	14	14	16
227	M^+	100	100	100	100	100	100	100	100
210	$(M - OH)^+$	4	4	7	3	1	2	1	4
209	$(M - H_2O)^+$	3				1		1	3
200		8	13	13	8	4	1	1	2
199	$(M - CO)^+$	47	56	29	32	28	8	9	24
198	$(M - CHO)^+$	12	31	44	9	20	11	11	22
185	$(M - CH_2CO)^+$		6	1			46		3
182	$(M - OH - CO)^+$	6	10	8		6	5	2	
181	$(M - OH - CHO)^+$	3	4	1		2		1	
171	$(M - CO - CO)^+$	41	41	52	12	13	11	29	24
170	$(M - CO - CHO)^+$	35	63	28	25	33	24	41	32
157	$(M - CH_2CO - CO)^+$	2	2	3			59	1	
154	$(M - OH - CO - CO)^+$	11	21	18	3	5	11	1	
153	$(M - OH - CO - HCO)^+$	14	4	4	3	4	5	3	
145	$(M - CO - CO - CN)^+$	6	21	18	5	3	9	41	
143	$(M - 3CO)$	11	10	9	3	9	8	5	10
142	$(M - 3CO - H)^+$	15	15	18	4	2	6	3	2
129	$(M - CH_2CO - 2CO)^+$		5	2		1	29	1	
115	$(M - 3CO - H_2CN)^+$	14	36	38	10	12	23	9	12

properties of the methoxydibenzoxazepines were similar to those of the corresponding methyldibenzoxazepines.[2]

4-Methoxydibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (22) was also prepared by treatment of the corresponding dibenz[*b*,*f*][1,4]oxazepine (41) with chromium trioxide in pyridine.[3] Oxidation of dibenz[*b*,*f*][1,4]oxazepines with peroxy-acids gives benzoxazoles and phenoxazines as well as dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones.[4]

It is possible to convert monohydroxydibenz[*b*,*f*][1,4]-oxazepin-11(10*H*)-ones into the corresponding dibenzoxazepines. Thus reduction of compound (29) with lithium aluminium hydride in dioxan afforded the dihydro-derivative (45), which was dehydrogenated when isolated from biological extracts. The subsequent discussion makes no attempt to describe definitive fragmentation patterns but merely to point out the salient correlative features of the spectra. The significant peaks are shown in Table 1. In each case, the molecular ion gave the base peak. With the exception of the 7-hydroxy-isomer (32), the spectra were qualitatively very similar, showing sequential loss of 28 or 29 mass units (C:O or HCO·, respectively). The 7-hydroxy-lactam (32) showed a strong initial loss of 42 mass units (keten). This was unique within the series and allowed ready characterisation of this isomer.

It is necessary to rely on relative peak intensities for

[2] A. W. H. Wardrop, G. L. Sainsbury, J. M. Harrison, and T. D. Inch, preceding paper.

[3] J. M. Harrison and T. D. Inch, unpublished results.

[4] K. Brewster, C. Brown, R. A. Chittenden, J. M. Harrison, and T. D. Inch, following paper.

the identification of the remaining isomers. The simplest approach is to establish whether the ratio of two close peaks is greater or smaller than unity. For this purpose, the pairs of peaks at $M - 28$ (*m/e* 199) and $M - 29$ (*m/e* 198), and $M - 56$ (*m/e* 171) and $M - 57$ (*m/e* 170) were selected. The results are given in Table 2, which shows that (27) (1-hydroxy) and (29) (3-hydroxy) may be identified. Similarly, (32) and (33) may be distinguished from the other isomers. Since (32) (7-hydroxy) can be uniquely identified, so also can (33) (8-hydroxy). This method fails to distinguish between the 2-, 4-, 6-, and 9-hydroxy-isomers [(28), (30), (31), and (34)] which required quantitative measurement of peak height ratios. By making use of multiple scans it was established that a peak height ratio could be determined with a standard deviation of 8%. Again the $M - 56$ and $M - 57$ peaks were used; the ratios for (28), (30), (31), and (34) are shown in Table 3. This allows the identification of (31) (6-hydroxy) with greater than 98% confidence and (28), (30), and (34) with 90% confidence.

TABLE 2

Comparison of relative intensities of $M - 28$ and $M - 29$, and $M - 56$ and $M - 57$ peaks for the hydroxylactams (27)—(34)

Compd.	$(M - 28)/(M - 29)$	$(M - 56)/(M - 57)$
(27) (1-OH)	>1	>1
(28) (2-OH)	>1	<1
(29) (3-OH)	<1	>1
(30) (4-OH)	>1	<1
(31) (5-OH)	>1	<1
(32) (7-OH)	<1	<1
(33) (8-OH)	<1	<1
(34) (9-OH)	>1	<1

TABLE 3

Intensity ratios of $M - 57$ and $M - 56$ peaks for the monohydroxydibenzoxazepines (28), (30), (31), and (34)

Compd.	$(M - 57)/(M - 56)$
(28) (2-OH)	1.81 ± 0.14
(30) (4-OH)	2.27 ± 0.18
(31) (6-OH)	3.51 ± 0.28
(34) (9-OH)	1.37 ± 0.11

By t.l.c. in a variety of solvent systems it was possible to obtain chromatographic separations of each of the individual isomers from the remaining seven (see Experimental section; Table 4). This technique, in conjunction with mass spectroscopy, allows unequivocal identification of all eight monohydroxydibenzoxazepinones (27)—(34). Thus these compounds can be identified unambiguously when isolated from biological extracts.

TABLE 4

R_F Values for the eight monohydroxydibenzoxazepinones (27)—(34)

Eluting solvent	1-OH (27)	2-OH (28)	3-OH (29)	4-OH (30)	6-OH (31)	7-OH (32)	8-OH (33)	9-OH (34)
Chloroform	0.35	0.1	0.1	0.25	0.25	0.1	0.05	0.15
Chloroform–methanol (19 : 1)	0.8	0.42	0.42	0.45	0.45	0.33	0.32	0.35
Chloroform–ethyl acetate (9 : 1)	0.68	0.15	0.19	0.28	0.28	0.15	0.1	0.22
Chloroform–ethyl acetate (8 : 2)	0.85	0.18	0.23	0.35	0.35	0.18	0.14	0.26

EXPERIMENTAL

N.m.r. spectra were measured with a JEOL JNM-4-H-100 n.m.r. spectrometer at 100 MHz for solutions in deuteriochloroform unless otherwise stated. The n.m.r. spectra of all the intermediates leading to the dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones were consistent with the assigned structures (no details are given but in most cases partial first-order analysis of the aromatic proton signals was possible). For the dibenz[*b,f*][1,4]oxazepin-11(10*H*)-ones all the spectra were consistent with the assigned structures—details are given only when first-order analysis of the aromatic pattern was possible.

Mass spectra were run on a Perkin-Elmer 270 spectrometer at 70 eV (scan speed 10 s; source temperature 250 °C; direct probe insertion).

1-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (27).—3-*Methoxy*-2-*methylphenol*. Dimethyl sulphate (75.5 g) was added dropwise to a cooled (5—10 °C) solution of 2-methylresorcinol (62 g) and sodium hydroxide (50 g) in water (300 ml), and the solution was stored for 1 h. The mixture was extracted with ether and the extract discarded. The aqueous solution was acidified and extracted with ether and the extract was dried, concentrated, and distilled. The product (36 g, 52%) was the fraction of b.p. 133° at 1.5 mmHg.

1-*Methoxy*-2-*methyl*-3-(2-*nitrophenoxy*)*benzene* (3).—A mixture of 3-methoxy-2-methylphenol (14 g), 1-chloro-2-nitrobenzene (15.8 g), potassium hydroxide (2.8 g), and a catalytic quantity of copper powder in dimethylformamide was stirred and boiled under reflux for 3.5 h, poured into water, and extracted with ether. The extract was dried and concentrated. The residue was recrystallised from ethanol (charcoal) to afford the *product* (3) (9.7 g, 27%), m.p. 88° (Found: C, 65.2; H, 5.1; N, 5.3. $C_{14}H_{13}NO_4$ requires C, 64.9; H, 5.1; N, 5.4%).

2-*Methoxy*-6-(2-*nitrophenoxy*)*benzoic acid* (11). A solution of the nitro-derivative (3) (15 g) and potassium permanganate (50 g) in pyridine (100 ml) and water (100 ml) was stirred at room temperature for 1 h. The precipitated manganese dioxide was filtered off and washed with aqueous pyridine and the combined filtrate and washings were concentrated. The residue was dissolved in water and extracted with ether. The aqueous layer was acidified and the precipitate filtered off, dried, and recrystallised from toluene to afford the *product* (11) (12.9 g, 81%), m.p. 152° (Found: C, 58.1; H, 3.8; N, 4.6. $C_{14}H_{11}NO_6$ requires C, 58.1; H, 3.8; N, 4.8%).

1-*Methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (19).—A solution of the acid (11) (5 g) in ethanol was hydrogenated over Adams catalyst. The solution was filtered and concentrated and the residue was heated at 180 °C under nitrogen for 10 min. The product was dissolved in chloroform and passed over silica in ethyl acetate. The eluate was concentrated and the residue was crystallised from ethanol to afford the *product* (19) (0.92 g, 22%), m.p.

245—247° (Found: C, 69.9; H, 4.8; N, 5.8. $C_{14}H_{11}NO_3$ requires C, 69.7; H, 4.6; N, 5.8%).

1-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (27). Ethanethiol (1.2 g) was added to a suspension of sodium hydride (0.85 g) in dimethylformamide (40 ml) at 0 °C, and the mixture was stirred at 0 °C for 90 min before addition of the lactam (19) (1 g) in dimethylformamide (15 ml). The mixture was boiled under reflux for 1 h, then concentrated *in vacuo*, and water was added to the residue. The aqueous mixture was filtered and the filtrate acidified with dilute hydrochloric acid. The precipitate was filtered off, dried, and recrystallised from ethanol to afford the *product* (27) (0.78 g, 83%), m.p. 218° (Found: C, 68.7; H, 4.0; N, 6.5. $C_{13}H_9NO_3$ requires C, 68.7; H, 4.0; N, 6.2%).

2-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (28).—5-*Methoxy*-2-(2-*nitrophenoxy*)*benzaldehyde* (4), prepared from 2-hydroxy-5-methoxybenzaldehyde (15.2 g) and 1-chloro-2-nitrobenzene (15.6 g) in 43% yield, had m.p. 96—97° (from ethanol) (Found: C, 61.7; H, 4.1; N, 4.93. $C_{14}H_{11}NO_5$ requires C, 61.5; H, 4.1; N, 5.1%). Compound (4) (3 g) on oxidation with potassium permanganate afforded 5-*methoxy*-2-(2-*nitrophenoxy*)*benzoic acid* (12) (2.6 g, 81%), m.p. 146—147° (from toluene) (Found: C, 58.2; H, 3.9; N, 4.9%). Reduction of (12) (7 g) with hydrogen over palladium–charcoal afforded 2-(2-*aminophenoxy*)-5-*methoxybenzoic acid* (5.5 g, 84%), m.p. 179—181° (from ethanol) (Found: C, 65.0; H, 5.1; N, 5.2. $C_{12}H_{13}NO_4$ requires C, 64.9; H, 5.1; N, 5.4%). The amino-acid (2.5 g) on heating at 200 °C for 10 min afforded 2-*methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (20) (1.68 g, 70%), m.p. 168° (from ethanol) (Found: C, 70.0; H, 4.7; N, 5.8%), δ 7.43 (H-1, $J_{1,3}$ 2.5 Hz). Demethylation of (20) (1 g) with sodium ethanethiolate afforded 2-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (28) (0.7 g, 75%), m.p. 228—230° (from ethanol) (Found: C, 68.4; H, 4.1; N, 6.0%).

3-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (29).—4-*Methoxy*-2-(2-*nitrophenoxy*)*benzaldehyde* (5), prepared from 2-hydroxy-4-methoxybenzaldehyde and 1-chloro-2-nitrobenzene in 35% yield, had m.p. 61—62° (from ethanol) (Found: C, 61.7; H, 4.2; N, 4.9%). Compound (5) (9.4 g) on oxidation with potassium permanganate afforded 4-*methoxy*-2-(2-*nitrophenoxy*)*benzoic acid* (13) (5.5 g, 55%), m.p. 172—174° (from ethanol) (Found: C, 57.9; H, 3.81; N, 5.0%). Reduction of (13) (5 g) over palladium–charcoal afforded 2-(2-*aminophenoxy*)-4-*methoxybenzoic acid* (3.7 g, 74%), m.p. 140—141° (from ethanol) (Found: C, 65.0; H, 5 3; N, 5.6%). The amino-acid (5 g) on heating at 200 °C under nitrogen for 10 min afforded 3-*methoxydibenz*[b,f][1,4]-*oxazepin*-11(10H)-*one* (21) (3.2 g, 68%), m.p. 178—180° (from ethanol) (Found: C, 69.9; H, 4.6; N, 3.6%), δ 7.74 (H-1, $J_{1,2}$ 9 Hz). Demethylation of (21) (1.5 g) afforded 3-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (29) (1.1 g, 73%), m.p. 229—231° (Found: C, 68 9; H, 4.1; N, 6.4%).

4-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (30).—3-*Methoxy*-2-(2-*nitrophenoxy*)*benzaldehyde* (6) prepared from *o*-vanillin (15.2 g) and 1-chloro-2-nitrobenzene (15.6 g) in 12.5% yield, had m.p. 116° [from light petroleum (b.p. 60—80°)] (Found: C, 61.5; H, 4.1; N, 5.2%). Compound (6) (4 g) on oxidation with potassium permanganate afforded 3-*methoxy*-2-(2-*nitrophenoxy*)*benzoic acid* (14) (3.6 g, 85%), m.p. 144—146° [from light petroleum (b.p. 80—100°)] (Found: C, 58.0; H, 3.9; N, 4.8%). Reduction of (14) over palladium charcoal afforded 2-(2-*aminophenoxy*)-3-*methoxybenzoic acid*, m.p. 181—183° (from ethanol) (Found: C, 64.5; H, 5.1; N, 5.4%). The amino-acid (1.5 g) on heating to 200 °C under nitrogen afforded 4-*methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (22) (1.1 g, 92%), m.p. 220—222° (from ethanol) (Found: C, 69.3; H, 4.7; N, 6.0%). Demethylation of (22) (0.9 g) afforded 4-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (30) (0.4 g, 49%), m.p. 250—252° (from aqueous ethanol) (Found: C, 68.5; H, 4.1; N, 6.0%)

6-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (31).—2-Chloro-3-nitroanisole (18 g) (prepared by methylation of 2-chloro-3-nitrophenol [5]) and copper powder were added to a stirred mixture of *o*-cresol (15 5 g) and potassium hydroxide pellets (12 g) at 120 °C. The mixture was heated for 41 min, cooled, diluted with water, and extracted with ether, and the extract was dried, concentrated, and distilled (b.p. 160—163° at 0.7 mmHg). The distillate solidified on cooling and the solid was recrystallised from light petroleum (b.p. 40—60°) to afford 1-*methoxy*-2-(2-*methylphenoxy*)-3-*nitrobenzene* (7) (11.8 g, 45%), m.p. 64—65° (Found: C, 65.0; H, 4.9; N, 5.2%). Oxidation of (7) (15 g) with potassium permanganate afforded 2-(2-*methoxy*-6-*nitrophenoxy*)*benzoic acid* (15) (9.7 g, 56%), m.p. 165° (from benzene) (Found: C, 58.4; H, 3.7; N, 4.5%) Reduction of (15) (3.5 g) over Adams catalyst in ethanol afforded 2-(2-*amino*-6-*methoxyphenoxy*)*benzoic acid* (3 g, 85%), m.p. 152° (from benzene) (Found: C, 65.0; H, 5.1; N, 5.3%). The amino-acid (1.25 g), heated above its m.p. under nitrogen afforded 6-*methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (23) (1.0 g, 86%), m.p. 218° (from ethanol) (Found: C, 69.6; H, 4.7; N, 5.7%). Demethylation of (23) (1 g) afforded 6-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (31) (0.75 g, 81%), m.p. 257—258° (from water) (Found: C, 68.8; H, 4.0; N, 6.1%), δ [$(CD_3)_2SO$] 7.73 (H-1, $J_{1,2}$ 8, $J_{1,3}$ 1.5 Hz), 6.98 (H-8, $J_{7,8} = J_{8,9} = 8$ Hz), 6.2 (H-7, $J_{7,8}$ 8, $J_{7,9}$ 1.5 Hz), and 6.62 (H-9, $J_{8,9}$ 8, $J_{7,9}$ 1.5 Hz).

7-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (32).—4-*Methoxy*-2-(2-*methylphenoxy*)-1-*nitrobenzene* (8), formed from *o*-cresol (8 g) and 3-chloro-4-nitroanisole [6] (8.75 g) in 46% yield by a similar procedure to that described for (7), had m.p. 47—48° [from light petroleum (b.p. 40—60°)] (Found: C, 64.7; H, 5.1; N, 5.3%). Oxidation of (8) (6 g) with potassium permanganate afforded 2-(5-*methoxy*-2-*nitrophenoxy*)*benzoic acid* (16) (3.6 g, 54%), m.p. 136—137° (from toluene) (Found: C, 58.1; H, 3.9; N, 4.6%). Reduction of (16) over Adams catalyst and subsequent heating at 180 °C under nitrogen afforded 7-*methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (24) [3.7 g, 44% from (16)], m.p. 202° (from toluene) (Found: C, 70.0; H, 4.8; N, 5.4%). Demethylation of (24) (0.6 g) gave 7-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (32) (0.19 g, 34%), m.p. 265° (from aqueous ethanol) (Found: C, 68.6; H, 4.3; N, 6.4%), δ [$(CD_3)_2SO$] 7.78 (H-1, $J_{1,2}$ 8, $J_{1,3}$ 1.5 Hz), 7.58 (H-4, $J_{3,4}$ 7, $J_{2,4}$ 1.5 Hz), 7.01 (H-9, $J_{8,9}$ 8 Hz), 6.75 (H-6, $J_{6,8}$ 2 Hz), and 6.63 (H-8, $J_{8,9}$ 8, $J_{6,8}$ 2 Hz).

8-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (33).—4-*Methoxy*-1-(2-*methylphenoxy*)-2-*nitrobenzene* (9), prepared [as for (7)] from *o*-cresol (15.5 g) and 4-chloro-3-nitroanisole (18 g) in 52% yield, had m.p. 53° [from light petroleum (b.p. 40—60°)] (Found: C, 64.8; H, 4.8; N, 5.1%). Oxidation of (9) (15 g) with potassium permanganate afforded 2-(4-*methoxy*-2-*nitrophenoxy*)*benzoic acid* (17) (11.7 g, 77%), m.p. 179—180° (from benzene) (Found: C, 58.1;

[5] H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 1925, 1599, p. 11.

[6] M. Tomita and H. Iwasaki, *J. Pharm. Soc. Japan*, 1955, **75**, 1128 (*Chem. Abs.*, 1956, **50**, 5560b).

H, 3.9; N, 4.7%). Compound (17) (7 g) with hydrogen over 10% palladium–charcoal afforded 2-(2-*amino*-4-*methoxyphenoxy*)*benzoic acid* (4.8 g, 70%), m.p. 128° (from benzene) (Found: C, 64.8; H, 4.9; N, 5.2%). The amino-acid (4.5 g), heated to 200 °C under nitrogen for 10 min, afforded 8-*methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (25) (3.6 g, 88%), m.p. 167—168° (from ethanol) (Found: C, 69.8; H, 4.6; N, 5.7%). Demethylation of (25) (1 g) afforded 8-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (33) (0.59 g, 59%), m.p. 288° (from aqueous ethanol) (Found: C, 68.6; H, 4.1; N, 6.0%), δ [$(CD_3)_2SO$] 7.81 (H-1, $J_{1,2}$ 9, $J_{2,3}$ 2 Hz), 7.6 (H-2 or H-3, J 8—9, 8—9, and 2 Hz), 7.13 (H-6, $J_{6,7}$ 8 Hz), 6.65 (H-9, $J_{7,9}$ 2 Hz), and 6.53 (H-7, $J_{7,9}$ 2, $J_{6,7}$ 8 Hz).

9-*Hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (34).—1-Methoxy-3-(2-methylphenoxy)-2-nitrobenzene [5] (10). prepared from 3-bromo-2-nitroanisole [5] (from 3-bromo-2-nitrophenol [5]) and *o*-cresol in 41% yield, had m.p. 67.5° [from light petroleum (b.p. 40—60°)]. Oxidation of (10) afforded 2-(3-*methoxy*-2-*nitrophenoxy*)*benzoic acid* (18), m.p. 178° (from toluene). Reduction of (18) (1 5 g) with hydrogen over 10% palladium–charcoal gave an amino-acid which was not isolated, but by heating at 200 °C under nitrogen for 10 min was converted into 9-*methoxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (26) (0.67 g, 54%), m.p. 172—174° (from benzene) (Found: C, 69.4; H, 4.6; N, 5.6%). Demethylation of (26) (0.4 g) afforded 9-*hydroxydibenz*[b,f][1,4]*oxazepin*-11(10H)-*one* (34) (0.18 g, 49%), m.p. 238° (from aqueous ethanol).

2-*Methoxydibenz*[b,f][1,4]*oxazepine* (39).—A suspension of the nitro-aldehyde (4) (7 g) and iron(II) sulphate (55 g) in water (125 ml) was heated to 70 °C. and ethanol (110 ml) and ammonia solution (s.g. 880; 35 ml) were added. After 5 min more ammonia solution (5 ml) was added, and the mixture was boiled under reflux for 45 min, cooled, concentrated, and filtered. The solid and aqueous solution were extracted with chloroform. The extract was concentrated and the residue dissolved in ethanol and added to ethanolic picric acid. The resulting picrate had m.p. 212° (from ethanol). A solution of the picrate in aqueous 5% sodium hydroxide was stirred at room temperature for 30 min and extracted with dichloromethane; the dichloromethane extract was dried and concentrated. The residue was recrystallised from light petroleum (b.p. 40—60°) to afford the *product* (39) (2.5 g. 43%), m.p. 71—72° (Found: C, 7.47; H, 5.1; N, 6.2%); δ 3.69 (OMe) and 8.45 (CH=N).

3-*Methoxydibenz*[b,f][1,4]*oxazepine* (40), b.p. 152—154° at 0.1 mmHg [δ 3·78 (OMe) and 8.40 (CH=N)] was similarly prepared from (5) in 47% yield *via* a picrate, m.p. 217—220° (from ethanol).

4-*Methoxydibenz*[b,f][1,4]*oxazepine* (41), m.p. 110—112° [from light petroleum (b.p. 60—80°)][δ 3.86 (OMe) and 8.57 (CH=N)] was similarly prepared from (6) in 55% yield *via* a picrate, m.p. 235—237° (from ethanol).

7-*Methoxydibenz*[b,f][1,4]*oxazepine* (43).—2-(4-*Methoxy*-2-*nitrophenoxy*)*benzaldehyde* (8a) [m.p. 78° (from cyclohexane)] was prepared in 30% yield by treatment of 3-chloro-4-nitroanisole with potassium salicylate in dimethylformamide. The nitro-aldehyde (8a) was treated with iron(II) sulphate and ammonia as described above to afford the product (43), b.p. 133—135° at 0.5 mmHg, δ 3.78 (OMe) and 8.40 (CH=N), which was purified *via* the picrate, m.p. 209—211° (from ethanol).

10,11-*Dihydrodibenz*[b,f][1,4]*oxazepin*-3-*ol* (45).—A mixture of compound (29) (0.75 g) and lithium aluminium hydride (1 g) in dry dioxan was boiled under reflux for 8 h. The excess of lithium aluminium hydride was decomposed with wet dioxan and the mixture was filtered. The solid residue was washed with hot dioxan and the combined filtrate and washings were concentrated. The residue was passed over silica in cyclohexane–ethyl acetate (1 : 1), and the major product was recrystallised from cyclohexane to give *compound* (45) (0 47 g, 67%), m.p. 144° (Found: C, 72.8; H, 5.2; N, 6.6. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%).

Dibenz[b,f][1,4]*oxazepin*-3-*ol* (46).—A mixture of the dihydro-compound (45) (1.2 g) and 10% palladium–charcoal (12 g) in mesitylene (15 ml) was heated until no starting material remained (t.l.c. in cyclohexane). The mixture was filtered and the filtrate was concentrated *in vacuo* to afford the *product* (46) (0.47 g, 40%), m.p. 202° (Found: C, 74.3; H, 4.5; N, 6.7. $C_{13}H_9NO_2$ requires C, 73.9; H, 4.3; N, 6.6%).

1-*Methoxydibenz*[b,f][1,4]*oxazepine* (38).—A solution of compound (19) (1 g) in dry dioxan (30 ml) was added to a suspension of lithium aluminium hydride (1 g) in dry dioxan. The mixture was boiled under reflux for 8 h, then cooled, and the excess of lithium aluminium hydride and alkoxides was decomposed with wet dioxan. The solution was filtered, the solid matter was washed with hot dioxan, and the combined filtrate and washings were concentrated *in vacuo*. The residue was passed over silica in cyclohexane–ethyl acetate (1 : 1) to afford 10,11-*dihydro*-1-*methoxydibenz*[b,f][1,4]*oxazepine* (35) (0.62 g, 66%), m.p. 62° (Found: C, 73.8; H, 5.6; N, 6.1. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.8; N, 6.2%), δ 3.85 (OMe) and 8.8 (CH_2·NH). A solution of (35) (0.25 g) in mesitylene (15 ml) to which 10% palladium–charcoal (0.1 g) had been added was boiled under reflux until no starting material remained (t.l.c. in cyclohexane–EtOAc, 7 : 3). The solution was filtered, concentrated, and passed over silica in cyclohexane–ethyl acetate (3 : 2), and the product was recrystallised from light petroleum to afford 1-*methoxydibenz*[b,f][1,4]*oxazepine* (38) (0.08 g, 33%), m.p. 110—111° (Found: C, 74.2; H, 5.1; N, 5.9. $C_{14}H_{12}NO_2$ requires C, 74.6; H, 4.9; N, 6.2%).

6-*Methoxydibenz*[b,f][1,4]*oxazepine* (42), m.p. 99—101° (from benzene), δ 3.91 (OMe) and 8.56 (C*H*=N), was prepared in 38% yield from (23) *via* 10,11-*dihydro*-6-*methoxydibenz*[b,f][1,4]*oxazepine* (36), m.p. 113—116° (from cyclohexane).

8-*Methoxydibenz*[b,f][1,4]*oxazepine* (44), m.p. 61—62° [from light petroleum (b.p. 40—60°)], δ 3.7 (OMe) and 8.48 (CH=N), was prepared in 46% yield from (25) *via* 10,11-*dihydro*-8-*methoxydibenz*[b,f][1,4]*oxazepine* (37), m.p. 110—111° [from light petroleum (b.p. 40—60°)].

Chromatographic Data for Monohydroxydibenzoxazepinones (27)—(34).—T.l.c. was performed by upward irrigation on microscope slides coated with Merck silica gel G. R_F Values in various solvent systems are shown in Table 4. The 4- and 6-hydroxy-isomers [(30) and (31)] could be separated from each other only by multiple irrigation (× 4), with chloroform as eluant. Many other systems were investigated but afforded no resolution.

[5/2195 *Received*, 11*th November*, 1975]