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Imidazo[1,2-*b*]pyridazines. XVIII* Syntheses and Central Nervous System Activities of Some 6-, 7- and 8-(Chloro and methoxy)imidazo[1,2-*a*]pyridine Analogues

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Abstract

Syntheses are reported for some 2-aryl-3-(benzamidomethyl and methoxy)-6(7 and 8)-chloro- and 6(and 8)-methoxy-imidazo[1,2-*a*]pyridines. In tests of the ability of these compounds to displace [^{3}H]diazepam from rat brain membrane, those with 6-chloro and 6-methoxy groups bound most strongly, and relatively small differences only were observed between corresponding imidazo[1,2-*a*]pyridines and imidazo[1,2-*b*]pyridazines.

Introduction

In this paper we examine the effect of relocating a chloro or methoxy group from the 6- to the 7- or the 8-position in imidazo[1,2-*a*]pyridines on the ability of such compounds to displace [^{3}H]diazepam from rat brain membrane. These compounds were chosen for study as models for imidazo[1,2-*b*]pyridazines because we have previously established[1] a close correlation between the binding abilities of 2,3,6-trisubstituted imidazo[1,2-*a*]pyridines and similarly substituted imidazo[1,2-*b*]pyridazines and also because the relevant substituted pyridines required for their synthesis were more readily available than the corresponding pyridazines.

Syntheses

The 3-benzamidomethyl-6(7 and 8)-chloroimidazo[1,2-*a*]pyridines required in this work were prepared from the relevant 5-, 4- or 3-chloropyridin-2-amines (1; X = Cl) by ring closure with α-bromoacetophenone (α-bromo-4-methylacetophenone or α-bromo-3,4-methylenedioxyacetophenone) to the 6-, 7- or 8-chloro-2-phenyl (or substituted phenyl)imidazo[1,2-*a*]pyridines (2; X = Cl, Y = H). The latter compounds, when heated with *N*-hydroxymethylbenzamide, gave the corresponding 3-benzamidomethyl derivatives (2; X = Cl, Y = $CH_2NHCOPh$).

The 6- and 8-methoxy-3-benzamidomethyl-2-phenyl(and substituted phenyl)imidazo[1,2-*a*]pyridines were prepared by a similar procedure; but 4-methoxypyridin-2-amine with α-bromoacetophenone did not give 7-methoxy-2-phenylimidazo[1,2-*a*]pyridine.

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[1] Barlin, G. B., Davies, L. P., Ireland, S. J., Ngu, M. M. L., and Zhang, J., *Aust. J. Chem.*, 1992, **45**, 877.

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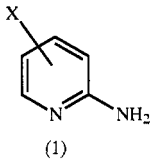
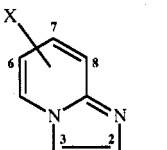
On the other hand, condensation of 5-, 4- or 3-chloropyridin-2-amine with phenylglyoxal in ethanol containing hydrochloric acid afforded the corresponding 3-hydroxyimidazo[1,2-*a*]pyridines (2; X = Cl, Y = OH) which were methylated with diazomethane to give the 3-methoxy compounds (2; X = Cl, Y = OMe). 3,6-Dimethoxy-2-(4′-tolyl)imidazo[1,2-*a*]pyridine had previously been prepared[1] in a similar manner but we could not prepare the 3,8-dimethoxy 2-phenyl analogue in this way.



(1)



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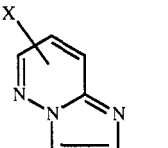

(3)

Some corresponding imidazo[1,2-*b*]pyridazines [3; X = Cl or OMe, Y = H, $CH_2NHCOPh$ or OMe, Ar = $C_6H_3(3',4'\text{-}OCH_2O)$] were prepared in an analogous manner.

Intermediates required for these syntheses either were from commercial sources or were prepared according to literature procedures as follows: 5-chloropyridin-2-amine (Aldrich), 4-chloropyridin-2-amine,[2,3] 3-chloropyridin-2-amine,[4] 5-methoxypyridin-2-amine,[1] 4-methoxypyridin-2-amine,[3] 3-methoxypyridin-2-amine (see Experimental section), α-bromo-4-methylacetophenone,[5] α-bromo-3,4-methylenedioxyacetophenone,[6] *N*-hydroxymethylbenzamide[7] and 6-methoxypyridazin-3-amine.[8,9]

Biological Activity

The compounds prepared in this work were examined for their ability to displace [^{3}H]diazepam from rat brain membrane as described in the Experimental section, and the results are presented in Table 1. Compound numbers (identified in Table 1) are given for ease of comparison in the text; and GBLD numbers are also recorded to simplify comparisons in previous and forthcoming publications.

Comparison of the results in Table 1 for the 2-aryl-6(7 and 8)-chloroimidazo[1,2-*a*]pyridines revealed that the 6-chloro compounds (4)–(6) bound more strongly than either the 7- or 8-chloro isomers: the general order of activity was 6 > 8 ≥ 7. The results for the 6- and 8-methoxy compounds (13)–(17) also indicated that, amongst the methoxy analogues, the 6-isomer was the most active. (The

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Table 1. Results for displacement of [^{3}H]diazepam from rat forebrain membrane benzodiazepine receptors by substituted imidazo[1,2-*a*]pyridines and substituted imidazo[1,2-*b*]pyridazines

Assays were conducted in the presence of 100 μM γ-aminobutyric acid under the standard conditions described in Barlin, G. B., Davies, L. P., and Ngu, M. M. L., *Aust. J. Chem.*, 1988, **41**, 1149. For some compounds tests were conducted over a range of concentrations in which case the results are given as IC_{50} values (nM); other results are given as percentage inhibitions of control binding at 1000 nM (in parentheses)

GBLD No.	Cpd No.	Substituents in formula (2) or (3) X	Y	Ar	IC_{50} (nM) (or percentage displacement)[A]
			Imidazo[1,2-*a*]pyridine (2)		
839	(4)	6-Cl	H	Ph	(26%)
648	(5)	6-Cl	H	C_6H_4Me-*p*	(49%)[B]
838	(6)	6-Cl	H	$C_6H_3(3',4'\text{-}OCH_2O)$	(42%)
832	(7)	7-Cl	H	Ph	(0%)
833	(8)	7-Cl	H	C_6H_4Me-*p*	(10%)
834	(9)	7-Cl	H	$C_6H_3(3',4'\text{-}OCH_2O)$	(21%)
840	(10)	8-Cl	H	Ph	(0%)
841	(11)	8-Cl	H	C_6H_4Me-*p*	(41%)
842	(12)	8-Cl	H	$C_6H_3(3',4'\text{-}OCH_2O)$	(20%)
658	(13)	6-OMe	H	C_6H_4Me-*p*	(9%)[B]
662	(14)	6-OMe	H	$C_6H_3(3',4'\text{-}OCH_2O)$	980[B]
851	(15)	8-OMe	H	Ph	(40·7%)
852	(16)	8-OMe	H	C_6H_4Me-*p*	(15·5%)
853	(17)	8-OMe	H	$C_6H_3(3',4'\text{-}OCH_2O)$	(0·13%)
830	(18)	6-Cl	$CH_2NHCOPh$	Ph	47
647	(19)	6-Cl	$CH_2NHCOPh$	C_6H_4Me-*p*	11[B]
831	(20)	6-Cl	$CH_2NHCOPh$	$C_6H_3(3',4'\text{-}OCH_2O)$	8·7
835	(21)	7-Cl	$CH_2NHCOPh$	Ph	(58%)
836	(22)	7-Cl	$CH_2NHCOPh$	C_6H_4Me-*p*	(68%)
837	(23)	7-Cl	$CH_2NHCOPh$	$C_6H_3(3',4'\text{-}OCH_2O)$	(79%)
843	(24)	8-Cl	$CH_2NHCOPh$	Ph	(12%)
869	(25)	8-Cl	$CH_2NHCOPh$	C_6H_4Me-*p*	(16·4%)
844	(26)	8-Cl	$CH_2NHCOPh$	$C_6H_3(3',4'\text{-}OCH_2O)$	(14%)
621	(27)	6-OMe	$CH_2NHCOPh$	C_6H_4Me-*p*	25[B]
661	(28)	6-OMe	$CH_2NHCOPh$	$C_6H_3(3',4'\text{-}OCH_2O)$	16[B]
854	(29)	8-OMe	$CH_2NHCOPh$	Ph	(32%)
855	(30)	8-OMe	$CH_2NHCOPh$	C_6H_4Me-*p*	(24·4%)
856	(31)	8-OMe	$CH_2NHCOPh$	$C_6H_3(3,4'\text{-}OCH_2O)$	(20·9%)
870	(32)	6-Cl	OMe	Ph	(61·2%)
319	(33)	6-Cl	OMe	C_6H_4Me-*p*	146[B]
871	(34)	7-Cl	OMe	Ph	(0%)
872	(35)	8-Cl	OMe	Ph	(14·9%)
628	(36)	6-OMe	OMe	C_6H_4Me-*p*	329[B]
			Imidazo[1,2-*b*]pyridazine (3)		
325	(37)	6-Cl	H	Ph	>3000[C]
594	(38)	6-Cl	H	C_6H_4Me-*p*	527[C]
539	(39)	6-Cl	H	$C_6H_3(3',4'\text{-}OCH_2O)$	1427[D]
566	(40)	6-OMe	H	C_6H_4Me-*p*	1704[B]
782	(41)	6-OMe	H	$C_6H_3(3',4'\text{-}OCH_2O)$	(58%)
302	(42)	6-Cl	$CH_2NHCOPh$	Ph	140[C]
593	(43)	6-Cl	$CH_2NHCOPh$	C_6H_4Me-*p*	18[C]
547	(44)	6-Cl	$CH_2NHCOPh$	$C_6H_3(3',4'\text{-}OCH_2O)$	25[D]
570	(45)	6-OMe	$CH_2NHCOPh$	C_6H_4Me-*p*	23[B]
819	(46)	6-OMe	$CH_2NHCOPh$	$C_6H_3(3,4'\text{-}OCH_2O)$	7·6
115	(47)	6-Cl	OMe	Ph	772[C]
173	(48)	6-Cl	OMe	C_6H_4Me-*p*	148[B]
857	(49)	6-OMe	OMe	C_6H_4Me-*p*	191

[A] At 1000 nM. [B] Ref. 1. [C] Ref. 10. [D] Ref. 11.

7-methoxy isomers were not available for study.) Examination of the results for the 2-aryl-3-benzamidomethyl-6(7 and 8)-chloroimidazo[1,2-*a*]pyridines revealed an interesting variation. As before, the 6-chloro compounds (18)–(20) bound the most strongly and were highly active (IC_{50} values 8·7–47 nM) but the 7-chloro compounds (21)–(23) were significantly more active than the 8-isomers (24)–(26).

The 2-aryl-3-benzamidomethyl-6-methoxyimidazo[1,2-*a*]pyridines (27) and (28) also exhibited strong binding (approaching that of the 6-chloro analogues) whereas the 8-isomers (29)–(31) bound much less strongly [but slightly more strongly than their 8-chloro analogues (24)–(26)].

Comparison of these results with those for the corresponding imidazo[1,2-*b*]pyridazines[1,10,11] revealed relatively small differences, but the 2-aryl-3-benzamidomethyl-6(7 and 8)-chloroimidazo[1,2-*a*]pyridines were slightly more active than the corresponding imidazo[1,2-*b*]pyridazines; whereas amongst the 6-methoxy derivatives the imidazo[1,2-*b*]pyridazines were the more active.

Amongst the 2-aryl-6(7 and 8)-chloro-3-methoxyimidazo[1,2-*a*]pyridines (32)–(35) the order of activity was 6 > 8 > 7 and the activity of compound (33) (IC_{50} 146 nM) was almost the same as the corresponding imidazo[1,2-*b*]pyridazine (48) (IC_{50} 148 nM); however, 3,6-dimethoxy-2-(4′-tolyl)imidazo[1,2-*b*]pyridazine (49) (IC_{50} 191 nM) bound more strongly than the analogous imidazo[1,2-*a*]pyridine[1] (36; IC_{50} 329 nM).

The similarity in binding affinity between the imidazo[1,2-*a*]pyridines and the corresponding imidazo[1,2-*b*]pyridazines discussed above, suggests that the presence of a ring nitrogen at position 5 does not significantly affect binding. However, the presence of a ring nitrogen atom at positions 7 or 8 as in imidazo[1,2-*a*]pyrimidines[1] and imidazo[1,2-*a*]pyrazines[1] has been found previously[1] to decrease binding ability, an effect currently under investigation.

Experimental

All compounds were examined for the presence of impurities by thin-layer chromatography on alumina (and silica) and by ^{1}H n.m.r. spectroscopy. The imidazo[1,2-*a*]pyridines on t.l.c. plates appeared as a fluorescent band; and the R_F of the 3-unsubstituted compounds was higher than that of the 3-benzamidomethyl derivative.

Solids for analysis were dried at 100°/710 mmHg for 24 h unless specified otherwise. Melting points are uncorrected and were taken in open Pyrex capillaries with an Electrothermal melting point apparatus.

Analyses were performed by the Australian National University Analytical Services Unit. The light petroleum used in this work had b.p. 60–80°.

^{1}H n.m.r. spectra (δ values) were recorded from $CDCl_3$ solution generally at 90 MHz and 30° with a Jeol FX90Q Fourier transform spectrometer with tetramethylsilane as internal standard.

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).

6-Chloro-2-phenylimidazo[1,2-a]pyridine (4)

A mixture of 5-chloropyridin-2-amine (0·19 g), α-bromoacetophenone (0·30 g) and ethanol (15·0 ml) was refluxed for 3 h, then sodium hydrogen carbonate (0·13 g) was added and the

[10] Barlin, G. B., Davies, L. P., Ireland, S. J., Ngu, M. M. L., and Zhang, J., *Aust. J. Chem.*, 1992, **45**, 731.

[11] Barlin, G. B., Davies, L. P., Glenn, B., Harrison, P. W., and Ireland, S. J., *Aust. J. Chem.*, 1994, **47**, 609.

refluxing continued for 3 h. The ethanol was evaporated under reduced pressure, the residue diluted with water, the product extracted into chloroform and the extract dried (Na_2SO_4). The solvent was evaporated to give a brown solid (0·29 g, 85%), part of which was recrystallized from light petroleum to give the *title compound*, m.p. 201–202° (Found: C, 68·1; H, 4·0; N, 12·1. $C_{13}H_9ClN_2$ requires C, 68·3; H, 4·0; N, 12·3%). ^{1}H n.m.r. δ 7·17, dd, $J_{7,8}$ 9 Hz, $J_{5,7}$ 2 Hz, H7; 7·34–7·60 and 7·89–7·98, complex, Ph; 7·67, d, $J_{7,8}$ 9 Hz, H8; 7·87, s, H3; 8·20, br s, H5.

7-Chloro-2-(p-tolyl)imidazo[1,2-a]pyridine (8)

A mixture of 4-chloropyridin-2-amine[2,3] (0·18 g) and bromo-4-methylacetophenone[5] in ethanol (15·0 ml) was refluxed for 3 h, then sodium hydrogen carbonate (0·13 g) was added and the refluxing continued for 3 h. The product was extracted as above and gave a yellow-brown solid (0·27 g, 75%), part of which was recrystallized from light petroleum and gave the *title compound*, m.p. 201–203° (Found: C, 69·0; H, 4·7; N, 11·3. $C_{14}H_{11}ClN_2$ requires C, 69·3; H, 4·6; N, 11·5%). ^{1}H n.m.r. δ 2·38, s, Me; 6·50–6·79, complex, 7·19–7·60, complex, and 7·85–7·91, complex, H6,8,2′,3′,5′,6′; 7·77, s, H3; 8·01, d, $J_{5,6}$ 7 Hz, H5.

8-Chloro-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (12) and Related Compounds

A mixture of 3-chloropyridin-2-amine[4] (0·19 g) and α-bromo-3,4-methylenedioxyacetophenone[6] (0·36 g) in ethanol (15·0 ml) with sodium hydrogen carbonate (0·13 g) was treated as above. It gave an orange solid (0·42 g) which after t.l.c. (alumina; chloroform/light petroleum, 3:1) gave the *title compound* (0·17 g, 42%), m.p. 172–173° (from light petroleum) (Found: C, 61·7; H, 3·2; N, 10·1. $C_{14}H_9ClN_2O_2$ requires C, 61·7; H, 3·3; N, 10·3%). ^{1}H n.m.r. δ 5·99, s, OCH_2O; 6·68, t, *J* 7 Hz, H6; 6·81–7·53, complex, H7(5),2′,5′,6′; 7·77, s, H3; 8·02, br d, *J* 7 Hz, H5(7).

The following analogues were prepared in a similar manner.

6-Chloro-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (6) (88%), m.p. 207–208° (from light petroleum) (Found: C, 61·4; H, 3·3; N, 10·2. $C_{14}H_9ClN_2O_2$ requires C, 61·7; H, 3·3; N, 10·3%). ^{1}H n.m.r. δ 6·00, s, OCH_2O; 6·88, d, *J* 7 Hz, H5′(6′); 7·18, dd, $J_{7,8}$ 9 Hz, $J_{5,7}$ 2 Hz, H7; 7·41–7·53, complex, H2′,6′(5′); 7·64, d, $J_{7,8}$ 9 Hz, H8; 7·74, s, H3; 8·17, br s, H5.

7-Chloro-2-phenylimidazo[1,2-a]pyridine (7) (99%), m.p. 180–181° (from light petroleum) (Found: C, 67·9; H, 3·9; N, 12·1. $C_{13}H_9ClN_2$ requires C, 68·3; H, 4·0; N, 12·3%). ^{1}H n.m.r. δ 6·66–6·82, complex, 7·30–7·63, complex, and 7·86–7·97, complex, H6,8, Ph; 7·81, s, H3; 8·02, d, $J_{5,6}$ 7 Hz, H5.

7-Chloro-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (9) (98%), m.p. 195–196° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from light petroleum (Found: C, 61·8; H, 3·3; N, 10·2. $C_{14}H_9ClN_2O_2$ requires C, 61·7; H, 3·3; N, 10·3%). ^{1}H n.m.r. δ 6·00, s, OCH_2O; 6·71–6·92, complex, and 7·40–7·60, complex, H6,8,2′,5′,6′; 7·71, s, H3; 8·01, d, $J_{5,6}$ 7 Hz, H5.

8-Chloro-2-phenylimidazo[1,2-a]pyridine (10) (39%), m.p. 98–100° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from light petroleum (Found, for a sample dried at 60°/1 mmHg for 6 h: C, 68·0; H, 3·9; N, 12·0. $C_{13}H_9ClN_2$ requires C, 68·3; H, 4·0; N, 12·3%). ^{1}H n.m.r. δ 6·71, t, *J* 7 Hz, H6; 7·20–7·45, complex, and 7·94–8·11, complex, H5,7, Ph; 7·91, s, H3.

8-Chloro-2-(4′-tolyl)imidazo[1,2-a]pyridine (11) (81%), m.p. 136–137° (from light petroleum) (Found: C, 69·5; H, 4·6; N, 11·5. $C_{14}H_{11}ClN_2$ requires C, 69·3; H, 4·6; N, 11·5%). ^{1}H n.m.r. δ 2·37, s, Me; 6·65, t, *J* 7 Hz, H6; 7·14–7·25, complex, and 7·83–7·92, complex, H7(5),2′,3′,5′,6′; 7·82, s, H3; 7·99, dd, *J* 7,1 Hz, H5(7).

3-Methoxy-2-nitropyridine[12]

A mixture of 2-nitropyridin-3-ol (0·56 g), dimethyl sulfate (0·9 ml, 1·14 g) and potassium carbonate (0·56 g) in acetone (40·0 ml) was refluxed for 2 h. The mixture was then diluted with water and the product was extracted into chloroform and gave an oil which slowly

[12] Ignatenko, A. G., and Yutilov, Yu. M., U.S.S.R. 598,891, from *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki*, 1978, **55** (11), 75 (*Chem. Abstr.*, 1978, **89**, 43127b).

crystallized. It was recrystallized from light petroleum to give the *title compound* (0·38 g, 61%), m.p. 72–73°(Found, for a sample dried at 30°/1 mmHg for 6 h: C, 46·3; H, 3·5; N, 17·6. $C_6H_6N_2O_3$ requires C, 46·8; H, 3·9; N, 18·2%). ^{1}H n.m.r. δ 3·98, s, MeO; 7·51, s, 7·55, s, H 4,6; 8·09, t, J 2·5 Hz, H 5.

8-Methoxy-2-phenylimidazo[1,2-a]pyridine (15) and Related Compounds

A mixture of 3-methoxy-2-nitropyridine (0·15 g) in methanol (10·0 ml) with palladium/charcoal (10%) was shaken with hydrogen until uptake ceased. The catalyst was filtered off and the solvent evaporated to leave an oil (0·11 g) (^{1}H n.m.r. δ 3·85, s, MeO; 6·92, m, H 4,5,6; 8·31, br s, NH_2).

This oil (0·11 g) and α-bromoacetophenone (0·18 g) in ethanol (10·0 ml) were refluxed for 3 h, sodium hydrogen carbonate (0·076 g) was added, and the mixture was refluxed for 3 h. It was then diluted with water and the product was extracted into chloroform, and the oil so obtained was subjected to t.l.c. (alumina; chloroform/light petroleum, 3:1). The product (0·12 g, 55%) recrystallized from light petroleum and gave the *title compound*, m.p. 106–108° (Found: for a sample dried at 50°/1 mmHg for 6 h: C, 74·9; H, 5·8; N, 12·4. $C_{14}H_{12}N_2O$ requires C, 75·0; H, 5·4; N, 12·5%). ^{1}H n.m.r. δ 4·01, s, MeO; 6·41, br d, $J_{6,7}$ 7 Hz, H 7; 6·64, t, J 7 Hz, H 6; 7·32–7·60, complex, and 7·67–7·76, complex, and 7·94–8·06, complex, H 5, Ph; 7·80, s, H 3.

8-Methoxy-2-(4′-tolyl)imidazo[1,2-a]pyridine (16) (68%) m.p. 141–142° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from light petroleum (Found: C, 75·2; H, 5·8; N, 11·4. $C_{15}H_{14}N_2O$ requires C, 75·6; H, 5·9; N, 11·8%). ^{1}H n.m.r. δ 2·37, s, Me; 4·02, s, MeO; 6·42, br d, $J_{6,7}$ 7 Hz, H 7; 6·65, t, J 7 Hz, H 6; 7·16–7·69, complex, and 7·84–7·94, complex, H 5,2′,3′,5′,6′; 7·78, s, H 3.

8-Methoxy-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (17) (43%) m.p. 168–169° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from a mixture of acetone and cyclohexane (Found: C, 67·2; H, 4·8; N, 10·4. $C_{15}H_{12}N_2O_3$ requires C, 67·2; H, 4·5; N, 10·4%). ^{1}H n.m.r. δ 4·03, s, MeO; 5·98, s, OCH_2O; 6·43, br d, $J_{6,7}$ 7 Hz, H 7; 6·66, t, J 7 Hz, H 6; 6·80–7·68, complex, and 7·72–7·77, complex, H 5,2′,5′,6′; 7·71, s, H 3.

3-Benzamidomethyl-7-chloro-2-phenylimidazo[1,2-a]pyridine (21)

A mixture of *N*-hydroxymethylbenzamide[7] (0·11 g), glacial acetic acid (5·0 ml) and 18 M sulfuric acid (0·18 ml) was heated in an oil bath at 50° for 15 min, then 7-chloro-2-phenylimidazo[1,2-*a*]pyridine was added and the mixture was refluxed at 120° for 24 h. The acetic acid was removed under vacuum and the residue was diluted with water (20 ml) and adjusted with aqueous ammonia to pH 10. The product was extracted into chloroform, and after washing with water the extract was dried (Na_2SO_4) and solvent removed to give an oil. This was subjected to t.l.c. (alumina; chloroform/light petroleum, 3:1) and gave the *title compound* (52%), as white crystals, m.p. 226–227° (from toluene) (Found: C, 70·0; H, 4·4; N, 11·5. $C_{21}H_{16}ClN_3O$ requires C, 69·7; H, 4·5; N, 11·6%). ^{1}H n.m.r. δ 5·05, d, J 5·5 Hz, CH_2N; 6·74, dd, J 7, 2 Hz, H 6(5); 7·27–7·91, complex, H 8, 2×Ph, 8·18, br d, J 7 Hz, H 5(6).

The following compounds were prepared by similar procedures.

3-Benzamidomethyl-6-chloro-2-phenylimidazo[1,2-a]pyridine (18) (55%), m.p. 237–238° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from toluene (Found: C, 69·9; H, 4·8; N, 11·8. $C_{21}H_{16}ClN_3O$ requires C, 69·7; H, 4·5; N, 11·6%). ^{1}H n.m.r. δ 5·09, d, J 5·5 Hz, CH_2N; 6·75, br, NH; 7·15, d; $J_{7,8}$ 9 Hz, $J_{5,7}$ 2 Hz, H 7; 7·33–7·90, complex, H 8, 2×Ph; 8·36, br s, H 5.

3-Benzamidomethyl-6-chloro-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (20) (21%), m.p. 227–228° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from toluene (Found: C, 65·1; H, 3·9; N, 10·3. $C_{22}H_{16}ClN_3O_3$ requires C, 65·1; H, 4·0; N, 10·4%). ^{1}H n.m.r. δ 5·04, d, J 5·5 Hz, CH_2N; 5·98, s, OCH_2O; 6·74–7·97, complex, H 7,8,2′,5′,6′, Ph; 8·34, br s, H 5.

3-Benzamidomethyl-7-chloro-2-(4′-tolyl)imidazo[1,2-a]pyridine (22) (43%), m.p. 245–246° after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from toluene (Found: C, 70·4; H, 5·1; N, 11·5. $C_{22}H_{18}ClN_3O$ requires C, 70·3; H, 4·8; N, 11·2%). ^{1}H

n.m.r. δ 2·35, s, Me; 5·06, d, J 5·5 Hz, CH_2N; 6·75, dd, J 7, 2 Hz, H6(5); 7·07–7·92, complex, H8,2′,3′,5′,6′, Ph; 8·20, br d, J 7 Hz, H5(6).

3-Benzamidomethyl-7-chloro-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (23) (75%), m.p. 260–261° after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene (Found: C, 64·6; H, 3·9; N, 10·1. $C_{22}H_{16}ClN_3O_3$ requires C, 65·1; H, 4·0; N, 10·4%). ^{1}H n.m.r. δ 5·09, d, J 5·5 Hz, CH_2N; 5·97, s, OCH_2O; 6·73–7·93, complex, H6(5),7,2′,5′,6′, Ph; 8·36, br d, J 7 Hz, H5(6).

3-Benzamidomethyl-8-chloro-2-phenylimidazo[1,2-a]pyridine (24) (50%), m.p. 226–228° after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene (Found: C, 69·9; H, 4·6; N, 11·4. $C_{21}H_{16}ClN_3O$ requires C, 69·7; H, 4·5; N, 11·6%). ^{1}H n.m.r. δ 5·09, d, J 5·5 Hz, CH_2N; 6·72, t, J 7 Hz, H6; 7·19–8·00, complex, H7(5), 2×Ph; 8·24, br d, J 7 Hz, H5(7).

3-Benzamidomethyl-8-chloro-2-(4′-tolyl)imidazo[1,2-a]pyridine (25) (30%), m.p. 259–261° after t.l.c. (alumina; chloroform/light petroleum) and recrystallization from toluene (Found: C, 70·8; H, 4·4; N, 11·5. $C_{22}H_{18}ClN_3O$ requires C, 70·3; H, 4·8; N, 11·2%). ^{1}H n.m.r. δ 2·31, s, Me; 5·09, d, J 5·5 Hz, CH_2N; 6·73, t, J 7 Hz, H6; 7·10–8·00, complex, H7(5),2′,3′,5′,6′, Ph; 8·24, br d, J 7 Hz, H5(7).

3-Benzamidomethyl-8-chloro-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (26) (32%), m.p. 248–249° after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene (Found: C, 64·9; H, 4·0; N, 10·3. $C_{22}H_{16}ClN_3O_3$ requires C, 65·1; H, 4·0; N, 10·4%). ^{1}H n.m.r. δ 5·06, d, J 5·5 Hz, CH_2N; 5·92, s, OCH_2O; 6·59–7·98, complex, H6,7(5),2′,5′,6′, Ph; 8·24, br d, J 7 Hz, H5(7).

3-Benzamidomethyl-8-methoxy-2-phenylimidazo[1,2-a]pyridine (29) (56%), m.p. 233–235° after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene (Found: C, 74·0; H, 5·4; N, 12·1. $C_{22}H_{19}N_3O_2$ requires C, 73·9; H, 5·4; N, 11·8%). ^{1}H n.m.r. δ 3·93, s, MeO; 5·07, d, J 5·5 Hz, CH_2N; 6·42, br d, J 7 Hz, H7; 6·66, t, J 7 Hz, H6; 7·23–7·95, complex, H5, 2×Ph.

3-Benzamidomethyl-8-methoxy-2-(4′-tolyl)imidazo[1,2-a]pyridine (30) (41%), m.p. 239–241° after t.l.c. (alumina; chloroform/light petroleum) and recrystallization from toluene (Found: C, 74·4; H, 6·0; N, 11·2. $C_{23}H_{21}N_3O_2$ requires C, 74·7; H, 5·7; N, 11·3%). ^{1}H n.m.r. δ 2·29, s, Me; 3·89, s, MeO; 5·01, d, J 5·5 Hz, CH_2N; 6·36, br d, J 7 Hz, H7; 6·60, t, J 7 Hz, H6; 6·98, d, J 8 Hz, H2′,6′(3′,5′); 7·37–8·01, complex, H5,3′,5′(2′,6′), Ph.

3-Benzamidomethyl-8-methoxy-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-a]pyridine (31) (13%), m.p. 251–253° after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) and recrystallization from toluene (Found: C, 68·9; H, 4·8; N, 10·4. $C_{23}H_{19}N_3O_4$ requires C, 68·8; H, 4·8; N, 10·5%). ^{1}H n.m.r. δ 3·95, s, MeO; 5·06, d, J 5·5 Hz, CH_2N; 5·94, s, OCH_2O; 6·45, br d, J 7 Hz, H7; 6·68, t, J 7 Hz, H6; 7·06–7·99, complex, H5,2′,5′,6′, Ph.

6-Chloro-3-methoxy-2-phenylimidazo[1,2-a]pyridine (32) and Related Compounds

A solution of 5-chloropyridin-2-amine (0·13 g), phenylglyoxal monohydrate (0·15 g), ethanol (10·0 ml) and 11 M hydrochloric acid (0·2 ml) was refluxed with stirring in an oil bath at 100° for 14 h. The solvent was evaporated and the residue stirred with ethereal diazomethane (from 1·03 g nitrosomethylurea) at 0° for 2 h and then at 20° overnight. The solvent and excess reagent were then evaporated and the residue subjected to t.l.c. (alumina; chloroform/light petroleum, 3 : 1). It gave the *title compound* (0·10 g, 38%) as a yellow oil (Found, for a sample dried at 40°/1 mmHg for 6 h: C, 63·7; H, 4·2; N, 10·6. $C_{14}H_{11}ClN_2O.0·05CHCl_3$ requires C, 63·8; H, 4·2; N, 10·6%). ^{1}H n.m.r. δ 3·97, s, MeO; 7·03–8·11, complex, H5,7,8, Ph. Mass spectrum *m/z* 260, 258 (M, 12, 34%), 217 (48), 215 (100), 112 (65), 84 (48).

In a similar manner the following compounds were prepared.

7-Chloro-3-methoxy-2-phenylimidazo[1,2-a]pyridine (34) (27%), as an oil, after t.l.c. (alumina; chloroform/light petroleum, 3 : 1) (Found, for a sample dried at 40°/1 mmHg for 6 h: C, 64·5; H, 4·5; N, 10·4. $C_{14}H_{11}ClN_2O.0·02CHCl_3$ requires C, 64·5; H, 4·3; N, 10·7%). ^{1}H n.m.r. δ 3·95, s, MeO; 6·75–6·94, complex, 7·31–7·54, complex, and 7·84–8·09, complex, H5,6,8, Ph. Mass spectrum *m/z* 260, 258 (M, 15, 35%), 217 (46), 215 (100), 112 (71), 76 (37).

8-Chloro-3-methoxy-2-phenylimidazo[1,2-a]pyridine (35) (50%), as an oil, after t.l.c. (alumina; chloroform/light petroleum, 1 : 1) (Found, for a sample dried at 35°/1 mmHg for 6 h: C, 64·2; H, 4·3; N, 10·3. $C_{14}H_{11}ClN_2O.0·04CHCl_3$ requires C, 64·0; H, 4·2; N, 10·6%). ^{1}H n.m.r.

δ 3·96, s, MeO; 6·73, t, J 7 Hz, H7; 7·15–8·17, complex, H5,8, Ph. Mass spectrum m/z 260, 258 (M, 15, 37%), 217 (47), 215 (100), 112 (59), 76 (32).

6-Methoxy-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-b]pyridazine (41) (28%), m.p. 193–194°, after recrystallization from toluene (Found: C, 62·8; H, 3·9; N, 15·4. $C_{14}H_{11}N_3O_3$ requires C, 62·4; H, 4·1; N, 15·6%). ^{1}H n.m.r. δ 3·99, s, MeO; 6·00, s, OCH_2O; 6·67, d, J 9·5 Hz, H7; 6·82–6·93, complex, 7·39–7·49, complex, H2′,5′,6′; 7·79, d, J 9·5 Hz, H8; 7·93, H3.

3-Benzamidomethyl-6-methoxy-2-(3′,4′-methylenedioxyphenyl)imidazo[1,2-b]pyridazine (46) (25%), m.p. 247–249°, after t.l.c. (alumina; chloroform/light petroleum, 3:1) and recrystallization from toluene (Found: C, 65·7; H, 4·5; N, 13·9. $C_{22}H_{18}N_4O_4$ requires C, 65·7; H, 4·5; N, 13·9%). ^{1}H n.m.r. δ 4·01, s, MeO; 5·17, d, J 5·5 Hz, CH_2N; 6·00, s, OCH_2O; 6·72, d, J 9·5 Hz, H7; 6·85–7·82, complex, H8,2′,5′,6′, Ph. Mass spectrum m/z 402 (M, 31%), 297 (81), 267 (100), 123 (50), 105 (35), 77 (24).

3,6-Dimethoxy-2-(4′-tolyl)imidazo[1,2-b]pyridazine (49) (57%), m.p. 98–101°, after t.l.c. (alumina; chloroform/light petroleum, 1:1) and recrystallization from cyclohexane (Found, for a sample dried at 60°/1 mmHg for 5 h: C, 66·9; H, 5·5; N, 15·4. $C_{15}H_{15}N_3O_2$ requires C, 66·9; H, 5·6; N, 15·6%). ^{1}H n.m.r. δ 2·39, s, MeC; 4·05, s, 3-OMe; 4·13, s, 6-OMe; 6·60, d, J 9·5 Hz, H7; 7·26, d, J 9 Hz, H3′,5′; 7·70, d, J 9·5 Hz, H8; 7·99, d, J 9 Hz, H2′,6′.

Biological Testing: Receptor Binding Assays

Evaluation of the compounds for their ability to displace [^{3}H]diazepam bound to rat brain membrane preparations in the presence of 100 μM γ-aminobutyric acid was carried out as described previously.[13]

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. 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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[13] Barlin, G. B., Davies, L. P., and Ngu, M. M. L., *Aust. J. Chem.*, 1988, **41**, 1149.