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Iminodiacetic Acid Derivatives of Benzimidazole. Synthesis of *N*-(Benzimidazol-2-ylmethyl)iminodiacetic Acids

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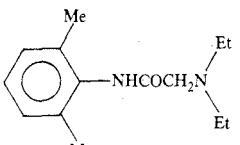
Abstract

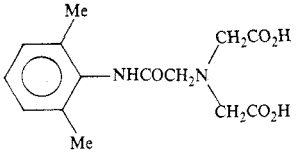
Ten new *N*-(2-benzimidazolylmethyl)iminodiacetic acids (BIMIDA)* have been synthesized from the corresponding *o*-phenylenediamines via intermediate 2-chloromethyl and 2-aminomethyl benzimidazoles as ligands for ^{99m}Tc. Anomalies associated with the synthesis of the iodo-substituted compound are described.

Introduction

Derivatives of iminodiacetic acid (IDA) have been widely used as ligands for ^{99m}Tc in hepatobiliary radiopharmaceuticals in recent years.[1,2] In their search for a heart imaging agent, Loberg and his coworkers[3,4] synthesized an analogue of lidocaine (1) in which the diethylamino group had been replaced by iminodiacetic acid to give HIDA (2) (hepatobiliary iminodiacetic acid, one of a series of derivatives of the parent compound). Lidocaine is an anti-arrhythmic drug that localizes in the viable myocardium, and HIDA was designed as a ligand for transporting ^{99m}Tc to the heart. The IDA group was chosen as the chelating function because it has a number of desirable features: it is relatively small, being roughly isosteric with diethylamine, and so



(1)



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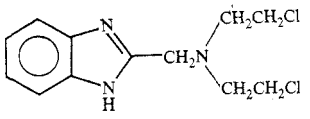

(3)

* Although Chemical Abstracts nomenclature is used in this paper, the new compounds are more commonly referred to as derivatives of iminodiacetic acid (IDA) and are denoted by acronyms derived therefrom.

[1] Fonseca, C., Rosenthall, L., Greenberg, D., Hernandez, M., and Arzoumanian, A., *Clin. Nucl. Med.*, 1979, **4**, 135.
[2] Wistow, B. W., Subramanian, G., and Grossman, G. M., *Radiology*, 1978, **128**, 793.
[3] Loberg, M. D., Cooper, M., Harvey, E., Callery, P., and Faith, W., *J. Nucl. Med.*, 1976, **17**, 633.
[4] Callery, P. S., Faith, W. T., Loberg, M. D., Fields, A. T., Harvey, E. B., and Cooper, M. D., *J. Med. Chem.*, 1976, **19**, 962.

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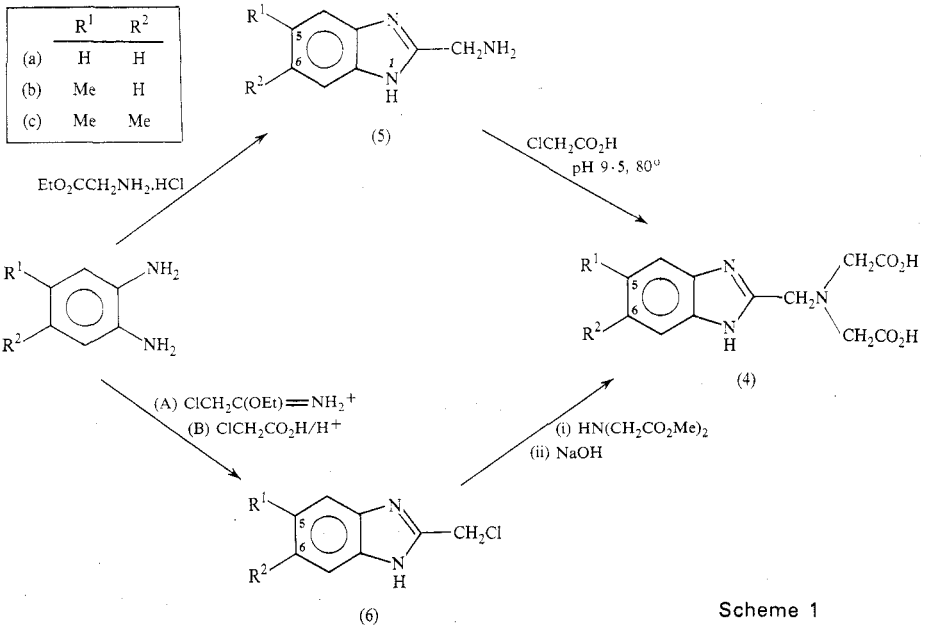
involved minimal departure in molecular size from lidocaine; it forms stable complexes with most metals; and it can be synthetically incorporated into organic molecules with relative ease.

The ^{99m}Tc-complex of HIDA, contrary to expectation, did not localize in the myocardium. After intravenous injection into mice it was rapidly excreted through the hepatobiliary route.[3] Subsequently, a number of derivatives of HIDA were synthesized and evaluated as hepatobiliary agents by several groups[5–7] with the result that 2,6-dimethyl-HIDA has since become the most widely used ligand for hepatobiliary scintigraphy.



Scheme 1

Adopting a similar approach, we attached the IDA moiety to a number of benzimidazoles as part of our search for ligands capable of complexing with ^{99m}Tc to give tumour-labelling radiopharmaceuticals. The benzimidazole nitrogen mustard (3),[8] known since 1957, has pronounced activity against several mouse tumours.[9] We therefore considered that substitution of IDA for the mustard group to give *N*-(2-benzimidazolylmethyl)iminodiacetic acid (4; $R^1 = R^2 = H$; BIMIDA) (Scheme 1) might provide the type of ligand likely to localize in a tumour as its ^{99m}Tc complex. When the compounds (4; $R^1 = R^2 = H$), and (4; $R^1 = R^2 = Me$) had been synthesized and the biological distribution of their ^{99m}Tc complexes in rats had been studied, it became obvious that we had discovered a series of ligands of considerable

[5] Subramanian, G., McAfee, J. G., Henderson, R. W., Rosenstreich, M., and Krokenberger, L., *J. Nucl. Med.*, 1977, **18**, 624.
[6] Wyk, A. J., van, Fourie, P. J., Zyl, W. H., van, Lötter, M. G., and Minnaar, P. C., *Eur. J. Nucl. Med.*, 1979, **4**, 445.
[7] Molter, M., and Kloss, G., Proc. 3rd Int. Symp. Radiopharm. Chem. St. Louis, U.S.A., 1980, p. 56.
[8] Hirschberg, E., Gellhorn, A., and Gump, W. S., *Cancer Res.*, 1957, **17**, 904.
[9] Hirschberg, E., Gellhorn, A., and Gump, W. S., *Ann. N.Y. Acad. Sci.*, 1958, **68**, 888.

potential as technetium hepatobiliary radiopharmaceuticals. The activity of the ^{99m}Tc complexes of several ligands of the series has been reported.[10,11] This paper describes the synthesis of these ligands and other members of the series.

Discussion

The BIMIDA compounds were accessible by either carboxymethylation of 2-aminomethylbenzimidazoles or alkylation of iminodiacetic acid with 2-chloromethylbenzimidazoles.

Table 1. 2-Chloromethylbenzimidazole (6) and hydrochlorides
Melting points printed in *italics* indicate decomposition

Substitution	Method	Recryst. Solvent	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	*m/z* (%)[A]
None	I	dioxan/hexane	65	161–163	160–161[B]	166 (M, 30)
5(6)-Methyl	I	toluene/hexane	98	127–131	121–123[C]	180 (M, 33)
5,6-Dimethyl	I	MeOH/H_2O	87	*160–168*	*165–168*[D]	194 (M, 28)
5(6)-Butyl	I	CH_2Cl_2/c-C_6H_{12}	43	90–94		222 (M, 22)
5(6)-Chloro		C_6H_6/hexane		132–134	*143–144*[D]	200 (M, 28)
5(6)-Chloro.HCl	II	EtOH/ether	65	*203–208*	*211–213*[D]	
5,6-Dichloro		EtOAc/hexane		172–175	186–187[E]	234 (M, 29)
5,6-Dichloro.HCl	II	EtOH/EtOAc	54	> 300	~ *280*[D]	
5(6)-Bromo		toluene/hexane		125–127		246 (M, 26)
5(6)-Bromo.HCl	II	MeOH/EtOAc	54	*240–242*		
5(6)-Iodo		toluene/hexane		125–128		292 (M, 98)
5(6)-Iodo.HCl		MeOH/EtOAc		*240–245*		
5(6)-Nitro	II	EtOH/H_2O	48	167–169	169–170[F]	211 (M, 100)
1-Methyl		c-C_6H_{12}		95–96	96[G]	180 (M, 28)
1-Methyl.HCl		EtOH/c-C_6H_{12}		*202–204*		
1-Benzyl	II	ligroin	68	105–107	97[H]	256 (M, 30)
1-Phenethyl	II	ligroin	75	95–96		270 (M, 40)

[A] M refers to the higher or highest peak of the halogen cluster.
[B] Mamalis, P., Petrow, V., and Sturgeon, B., *J. Chem. Soc.*, 1950, 1600.
[C] Tatsuoka, S., and Hitomi, H., *J. Pharm. Soc., Japan*, 1951, **71**, 871.
[D] Lettré, H., Fritsch, W., and Parath, J., *Chem. Ber.*, 1951, **84**, 719.
[E] Knobloch, W., *Chem. Ber.*, 1958, **91**, 2557.
[F] Ozegowski, W., Krebs, D., and Wunderwald, M., *J. Prakt. Chem.*, 1963, **20**, 166.
[G] Matrick, H., and Day, A. R., *J. Org. Chem.*, 1961, **26**, 1646.
[H] Jerchel, D., Fischer, H., and Kracht, M., *Justus Liebigs Ann. Chem.*, 1952, **575**, 162.

Methods of preparing 2-aminomethylbenzimidazoles were investigated first. The parent compound (5a) had already been obtained in 58% yield by fusing glycine ester hydrochloride with *o*-phenylenediamine in an atmosphere of nitrogen.[12] This reaction, however, proved unsatisfactory with 4-methyl- and 4,5-dimethyl-*o*-phenylenediamines, as the products were always contaminated with starting diamine hydrochloride which was difficult to remove. With halogen- and nitro-substituted *o*-phenylenediamines highly coloured, intractable products resulted. By employing the method

[10] Hunt, F. C., Maddalena, D. J., and Wilson, J. G., Proc. 2nd Int. Symp. Radiopharm., Seattle, U.S.A., 1979, p. 587.
[11] Hunt, F. C., Maddalena, D. J., and Wilson, J. G., Proc. 3rd Int. Symp. Radiopharm. Chem., St. Louis, U.S.A., 1980, p. 191.
[12] Lane, E. S., *J. Chem. Soc.*, 1957, 3313.

of Cescon and Day,[13] who used 5·5 N hydrochloric acid, and extending the reflux time to over 70 hours, the simple alkyl aminomethylbenzimidazoles (5a,b,c) were obtained in satisfactory yields, although in the case of the dimethyl compound (5c) unchanged diamine was still present to a significant extent. The low yield and difficulty in removing coloured impurities from the product obtained from the chloro compound led to the abandonment of this approach.

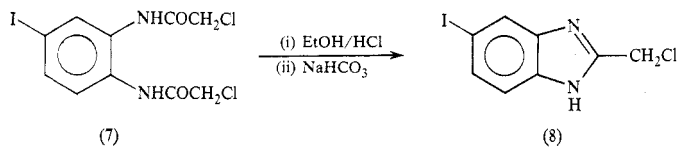
Table 2. Analyses of new compounds listed in Table 1

Sub-stitution	Molecular formula	Found (%)			Required (%)		
		C	H	N	C	H	N
5(6)-Methyl	$C_9H_9ClN_2$	59·5	5·1	15·6	59·8	5·0	15·5
5,6-Dimethyl	$C_{10}H_{11}ClN_2$	61·5	5·7	14·4	61·7	5·7	14·4
5(6)-Butyl	$C_{12}H_{15}ClN_2$	64·7	7·0	12·6	64·7	6·7	12·6
5(6)-Chloro	$C_8H_6Cl_2N_2$	48·0	3·0	13·8	47·8	3·0	13·9
5(6)-Chloro.HCl	$C_8H_6Cl_2N_2.HCl$	40·5	3·0	11·8	40·5	3·2	11·9
5,6-Dichloro	$C_8H_5Cl_3N_2$	40·7	2·2	12·1	40·8	2·1	11·9
5,6-Dichloro.HCl	$C_8H_5Cl_3N_2.HCl$	35·6	2·4	10·6	35·3	2·2	10·3
5(6)-Bromo	$C_8H_6BrClN_2$	39·1	2·5	11·5	39·1	2·4	11·4
5(6)-Bromo.HCl	$C_8H_6BrClN_2.HCl.0·5H_2O$	33·1	2·4	9·8	33·0	2·7	9·6
5(6)-Iodo	$C_8H_6ClIN_2$	33·0	2·1	9·4	32·8	2·1	9·6
5(6)-Iodo.HCl	$C_8H_6ClIN_2.HCl$	29·5	2·4	8·7	29·2	2·1	8·5
1-Methyl.HCl	$C_9H_9ClN_2.HCl.0·125H_2O$	49·3	4·6	12·6	49·3	4·7	12·7
1-Benzyl	$C_{15}H_{13}ClN_2$	70·0	5·2	10·7	70·2	5·1	10·9
1-Phenethyl	$C_{16}H_{15}ClN_2$	70·8	5·8	10·3	71·0	5·6	10·4

The 2-chloromethylbenzimidazole intermediates (Tables 1 and 2) for the second route to the BIMIDA compounds were obtained by either the method of King and Acheson,[14] (method I in the Table) in which the diamine reacts with chloroacetimino ethyl ether hydrochloride in absolute ethanol, or the classical Phillips reaction (method II).[15] The first method was preferred for the preparation of the alkylbenzimidazoles; with halogen substituted *o*-phenylenediamines, however, less pure products were obtained in lower yields. The Phillips reaction,[15] in which chloroacetic acid and the appropriate *o*-phenylenediamine reacted in refluxing 4 N hydrochloric acid, permitted isolation of the 2-chloromethylbenzimidazoles (Tables 1 and 2) in most cases as their hydrochlorides which could be purified by recrystallization. Conversion into the free bases, which were obtained as pale cream to off-white crystalline solids, was effected by addition of sodium bicarbonate to an aqueous solution or suspension of the hydrochlorides at or below 15°. Except in the case of the *N*-alkyl derivatives recrystallization was usually attended by considerable losses. The free bases are very reactive and tend to undergo self-quaternization. Nevertheless, even in their crude state they were used successfully in the reaction with IDA dimethyl ester to give the BIMIDA compounds.

In the case of 4-iodo-*o*-phenylenediamine, the Phillips reaction with chloroacetic acid failed. Decomposition occurred a few minutes after reaction had begun and iodine was observed to collect in the condenser. It was recently reported that attempts to obtain benzimidazoles from this diamine in the Phillips reaction, though successful

[13] Cescon, L. A., and Day, A. R., *J. Org. Chem.*, 1962, **27**, 581.
[14] King, F. E., and Acheson, R. M., *J. Chem. Soc.*, 1949, 1396.
[15] Phillips, M. A., *J. Chem. Soc.*, 1928, 2393.



(7) (8) Scheme 2

Table 3. *N*-(Benzimidazol-2-ylmethyl)iminodiacetic acids (4)

All compounds listed melt with decomposition

Substitution	Method	Yield (%)	M.p. (°C)	ν(C=O) (KBr) (cm^{-1})	*m/z* (%)[C]
None	I	65	213–215[A]	1745	245 (M−18, 31)
	II	53			
5(6)-Methyl	I		196–198	1723	259 (M−18, 55)
	II	44			
5,6-Dimethyl	I	50	209–210	1720	273 (M−18, 50)
	II	41			
5(6)-n-Butyl	II	72	184–186	1720	301 (M−18, 40)
5(6)-Chloro	II	60	193–195	1720	279 (M−18, 19)
5,6-Dichloro	II	15	203–205	1724	323 (M−18, 10)
5(6)-Bromo	II	63	200–202	1720	313 (M−18, 12)
5(6)-Iodo	II	40	204–205	1722	371 (M−18, 73)
5(6)-Nitro	II	58	196–198	1720	290 (M−18, 1)
1-Methyl	II	54	206–208[B]	1718	[D]
1-Benzyl	II	46	199–201	1729	[D]
1-Phenethyl	II	56	163–165	1726	[D]

[A] Irving, H., and Weber, O., *J. Chem. Soc.*, 1959, 2296; m.p. 212°.

[B] Ref.[A]; m.p. 186–188°.

[C] When the compound has chlorine or bromine, M refers to the higher or highest peak of the halogen cluster.

[D] No peaks corresponding to M or M−18. The first significant peak in the spectrum corresponds to the loss of the iminodiacetic acid group from the molecular ion.

Table 4. Analyses for compounds in Table 3

Sub-stitution	Molecular formula	Found (%)			Required (%)		
		C	H	N	C	H	N
None	$C_{12}H_{13}N_3O_4.0{\cdot}25H_2O$	53·7	5·3	15·6	53·9	5·1	15·7
5(6)-Methyl	$C_{13}H_{15}N_3O_4$	55·9	5·6	15·1	56·3	5·4	15·2
5,6-Dimethyl	$C_{14}H_{17}N_3O_4$	57·7	5·9	14·2	57·7	5·8	14·4
5(6)-Butyl	$C_{16}H_{21}N_3O_4$	60·2	6·6	13·1	60·1	6·6	13·2
5(6)-Chloro	$C_{12}H_{12}ClN_3O_4.0{\cdot}5H_2O$	47·5	4·0	14·1	47·7	4·1	13·9
5,6-Dichloro	$C_{12}H_{11}Cl_2N_3O_4$	43·3	3·2	12·6	43·4	3·3	12·7
5(6)-Bromo	$C_{12}H_{12}BrN_3O_4$	42·4	3·8	12·7	42·1	3·5	12·3
5(6)-Iodo	$C_{12}H_{12}IN_3O_4$	37·2	3·2	10·9	37·0	3·1	10·8
5(6)-Nitro	$C_{12}H_{12}N_4O_6$	46·8	4·1	18·1	46·8	3·9	18·2
1-Methyl	$C_{13}H_{15}N_3O_4$	56·6	5·3	15·2	56·3	5·4	15·2
1-Benzyl	$C_{19}H_{19}N_3O_4$	64·5	5·3	11·7	64·6	5·4	11·9
1-Phenethyl	$C_{20}H_{21}N_3O_4$	65·6	5·8	11·2	65·3	5·7	11·4

with formic acid, failed with acetic and isobutyric acids, the use of these two acids leading to decomposition of the iodo derivatives.[16] No mention was made of the formation of elemental iodine. As an alternative approach to 2-chloromethyl-5-iodobenzimidazole (8) the cyclization of the *N,N'*-bischloroacetyl derivative of 4-iodo-*o*-phenylene diamine (7) was examined (Scheme 2). This derivative of 4-nitro-*o*-phenylenediamine was already known to cyclize to the chloromethyl compound in boiling 3 N hydrochloric acid.[17] By using this procedure, therefore, but maintaining the temperature at 70–75° for 2 h, a modest yield of 5(6)-iodo-2-chloromethylbenzimidazole was obtained. The quality of the product was noticeably improved when cyclization was carried out in 20% ethanolic hydrogen chloride at reflux temperature for 30 min. In this way the hydrochloride was obtained in 90% yield.

The *N*-(benzimidazol-2-ylmethyl)iminodiacetic acids (4) listed in Tables 3 and 4 were obtained by direct carboxymethylation of the 2-aminomethylbenzimidazoles (5) by means of an appropriate modification of the established methods[18] or by alkylation of the dimethyl ester of iminodiacetic acid with the 2-chloromethylbenzimidazoles (6) followed by alkaline hydrolysis of the resulting tertiary iminoesters to the amino acids.[19] Although in the second method the choice of toluene or ethyl acetate for the reaction solvent usually had little effect on the yield of product, a better separation of solvent and concentrated aqueous potassium carbonate solution in the conversion of IDA methyl ester hydrochloride was achieved with ethyl acetate. The intermediate benzimidazole IDA esters were not isolated but directly hydrolysed to the amino acids.

Experimental

^{1}H n.m.r. spectra were recorded in $CDCl_3$ on a Varian XL100 spectrometer with Me_4Si as an internal standard by Dr W. Bubb, School of Chemistry, Sydney University. Mass spectra were run on an AEI MS902 spectrometer by the Mass Spectrometry Unit in the same School. Infrared spectra were recorded on a Perkin–Elmer 237 instrument as KBr discs. Elemental analyses were performed by the Australian Microanalytical Service, Melbourne.

Commercially available *o*-phenylenediamines were purchased and used without further treatment. Other starting materials were prepared according to procedures described in the literature: *N*-butyl-*o*-phenylenediamine,[20] *N*-benzyl-*o*-phenylenediamine,[21,22] *N*-phenethyl-*o*-phenylenediamine,[21,23] (1-methylbenzimidazol-2-yl)methanol[24] and 2-chloromethyl-1-methylbenzimidazole.[25]

o-Phenylenediamines

4-Bromo-1,2-phenylenediamine

(i) *Bromination of* o-*nitroaniline*.—It was essential to use less than 1 equiv. of bromine in order to prevent the formation of dibromination products which were difficult to remove from the monobromo compound.[25] Bromine (30·4 g, 0·19 mol) in glacial acetic acid (80 ml) was added dropwise

[16] Kazimierczuk, Z., Dudycz, L., Stolarski, R., and Shugar, D., *J. Carbohydr., Nucleosides, Nucleotides*, 1981, **8**, 101.
[17] Ozegowski, W., Krebs, D., and Wunderwald, M., *J. Prakt. Chem.*, 1963, **20**, 166.
[18] Yashunsky, V. G., and Samoilova, O. I., *Russ. Chem. Rev.*, 1976, **45**, 777; *Usp. Khim.*, 1976, **45**, 1537.
[19] Shtacher, G., and Taub, W., *J. Med. Chem.*, 1966, **9**, 197.
[20] Clark, R. L., and Pessolano, A. A., U.S. Pat. 2,933,503 (*Chem. Abstr.*, 1960, **54**, 19716^i).
[21] Ashton, B. W., and Suschitsky, H., *J. Chem. Soc.*, 1957, 4559.
[22] Schering, A.-G., Br. Pat. 703,272 (1954) (*Chem. Abstr.*, 1955, **49**, 1816^e).
[23] Matrick, H., and Day, A. R., *J. Org. Chem.*, 1961, **26**, 1646.
[24] Mamalis, P., Petrow, V., and Sturgeon, B., *J. Chem. Soc.*, 1950, 1600.
[25] Hughes, G. K., and Lions, F., *Proc. R. Soc. New South Wales*, 1938, **17**, 209.

over 45 min to a stirred solution of *o*-nitroaniline (27·6 g, 0·20 mol) in the same solvent (80 ml) containing anhydrous sodium acetate (16·5 g, 0·20 mol). Stirring was continued for 1·5 h, water (180 ml) was added and the mixture was stirred for another hour. The product was washed well with water and on recrystallization from ethanol (130 ml) and water (30 ml) was obtained as small cinnamon needles (33·0 g, 76%), m.p. 107–108° (lit.[26] 109°). ^{1}H n.m.r. (δ) 6·74, d, J_{ortho} 9 Hz, H 6; 7·41, q, J_{meta} 2 Hz, J_{ortho} 9 Hz, H 5; 8·26, d, J_{meta} 2 Hz, H 3.

(ii) *Reduction to the* o-*phenylenediamine.*—4 Bromo-2-nitroaniline (21·7 g, 0·1 mol) was added in aliquots over 1 h to a stirred solution of stannous chloride (84·8 g, 0·375 mol) in conc. hydrochloric acid (160 ml), the temperature being maintained at 65–70°. Stirring was continued at this temperature for a further hour; then the solution was cooled at 0° for 16 h to allow crystallization of the tin complex. A vigorously stirred solution of the complex in water (100 ml) was basified to pH 12 with sodium hydroxide (*c.* 25 g) added as a 50% aqueous solution, the temperature being maintained at 10–20°. The diamine was washed free of alkali and dried in a vacuum to give 17·9 g (96%), m.p. 60–62°. Recrystallization of a sample from cyclohexane afforded flat, pinkish needles, m.p. 64° (lit.[27] 63°).

*4-Iodo-*o*-phenylenediamine*

(i) *Iodination of* o-*nitroaniline.*—To a stirred solution of *o*-nitroaniline (13·8 g, 0·1 mol) in glacial acetic acid (50 ml) containing anhydrous sodium acetate (9·3 g, 1·125 mol), iodine monochloride (18·3 g, 1·125 mol) in acetic acid (30 ml) was added over 30 min. The reaction mixture was heated on the water bath for 30 min, stirred for another 30 min at room temperature, then diluted slowly with water (100 ml) which caused the separation of the red-brown crystalline product. Stirring was continued for 1 h and after 16 h the product was washed free of acetic acid and dried in air (24·8 g), m.p. 119–121°. On crystallization from ethanol (120 ml) and water (25 ml), 4-iodo-2-nitroaniline was obtained as cinnamon microcrystals (21·3 g, 81%), m.p. 121–122° (lit.[28] 123°). ^{1}H n.m.r.: δ 6·64, d, J_{ortho} 9 Hz, H 6; 7·57, q, J_{meta} 2 Hz, J_{ortho} 9 Hz, H 5; 8·43, d, J_{meta} 2 Hz, H 3.

(ii) *Reduction to the* o-*phenylenediamine.*—To a stirred solution of stannous chloride (78·0 g, 0·346 mol) in conc. hydrochloric acid (160 ml) was added 4-iodo-2-nitroaniline (25·4 g, 0·092 mol) over 40 min, the temperature being held at 65–70°. After an additional hour at this temperature the reaction mixture was cooled at 0–5° for 16 h to allow the tin complex to crystallize. The complex dissolved in water (150 ml) was treated with sodium hydroxide (25 ml) in water (50 ml) while being vigorously stirred and kept at or below 20°. The product was washed with water to neutral pH and dried in a vacuum; yield 16·7 g (71%), m.p. 72–75°. Recrystallization of a small amount from cyclohexane gave pinkish needles, m.p. 75–77° (lit.[29] 73°). The *diacetyl derivative* crystallized from ethanol in tightly packed felted needles, m.p. 209–211° (Found: C, 37·5; H, 3·5; N, 8·9. $C_{10}H_{11}IN_2O_2$ requires C, 37·7; H, 3·5; N, 8·8%).

2-Aminomethylbenzimidazoles

The method of Cescon and Day[13] as modified by Revankar, Siddappa and Umarani[30] was used and is illustrated by the preparation that follows.

2-Aminomethyl-5,6-dimethylbenzimidazole

4,5-Dimethyl-*o*-phenylenediamine (27·2 g, 0·2 mol) and glycine (18·75 g, 0·25 mol) in 5 N hydrochloric acid (200 ml) were heated under reflux for 70 h. A few drops of decan-1-ol was added to prevent frothing. The diamine was completely dissolved after 15 h. The filtered solution was cooled and deposited the dihydrochloride of the diamine (9·5 g). Evaporation of the filtrate with ethanol left a residue which, on being stirred with warm ethanol (*c.* 80 ml), gave the dihydrochloride of the

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product (20 g) which was collected and washed with a little cold ethanol. On standing the filtrate deposited a second fraction (6·7 g) of glycine ester hydrochloride. The filtrate was again evaporated to a residual gum which on trituration with cold ethanol gave a second fraction of the product (4·0 g). The *2-aminomethylbenzimidazole dihydrochloride* was recrystallized from ethanol (500 ml) containing concentrated hydrochloric acid (12 ml) and ether (200 ml) and obtained as small off-white felted needles (18·4 g), m.p. 265–268° (dec.) (lit.[24] 266–268°). The benzoyl derivative was obtained as hairy needles from ethanol, m.p. 233–234° (lit.[23] 235°). *2-Aminomethyl-5(6)-methylbenzimidazole dihydrochloride* was obtained in 60% yield and crystallized as very pale grey needles from ethanol/ether containing a little conc. hydrochloric acid, m.p. 253–235° (dec.) (Found: C, 46·4; H, 5·8; N, 18·1. $C_9H_{11}N_3.2HCl$ requires C, 46·2; H, 5·6; N, 18·0%). The *benzoyl derivative* formed felted needles from aqueous ethanol, m.p. 201° (Found: C, 72·7; H, 5·7; N, 15·9. $C_{16}H_{15}N_3O$ requires C, 72·5; H, 5·7; N, 15·9%).

2-Chloromethylbenzimidazoles

Method I (a modification of the method of King and Acheson[14]).—To a solution or suspension of the *o*-phenylenediamine (0·10 mol) in absolute ethanol (*c.* 50 ml) was added in several portions and with vigorous stirring a suspension of chloroacetiminoethyl ether hydrochloride (0·11 mol) in the same solvent (*c.* 50 ml). Residual hydrochloride was washed in with a little solvent. Reaction occurred immediately with the generation of considerable heat and the separation of ammonium chloride. After several hours at room temperature the mixture was diluted with water (*c.* 200 ml). The precipitated product was washed with water and dried in air. It was usually sufficiently pure for subsequent reactions. Further purification, when necessary, was achieved by chromatography on either slightly basic alumina or silica.

A sample was recrystallized for analysis from the appropriate solvent, as shown in Table 1.

Method II (a modification of the method of Phillips[15]).—The *o*-phenylenediamine (0·10 mol) and chloroacetic acid (0·15 mol) were refluxed in 5 N hydrochloric acid (70–80 ml) for 45–60 min. The filtered (charcoal) reaction mixture was cooled at 0°C for 1–3 days and the hydrochloride was collected and recrystallized. Conversion into the free base was effected by addition of sodium carbonate in small aliquots to a vigorously stirred aqueous suspension of the hydrochloride. The chloromethyl compound was usually sufficiently pure for the next reaction. Further purification, when necessary, was achieved by chromatography on slightly basic alumina (Woelm). A sample was recrystallized for analysis as indicated in Table 1.

N,N′-Bis(chloroacetyl)-4-iodo-1,2-phenylenediamine

4-Iodo-*o*-phenylenediamine (23·4 g, 0·1 mol) was dissolved in benzene (250 ml) and with vigorous agitation treated with chloroacetyl chloride (45·2 g, 0·04 mol) added in several aliquots. The reaction mixture was refluxed for 2 h (guard-tube) and as it cooled more of the crystalline solid that formed during the reflux period separated. This fraction amounted to 20·7 g, m.p. 160–163°. Removal of the solvent and excess of reagent from the filtrate and trituration of the residue with ethanol gave a second fraction of the product, (9·1 g), m.p. 160–162° (total yield: 84%). It crystallized from ethanol as minute, lustrous *plates*, m.p. 161–163° (Found: C, 30·8; H, 2·4; N, 7·4. $C_{10}H_9Cl_2IN_2O_2$ requires C, 31·0; H, 2·3; N, 7·2%).

2-Chloromethyl-5(6)-iodobenzimidazole

Hydrogen chloride gas was passed into absolute ethanol (250 ml) until 64 g had been absorbed. *N,N′*-Bis(chloroacetyl)-4-iodo-1,2-phenylenediamine (41·0 g, 0·016 mol) was then added to the ethanolic solution and dissolved when the mixture was gently heated (2–3 min). Heating at reflux temperature was continued and crystals of the hydrochloride began to separate (2–3 min) until the reaction mixture was quite thick. After further gently refluxing (25 min) with occasional shaking, the flask was chilled at 0–5° for 3 hours. The product after being dried in a vacuum was obtained as soft, off-white needles (31·7 g, 91%), m.p. 188–192° (dec.) Recrystallization from ethanol/ethyl acetate gave lilac crystals (20·5 g, 53%), m.p. 240–245°d. The free base (79%) was obtained by method I above as a cream solid which was kept in a desiccator and used within a few days. A sample recrystallized from toluene/hexane afforded 2-chloromethyl-5(6)-iodobenzimidazole as almost white rosettes, m.p. 125–128°.

N-(2-Benzimidazolylmethyl)iminodiacetic Acids

Method I: Carboxymethylation of 2-Aminomethylbenzimidazoles

A solution of chloroacetic acid (11·4 g; 0·12 mol) in water (100 ml) was neutralized with sodium carbonate (6·4 g; 0·06 mol) and added to a solution of the 2-aminomethylbenzimidazole dihydrochloride (0·04 mol) in water (25 ml) and ethanol (25 ml) neutralized with a solution of sodium hydroxide (3·2 g; 0·08 mol). The stirred reaction mixture containing some solid amine was slowly heated to 80–85° while the pH was maintained at 9·0–9·5 (pH meter electrode in the reaction mixture) by constant addition of sodium hydroxide (4·8 g; 0·17 mol) in water (*c.* 15 ml). When most of the amine had dissolved at *c.* 50–60°, the reaction began to accelerate, but slowed down perceptibly after 0·75 h. Heating and stirring were continued for 2 h when almost all the alkali had been added. The hot solution was filtered (charcoal) and after the addition of ethanol (20–30 ml) the pH was brought to 3·5 with concentrated hydrochloric acid. The iminodiacetic acid derivative readily separated as a finely crystalline solid and after several hours at 5° was collected, washed with cold water and cold ethanol, and dried in air. The product was purified by dissolving a suspension of the crude material in methanol/water (1 : 3) by addition of sufficient aqueous sodium hydroxide. The warm solution was treated with charcoal, if necessary, filtered and acidified to pH *c.* 3·0. The iminodiacetic acids were obtained as pale cream to white crystalline solids (Table 2).

Method II: Reaction of 2-Chloromethylbenzimidazoles with Iminodiacetic Dimethyl Ester

Iminodiacetic acid dimethyl ester hydrochloride (9·8 g, 0·05 mol) was converted into the free base by suspending it in ethyl acetate (30 ml) and adding a solution of potassium carbonate (4·0 g) in water (7 ml), the operation being conducted in the cold. The ethyl acetate solution was decanted and the aqueous layer extracted again with the same volume solvent. To the dried ($MgSO_4$) ethyl acetate solution the 2-chloromethylbenzimidazole (0·02 mol) was added and the mixture refluxed for 3 h. Iminodiacetic ester hydrochloride usually began to separate in 20–30 min. The hydrochloride was filtered from the well cooled mixture and washed with solvent. The filtrate was freed of solvent and the residue in 50% methanol (25 ml) was treated dropwise with sodium hydroxide (4·0 g, 0·1 mol), also in 50% methanol (25 ml), over 30 min. The solution was stirred for an additional 30 min, diluted with water (*c.* 25 ml), extracted with ether and carefully acidified with concentrated hydrochloric acid to pH *c.* 3·0. Thereafter the procedure was the same as for method I.

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