Synthesis and Reactions of Some Novel Imidazobenzoxazines and Related Systems

By **Geoff W. Danswan, Peter W. Hairsine, David A. Rowlands,* John B. Taylor,** and **Robert Westwood,**
Roussel Laboratories Limited, Kingfisher Drive, Covingham, Swindon SN3 5BZ

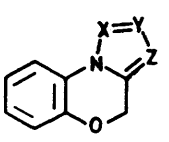
A novel synthesis of the new 4*H*-imidazo[2,1-*c*][1,4]benzoxazine system (2) has been carried out under two sets of conditions, leading to products with differing functionalities. The effect of substituents on the cyclization step has been investigated and the reactions of the functional groups of the new ring system have been studied. Derivatives of the related 4,5-dihydroimidazo[2,1-*d*][1,5]benzoxazepine (3) have also been prepared.

Our interest in the preparation of carboxy-substituted tricyclic compounds [1] as potential antiallergic drugs led us to consider the nitrogen-containing ring systems based on 1,4-benzoxazine and described by formula (1) (X, Y, Z = CH or N). Although these angular 6,6,5-tricyclic systems have been studied widely,[2-9] the 4*H*-imidazo[2,1-*c*][1,4]benzoxazine system (2) has not been described previously. This paper reports the synthesis of the new ring system (2), its derivatives, and derivatives of the homologue (3) *via* a novel rearrangement.

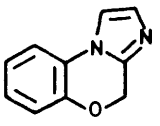
The diamine (4) was the crucial intermediate for our work. Previous workers [9] had used the corresponding diamine ethyl ester (5) as an intermediate for the synthesis of the 4*H*-*v*-triazolo[5,1-*c*][1,4]benzoxazine (6). To make the diamine (4), *o*-aminophenol was condensed with dimethyl acetylenedicarboxylate in ethanol to give the benzoxazinone (7).[10] Pentyl nitrite in glacial acetic acid converted the benzoxazinone (7) into the oxime (8), catalytic hydrogenation of which gave the diamine (4) as a brick-red solid. Mono(chloroacetyl)ation of the diamine (4) under controlled conditions with chloroacetyl chloride in dimethylformamide gave the yellow chloroacetyl derivative (9), thus avoiding the diacetylation found previously [9] with the use of acetic anhydride. When a solution of the chloroacetyl compound (9) in methanol and triethylamine was heated under reflux, the diester (10) was formed in 80% yield. If ethanol was used as solvent, the corresponding diester (11) was obtained in 84% yield. Scheme 1 shows the mechanism proposed for this novel rearrangement (Method A). Isolation of the intermediate phenolic diesters (12) and (13) from incomplete reactions gives further evidence for this mechanism.

Alternatively (Method B), the chloroacetyl compound (9) was dissolved in a warm solution of sodium carbonate in aqueous acetone and the solution was then rapidly acidified to pH 2 with concentrated hydrochloric acid. Under these conditions the precipitated crystalline product was the acid ester (14), obtained in 69% yield. Thus the rearrangement reaction conditions could be controlled to give the diesters (10) and (11) or the acid ester (14) as products from the chloroacetyl compound (9).

The scope of the reaction was then extended to a series of substituted analogues of the chloroacetyl compound (9), *i.e.* compounds (15)—(24), prepared by the methods already described (Table 1 and Experimental section).



(1)



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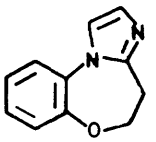

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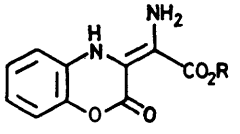
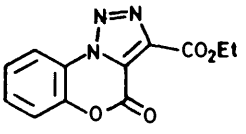


(4) R = Me
(5) R = Et



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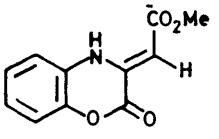
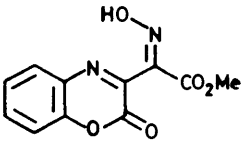


(7)



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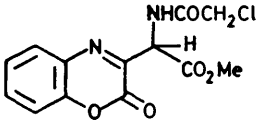
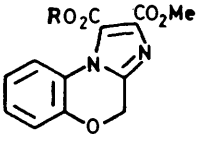
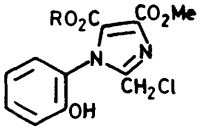


(9)



(10) R = Me
(11) R = Et



(12) R = Me
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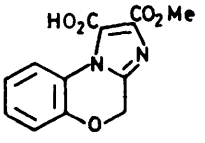
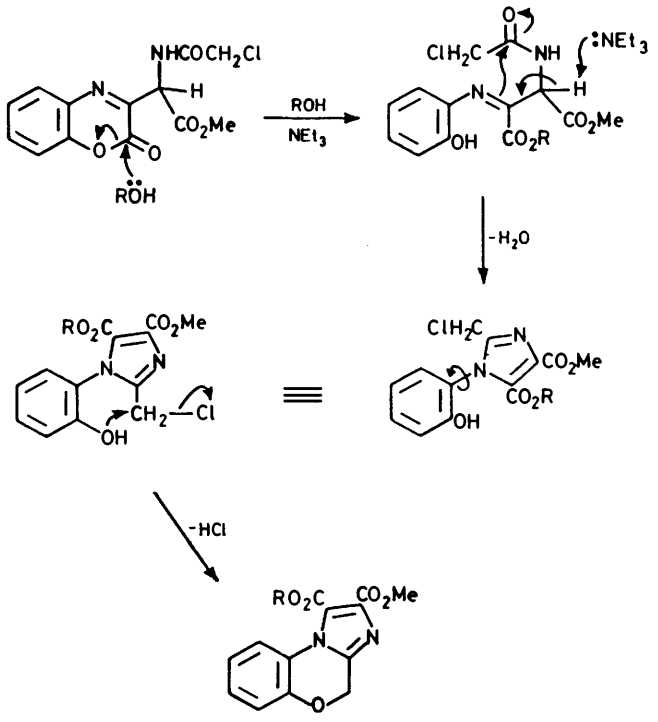


(14)

Results of the treatment of these compounds by Method A or Method B are shown in Tables 2 and 3, respectively.

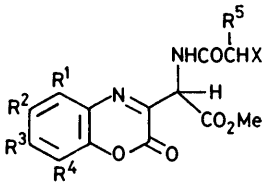


SCHEME 1

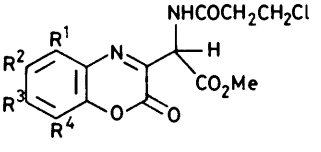
Yields are generally good by both methods and are not much affected by the presence of substituents in the aromatic ring. The only exceptions were compounds (20)—(22), for which Method B failed completely, probably because of steric hindrance. In these cases, however, the more forcing conditions of Method A gave the diesters (26)—(28). The lower yield of the diester (28) from (22) as compared with the diester (27) from (21) (Method A) may be attributed partly to steric reasons,

TABLE 1

Starting materials



(9),(15)-(22)



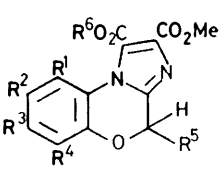
(23), (24)

Compound no.	R¹	R²	R³	R⁴	R⁵	X	% Yield [a]
(9)	H	H	H	H	H	Cl	54
(15)	H	Cl	H	H	H	Cl	52
(16)	H	Me	H	H	H	Cl	53
(17)	H	H	Me	H	H	Cl	43
(18)	H	Cl	Me	H	H	Cl	49
(19)	H	H	H	OMe	H	Cl	44
(20)	Me	H	H	H	H	Cl	51
(21)	H	H	H	H	Me	Cl	57
(22)	H	H	H	H	Et	Br	47
(23)	H	H	H	H			55
(24)	H	Me	H	H			55

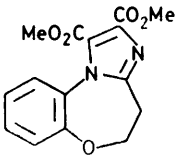
[a] Overall yield; four stages from the corresponding substituted *o*-aminophenols.

TABLE 2

Products from Method A (alcohol ROH + NEt_3; reflux)



(10),(11),(25)-(28)

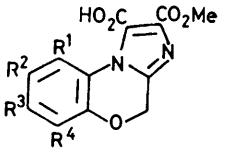


(29)

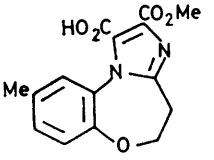
Starting material	Product no.	R¹	R²	R³	R⁴	R⁵	R⁶	% Yield
(9)	(10)	H	H	H	H	H	Me	80
(9)	(11)	H	H	H	H	H	Et	84
(15)	(25)	H	Cl	H	H	H	Et	74
(20)	(26)	Me	H	H	H	H	Et	63
(21)	(27)	H	H	H	H	Me	Et	72
(22)	(28)	H	H	H	H	Et	Et	24
(23)	(29)							5

TABLE 3

Products from Method B [a] (Na_2CO_3–H_2O–Me_2CO; H^+)



(14),(30)-(34)



(35)

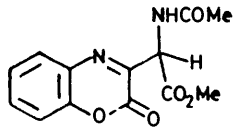
Starting material	Product no.	R¹	R²	R³	R⁴	% Yield
(9)	(14)	H	H	H	H	69
(15)	(30)	H	Cl	H	H	74
(16)	(31)	H	Me	H	H	83
(17)	(32)	H	H	Me	H	77
(18)	(33)	H	Cl	Me	H	71
(19)	(34)	H	H	H	OMe	88
(24)	(35)					16

[a] Method B gave none of the expected products from (20), (21), and (22) as starting materials.

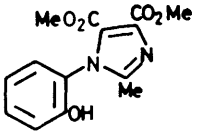
but may also be due to the greater ease of elimination of hydrogen bromide. Likewise the very low yields in the formation of the homologous seven-membered-ring compounds (29) and (35) from the chloropropionyl compounds (23) and (24) are probably caused by elimination of hydrogen chloride to give vinylic side products. The 6,7,5-tricyclic compounds (29) and (35) are also examples of a new ring system. In general, the aqueous Method B is the more convenient, and moreover gives products with mixed acid ester functionality. In those cases where steric hindrance is a problem, Method A is to be preferred.

Treatment of the *N*-acetyl compound (36) with methanol and triethylamine gave only the phenolic product (37), as expected. On melting, (37) cyclised to the benzoxazinone (38), which was also formed by reaction of the diamine (4) with triethyl orthoacetate.

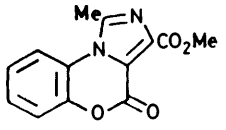
Modification of the functional groups in the new 4*H*-



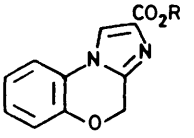
(36)



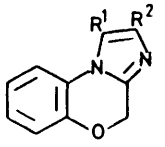
(37)



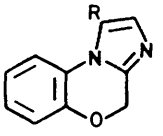
(38)



(39) R = Me
(40) R = H



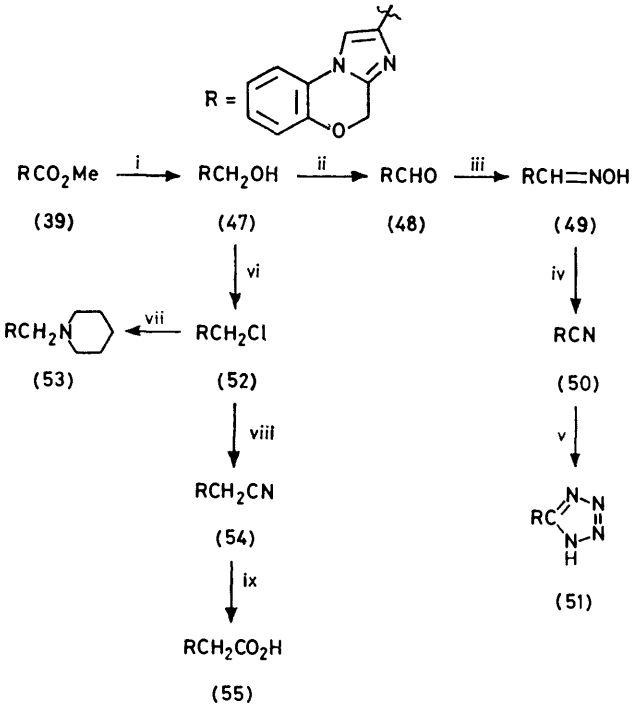
(41) $R^1 = R^2 = CO_2H$
(42) $R^1 = COCl$, $R^2 = CO_2Me$
(43) R^1 =  , $R^2 = CO_2Me$
(44) R^1 =  , $R^2 = CO_2H$



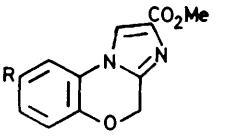
(45) R = 
(46) R = CO_2H

imidazo[2,1-*c*][1,4]benzoxazine system was also investigated. Carboxy-groups in both the 1- and 2-positions in the imidazole ring were susceptible to decarboxylation. Thus, heating the acid ester (14) at 180 °C gave the monoester (39). This was readily hydrolysed by base to the acid (40), which again could be decarboxylated at >260 °C to give the parent heterocycle (2). Hydrolysis of the diester (10) or (11) gave the diacid (41), which on decarboxylation preferentially lost the 1-carboxy-group to give the acid (40). The isomeric acid (46) was prepared by first protecting the 1-carboxy-group of the acid ester (14) [by formation of the morpholide (43), which could be obtained from the acid chloride (42)]. Selective hydrolysis of the amide ester (43) gave the amide acid (44), which was decarboxylated to the amide (45). Finally, hydrolysis of the amide (45) gave the 1-acid (46).

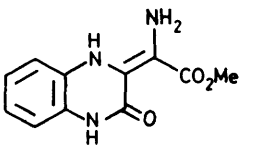
Reduction of the ester (39) using lithium borohydride gave the alcohol (47), which underwent the expected con-



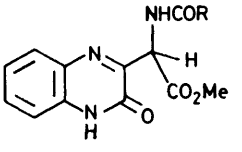
SCHEME 2 *Reagents*: i, $LiBH_4$–THF; ii, MnO_2–$CHCl_3$; iii, NH_2OH,HCl–NaOAc–H_2O–EtOH; iv, Ac_2O; v, NaN_3–DMF; vi, $SOCl_2$–CH_2Cl_2–NEt_3; vii, piperidine–diethyl ketone; viii, KCN–DMF; ix, NaOH–H_2O–MeOH,H^+



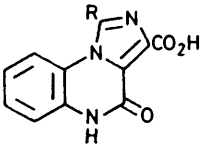
(56) R = NO_2
(57) R = NH_2
(58) R = NHCOMe
(59) R = $NHCOCO_2Et$



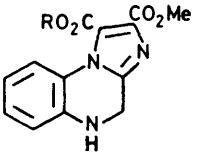
(60)



(61) R = Et
(62) R = Ph
(63) R = CH_2Ph
(64) R = CH_2Cl



(65) R = Et
(66) R = Ph
(67) R = CH_2Ph



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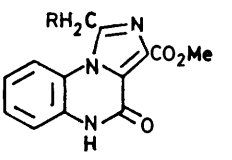
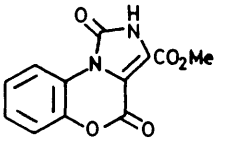


(69) R = Cl
(70) R = N



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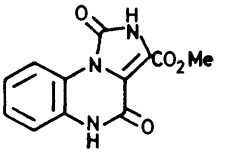


(72)

versions shown in Scheme 2, giving derivatives (48)—(55). Nitration of the ester (39) gave as the only isolated product the 8-nitro-derivative (56), reduction of which gave the amino-ester (57). Acylation of the amino-ester (57) with acetyl chloride and ethyl oxalyl chloride gave the amides (58) and (59) respectively.

A limited amount of work was also carried out in the analogous quinoxaline series. Thus the diamine (60) [11] was prepared in the usual way from *o*-phenylenediamine and acylated to give the amides (61)—(64). Treatment of the amides (61)—(63) under basic conditions using sodium hydroxide solution caused cyclisation and hydrolysis to the acids (65)—(67). However when the chloroacetyl compound (64) was treated under the conditions used (Method A or B) for the analogue (9) from the corresponding benzoxazinone series, none of the hoped-for rearrangement products, the 4,5-dihydroimidazo-[1,2-*a*]quinoxalines (68; R = H or Et), were obtained, presumably because of the much greater stability of the quinoxalinone amide group than of the benzoxazinone lactone group. Treatment of the diamine (60) with triethyl orthochloroacetate gave the chloromethyl-imidazole (69), which also could not be induced to rearrange to (68), but which gave the amine (70) on reaction with piperidine. Reactions of the diamines (4) and (60) with 1,1'-carbonyldi-imidazole gave the corresponding imidazolones (71) and (72).

Significant antiallergic activity has been found in this series of 4*H*-imidazo[2,1-*c*][1,4]benzoxazines, especially the 2-carboxylic acids, and is the subject of a patent.[12] A full description of the antiallergic structure–activity relationships found in this and related tricyclic series will be published elsewhere.

EXPERIMENTAL

M.p.s were determined with a Townson and Mercer capillary apparatus. I.r. spectra were determined for potassium bromide discs with a Pye–Unicam SP 1000 spectrophotometer. N.m.r. spectra were determined with a Perkin-Elmer R12A spectrometer at 60 MHz, with tetramethylsilane as internal standard; all OH and NH peaks were removed by addition of D_2O. All organic extracts were dried over magnesium sulphate and solid products were dried under vacuum over P_2O_5.

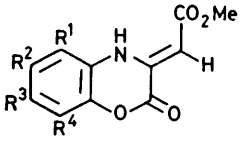
Methyl 2-Oxo-2H-1,4-benzoxazin-3(4H)-ylideneacetate (7).—*o*-Aminophenol (61 g) dissolved in hot absolute ethanol (900 ml) was decolourised with charcoal and filtered. To the filtrate was added dimethyl acetylenedicarboxylate (82 g) and the mixture was then cooled in an ice-bath for 3 h. The product was filtered off and washed well with ether, then dried giving the benzoxazinone (7) (115 g, 94%), as yellow needles (from ethanol), m.p. 170—172 °C (lit.,[10] 170—171 °C) (Found: C, 60.3; H, 4.15; N, 6.4. Calc. for $C_{11}H_9NO_4$: C, 60.3; H, 4.1; N, 6.35%). Table 4 gives details of six substituted *benzoxazinones* prepared in the same manner from the corresponding *o*-aminophenols.

Methyl 2-Hydroxyimino-2-[2-oxo-2H-1,4-benzoxazin-3-yl]-acetate (8).—The ester (7) (82 g) suspended in glacial acetic acid (900 ml) and trichloroacetic acid (15 g) was treated with pentyl nitrite (48 g). The mixture became warm (*ca.* 60 °C) and after 2 h more pentyl nitrite (3 g) was added. After cooling in an ice-bath for 3 h the product was filtered off and washed well with ether until the filtrate was colourless. The product was dried giving the *oxime* (8) (77 g, 83%), as buff needles (from acetic acid–ether), m.p. 175—176 °C (Found: C, 53.5; H, 3.25; N, 11.25. $C_{11}H_8N_2O_5$ requires C, 53.25; H, 3.25; N, 11.3%); $\nu_{max.}$ 1 754 and 3 310 cm^{-1}; τ [$(CD_3)_2SO$] −3.10 (1 H, s, oxime OH), 2.10—2.75 (4 H, m, ArH), and 6.15 (3 H, s, ester CH_3). Table 5 gives details of six substituted *oximes* prepared in the same manner.

Methyl 2-Amino-2-[2-oxo-2H-1,4-benzoxazin-3-ylidene]-acetate (4).—The oxime (8) (42.5 g) was suspended in tetrahydrofuran (THF) (500 ml; dried over KOH pellets) and platinum oxide (1.0 g) was added. The mixture was hydrogenated at 4 atm; the uptake of hydrogen was rapid and steady and ceased after 1.5 h. The dark red solution was then filtered through Celite, the filter pad being washed well with chloroform. The filtrate was evaporated to dryness at 45 °C and ethanol (100 ml; cold) was added. Trituration gave a red crystalline product which was filtered off, washed with a little cold ethanol and ether, and then dried giving the *diamine* (4) (35.5 g, 88%) as brick red needles (from ethanol), m.p. 132—134 °C (Found: C, 56.45; H, 4.3; N, 11.9. $C_{11}H_{10}N_2O_4$ requires C, 56.4; H, 4.3; N, 11.95%); $\nu_{max.}$ 1 695, 1 728, 3 300, 3 360, and 3 470 cm^{-1}; τ ($CDCl_3$) 0.45—0.85 (1 H, br, s, ArNH), 2.85—3.5 (4 H, m, ArH), 4.15—4.85 (2 H, br, s, NH_2), and 6.15 (3 H, s, ester

TABLE 4

Methyl 2-oxo-2*H*-1,4-benzoxazin-3(4*H*)-ylideneacetates

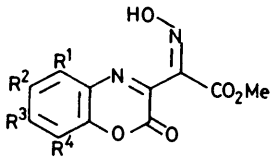


R¹	R²	R³	R⁴	Yield (%)	M.p. (°C) [a]	Formula	% Found (required) C	H	Cl	N
H	Cl	H	H	90	169—170	$C_{11}H_8ClNO_4$	51.9(52.1)	3.2(3.2)	13.9(14.0)	5.55(5.5)
H	Me	H	H	93	141—142	$C_{12}H_{11}NO_4$	61.6(61.8)	4.8(4.75)		6.05(6.0)
H	H	Me	H	92	175—176	$C_{12}H_{11}NO_4$	61.7(61.8)	4.8(4.75)		6.05(6.0)
H	Cl	Me	H	86	195—196	$C_{12}H_{10}ClNO_4$	53.8(53.85)	3.75(3.75)	13.25(13.25)	5.3(5.25)
H	H	H	OMe	87	197—199	$C_{12}H_{11}NO_5$	57.55(57.85)	4.5(4.45)		5.65(5.6)
Me	H	H	H	91	189—190	$C_{12}H_{11}NO_4$	61.7(61.8)	4.85(4.75)		6.05(6.0)

[a] From ethanol.

TABLE 5

Methyl 2-hydroxyimino-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)acetates

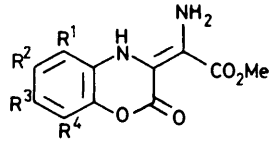


				Yield	M.p. [a]		% Found (required)			
R^1	R^2	R^3	R^4	(%)	(°C)	Formula	C	H	Cl	N
H	Cl	H	H	81	176—177	$C_{11}H_7ClN_2O_5$	46.9(46.75)	2.6(2.5)	12.6(12.55)	9.8(9.9)
H	Me	H	H	86	176—177	$C_{12}H_{10}N_2O_5$	55.0(54.95)	3.9(3.85)		10.7(10.7)
H	H	Me	H	89	189—190	$C_{12}H_{10}N_2O_5$	54.9(54.95)	3.9(3.85)		10.75(10.7)
H	Cl	Me	H	82	190—191	$C_{12}H_9ClN_2O_5$	48.7(48.6)	3.2(3.05)	11.9(11.95)	9.35(9.45)
H	H	H	OMe	88	171—172	$C_{12}H_{10}N_2O_6$	51.6(51.8)	3.75(3.6)		10.05(10.05)
Me	H	H	H	58	191—192	$C_{12}H_{10}N_2O_5$	54.85(54.95)	3.8(3.85)		10.7(10.7)

[a] From acetic acid/ether.

TABLE 6

Methyl 2-amino-2-[2-oxo-2*H*-1,4-benzoxazin-3(4*H*)-ylidene]acetates

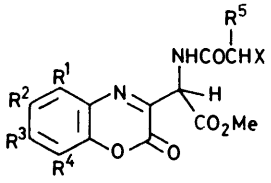


				Yield	M.p.		% Found (required)			
R^1	R^2	R^3	R^4	(%)	(°C) [a]	Formula	C	H	Cl	N
H	Cl	H	H	80	203—206	$C_{11}H_9ClN_2O_4$	49.0(49.2)	3.4(3.4)	13.4(13.2)	10.4(10.45)
H	Me	H	H	72	145—146	$C_{12}H_{12}N_2O_4$	57.95(58.05)	4.85(4.85)		11.3(11.3)
H	H	Me	H	63	140—141	$C_{12}H_{12}N_2O_4$	58.1(58.05)	4.8(4.85)		11.4(11.3)
H	Cl	Me	H	77	163—165	$C_{12}H_{11}ClN_2O_4$	51.0(51.0)	3.9(3.9)	12.55(12.55)	9.9(9.9)
H	H	H	OMe	75	175—178	$C_{12}H_{12}N_2O_5$	54.45(54.55)	4.6(4.6)		10.3(10.6)
Me	H	H	H	85	167—170	$C_{12}H_{12}N_2O_4$	58.05(58.05)	4.9(4.85)		11.1(11.3)

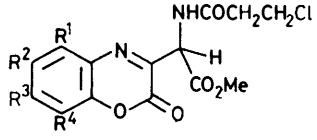
[a] From ethanol.

TABLE 7

Methyl 2-(substituted amino)-2-[2-oxo-2*H*-1,4-benzoxazin-3-yl]acetates



(15)–(22), (36)



(23), (24)

Compd.							Yield [a]	M.p.		% Found (required)			
no.	R^1	R^2	R^3	R^4	R^5	X	(%)	(°C) [b]	Formula	C	H	Halogen	N
(15)	H	Cl	H	H	H	Cl	89	170—176	$C_{13}H_{10}Cl_2N_2O_5$	45.15(45.25)	2.95(2.9)	20.55(20.55)	8.15(8.1)
(16)	H	Me	H	H	H	Cl	91	160—165	$C_{14}H_{13}ClN_2O_5$	51.7(51.8)	4.0(4.05)	10.9(10.9)	8.65(8.65)
(17)	H	H	Me	H	H	Cl	84	172—173	$C_{14}H_{13}ClN_2O_5$	51.75(51.8)	3.95(4.05)	10.9(10.9)	8.55(8.65)
(18)	H	Cl	Me	H	H	Cl	89	184—186	$C_{14}H_{12}Cl_2N_2O_5$	46.85(46.8)	3.35(3.35)	19.75(19.75)	7.85(7.8)
(19)	H	H	H	OMe	H	Cl	76	152—154	$C_{14}H_{13}ClN_2O_6$	49.4(49.35)	3.85(3.85)	10.5(10.4)	8.3(8.2)
(20)	Me	H	H	H	H	Cl	92	159—164	$C_{14}H_{13}ClN_2O_5$	51.7(51.8)	4.05(4.05)	11.0(10.9)	8.7(8.65)
(21)	H	H	H	H	Me	Cl	82	184—185	$C_{14}H_{13}ClN_2O_5$	51.55(51.8)	3.95(4.05)	10.9(10.9)	8.6(8.65)
(22)	H	H	H	H	Et	Br	69	122—127	$C_{15}H_{15}BrN_2O_5$	47.3(47.0)	4.0(3.95)	20.5(20.85)	7.35(7.3)
(23)	H	H	H	H			80	136—138	$C_{14}H_{13}ClN_2O_5$	51.65(51.8)	3.95(4.05)	10.95(10.9)	8.55(8.65)
(24)	H	Me	H	H			96	149—153	$C_{15}H_{15}ClN_2O_5$	53.15(53.2)	4.45(4.45)	10.55(10.45)	8.25(8.25)
(36)	H	H	H	H	H	H	73	152—154	$C_{13}H_{12}N_2O_5$	56.4(56.5)	4.25(4.4)		10.15(10.15)

[a] Reactions to give (15)—(22) were carried out in dimethylformamide as solvent, but for (23), (24), and (36) acetic acid was used as solvent. [b] From ethyl acetate–ether.

CH_3). Table 6 gives details of six substituted *diamines* prepared in the same manner.

Methyl 2-(*Chloroacetamido*)-2-[2-*oxo*-2H-1,4-*benzoxazin*-3-*yl*]*acetate* (9).—The diamine (4) (50 g) was suspended in dimethylformamide (500 ml) and chloroacetyl chloride (30 g) was added. The mixture was stirred at room temperature for 2 h, then water (500 ml) and ethyl acetate (750 ml) were added. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (2 × 250 ml). The combined organic layer was washed once more with water (300 ml), dried, and evaporated to dryness. Trituration with ether gave the product, which was filtered off and dried giving the *chloroacetamide* (9) (53 g, 79%), as yellow needles (from ethyl acetate–ether), m.p. 133—134 °C (Found: C, 50.15; H, 3.6; Cl, 11.45; N, 8.95. $C_{13}H_{11}ClN_2O_5$ requires C, 50.25; H, 3.55; Cl, 11.4; N, 9.0%); $\nu_{max.}$ 1 670, 1 745, 1 767, and 3 295 cm^{-1}; τ ($CDCl_3$) 2.21 (1 H, br, d, *J* 9 Hz, amide NH), 2.2—2.8 (4 H, m, ArH), 3.9 (1 H, d, *J* 9 Hz, acetic ester α-H), 5.92 (2 H, s, CH_2Cl), and 6.23 (3 H, s, ester CH_3). Table 7 gives details for the preparation in the same manner of the analogous *acetyl* and *propionyl derivatives* (15)—(24) and (36); see also footnote to Table 7.

Rearrangement of Methyl 2-(*Chloroacetamido*)-2-[2-*oxo*-2H-1,4-*benzoxazin*-3-*yl*]*acetate* (9).—*Method A*. The chloroacetyl compound (9) (2.0 g) was suspended in methanol (20 ml) and triethylamine (1 ml) was added. The mixture was heated under reflux for 6 h, then diluted with water (50 ml) and extracted with chloroform (3 × 50 ml). The combined organic extract was washed once with water, dried, and evaporated to dryness. Trituration with ether gave a crystalline product, which was filtered off and dried giving *dimethyl* 4H-*imidazo*[2,1-c][1,4]*benzoxazine*-1,2-*dicarboxylate* (10) (1.48 g, 80%), as colourless needles (from ethyl acetate–ether), m.p. 177—179 °C (Found: C, 58.4; H, 4.2; N, 9.75. $C_{14}H_{12}N_2O_5$ requires C, 58.35; H, 4.2; N, 9.7%); $\nu_{max.}$ 1 714 and 1 750 cm^{-1}; τ ($CDCl_3$) 2.5—3.0 (4 H, m, ArH), 4.80 (2 H, s, OCH_2), 5.99 (3 H, s, ester CH_3), and 6.09 (3 H, s, ester CH_3).

Using ethanol as solvent, the reaction was repeated to give *ethyl* 2-*methoxycarbonyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine*-1-*carboxylate* (11) (84%), as colourless needles (from ethyl acetate–ether), m.p. 109—110 °C (Found: C, 59.65; H, 4.65; N, 9.25. $C_{15}H_{14}N_2O_5$ requires C, 59.6; H, 4.65; N, 9.25%); $\nu_{max.}$ 1 712 and 1 741 cm^{-1}; τ ($CDCl_3$) 2.5—3.0 (4 H, m, ArH), 4.80 (2 H, s, OCH_2), 5.50 (2 H, q, *J* 7 Hz, ethyl CH_2), 6.09 (3 H, s, ester CH_3), and 8.60 (3 H, t, *J* 7 Hz, ethyl CH_3).

When repeats of the above reactions were stopped after 0.5 h, the mixtures worked up in the way described, and the products chromatographed on silica using ethyl acetate as eluant, the major lower R_F products isolated were, respectively, the phenols (12) and (13). *Dimethyl* 2-*chloromethyl*-1-(2-*hydroxyphenyl*)*imidazole*-4,5-*dicarboxylate* (12) (62%) formed colourless needles (from ethyl acetate–ether), m.p. 160—162 °C (Found: C, 51.95; H, 3.95; Cl, 10.85; N, 8.6. $C_{14}H_{13}ClN_2O_5$ requires C, 51.8; H, 4.05; Cl, 10.9; N, 8.65%); $\nu_{max.}$ 1 736 and 1 746 cm^{-1}; τ ($CDCl_3$) 0.7—1.6 (1 H, vbr, OH), 2.5—3.1 (4 H, m, ArH), 5.5 (2 H, ABq, *J* 12 Hz, CH_2Cl), 6.16 (3 H, s, ester CH_3), and 6.31 (3 H, s, ester CH_3); *methyl* 2-*chloromethyl*-5-*ethoxycarbonyl*-1-(2-*hydroxyphenyl*)*imidazole*-4-*carboxylate* (13) (57%) gave colourless needles (from ethyl acetate–ether), m.p. 129—131 °C (Found: C, 53.2; H, 4.45; Cl, 10.5; N, 8.25. $C_{15}H_{15}ClN_2O_5$ requires C, 53.2; H, 4.45; Cl, 10.45; N, 8.25%); $\nu_{max.}$ 1 726 and 1 746 cm^{-1}; τ ($CDCl_3$) 1.0—2.0 (1 H, vbr, OH), 2.5—3.1 (4 H, m, ArH), 5.60 (2 H, ABq, *J* 12 Hz, CH_2Cl), 5.83 (2 H, q, *J* 7 Hz, ethyl CH_2), 6.14 (3 H, s, ester CH_3), and 8.93 (3 H, t, *J* 7 Hz, ethyl CH_3).

Method B. The chloroacetyl compound (9) (72 g) was suspended in water (400 ml) and acetone (50 ml) and sodium carbonate (40 g) were added. The mixture was heated on a water-bath for 0.25 h (until a clear yellow solution was obtained). Concentrated hydrochloric acid was then dripped slowly into the solution until the pH reached 2. A colourless crystalline product appeared which after cooling was filtered off, washed well with water, and dried giving 2-*methoxycarbonyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine*-1-*carboxylic acid* (14) (43.5 g, 69%), as colourless needles (from ethanol–water), m.p. 167—168 °C (decarboxylates) (Found: C, 56.9; H, 3.65; N, 10.15. $C_{13}H_{10}N_2O_5$ requires C, 56.95; H, 3.7; N, 10.2%); $\nu_{max.}$ 1 722 and 2 200—2 800 w cm^{-1}; τ [$(CD_3)_2SO$] −2.0 to −1.0 (1 H, vbr, acid OH), 2.3—2.8 (4 H, m, ArH), 4.69 (2 H, s, OCH_2), and 6.19 (3 H, s, ester CH_3).

Table 8 lists the other *imidazo*[2,1-c][1,4]*benzoxazines* (25)—(28) and (30)—(34) prepared as above by either Method A or Method B, and includes the two 4,5-*dihydroimidazo*[2,1-d][1,5]*benzoxazepines* (29) and (35) also prepared under these conditions.

Dimethyl 1-(2-*Hydroxyphenyl*)-2-*methylimidazole*-4,5-*dicarboxylate* (37).—The acetyl compound (36) (Table 7) (1.5 g) was suspended in methanol (20 ml) and triethylamine (2 ml) and heated under reflux for 5 h. Water (100 ml) was added and the mixture was extracted with chloroform (3 × 50 ml). The combined extract was washed once with water (100 ml) and dried, filtered, and evaporated to dryness. Trituration with ether then gave the *phenolic diester* (37) (1.25 g, 79%), as colourless needles (from ethyl acetate–ether), m.p. 162—163 °C (Found: C, 57.75; H, 4.8; N, 9.55. $C_{14}H_{14}N_2O_5$ requires C, 57.95; H, 4.85; N, 9.65%); $\nu_{max.}$ 1 731br cm^{-1}; τ ($CDCl_3$) 2.35—3.35 (5 H, m, 4 ArH and phenolic OH), 6.19 and 6.34 (2 × 3 H, 2 × s, ester CH_3), and 7.83 (3 H, s, imidazole CH_3).

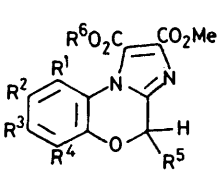
Methyl 1-*Methyl*-4-*oxo*-4H-*imidazo*[5,1-c][1,4]*benzoxazine*-3-*carboxylate* (38).—The phenolic diester (37) (500 mg) was heated to 180 °C; after cooling, the product was triturated with chloroform and ether to give the 4H-*imidazo*[5,1-c]-[1,4]*benzoxazine* (38) (220 mg, 50%), as buff needles (from chloroform–ether), m.p. 244—247 °C (decomp.) (Found: C, 60.25; H, 3.9; N, 10.85. $C_{13}H_{10}N_2O_4$ requires C, 60.45; H, 3.9; N, 10.85%); $\nu_{max.}$ 1 731 and 1 775 cm^{-1}; τ (CF_3CO_2-H) 2.0—2.3 (1 H, m, 9-H), 2.4—2.9 (3 H, m, ArH), 6.15 (3 H, s, ester CH_3), and 6.94 (3 H, s, imidazole CH_3).

Alternatively, the diamine (4) was heated under reflux for 3 h with a little toluene-*p*-sulphonic acid in triethyl orthoacetate (10 volumes); the mixture was then cooled and filtered, and the solid washed with ethyl acetate to give (38) (88%) as buff needles, identical (m.p., i.r., n.m.r.) with the foregoing material.

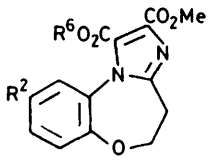
Methyl 4H-*Imidazo*[2,1-c][1,4]*benzoxazine*-2-*carboxylate* (39).—The acid ester (14) (20 g) was added to a flask with a magnetic stirrer. The flask was placed in an oil-bath at 175—180 °C and stirring was continued for about 20 min (until effervescence ceased). After cooling, the product was dissolved in chloroform and then passed down a short silica column to remove low R_F impurities. The fractions collected containing (39) were combined and evaporated to dryness. Trituration with ether gave the *ester* (39) (14.0g, 83%), as off-white needles (from ethyl acetate–ether), m.p. 133—134 °C (Found: C, 62.55; H, 4.35; N, 12.15. $C_{12}H_{10}N_2O_3$ requires C, 62.6; H, 4.4; N, 12.15%); $\nu_{max.}$ 1 715 and

TABLE 8

4*H*-Imidazo[2,1-*c*][1,4]benzoxazines and 4,5-dihydroimidazo[2,1-*d*][1,5]benzoxazepines



(25)-(28),(30)-(34)



(29),(35)

Method	Compd. no.	R¹	R²	R³	R⁴	R⁵	R⁶	Yield (%)	M.p. (°C) [a]	Formula	% Found (required) C	H	Cl	N
A	25	H	Cl	H	H	H	Et	74	135—136	$C_{15}H_{13}ClN_2O_5$	53.35(53.5)	3.9(3.9)		8.25(8.3)
A	26	Me	H	H	H	H	Et	63	113—114	$C_{16}H_{16}N_2O_5$	60.8(60.75)	5.15(5.1)		8.8(8.85)
A	27	H	H	H	H	Me	Et	72	130—131	$C_{16}H_{16}N_2O_5$	60.7(60.75)	5.05(5.1)		8.9(8.85)
A	28	H	H	H	H	Et	Et	24	124—126	$C_{17}H_{18}N_2O_5$	61.85(61.8)	5.45(5.5)		8.5(8.5)
A	29 [b]		H				Me	5	128—129	$C_{15}H_{14}N_2O_5$	59.65(59.6)	4.7(4.65)		9.15(9.25)
B	30	H	Cl	H	H	H	H	74	236—238	$C_{13}H_9ClN_2O_5$	50.3(50.6)	2.9(2.95)	11.5(11.5)	9.0(9.05)
B	31	H	Me	H	H	H	H	83	178—179	$C_{14}H_{12}N_2O_5$	58.1(58.35)	4.3(4.2)		9.7(9.7)
B	32	H	H	Me	H	H	H	77	176—177	$C_{14}H_{12}N_2O_5$	58.2(58.35)	4.25(4.2)		9.75(9.7)
B	33	H	Cl	Me	H	H	H	71	240—244	$C_{14}H_{11}ClN_2O_5$	51.75(52.1)	3.4(3.45)	11.0(11.0)	8.85(8.7)
B	34	H	H	H	OMe	H	H	88	167—168	$C_{14}H_{12}N_2O_6 \cdot H_2O$	51.95(52.2)	4.35(4.4)		8.75(8.7)
B	35		Me				H	16	182—184	$C_{15}H_{14}N_2O_5$	59.4(59.6)	4.65(4.65)		9.2(9.3)

[a] Compounds (25)–(29) recrystallised from ethyl acetate–ether; (30)—(35) from ethanol–water. [b] Spectral data for (29): $\nu_{max.}$ 1 203, 1 238, 1 506, 1 731, and 1 743 cm^{-1}; τ ($CDCl_3$) 2.55—2.8 (4 H, m, aryl H), 5.43 (2 H, t, *J* 7 Hz, OCH_2), 6.08 and 6.19 (2 × 3 H, s, ester Me), and 6.99 (2 H, t, *J* 7 Hz, OCH_2CH_2).

3 135 cm^{-1}; τ ($CDCl_3$) 1.94 (1 H, s, imidazole 1-H), 2.5—3.05 (4 H, m, ArH), 4.72 (2 H, s, OCH_2), and 6.09 (3 H, s, ester CH_3).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine-2-carboxylic Acid* (40). —The ester (39) (10 g) was suspended in methanol (100 ml) and water (50 ml), and sodium hydroxide pellets (2 g) were added. The mixture was warmed on a water-bath for 2 h and then acidified to pH 2—3 with concentrated hydrochloric acid. The product crystallised out, and was filtered off, washed with water, and dried giving the *acid* (40) (8.5 g, 91%), as colourless needles (from ethanol), m.p. 257—259 °C (decarboxylates) (Found: C, 61.15; H, 3.75; N, 12.95. $C_{11}H_8N_2O_3$ requires C, 61.1; H, 3.75; N, 12.95%); $\nu_{max.}$ 1 695, 2 300—3 500, and 3 135 cm^{-1}; τ [$(CD_3)_2SO$] 1.39 (1 H, s, imidazole 1-H), 2.20—2.25 (1 H, m, H-9), 2.6—3.0 (3 H, br, m, ArH), and 4.68 (2 H, s, OCH_2) (acid H not seen).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine* (2).—The acid (40) (500 mg) was heated in a small flask on an isomantle at >260 °C for 10 min until effervescence had ceased. Chloroform (10 ml) was added after cooling, and the solution was chromatographed on silica with ether–light petroleum (b.p. 40—60 °C) as eluant. The fractions containing the product were combined and evaporated to give a colourless oil. Trituration with light petroleum gave the product as colourless needles, which were filtered off and dried. Recrystallisation from light petroleum gave 4H-*imidazo*[2,1-c][1,4]-*benzoxazine* (2) (350 mg, 88%), as long colourless needles, m.p. 108—111 °C (Found: C, 69.7; H, 4.75; N, 16.2. $C_{10}H_8N_2O$ requires C, 69.75; H, 4.7; N, 16.25%); $\nu_{max.}$ 1 520, 3 107, and 3 140 cm^{-1}; τ ($CDCl_3$) 2.61 (1 H, d, $J_{1,2}$ 1 Hz, imidazole H), 2.79 (1 H, d, $J_{1,2}$ 1 Hz, imidazole H), 2.70 —3.0 (4 H, br, m, ArH), and 4.72 (2 H, s, OCH_2).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine-1,2-dicarboxylic Acid* (41).—The diester (10) (2.1 g) was heated under reflux for 1 h in ethanol (30 ml) and water (80 ml) containing sodium hydroxide (2 g). The solution was then acidified to pH 2—3 and cooled. The *diacid* (41) crystallised out and was filtered off and dried after washing with water to give colourless needles (1.57 g, 83%) (from ethanol), m.p. 220—222 °C (decarboxylates) (Found: C, 55.2; H, 3.1; N, 10.75. $C_{12}H_8N_2O_5$ requires C, 55.4; H, 3.1; N, 10.75%); $\nu_{max.}$ 1 740 and 2 200—2 800 cm^{-1}; τ [$(CD_3)_2SO$] −0.65 (2 H, br, s, acid H), 2.3—2.8 (4 H, m, ArH), and 4.70 (2 H, s, OCH_2).

Methyl 1-*Chloroformyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine-2-carboxylate* (42).—The acid ester (14) (5 g) suspended in thionyl chloride (15 ml) was heated under reflux for 2 h, during which time the starting material went into solution. The excess of thionyl chloride was removed by azeotropic evaporation with benzene (rotary evaporator), and trituration with ether gave the product as a crystalline off-white solid. The product was filtered off, washed well with ether, and dried, giving the *acid chloride* (42) (4.06 g, 76%) as colourless crystals (from ethyl acetate–ether), m.p. 150—151 °C (Found: C, 53.3; H, 3.1; Cl, 12.3; N, 9.35. $C_{13}H_9ClN_2O_4$ requires C, 53.5; H, 3.1; Cl, 12.1; N, 9.55%); $\nu_{max.}$ 1 723 and 1 769 cm^{-1}; τ ($CDCl_3$) 2.45—2.95 (4 H, m, ArH), 4.77 (2 H, s, OCH_2), and 6.05 (3H, s, ester CH_3).

Methyl 1-*Morpholinocarbonyl*-4H-*imidazo*[2,1-*c*][1,4]-*benzoxazine-2-carboxylate* (43).—The acid chloride (42) (3.0 g) was suspended in dichloromethane (50 ml) and morpholine (3.0 g) was added. The mixture was stirred at room temperature for 3 h, and water (100 ml) was added. The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 × 50 ml). The combined organic layer was washed once more with water (100 ml) then dried, filtered, and evaporated to dryness. Trituration with ether gave the *amide ester* (43) (2.2 g, 62%) as colourless needles (from ethyl acetate–ether), m.p. 174—175 °C (Found: C, 59.6; H, 4.95; N, 12.2. $C_{17}H_{17}N_3O_5$ requires C, 59.45; H, 5.0; N, 12.25%); $\nu_{max.}$ 1 650 and 1 720 cm^{-1}; τ ($CDCl_3$) 2.4—3.0 (4 H, m, ArH), 4.76 (2 H, ABq, *J* 14 Hz, non-equivalent OCH_2), 6.06 (3 H, s, ester Me), and 6.0—6.8 (8 H, m, morpholine CH_2).

1-*Morpholinocarbonyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine-2-carboxylic Acid* (44).—The hydrolysis of the ester (43) was

carried out as for the ester (39) giving the *amide acid* (44) (76%), as colourless needles (from ethyl acetate–chloroform), m.p. 228—229 °C (decarboxylates) (Found: C, 56.95; H, 4.55; N, 12.1. $C_{16}H_{15}N_3O_5,0.5H_2O$ requires C, 56.8; H, 4.75; N, 12.4%); $\nu_{max.}$ 1 646, 1 732, and 2 100—3 200 cm^{-1}; τ [$(CD_3)_2SO$] 2.4—3.3 (5 H, m, ArH + acid H), 4.78 (2 H, s, OCH_2), 6.20 (4 H, br, s, morpholine OCH_2), and 6.3—6.8 (4 H, m, morpholine NCH_2).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine*-1-*carbomorpholide* (45).—The amide acid (44) (1.3 g) was heated in an oil-bath at 240 °C until effervescence ceased. After cooling, the product was dissolved in chloroform (10 ml) and passed through a short silica column to remove low R_F impurities. The fractions containing the product were then combined, evaporated, and triturated with ether, giving the *amide* (45) (0.7 g, 62%), as colourless needles (from ethyl acetate–ether), m.p. 163—164 °C (Found: C, 63.05; H, 5.3; N, 14.8. $C_{15}H_{15}N_3O_3$ requires C, 63.15; H, 5.3; N, 14.75%); $\nu_{max.}$ 1 505, 1 625, and 2 850 cm^{-1}; τ ($CDCl_3$) 2.5—3.0 (5 H, m, ArH + imidazole 2-H), 4.69 (2 H, s, OCH_2), and 6.32 (8 H, vbr, s, morpholine CH_2).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine*-1-*carboxylic Acid* (46).—The amide (45) (0.6 g) was suspended in ethanol (20 ml) and water (10 ml), and sodium hydroxide pellets (1.0 g) were added. The mixture was heated under reflux for 5 h, then cooled and acidified to pH 2 with concentrated hydrochloric acid. The precipitate was filtered off, washed with water, and dried giving the *acid* (45) (0.4 g, 88%) as colourless needles (from methanol–water), m.p. 224—225 °C (decarboxylates) (Found: C, 61.0; H, 3.8; N, 12.85. $C_{11}H_8N_2O_3$ requires C, 61.1; H, 3.75; N, 12.95%); $\nu_{max.}$ 1 508, 1 726, and 2.200—3 600 cm^{-1}; τ [$(CD_3)_2SO$] 2.0 (1 H, m, 9-H), 2.21 (1 H, s, imidazole 2-H), 2.6—2.9 (3 H, m, 6-, 7-, 8-H), and 4.78 (2 H, s, OCH_2) (acid H not seen).

4H-*Imidazo*[2,1-c][1,4]*benzoxazin*-2-*ylmethanol* (47).—The ester (39) (23 g) was stirred at room temperature in dry tetrahydrofuran (250 ml), while lithium borohydride (6.0 g) was slowly added. The mixture became warm (*ca.* 70 °C) and stirring was continued for 5 h. Dilute hydrochloric acid (2N; 500 ml) was added and the mixture was then neutralised with sodium hydrogencarbonate. The solution was extracted with ethyl acetate (3 × 250 ml), and the combined organic extract was washed once with water (250 ml) before drying and evaporation to dryness. Trituration with ether gave the *alcohol* (18.3 g, 90%), as colourless needles (from ethyl acetate–ether), m.p. 168—169 °C (Found: C, 65.15; H, 5.1; N, 13.75. $C_{11}H_{10}N_2O_2$ requires C, 65.35; H, 5.0; N, 13.85%); $\nu_{max.}$ 1 606 and 3 000—3 300 cm^{-1}; τ ($CDCl_3$) 2.70 (1 H, s, imidazole 1-H), 2.7—3.2 (4 H, m, ArH), 4.82 (2 H, s, OCH_2), 5.41 (2 H, s, CH_2OH), and 6.32 (1 H, s, CH_2OH).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine*-2-*carbaldehyde* (48).—The alcohol (47) (4.9 g) was stirred at room temperature with activated manganese dioxide (30 g) in chloroform (200 ml) for 3 h. The mixture was filtered and the filter pad was well washed with chloroform. The chloroform extract was evaporated to dryness; trituration with ether gave the *aldehyde* (48) (3.9 g, 80%) as colourless needles (from ethyl acetate–ether), m.p. 180—182 °C (Found: C, 65.75; H, 4.15; N, 13.9. $C_{11}H_8N_2O_2$ requires C, 66.0; H, 4.05; N, 14.0%); $\nu_{max.}$ 1 560 and 1 698 cm^{-1}; τ ($CDCl_3$) 0.20 (1 H, s, aldehyde H), 2.07 (1 H, s, imidazole 1-H), 2.7—3.1 (4 H, m, ArH), and 4.78 (2 H, s, OCH_2).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine*-2-*carbaldehyde Oxime* (49).—The aldehyde (48) (2.0 g) was suspended in ethanol (50 ml) and a solution of hydroxylamine hydrochloride (0.8 g) and sodium acetate (1.1 g) in water (20 ml) was added. After warming on a water-bath for 1 h, the solution was evaporated to *ca.* 20 ml. The product crystallised out and was filtered off, washed with water, and dried giving the *oxime* (49) (2.05 g, 95%) as colourless needles (from ethanol–water), m.p. (softens 210 °C) 232—233 °C (Found: C, 61.5; H, 4.3; N, 19.6. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); $\nu_{max.}$ 1 518 and 2 500—3 300 cm^{-1}; τ [$(CD_3)_2SO$] −1.58 (0.33 H, s, oxime OH), −0.86 (0.67 H, s, oxime OH), 1.64 and 2.66 (2 × 0.33 H, s, imidazole 1-H and oxime CH), 1.96 and 2.11 (2 × 0.67 H, s, imidazole 1-H and oxime CH), 2.2—2.5 (1 H, br, m, 9-H), 2.8—3.2 (3 H, br, m, 6-, 7-, 8-H), and 4.79 (2 H, s, OCH_2) (mixture of *syn*- and *anti*-oximes).

4H-*Imidazo*[2,1-c][1,4]*benzoxazine*-2-*carbonitrile* (50).—The oxime (49) (1.9 g) was heated under reflux for 3 h in acetic anhydride (20 ml). The mixture was then poured into aqueous sodium carbonate (20 g in 100 ml) and extracted with ethyl acetate (3 × 100 ml). The combined ethyl acetate layer was washed once with water, then was dried, filtered, and evaporated to dryness. Trituration with ether gave the product, which was filtered off and dried giving the *cyanide* (50) (1.45 g, 83%) as buff needles (from ethyl acetate–ether), m.p. 226—228 °C (Found: C, 66.7; H, 3.7; N, 21.2. $C_{11}H_7N_3O$ requires C, 67.0; H, 3.6; N, 21.3%); $\nu_{max.}$ 1 508, 2 220, and 3 120 cm^{-1}; τ [$(CD_3)_2SO$] 1.56 (1 H, s, imidazole 1-H), 2.3—2.7 (1 H, br, m, 9-H), 2.7—3.2 (3 H, br, m, 6-, 7-, 8-H), and 4.82 (2 H, s, OCH_2).

2-(1H-*Tetrazol*-5-*yl*)-4H-*imidazo*[2,1-c][1,4]*benzoxazine* (51).—The cyanide (50) (1.05 g) was dissolved in dimethylformamide (50 ml) and sodium azide (0.45 g) and ammonium chloride (0.4 g) were added. The mixture was stirred at 125 °C in an oil-bath for 24 h. After cooling, the mixture was poured into water (200 ml) and the crude product was filtered off and recrystallised from methanol (charcoal). The *tetrazole* (51) (0.55 g, 43%) was obtained as off-white needles (from methanol), m.p. 282—285 °C (decomp.) (Found: C, 55.2; H, 3.5; N, 34.75. $C_{11}H_8N_6O$ requires C, 55.0; H, 3.35; N, 35.0%); $\nu_{max.}$ 1 501, 1 634, and 2 200—3 600 cm^{-1}; τ [$(CD_3)_2SO$] 1.34 (1 H, s, imidazole 1-H), 2.0—2.4 (1 H, br, m, 9-H), 2.5—3.1 (3 H, br, m, 6-, 7-, 8-H), and 4.65 (2 H, s, OCH_2) [tetrazolyl NH probably with $(CD_3)_2SO,H_2O$ peak at 4.97].

2-*Chloromethyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine* (52).—The alcohol (47) (10 g) was dissolved in dichloromethane (500 ml) and triethylamine (7.5 ml) and the solution was stirred while thionyl chloride (4 ml) was slowly added. After a further 0.5 h, the mixture was poured into water (500 ml). The organic layer was separated and the aqueous layer was further extracted (2 × 200 ml) with chloroform. The combined organic extract was washed once with water (200 ml), then dried, filtered, and evaporated. Trituration with ether gave a crude product, which was recrystallised from ethyl acetate–ether, giving the *chloromethyl compound* (52) (7.1 g, 65%) as off-white needles (from ethyl acetate–ether), m.p. 137—138 °C (Found: C, 59.95; H, 4.15; Cl, 15.65; N, 12.55. $C_{11}H_9ClN_2O$ requires C, 59.85; H, 4.1; Cl, 16.1; N, 12.7%); $\nu_{max.}$ 1 540 and 3 065 cm^{-1}; τ ($CDCl_3$) 2.70 (1 H, s, imidazole 1-H), 2.8—3.0 (4 H, m, ArH), 4.83 (2 H, s, OCH_2), and 5.43 (2 H, s, CH_2Cl).

2-*Piperidinomethyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine* (53).—The chloromethyl compound (52) (1.0 g) was stirred with piperidine (4 ml) in diethyl ketone (20 ml) at 80 °C for 2 h. Water (100 ml) was then added and the mixture was

extracted with ethyl acetate (2 × 100 ml). The organic extract was washed with water, then dried, filtered, and evaporated to a small volume. A solution of hydrogen chloride in ether was then added dropwise until precipitation of the hydrochloride salt was complete. The product was filtered off and recrystallised from ethanol–ether giving the *amine* (53) *hydrochloride salt* (0.98 g, 71%) as colourless needles (from ethanol–ether), m.p. 221—224 °C (Found: C, 62.6; H, 6.55; Cl, 11.6; N, 13.75. $C_{16}H_{19}ClN_3O$ requires C, 62.85; H, 6.55; Cl, 11.6; N, 13.75%); $\nu_{max.}$ 1 540, 2 640, 2 945, and 3 440 cm^{-1}; τ (D_2O) 2.25 (1 H, s, imidazole 1-H), 2.5—3.1 (4 H, m, ArH), 4.87 (2 H, s, OCH_2), 5.80 (2 H, s, 2-CH_2N), 6.75 (4 H, br, s, piperidine CH_2 next to N), and 8.25 (6 H, br, s, remaining piperidine CH_2).

2-*Cyanomethyl*-4H-*imidazo*[2,1-c][1,4]*benzoxazine* (54).—The chloromethyl compound (52) (1.0 g) and potassium cyanide (0.5 g) were dissolved in dimethylformamide (20 ml). The mixture was stirred at room temperature for 16 h, then poured into water (100 ml) and extracted with ethyl acetate (2 × 100 ml). The organic extract was washed once with water (50 ml), then dried, filtered, and evaporated to a small volume. Addition of light petroleum (b.p. 40—60 °C) caused crystallisation of the product, which was filtered off and dried giving the *cyanomethyl compound* (54) (0.85 g, 88%) as buff crystals (from ethyl acetate–ether), m.p. 101—104 °C (Found: C, 68.05; H, 4.3; N, 19.9. $C_{12}H_9N_3O$ requires C, 68.25; H, 4.25; N, 19.9%); $\nu_{max.}$ 1 541 and 2 243 cm^{-1}; τ ($CDCl_3$) 2.69 (1 H, s, imidazole 1-H), 2.8—3.1 (4 H, br, m, ArH), 4.87 (2 H, s, OCH_2), and 6.31 (2 H, s, CH_2CN).

4H-*Imidazo*[2,1-c][1,4]*benzoxazin*-2-*ylacetic Acid* (55).—The cyanomethyl compound (54) (0.42 g) was dissolved in a mixture of methanol (10 ml) and sodium hydroxide (0.3 g) in water (5 ml). The mixture was heated on a water-bath for 7 h, then cooled and acidified with dilute acetic acid. The precipitate was filtered off and dried giving the *acid* (55) (0.45 g, 98%) as colourless needles (from ethanol–water), m.p. 202—205 °C (Found: C, 62.35; H, 4.55; N, 12.05. $C_{12}H_9N_2O_3$ requires C, 62.6; H, 4.35; N, 12.15%); $\nu_{max.}$ 1 540, 1 679, 3 240, and 3 360 cm^{-1}; τ ($CDCl_3$–CD_3OH) 2.67 (1 H, s, imidazole 1-H), 2.7—3.1 (4 H, br, m, ArH), 4.81 (2 H, s, OCH_2), 5.8 (1 H, br, s, acid H), and 6.37 (2 H, s, CH_2CO_2H).

Methyl 8-*Nitro*-4H-*imidazo*[2,1-c][1,4]*benzoxazine*-2-*carboxylate* (56).—The ester (39) (8.0 g) was added slowly to a stirred mixture of concentrated sulphuric acid (25 ml) and concentrated nitric acid (25 ml) at 5 °C. When all the ester had gone into solution, the yellow solution thus obtained was stirred at room temperature for 3 h, then diluted with water (500 ml). The yellow precipitate was filtered off and dried giving the *nitro-ester* (56) (7.5 g, 79%), as yellow crystals (from ethyl acetate–chloroform), m.p. 270—272 °C (decomp.) (Found: C, 52.3; H, 3.25; N, 15.15. $C_{12}H_8N_3O_5$ requires C, 52.35; H, 3.3; N, 15.25%); $\nu_{max.}$ 1 276, 1 348, 1 541, 1 571, 1 728, and 3 150 cm^{-1}; τ [$(CD_3)_2SO$] 1.23 (1 H, s, imidazole 1-H), 1.30 (1 H, d, $J_{7,9}$ 3 Hz, 9-H), 1.70 (1 H, dd, $J_{7,9}$ 3, $J_{6,7}$ 9 Hz, 7-H), 2.63 (1 H, d, $J_{6,7}$ 9 Hz, 6-H), 4.30 (2 H, s, OCH_2), and 6.03 (3 H, s, ester CH_3).

Methyl 8-*Amino*-4H-*imidazo*[2,1-c][1,4]*benzoxazine*-2-*carboxylate* (57).—The nitro-ester (56) (5.0 g) was suspended in acetic acid (20 ml) and concentrated hydrochloric acid (15 ml). Tin(II) chloride (15 g) was added and the mixture was stirred and warmed to *ca.* 40 °C. After 1 h a crystalline precipitate appeared. The mixture was cooled in an ice-bath for 2 h then filtered, the product being washed well with ether. The chlorostannate salt was dissolved in water (100 ml) and the pH was adjusted to 9 using dilute sodium hydroxide solution. The solution was then extracted with chloroform (2 × 100 ml). The combined extract was washed once with water (100 ml), then dried, filtered, and evaporated to an oil. Trituration with ether gave the *amine* (57) (2.7 g, 61%), as brown crystals (from ethyl acetate–ether), m.p. 213—214 °C (Found: C, 58.6; H, 4.55; N, 16.95. $C_{12}H_{11}N_3O_3$ requires C, 58.75; H, 4.5; N, 17.15%); $\nu_{max.}$ 1 740, 3 135, 3 215, 3 320, and 3 440 cm^{-1}; τ ($CDCl_3$) 2.02 (1 H, s, imidazole 1-H), 3.07 (1 H, d, $J_{6,7}$ 8 Hz, 6-H), 3.33 (1 H, d, $J_{7,9}$ 2 Hz, 9-H), 3.48 (1 H, dd, $J_{6,7}$ 8, $J_{7,9}$ 2 Hz, 7-H), 4.85 (2 H, s, OCH_2), 6.10 (3 H, s, ester CH_3), and 6.0—6.5 (2 H, br, m, NH_2).

Methyl 8-*Acetamido*-4H-*imidazo*[2,1-c][1,4]*benzoxazine*-2-*carboxylate* (58).—The amino-ester (57) (1.5 g) was dissolved in chloroform (50 ml), and sodium carbonate (2.0 g) and acetyl chloride (1.0 g) were added. The mixture was stirred at room temperature for 2 h, then water (200 ml) was added. The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 50 ml). The combined extract was then dried, filtered, and evaporated to dryness. Trituration with ether gave the *acetamido-ester* (58) (1.3 g, 74%), as colourless needles (from methanol–ether), m.p. 288—290°C (decomp.) (Found: C, 58.2; H, 4.55; N, 14.55. $C_{14}H_{13}N_3O_4$ requires C, 58.5; H, 4.55; N, 14.65%); $\nu_{max.}$ 1 689, 1 730, 3 140, and 3 360 cm^{-1}; τ [$(CD_3)_2SO$] 1.57 (1 H, s, imidazole 1-H), 1.93 (1 H, d, $J_{7,9}$ 1.5 Hz, 9-H), 2.62 (1 H, dd, $J_{7,9}$ 1.5, $J_{6,7}$ 9 Hz, 7-H), 2.9 (1 H, d, $J_{6,7}$ 9 Hz, 6-H), 4.72 (2 H, s, OCH_2), 6.21 (3 H, s, ester CH_3), and 7.94 (3 H, s, amide CH_3).

Under similar conditions using ethyl oxalyl chloride was prepared *methyl* 8-*ethoxalylamino*-4H-*imidazo*[2,1-c][1,4]-*benzoxazine*-2-*carboxylate* (59) (75%), as colourless needles (from ethyl acetate–ether), m.p. 186—188 °C (Found: C, 55.45; H, 4.4; N, 12.0. $C_{16}H_{15}N_3O_6$ requires C, 55.65; H, 4.4; N, 12.15%); $\nu_{max.}$ 1 712, 1 739, 3 150, and 3 300 cm^{-1}.

Methyl 2-*Amino*-2-[3,4-*dihydro*-3-*oxoquinoxalin*-2(1H)-*ylidene*]*acetate* (60).—Methyl 3,4-dihydro-3-oxoquinoxalin-2(1*H*)-ylideneacetate [13] (128 g) was suspended in glacial acetic acid (1 250 ml), and trichloroacetic acid (22.2 g) in glacial acetic acid (150 ml) was added with stirring, followed by pentyl nitrite (75 ml). The starting material slowly went into solution and the solution was stirred for a further 3 h at room temperature. The product precipitated out, and after cooling was filtered off and washed well with ether before drying to give *methyl* 2-*hydroxyimino*-2-(3,4-*dihydro*-3-*oxoquinoxalin*-2-*yl*)*acetate* (145.5 g, 96%), as pale yellow needles (from ethanol), m.p. (discolours *ca.* 220 °C) 249—250 °C (Found: C, 53.6; H, 3.85; N, 16.85. $C_{11}H_9N_3O_4$ requires C, 53.45; H, 3.65; N, 17.0%); $\nu_{max.}$ 1 649, 1 749, 2 890, 3 040, and 3 175 cm^{-1}; τ [$(CD_3)_2SO$] −2.83 (1 H, br, m, oxime OH), 2.0—2.8 (4 H, m, ArH), and 6.20 (3 H, s, ester CH_3) (NH not seen).

This oxime (25 g) was suspended in tetrahydrofuran (200 ml) and ethanol (200 ml) containing platinum oxide (1.5 g). The mixture was hydrogenated for 4 h at atmospheric pressure, then filtered through Celite. The filter pad was washed well with chloroform and the filtrate was evaporated to dryness. Trituration with ethanol gave the product, which was filtered off, washed with ether and dried giving the *diamine* (60) (14.0 g, 59%), as red needles (from ethanol), m.p. 170—173 °C (Found: C, 56.25; H, 4.7; N, 17.8. $C_{11}H_{11}N_3O_3$ requires C, 56.65; H, 4.75; N, 18.0%); $\nu_{max.}$ 1 200, 1 345, 1 655, and 2 800—3 500 cm^{-1}; τ [$(CD_3)_2$-

SO] 0.16 (1 H, br, m, NH), 3.0—3.3 (4 H, br, m, ArH), and 6.20 (3 H, s, ester CH_3) [other NH and NH_2 not seen, probably in H_2O peak of $(CD_3)_2SO$].

Methyl 2-Propionamido-2-(3,4-dihydro-3-oxoquinoxalin-2-yl)acetate (61).—The diamine (60) (2 g) in dimethylformamide (20 ml) was treated with propionyl chloride (1.5 g). After 2 h at room temperature, water (100 ml) and ethyl acetate (200 ml) were added. The organic layer was separated, dried, filtered, and evaporated to dryness. The solid obtained was recrystallised from chloroform and light petroleum (b.p. 60—80 °C), giving the *propionamido-compound* (61) (2.0 g, 81%), as pale yellow crystals (from ethyl acetate), m.p. 232—235 °C (Found: C, 57.95; H, 5.2; N, 14.45. $C_{14}H_{15}N_3O_4$ requires C, 58.15; H, 5.25; N, 14.55%); $\nu_{max.}$ 1 676, 1 760, and 3 285 cm^{-1}; τ [$(CD_3)_2SO$] 1.55 (1 H, d, J 8.5 Hz, amide NH), 2.1—2.85 (5 H, m, ArH + quinoxalinone NH), 4.06 (1 H, d, J 8.5 Hz, methine H), 6.34 (3 H, s, ester CH_3), 7.78 (2 H, q, $COCH_2CH_3$), and 8.98 (3 H, t, $COCH_2CH_3$).

Similarly prepared were the *amide* (62) (50%), as pale yellow crystals (from ethyl acetate), m.p. 233—236 °C (Found: C, 64.1; H, 4.5; N, 12.55. $C_{18}H_{15}N_3O_4$ requires C, 64.1; H, 4.5; N, 12.45%); $\nu_{max.}$ 1 675, 1 754, and 3 295 cm^{-1}; and the *amide* (63) (66%), as light buff crystals (from ethyl acetate), m.p. 241—243 °C (Found: C, 64.85; H, 4.8; N, 11.9. $C_{19}H_{17}N_3O_4$ requires C, 64.95; H, 4.9; N, 11.95%); $\nu_{max.}$ 1 679, 1 745, and 3 285 cm^{-1}; and the *amide* (64) (76%), as pale yellow crystals (from ethyl acetate), m.p. 242—245 °C (Found: C, 50.25; H, 3.8; Cl, 11.2; N, 13.45. $C_{13}H_{12}ClN_3O_4$ requires C, 50.4; H, 3.9; Cl, 11.45; N, 13.55%); $\nu_{max.}$ 1 670, 1 686, 1 766, and 3 280 cm^{-1}.

4,5-Dihydro-1-ethyl-4-oxoimidazo[1,5-a]*quinoxaline-3-carboxylic Acid* (65).—The propionamido-compound (61) (1.5 g) was suspended in ethanol (20 ml) and water (10 ml) containing potassium hydroxide (1.0 g), and the mixture was heated under reflux for 4 h. After cooling and filtering, the solution was acidified with concentrated hydrochloric acid giving a white precipitate. The product was filtered off, washed well with water, and dried giving the *acid* (65) (0.8 g, 60%), as colourless needles (from ethanol–water), m.p. 214—216 °C (Found: C, 60.65; H, 4.4; N, 16.1. $C_{13}H_{11}N_3O_3$ requires C, 60.7; H, 4.3; N, 16.35%); $\nu_{max.}$ 1 655, 1 740, 2 500—2 900, and 3 300 cm^{-1}; τ [$(CD_3)_2SO$] 0.33 (1 H, m, quinoxalinone NH), 2.1—2.6 (4 H, m, ArH), 7.75 (2 H, q, CH_2CH_3), and 8.90 (3 H, t, CH_2CH_3) (acid OH not seen).

Similarly prepared were the *acid* (66) (52%), as colourless needles (from ethanol–water), m.p. 245—247 °C (Found: C, 66.8; H, 3.6; N, 13.7. $C_{17}H_{11}N_3O_3$ requires C, 66.9; H, 3.65; N, 13.75%); $\nu_{max.}$ 1 670, 1 725, 2 500—2 900, and 3 300 cm^{-1}; and the *acid* (67) (47%), as colourless needles (from ethanol–water), m.p. 181—183 °C (Found: C, 67.5; H, 4.2; N, 13.1. $C_{18}H_{13}N_3O_3$ requires C, 67.7; H, 4.1; N, 13.15%); $\nu_{max.}$ 1 675, 1 710, 2 500—2 900, and 3 280 cm^{-1}.

Methyl 1-Chloromethyl-4,5-dihydro-4-oxoimidazo[1,5-a]*quinoxaline-3-carboxylate* (69).—The diamine (60) (6.5 g) was suspended in toluene (30 ml) and triethyl orthochloroacetate (5.9 g) and toluene-*p*-sulphonic acid (0.2 g) were added; the mixture was heated under reflux for 3 h. After filtering, the solution volume was reduced to *ca.* 10 ml. The product crystallised out and was filtered off and washed with ether then dried giving the *chloromethyl compound* (69) (5.9 g, 72%), as buff crystals (from toluene), m.p. 145—150 °C (decomp.) (Found: C, 53.4; H, 3.4; Cl, 12.2; N, 14.2. $C_{13}H_{10}ClN_3O_3$ requires C, 53.55; H, 3.45; Cl, 12.15; N, 14.4%); $\nu_{max.}$ 1 682 and 1 749 cm^{-1}; τ [$(CD_3)_2SO$] 2.0 (1 H, m, 9-H), 2.5—3.0 (3 H, m, 6-, 7-, 8-H), 4.56 (2 H, s, CH_2Cl), and 6.21 (3 H, s, ester CH_3) (NH not seen).

Methyl 4,5-Dihydro-4-oxo-1-piperidinomethylimidazo[1,5-a]*quinoxaline-3-carboxylate* (70).—The chloromethyl-compound (69) (1.35 g) was dissolved in dimethylformamide (20 ml), and piperidine (1 ml) was added. The mixture was warmed on a water-bath at *ca.* 80 °C for 3 h. Water (100 ml) and ethyl acetate (100 ml) were then added and the organic layer was separated, dried, and evaporated. Trituration with ether gave the product, which was filtered off, washed with ether, and dried giving the *piperidinomethyl compound* (70) (0.46 g, 29%), as buff needles (from ethyl acetate), m.p. 239—241 °C (Found: C, 63.5; H, 5.9; N, 16.55. $C_{18}H_{20}N_4O_3$ requires C, 63.5; H, 5.9; N, 16.45%); $\nu_{max.}$ 1 676 and 1 740 cm^{-1}; τ [$(CD_3)_2SO$] 1.88 (1 H, m, 9-H), 2.5—3.0 (3 H, m, 6-, 7-, 8-H), 6.16 (2 H, s, CH_2), 6.21 (3 H, s, ester CH_3), 7.50 (4 H, br, m, CH_2 next to N), and 8.59 (6 H, br, m, remaining piperidine CH_2) (NH not seen).

Methyl 1,2-Dihydro-1,4-dioxo-4H-imidazo[5,1-c][1,4]*benzoxazine-3-carboxylate* (71).—The diamine (4) (2.0 g) was suspended in dry toluene (25 ml) and 1,1′-carbonyldiimidazole (1.6 g) was added. The mixture was heated under reflux for 3 h, then cooled, and the product was filtered off. The product was washed with methanol and ether and then dried giving the *imidazolone* (71) (0.9 g, 40%), as brown needles (from toluene), m.p. 218—220 °C (Found: C, 55.35; H, 3.15; N, 10.9. $C_{12}H_8N_2O_5$ requires C, 55.4; H, 3.1; N, 10.75%); $\nu_{max.}$ 1 700, 1 716, and 1 772 cm^{-1}; τ [$(CD_3)_2SO$] 1.40 (1 H, m, 9-H), 2.5—2.9 (3 H, br, m, 6-, 7-, 8-H), and 6.16 (3 H, s, ester CH_3) (NH not seen).

Methyl 1,4-Dioxo-1,2,4,5-tetrahydroimidazo[1,5-a]*quinoxaline-3-carboxylate* (72).—This was prepared in an analogous way (53%), as light brown *crystals* (from toluene), m.p. 271—274 °C (Found: C, 55.4; H, 3.4; N, 16.1. $C_{12}H_9N_3O_4$ requires C, 55.6; H, 3.5; N, 16.2%); $\nu_{max.}$ 1 685, 1 711, 1 754, and 3 275 cm^{-1}; τ [$(CD_3)_2SO$] 1.20 (1 H, m, 9-H), 2.5—3.1 (3 H, m, 6-, 7-, 8-H), and 6.15 (3 H, s, ester CH_3) [NH not seen; in with $(CD_3)_2SO$ water peak?].

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