Synthesis of 5,6-Dihydro-4*H*-imidazo[1,5-*a*][4,1]benzoxazepin-6-ones and their Transformation into 5,6-Dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-ones

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Novel 5,6-dihydro-4*H*-imidazo[1,5-*a*][4,1]benzoxazepin-6-ones have been prepared from benzoxazepindiones by 1,3-dipolar cycloadditions. Ring opening of the oxygen analogues with amines, chlorination followed by base promoted recyclisation provided 5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-ones by a novel route.

Efforts to improve the biological activity of the 1,4-benzodiazepine antianxiety agents[1] have included the preparation of tricyclic 5,6-dihydro-4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-one derivatives.[2,3] We now report the synthesis of compounds of an analogous oxygen ring system, namely 5,6-dihydro-4*H*-imidazo[1,5-*a*][4,1]benzoxazepin-6-ones, Scheme 1.

Cyclisation of chloroacetamidobenzoic acids (**1**) under basic conditions initially gave 4,1-benzoxazepin-2,5-diones[4] (**2a, b**) accompanied by the benzoxazinones (**3**) as by-products (*ca.* 10%) which were difficult to remove. However, alteration of the reaction solvent composition led to the pure uncontaminated diones (**2a, b**) crystallising directly from the reaction mixture in *ca.* 90% yield. Formation of the imidazole ring was accomplished by the established procedure[2] of 1,3-dipolar cycloaddition of a methyl isocyanide anion with imine derivatives. Previously, annulated cyanoimidazoles had been prepared from the corresponding esters which were obtained in poor yield from ethyl isocyanoacetate. It was thought that a contributing factor to the low yields was the strong base, required to deprotonate the isocyanoacetate, causing side reactions. Therefore, it was considered that the direct preparation of the cyanides (**5**) would reduce the number of steps in the reaction sequence and since cyanomethyl isocyanide is readily deprotonated (NEt_3 in CH_2Cl_2 at 15 °C)[5] the use of mild conditions would lead to good yields. Indeed the cyanoimidazoles (**5**) required for the construction of the oxadiazoles were obtained from imidoyl chlorides (**4a, b**) by reaction with cyanomethyl isocyanide and triethylamine at room temperature in 46 and 60% yield respectively.

Reaction of the cyanides (**5**) with hydroxylamine followed by cyclisation of the amidoximes (**6**) with carboxylic acid anhydrides gave the novel 5,6-dihydro-3-oxadiazolyl-4*H*-imidazo[1,5-*a*][4,1]benzoxazepin-6-ones (**7a—f**) in 50—70% yield, *i.e. ca.* 25% overall yield from diones (**2**). The isopropyl derivative (**7e**) was obtained in higher overall yield (44—62%) by addition of lithium di-isopropylamide or potassium hexamethyldisilazane to a solution of 3-isocyanomethyl-5-isopropyl-1,2,4-oxadiazole and the imidoyl chloride (**4b**) or imidothiolic ester (**4c**).

The benzoxazepinones (**7**) are convenient starting materials for the preparation of imidazo[1,5-*a*][1,4]benzodiazepinones (**9**) thereby introducing a variety of substituents at the 5-position. Reaction of the benzoxazepinone (**7e**) with methylamine or butylamine gave the hydroxymethylamines (**8b**) and (**8d**) in good yield (93 and 60%). However, although the reaction of amides with alcohols under the Mitsunobu conditions[6] is reported to result in *N*-alkylation[7] (and O-alkylation),[8] attempted direct cyclisation of the hydroxy compound (**8b**) by treatment with diethyl azodicarboxylate and triphenylphosphine gave the hydrazine derivative (**8e**). Cyclisation of the hydroxy compounds was achieved, after conversion into the chloromethyl compounds, in a two-step process. Reaction of compound (**8d**) with thionyl chloride gave the chloromethyl compound (**8i**) in 95% yield. More conveniently the hydroxy compounds (**8a—c**) may be prepared in DMF solution from the benzoxazepinones (**7b**) and (**7e**) by reaction with primary amines, and converted into the chloromethyl derivatives (**8f—h**) by addition of thionyl chloride in 44—93% yield. Cyclisation of the chloro compounds (**8f—i**) by treatment with base gave the 4*H*-imidazo[1,5-*a*][1,4]benzodiazepin-6-ones (**9a—d**) in 64—85% yield, demonstrating a new method for the preparation of these compounds.

Experimental

M.p.s were determined on a Buchi 510 apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 781 spectrometer. ^1H N.m.r. spectra were obtained on a Bruker AM-250 spectrometer with tetramethylsilane as internal standard in [$^2H_6$]acetone unless otherwise stated. Mass spectra were obtained on a VG-Micromass-16F spectrometer.

4,1-*Benzoxazepin*-2,5-(1H,3H)-*dione* (**2a**).—A solution of sodium hydroxide (2 g, 50 mmol) in water (12 ml) was added to a suspension of 2-chloroacetamidobenzoic acid[4] (10.3 g, 48 mmol) in a mixture of isopropyl alcohol (22.5 ml) and water (87.5 ml). The acid dissolved and the solution was heated at 80 °C for 4 h. The reaction mixture was cooled to 0 °C and the crystalline solid collected to give the *dione* (**2a**) (20.7 g, 97%), m.p. 200—201 °C (lit.,[4] m.p. 200—201 °C).

6-*Chloro*-4,1-*benzoxazepin*-2,5-(1H,3H)-*dione* (**2b**).—Chloroacetyl chloride (51 ml, 0.64 mol) was added over 20 min to a solution of 2-amino-6-chlorobenzoic acid (100 g, 0.58 mol) in dimethylformamide (150 ml) the temperature being maintained < 30 °C. The solution was stirred for 1 h and then a solution of sodium hydroxide (52.2 g, 1.3 mol) in water (1 250 ml) added at < 35 °C. The mixture was slowly heated to 90 °C over 30 min, maintained at 90 °C for 2 h, and then cooled to 5 °C. The crystalline solid was collected to give the *dione* (**2b**) (111.7 g, 91%), m.p. 193—196 °C (Found: C, 51.0; H, 2.9; N, 6.6. $C_9H_6ClNO_3$ requires C, 51.1; H, 2.85; N, 6.6%); $\nu_{max.}$(Nujol) 3 200 and 3 115 (NH), 1 735, 1 700, and 1 675 cm^{-1} (C=O); δ_H 4.77 (s, 2 H, CH_2), 7.23 (dd, 1 H, *J* 1 and 8 Hz, 9-H), 7.39 (dd, 1 H, *J* 1 and 8 Hz, 7-H), 7.56 (t, 1 H, *J* 8 Hz, 8-H); *m/z* 211 (20%, $M^{+\bullet}$), and 119 (100%).

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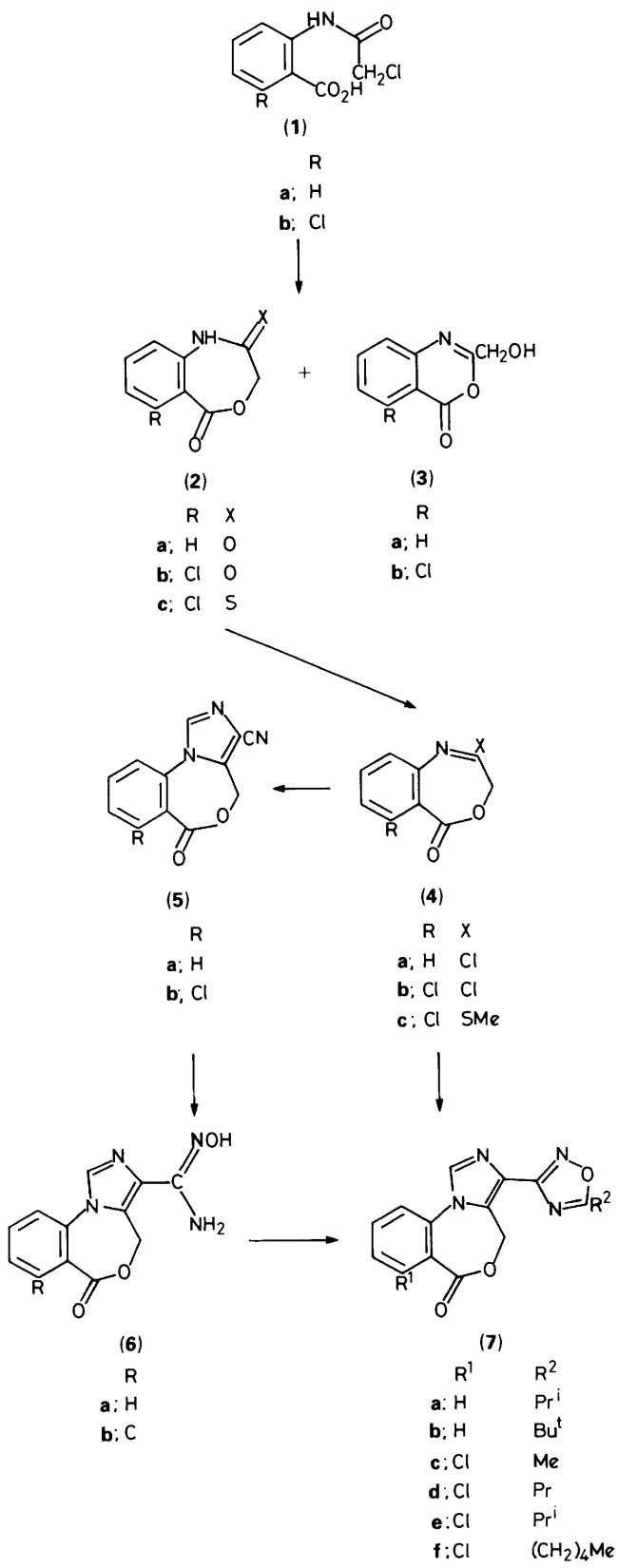


Scheme 1.

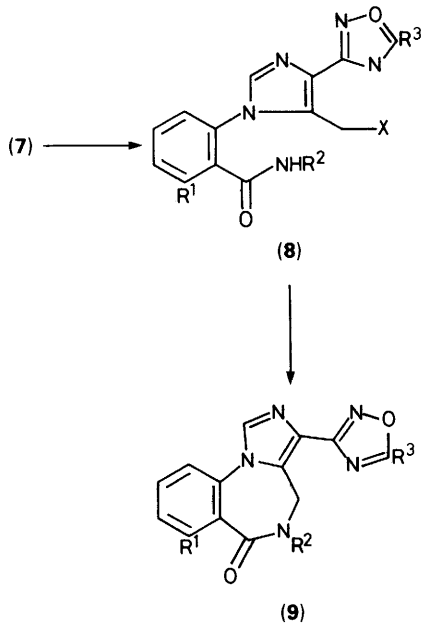
6-*Chloro*-2-*thioxo*-1,2-*dihydro*-4,1-*benzoxazepin*-5-(3H)-*one* (**2c**).—Lawesson's reagent (38 g, 94 mmol) was added to a solution of the dione (**2b**) (20 g, 95 mmol) in dimethoxyethane (472 ml) and the suspension stirred at room temperature for 18 h. The mixture was filtered, the filtrate evaporated, and the residue chromatographed on silica with ethyl acetate–hexane to give the *thione* (**2c**) (20.9 g, 97%), m.p. 177—180 °C (from ethyl acetate) (Found: C, 47.5; H, 2.7; N, 6.05; S, 13.85. $C_9H_6ClNO_2S$ requires C, 47.5; H, 2.65; N, 6.15; S, 14.1%); $\nu_{max.}$(Nujol) 3 140 and 3 070 (NH) and 1 735 cm^{-1} (C=O); δ_H 5.09 (s, 1 H, CH_2), 7.39 (dd, 1 H, *J* 1 and 8 Hz, 9-H), 7.52 (dd, 1 H, *J* 1 and 8 Hz, 7-H), and 7.65 (t, 1 H, *J* 8 Hz, 8-H); *m/z* 227 (100%, $M^{+\cdot}$).

3-*Cyano*-5,6-*dihydro*-4H-*imidazo*[1,5-a][4,1]*benzoxazepin*-6-*one* (**5a**).—A solution of the dione (**2a**) (2.1 g, 12 mmol) and *N*,*N*-dimethylaniline (14 ml, 110 mmol) in dichloromethane (20 ml) was treated with phosphoryl chloride (1.75 ml, 18 mmol) and the solution heated under reflux for 18 h. The solution was cooled and poured into water (50 ml) containing sodium hydrogen carbonate (8 g). The organic layer was separated, and the aqueous layer extracted with dichloromethane. The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated to give a solution of the imidoyl chloride (**4a**) in *N*,*N*-dimethylaniline. A solution of formamidoacetonitrile[9] (2.2 g, 26 mmol) and triethylamine (8.7 ml, 62 mmol) in dichloromethane (26 ml) was treated with phosphoryl chloride (2.5 ml, 25 mmol) at −25 °C. The mixture was stirred for 1 h at −25 °C and then sodium carbonate (5.3 g) in water (25 ml) added. The mixture was stirred for 45 min after which the organic layer was separated and washed with water. The solution of isocyanoacetonitrile in dichloromethane was dried (Na_2SO_4) and added to the imidoyl chloride solution containing triethylamine (4.5 ml, 32 mmol). The mixture was stirred at room temperature for 18 h and poured into 2M hydrochloric acid. The organic phase was separated, washed with 2M hydrochloric acid and saturated aqueous sodium hydrogen carbonate and dried (Na_2SO_4). The solution was evaporated and the residue chromatographed on silica with ethyl acetate–hexane to give the *product* (**5a**) (1.2 g, 46%), m.p. 201—222 °C (from ethyl acetate) (Found: C, 63.95; H, 3.25; N, 18.6. $C_{12}H_7N_3O_2$ requires C, 64.0; H, 3.15; N, 18.65%); $\nu_{max.}$(Nujol) 2 230 (CN) and 1 730 and 1 715 (CO); δ_H 5.44 (s, 1 H, CH_2), 7.70 (m, 1 H, 9-H), 7.85—7.95 (m, 2 H, 8- and 10-H), 8.06 (dt, 1 H, *J* 1 and 8 Hz, 7-H), and 8.60 (s, 1 H, 1-H); *m/z* 226 (60%, *M* + 1) and 177 (100).

7-*Chloro*-3-*cyano*-5,6-*dihydro*-4H-*imidazo*[1,5-a][4,1]*benzoxazepin*-6-*one* (**5b**).—This compound was prepared from imidoyl chloride (**4b**) [obtained from the dione (**2b**) (25 g, 0.12 mmol)] and isocyanoacetonitrile to give the *product* (**5b**) (18.3 g, 60%), m.p. 217—219 °C (from ethyl acetate–hexane) (Found: C, 55.5; H, 2.5; N, 16.05. $C_{12}H_6ClN_3O_2$ requires C, 55.5; H, 2.35; N, 16.2%); $\nu_{max.}$(Nujol) 2 230 (CN) and 1 740 and 1 720 cm^{-1} (CO); δ_H 4.79 (s, 2 H, CH_2), 7.7—7.9 (m, 3 H, ArH), and 8.51 (s, 1 H, 1-H); *m/z* 259 (37%, $M^{+\cdot}$) and 180 (100).

3-*Amidoximido*-5,6-*dihydro*-4H-*imidazo*[1,5-a]*benzoxazepin*-6-*one* (**6a**).*—A mixture of the cyanide (**5a**) (3.8 g, 17 mmol), potassium carbonate (2.9 g, 20 mmol), hydroxylamine hydrochloride (1.5 g, 20 mmol), and water (3 ml) in isopropyl alcohol (190 ml) was stirred at room temperature for 4 days. The reaction mixture was heated under reflux for 6 h and then concentrated to 50 ml. Water (50 ml) was slowly added and the mixture cooled to 5 °C. The solid was collected to give the *amidoxime* (**6a**) (3.8 g, 86%), m.p. 222—224 °C (Found: C, 55.9; H, 4.0; N, 21.3. $C_{12}H_{10}N_4O_3$ requires C, 55.8; H, 3.9; N, 21.7%); $\nu_{max.}$(Nujol) 3 520, 3 460, 3 320 (NH_2, OH), and 1 700 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 5.60 (s, 2 H, CH_2), 7.65 (m, 1 H, 9-H),

* The prefix 'amidoximido' has been used for convenience only, the correct IUPAC name for this group being amino(hydroxyimino)methyl.



(8)

(9)

	(8)					(9)		
	R^1	R^2	R^3	X		R^1	R^2	R^3
a;	H	Pr	Bu^t	OH	**a**;	H	Pr	Bu^t
b;	Cl	Me	Pr^i	OH	**b**;	Cl	Me	Pr^i
c;	Cl	Pr	Pr^i	OH	**c**;	Cl	Pr	Pr^i
d;	Cl	Bu	Pr^i	OH	**d**;	Cl	Bu	Pr^i
e;	Cl	Me	Pr^i	N(CO_2Et)-NHCO_2Et				
f;	H	Pr	Bu^t	Cl				
g;	Cl	Me	Pr^i	Cl				
h;	Cl	Pr	Pr^i	Cl				
i;	Cl	Bu	Pr^i	Cl				

Scheme 2.

7.8—7.95 (m, 2 H, 8- and 10-H), 8.01 (dt, 1 H, *J* 1 and 8 Hz, 7-H), and 8.41 (s, 1 H, 1-H); *m/z* 258 (34%, $M^{+\bullet}$) and 77 (100).

3-*Amidoximido*-7-*chloro*-5,6-*dihydro*-4H-*imidazo*[1,5-a]-[4,1]*benzoxazepin*-6-*one* (**6b**).—Reaction of the cyanide (**5b**) (16.9 g, 57 mmol) and hydroxylamine hydrochloride (4.6 g, 66 mmol) gave the *product* (**6b**) (11 g, 58%), m.p. 252 °C (Found: C, 49.2; H, 3.15; N, 18.9. $C_{12}H_9N_4O_3$ requires C, 49.25; H, 3.1; N, 19.15%); $\nu_{max.}$(Nujol) 3 540, 3 300br (NH_2, OH), and 1 740 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 4.08 (s, 2 H, CH_2), 7.6—7.9 (m, 3 H, ArH), and 8.37 (s, 1 H, 1-H); *m/z* 293 (89%, *M* + 1) and 228 (100).

5,6-*Dihydro*-3-(5-*isopropyl*-1,2,4-*oxadiazol*-3-*yl*)-4H-*imidazo*-[1,5-a][4,1]*benzoxazepin*-6-*one* (**7a**).—The amidoxime (**6a**) (2 g, 8 mmol) in isobutyric anhydride (6 ml) was heated at 150 °C for 2 h. The mixture was concentrated and chromatographed on silica with ethyl acetate–hexane to give the *oxadiazole* (**7a**) (1.4 g, 58%), m.p. 143 °C (from ethyl acetate–hexane) (Found: C, 61.9; H, 4.6; N, 18.0. $C_{16}H_{14}N_4O_3$ requires C, 61.95; H, 4.55; N, 18.05%); $\nu_{max.}$(Nujol) 1 715 cm^{-1} (C=O); δ_H 1.45 (d, 6 H, *J* 7 Hz, Me_2), 3.33 (septet, 1 H, *J* 7 Hz, CH), 5.78 (s, 2 H, CH_2), 7.65 (m, 1 H, 9-H), 7.85—7.95 (m, 2 H, 8- and 10-H), 8.04 (ddd, 1 H, *J* 0.5, 1, and 8 Hz, 7-H), and 8.50 (s, 1 H, 1-H); *m/z* 310 (47%, $M^{+\bullet}$) and 196 (100).

3-(5-t-*Butyl*-1,2,4-*oxadiazol*-3-*yl*)-5,6-*dihydro*-4H-*imidazo*-[1,5-a][4,1]*benzoxazepin*-6-*one* (**7b**).—Reaction of the amidoxime (**6a**) (1.9 g, 7 mmol) and trimethylacetic anhydride gave the *product* (**7b**) (1.6 g, 66%), m.p. 210 °C (from ethyl acetate) (Found: C, 63.0; H, 5.05; N, 17.25. $C_{17}H_{10}N_4O_3$ requires C, 63.0; H, 4.95; N, 17.3%); $\nu_{max.}$(Nujol) 1 710 cm^{-1} (C=O); δ_H 1.51 (s, 9 H, Me_3), 5.80 (s, 2 H, CH_2), 7.65 (m, 1 H, 9-H), 7.85—7.95 (m, 2 H, 8- and 10-H), 8.04 (ddd, 1 H, *J* 0.5, 1, and 8 Hz, 7-H), and 8.42 (s, 1 H, 1-H); *m/z* 324 (28%, $M^{+\bullet}$) and 196 (100).

7-*Chloro*-5,6-*dihydro*-3-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)-4H-*imidazo*[1,5-a][4,1]*benzoxazepin*-6-*one* (**7c**).—Reaction of the amidoxime (**6b**) (3 g, 10 mmol) and acetic anhydride gave the *product* (**7c**) (2.1 g, 66%), m.p. 253—255 °C (from acetone) (Found: C, 53.2; H, 3.0; N, 17.6. $C_{14}H_9ClN_4O_3$ requires C, 53.1; H, 2.85; N, 17.7%); $\nu_{max.}$(Nujol) 1 710 cm^{-1} (C=O); δ_H 2.71 (s, 3 H, Me), 5.78 (br s, 2 H, CH_2), 7.75—7.85 (m, 3 H, ArH), and 8.61 (s, 1 H, 1-H); *m/z* 317 (58%, *M* + 1) and 91 (100).

7-*Chloro*-5,6-*dihydro*-3-(5-*propyl*-1,2,4-*oxadiazol*-3-*yl*)-4H-*imidazo*[1,5-a][4,1]*benzoxazepin*-6-*one* (**7d**).—Reaction of the amidoxime (**6b**) (2 g, 7 mmol) and butyric anhydride gave the *product* (**7d**) (1.2 g, 50%), m.p. 130—132 °C (from ethyl acetate–cyclohexane) (Found: C, 55.8; H, 3.9; N, 16.15. $C_{16}H_{13}ClN_4O_3$ requires C, 55.75; H, 3.8; N, 16.25%); $\nu_{max.}$(Nujol) 1 730 cm^{-1} (CO); δ_H 1.06 (t, 3 H, *J* 7 Hz, Me), 1.91 (sextet, 2 H, *J* 7 Hz, CH_2), 3.0 (t, 2 H, *J* 7 Hz, CH_2), 5.80 (br s, 2 H, CH_2), 7.7—7.85 (m, 3 H, ArH), and 8.45 (s, 1 H, 1-H); 344 (27%, $M^{+\bullet}$), 315 (93), and 84 (100).

7-*Chloro*-4,5-*dihydro*-3-(5-*isopropyl*-1,2,4-*oxadiazol*-3-*yl*)-4H-*imidazo*[1,5-a][4,1]*benzoxazepin*-6-*one* (**7e**).—(a) *From amidoxime* (**6b**). The reaction of amidoxime (**6b**) (12.6 g, 44 mmol) with isobutyric anhydride gave the *product* (**7e**) (10.2 g, 70%), m.p. 167—168 °C (from ethyl acetate) (Found: C, 55.65; H, 3.9; N, 16.15. $C_{16}H_{13}ClN_4O_3$ requires C, 55.75; H, 3.8; N, 16.25%); $\nu_{max.}$(Nujol) 1 735 cm^{-1} (CO); δ_H 1.45 (d, 6 H, *J* 7 Hz, Me_2), 3.38 (sept, 1 H, *J* 7 Hz, CH), 5.80 (br s, 2 H, CH_2), 7.7—7.85 (m, 3 H, ArH), 8.45 (s, 1 H, 1-H); 344 (21%, $M^{+\bullet}$), 315 (46), and 43 (100).

(b) *From imidoyl chloride* (**4b**). A solution of the imidoyl chloride (**4b**) [obtained from the dione (**2b**) (1.9 g, 9 mmol) in *N*,*N*-dimethylaniline] was added to a solution of 3-isocyanomethyl-5-isopropyl-1,2,4-oxadiazole[2] (1.5 g, 10 mmol) in THF (33 ml) and the mixture cooled to −78 °C. A solution of potassium hexamethyldisilazane (0.2 g, 10 mmol) in toluene (10 ml) was added and the mixture stirred at −78 °C for 30 min and then at 20 °C for 4 h. The mixture was poured into 2M hydrochloric acid (50 ml) and the layers separated. The aqueous layer was extracted with ethyl acetate and the combined organic phases were washed with aqueous saturated sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica with ethyl acetate–hexane to give the *product* (**7e**) (1.3 g, 44%), m.p. 167—168 °C (from ethyl acetate) identical (n.m.r.) with a previous sample.

(c) *From the imidothiolic ester* (**4c**). A solution of the thione (**2c**) (19.8 g, 87 mmol) in THF (150 ml) at < 10 °C was treated with sodium hydride (4.7 g, 96 mmol) suspended in THF (150 ml). The solution was stirred for 1 h and iodomethane (6 ml, 92 mmol) added. The mixture was stirred for 1 h and then the resulting solution of the imidothiolic ester (**4c**) cooled to −78 °C. 3-Isocyanomethyl-5-isopropyl-1,2,4-oxadiazole (16.4 g, 107 mmol) was added followed by lithium di-isopropylamide [from butyl-lithium in hexane (2.4M; 64 ml) and di-isopropylamine (22 ml) in THF (120 ml)]. The mixture was stirred at < −65 °C for 1 h 30 min and then poured into a mixture of acetic acid (15 ml), ethyl acetate (300 ml), and water (300 ml). The organic layer was separated, washed with water, and evaporated. The residue was chromatographed on silica with ethyl acetate–hexane to give the *product* (**7e**) (18.5 g, 62%), m.p. 167—168 °C (from ethyl acetate) identical (n.m.r.) with previous samples.

7-*Chloro*-5,6-*dihydro*-3-(5-*pentyl*-1,2,4-*oxadiazol*-3-*yl*)-4H-*imidazo*[1,5-a][4,1]*benzoxazepin*-6-*one* (**7f**).—The reaction of the amidoxime (**6b**) (2 g, 7 mmol) with caproic anhydride gave the *product* (**7f**) (1.6 g, 63%), m.p. 110—112 °C (from ethyl acetate–hexane) (Found: C, 58.0; H, 4.7; N, 14.95. $C_{18}H_{17}ClN_4O_3$ requires C, 58.0; H, 4.55; N, 15.05%); $\nu_{max.}$(Nujol) 1 735 cm^{-1} (CO); δ_H 0.92 (t, 3 H, *J* 7 Hz, Me), 1.4 (m, 4 H, $[CH_2]_2$), 1.88 (m, 2 H, CH_2), 3.02 (t, 2 H, *J* 7 Hz, CH_2), 5.82 (br s, 2 H, CH_2), 7.7—7.85 (m, 3 H, ArH), and 8.45 (s, 1 H, 1-H); *m*/*z* 372 (24%, $M^{+\cdot}$) and 343 (100).

3-[1-(3-*Chloro*-2-N-*methylcarbamoylphenyl*)-2-*hydroxymethylimidazol*-3-*yl*]-5-*isopropyl*-1,2,4-*oxadiazole* (**8b**).—A solution of the benzoxazepin-6-one (**7e**) (2.65 g, 7.5 mmol) in DMF (15 ml) was treated with an excess of methylamine and the solution stirred for 3 h. The solution was poured into water and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated and the residue crystallised from ethyl acetate to give the *product* (**8b**) (2.7 g, 93%), m.p. 184 °C (Found: C, 54.3; H, 4.9; N, 18.5. $C_{17}H_{18}ClN_5O_3$ requires C, 54.35; H, 4.85; N, 18.65%); $\nu_{max.}$($CHCl_3$) 3 450 (OH), 3 300 (NH), and 1 665 cm^{-1} (CO); δ_H 1.43 (d, 6 H, *J* 7 Hz, Me_2), 2.66 (d, 3 H, *J* 5 Hz, NMe), 3.33 (septet, 1 H, *J* 7 Hz, CH), 4.70 (t, 1 H, *J* 5 Hz, OH), 4.84 (d, 2 H, *J* 5 Hz, CH_2O), 7.56 (dd, 1 H, *J* 2 and 8 Hz, 6-H), 7.65 (t, 1 H, *J* 8 Hz, 5-H), 7.65 (s, 1 H, imidazole H), 7.70 (dd, 1 H, *J* 2 and 8 Hz, 4-H), and 7.84 (q, 1 H, *J* 5 Hz, NH); *m*/*z* 375 (6%, $M^{+\cdot}$), 317 (75) and 43 (100).

3-[1-(2-N-*Butylcarbamoyl*-3-*chlorophenyl*)-2-*hydroxymethylimidazol*-3-*yl*]-5-*isopropyl*-1,2,4-*oxadiazole* (**8d**).—The benzoxazepin-6-one (**7e**) (3.5 g, 10 mmol) and butylamine gave the *product* (**8d**) (2.5 g, 60%), m.p. 127—128 °C (from ethyl acetate) (Found: C, 57.4; H, 5.8; N, 16.7. $C_{20}H_{24}ClN_5O_3$ requires C, 57.5; H, 5.8; N, 16.75%); $\nu_{max.}$(Nujol) 3 350 (OH), 3 220 (NH), and 1 640 cm^{-1} (CO); δ_H 0.76 (t, 3 H, *J* 7 Hz, Me), 1.1—1.35 (m, 4 H, $[CH_2]_2$), 1.43 (d, 6 H, *J* 7 Hz, Me_2), 3.13 (q, 2 H, *J* 7 Hz, CH_2), 3.34 (septet, 1 H, *J* 7 Hz, CH), 4.65 (t, 1 H, *J* 5 Hz, OH), 4.86 (d, 2 H, *J* 5 Hz, CH_2O), 7.57 (dd, 1 H, *J* 2 and 8 Hz, 6-H), 7.64 (t, 1 H, *J* 8 Hz, 5-H), 7.65 (s, 1 H, imidazole H), 7.70 (dd, 1 H, *J* 2 and 8 Hz, 4-H), and 7.80 (t, 1 H, *J* 5 Hz, NH); *m*/*z* 418 (11%, $M + 1$), 400 (13%, $M + 1 - H_2O$), and 29 (100).

5-*t*-*Butyl*-2-*chloromethyl*-3-[1-(2-N-*propylcarbamoylphenyl*)-*imidazol*-3-*yl*]-1,2,4-*oxadiazole* (**8f**).—A solution of the benzoxazepin-6-one (**7b**) (1.0 g, 3.09 mmol) and propylamine (6 ml, 73 mmol) in DMF (5 ml) was stirred at room temperature for 18 h. The excess of propylamine was removed at 40 °C *in vacuo* and the resulting solution of the hydroxymethyl compound (**8a**) cooled to 0 °C. Thionyl chloride (1.46 ml, 19.7 mmol) was added and the solution stirred at room temperature for 15 min. The solution was poured into water and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated and the residue crystallised from ethyl acetate to give the *chloromethyl compound* (**8f**) (0.55 g, 44%), m.p. 158—160 °C (Found: C, 59.65; H, 6.05; N, 17.35. $C_{20}H_{24}ClN_5O_2$ requires C, 59.75; H, 6.0; N, 17.45%); $\nu_{max.}$(Nujol) 3 200br (NH) and 1 660 cm^{-1} (C=O); δ_H 0.79 (t, 3 H, *J* 7.5 Hz, Me), 1.37 (m, 2 H, CH_2), 1.49 (s, 9 H, Me_3), 3.13 (q, 2 H, *J* 7 Hz, NCH_2), 5.08 (s, 2 H, CH_2Cl), 6.34 (t, 1 H, *J* 7 Hz, NH), 7.62 (s, 1 H, imidazole H), and 7.4—7.8 (m, 4 H, ArH); *m*/*z* 401 (70%, $M^{+\cdot}$), 317 (74) and 57 (100).

3-[2-*Chloromethyl*-1-(3-*chloro*-2-N-*methylcarbamoylphenyl*)-*imidazol*-3-*yl*]-5-*isopropyl*-1,2,4-*oxadiazole* (**8g**).—The benzoxazepin-6-one (**7e**) (5 g, 14.5 mmol) with methylamine gave a solution of the hydroxymethyl compound (**8b**) in DMF which with thionyl chloride gave the *product* (**8g**) (5.3 g, 93%), m.p. 176—178 °C (from ethyl acetate) (Found: C, 51.7; H, 4.4; N, 17.65. $C_{17}H_{17}Cl_2N_5O_2$ requires C, 51.8; H, 4.35; N, 17.75%); $\nu_{max.}$(Nujol) 3 250br (NH) and 1 660 cm^{-1} (CO); δ_H 1.44 (d, 6 H, *J* 7 Hz, Me_2), 2.68 (d, 3 H, *J* 5 Hz, NMe), 3.33 (septet, 1 H, *J* 7 Hz, CH), 5.13 (br s, 2 H, CH_2Cl), 7.62 (dd, 1 H, *J* 2 and 8 Hz, 6-H), 7.68 (t, 1 H, *J* 8 Hz, 5-H), 7.75 (dd, 1 H, *J* 2 and 8 Hz, 4-H), and 7.79 (s, 1 H, imidazole H); *m*/*z* 394 (100%, $M + 1$).

3-[1-(3-*Chloro*-2-N-*propylcarbamoylphenyl*)-2-*chloromethylimidazol*-3-*yl*]-5-*isopropyl*-1,2,4-*oxadiazole* (**8h**).—The benzoxazepin-6-one (**7e**) (2 g, 6 mmol) with propylamine gave a solution of the hydroxymethyl compound (**8c**) in DMF which with thionyl chloride gave the *product* (**8h**) (1.8 g, 75%), m.p. 157—158 °C (from ethyl acetate) (Found: C, 53.95; H, 5.0; N, 16.5. $C_{19}H_{21}Cl_2N_5O_2$ requires C, 54.05; H, 5.0; N, 16.6%); $\nu_{max.}$(Nujol) 3 270 (NH) and 1 635 cm^{-1} (CO); δ_H 0.77 (t, 3 H, *J* 7 Hz, Me), 1.35 (quintet, 2 H, *J* 7 Hz, CH_2), 1.44 (d, 6 H, *J* 7 Hz, Me_2), 3.11 (m, 2 H, NCH_2), 3.33 (septet, 1 H, *J* 7 Hz, CH), 5.14 (br s, 2 H, CH_2Cl), 7.62 (dd, 1 H, *J* 2 and 8 Hz, 6-H), 7.68 (t, 1 H, *J* 8 Hz, 5-H), 7.76 (dd, 1 H, *J* 2 and 8 Hz, 4-H), 7.78 (s, 1 H, imidazole H); *m*/*z* 421 (10%, $M^{+\cdot}$) and 43 (100).

3-[1-(2-N-*Butylcarbamoyl*-3-*chlorophenyl*)-2-*chloromethylimidazol*-3-*yl*]-5-*isopropyl*-1,2,4-*oxadiazole* (**8i**).—A solution of the hydroxymethyl compound (**8d**) (2.4 g, 6 mmol) in THF (20 ml) was treated with thionyl chloride (0.5 ml, 7 mmol) and the solution stirred for 1 h. The solution was diluted with water (50 ml) and the solid collected and recrystallised from ethyl acetate to give the *chloro compound* (**8i**) (2.4 g, 95%), m.p. 149—150 °C (Found: C, 55.15; H, 5.35; N, 16.0. $C_{20}H_{23}Cl_2N_5O_2$ requires C, 55.05; H, 5.3; N, 16.05%); $\nu_{max.}$(Nujol) 3 260 (NH) and 1 635 cm^{-1} (CO); δ_H 0.75 (t, 3 H, *J* 7 Hz, Me), 1.17 (m, 2 H, CH_2), 1.29 (m, 2 H, CH_2), 1.44 (d, 6 H, *J* 7 Hz, Me_2), 3.16 (q, 2 H, *J* 7 Hz, NCH_2), 3.36 (septet, 1 H, *J* 7 Hz, CH), 5.14 (br s, 2 H, CH_2Cl), 7.61 (dd, 1 H, *J* 2 and 8 Hz, 6-H), 7.68 (t, 1 H, *J* 8 Hz, 5-H), 7.75 (dd, 1 H, *J* 2 and 8 Hz, 4-H), 7.78 (s, 1 H, imidazole H); *m*/*z* 436 (100%, $M + 1$).

3-(5-*t*-*Butyl*-1,2,4-*oxadiazol*-3-*yl*)-5,6-*dihydro*-5-*propyl*-4H-*imidazo*[1,5-a][1,4]*benzodiazepin*-6-*one* (**9a**).—Potassium t-butoxide (0.11 g, 0.94 mmol) in THF (12 ml) was added to a solution of the chloromethyl compound (**8f**) (0.3 g, 0.75 mmol) in THF (16.5 ml) maintained at −30 °C. The solution was poured into water and extracted into ethyl acetate. The extract was evaporated and chromatographed on silica with ethyl acetate–hexane to give the *product* (**9a**) (0.22 g, 81%), m.p. 206—207 °C (from diethyl ether) (Found: C, 65.75; H, 6.4; N, 19.15. $C_{20}H_{23}N_5O_2$ requires C, 65.75; H, 6.35; N, 19.15%); $\nu_{max.}$(Nujol) 1 645 and 1 630 cm^{-1} (CO); δ_H 0.87 (t, 3 H, *J* 7.5 Hz, Me), 1.51 (s, 9 H, Me_3), 1.68 [m, 4 H, $(CH_2)_2$], 3.63 (dt, 2 H, *J* 2 and 7.5 Hz, CH_2N), 4.51 (d, 1 H, *J* 16 Hz, NCH_A), 5.41 (d, 1 H, *J* 16 Hz, NCH_B), 7.58 (ddd, 1 H, *J* 3, 6, and 9 Hz, 9-H), 7.65—7.8 (m, 2 H, 8- and 10-H), 8.01 (ddd, 1 H, *J* 1, 2, and 8 Hz, 7-H), and 8.32 (s, 1 H, 1-H); *m*/*z* 365 (56%, $M^{+\cdot}$) and 42 (100%).

7-*Chloro*-5,6-*dihydro*-3-(5-*isopropyl*-1,2,4-*oxadiazol*-3-*yl*)-5-*methyl*-4H-*imidazo*[1,5-a][1,4]*benzodiazepin*-6-*one* (**9b**).—(a) *From chloromethyl compound* (**8g**). Reaction of the chloromethyl compound (**8g**) (2 g, 5 mmol) with potassium t-butoxide gave the *benzodiazepinone* (**9b**) (1.5 g, 85%), m.p. 165 °C (from ethyl acetate) (Found: C, 57.05; H, 4.55; N, 19.6. $C_{17}H_{16}ClN_5O_2$ requires C, 57.05; H, 4.5; N, 19.55%); $\nu_{max.}$(Nujol) 1 660 cm^{-1} (CO); δ_H 1.46 (2 × d, 6 H, *J* 7 Hz, Me_2), 3.15 (s, 3 H, NMe), 3.36 (septet, 1 H, *J* 7 Hz, CH), 4.64 (d, 1 H, *J* 16 Hz, NCH), 5.28 (dd, 1 H, *J* 0.5 and 16 Hz, NCH), 7.63 (dd, 1 H, *J* 2 and 8 Hz, 10-H), 7.68 (t, 1 H, *J* 8 Hz, 9-H), 7.72 (dd, 1 H, *J* 2 and 8 Hz, 8-H), 8.33 (d, 1 H, *J* 0.5 Hz, 1-H); *m*/*z* 357 (88% $M^{+\cdot}$) and 43 (100).

(b) *Attempted preparation from hydroxymethyl compound* (**8b**). A solution of the hydroxymethyl compound (**8b**) (0.4 g, 1 mmol) and triphenylphosphine (0.7 g, 2.6 mmol) in THF (10 ml)

was treated with diethyl azodicarboxylate (0.4 ml, 2.6 mmol). An exothermic reaction occurred and the mixture was left overnight. The solution was evaporated and chromatographed on silica with ethyl acetate–hexane to give triphenylphosphine oxide (1 g) and the *product* (**8e**) (0.5 g), m.p. 199 °C (from ethyl acetate–hexane) (Found: C, 51.7; H, 5.3; N, 18.25. $C_{23}H_{28}ClN_7O_6$ requires C, 51.75; H, 5.3; N, 18.35%); $\nu_{max.}$(CHCl$_3$) 3 300br (NH) 1 735, 1 705, and 1 660 cm^{-1} (CO); δ_H 1.09 (t, 3 H, *J* 7 Hz, Me), 1.1 (br t, 3 H, *J* ~7 Hz, Me), 1.42 (d, 6 H, *J* 7 Hz, Me_2), 2.83 (br d, 3 H, *J* ~5 Hz, NMe), 3.30 (septet, 1 H, *J* 7 Hz, CH), 3.8 (br s, 2 H, CH_2O), 3.97 (br q, 2 H, *J* ~7 Hz, CH_2O), 5.25 (br s, 2 H, CH_2N), 7.6 (m, 4 H, ArH), 7.73 (s, 1 H, imidazole H), 8.07 (br s, 1 H, NH), and 8.68 (br s, 1 H, NH); *m/z* 533 (3%, $M^{+\cdot}$) and 43 (100).

7-*Chloro*-5,6-*dihydro*-3-(5-*isopropyl*-1,2,4-*oxadiazol*-3-*yl*)-5-*propyl*-4H-*imidazo*[1,5-a][1,4]*benzodiazepin*-6-*one* (**9c**).—Reaction of the chloromethyl compound (**8h**) (0.9 g, 2 mmol) with potassium t-butoxide gave the *benzodiazepinone* (**9c**) (0.5 g, 65%), m.p. 132—133 °C (from ethyl acetate–hexane) (Found: C, 58.85; H, 5.25; N, 17.85. $C_{19}H_{20}ClN_5O_2$ requires C, 59.15; H, 5.2; N, 18.15%); $\nu_{max.}$(Nujol) 1 650 cm^{-1} (CO); δ_H 0.90 (t, 3 H, *J* 7.5 Hz, Me), 1.45 (2 × d, 6 H, *J* 7 Hz, Me_2), 1.68 (m, 2 H, CH_2), 3.36 (m, 1 H, NCH), 3.38 (septet, 1 H, *J* 7 Hz, CH), 3.78 (dt, 1 H, *J* 7 and 13.5 Hz, NCH), 4.56 (d, 1 H, *J* 16 Hz, NCH_A), 5.35 (d, 1 H, *J* 16 Hz, NCH_B), 7.65 (dd, 1 H, *J* 2 and 8 Hz, 10-H), 7.65 (t, 1 H, *J* 8 Hz, 9-H), 7.72 (dd, 1 H, *J* 2 and 8 Hz, 8-H), and 8.39 (s, 1 H, 1-H); *m/z* 385 (5%, $M^{+\cdot}$) 43 (100).

5-*Butyl*-7-*chloro*-5,6-*dihydro*-3-(5-*isopropyl*-1,2,4-*oxadiazol*-3-*yl*)-4H-*imidazo*[1,5-a][1,4]*benzodiazepin*-6-*one* (**9d**).—Reaction of the chloromethyl *compound* (**8i**) (1.75 g, 4 mmol) with potassium t-butoxide gave the benzodiazepinone (**9d**) (1.0 g, 64%), m.p. 118—119 °C (from ethyl acetate–hexane) (Found: C, 60.1; H, 5.6; N, 17.45. $C_{20}H_{22}ClN_5O_2$ requires C, 60.05; H, 5.55; N, 17.5%); $\nu_{max.}$(Nujol) 1 650 cm^{-1} (CO); δ_H 0.90 (t, 3 H, *J* 7.5 Hz, Me), 1.46 (m, 2 H, CH_2), 1.46 (2 × d, 6 H, *J* 7 Hz, Me_2), 1.63 (m, 2 H, CH_2), 3.37 (septet, 1 H, *J* 7 Hz, CH), 3.42 (m, 1 H, NCH), 3.85 (dt, 1 H, *J* 7 and 13 Hz, NCH), 4.55 (d, 1 H, *J* 16 Hz, NCH_A), 5.36 (d, 1 H, *J* 16 Hz, NCH_B), 7.61 (dd, 1 H, *J* 2 and 8 Hz, 10-H), 7.65 (t, 1 H, *J* 8 Hz, 9-H), 7.70 (dd, 1 H, *J* 2 and 8 Hz, 8-H), and 8.33 (s, 1 H, 1-H); *m/z* 400 (100%, *M* + 1).

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