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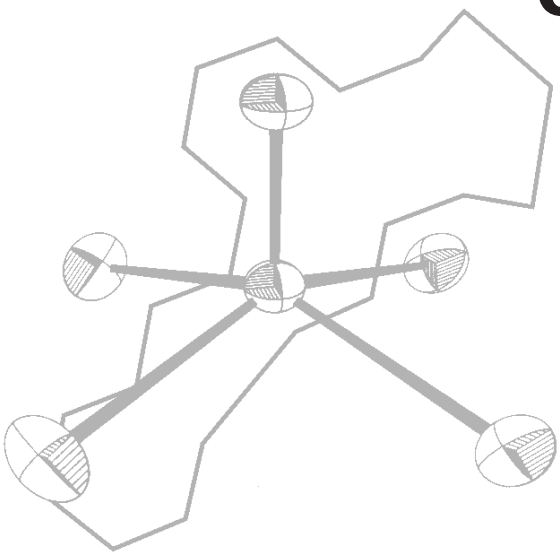

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Imidazo[1,2-*b*]pyridazines. XXI*
Syntheses of Some 3-Acylaminomethyl-6-(chloro and iodo)-2-(substituted phenyl)-imidazo[1,2-*b*]pyridazines and -imidazo[1,2-*a*]pyridines and Their Interaction with Central and Mitochondrial Benzodiazepine Receptors

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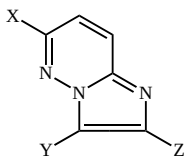
A series of 3-acylaminomethyl-6-(chloro, iodo and methyl)-2-(phenyl, 4′-t-butylphenyl, 4′-cyclohexylphenyl, biphenyl-4′-yl, 4′-chlorophenyl and 4′-iodophenyl)imidazo[1,2-*b*]pyridazines and imidazo[1,2-*a*]pyridines has been prepared and examined for interaction with central and mitochondrial (peripheral-type) benzodiazepine receptors. The imidazo[1,2-*b*]pyridazines were generally more selective for the mitochondrial receptors than the corresponding imidazo[1,2-*a*]pyridines. Of these compounds, 3-acetamidomethyl-2-(biphenyl-4′-yl)-6-chloroimidazo[1,2-*b*]pyridazine (9) proved to be the most selective in studies of the displacement of [^{3}H]diazepam from peripheral-type and central benzodiazepine receptors (IC_{50} 2·8 nM and 0% displacement at 1000 nM, respectively).

Introduction

In Part XX[1] we reported the synthesis of some 3-acylaminomethyl-6-(chloro, fluoro, methoxy, methylthio, phenoxy and phenylthio)-2-(phenyl, 4-t-butylphenyl, 4-cyclohexylphenyl, β-naphthyl and styryl)imidazo[1,2-*b*]pyridazines and their interaction with central and mitochondrial (peripheral-type) benzodiazepine receptors (BZR and PBR, respectively). Some of the 3-acylaminomethyl-6-chloroimidazo[1,2-*b*]pyridazines with relatively large substituents at the 2-position were found to bind strongly and selectively to mitochondrial receptors. We now describe an extension of this work to some new 3-acylaminomethyl-6-(chloro and iodo)-2-(substituted phenyl)imidazo[1,2-*b*]pyridazines and imidazo[1,2-*a*]pyridines (for comparison) and we report the results of binding to both the BZR and the PBR.

Syntheses

The imidazo[1,2-*b*]pyridazines reported in this paper were prepared by procedures similar to those previously used by us for analogous compounds.[1–3] The 6-chloro-[4] and 6-methyl-pyridazin-3-amines,[5] and 6-iodopyridazin-3-amine (previously reported as the hydriodide[6]) were condensed with the bromoacetyl compounds, namely α-bromoacetophenone, α-bromo-4′-methylacetophenone,[7] α-bromo-4′-t-butylacetophenone,[2] α-bromo-4′-cyclohexylacetophenone,[2] α-bromo-4′-phenylacetophenone,[8,9] α-bromo-4′-chloroacetophenone,[10] and α-bromo-4′-iodoacetophenone,[11] to give the 2,6-disubstituted imidazo[1,2-*b*]pyridazines (**1**; Y = H).



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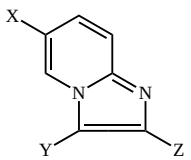

(2)

When these compounds (**1**; Y = H) were heated with *N*-hydroxymethylacylamides, namely the *N*-hydroxymethyl derivatives of formamide,[12] acetamide,[13] propionamide,[14] butyramide,[15] benzamide,[13] or *o*-, *m*- or *p*-chlorobenzamide,[16,17] in acetic acid containing a catalytic amount of sulfuric acid, they gave the 3-acylaminomethylimidazo[1,2-*b*]pyridazines (**1**; Y = CH_2NHCOR).

The substituted imidazo[1,2-*a*]pyridines (**2**; Y = H and CH_2NHCOR) were prepared in an analogous manner from pyridin-2-amine and 5-chloro- or 5-iodopyridin-2-amine.[18]

* Part XX, *Aust. J. Chem.*, 1996, **49**, 451.

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Biological Activity

The compounds reported in this paper were tested for their ability to displace [^{3}H]diazepam from the BZR in rat forebrain membranes and from the PBR in rat kidney membranes. Details of the test procedure for the determination of binding to the BZR[19,20] and the PBR[1,20,21] have been reported previously. The results of these tests are recorded in Table 1 as IC_{50} values (nM) or as the percentage inhibition of binding at specific concentrations (in parentheses). The PBR binding data have been measured also for some compounds for which we have previously described the syntheses and BZR affinities. Formula numbers are given for ease of comparison in the text and substituents are defined in Table 1. GBLD numbers are also recorded (as in earlier publications) in order to simplify comparisons in forthcoming publications.

An examination of the data for the imidazo[1,2-*b*]pyridazines in Table 1 reveals a very low affinity of binding to the BZR for the 6-chloro-2-(biphenyl-4′-yl)imidazo-[1,2-*b*]pyridazines (8)–(10) compared to their 2-phenyl analogues (2)–(4), or their 2-(4′-t-butylphenyl) analogues (5)–(7) [and the 2-(4′-cyclohexyl)phenyl analogues].[1] However, compounds (9) and (10) bound strongly to the PBR: compound (9) bound more strongly than its 2-(4′-t-butylphenyl) analogue (6), whereas compound (10) bound less strongly than compound (7). Of the compounds (1)–(10), the 2-(biphenyl-4′-yl) compounds (9) and (10) were the most selective for the PBR and of these the more active was compound (9) (IC_{50} 2·8 nM).

Compound (1), which lacked the 6-chloro substituent, bound moderately to the BZR but not to the PBR, and compounds (2), (5) and (8), which lacked the 3-acylaminomethyl group, did not interact significantly with either the BZR or the PBR.

The 6-chloro-2-(4′-chlorophenyl) compounds (11), (13) and (16) bound more strongly than their 6-chloro-2-phenyl analogues (2), (3) and (4) to both the BZR and PBR; binding was stronger to the PBR. The selectivity of the 2-(4′-chlorophenyl) compounds (12)–(16), relative to their 2-phenyl analogues, for the PBR was relatively modest, and decreased progressively in compounds (12)–(15) with increasing size of the 3-acylaminomethyl group. The selectivity in the series (11)–(19) was greatest in compounds (17) and (19).

The 6-chloro-2-(4′-iodophenyl)imidazo[1,2-*b*]pyridazines (21)–(25) bound to the PBR with IC_{50} values little different from those for their 2-(4′-chlorophenyl) analogues, but their higher IC_{50} values for interaction with the BZR increased their selectivity for interaction with the PBR. Of these compounds, the most selective was compound (21) with IC_{50} values for the BZR and PBR of 235 and 1·6 nM, respectively.

Amongst the 6-iodo compounds (26)–(40) the preference is for stronger binding to the PBR. This was enhanced in the 3-acylaminomethyl-2-(4′-t-butylphenyl) [(30) and (31)], 2-(4′-cyclohexylphenyl) [(33) and (34)] and 2-(biphenyl-4′-yl) [(36) and (37)] compounds. The 6-iodo-2-(4′-iodophenyl)imidazo[1,2-*b*]pyridazines (38)–(40) exhibited very strong binding to the PBR: compounds (39) and (40) had IC_{50} values of 4·9 and 7·1 nM, respectively.

Amongst the 6-methylimidazo[1,2-*b*]pyridazines (41)–(46), little selectivity was apparent between binding to the BZR or the PBR.

A comparison of the 3-unsubstituted imidazo[1,2-*a*]pyridines (49), (51) and (53) listed in Table 1 with the corresponding imidazo[1,2-*b*]pyridazines (2), (5) and (11) reveals that the imidazo[1,2-*a*]pyridines interacted more stongly with both the BZR and the PBR. Whereas the 3-benzamidomethyl derivatives of 2-phenyl- and 6-chloro-2-phenyl-imidazo[1,2-*a*]pyridine [(48) and (50) respectively] were stronger ligands for the BZR than for the PBR, the reverse applied to 3-benzamidomethyl-6-chloro-2-phenylimidazo[1,2-*b*]pyridazine (4). Also, 3-benzamidomethyl-2-(4′-t-butylphenyl)-6-chloroimidazo[1,2-*a*]pyridine (52) showed enhanced binding to the PBR relative to the 2-phenyl analogue (50) but it was significantly less than that shown by the imidazo[1,2-*b*]pyridazine (7). The results for the 6-chloro-2-(4′-chlorophenyl)- [(53) and (54)] and 6-iodo-2-(4′-t-butylphenyl)-imidazo[1,2-*a*]pyridines [(55)–(57)] did not indicate a significantly enhanced preference for the PBR.

In summary, appropriately substituted imidazo[1,2-*b*]pyridazines examined in this work were found to be better selective ligands for the PBR (relative to the BZR) than the corresponding imidazo[1,2-*a*]pyridines.

Experimental

All compounds were examined for the presence of impurities by thin-layer chromatography on alumina and by ^{1}H n.m.r. spectroscopy. Many compounds, as indicated in the descriptions below, were purified by preparative t.l.c. on aluminium oxide 60 $PF_{254+366}$ (type E).

Solids for analysis were dried at 100–120°/710 mmHg for 3–24 h unless specified otherwise. Melting points are uncorrected and were taken in open Pyrex capillaries. The light petroleum used had a b.p. of 60–80°.

Analyses were performed by the Australian National University Analytical Services Unit.

^{1}H n.m.r. spectra (δ values) were recorded from $CDCl_3$ solutions (unless specified otherwise), with tetramethylsilane as internal standard, and at 90 MHz and 30° with a Jeol FX90Q Fourier-transform spectrometer possessing a digital resolution of 0·12 Hz, or at 300 MHz on a Varian VXR 300 Fourier-transform spectrometer.

Low-resolution mass spectra were recorded on an Incos data system attached to a VG-Micromass 7070 double-focusing mass spectrometer by using electron ionization (e.i.) at 70 eV (under the supervision of Dr J. K. MacLeod at the Research School of Chemistry).

α-Bromo-4′-iodoacetophenone

Bromine (0·64 g, 4 mmol) was added dropwise over 15 min to a solution of 4′-iodoacetophenone (1·97 g, 4 mmol) in dry ether (20·0 ml) containing anhydrous aluminium chloride (0·02 g) at 0° and the stirring continued for 45 min. The ether was removed under vacuum and the residue (2·53 g) was washed with water, then ethanol, and dried. It was recrystallized from

Table 1. Results for the displacement of [^{3}H]diazepam from the BZR and the PBR by substituted imidazo[1,2-*b*]pyridazines and imidazo[1,2-*a*]pyridines

Assays for displacements from the BZR were conducted in the presence of 100 μM γ-aminobutyric acid under the standard assay conditions described in Barlin, G. B., Davies, L. P., and Ngu, M. M. L., *Aust. J. Chem.*, 1988, **41**, 1149. Assays for displacements from the PBR were conducted in the absence of γ-aminobutyric acid as described in Barlin, G. B., Davies, L. P., Harrison, P. W., Ireland, S. J., and Willis, A. C., *Aust. J. Chem.*, 1996, **49**, 451. The results are given as IC_{50} values (nM), or as percentage inhibitions of control binding at 1000 nM (in parentheses)

Class of compound	Compound No.	GBLD No.	Substituents in **(1)** or **(2)** X (position 6)	Y (position 3)	Z (position 2)	IC_{50} (nM) (or percentage displacement[A]) BZR	PBR
Imidazo[1,2-*b*]pyridazine **(1)**	(1)	331	H	$CH_2NHCOPh$	Ph	214[B]	>1000
	(2)	325	Cl	H	Ph	>3000[C]	(0%)[D]
	(3)	318	Cl	$CH_2NHCOMe$	Ph	474[C]	177[D]
	(4)	302	Cl	$CH_2NHCOPh$	Ph	140[C]	114[D]
	(5)	699	Cl	H	$C_6H_4Bu^t$-*p*	(12%)[B]	(4%)[D]
	(6)	934	Cl	$CH_2NHCOMe$	$C_6H_4Bu^t$-*p*	(39%)[D]	10[D]
	(7)	700	Cl	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(8%)[B]	6·2[D]
	(8)[E]	677	Cl	H	$C_6H_4C_6H_5$-*p*	(5%)	(19%)
	(9)	471	Cl	$CH_2NHCOMe$	$C_6H_4C_6H_5$-*p*	(0%)	2·8
	(10)[E]	470	Cl	$CH_2NHCOPh$	$C_6H_4C_6H_5$-*p*	(0·6%)	13·3
	(11)	584	Cl	H	C_6H_4Cl-*p*	(46%)[C]	(14%)
	(12)	945	Cl	CH_2NHCOH	C_6H_4Cl-*p*	(71%)	59
	(13)	943	Cl	$CH_2NHCOMe$	C_6H_4Cl-*p*	92	4
	(14)	938	Cl	$CH_2NHCOEt$	C_6H_4Cl-*p*	40	5
	(15)	940	Cl	$CH_2NHCOPr$	C_6H_4Cl-*p*	11	6
	(16)	812	Cl	$CH_2NHCOPh$	C_6H_4Cl-*p*	26	8
	(17)	932	Cl	$CH_2NHCOC_6H_4Cl$-*o*	C_6H_4Cl-*p*	488	13
	(18)	930	Cl	$CH_2NHCOC_6H_4Cl$-*m*	C_6H_4Cl-*p*	67	20
	(19)	931	Cl	$CH_2NHCOC_6H_4Cl$-*p*	C_6H_4Cl-*p*	401	10
	(20)	946	Cl	H	C_6H_4I-*p*	(41%)	(54%)
	(21)	951	Cl	$CH_2NHCOMe$	C_6H_4I-*p*	235	1·6
	(22)	947	Cl	$CH_2NHCOPh$	C_6H_4I-*p*	3362	15
	(23)	948	Cl	$CH_2NHCOC_6H_4Cl$-*o*	C_6H_4I-*p*	329, (80%)	4·1
	(24)	949	Cl	$CH_2NHCOC_6H_4Cl$-*m*	C_6H_4I-*p*	233, (85%)	15
	(25)	950	Cl	$CH_2NHCOC_6H_4Cl$-*p*	C_6H_4I-*p*	370, (85%)	3·0
	(26)	960	I	H	Ph	(18%)	(26%)
	(27)	979	I	$CH_2NHCOMe$	Ph	(43%)	(90%)
	(28)	959	I	$CH_2NHCOPh$	Ph	229, (76%)	(90%)
	(29)	953	I	H	$C_6H_4Bu^t$-*p*	(2%)	(8%)
	(30)	955	I	$CH_2NHCOMe$	$C_6H_4Bu^t$-*p*	(8%)	11
	(31)	952	I	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(9%)	4·2
	(32)	980	I	H	$C_6H_4C_6H_{11}$-*p*	(0%)	(0%)
	(33)	957	I	$CH_2NHCOMe$	$C_6H_4C_6H_{11}$-*p*	(2%)	88
	(34)	956	I	$CH_2NHCOPh$	$C_6H_4C_6H_{11}$-*p*	(5%)	67
	(35)	981	I	H	$C_6H_4C_6H_5$-*p*	(0%)	(8%)
	(36)	958	I	$CH_2NHCOMe$	$C_6H_4C_6H_5$-*p*	(7%)	173
	(37)	954	I	$CH_2NHCOPh$	$C_6H_4C_6H_5$-*p*	(0%)	37
	(38)	988	I	H	C_6H_4I-*p*	(0%)	(47%)
	(39)	987	I	$CH_2NHCOMe$	C_6H_4I-*p*	(30%)	4·9, (93%)
	(40)	982	I	$CH_2NHCOPh$	C_6H_4I-*p*	(61%)	7·1, (97%)
	(41)	692	Me	H	Ph	(24%)	(0%)
	(42)	998	Me	$CH_2NHCOMe$	Ph	(62%)	(51%)
	(43)	996	Me	$CH_2NHCOPh$	Ph	(85%)	(59%)
	(44)	999	Me	H	C_6H_4Me-*p*	(57%)	(2%)
	(45)	1009	Me	$CH_2NHCOMe$	C_6H_4Me-*p*	(81%)	(84%)
	(46)	1001	Me	$CH_2NHCOPh$	C_6H_4Me-*p*	25, (95%)	(89%)
Imidazo[1,2-*a*]pyridine **(2)**	(47)[F]	1007	H	H	Ph	(6%)	(17%)
	(48)	1002	H	$CH_2NHCOPh$	Ph	(88%)	(20%)
	(49)	839	Cl	H	Ph	(26%)[G]	(64%)
	(50)	830	Cl	$CH_2NHCOPh$	Ph	47[G]	(65%)

Table 1 (*Continued*)

Class of compound	Compound No.	GBLD No.	Substituents in **(1)** or **(2)** X (position 6)	Y (position 3)	Z (position 2)	IC50 (nM) (or percentage displacement[A]) BZR	PBR
Imidazo[1,2-*a*]pyridine **(2)** (*continued*)	(51)	873	Cl	H	$C_6H_4Bu^t$-*p*	(47%)[H]	134[D]
	(52)	877	Cl	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(7%)[H]	487[D]
	(53)[I]	1003	Cl	H	C_6H_4Cl-*p*	(42%)	(84%)
	(54)	1000	Cl	$CH_2NHCOPh$	C_6H_4Cl-*p*	17, (96%)	(86%)
	(55)	1004	I	H	$C_6H_4Bu^t$-*p*	(11%)	(62%)
	(56)	1005	I	$CH_2NHCOMe$	$C_6H_4Bu^t$-*p*	(19%)	(71%)
	(57)	1006	I	$CH_2NHCOPh$	$C_6H_4Bu^t$-*p*	(13%)	(62%)
Diazepam						4·3	73

[A] At 1000 nM. [B] Ref. 2. [C] Ref. 17. [D] Ref. 1. [E] Syntheses reported in ref. 9. [F] Ref. 23. [G] Barlin, G. B., Davies, L. P., and Harrison, P. W., *Aust. J. Chem.*, 1995, **48**, 1031. [H] The values given in ref. 1 for GBLD 873 and 877 are 43 and 3% respectively. [I] Ref. 24.

light petroleum and gave the title compound (1·20 g, 46%), m.p. 111–113° (lit.[11] 113·5°) (Found, for a sample dried at 50° and 1 mmHg for 6 h: C, 29·8; H, 1·6. Calc. for C_8H_6BrIO: C, 29·6; H, 1·9%). ^{1}H n.m.r.: δ 4·39, s, CH_2; 7·68, d, *J* 8·5 Hz, H 3′,5′ (or 2′,6′); 7·88, d, *J* 8·5 Hz, H 2′,6′ (or 3′,5′).

6-Iodopyridazin-3-amine

6-Chloropyridazin-3-amine[4] (1·04 g, 8 mmol) and 50% hydriodic acid (8·0 ml) were heated with stirring in an oil bath at 110° for 14 h and then cooled. The precipitate (1·80 g) was filtered off and washed with ethyl acetate. This solid was suspended in 1 N sodium hydroxide (30 ml) and the mixture stirred for 10 min. The pale yellow *6-iodopyridazin-3-amine* (1·18 g, 67%) was filtered off and dried. It had m.p. 161–161·5° (Found: C, 21·8; H, 1·5; N, 19·1. $C_4H_4IN_3$ requires C, 21·7; H, 1·8; N, 19·0%). ^{1}H n.m.r. (CD_3SOCD_3): δ 4·64, br s, NH_2; 6·75, d, *J* 9·5 Hz, H 5; 7·70, d, *J* 9·5 Hz, H 4.

*6-Chloro-2-(4′-iodophenyl)imidazo[1,2-*b*]pyridazine (20) and Related Compounds*

A mixture of 6-chloropyridazin-3-amine[4] (0·19 g, 1·5 mmol) and α-bromo-4′-iodoacetophenone[11] (0·49 g, 1·5 mmol) in ethanol (15 ml) was refluxed for 3 h. Sodium hydrogen carbonate (0·12 g, 1·5 mmol) was then added and the refluxing continued for 3 h. After being cooled, the precipitate (0·14 g, 77%) was collected and recrystallized from ethanol to give the *title compound* (20) (0·28 g), m.p. 228–229° (Found: C, 40·9; H, 1·6; N, 11·8. $C_{12}H_7ClIN_3$ requires C, 40·5; H, 2·0; N, 11·8%). ^{1}H n.m.r.: δ 7·06, d, *J* 9·5 Hz, H 7; 7·67, d, 7·80, d, *J* 8 Hz, H 2′,3′,5′,6′; 7·89, d, *J* 9·5 Hz, H 8; 8·19, s, H 3. Mass spectrum: *m/z* 357 (45%), 355 (M, 100), 228 (21), 193 (40), 107 (48).

In a similar manner from the compounds mentioned above (or from the compounds under Syntheses) the following compounds were prepared.

*6-Iodo-2-phenylimidazo[1,2-*b*]pyridazine* (26) (53%), m.p. 194–196° (from ethanol) (Found: C, 45·2; H, 2·4; N, 13·0. $C_{12}H_8IN_3$ requires C, 44·9; H, 2·5; N, 13·1%). ^{1}H n.m.r.: δ 7·31, d, *J* 9·5 Hz, H 7; 7·38–7·48 and 7·90–8·02, complex, Ph; 7·65, d, *J* 9·5 Hz, H 8; 8·24, s, H 3.

*2-(4′-t-Butylphenyl)-6-iodoimidazo[1,2-*b*]pyridazine* (29) (49%), m.p. 174–175° (from ethanol) (Found: C, 51·1; H, 4·2; N, 11·0. $C_{16}H_{16}IN_3$ requires C, 50·9; H, 4·3; N, 11·1%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 7·28, d, *J* 9·5 Hz, H 7; 7·49, d, *J* 8 Hz, H 3′,5′ (or 2′,6′); 7·63, d, *J* 9·5 Hz, H 8; 7·89, d, *J* 8 Hz, H 2′,6′ (or 3′,5′); 8·22, s, H 3.

*2-(4′-Cyclohexylphenyl)-6-iodoimidazo[1,2-*b*]pyridazine* (32) (48%), m.p. 244–246° (from ethanol) (Found: C, 54·1; H, 4·5; N, 10·4. $C_{18}H_{18}IN_3$ requires C, 53·6; H, 4·5; N, 10·4%). ^{1}H n.m.r.: δ 7·28, d, *J* 9·5 Hz, H 7; 7·28, d, *J* 8·5 Hz, H 3′,5′ (or 2′,6′); 7·61, d, *J* 9·5 Hz, H 8; 7·87, d, *J* 8·5 Hz, H 2′,6′ (or 3′,5′); 8·20, s, H 3.

*2-(Biphenyl-4′-yl)-6-iodoimidazo[1,2-*b*]pyridazine* (35) (70%), m.p. 252–253° (from toluene) (Found: C, 54·2; H, 2·8. $C_{18}H_{10}IN_3$ requires C, 54·4; H, 3·0%). ^{1}H n.m.r.: δ 7·31, d, *J* 9·5 Hz, H 7; 7·38–7·74, complex, H 8,3′,5′ (or 2′,6′) and Ph; 8·02, d, *J* 8·5 Hz, H 2′,6′ (or 3′,5′); 8·28, s, H 3. Mass spectrum: *m/z* 397 (M, 100%), 368 (14), 313 (9), 270 (15).

*6-Iodo-2-(4′-iodophenyl)imidazo[1,2-*b*]pyridazine* (38) (60%), m.p. 266–267° (from toluene) (Found: C, 32·4; H, 1·3; N, 9·2. $C_{12}H_7I_2N_3$ requires C, 32·2; H, 1·6; N, 9·4%). ^{1}H n.m.r.: δ 7·31, d, *J* 9·5 Hz, H 7; 7·63, d, *J* 9·5 Hz, H 8; 7·67, d, *J* 8·5 Hz, H 3′,5′ (or 2′,6′); 7·81, d, *J* 8·5 Hz, H 2′,6′ (or 3′,5′); 8·22, s, H 3.

*6-Methyl-2-phenylimidazo[1,2-*b*]pyridazine* (41) (78%), m.p. 162–163° (from ethanol) (lit.[22] 157–158°) (Found: C, 74·2; H, 5·7; N, 20·1. Calc. for $C_{13}H_{11}N_3$: C, 74·6; H, 5·3; N, 20·1%). ^{1}H n.m.r.: δ 2·55, s, CH_3; 6·87, d, *J* 9·5 Hz, H 7; 7·81, d, *J* 9·5 Hz, H 8; 7·30–7·55 and 7·86–8·02, complex, Ph; 8·16, s, H 3.

*6-Methyl-2-(4′-methylphenyl)imidazo[1,2-*b*]pyridazine* (44) (54%), m.p. 165·5–166·5° (from ethanol) (Found: C, 74·9; H, 5·8; N, 18·7. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·8%). ^{1}H n.m.r.: δ 2·39, s, 4′-Me; 2·56, s, 6-Me; 6·89, d, *J* 9·5 Hz, H 7; 7·25, d, *J* 8·5 Hz, H 2′,6′ (or 3′,5′); 7·82, d, *J* 9·5 Hz, H 8; 7·85, d, *J* 8·5 Hz, H 3′,5′ or (2′,6′); 8·13, s, H 3.

*3-Acetamidomethyl-2-(biphenyl-4′-yl)-6-chloroimidazo-[1,2-*b*]pyridazine (9)*

2-(Biphenyl-4′-yl)-6-chloroimidazo[1,2-*b*]pyridazine[9] (4·0 g, 13 mmol) was added to a mixture of *N*-hydroxymethylacetamide[13] (2·3 g, 26 mmol) in acetic acid (100 ml) containing concentrated sulfuric acid (0·20 ml) and the mixture was refluxed with stirring in an oil bath at 120° for 14 h. The acetic acid was then evaporated under reduced pressure, the residue diluted with water, aqueous 25% ammonium hydroxide added to pH 10, and the mixture was extracted with chloroform. The solvent was evaporated and the product was recrystallized from toluene to give the *title compound* (9) (1·317 g, 27%), m.p. 276–278° (Found: C, 66·8; H, 4·4; N, 14·7. $C_{21}H_{17}ClN_4O$ requires C, 66·9; H, 4·5; N, 14·9%). ^{1}H n.m.r.: δ 2·08, s, Me; 5·10, d, *J* 5·5 Hz, CH_2; 6·38, br s, NH; 7·15, d, *J* 9·5 Hz, H 7; 7·36–7·79, complex, and 8·10, d, *J* 8 Hz, C_6H_4Ph; 7·98, d, *J* 9·5 Hz, H 8.

*6-Chloro-2-(4′-chlorophenyl)-3-formamidomethylimidazo-[1,2-*b*]pyridazine (12)*

A mixture of 6-chloro-2-(4′-chlorophenyl)imidazo[1,2-*b*]-pyridazine[17] (0·2 g, 0·76 mmol), *N*-hydroxymethylformamide[12] (0·2 g, 2·7 mmol), acetic acid (4 ml) and concentrated sulfuric

acid (0·05 ml) was heated with stirring under reflux in an oil bath at 120° for 14 h. The acetic acid was evaporated under vacuum, the residue diluted with water, adjusted to pH 10, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and the solvent evaporated. The product was subjected to t.l.c. (alumina; chloroform) and recrystallized from toluene to give the *title compound* (12) (0·054 g, 22%), m.p. 237–239° (Found: C, 52·5; H, 2·9; N, 17·1. $C_{14}H_{10}Cl_2N_4O$ requires C, 52·4; H, 3·1; N, 17·4%). ^{1}H n.m.r.: δ 5·03, d, J 5·5 Hz, CH_2; 7·12, d, J 9·5 Hz, H 7; 7·47, d, 7·94, d, J 8·5 Hz, H 2′,3′,5′,6′; 7·82, d, J 9·5 Hz, H 8; 8·26, br s, CHO.

*3-Benzamidomethyl-6-chloro-2-(4′-iodophenyl)imidazo-[1,2-*b*]pyridazine (22) and Related Compounds*

A mixture of 6-chloro-(4′-iodophenyl)imidazo[1,2-*b*]pyridazine (0·18 g, 0·5 mmol), *N*-hydroxymethylbenzamide[13] (0·076 g, 0·5 mmol), glacial acetic acid (5 ml) and concentrated sulfuric acid (0·09 ml) was heated with stirring under reflux in an oil bath at 120° for 14 h. The acetic acid was evaporated under vacuum, the residue diluted with water, adjusted to pH 10, and extracted with chloroform. The product obtained was subjected to t.l.c. (alumina; chloroform/light petroleum, 2 : 1) and recrystallized from toluene to give the *title compound* (22) (0·08 g, 33%), m.p. 267–268° (Found: C, 49·4; H, 2·7. $C_{20}H_{14}ClIN_4O$ requires C, 49·1; H, 2·9%). ^{1}H n.m.r.: δ 5·22, d, J 5·5 Hz, CH_2; 7·15, d, J 9·5 Hz, H 7; 7·40–7·55 and 7·80–7·90, complex, Ph and H 2′,3′,5′,6′; 7·95, d, J 9·5 Hz, H 8. Mass spectrum: *m/z* 490, 488 (M, 3, 11%), 385 (37), 383 (100), 105 (50), 91 (40), 77 (45).

In a similar manner the following compounds were prepared.

*3-Acetamidomethyl-6-chloro-2-(4′-chlorophenyl)imidazo-[1,2-*b*]pyridazine* (13) (62%), m.p. 258–261° [after t.l.c. (alumina; chloroform) and recrystallization from ethanol] (Found: C, 53·6; H, 3·6; N, 16·5. $C_{15}H_{12}Cl_2N_4O$ requires C, 53·7; H, 3·6; N, 16·7%). ^{1}H n.m.r.: δ 2·02, s, CH_3; 4·98, d, J 5·5 Hz, CH_2; 6·37, br s, NH; 7·11, d, J 9·5 Hz, H 7; 7·46, d, 7·96, d, J 8·5 Hz, H 2′,3′,5′,6′; 7·83, d, J 9·5 Hz, H 8.

*6-Chloro-2-(4′-chlorophenyl)-3-propionamidomethylimidazo[1,2-*b*]pyridazine* (14) (77%), m.p. 227·5–229° [after t.l.c. (alumina; chloroform/light petroleum, 2 : 3 then 1 : 1) and recrystallization from ethanol] (Found: C, 54·7; H, 4·3; N, 15·8. $C_{16}H_{14}Cl_2N_4O$ requires C, 55·0; H, 4·0; N, 16·0%). ^{1}H n.m.r.: δ 1·23, t, J 7 Hz, CH_3; 2·25, q, J 7 Hz, $CH_3C\mathbf{H}_2$; 4·99, d, J 5·5 Hz, CH_2N; 6·39, br s, NH; 7·12, d, J 9·5 Hz, H 7; 7·45, d, 7·96, d, J 8·5 Hz, H 2′,3′,5′,6′; 7·91, d, J 9·5 Hz, H 8.

*3-Butyramidomethyl-6-chloro-2-(4′-chlorophenyl)imidazo-[1,2-*b*]pyridazine* (15) (43%), m.p. 194–195° [after t.l.c. (alumina; chloroform/light petroleum, 1 : 1) and recrystallization from ethanol] (Found: C, 55·8; H, 4·4; N, 15·4. $C_{17}H_{16}Cl_2N_4O$ requires C, 56·2; H, 4·4; N, 15·4%). ^{1}H n.m.r.: δ 0·93, t, J 7 Hz, CH_3; 1·67, q, J 7 Hz, $CH_3C\mathbf{H}_2$; 2·16, dt, J 7 Hz, $CH_3CH_2C\mathbf{H}_2$; 5·99, d, J 5·5 Hz, CH_2N; 6·33, br s, NH; 7·09, d, J 9·5 Hz, H 7; 7·45, d, 7·95, d, J 8·5 Hz, H 2′,3′,5′,6′; 8·90, d, J 9·5 Hz, H 8.

*3-Benzamidomethyl-6-chloro-2-(4′-chlorophenyl)imidazo-[1,2-*b*]pyridazine* (16) (29%), m.p. 237–238° [after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene] (Found: C, 60·6; H, 3·5; N, 14·1. $C_{20}H_{14}Cl_2N_4O$ requires C, 60·5; H, 3·6; N, 14·1%). ^{1}H n.m.r.: δ 5·20, d, J 5·5 Hz, CH_2; 7·11, d, J 9·5 Hz, H 7; 7·40–7·52 and 7·72–8·06, complex, H 8,2′,3′,5′,6′ and Ph. Mass spectrum: *m/z* 400, 398, 396 (M, 2, 6, 8%), 295 (17), 293 (70), 291 (100), 105 (38).

*6-Chloro-3-(2′-chlorobenzamidomethyl)-2-(4′′-chlorophenyl)imidazo[1,2-*b*]pyridazine* (17) (68%), m.p. 239–240° [after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene] (Found: C, 56·0; H, 2·9; N, 12·9. $C_{20}H_{13}Cl_3N_4O$ requires C, 55·6; H, 3·0; N, 13·0%). ^{1}H n.m.r.: δ 5·21, d, J 5·5 Hz, CH_2; 7·13, d, J 9·5 Hz, H 7; 7·30–8·08, complex, H 8,3′,4′,5′,6′,2′′,3′′,5′′,6′′. Mass spectrum: *m/z* 432, 430 (M, 8%), 293 (75), 291 (100), 139 (45).

*6-Chloro-3-(3′-chlorobenzamidomethyl)-2-(4′′-chlorophenyl)imidazo[1,2-*b*]pyridazine* (18) (35%), m.p. 234–235° [after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene] (Found: C, 55·7; H, 3·0; N, 12·8. $C_{20}H_{13}Cl_3N_4O$ requires C, 55·6; H, 3·0; N, 13·0%). ^{1}H n.m.r.: δ 5·19, d, J 5·5 Hz, CH_2N; 7·14, d, J 9·5 Hz, H 7; 7·27–8·04, complex, H 8,2′,4′,5′,6′,2′′,3′′,5′′,6′′. Mass spectrum: *m/z* 432, 430 (M, 10%), 293 (75), 291 (100), 255 (15), 139 (42).

*6-Chloro-3-(4′-chlorobenzamidomethyl)-2-(4′′-chlorophenyl)imidazo[1,2-*b*]pyridazine* (19) (35%), m.p. 236–237° [after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene] (Found: C, 55·9; H, 2·9; N, 12·7. $C_{20}H_{13}Cl_3N_4O$ requires C, 55·6; H, 3·0; N, 13·0%). ^{1}H n.m.r.: δ 5·18, d, J 5·5 Hz, CH_2N; 7·13, d, J 9·5 Hz, H 7; 7·35–8·05, complex, H 8,2′,3′,5′,6′,2′′,3′′,5′′,6′′. Mass spectrum: *m/z* 432, 430 (M, 8%), 293 (72), 291 (100), 255 (13), 139 (45).

*3-Acetamidomethyl-6-chloro-2-(4′-iodophenyl)imidazo[1,2-*b*]pyridazine* (21) (33%), m.p. 300–301° [after t.l.c. (alumina; chloroform/light petroleum, 2 : 1) and recrystallization from toluene] (Found: C, 42·7; H, 2·6. $C_{15}H_{12}ClIN_4O$ requires C, 42·2; H, 2·8%). ^{1}H n.m.r.: δ 2·07, s, CH_3; 5·02, d, J 5·5 Hz, CH_2; 6·35, br s, NH; 7·16, d, J 9·5 Hz, H 7; 7·81, d, 7·88, d, J 8 Hz, H 2′,3′,5′,6′; 7·96, d, J 9·5 Hz, H 8. Mass spectrum: *m/z* 428 (9%), 426 (M, 25), 383 (100), 349 (20), 256 (21).

*6-Chloro-3-(2′-chlorobenzamidomethyl)-2-(4′′-iodophenyl)-imidazo[1,2-*b*]pyridazine* (23) (4%), as cream crystals, m.p. 218–220° [after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene] (Found: C, 46·1; H, 2·8; N, 10·5. $C_{20}H_{13}Cl_2IN_4O$ requires C, 45·9; H, 2·5; N, 10·7%). ^{1}H n.m.r.: δ 5·21, d, J 5·5 Hz, CH_2; 7·13, d, J 9·5 Hz, H 7; 7·30–7·42, 7·66–7·74 and 7·76–7·89, complex, H 3′,4′,5′,6′ and ArH; 7·92, d, J 9·5 Hz, H 8. Mass spectrum: *m/z* 524, 522 (M, 1·5, 3%), 347 (100), 278 (45), 187 (67), 172 (40), 128 (55).

*6-Chloro-3-(3′-chlorobenzamidomethyl)-2-(4′′-iodophenyl)-imidazo[1,2-*b*]pyridazine* (24) (27%), as yellow crystals, m.p. 222–224° [after t.l.c. (alumina; chloroform/light petroleum, 2 : 1) and recrystallization from toluene] (Found: C, 46·5; H, 2·1; N, 10·4. $C_{20}H_{13}Cl_2IN_4O$ requires C, 45·9; H, 2·5; N, 10·7%). ^{1}H n.m.r.: δ 5·19, d, J 5·5 Hz, CH_2; 7·15, d, J 9·5 Hz, H 7; 7·30–7·68, complex, H 2′,4′,5′,6′; 7·78, d, J 8 Hz, 7·85, d, J 8 Hz, H 2′′,3′′,5′′,6′′; 7·93, d, J 9·5 Hz, H 8. Mass spectrum: *m/z* 524, 522 (M, 31, 50%), 383 (100), 149 (60), 57 (30).

*6-Chloro-3-(4′-chlorobenzamidomethyl)-2-(4′′-iodophenyl)-imidazo[1,2-*b*]pyridazine* (25) (58%), as a white solid, m.p. 260–261° [after t.l.c. (alumina; chloroform/light petroleum, 2 : 1) and recrystallization from toluene] (Found: C, 45·7; H, 2·7; N, 10·5. $C_{20}H_{13}Cl_2IN_4O$ requires C, 45·9; H, 2·5; N, 10·7%). ^{1}H n.m.r.: δ 5·19, d, J 5·5 Hz, CH_2; 7·14, d, J 9·5 Hz, H 7; 7·43, d, 7·75, d, J 8 Hz, H 2′,3′,5′,6′; 7·85, d, J 8 Hz, H 2′′,3′′,5′′,6′′; 7·92, d, J 9·5 Hz, H 8. Mass spectrum: *m/z* 524, 522 (M, 7, 13%), 385 (46), 383 (100), 139 (42).

*3-Acetamidomethyl-6-iodo-2-phenylimidazo[1,2-*b*]pyridazine* (27) (15%), m.p. 251–252° (from toluene) (Found: C, 45·9; H, 3·2; N, 13·7. $C_{15}H_{13}IN_4O$ requires C, 45·9; H, 3·3; N, 14·3%). ^{1}H n.m.r.: δ 2·03, s, Me; 5·03, d, J 5·5 Hz, CH_2; 6·24, br s, NH; 7·36, d, J 9·5 Hz, H 7; 7·43–7·60 and 7·91–8·02, complex, Ph; 7·66, d, J 9·5 Hz, H 8. Mass spectrum: *m/z* 392 (M, 26%), 349 (100), 301 (4), 223 (49).

*3-Benzamidomethyl-6-iodo-2-phenylimidazo[1,2-*b*]pyridazine* (28) (43%), m.p. 223–224° (from toluene) (Found: C, 52·8; H, 3·2; N, 12·0. $C_{20}H_{15}IN_4O$ requires C, 52·9; H, 3·3; N, 12·3%). ^{1}H n.m.r.: δ 5·24, d, J 5·5 Hz, CH_2; 7·19, br s, NH; 7·34, d, J 9·5 Hz, H 7; 7·40–7·51 and 7·74–8·05, complex, 2×Ph; 7·63, d, J 9·5 Hz, H 8.

3-Acetamidomethyl-2-(4′-t-butylphenyl)-6-iodoimidazo[1,2-b]pyridazine (30) (22%), m.p. 223–224° (from toluene) (Found: C, 50·9; H, 4·7; N, 12·5. $C_{19}H_{21}IN_4O$ requires C, 50·9; H, 4·7; N, 12·5%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 2·02, s, Me; 5·02, d, J 5·5 Hz, CH_2; 6·33, br s, NH; 7·32, d, J 9·5 Hz, H 7; 7·51, d, J 9 Hz, H 3′,5′ (or 2′,6′); 7·62, d, J 9·5 Hz, H 8; 7·89, d, J 9 Hz, H 2′,6′ (or 3′,5′).

3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-iodoimidazo[1,2-b]pyridazine (31) (54%), m.p. 216–218° (from toluene) (Found: C, 56·8; H, 4·2; N, 10·9. $C_{24}H_{23}IN_4O$ requires C, 56·5; H, 4·5; N, 11·0%). ^{1}H n.m.r.: δ 1·35, s, CMe_3; 5·25, d, J 5·5 Hz, CH_2; 7·31, d, J 9·5 Hz, H 7; 7·35–7·83, complex, Ph; 7·52, d, J 9 Hz, H 3′,5′ (or 2′,6′); 7·72, d, J 9·5 Hz, H 8; 7·93, d, J 9 Hz, H 2′,6′ (or 3′,5′).

3-Acetamidomethyl-2-(4′-cyclohexylphenyl)-6-iodoimidazo-[1,2-b]pyridazine (33) (32%), m.p. 235–236° (from toluene) (Found: C, 52·9; H, 4·8; N, 11·5. $C_{21}H_{23}IN_4O$ requires C, 53·2; H, 4·9; N, 11·8%). ^{1}H n.m.r.: δ 1·25–1·90, complex, cyclohexyl; 2·02, s, Me; 5·02, d, J 5·5 Hz, CH_2; 6·29, br s, NH; 7·34, d, J 9·5 Hz, H 7; 7·34, d, J 8·5 Hz, H 3′,5′ (or 2′,6′); 7·63, d, J 9·5 Hz, H 8; 7·87, d, J 8·5 Hz, H 2′,6′ (or 3′,5′).

3-Benzamidomethyl-2-(4′-cyclohexylphenyl)-6-iodoimidazo-[1,2-b]pyridazine (34) (52%), m.p. 239–241° (from toluene) (Found: C, 58·2; H, 4·6; N, 10·3. $C_{26}H_{25}IN_4O$ requires C, 58·2; H, 4·7; N, 10·4%). ^{1}H n.m.r.: δ 1·25–1·90, complex, cyclohexyl; 5·23, d, J 5·5 Hz, CH_2; 7·30, d, J 9·5 Hz, H 7; 7·27–7·50 and 7·74–7·80, complex, H 3′,5′ (or 2′,6′) and Ph; 7·60, d, J 9·5 Hz, H 8; 7·88, d, J 8·5 Hz, H 2′,6′ (or 3′,5′).

3-Acetamidomethyl-2-(biphenyl-4′-yl)-6-iodoimidazo[1,2-b]pyridazine (36) (21%), m.p. 247–248° (from toluene) (Found: C, 54·9; H, 3·6; N, 11·6. $C_{21}H_{17}IN_4O.0{\cdot}15C_7H_8$ requires C, 54·9; H, 3·8; N, 11·6%). ^{1}H n.m.r.: δ 2·05, s, Me; 5·07, d, J 5·5 Hz, CH_2; 7·26–8·13, complex, H 7,8,2′,3′,5′,6′ and ArH.

3-Benzamidomethyl-2-(biphenyl-4′-yl)-6-iodoimidazo[1,2-b]pyridazine (37) (19%), m.p. 223–225° (from toluene) (Found: C, 59·0; H, 3·3. $C_{26}H_{19}IN_4O$ requires C, 58·9; H, 3·6%). ^{1}H n.m.r.: δ 5·28, d, J 5·5 Hz, CH_2; 7·35, d, J 9·5 Hz, H 7; 7·38–7·88, complex, H 3′,5′ (or 2′,6′) and 2×Ph; 7·65, d, J 9·5 Hz, H 8; 8·09, d, J 8 Hz, H 2′,6′ (or 3′,5′).

3-Acetamidomethyl-6-iodo-2-(4′-iodophenyl)imidazo[1,2-b]pyridazine (39) (19%), m.p. 242–243° (from toluene) (Found: C, 34·3; H, 2·0. $C_{15}H_{12}I_2N_4O$ requires C, 34·8; H, 2·3%). Mass spectrum: m/z 518 (M, 43%), 475 (100), 447 (9), 394 (4), 368 (12), 349 (45).

3-Benzamidomethyl-6-iodo-2-(4′-iodophenyl)imidazo[1,2-b]pyridazine (40) (9%), m.p. 237–238° (from toluene) (Found: C, 41·7; H, 2·4. $C_{20}H_{14}I_2N_4O$ requires C, 41·4; H, 2·4%). ^{1}H n.m.r.: δ 5·21, d, J 5·5 Hz, CH_2; 7·38, d, J 9·5 Hz, H 7; 7·30–7·52 and 7·74–7·85, complex, H 2′,3′,5′,6′ and Ph; 7·67, d, J 9·5 Hz, H 8. Mass spectrum: m/z 580 (M, 18%), 475 (100), 349 (12), 105 (60).

3-Acetamidomethyl-6-methyl-2-phenylimidazo[1,2-b]pyridazine (42) (29%), m.p. 240–242° [after t.l.c. (alumina; chloroform) and recrystallization from toluene] (Found: C, 68·5; H, 5·6; N, 19·9. $C_{16}H_{16}N_4O$ requires C, 68·6; H, 5·8; N, 20·0%). ^{1}H n.m.r.: δ 2·04, s, MeCO; 2·62, s, 6-Me; 5·03, d, J 5·5 Hz, CH_2; 6·42, br, NH; 6·96, d, J 9·5 Hz, H 7; 7·38–7·52, complex, and 7·92–7·96, complex, Ph; 7·84, d, J 9·5 Hz, H 8.

3-Benzamidomethyl-6-methyl-2-phenylimidazo[1,2-b]pyridazine (43) (65%), m.p. 219–220° [after t.l.c. (alumina; chloroform) and recrystallization from toluene] (Found: C, 73·7; H, 5·3; N, 16·1. $C_{21}H_{18}N_4O$ requires C, 73·7; H, 5·3; N, 16·4%). ^{1}H n.m.r.: δ 2·66, s, Me; 5·27, d, J 5·5 Hz, CH_2; 7·00, d, J 9·5 Hz, H 7; 7·19, br s, NH; 7·41–7·56, 7·77–7·81 and 7·99–8·04, complex, 2×Ph; 7·89, d, J 9·5 Hz, H 8.

3-Acetamidomethyl-6-methyl-2-(4′-methylphenyl)imidazo-[1,2-b]pyridazine (45) (5%), m.p. 249–251° [after t.l.c. (alumina; chloroform, developed twice) and recrystallization from toluene] (Found: C, 69·5; H, 6·0; N, 19·1. $C_{17}H_{18}N_4O$ requires C, 69·4; H, 6·2; N, 19·0%). ^{1}H n.m.r.: δ 2·05, s, CH_3CO; 2·42, s, 4′-CH_3; 2·60, s, 6-CH_3; 5·00, d, J 5·5 Hz, CH_2; 6·58, br s, NH; 6·92, d, J 9·5 Hz, H 7; 7·27, d, J 8 Hz, 7·79, d, J 9 Hz, H 8,2′,3′,5′,6′.

3-Benzamidomethyl-6-methyl-2-(4′-methylphenyl)imidazo-[1,2-b]pyridazine (46) (70%), m.p. 203–204° [after t.l.c. (alumina; chloroform) and recrystallization from cyclohexane or toluene] (Found: C, 74·0; H, 5·6; N, 15·4. $C_{22}H_{20}N_4O$ requires C, 74·1; H, 5·7; N, 15·7%). ^{1}H n.m.r.: δ 2·42, s, 4′-Me; 2·65, s, 6-Me; 5·26, d, J 5·5 Hz, CH_2; 6·99, d, J 9·5 Hz, H 7; 7·12, br s, NH; 7·31–7·50 and 7·77–7·92, complex, H 8,2′,3′,5′,6′ and Ph.

3-Benzamidomethyl-2-phenylimidazo[1,2-a]pyridine (48)

A mixture of 2-phenylimidazo[1,2-*a*]pyridine[23] (0·2 g, 1 mmol), *N*-hydroxymethylbenzamide[13] (0·233 g, 1·5 mmol), acetic acid (5 ml) and concentrated sulfuric acid (0·05 ml) was heated under reflux with stirring in an oil bath at 116° for 14 h. The acetic acid was evaporated, the residue diluted with water, adjusted with ammonium hydroxide to pH 10, and the mixture extracted with chloroform. The product obtained was subjected to t.l.c. (alumina; chloroform) and recrystallized from toluene to give the *title compound* (0·180 g, 53%), m.p. 199–200° (Found: C, 77·1; H, 5·4; N, 12·9. $C_{21}H_{17}N_3O$ requires C, 77·0; H, 5·2; N, 12·8%). ^{1}H n.m.r.: δ 4·94, d, J 5·5 Hz, CH_2; 6·65, t, J 6·5 Hz, 7·05, t, J 6·5 Hz, 7·18–7·49, 7·77, t, J 6·5 Hz, 7·84, d, J 7 Hz, 8·08, d, J 7 Hz, H 5,6,7,8 and 2×Ph.

3-Benzamidomethyl-6-chloro-2-(4′-chlorophenyl)imidazo-[1,2-a]pyridine (54)

A mixture of 6-chloro-2-(4′-chlorophenyl)imidazo[1,2-*a*]pyridine[24] [^{1}H n.m.r.: δ 7·17, dd, $J_{7,8}$ 9·5 Hz, $J_{5,7}$ 2 Hz, H 7; 7·42, d, J 8 Hz, H 2′,6′ (or 3′,5′); 7·59, d, J 9·5 Hz, H 8; 7·83, s, H 3; 7·87, d, J 8 Hz, H 3′,5′ (or 2′,6′); 8·18, br s, H 5] (0·20 g, 0·87 mmol), *N*-hydroxymethylbenzamide (0·198 g, 1·3 mmol), acetic acid (5 ml) and concentrated sulfuric acid (0·05 ml) was heated under reflux with stirring in an oil bath at 116° for 4 h. The acetic acid was evaporated, the residue diluted with water, adjusted with ammonium hydroxide to pH 10, and extracted with chloroform. The product was recrystallized from toluene and the crystalline solid (0·240 g, 69%) after t.l.c. (alumina; chloroform) and recrystallization from toluene gave the *title compound* (54), m.p. 260–261° (Found: C, 64·0; H, 4·1; N, 10·4. $C_{21}H_{15}Cl_2N_3O$ requires C, 63·6; H, 3·8; N, 10·6%). ^{1}H n.m.r.: δ 5·12, d, J 5·5 Hz, CH_2; 6·61, br s, NH; 7·23, d, J 9 Hz, H 7; 7·42–7·57, complex, 7·86, d, J 8 Hz, H 2′,3′,5′,6′ and Ph; 7·66, d, J 9 Hz, H 8; 8·41, br s, H 5.

2-(4′-t-Butylphenyl)-6-iodoimidazo[1,2-a]pyridine (55)

A mixture of 5-iodopyridin-2-amine[18] (1·0 g, 4·5 mmol), α-bromo-4′-t-butylacetophenone[2] (1·15 g, 4·5 mmol) in ethanol (25 ml) was refluxed with stirring in an oil bath at 105° for 4 h. Sodium hydrogen carbonate (0·38 g, 4·5 mmol) was then added and the refluxing continued for 12 h. The solvent was removed under reduced pressure, the residue diluted with water and the product (1·93 g) extracted into chloroform. It was recrystallized from cyclohexane with charcoal filtration to give the *title compound* (55) (0·783 g, 46%), m.p. 110–112° (Found, for a sample dried at 80° and 710 mmHg for 4 h: C, 54·2; H, 4·5; N, 7·2. $C_{17}H_{17}IN_2$ requires C, 54·3; H, 4·6; N, 7·4%). ^{1}H n.m.r.: δ 1·39, s, CMe_3; 7·34–7·39, 7·46–7·52, 7·88–7·92, complex, H 7,8,2′,3′,5′,6′; 7·81, s, H 3; 8·41, m, H 5.

3-Acetamidomethyl-2-(4′-t-butylphenyl)-6-iodoimidazo-[1,2-a]pyridine (56)

A mixture of the imidazo[1,2-*a*]pyridine (55) (0·2 g, 0·5 mmol), *N*-hydroxymethylacetamide (0·122 g, 1·4 mmol),

acetic acid (4 ml) and concentrated sulfuric acid (0·05 ml) was heated with stirring under reflux in an oil bath at 120° for 14 h. The acetic acid was evaporated under reduced pressure, the residue diluted with water, ammonium hydroxide added to pH 10–11, and the mixture extracted with chloroform. The glassy product (0·267 g) obtained from the extract was subjected to t.l.c. (alumina; chloroform/light petroleum, 1 : 1, developed twice), and the solid (0·126 g) from the band at low R_F was recrystallized from toluene to give the *title compound* (56) (0·038 g, 16%), m.p. 253–255° (Found: C, 53·7; H, 4·7; N, 9·1. $C_{20}H_{22}IN_3O$ requires C, 53·7; H, 5·0; N, 9·4%). ^{1}H n.m.r.: δ 1·33, s, CMe_3; 2·02, s, CH_3; 4·71, d, J 5·5 Hz, CH_2; 7·09, t, NH; 7·17–7·41, complex, H 7,8,2′,3′,5′,6′; 8·36, s, H 5.

*3-Benzamidomethyl-2-(4′-t-butylphenyl)-6-iodoimidazo[1,2-*a*]-pyridine (57)*

This compound was prepared in a similar manner from 2-(4′-t-butylphenyl)-6-iodoimidazo[1,2-*a*]pyridine (0·2 g, 0·5 mmol) and *N*-hydroxymethylbenzamide (0·12 g, 0·79 mmol). The product was extracted into chloroform and the glass-like material (0·309 g) was recrystallized from toluene to give a white solid (0·214 g, 79%). Part of this material was subjected to t.l.c. (alumina; chloroform, developed twice), and the major product was recrystallized from cyclohexane to give the *title compound* (57), m.p. 230° (with prior softening) (Found: C, 59·2; H, 4·5; N, 8·1. $C_{25}H_{24}IN_3O$ requires C, 58·9; H, 4·7; N, 8·2%). ^{1}H n.m.r.: δ 1·36, s, CMe_3; 5·07, d, J 5·5 Hz, CH_2; 6·96, br s, NH; 7·29–7·90; complex, H 6,7,2′,3′,5′,6′ and Ph; 8·52, s, H 5. Mass spectrum: m/z 509 (M, 100%), 389 (82), 105 (78).

Biological Testing: BZR *and* PBR *Binding Assays*

Evaluation of the compounds for their ability to displace [^{3}H]diazepam bound to rat brain membrane (BZR) preparations in the presence of 100 μM γ-aminobutyric acid[19,20] and to displace [^{3}H]diazepam bound to rat kidney membrane (PBR) preparations in the absence of γ-aminobutyric acid[1] was carried out as described previously.[1,20,21]

Percentage inhibitions of control binding at 1000 nM were measured firstly, and in appropriate cases IC_{50} values (nM) were determined. In the latter, tests were conducted over a range of four concentrations which were selected to span the estimated IC_{50} value and, within each determination, assays were performed in triplicate or quadruplicate. In all experiments the correlation coefficients of the lines of best fit to log–logit curves were greater than 0·95.

The results are listed in Table 1 as IC_{50} values (nM), or in parentheses as percentage displacement at 1000 nM.

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