One-step Synthesis and Spectral Study of Some 1-Methylbenzimidazoles, including Use of a Lanthanide Shift Reagent

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Substituted *o*-phenylenediamines (1) or their monoacetyl derivatives react with formaldehyde in boiling ethanol containing hydrochloric acid to give moderate yields of the corresponding 1-methylbenzimidazoles in one step. 4-Nitro-*o*-phenylenediamine gives the 6-nitro-derivative (2a; R = NO_2); 4-chloro-*o*-phenylenediamine produces the 5-chlorobenzimidazole (2b; R = Cl), but a mixture of the isomers (2a) and (2b) is obtained when R is another substituent. The synthesis of several new 1-methylbenzimidazoles is described and a comparison is made of the spectra of several isomeric pairs. They are most easily distinguished by their n.m.r. spectra: it is usually necessary to use a lanthanide shift reagent in order to analyse the spectra. The latter show that tris(pivaloylmethanato)-europium(III) complexes at N-3 in the presence of various substituents on the benzene ring, *e.g.*, methyl, halogeno, cyano, nitro, ethoxycarbonyl, or amino.

THE reaction of *o*-phenylenediamine with an aldehyde gives substituted benzimidazoles;[1] the course of the reaction depends on the pH[2] and on the presence[3] or absence[4] of an oxidizing agent. Formaldehyde was first used in this reaction[5] in 1892. In acid solution, *o*-phenylenediamine (1; $R^1 = R^2 = H$) reacts with two

[1] (*a*) J. B. Wright, *Chem. Rev.*, 1951, **48**, 434; (*b*) K. Hofmann, 'Imidazole and its Derivatives,' Interscience, New York, 1953, pp. 267—273; (*c*) A. F. Pozharskii, A. D. Garnovskii, and A. M. Simonov, *Russ. Chem. Rev.*, 1966, **35**, 122.

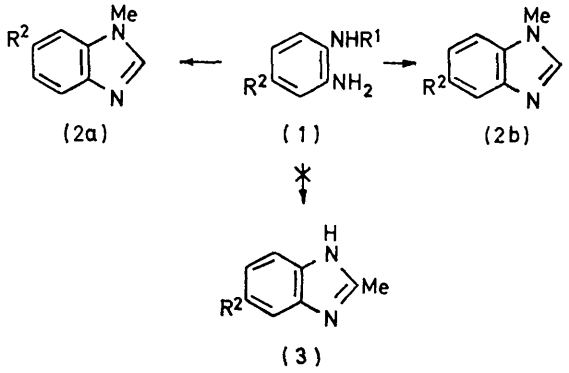
[2] O. Hinsberg and P. Koller, *Ber.*, 1896, **29**, 1497.

[3] R. Weidenhagen, *Ber.*, 1936, **69B**, 2263; F. F. Stephens and J. D. Bower, *J. Chem. Soc.*, 1949, 2971; 1950, 1722.

[4] O. Hinsberg, *Ber.*, 1887, **20**, 1585.

[5] O. Fischer and H. Wreszinski, *Ber.*, 1892, **25**, 2711.

moles of formaldehyde in boiling ethanol to give 1-methylbenzimidazole (2a; $R^2 = H$); higher aldehydes



often give [6] a mixture of 1- and 1,2-substituted benzimidazoles. The reaction with formaldehyde, in contrast with the Phillips and related reactions,[7] is unique in producing 1-methylbenzimidazole in one step from the diamine. When ring-substituted diamines are employed there are two possible structures, (2a) or (2b), for the product. Morgan and Challenor [8] described the condensation of 4-chloro-5-methyl-*o*-phenylenediamine with formaldehyde to give 5-chloro-1,6-dimethylbenzimidazole. Although the bisulphite addition products of many aldehydes react with diamines to give benzimidazoles, that of formaldehyde does not.[9]

Earlier workers [5,8] condensed the free diamine with the aldehyde but we find that the more accessible *N*-monoacetyl derivative (1; $R^1 = Ac$) behaves similarly, the formaldehyde cyclization [to give (2)] taking precedence over the possible Phillips-type condensation [7] which would yield the 2-methylbenzimidazole (3). The products obtained from the diamine–formaldehyde cyclization by this method are listed in Table 1 which shows that whereas in some condensations one isomer was produced, in others a mixture of (2a) and (2b) was formed. Moderately good yields were obtained although formaldehyde is known to give secondary products with amines.[9,10] A number of new benzene-ring substituted 1-methylbenzimidazoles were unequivocally synthesized; these and others which were required for spectroscopic comparison or biological studies are listed in Table 2. Some of these were synthesized by routes which are different from and more convenient than those previously published.

The product of the formaldehyde cyclization is either of type (2b) or a mixture of (2a) and (2b) except in the case of the nitro-diamine (1; $R^2 = NO_2$) from which only the 6-nitro-derivative (2a; $R^2 = NO_2$) was isolated. This one-step synthesis is thus more convenient than the existing multi-step method [11] which requires N^1-methyl-5-nitro-*o*-phenylenediamine as an intermediate, or alkylation [12] (5·25% yield) of 5-nitrobenzimidazole. Reduction of the nitro-group followed by diazotization provides a useful route to several otherwise rather inaccessible 6-substituted 1-methylbenzimidazoles; some of the compounds listed in Table 2 may be prepared in this way. 6-Chloro-1-methylbenzimidazole, for instance, is more easily synthesized in this way than through 5-chloro-*N*-methyl-2-nitroaniline.[13] After the completion of this work, a Russian report [14] described the conversion of 5-amino-1-methylbenzimidazole into the 6-amino-isomer which was described as an oil, b.p. 180—185° at 4 mmHg, and was characterized as the picrate, m.p. 225—227°. In the present work, reduction of 1-methyl-6-nitrobenzimidazole gave the 6-amino-compound, m.p. 160° [picrate, m.p. 251° (decomp.)]. Its structure was confirmed by n.m.r. spectroscopy (see later).

The formaldehyde cyclization also proceeds under mild conditions. Plotting the u.v. spectrum of the reaction mixture at intervals gave evidence that the reactants gradually change into products without the formation of stable intermediates. Using formaldehyde free of traces of methanol and formic acid gave identical results but in the absence of mineral acid, no reaction occurred.

Samples of 1-methylbenzimidol-5- and -6-ol were required for another study; the two isomers were synthesized in small quantities by Friedrich and Bernhauer [15] from 4- and 5-alkoxy-2-nitroaniline in a multi-stage process. The formaldehyde cyclization cannot be applied to a diaminophenol, however because of competing hydroxymethylation of the ring. Attempts were made to suppress this reaction by acylating the phenolic group of 3,4-diaminophenol and of *N*-acetyl-4-amino-3-nitrophenol. Benzoylation of the latter gave mainly *NO*-dibenzoyl-3-amino-4-nitrophenol. However, neither acetates nor benzoates of this kind gave benzimidazoles on reaction with formaldehyde. The benzimidazolols were synthesized from the appropriate amino-1-methylbenzimidazole by diazotization and hydrolysis.

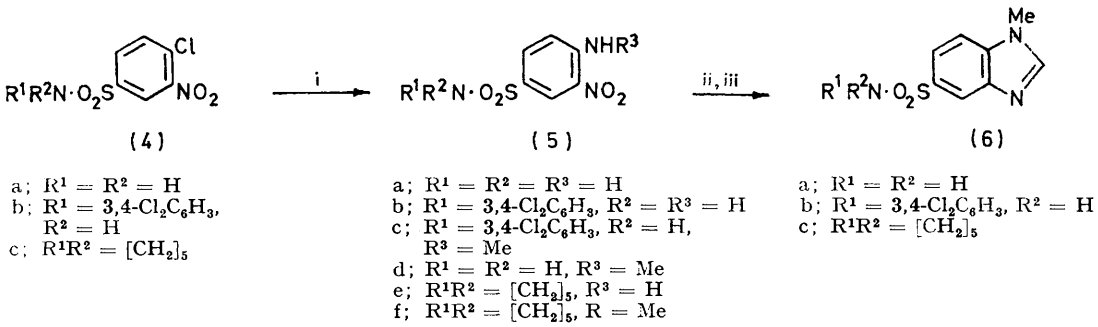
Three new sulphonamides (6) of biological interest were synthesized by the route shown in Scheme 1. The diamine from (5a) could not be cyclized with formaldehyde because of the competing *N*-hydroxymethylation on the sulphonamide but when (5b) was reduced and cyclized with formaldehyde a mixture of the benzimidazole (6b) and its 6-sulphamoyl isomer was isolated.

The availability of several pairs of 5- and 6-substituted 1-methylbenzimidazoles encouraged us to consider the

[6] Ref. 1*b*, p. 267.
[7] Ref. 1*a*, p. 406; N. V. S. Rao and C. V. Ratman, *J. Indian Chem. Soc.*, 1961, **38**, 631, and references therein.
[8] G. T. Morgan and W. A. P. Challenor, *J. Chem. Soc.*, 1921, **119**, 1537.
[9] H. F. Ridley, R. G. W. Spickett, and G. M. Timmis, *J. Heterocyclic Chem.*, 1965, **2**, 453.
[10] O. Y. Fedotova, M. A. Askarov, and I. P. Losev, *J. Gen. Chem.* (*U.S.S.R.*), 1957, **27**, 849.
[11] G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazzetta*, 1955, **85**, 769.
[12] B. Aliprandi, F. Cacace, and E. Possagno, *Ann. Chim.* (*Italy*), 1958, **48**, 1349.
[13] M. T. Davies, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, 1951, **3**, 420.
[14] V. M. Mar'yanovskii, A. F. Pozharskii, and A. M. Simonov, *Chem. Heterocyclic Compounds*, 1970, 202.
[15] W. Friedrich and K. Bernhauer, *Chem. Ber.*, 1956, **89**, 2030.

possibility of identifying each isomer spectroscopically. Examination of the u.v. spectra of several pairs * gave no characteristic features.

Most studies of the i.r. spectra of benzimidazoles [16-21] have been concerned with 1-unsubstituted compounds (except those containing the nitro-group) absorbed in the 1560—1520 cm^{-1} region where the N=C–N group is claimed [19] to absorb in 2-alkylbenzimidazoles. In our compounds, the N=C–N group [17] probably accounts for the absorption at 1500 ± 10 cm^{-1}.



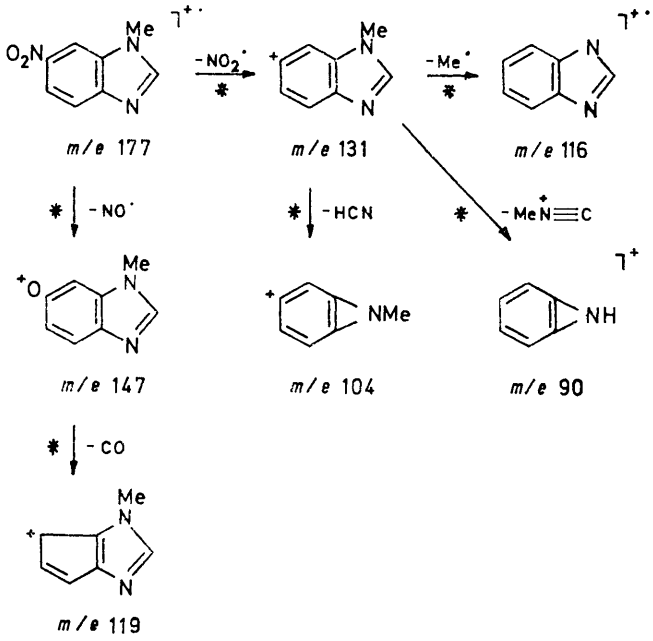
a; $R^1 = R^2 = H$
b; $R^1 = 3,4\text{-}Cl_2C_6H_3$, $R^2 = H$
c; $R^1R^2 = [CH_2]_5$

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = 3,4\text{-}Cl_2C_6H_3$, $R^2 = R^3 = H$
c; $R^1 = 3,4\text{-}Cl_2C_6H_3$, $R^2 = H$, $R^3 = Me$
d; $R^1 = R^2 = H$, $R^3 = Me$
e; $R^1R^2 = [CH_2]_5$, $R^3 = H$
f; $R^1R^2 = [CH_2]_5$, $R = Me$

a; $R^1 = R^2 = H$
b; $R^1 = 3,4\text{-}Cl_2C_6H_3$, $R^2 = H$
c; $R^1R^2 = [CH_2]_5$

SCHEME 1 Reagents: i, NH_3 or $MeNH_2$; ii, H_2–PtO_2; iii, HCO_2H

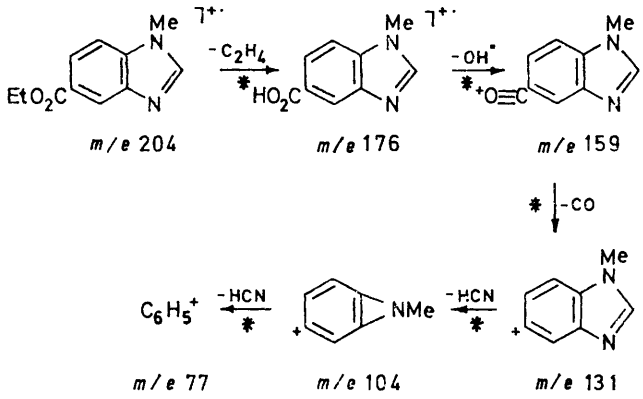
or have considered benzimidazoles containing 2-aryl or -aralkyl groups.[17,21] No useful conclusions could be drawn from comparisons of their spectra of pairs of benzimidazoles.* None of the present compounds



SCHEME 2

* Fragmentation indicated by a metastable peak at the calculated *m/e* value.

The mass spectra of isomeric benzimidazoles have not been compared although those of several members of the series have been described.[22-24] The main peaks of pairs of isomers are listed in Supplementary Publication No. SUP 20932. The difference between the spectra of the two amino-1-methylbenzimidazoles is negligible; the isomeric nitrobenzimidazoles also have very similar spectra which may be formulated as in Scheme 2. In most of the compounds studied, the considerable stability of the ring system resulted in the molecular ion being the



SCHEME 3

* Fragmentation indicated by a metastable peak at the calculated *m/e* value.

* These data are listed in Supplementary Publication No. SUP 20932 (6 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1972, Index issue (items less than 10 pp. are sent full size).

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[17] A. Jurasek, R. Kada, and T. Sticzay, *Coll. Czech. Chem. Comm.*, 1969, **34**, 572.
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[23] T. Nishiwaki, *J. Chem. Soc. (C)*, 1968, 428.
[24] S. O. Lawesson, E. Schroll, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, 1968, **24**, 1875.

most intense peak in the spectrum [22] but this was not so for the ethoxycarbonyl isomers (2a and 2b; R = CO_2Et) in which the most intense peak was due to $(M - 28 - 17)^+$ (Scheme 3). Although there were a few differences in the intensities of individual peaks from the isomeric esters, mass spectrometry is not generally useful for identifying isomers of this series.

A study of the chemical shifts of the protons in several pairs of 5- and 6-substituted 1-methylbenzimidazoles (Table 3 †) showed that the *N*-methyl and C-2 protons absorb over a comparatively small range (δ 3·63 ± 0·27 and 7·59 ± 0·58 p.p.m. respectively). The chemical shift of the easily recognized C-2 proton signal is slightly greater in the 5- than in the 6-substituted isomer. This difference is too small to be of value for identification; there is often considerable overlapping of signals in the aromatic region. However, the addition of a lanthanide shift reagent (LSR) simplifies the interpretation of the spectrum.[25] Even when substituents of different electronic character (*e.g.*, Me, Br, CO_2Et, CN, NO_2, or NH_2) were attached to the benzene ring, the LSR complexed at N-3. Therefore the C-4 proton suffers a greater paramagnetic shift than the more remote protons. As may be seen from the examples in Table 3, the minimum amount of LSR which is required to separate the signals in the aromatic region varies with the substituent and its position. From the characteristics of the lanthanide-modified spectrum, the identity of a substituted 1-methylbenzimidazole may be readily determined. The low solubility of a few benzimidazoles in deuteriochloroform prevented this useful technique from being applied, for instance, to the product formed when 3-amino-4-acetamidobenzamide was cyclized with formaldehyde. The latter also reacts with the amide function to form a $CO{\cdot}NH{\cdot}CH_2{\cdot}OH$ group.

General pharmacological screening of the benzimidazoles gave the following results after an oral dose of 100 mg kg^{-1}; 6-nitro-, 5-trifluoromethyl-, and 6-chloro-1-methylbenzimidazoles inhibited phenylquinone-induced writhing in mice but were slightly less effective than aspirin; the 5-piperidinosulphonyl- and 5-carboxy-compounds showed slight analgesic activity in the tail-clip test for analgesic action.

TABLE 1

Condensation of *o*-phenylenediamines (1) with formaldehyde

Diamine (1) R¹	R²	Reaction time (min)	Isomer formed	Yield (%)	Isolated as	M.p. (lit. m.p.) (°C)	Solvent
H	NO_2	30	(2a)	42	Base	182 (182) [a]	aq. EtOH
H	Me	30	(2a) + (2b)	49	Picrate	192—194 (decomp.) [b]	EtOH
Ac	CO_2H	30	(2b)	56	Base	312 (308—310) [c]	H_2O
Ac	Cl	30	(2b)	49	Picrate	241—243 (242—243) [d]	$MeCO_2Et$–MeOH
					HCl	260—261 (261) [d]	EtOH
H	Cl	30	(2b)	43	Picrate	240—241 (242—243) [d]	$MeCO_2Et$–MeOH
					HCl	260—261 (261) [d]	EtOH
Ac	Br	90	(2a) + (2b)	59	Picrate	226—230 [e]	EtOH
Ac	$CONH_2$	20	*f*	47	Base	297—298	DMF–H_2O
H	CF_3	30	(2a) + (2b)	48	Base	58—60 [g]	aq. EtOH
H	$3,4\text{-}Cl_2C_6H_3NHSO_2$	30	(2a) + (2b)	48	Base	95 (decomp.) [h]	DMF–H_2O

[a] Ref. 11. [b] 1,5-Dimethylbenzimidazole picrate, m.p. 244—245°; 1,6-isomer picrate, m.p. 250—252° (ref. 12). [c] Ref. 26. [d] Ref. 13. [e] 5-Bromo-1-methylbenzimidazole picrate, m.p. 264° (decomp.) (ref. 27); 6-bromo-isomer picrate, see Table 2. [f] Product is 5- or 6-(N-*hydroxymethylcarbamoyl*)-1-*methylbenzimidazole* (Found: C, 58·3; H, 5·4; N, 20·5. $C_{10}H_{11}N_3O_2$ requires C, 58·5; H, 5·4; N, 20·5%). [g] G.l.c. showed the presence of two isomers in the ratio of 2 : 3. Comparison with 1-methyl-5-trifluoromethylbenzimidazole (Table 2) showed that the 6-isomer predominated. [h] T.l.c. of product showed presence of two isomers (*cf.* Table 2).

† Table 3 shows the n.m.r. data for two 1-methylbenzimidazoles; the data for the others are listed in Supplementary Publication No. SUP 20932 (6 pp.).

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. U.v. spectra were determined in ethanol solutions with Unicam SP 700A and SP 800 spectrophotometers. I.r. data were obtained for potassium bromide discs with Perkin-Elmer model 521 and 237 spectrophotometers. N.m.r. spectra (in deuteriochloroform) were determined with a Perkin-Elmer R10 (60 MHz) instrument (tetramethylsilane as internal reference).

Intermediates required for the Cyclizations listed in Table 1.—The following compounds were synthesized as described

[25] B. C. Mayo, *Chem. Soc. Rev.*, 1973, **2**, 49.
[26] A. M. Simonov and A. N. Lomakin, *J. Gen. Chem.* (*U.S.S.R.*), 1962, **32**, 2194.
[27] B. N. Feitelson, P. Mamalis, R. J. Moualim, V. Petrow, O. Stephenson, and B. Sturgeon, *J. Chem. Soc.*, 1952, 2389.

TABLE 2

Substituted 1-methylbenzimidazoles

Substituent	M.p. (°C)	Solvent	Yield (%)	Method [a]	Found (%) C	H	N	Formula	Required (%) C	H	N
5-Me	93—94 [b]	Light petroleum	88	1	73·7	7·1	18·9	$C_9H_{10}N_2$	74·0	6·85	19·2
6-Me	73—74 [c]	Light petroleum	84	1	74·4	6·6	19·5	$C_9H_{10}N_2$	74·0	6·85	19·2
5-NH_2	156—157 [d]	PhH	78	2	65·6	6·4	28·6	$C_8H_9N_3$	65·3	6·1	28·6
6-NH_2 [e]	160	PhH	97	2	65·7	6·1	28·9	$C_8H_9N_3$	65·3	6·1	28·6
5-OH	266 [f]	H_2O	83	3	64·8	5·8	19·1	$C_8H_8N_2O$	64·8	5·4	18·9
6-OH	242 [g]	H_2O	50	3	64·4	5·5	19·1	$C_8H_8N_2O$	64·8	5·4	18·9
5-CN	139—141	PhH	50	4	68·5	4·4	26·8	$C_9H_7N_3$	68·8	4·5	26·8
6-CN	170—172	PhH	47	4	68·6	4·2	26·7	$C_9H_7N_3$	68·8	4·5	26·8
5-Br	86 [h]	aq. EtOH	65	4, 4a	45·9	3·2	13·5	$C_8H_7BrN_2$	45·5	3·3	13·3
6-Br [i]	123—125	aq. EtOH	67	4	45·9	3·7	13·5	$C_8H_7BrN_2$	45·5	3·3	13·3
5-Cl	23—24	aq. EtOH	74	4	58·1	4·2	16·8	$C_8H_7ClN_2$	57·7	4·2	16·8
6-Cl	121—122 [j]	aq. EtOH	80	4	58·0	4·2	16·9	$C_8H_7ClN_2$	57·7	4·2	16·8
5-CO_2H	312 [k]	H_2O	49	5	61·3	4·6	16·0	$C_9H_8N_2O_2$	61·4	4·55	15·9
6-CO_2H	280 (decomp.)	H_2O	77	5	61·1	4·6	16·1	$C_9H_8N_2O_2$	61·4	4·55	15·9
5-CO_2Et	82—83 [l]	Light petroleum	65	6	64·9	6·0	13·8	$C_{11}H_{12}N_2O_2$	64·7	5·9	13·8
6-CO_2Et	123	aq. EtOH	78	6	64·9	6·2	13·8	$C_{11}H_{12}N_2O_2$	64·7	5·9	13·8
5-NO_2	212 [m]	aq. EtOH	71	1, 7	54·6	4·3	23·8	$C_8H_7N_3O_2$	54·2	4·0	23·7
5-CF_3	110	aq. EtOH	65	1	54·0	3·6	14·2	$C_9H_7F_3N_2$	54·0	3·5	14·0
5-SO_2NH_2	266—267	H_2O	97	1	45·9	4·3	20·3	$C_8H_9N_3O_2S$	45·5	4·3	19·9
5-$SO_2NHC_6H_3Cl_2$-*m*, *p*	243—245 (decomp.)	aq. DMF	60	1	46·9	3·2	11·6	$C_{14}H_{11}Cl_2N_3O_2S$	47·2	3·2	11·8
5-$SO_2NC_5H_{10}$ [n]	189—190 (decomp.)	aq. EtOH	93	1	55·9	6·1	15·2	$C_{13}H_{17}N_3O_2S$	55·9	6·1	15·05

[a] 1, Cyclization of the *N*-methylaniline with formic acid; 2, reduction of the nitro-compound; 3, diazotization followed by hydrolysis; 4, Sandmeyer reaction; 4a, from 2,5-dibromonitrobenzene; 5, oxidation of the methyl group; 6, esterification of the carboxylic acid; 7, cyclization of the *N*-methylaniline with ethyl orthoformate. [b] Lit.,[28] m.p. 96°. [c] Lit.,[28] m.p. 74—75°. [d] Lit.,[29] m.p. 158—159°. [e] *Picrate*, m.p. 250° (decomp.) (Found: C, 44·9; H, 3·1; N, 22·1. $C_{14}H_{12}N_6O_7$ requires C, 44·7; H, 3·2; N, 22·3%). [f] Lit.,[15] m.p. 263—265°. [g] Lit.,[15] m.p. 246—248°. Lit.,[27] m.p. 86—87°. [h] *Picrate*, m.p. 251° (Found: C, 38·0; H, 2·0; N, 15·8. $C_{14}H_{10}BrN_5O_7$ requires C, 38·2; H, 2·3; N, 15·9%). [i] Lit.,[13] m.p. 123—124°. [k] Lit.,[13] m.p. 308—310°. [l] Lit.,[27] m.p. 84—85°. [m] Lit.,[12] m.p. 209°. [n] Piperidine.

in the literature: 4-acetamido-3-nitrobenzoic acid,[30] N^1-acetyl-4-chloro-*o*-phenylenediamine,[31] N^1-acetyl-4-bromo-*o*-phenylenediamine,[32] and 2-nitro-4-trifluoromethylaniline.[33]

TABLE 3

Examples of the effect of lanthanide shift reagent on n.m.r. spectra of some substituted 1-methylbenzimidazoles (δ values in $CDCl_3$; *J* in Hz)

5- or 6-R	Proton attached to N-1	C-2	C-4	C-5	C-6	C-7
6-Me	3·36	7·01	← 7·38—6·80 [a] →			
	4·40	9·88	8·50	7·54	2·74 (Me)	7·70 [b]
			$J_{4,5}$ 9·0; $J_{5,7}$ 0·8			
6-NO_2	3·95	← 8·40—7·75 →				
	7·34	15·44	11·80	10·72		11·54 [c]
			$J_{4.5}$ 8·0; $J_{5.7}$ 2·5			

[a] 6-Me δ 2·35. [b] With 0·066 mol of $Eu(dpm)_3$ per mol. [c] With 0·674 mol of $Eu(dpm)_3$ per mol.

The nitro-compounds were reduced (either with hydrogen and Adams catalyst or with hydrazine hydrate and palladium–charcoal) to the amines which were treated *in situ* with formaldehyde (see below). 4-*Acetamido*-3-*aminobenzamide*, m.p. 193° (from ethanol) (Found: C, 56·1; H, 5·8; N, 21·6 $C_9H_{11}N_3O_2$ requires C, 56·0; H, 5·7; N, 21·8%) was prepared by catalytic hydrogenation (Adams catalyst) of the 3-nitro-compound.[34]

[28] G. H. Beaven, E. R. Holiday, E. A. Johnson, B. Ellis, P. Mamalis, V. Petrow, and B. Sturgeon, *J. Pharm. Pharmacol.*, 1949, **1**, 957.
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[30] E. Borel and H. Deuel, *Helv. Chim. Acta*, 1953, **36**, 801.
[31] M. A. Phillips, *J. Chem. Soc.*, 1931, 1143.

4-*Amino*-N-(3,4-*dichlorophenyl*)-3-*nitrobenzenesulphonamide*.—To 4-chloro-3-nitrobenzenesulphonyl chloride [35] (50 g) dissolved in dry acetone (100 cm³) was added dropwise and with stirring at room temperature a solution of 3,4-dichloroaniline (32·4 g) in dry acetone (100 cm³). The mixture was poured into ice–water and the brown oil solidified on standing to give 4-*chloro*-N-(3,4-*dichlorophenyl*)-3-*nitrobenzenesulphonamide* (4b) (60 g, 81%), m.p. 138° (from aqueous methanol) (Found: C, 37·8; H, 1·8; N, 7·1. $C_{12}H_7Cl_3N_2O_4S$ requires C, 37·75; H, 1·8; N, 7·3%). This compound (18 g) was heated at 120—130° for 4 h under autogeneous pressure in an autoclave with a saturated solution of ethanolic ammonia (300 cm³). Concentrating the solution under reduced pressure gave 4-*amino*-N-(3,4-*dichlorophenyl*)-3-*nitrobenzenesulphonamide* (14 g, 82%), m.p. 249—251° (from ethanol) (Found: C, 39·8; H, 2·6; N, 11·4. $C_{12}H_9Cl_2N_3O_4S$ requires C, 39·8; H, 2·5; N, 11·6%).

4-*Acetamido*-3-*nitrophenyl Benzoate*.—(a) 4-Acetamidophenyl benzoate (5 g) in glacial acetic acid (40 cm³) was treated with a mixture of fuming nitric acid (20 cm³) and glacial acetic acid (20 cm³) and then warmed to 60°. Cooling and pouring into ice gave the *nitro-derivative* (4·5 g, 77%) m.p. 125—126° (from aqueous ethanol) (Found: C, 60·2; H, 4·3; N, 9·5. $C_{15}H_{12}O_5$ requires C, 60·0; H, 4·0; N, 9·3%).

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[35] M. E. Hultquist, R. P. Germann, J. S. Webb, W. B. Wright, B. Roth, J. M. Smith, and Y. S. Row, *J. Amer. Chem. Soc.*, 1951, **73**, 2558.

When the nitration was attempted using a 1 : 1 mixture of concentrated nitric and sulphuric acids at room temperature, the main product was *4-acetamido-3-nitrophenyl 4-nitrobenzoate* (57% yield), m.p. 180° (from aqueous ethanol) (Found: C, 52·2; H, 3·5; N, 12·1. $C_{15}H_{11}N_3O_7$ requires C, 52·2; H, 3·2; N, 12·2%). Its structure was proved by hydrolysis with concentrated sulphuric acid to 4-amino-3-nitrophenol and 3-nitrobenzoic acid, m.p.s and mixed m.p.s with authentic specimens not depressed.

(b) 4-Acetamido-3-nitrophenol (1 g) was converted into its *O*-benzoyl derivative (0·75 g, 49%), m.p. 125° (from aqueous ethanol), by means of the Schotten–Baumann procedure.

4-Acetamido-3-aminophenyl Benzoate.—The foregoing nitro-benzoate (5 g) in ethanol (100 cm³) was hydrogenated (Adams catalyst) at room temperature and 1·5 atm. to give the *amine* (3·5 g, 78%), m.p. 210° (from aqueous ethanol) (Found: C, 66·7; H, 5·4; N, 10·4. $C_{15}H_{14}N_2O_3$ requires C, 66·7; H, 5·2; N, 10·4%).

4-Amino-3-nitrobenzenesulphonamide.— 4-Chloro-3-nitrobenzenesulphonamide [35] (10 g) was heated for 3 h with a saturated ethanolic ammonia solution (300 cm³) at 120—130° under autogeneous pressure. Ethanol was distilled off to give the amine (6·5 g, 71%), m.p. 209° (from aqueous ethanol) (lit.,[36] 209—209·5°).

Condensation of Substituted o-*Phenylenediamines with Formaldehyde.*—(a) *General procedure.* The substituted diamine or its *N*-monoacetyl derivative (0·01 mol) was dissolved in ethanol (*ca.* 30 cm³) and concentrated hydrochloric acid (*ca.* 10 cm³). After adding formaldehyde (40% solution in water, 0·02 mol), the mixture was refluxed for a time (see Table 1) and then allowed to cool before being basified with ammonia solution or aqueous sodium hydroxide. The benzimidazole precipitated out in some cases but in others the product was isolated as an oil (and characterized as the picric acid salt or hydrochloride) or was isolated in other ways: for example, the carboxylic acid was precipitated by carefully acidifying the reaction mixture.

The identity of the product was determined by comparison of its m.p. and spectra with those of known compounds where possible. Authentic samples of many of these and of some new compounds (Table 2) were synthesized. The presence of a mixture was also demonstrated by t.l.c. or g.l.c.

Several attempts to condense 4-acetamido-3-aminophenyl acetate or benzoate in this way did not produce an identifiable product.

(b) *Using paraformaldehyde.* A solution of formaldehyde (4 g) (generated from paraformaldehyde) in absolute ethanol (40 cm³) was heated under reflux for 30 min with 4-nitro-*o*-phenylenediamine (7·1 g) and concentrated hydrochloric acid (3 cm³). On basification with ammonia, 1-methyl-6-nitrobenzimidazole (2 g, 25%), m.p. and mixed m.p. with an authentic sample, 182°.

(c) *Reaction at high dilution.* 4-Nitro-*o*-phenylenediamine (0·151 g) was dissolved in absolute ethanol (100 cm³), concentrated hydrochloric acid (1 cm³) and formaldehyde (40% aqueous solution; 0·15 cm³). The well mixed solution was diluted one hundred-fold with ethanol and a sample of this was placed in a u.v. spectrophotometer. The solution was scanned at intervals until no further spectral change occurred. Initially, maxima were observed at 207 (absorbance 0·83), 225 (0·81), and 347 nm (1·25). At the end of the experiment (5 h), there were maxima at 230 (1·36) and 277 nm (0·69). Because of the slow rate of reaction, the temperature was raised slowly to 29° after 30 min and reached 61·5° after 4·5 h.

Reaction of 4-Acetamido-3-nitrophenol with Benzoyl Chloride.—The phenol (1 g), dissolved in pyridine (20 cm³), was refluxed for 0·5 h with benzoyl chloride (2 cm³). On pouring the mixture into 2N-hydrochloric acid, crystals were obtained of 4-benzamido-3-nitrophenyl benzoate (1·2 g, 65%), m.p. 145—146° (from ethanol) (lit.,[37] 147°) (Found: C, 66·5; H, 3·9; N, 7·6. Calc. for $C_{20}H_{14}N_2O_5$: C, 66·3; H, 3·9; N, 7·7%). When this reaction was repeated on a larger scale, some of the expected 4-acetamido-3-nitrophenyl benzoate was also isolated.

3-Amino-4-benzamidophenyl Benzoate.—Catalytic hydrogenation of the foregoing dibenzoyl-nitro-compound gave the *amine*, m.p. 193—194° (from ethanol) (Found: C, 74·2; H, 5·0; N, 8·7. $C_{20}H_{16}N_2O_3$ requires C, 74·5; H, 5·0; N, 8·7%).

Synthesis of 1-*Methylbenzimidazoles Listed in Table* 2.—*1-Methyl-5-nitrobenzimidazole.* In the cyclization [13] of *N*-methyl-4-nitro-*o*-phenylenediamine, formic acid was replaced by ethyl orthoformate (71% yield).

1-Methyl-5- and 6-aminobenzimidazole. The nitro-compound was hydrogenated in the presence of Adams catalyst (2 atm at room temperature).

1-Methylbenzimidazole-6-carboxylic acid and ethyl ester. The *acid* was prepared by oxidation of 1,6-dimethylbenzimidazole with potassium permanganate; refluxing the acid with ethanol and concentrated sulphuric acid for 10 h gave the *ethyl ester.*

Bromo- and chloro-1-methylbenzimidazole. (a) Diazotization and Sandmeyer reaction of 5- or 6-amino-1-methylbenzimidazole gave the corresponding 5- or 6-halogeno-compound in good yields.

(b) 5-Bromo-1-methylbenzimidazole. 2,5-Dibromonitrobenzene (70 g), anhydrous copper(II) chloride (1·75 g) and ethanolic methylamine (33% w/w; 120 cm³) were heated under reflux for 30 h. On cooling, 4-bromo-*N*-methyl-2-nitroaniline (42 g, 73%), m.p. 101—102° (from light petroleum, b.p. 60—80°) (lit.,[38] 103°) separated (Found: C, 36·0; H, 2·7; N, 11·9. Calc. for $C_7H_7BrN_2O_2$: C, 36·4; H, 3·0; N, 12·1%). This was reduced catalytically and cyclized with formic acid to give the benzimidazole.

1-Methylbenzimidazol-5- and 6-ol. 5- or 6-Amino-1-methylbenzimidazole (5 g) was dissolved in concentrated sulphuric acid (40 cm³) and water (120 cm³) and the solution cooled to 0°. Sodium nitrite (2·5 g) in ice-cold water (20 cm³) was added dropwise through a tap-funnel whose tip was just below the surface of the stirred acid solution; the temperature was kept at 0—5° throughout the addition and while stirring for another 10 min. The diazotized solution was added slowly to a boiling mixture of concentrated sulphuric acid (35 cm³) and water (70 cm³). Boiling was continued until no more nitrogen was evolved. The red solution was cooled and basified below 30° with ammonia solution (*d* 0·88) to precipitate the product.

1-Methyl-5-trifluoromethylbenzimidazole. A mixture of *N*-methyl-2-nitro-4-trifluoromethylaniline (9 g) and Adams catalyst (300 mg) in ethanol (100 cm³) was stirred under hydrogen at 2·5 atm. at room temperature. Ethanol was

[36] V. A. Lavrishchev, V. L. Plakidin, and A. E. Kretov, *Izvest. Vysshikh Ucheb. Zavedenii, Khim. i Khim. Tekhnol.*, 1960, **3**, 127.

[37] Beilsteins Handbuch der Organischen Chemie, 4th edn., 1930, Vol. 13, p. 523.

[38] Heilbron's Dictionary of Organic Compounds, ed. G. Harris, 4th edn., Eyre and Spottiswoode, London, 1965, p. 467.

then distilled off and the residue was refluxed for 2 h on a steam-bath with an excess of formic acid. The solution was cooled and basified with ammonia (*d* 0·88) to give an oil which later solidified to give the *benzimidazole* (5·5 g, 65%), m.p. 110°.

Other *N*-methyl-2-nitroanilines were similarly treated.

4-Methylamino-3-nitrobenzenesulphonamide (5d).—4-Chloro-3-nitrobenzenesulphonamide [39] (10 g) was heated with ethanolic methylamine solution (33% w/v; 10 cm³) for 4 h at 120—130° in an autoclave. Cooling and evaporating the ethanol gave the methylamino-compound (8·0 g, 82%), m.p. 213° (lit.,[40] 212—213°).

1-(4-Methylamino-3-nitrophenylsulphonyl)piperidine (5e).—1-(4-Chloro-3-nitrophenylsulphonyl)piperidine [41] (20 g) was converted into the *4-methylamino-compound* (16 g, 82%), m.p. 140° (from ethanol) (Found: C, 47·9; H, 5·7; N, 14·0. $C_{12}H_{17}N_3O_4S$ requires C, 48·2; H, 5·7; N, 14·05%), in the same way as for the unsubstituted sulphonamide (5d) (see above).

N-(3,4-Dichlorophenyl)-4-methylamino-3-nitrobenzenesulphonamide (5c).—Reaction of 4-chloro-*N*-(3,4-dichlorophenyl)-3-nitrobenzenesulphonamide (30 g) with ethanolic methylamine solution as described above for similar compounds gave the *4-methylamino-compound* (24 g, 81%), m.p. 180° (from ethanol) (Found: C, 41·2; H, 2·9; N, 10·8. $C_{13}H_{11}Cl_2N_3O_4S$ requires C, 41·5; H, 2·95; N, 11·2%).

6-Cyano-1-methylbenzimidazole.—To a solution of 6-amino-1-methylbenzimidazole (10 g) in concentrated hydrochloric acid (30 cm³) and water (30 cm³) was added dropwise an ice-cold solution of sodium nitrite (6·4 g) in water (15 cm³). When addition was complete, the solution was neutralized with sodium carbonate and then slowly added to a solution of copper(I) cyanide (4 g) and sodium cyanide (10 g) in water (25 cm³) at 50°. This gave the *6-cyano-compound* (5 g, 47%), m.p. 170—172°, $\nu_{max.}$ (KBr) 2210, 1608, and 1495 cm^{-1}.

The 5-cyano-isomer was similarly prepared.

Experiments with LSR.—To a 10% solution of the benzimidazole in deuteriochloroform was added $Eu(dpm)_3$ (5 mg). The spectrum was plotted and if a satisfactory separation of signals was not achieved, further quantities (5 or 10 mg) of the LSR were added. The results for two benzimidazoles are shown in Table 3 (the remainder of the data is deposited in Supplementary Publication No. SUP 20932).

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