

Condensed heterotricycles: Pyrido(1,2,3-*de*)(1,4)benzoxazines, pyrido(1,2,3-*ef*)(1,5)benzoxazepines and pyrido(1,2,3-*fg*)(1,6)benzoxazocines⁺

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Abstract. Cyclization of N-(2-haloacyl)-8-hydroxy-1,2,3,4-tetrahydroquinolines **4-7** and **9** with alkali affords pyridobenzoxazinones **21-24** and **26** respectively and of the 4-chlorobutyramide **13** with NaH, the benzoxazocinone **31**. Exposure of 3-chloropropionamide **12** to NaH affords acrylamide **15**, benzoxazepinone **28** or methyl benzoxazinone **22** or mixtures thereof under various conditions. **28** undergoes rapid base-catalysed ring contraction to **22**. NaH-catalysed ring closure of acrylamide **15** affords mixtures of **22** and **28**, while from the crotonamides **16** and **17**, the methylbenzoxazepinones **29** and **30** are obtained preponderantly, the former amide yielding only traces of the ethyl benzoxazinone **23**. **29** shows no propensity for ring contraction to give **23**. The cinnamoyl derivatives **18**, **19** and **20** are cyclized to benzyl benzoxazinones **24**, **27** and **25**, respectively. The intermediacy of the phenyl benzoxazepinone **39** in the formation of **24** has been established by deuteration studies. Benzylidene benzoxazinone **41** is obtained from dibromocinnamamide **14** and propiolamide **40**. Dichloracetamides **8** and **10** undergo interesting ring closure to compounds **45-54** upon treatment with amines. The course of electrophilic reactions of the lactams depends upon the ring size.

Keywords. Ring size and stability; deuteration studies; ¹H and ¹³C NMR studies.

1. Introduction

Pyrido(4,3-*b*)(1,5)benzoxazepines (Kaiser and Setler 1981) and dibenzoxazepines (Nagarajan *et al* 1985, 1986) e.g. Sintamil (Nagarajan 1979), amoxapine (Howell *et al* 1968) are ring systems studied extensively for their effects on the central nervous system. Pyrido(1,2,3-*de*)benzoxazine derivatives exemplified by ofloxacin (Hayakawa *et al* 1982) have recently become important as antibacterial agents (Fernandes and Chu 1987). As part of our work on the Sintamil series (Nagarajan 1972), we had synthesized a number of candidate drugs incorporating the pyrido(1,2,3-*de*)(1,4)benzoxazine,

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pyrido(1,2,3-*ef*)(1,5)-benzoxazepine and pyrido(1,2,3-*fg*)(1,6)benzoxazocine ring systems from 8-hydroxy-1,2,3,4-tetrahydroquinolines and observed good analgesic activity for members of all the three ring systems (Nagarajan *et al* 1974). The work also led to a considerable amount of interesting chemistry which is presented in this paper.

2. Cyclization reactions

2.1 Cyclization of *N*-(α -haloacyl)-8-hydroxy-1,2,3,4-tetrahydroquinolines—formation of pyrido(1,2,3-*de*)(1,4)benzoxazin-3-ones

8-Hydroxyquinolines were reduced catalytically to the known tetrahydroquinolines 1–3. These were acylated in ether solution with α -haloacid chlorides in the presence of aqueous sodium bicarbonate to afford amides 4–7 and 9 (table 1). Treatment of these amides with aqueous potassium or sodium hydroxide led to the formation of the benzoxazinones 21–24 and 26, respectively, in moderate to high yields (table 2).

The ring system has been synthesised earlier (Isler 1944) by internal alkylation of 8-(2-haloethoxy)-1,2,3,4-tetrahydroquinolines and cyclization of *N*-(3-carboxypropyl)-(1,4)benzoxazin-2-one (Techer *et al* 1969). Ofloxacin is obtained by displacement of the fluorine atom in 8-fluoro-*N*-(2-hydroxypropyl)-quinoline (Hayakawa *et al* 1982). Halopyridobenzoxazinones with antifungal properties have been obtained recently by Naumann *et al* (1984) and Brandes *et al* (1985) by cyclocondensation of 8-hydroxy-1,2,3,4-tetrahydroquinolines with chloroacetyl chloride.

Table 1. Physical data for *N*-acyl-8-hydroxy-1,2,3,4-tetrahydroquinolines.

Compound no.	Yield (%)	Crystallized from	Mol. formula	Mol. wt.	m.p. (°C)
<u>4</u>	82	EtOH-H ₂ O	C ₁₁ H ₁₂ ClNO ₂	225.7	133–4
<u>5</u>	73	EtOH-H ₂ O	C ₁₂ H ₁₄ ClNO ₂	239.7	148–50
<u>6</u>	85		C ₁₃ H ₁₆ BrNO ₂	298.3	Oil
<u>7</u>	73	C ₆ H ₁₄	C ₁₈ H ₁₈ ClNO ₂	315.8	124–6
<u>8</u>	74	EtOH-H ₂ O	C ₁₁ H ₁₁ Cl ₂ NO ₂	260.1	186–7(<i>d</i>)
				(<i>M</i> ⁺ 259, 261)	
<u>9</u>	83	EtOH	C ₁₂ H ₁₄ ClNO ₂	239.7	151–2
<u>10</u>	77	MeOH	C ₁₁ H ₁₀ Cl ₃ NO ₂	294.6	200–3
<u>11</u>	24	C ₆ H ₆ -C ₆ H ₁₄	C ₁₁ H ₁₀ Cl ₃ NO ₂	294.6	114–6
<u>12</u>	87	EtOH-H ₂ O	C ₁₂ H ₁₄ ClNO ₂	239.7	129–31
<u>13</u>	71	EtOH-H ₂ O	C ₁₃ H ₁₆ ClNO ₂	253.7	104–6
<u>14</u>	57	EtOH	C ₁₈ H ₁₇ Br ₂ NO ₂	439.2	162–3
<u>15</u>	55	EtOH	C ₁₂ H ₁₃ NO ₂	203.2	152–3
<u>16</u>	58	EtOH-H ₂ O	C ₁₃ H ₁₅ NO ₂	217.3	109–10
				(<i>M</i> ⁺ 217)	
<u>17</u>	49	MeOH-H ₂ O	C ₁₃ H ₁₄ ClNO ₂	251.7	142–3
<u>18</u>	83	MeOH-C ₆ H ₆	C ₁₈ H ₁₇ NO ₂	279.3	182–4
				(<i>M</i> ⁺ 279)	
<u>19</u>	81	MeOH	C ₁₉ H ₁₉ NO ₂	293.4	173–5
<u>20</u>	66	EtOH-C ₆ H ₆	C ₁₉ H ₁₉ NO ₃	309.4	185–8
<u>40</u>	85	MeOH	C ₁₈ H ₁₅ NO ₂	277.3	116–8
				(<i>M</i> ⁺ 277)	

Table 2. Physical data for pyridobenzoxazinones, oxazepinones and oxazocinone.

Compound no.	Yield (%)	Crystallized from	Mol. formula	Mol. wt.	m.p. (°C)	¹ H NMR data (δ in ppm)
<u>21</u>	80	Hexane	C ₁₁ H ₁₁ NO ₂	189.2 (M ⁺ 189)	113-4	1.90(<i>qui</i> , C-6 H ₂), 2.77(<i>t</i> , C-7 H ₂), 3.80(<i>t</i> , C-5 H ₂), 4.50(<i>s</i> , C-2 H ₂), 6.65-6.90(<i>m</i> , 3 ArH)
<u>22</u>	83	Hexane	C ₁₂ H ₁₃ NO ₂	203.2	94-5	1.55(<i>d</i> , Me), 1.93(<i>qui</i> , C-6 H ₂), 2.80(<i>t</i> , C-7 H ₂), 3.50-4.20(<i>m</i> , C-5 H ₂), 4.58(<i>q</i> , C-2H), 6.65-7.00(<i>m</i> , 3 ArH)
<u>23</u>	65	Hexane	C ₁₃ H ₁₅ NO ₂	217.3 (M ⁺ 217)	44-6	1.05(<i>t</i> , Me), 1.6-2.2(<i>m</i> , C-6 H ₂ ⁺ CH ₂ Me), 2.75(<i>t</i> , C-7 H ₂), 3.78(<i>t</i> , C-5 H ₂), 4.32(<i>d</i> × <i>d</i> C-2 H), 6.5-6.9(<i>m</i> , 3 ArH)
<u>24</u>	82		C ₁₈ H ₁₇ NO ₂	279.3 (M ⁺ 279)	Oil	1.70(<i>qui</i> , C-6 H ₂), 2.57(<i>t</i> , C-7 H ₂), 2.70-3.40(<i>m</i> , ArCH ₂), 3.65(<i>t</i> , C-5 H ₂), 4.58(<i>d</i> × <i>d</i> , C-2H), 6.4-6.8(<i>m</i> , 3 ArH), 7.13(<i>s</i> , C ₆ H ₅)
<u>25</u>	50	MeOH	C ₁₉ H ₁₉ NO ₃	309.4	83-5	1.75(<i>qui</i> , C-6 H ₂), 2.62(<i>t</i> , C-7 H ₂), 2.75-3.33(<i>m</i> , ArCH ₂), 3.62(<i>s</i> , OMe), 3.67(<i>t</i> , C-5 H ₂), 4.55(<i>d</i> × <i>d</i> , C-2H), 6.5-6.85(<i>m</i> , 5 ArH), 6.90-7.25(<i>m</i> , 2 ArH)
<u>26</u>	74		C ₁₂ H ₁₃ NO ₂	203.2	Oil 120-5/ 0.7 mm	1.17(<i>d</i> , Me), 1.90(<i>m</i> , C-6 H ₂), 2.40-3.20(<i>m</i> , C-7 H ₂), 4.30(<i>d</i> , C-2H), 4.57(<i>d</i> , C-2H), 4.85(<i>m</i> , C-5 H), 6.60-7.00(<i>m</i> , 3 ArH)
<u>27</u>	71	Hexane	C ₁₉ H ₁₉ NO ₂	293.3	65-7	1.40(<i>s</i> , Me), 1.70(<i>qui</i> , C-6 H ₂), 2.55(<i>t</i> , C-7 H ₂), 2.82(<i>d</i> , PhCH), 3.20(<i>d</i> , PhCH), 3.45-3.90(<i>m</i> , C-5 H ₂), 6.4-6.8(<i>m</i> , 3 ArH), 7.10(<i>s</i> , Ph)
<u>28</u>	23	Hexane	C ₁₂ H ₁₃ NO ₂	203.2	84-5	1.85(<i>qui</i> , 2H, C-7 H ₂), 2.57(<i>t</i> , C-3 H ₂), 2.70(<i>t</i> , C-8H ₂), 3.67(<i>t</i> , C-6 H ₂), 4.53(<i>t</i> , C-2 H ₂), 6.75-7.0(<i>m</i> , 3 ArH)
<u>29</u>	70	Hexane	C ₁₃ H ₁₅ NO ₂	217.3 (M ⁺ 217)	81-2	1.35(<i>d</i> , Me), 1.83(<i>qui</i> , C-7 H ₂), 2.08-2.90(<i>m</i> , C-8 H ₂ , C-3 H ₂), 3.68(<i>t</i> , C-6 H ₂), 4.80(<i>m</i> , C-2 H), 6.70-7.00(<i>m</i> , 3 ArH)
<u>30</u>	85		C ₁₃ H ₁₄ ClNO ₂	251.8	Oil	1.37(<i>d</i> , Me), 1.90(<i>qui</i> , C-7 H ₂), 2.15-3.00(<i>m</i> , C-8 H ₂ , C-3 H ₂), 3.70(<i>t</i> , C-6 H ₂), 4.72(<i>m</i> , C-2H), 6.80(<i>d</i> , ArH), 7.05(<i>d</i> , ArH)
<u>31</u>	69	Hexane	C ₁₃ H ₁₅ NO ₂	217.3 (M ⁺ 217)	78-9	1.50-5.00(all CH ₂ , as humps), 6.70-7.40(<i>m</i> , 3 ArH)
<u>41</u>	65	MeOH	C ₁₈ H ₁₅ NO ₂	277.3 (M ⁺ 277)	125-6	1.97(<i>qui</i> , C-6 H ₂), 2.77(<i>t</i> , C-7 H ₂), 3.90(<i>m</i> , C-5 H ₂), 6.50-6.92(<i>m</i> , 3 ArH), 6.87(=CH), 7.0-7.46(<i>m</i> , 3 ArH), 7.5-8.7(<i>m</i> , 2 ArH)

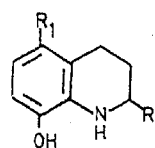
2.2 Cyclization of 3-chloropropionyl derivative 12 - formation of acrylamide 15, pyrido(1,2,3-*ef*) (1,5)benzoxazepin-4-one 28 and pyridobenzoxazinone 22

The amide 12 (table 1) was obtained from 1 and 3-chloropropionyl chloride. Treatment with aqueous NaOH led to elimination of HCl and formation of 15, derived from 1 and acryloyl chloride (table 1). Refluxing of 12 with 1.03 molar equivalents of sodium

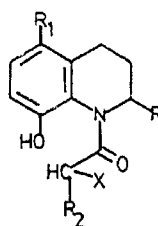
hydride (NaH) in DMF for 5 min gave a mixture of the desired benzoxazepinone 28 (table 2) and the methylbenzoxazinone 22, separated by fractional crystallization. The former was characterized by the presence in the ^1H NMR spectrum of signals due to $-\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2\text{CH}_2\text{CH}_2-$ as against $\text{CH}-\text{CH}_3$ and $\text{CH}_2\text{CH}_2\text{CH}_2$ units in that of the latter. The proportion of 22 in the product mixture increased considerably when the reaction time was extended to 1 h allowing isolation of pure 22. Reaction of 12 with NaH in DMF at ambient temperature was sluggish, but the formation of the acrylamide 15 was observed. 28 was unambiguously synthesized from 8-hydroxyquinoline via propionic acid 32 and its tetrahydro derivative 33.

The ring system has been synthesized by PPA cyclization of N-carboxypropyl-1,5-benzoxazepin-4-one (Katekar 1972) and the 7-carboxylic acid derivatives reported to be antibacterial (Schriewer *et al* 1987).

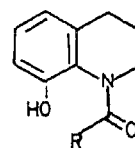
Reaction of amide 12 with a little less than one molar equivalent of NaH gave only the acrylamide 15. While the benzoxazepinone 28 was stable in hot DMF alone, it rapidly underwent ring contraction in the presence of NaH to afford 22, presumably by ring opening to form 15 and readdition of the resultant phenolate ion to the carbon α to the $\text{C}=\text{O}$ group in an 'anti-Michael' fashion. Formation of 22 was



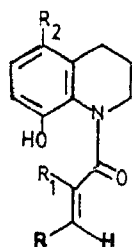
- 1 $\text{R} = \text{R}_1 = \text{H}$
2 $\text{R} = \text{Me}; \text{R}_1 = \text{H}$
3 $\text{R} = \text{H}; \text{R}_1 = \text{Cl}$



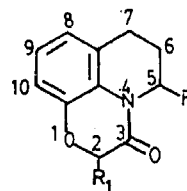
- $\text{R} = \text{R}_1 = \text{H}$
4 $\text{R}_2 = \text{H}; \text{X} = \text{Cl}$
5 $\text{R}_2 = \text{Me}; \text{X} = \text{Cl}$
6 $\text{R}_2 = \text{Et}; \text{X} = \text{Br}$
7 $\text{R}_2 = \text{PhCH}_2; \text{X} = \text{Cl}$
8 $\text{R}_2 = \text{X} = \text{Cl}$



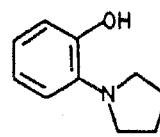
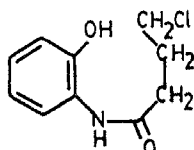
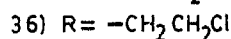
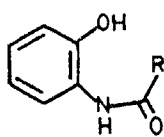
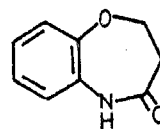
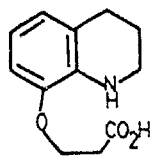
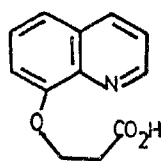
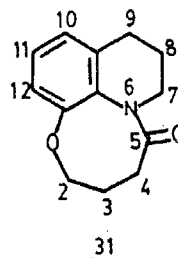
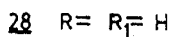
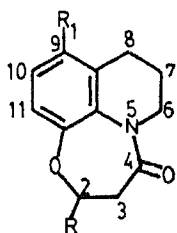
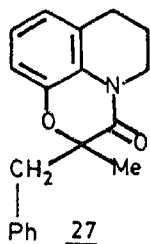
- 11 $\text{R} = \text{CCl}_3$
12 $\text{R} = \text{CH}_2\text{CH}_2\text{Cl}$
13 $\text{R} = \text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$
14 $\text{R} = \text{---CH(Br)---CH(Br)---Ph}$



- $\text{R} = \text{Me}; \text{R}_1 = \text{H}$
9 $\text{R}_2 = \text{H}; \text{X} = \text{Cl}$
10 $\text{R}_2 = \text{X} = \text{Cl}$
15 $\text{R} = \text{R}_1 = \text{R}_2 = \text{H}$
16 $\text{R} = \text{Me}; \text{R}_1 = \text{R}_2 = \text{H}$
17 $\text{R} = \text{Me}; \text{R}_1 = \text{H}; \text{R}_2 = \text{Cl}$
18 $\text{R} = \text{Ph}; \text{R}_1 = \text{R}_2 = \text{H}$
19 $\text{R} = \text{Ph}; \text{R}_1 = \text{Me}; \text{R}_2 = \text{H}$
20 $\text{R} = 4\text{-MeO-C}_6\text{H}_4; \text{R}_1 = \text{R}_2 = \text{H}$



- 21 $\text{R} = \text{R}_1 = \text{H}$
22 $\text{R} = \text{H}; \text{R}_1 = \text{Me}$
23 $\text{R} = \text{H}; \text{R}_1 = \text{Et}$
24 $\text{R} = \text{H}; \text{R}_1 = \text{PhCH}_2$
25 $\text{R} = \text{H}; \text{R}_1 = 4\text{-MeOC}_6\text{H}_4\text{CH}_2$
26 $\text{R} = \text{Me}; \text{R}_1 = \text{H}$



observed to the extent of 16% in 5 min and 70% in 1 h. Under similar conditions, 22 had no tendency to form 28.

It is interesting to note that the bicyclic 1,5-benzoxazepinone 34 (Huckle *et al* 1965) upon treatment with NaH in hot DMF does not undergo a similar ring contraction but only yields the acrylamide 35, also obtained from 2-(3-chloropropionamido)phenol 36 with aqueous NaOH or methanolic KOH.

2.3 Cyclization of 4-chlorobutyryl derivative 13 - formation of pyrido(1,2,3-fg)(1,6)benzoxazocin-5-one 31

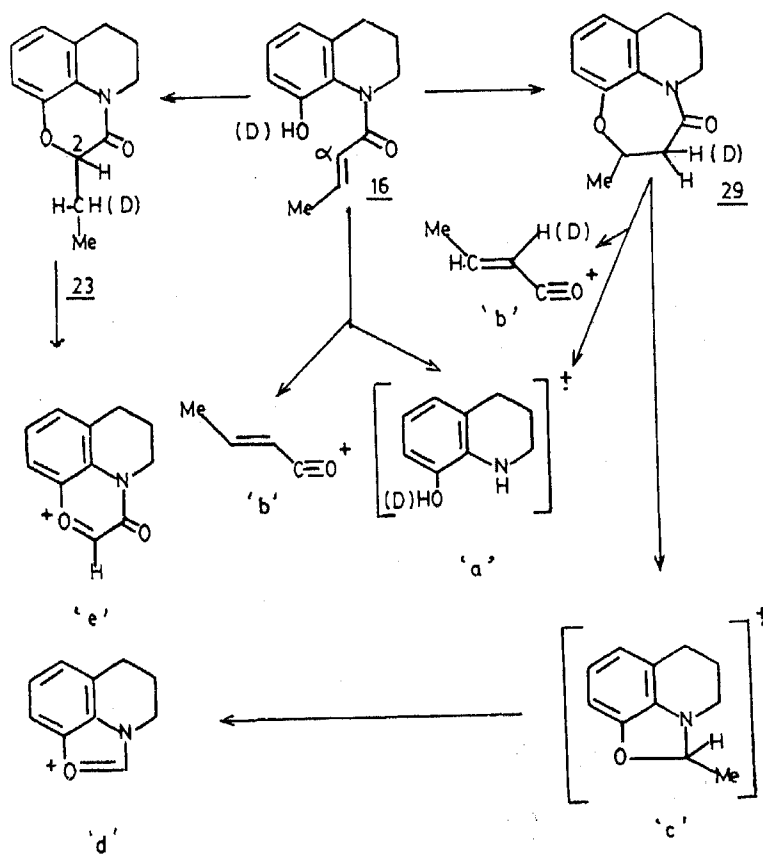
Smooth cyclization of the amide 13 (table 1) with NaH in DMF occurred to afford in 69% yield, the novel benzoxazocinone 31 (table 2). In contrast to the lower ring homologues 21 and 28, the 60 MHz ¹H NMR spectrum of 31 gave rise to a featureless envelope as the signal for the protons of the five methylene groups, implying slow ring inversion. Attempts to cyclize 13 with methanolic KOH at room or elevated temperature gave negative results. 31 was stable to heating with NaH in DMF. Interestingly 2-(4-chlorobutyramido) phenol 37 is reported to undergo cyclization only to the pyrrolidine 38 (Badilescu 1968).

2.4 Cyclization of acryloyl derivatives 15–20

The acrylamides were prepared by the general procedure outlined earlier and are listed in table 1. Heating of a DMF solution of 15 in the presence of NaH (18 mol%) for 5 min gave in 67% yield a gum as the neutral product which was a mixture of 22 and 28 in the ratio of 1:3. 28 could be obtained pure from the gum in about 34% yield by fractional crystallization. Heating for 15, 30, 60 and 240 min gave a mixture in which the presence of 28 decreased to 60, 42, 37 and 35% respectively. Cyclization of 15 was not catalyzed by *p*-toluenesulphonic acid.

Similar cyclization of the crotonyl derivatives 16 and 17 under NaH catalysis gave rise to the pyridobenzoxazepines 29 and 30 respectively (table 2) as the neutral products. These were readily characterized by the presence of Me doublet due to CH₃–CH in their ¹H NMR spectra. Reaction times of 5 min to 1 h gave only increasing yields of 29 and 30. From the cyclization of the amide 16, a trace of the ethylbenzoxazinone 23 was obtained. This did not exhibit any tendency towards ring enlargement to 29 under base catalysis.

It is conceivable that 29 is in equilibrium with 16 in the presence of NaH and that 29 and 23 are continuously formed, the former preponderantly and the latter irreversibly by an 'anti-Michael' addition. This hypothesis was tested and eliminated by subjecting the O-deuterated derivative of 16 to cyclization and isolating as before the monodeutero-derivative of 29 as the major product and the monodeutero derivative of 23 in traces. The deuterium atoms were located as shown in scheme 1 by a study of their



Scheme 1.

Table 3. Mass spectral fragmentation of 16, 23 and 29 and their deuterio derivatives (scheme 1).

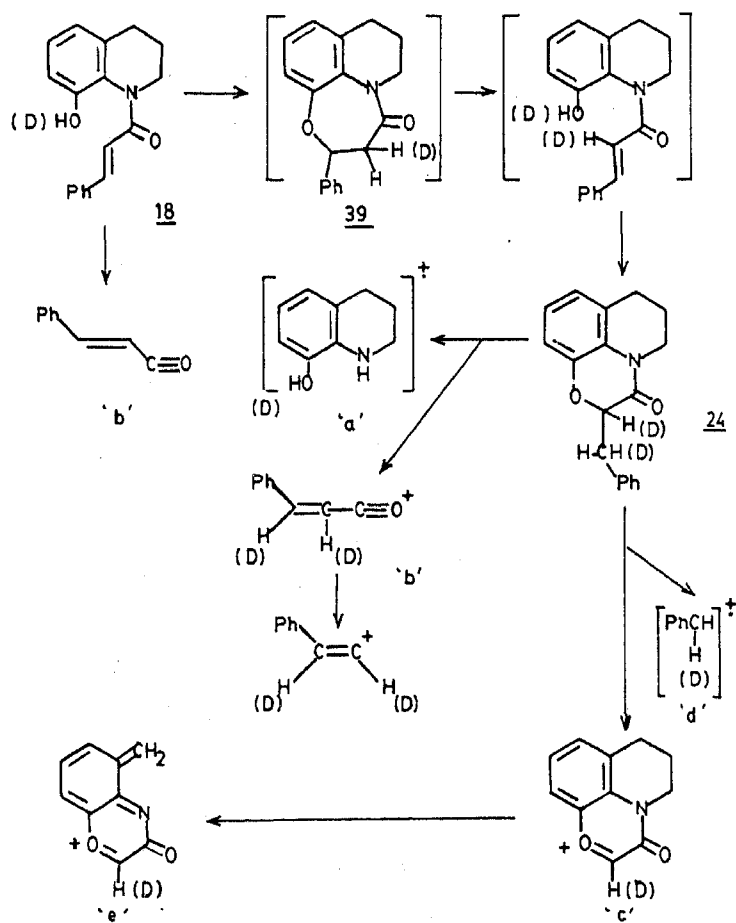
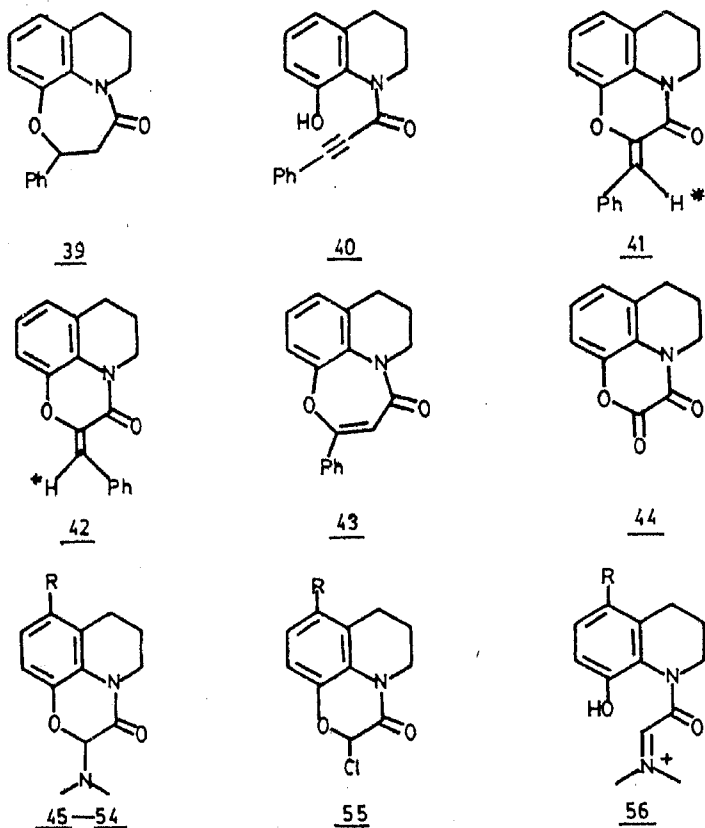
Compound no.	<i>m/z</i> (% abundance)		Fragments <i>m/z</i> (% abundance)				
	<i>M</i> ⁺	(<i>M</i> + 1) ⁺	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>
<u>16</u>	217(4.9)	218(1)	149(100), 150(12)	69(63), 70(3)			
<u>16(D)</u>	217(4.9)	218(24)	149(100), 150(95)	69(70), 70(4)			
<u>23</u>	217(100)	218(20)					183(35), 189(50)
<u>23(D)</u>	217(100)	218(66)					188(35), 189(41)
<u>29</u>	217(90)	218(19)	149(100), 150(14)	69(49), 70(3)	175(22), 176(9)	161(25), 162(10)	
<u>29(D)</u>	217(90)	218(85)	149(100), 150(47)	69(27), 70(16)	175(25), 176(14)	161(12), 162(5)	

mass spectral fragmentation (table 3). Fragments 'a' and 'b' of the monodeutero 29 had a D atom in them, while 'c' did not. Fragment 'e' of the monodeutero 23 did not carry a D atom. If there were an equilibrium between 29 and 16, the latter would have acquired a D atom at the carbon atom α and this would have landed at position 2 in 23, which in turn would have been left in 'e' during fragmentation.

The process of exchange of proton for deuterium in 16 did not lead to its introduction into the crotonyl moiety as revealed by one of its significant fragments 'a' carrying the D atom but not 'b' (scheme 1, table 3).

Cyclization of the cinnamoyl derivative 18 under NaH catalysis for 5 min gave the benzylbenzoxazinone 24 as an oily neutral product in 30% yield which increased to 82% in 1 h. This was identical with the product obtained by cyclization of the 2-chlorophenylpropionyl derivative 7. There was no evidence for the formation of the (normally) expected phenylbenzoxazepinone 39. The structure of 24 was based upon the formation of a strong (100%) fragment due to the loss of PhCH₂ group upon electron impact and also upon signals in the ¹H NMR spectrum at δ 4.58 ppm (*dd*, $J = 8, 4$ Hz) due to the methine proton at C-2 and to a multiplet for the benzylic CH₂ at 2.75–3.33 ppm. NaH-catalysed cyclization of the α -methylcinnamoyl derivative 19 for 15 min–1 h gave a neutral product in 82–90% yield from which 2-methyl-2-benzylbenzoxazinone 27 was obtained as a crystalline compound (71%) (table 2). Evidence for the structure was provided by its ¹H NMR spectrum showing a methyl group as a singlet at δ 1.40 ppm and the benzylic CH₂ as a quartet at δ 2.82 and 3.20 ppm ($J = 14$ Hz).

Although the phenyl pyridobenzoxazepinone 39 could not be isolated from the cyclization of the cinnamamide 18, its putative formation was demonstrated by cyclization of the O-deutero derivative of 18. The deuterated benzylbenzoxazinone 24 was isolated and its mass spectral fragmentation compared with that of the product from undeuterated 18. If 24 were the product of direct addition of the deuterophenol to the (unfavoured) carbon α to the C=O in 18, the resultant product would be monodeutero 24, with the D atom only on the benzylic carbon atom. However, the product from our experiment was the dideutero derivative of 24 with the D atoms as



Scheme 2.

Table 4. Mass spectral fragmentation of 18 and 24 and their deuterio derivatives (scheme 2).

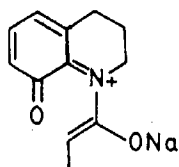
Com- pound no.	<i>m/z</i> (abundance)			Fragments <i>m/z</i> (% abundance)				
	<i>M</i> ⁺	(<i>M</i> + 1) ⁺	(<i>M</i> + 2) ⁺	<i>a</i>	<i>b</i>	<i>c</i>	<i>d</i>	<i>e</i>
<u>18</u>	279(36)	280(9)			131(100), 132(14)			
<u>18(D)</u>	279(35)	280(49)			131(100), 132(15)			
<u>24</u>	279(84)	280(28)	281(4)	149(65), 150(8)	131(91), 132(49), 133(11)	188(100), 189(14)	91(68), 92(8)	160(64), 161(9)
<u>24(D)</u>	279(84)	280(87)	281(35)	149(65), 150(39)	131(91), 132(73), 133(29)	188(100), 189(54)	91(68), 92(31)	160(64), 161(33)

shown in scheme 2. Thus the major fragments of the deuterated product upon electron impact (table 4) at *m/z* 91(d), 188(c) and 149(a) had one excess deuterium in them, while fragment 'b' as expected had two D atoms. This would be only possible if 39 were formed from 18 in a reversible reaction ending in the irreversible production of 24. The possibility of the cinnamoyl group in 18 acquiring a deuterium atom during the preparation of monodeutero 18 was ruled out readily since its mass spectrum showed the same base fragment at *m/z* 131 as 18 did (scheme 2, table 4).

The formation of 24 from the anion of 18 is apparently 'anti-Michael' addition and would imply that the benzylic carbanion has greater stability than COCH⁽⁻⁾. The former would be expected to be destabilized with respect to the latter by positioning an electron-donating methoxyl group para to the side chain in 18. However, the cyclization of the *p*-methoxycinnamamide 20 also resulted only in the formation of the *p*-methoxybenzylbenzoxazinone 25 (¹H NMR, table 2).

It would thus appear that the pyridobenzoxazepinones 28 and 39 are unstable in the presence of base and undergo irreversible ring contraction to the benzoxazinones 22 and 24, respectively, while the methylpyridobenzoxazepinone 29 does not get transformed into the ethylbenzoxazinone 23. These observations defy a cogent explanation. We propose reluctantly that the seven-membered rings in this series are relatively unstable; hence they undergo ring opening followed by an "anti-Michael" addition irreversibly. The stability of 29 (and 30) would require that the CH₃CH⁽⁻⁾ is considerably less stable and hence its formation is not favoured compared to CH₂⁽⁻⁾ or PhCH₂^{(-)*}.

* A referee has suggested that 15 can give rise to the following species which can then undergo a π₂s + π₂s + π₂s cyclization, to afford 22. The authors do not favour this not only because of its high energy but also because it does not explain several observations including the formation of 29 from 16 and its stability, the nonisolability of 39 etc.



2.5 Cyclization of 2,3-dibromocinnamamide 14 and phenylpropiolamide 40 – formation of benzylidenepyridobenzoxazinone 41

The amide 14 (table 1), was prepared from 1 and 2,3-dibromo-3-phenylpropionyl chloride and cyclized with methanolic KOH to give 41 (table 2) in 65% yield. The same product was obtained by using morpholine or 3-aminopropylmorpholine instead of methanolic KOH, and also in the NaH-catalysed cyclization of phenylpropiolamide 40 (table 1). The isomeric structure 43 was ruled out by ozonolysis which afforded the benzoxazinedione 44 and benzaldehyde. Authentic 44 was readily obtained for comparison from 1 and oxalyl chloride. The Z-structure 41 was favoured over the E-configuration 42 on the basis of ^{13}C spectral consideration. Thus the signal due the carbonyl carbon of 41 observed at 155.37 ppm was split into a doublet by a three-bond coupling with the starred H ($J = 3.6$ Hz). This is consistent with a *cis*-arrangement of the two nuclei as in 41, while in 42, the relation would be *trans* and the coupling expected to be 10–12 Hz (Vögeli *et al* 1978).

Addition of 1 to diethylacetylene dicarboxylate has been shown by us earlier to yield a mixture of E and Z forms of 3-carbethoxy methylidenepyridobenzoxazin-2-ones (Nair *et al* 1979).

2.6 Cyclization of N-dichloroacetyl-8-hydroxy-1,2,3,4-tetrahydroquinolines 8 and 10

Reaction of 8 with morpholine gave the 2-morpholinopyridobenzoxazinone 45 (53% yield). The structure was supported by elemental analysis, mass spectrum (M^+ 274; base peak at m/z 188 due to loss of morpholino moiety corresponding to fragment 'c', scheme 2) and IR spectrum ($\nu_{\text{C=O}}$ 1680 cm^{-1}). Especially diagnostic was the presence of a singlet in the ^1H NMR spectrum at δ 5.13 ppm for C-2 H. The formation of 45 from 8 may be visualized as proceeding through species 55 or 56. Similar products (46–54) were obtained from 8 and 10 with various primary and-secondary amines (table 5).

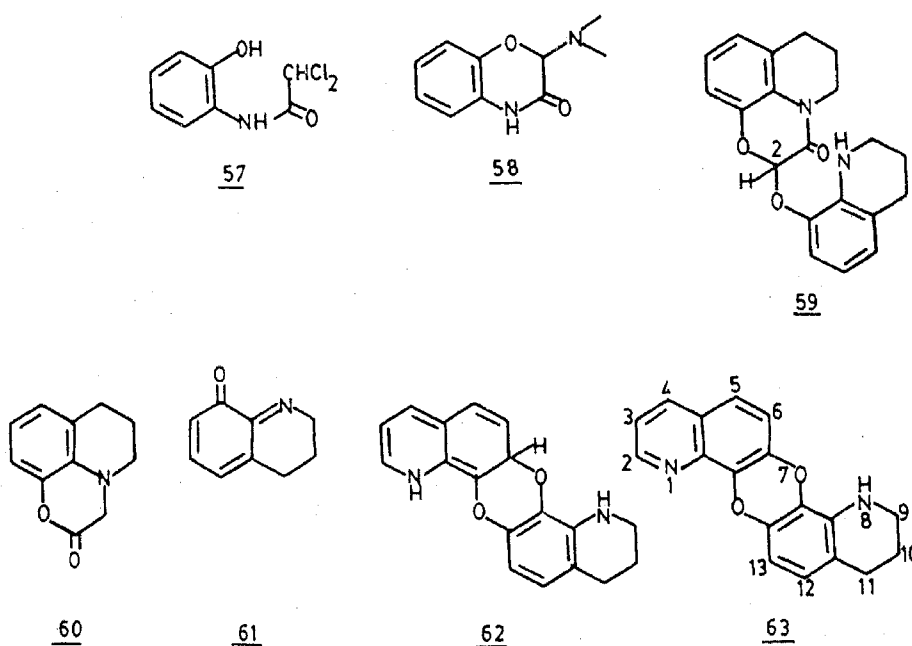


Table 5. Physical data for 2-aminopyridobenzoxazinones.

Com- pound no.	R	R ₁	Yield (%)	Crystal- lized from	Mol. formula	Mol. wt.	m.p. (°C)	¹ H NMR data* (δ in ppm)
<u>45</u>	Morpholino	H	53	Et ₂ O	C ₁₅ H ₁₈ N ₂ O ₃	274.3 (M ⁺ 274)	94-5	1.95(<i>qui</i> , C-6H ₂), 2.40-3.15 (<i>m</i> , C-7H ₂ + CH ₂ NCH ₂), 3.3-4.3 (<i>m</i> , C-5H ₂ + CH ₂ OCH ₂), 6.7-7.0(<i>m</i> , 3 ArH); 5.13(<i>s</i> , C-2H)
<u>46</u>	Piperidino	H	79	Et ₂ O- C ₆ H ₁₄	C ₁₆ H ₂₀ N ₂ O ₂	272.3 (M ⁺ 272)	76-8	1.33(<i>br s</i> , C-(CH ₂)C), 1.93(<i>m</i> , C-6H ₂), 2.3-3.0(<i>m</i> , C-7H ₂ , CH ₂ NCH ₂), 3.87(<i>m</i> , C-5H ₂), 5.12(<i>s</i> , C-2H), 6.77(<i>br s</i> , 3 ArH)
<u>47</u>	4-Carboethoxy- piperazino	H	73	EtOH	C ₁₈ H ₂₃ N ₃ O ₄	345.4	103-4	1.23(<i>t</i> , Me), 1.97(<i>m</i> , C-6H ₂), 2.4-3.0(<i>m</i> , C-7H ₂ , CH ₂ NCH ₂), 3.47(<i>t</i> , CH ₂ (CO)NCH ₂), 3.93(<i>m</i> , C-5H ₂), 4.1(<i>g</i> , CO ₂ CH ₂), 5.17(<i>s</i> , C-2H), 6.73(<i>br s</i> , 3 ArH)
<u>48</u>	<i>m</i> -BrC ₆ H ₄ NH	H	32	MeOH	C ₁₇ H ₁₃ BrN ₂ O ₂	359.2	134-5	1.93(<i>qui</i> , C-6H ₂), 2.77(<i>t</i> , C-7H ₂), 3.55(<i>m</i> , C-5H), 4.0(<i>m</i> , C-5H), 5.42(<i>s</i> , C-2H), 6.60-7.00(<i>m</i> , 7 ArH), 1.90(<i>m</i> , C-6H ₂), 2.90(<i>s</i> , 2 Me), 5.50(<i>s</i> , C-2H), 6.80(<i>s</i> , 3 ArH)
<u>49</u>	Me ₂ NCH ₂ CH ₂ · NH(HCl·H ₂ O)	H	81	EtOH- Et ₂ O	C ₁₅ H ₂₂ ClN ₃ O ₂ · 2H ₂ O	311.8	165-70	1.5-1.8(<i>m</i> , C-CH ₂ CH ₂ -C), 2.0(<i>m</i> , C-6H ₂), 2.6-3.1(<i>m</i> , C-7H ₂ , CH ₂ NCH ₂), 3.8(<i>m</i> , C-5H ₂), 5.23(<i>s</i> , C-2H), 6.70(<i>d</i> , ArH), 6.95(<i>d</i> , ArH)
<u>50</u>	Pyrrolidino	Cl	57	95% EtOH	C ₁₅ H ₁₇ ClN ₂ O ₂	292.8 (M ⁺ 292) 294)	110-2	1.90(<i>qui</i> , C-6H ₂), 2.70(<i>m</i> , CH ₂ NCH ₂), 2.77(<i>m</i> , C-7H ₂), 3.5(<i>m</i> , CH ₂ OCH ₂), 3.90(<i>t</i> , C-5H ₂), 5.20(<i>s</i> , C-2H), 6.80(<i>d</i> , ArH), 7.03(<i>d</i> , ArH)
<u>51</u>	Morpholino	Cl	53	MeOH	C ₁₅ H ₁₇ ClN ₂ O ₃	308.8	106-7	2.0(<i>m</i> , C-6H ₂), 5.47(<i>s</i> , C-2H), 6.80(<i>d</i> , ArH), 7.0(<i>d</i> , ArH)
<u>52</u>	4-Methylpipe- razino	Cl	31	EtOH- H ₂ O	C ₁₆ H ₂₀ ClN ₃ O ₂	321.8	138-9	
<u>53</u>	3-Morpholino- propylamino (2HCl)	Cl	47	MeOH- Et ₂ O	C ₁₈ H ₂₆ Cl ₃ N ₃ O ₃	438.8	243-4	
<u>54</u>	Me ₂ N NH	Cl	55	C ₆ H ₆ - MeOH	C ₁₃ H ₁₆ ClN ₃ O ₂ · H ₂ O	281.7	185-6	

*45-48, 50 in CDCl₃; 49, 51, 53 in DMSO-*d*₆

In contrast, treatment of 2-dichloroacetamidophenol 57 with amines did not lead to the formation of 58. With aniline 57 was recovered, while with morpholine, gummy unidentified products were produced.

Treatment of 8 with methanolic NaOH produced a product having the composition $C_{20}H_{20}N_2O_3$ formulated as 59 (M^+ 336; fragments at m/z 148 due to the radical cation from 1 and 'c', scheme 2; IR $\nu_{C=O}$ 1650; ν_{NH} , 3380 cm^{-1} ; 1H NMR singlet at δ 5.70 due to C-2H). Its formation is easily visualised as arising from hydrolysis of 8 to the anion of 1 which reacts with a second molecule of 8 as other aminonucleophiles do.

2.7 Reaction of 1 with chloroacetic acid – formation of pyridobenzoxazin-2-one 60 and dimeric product 61

Fusion of 1 and chloroacetic acid at 100–110° for 2 h led to the formation of two neutral products. The minor one was identified as the lactone 60 (M^+ 189, ν_{CO} 1760 cm^{-1}). The major product, $C_{18}H_{14}N_2O_2$, is tentatively structured as 63, M^+ 290; 1H NMR – pyridine proton signals at δ 8.50(*d*), 8.08(*d*) and 7.25(*dd*) and dihydro pyridine proton signals at 3.52(*t*), 2.73(*t*) and 2.13 ppm(*qui*). The formation of 63 is visualised through the formation of quinonimine 61, probably by aerial oxidation, addition of 1 to 61 to yield 62 and further oxidative aromatisation.

2.8 Electrophilic substitution reactions of pyridobenzoxazinones, benzoxazepinones and benzoxazocinone

Addition of the benzoxazinones 21, 24 and 26 to nitric acid led to the formation of the dinitro derivatives 64–66 in 33, 50 and 85% yield, respectively (table 6). The alternative structure 67 is considered less likely on the basis of mass spectral data. In the spectra of the dinitro derivatives 64 and 66, strong fragments are seen due to the loss of 17 and 18 mass units, which are conspicuously absent in the mass spectra of the mono nitrocompounds 71–73. The phenomenon arises when a nitro group has an adjacent CH or CH_2 moiety (Nagarajan *et al* 1982). Since the two amino groups in 69 have been shown to be vicinal (*vide infra*), it follows that in 66 and by analogy in 64 and 65, the two nitro groups occupy positions 8 and 9.

The dinitro derivatives 65 and 66 were reduced catalytically to the diamines 68 and 69 in good yield (table 6). Condensation of 69 with benzil in acetic acid afforded the tetracyclic quinoxaline 70, confirming the proximity of the two nitro groups in 66.

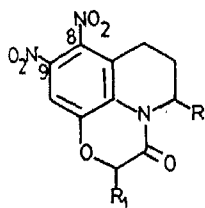
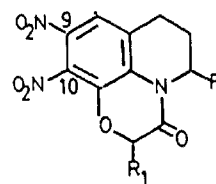
In contrast to the benzoxazinones, nitration of the pyridobenzoxazepinones 28 and 29 and the benzoxazocinone 31 afforded in good yields the mono nitro derivatives 71–73 (table 6). The structures were supported by their 1H NMR spectra. The two aromatic protons were either seen together as a singlet or as two doublets with meta coupling. 71–73 were reduced to the mono amines 74–76, respectively (table 6).

The differential behaviour of the pyridobenzoxazinones on the one hand and of the benzoxazepinones and benzoxazocinones on the other deserves comment. The former have a fully planar arrangement with both N and O atoms well disposed to donate electrons into the aromatic ring (Nagarajan *et al* 1973). In the latter group, the O,N-containing ring is buckled with the result that the oxygen atom is inhibited from activating its para position. The C=O group is also twisted out of the aryl plane, thus leaving the N-atom in a better position to donate electrons to the aromatic ring.

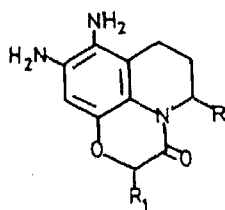
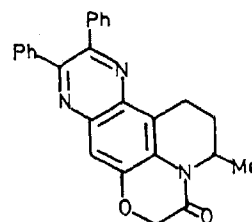
Table 6. Nitro, amino and bromo pyridobenzoxazinones, oxazepinones and oxazocinone.

Com- pound no.	Yield (%)	Crystal- lised from	Mol. formula	Mol. wt.	m.p. (°C)	¹ HNMR* (δ in ppm)
<u>64</u>	33	MeOH— C ₆ H ₆	C ₁₁ H ₉ N ₃ O ₆	279.2 (M ⁺ 279)	170–2	1.92(<i>qui</i> , C-6 H ₂), 2.68(<i>m</i> , C-7 H ₂), 3.73(<i>m</i> , C-5 H ₂), 4.83(<i>s</i> , C-2 H ₂), 7.72(<i>s</i> , ArH)
<u>65</u>	50	C ₆ H ₆	C ₁₈ H ₁₅ N ₃ O ₆	369.3 (M ⁺ 369)	153–5	1.95(<i>m</i> , C-6 H ₂), 2.55(<i>m</i> , C-7 H ₂), 3.17(<i>m</i> , ArCH ₂), 3.77(<i>m</i> , C-5 H ₂), 5.00(<i>m</i> , C-2 H), 7.15(<i>s</i> , C ₆ H ₅), 7.48(<i>s</i> , ArH)
<u>66</u>	85	MeOH	C ₁₂ H ₁₁ N ₃ O ₆	293.2 (M ⁺ 293)	152–3	1.20(<i>d</i> , Me), 1.5–2.3(<i>m</i> , C-6 H ₂), 2.4–3.2(<i>m</i> , C-7 H ₂), 4.55(<i>d</i> , C-2 H) 4.90(<i>d</i> , C-2 H), 4.97(<i>m</i> , C-5 H), 7.57(<i>s</i> , ArH)
<u>68</u>	76	MeOH	C ₁₈ H ₁₉ N ₃ O ₂	309.4	100–3	1.0(<i>d</i> , Me), 1.83(<i>m</i> , C-6 H ₂), 2.40(<i>m</i> , C-7 H ₂), 4.23(<i>s</i> , C-2 H ₂), 4.57(<i>m</i> , C-5 H), 6.0(<i>s</i> , C-10 H)
<u>69</u>	59	MeOH	C ₁₂ H ₁₅ N ₃ O ₂	233.3 (M ⁺ 233)	160–3	2.0(<i>qui</i> , C-7 H ₂), 2.78(<i>t</i> , C-3 H ₂), 2.90(<i>t</i> , C-8 H ₂), 3.85(<i>t</i> , C-6 H ₂), 4.72(<i>t</i> , C-2 H ₂), 7.85(<i>s</i> , 2 ArH)
<u>71</u>	62	EtOH	C ₁₂ H ₁₂ N ₂ O ₄	248.2 (M ⁺ 248)	188–90	1.50(<i>d</i> , Me), 2.0(<i>qui</i> , C-7 H ₂), 2.3–3.1(<i>m</i> , C-8 H ₂ , C-3 H ₂), 3.87(<i>t</i> , C-6 H ₂), 5.05(<i>m</i> , C-2 H), 7.85(<i>d</i> , J = 3 Hz, ArH), 7.8(<i>d</i> , J = 3 Hz, ArH)
<u>72</u>	57	EtOH	C ₁₃ H ₁₄ N ₂ O ₄	262.3 (M ⁺ 262)	123–5	1.87–2.70(<i>br m</i> , C-3 H ₂ , C-4 H ₂ , C-8 H ₂), 2.83(<i>t</i> , C-9 H ₂), 3.25–5.0(<i>p br s</i> , C-7 H ₂), 7.88(<i>sl br s</i> , 2 ArH)
<u>73</u>	72	MeOH	C ₁₃ H ₁₄ N ₂ O ₄	262.3 (M ⁺ 262)	165–8	1.27(<i>d</i> , Me), 1.73(<i>q</i> , C-7 H ₂), 2.43(<i>t</i> , C-8 H ₂), 2.53(<i>m</i> , C-3 H ₂), 3.53(<i>t</i> , C-6 H ₂), 4.5(<i>br s</i> , NH ₂), 4.80(<i>m</i> , C-2 H), 6.2(<i>s</i> , 2 ArH)
<u>74</u>	86	EtOH	C ₁₂ H ₁₄ N ₂ O ₂	218.3	220–5	6.17(<i>s</i> , 2 ArH)
<u>75</u>	81	EtOH	C ₁₃ H ₁₆ N ₂ O ₂	232.3	179–81	1.93(<i>qui</i> , C-6 H ₂), 2.80(<i>t</i> , C-7 H ₂), 3.82(<i>m</i> , C-5 H ₂), 4.52(<i>s</i> , C-2 H ₂), 6.62(<i>d</i> , J = 8 Hz, ArH), 7.07(<i>d</i> , J = 8 Hz, ArH)
<u>76</u>	75	MeOH	C ₁₃ H ₁₆ N ₂ O ₂	232.3	204–5	1.17(<i>d</i> , Me), 1.7–2.1(<i>m</i> , C-6 H ₂), 2.2–3.2(<i>m</i> , C-7 H), 4.40(<i>d</i> , C-2 H), 4.72(<i>d</i> , C-2 H), 5.0(<i>m</i> , C-5 H), 6.68(<i>d</i> , J = 8 Hz, ArH), 7.15(<i>d</i> , J = 8 H, ArH)
<u>77</u>	40	MeOH	C ₁₁ H ₁₀ BrNO ₂	268.1	133–4	
<u>78</u>	57	MeOH	C ₁₂ H ₁₂ BrNO ₂	282.1 (M ⁺ 281, 283)	98–100	1.45(<i>s</i> , Me), 1.85(<i>qui</i> , C-6 H ₂), 2.70(<i>t</i> , C-7 H ₂), 2.88(<i>d</i> , PhCH), 3.23(<i>d</i> , PhCH), 3.77(<i>m</i> , C-5 H ₂), 6.65(<i>d</i> , J = 9 Hz, ArH), 7.10(<i>d</i> , J = 9 Hz, ArH), 7.15(<i>s</i> , C ₆ H ₅).
<u>79</u>	84	MeOH	C ₁₉ H ₁₈ BrNO ₂	372.3	108–10	

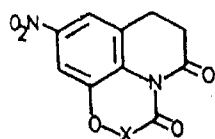
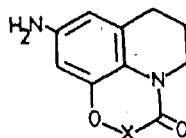
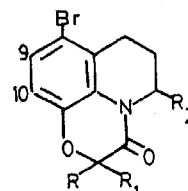
*All spectra were run in CDCl₃ except for 65(CDCl₃ + DMSO-*d*₆) and 64, 69, 71, 75 and 76 (DMSO-*d*₆).

64 R = R₁ = H65 R = H; R₁ = CH₂Ph66 R = Me; R₁ = H

67

68 R = H; R₁ = PhCH₂69 R = Me; R₁ = H

70

71 X = -CH₂CH₂72 X = -CH(Me)-CH₂73 X = -(CH₂)₃74 X = -CH₂CH₂75 X = -CH(Me)-CH₂76 X = -(CH₂)₃77 R = R₁ = R₂ = H78 R = R₁ = H; R₂ = Me79 R = Ph; R₁ = Me; R₂ = H

The relatively softer nucleophilic Br⁺, gave mono bromo derivatives with 21, 26 and 27 in modest yields. The products are formulated as 77–79 (table 6), with their ¹H NMR spectra showing strong (ortho) coupling for the vicinal aromatic protons. In the product mixture from the bromination of 21, the 9-bromo derivative was present as seen in the ¹H NMR spectrum (meta-coupled AB quartet in the aromatic region at δ 6.80 ppm). Addition of 1 molar equivalent of bromine to the pyridobenzoxazepinone 29 gave a mixture of recovered starting material (37%), the 8-bromo (44%) and probably the 9-bromo derivative (19%) (¹H NMR) which defied easy separation into the components.

3. Experimental

Melting points are uncorrected. IR spectra were run as nujol mulls on a Perkin-Elmer M 337 or 681 spectrophotometer. Mass spectra were recorded on a Varian Mat CH7 or Shimadzu QP 1000 GC-MS spectrometer. ¹H NMR spectra were measured on a Varian A60 or EM 360 NMR spectrometer and ¹³C on a Bruker WH 90 spectrometer at 22.63 MHz or Varian XL 200 at 50 MHz. Chemical shifts are quoted in ppm downfield from TMS as internal standard. Signal multiplicities are abbreviated as

usual: *s*-singlet; *d*-doublet, *t*-triplet, *q*-quartet, *qui*-quintet, *m*-multiplet; *br*-broad; *sl*-slight; *v*-very. All new compounds reported in the tables had appropriate C,H,N analyses.

3.1 General synthesis of amides 4–20 and 40

To a stirred mixture of sodium bicarbonate (15 g) in water (100 ml) and 8-hydroxy-1,2,3,4-tetrahydroquinoline 1 (7.45 g, 50 m mol) in ether (75 ml) chloroacetylchloride (5.65 g, 50 m mol) in dry ether (25 ml) was added slowly and with stirring over a period of half an hour. After stirring for 2 h, the mixture was filtered and the precipitate washed with water and ether to give the bulk of the product. From the filtrate, the ether layer was separated and washed with dilute HCl and then water, and finally dried. Concentration of the solution gave a second crop of the product. The total material was recrystallized to give 4 in 82% yield. Other amides were synthesized similarly (table 1).

3.2 Synthesis of pyrido benzoxazinones from α -chloro amides

N-chloroacetyl-8-hydroxy-1,2,3,4-tetrahydroquinoline 4 or quinaldine 9 (10 m mol) was added to a solution of potassium hydroxide (11 m mol) in methanol (25 ml) and the mixture heated under reflux for 20 min. Solvent was then evaporated off and the residue taken into ether. The ethereal layer was washed successively with 10% aqueous NaOH, water, 2N HCl and water. It was then dried and evaporated. The residue was crystallized from a suitable solvent to afford 21 or 26 (table 2).

In the case of α -chloropropionyl derivatives 5 and 7 and α -bromobutyroyl derivative 6, a suspension of the amide (12.5 mmole) was stirred with 10% aqueous NaOH (25 ml) and ether (50 ml) till the solid completely dissolved (10 min). The ether layer was washed with water, 2N HCl and water.

It was then dried and evaporated. The residue was crystallised to yield 22–24 (table 2).

3.3 Cyclization of β -chloropropionyl derivative 12

To a solution of the amide 12 (7.9 g, 33 m mol) in DMF (35 ml), was added 50% NaH suspension in kerosine (1.65 g) and the mixture heated under reflux for 5 min. Water (100 ml) was added and the solution extracted with ether. The ether layer was washed with 10% aq. NaOH and water and then dried. Evaporation gave a residue (4.3 g) which was crystallised twice from hexane to give 28 (1.65 g), m.p. 80–5°C (table 2). The mother liquor after some days gave 22 (0.5 g), m.p. 95–6°C. When the reaction time was extended, the benzoxazinone predominated.

If the β -chloropropionyl derivative 12 (1 g) was added to a solution of NaOH (1 g) in water (20 ml) and set aside for half an hour and then acidified, the acryloyl derivative 15 (0.65 g) was obtained: m.p. 152–3°C.

3.4 Cyclization of γ -chlorobutyroyl derivative 13

The amide (2.53 g) was added to DMF (20 ml) containing sodium hydride (50% suspension, 2 g) and the mixture heated under reflux for one and a quarter hours. DMF was then removed *in vacuo*. The residue was treated with water and the ether extract worked up as usual to give the benzoxazocinone 31 (1.5 g) (table 2).

3.5 Cyclization of the acryloyl derivatives 15-17

Amide 15 (16.2 g, 80 mmole) was heated in DMF (70 ml) containing NaH (50% suspension; 0.7 g) for 5 min. The product was worked up as usual to give a gum (9.2 g) which was a mixture of oxazepinone 28 and oxazinone 22 with the former as the major product. Fractional crystallization from hexane gave the oxazepinone 28 (5.5 g), m.p. 84–85°C (table 2).

Increasing the reaction time upto 1 h gave a mixture in which the oxazinone 22 predominated. Cyclization of the crotonyl derivatives 16 and 17 with NaH as above gave the methyl benzoxazepinones 29 and 30 with reaction times of 5 min–1 h, the latter tending to give better yields.

3.6 Cyclization of cinnamoyl derivatives 18-20

Cinnamamide 18 (16.7 g, 60 mmol) was cyclized in DMF (120 ml) using NaH (50% suspension, 0.9 g) for 1 h. Workup as usual gave the product 24 (13.7 g) as an oil identical to the one from cyclization of 7. The same product was obtained in poorer yield when the reaction was carried out for 5 min.

The α -methyl cinnamamide 19 was cyclized similarly to 27 (table 2), the yields being high whether the reaction time was 5 min or 1 h.

In one experiment on the cyclization of the methoxy cinnamamide 20, a byproduct was obtained in 5% yield, considered to be the O-(4-methoxycinnamoyl)-derivative of 1, m.p. 142°C (Found: C, 74.00, H, 6.39, N, 4.32; $C_{19}H_{19}NO_3$ requires C, 73.76, H, 6.19, N, 4.53%.)

3.7 Alternative synthesis of benzoxazepinone 28

8-Hydroxyquinoline (14.5 g, 0.1 mol) was added to methanol (225 ml) containing 3-chloropropionic acid (16.4 g), KOH (8.2 g) and $NaHCO_3$ (5 g) and the mixture heated under reflux for 2 days. It was then filtered and the filtrate evaporated. The residue was dissolved in water and the solution acidified to pH 6 by acetic acid. The precipitate was filtered off and crystallised three times from methanol to give β -(8-quinolyloxy) propionic acid 32 (3.5 g), m.p. 223–224°C. (Found: C, 66.67, H, 4.71, N, 6.78; $C_{12}H_{11}NO_3$ requires C, 66.35, H, 5.10, N, 6.45%.)

The above acid (2.7 g) was reduced catalytically in acetic acid solution at 29°C for 17 h with hydrogen at 1 atm pressure using platinum catalyst from PtO_2 (0.15 g) to give the tetrahydro acid 33 (2.4 g, 88%), m.p. 131–2°C. (Found: C, 64.75, H, 6.90, N, 6.21; $C_{12}H_{15}NO_3$ requires C, 65.14, H, 6.83, N, 6.33%.)

33 (1.8 g) was heated in vacuum (0.7 mm) at 150°C for one and a half hours and the distillate collected. This was taken up in ether and washed with alkali. Evaporation of the ether layer gave 28 (1.2 g), m.p. 84–6°C (from Et_2O -hexane) identical to the one described earlier.

3.8 Preparation of deuterio derivatives of amides 16 and 18

A solution of the amide (0.5 g) in dry dioxane (10 ml) was heated with deuterium oxide (2 ml) at 60°C for half an hour and then evaporated to dryness *in vacuo*. The process was repeated twice and the final products used for cyclization studies with NaH.

3.9 Treatment of 2-(3-chloropropionamido)phenol 36 with alkali

Amide 36 (2 g) in methanol (25 ml) was treated with potassium methoxide (from 0.4 g in 25 ml methanol) under reflux for 1 h (Sidhu *et al* 1964). Methanol was removed and water and dilute HCl added to give the acrylamide 35 (1.45 g) m.p. 126–8°C. The same product was obtained when 36 (1 g) was mixed with 10% aq. NaOH (20 ml) and the solution heated at 100°C for a few minutes.

3.10 Cyclization of the dibromo amide 14

The amide 14 (4.4 g) was added to KOH (1.6 g) in methanol (50 ml) and the mixture heated under reflux for 10 min. The solvent was partly evaporated off and water added to give a sticky solid. This was dissolved in hot methanol and cooled to give 41 (1.8 g), m.p. 125–126°C. The same product was obtained using morpholine and aminopropyl morpholine. Cyclization of the phenyl propiolamide 40 (6.5 g) in DMF (50 ml) using NaH suspension (3.1 g) also afforded 41 (60%).

3.11 Ozonolysis of benzylidenebenzoxazinone 41

41 (0.4 g) in methylene chloride (50 ml) was cooled to 0°C and treated with ozonised oxygen for 1 h. The solvent was removed *in vacuo* and the residue smelling of benzaldehyde was heated with Zn dust (0.2 g) in water (20 ml) for half an hour. The aqueous layer was decanted off and the residue extracted with paper. This was added to the ether extract of the aqueous layer and the organic layer was separated and evaporated. The remaining oil was converted to the 2,4-dinitrophenyl hydrazone (0.15 g); m.p. and mixed m.p. with benzaldehyde derivative, 245°C. The ether insoluble portion was extracted with CHCl₃ to give crystals of 44 (0.2 g), m.p. 201–203°C; mixed m.p. with authentic sample undepressed. (Found: C, 65.05, H, 4.60, N, 6.88; C₁₁H₉NO₃ requires C, 65.02, H, 4.46, N, 6.89%.)

3.12 Synthesis of benzoxazinedione 44

8-Hydroxytetrahydroquinoline 1 (3 g) was dissolved in ether (75 ml) containing triethyl amine (2.1 g). The solution was cooled in an icebath and treated with oxalyl chloride (2.6 g) in ether (5 ml). The mixture was left at 28°C for 16 h and filtered. The precipitate was washed with water and ether to give 44 (2.2 g). Additional 0.8 g was obtained by chloroform extraction of the filtrate. The total was crystallised from chloroform–ether to give 44 (2.1 g), m.p. 198–200°C. (Found: C, 64.95, H, 4.70, N, 7.13; C₁₁H₉NO₃ requires C, 65.02, H, 4.46, N, 6.89%.)

3.13 Reaction of dichloroacetamides 8 and 10 with amines – General procedure for the synthesis of aminobenzoxazinones 45–54

The dichloroacetyl derivative 8 or 10 (20 m mole) was added to the amine (60 m mole) when generally an exothermic reaction occurred. After this subsided, the mixture was heated for 5 more min on the steam bath and treated with water. In those cases, when the initial reaction was sluggish the mixture was heated at 100°C for half an hour. The product was extracted into ether and washed with 10% aqueous NaOH and

water. On drying and evaporation, the aminobenzoxazinone was generally obtained crystalline and was recrystallized from a suitable solvent. In the case of 52, the basic product was purified by passage through 2N HCl. The compounds are listed in table 5.

3.14 2-(Dichloroacetamido)phenol 57

2-Aminophenol (21 g) was converted into amide 57 by the usual method; yield 35.9 g. m.p. 134–136°C. This was recovered unchanged by treatment with hot aniline. Hot morpholine gave no isolable product.

3.15 Formation of 59 from 8

Amide 8 (1.3 g, 5 mmol) was warmed with 5% aq. NaOH (4.4 ml, 5.5 mmol) on the water bath for half an hour. The resultant gum was left in MeOH for 2 days to provide crystals which were recrystallized from a large volume of the same solvent to give 59, m.p. 158–60°C; $C_{20}H_{20}N_2O_3$; M^+ 336, $r_{C=O}$ 1650 cm^{-1} ; 1H NMR ($CDCl_3 + DMSO-d_6$): 1.50–2.20 (m, C-6H₂, C-3'H₂), 2.27–3.07 (m, C-7H₂, C-4' H₂), 3.07–3.30 (m, C-2'H₂), 3.33 (s, NH), 3.37–3.77 (m, C-5H), 3.77–4.43 (m, C-5H), 5.70 (s, C-2H), 6.10–6.75 (m, 3H at C-5', 6', 7'); 6.67 (s, 3H at C-8,9,10).

3.16 Reaction of 8-hydroxy-1,2,3,4-tetrahydroquinoline 1 with chloroacetic acid

1 (1.5 g, 10 mmol) and chloroacetic acid (1.9 g, 20 mmol) were heated together at 100–110°C for two hours. The melt was cooled and treated with water and ether. The aqueous acidic layer on neutralization with sodium bicarbonate gave recovered starting material (0.7 g), m.p. 105–115°C. The ether extract was washed with sodium bicarbonate solution, dried and concentrated to give reddish crystals of 63 (0.8 g), m.p. 135–8°C. (Found: C, 74.59, 74.37, H, 5.28, 4.98, N, 9.03, 9.28. $C_{18}H_{14}N_2O_2$ requires C, 74.48, H, 4.8, N, 9.65%) M^+ 290; 1H NMR ($CDCl_3$): 8.50 (d, $J = 4$ Hz; C-2H), 8.08 (d, $J = 9$ Hz; C-4H); 7.25 (d × d, $J = 9, 4$ Hz; C-3H); 6.50–6.85 (m, 4 ArH); 3.52 (t, $J = 6$ Hz; C-9 H₂); 2.73 (t, $J = 6$ Hz; C-11 H₂); 2.13 (qui, $J = 6$ Hz, C-10 H₂). The ether mother liquor was evaporated and the residue extracted with hexane to give 60 (0.1 g). m.p. 69–70°C; $r_{C=O}$ 1760 cm^{-1} ; M^+ : 189 1H NMR ($CDCl_3$). 6.75 (br s, 3 Ar-H); 3.67 (s, C-3 H₂); 3.05 (t, C-5 H₂); 2.85 (t, C-7 H₂); 2.05 (qui, C-6 H₂).

3.17 General procedure for nitration

The lactam (50 mmol) was added portionwise to concentrated nitric acid (50 ml) at 0°C over a period of 45 min. The solution was stirred at 28°C for 1 h and poured into a mixture of ice and water. The precipitate was collected and recrystallised to constant m.p. In the case of 27, nitration was done on an acetic acid solution of the substrate. The di and mono nitro derivatives are listed in table 6. 71 was found to be contaminated with very small amounts of impurities, possibly an isomeric mononitro and a dinitro derivative.

3.18 General procedure for reduction of nitro lactams

The dinitro derivative 66 (6 g) was dissolved in methanol (300 ml) and shaken with hydrogen at 1 atm pressure and 29°C in the presence of platinum catalyst (from 0.2 g PtO₂) till absorption of hydrogen ceased. The mixture was filtered and the filtrate evaporated to give the diamine 69. 72 and 73 were reduced likewise to 75 and 76. In the case of sparingly soluble nitro compounds, ethyl acetate (for 65) or tetrahydrofuran (for 71) was used for reduction respectively to 68 and 74 (table 6).

3.19 General procedure for bromination

To a solution of lactam (20 mmol) in acetic acid (20 ml), bromine (20 mmol) in acetic acid (5 ml) was added slowly. The mixture was set aside for 5 min. The solid was filtered off, washed with acetic acid and water and crystallised. The products 77–79 are listed in table 6.

3.20 Condensed quinoxaline 70 from 69

Diamine 69 (2.4 g) and benzil (2.1 g) were heated together in glacial acetic acid (35 ml) under reflux for 24 h and the resultant solution diluted with water. The precipitate was collected and crystallised from MeOH–benzene to afford 70 (3.0 g), m.p. 214–15°C. (Found: C, 76.64, H, 5.20, N, 10.31. C₂₆H₂₁N₃O₂ requires C, 76.64, H, 5.39, N, 10.61%).

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