115. *Organic Complex-forming Agents for Metals. Part I. Preparation of 4-Hydroxy- and 4 : 7-Dihydroxy-benziminazoles and Related Compounds.*

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Methods are detailed for the synthesis and characterisation of 4-hydroxy-, 4 : 7-dihydroxy-, and 4 : 7-dihydroxy-1-methyl-2-substituted benziminazoles. Syntheses of 4-hydroxy-benzoxazoles, -benzotriazoles, and -benzo-2 : 1 : 3-selenadiazoles are included.

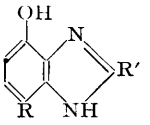
4-Hydroxybenziminazole (I; R = R′ = H) was first synthesised by Sorkin, Roth, and Erlenmeyer,[1] and substituted compounds of this type were later described by Gillespie and Graff.[2] These compounds were required for biological examination, and their analytical applications have not been reported. This paper reports the preparation of a series of compounds based on, and including, 4-hydroxybenziminazole and it is hoped to examine their analytical behaviour especially in view of the manifold application of the somewhat similar 8-hydroxyquinoline and its substituted derivatives.

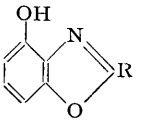
The chelating system, 4-hydroxybenziminazole, is of interest from a theoretical viewpoint since considerable modification of the basicity of the tertiary nitrogen atom of the benziminazole ring system can be effected by varying the substituent in the 2-position.[3] Furthermore, the corresponding 4 : 7-dihydroxybenziminazoles (I; R = OH) are of interest since the additional possibility exists of metals forming a complex with the 1-hydrogen atom and the 7-hydroxyl group. Some members of this series have been synthesised including some where a methyl group has been inserted in the 1-position to remove complex-forming power from that position. The corresponding 4-hydroxybenzoxazoles (II; R = H, Me), -benzotriazole (III), and -benzo-2 : 1 : 3-selenadiazole (IV; R = OH), which possess essentially the same complex-forming groups, but with different relative donor and acceptor properties, have also been synthesised.

The benziminazoles were prepared by Phillips's method [4] from a variety of acids and

[1] Sorkin, Roth, and Erlenmeyer, *Helv. Chim. Acta*, 1952, **35**, 1736.
[2] Gillespie and Graff, *J. Amer. Chem. Soc.*, 1954, **76**, 3531.
[3] Lane, *J.*, 1955, 534; Belcher, Sykes, and Tatlow, *J.*, 1954, 4159.
[4] Phillips, *J.*, 1928, 2397.

2 : 3-diaminoanisole, 2 : 3-diaminoquinol diethyl ether, and 2-amino-3-methylaminoquinol diethyl ether, respectively. The last base had been prepared by Nelson and Brown's alkylation method [5] from the unsubstituted base and methyl iodide. Perfluoroalkyl groups and lower alkyl groups were introduced into the 2-position, the object being first to decrease


(I)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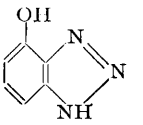
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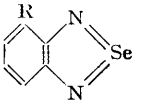
(IV)

and then to increase the basicity of the tertiary nitrogen atom. With the exception of the perfluoroalkyl derivatives these benziminazoles were all basic compounds, forming well-defined salts with dilute acids; their properties are detailed in the Tables. The chemical behaviour of the perfluoroalkyl derivatives was appreciably different from that of the unsubstituted analogues. Whereas the alkylbenziminazoles were smoothly demethylated with anhydrous aluminium chloride in boiling benzene, concentrated hydrobromic acid gave better yields from the perfluoro-compounds. Mineral acid salts formed by the latter were hydrolysed by water to the parent base, indicating a considerably weakened basic nitrogen atom. All the 4-hydroxy-benziminazoles were stable in air, but with the exception of the perfluoro-derivatives the 4 : 7-dihydroxy-benziminazoles were obtained only as salts. 4 : 7-Dihydroxybenziminazole, obtained on basification of a solution of its hydrochloride, was rapidly oxidised on exposure to air. No further attempt was made to prepare the free higher homologues, since with increasing basicity the instability is also likely to increase. The characterisation of these hydroxy-benziminazoles was attempted by the formation of their acetates. The 4 : 7-dihydroxy-series formed normal diacetates with pyridine and acetic anhydride. Of the 4-hydroxy-benziminazoles only the perfluoroalkyl-derivatives gave stable products; others gave unstable crystalline compounds of indeterminate constitution, which evolved acetic acid and left a gum on storage. The compound formed from 4-hydroxybenziminazole was 4(7)-acetoxy-1-acetylbenziminazole.

The corresponding hydroxy-benzoxazoles, -benzotriazoles, and -benzo-2 : 1 : 3-selenadiazoles were prepared by extensions of known reactions. In the dealkylation of 4-methoxy- and 4 : 7-diethoxy-benzo-2 : 1 : 3-selenadiazoles by anhydrous aluminium chloride in benzene, the former compound was recovered unchanged after refluxing with 1 mol. of aluminium chloride, but use of 2 mols. gave the required hydroxy-compound in high yield. When 4 : 7-diethoxybenzo-2 : 1 : 3-selenadiazole was similarly treated with 2 mols. of aluminium chloride only one ethoxy-group was de-ethylated. When 3 mols. were used a very easily oxidizable compound, believed to be the 4 : 7-dihydroxy-derivative, was obtained, but was too labile for isolation and characterisation. Both this compound and the 4 : 7-dihydroxy-benziminazoles described above would be expected to form the corresponding *p*-quinone on oxidation. It appears that in the dealkylation 1 mol. of aluminium chloride is rendered unavailable owing to co-ordination to the selenium atom which, in the conventional formulation of benzo-2 : 1 : 3-selenadiazoles (IV), is co-ordinatively unsaturated.

Experimental

Determination of the Equivalent Weight of Benziminazoles and Related Substances.—Two methods were used: (*a*) Titration with perchloric acid in glacial acetic acid, (i) crystal-violet or (ii) a high-frequency conductometric procedure [6] being used for determination of the end-point; (*b*) titration with sodium methoxide in methanol–benzene with ethylenediamine as solvent and the high-frequency conductometric end-point procedure. Some compounds were suitable for determination by both methods; letters in parentheses below indicate which method was used.

Preparation of Perchlorates for Characterisation.—Base perchlorates were obtained by adding slightly more than 1 equiv. of 0·1N-perchloric acid in glacial acetic acid to the base in solution

[5] Nelson and Brown, *J. Amer. Chem. Soc.*, 1953, **75**, 24.
[6] Lane, *Analyst*, 1955, **80**, 675.

in the same solvent. Precipitation of the salt was completed by addition of light petroleum. For results see Table 1.

2-Amino-3-methylaminoquinol Diethyl Ether.—2 : 3-Diaminoquinol diethyl ether (58 g.), methyl iodide (50 ml.), and methanol (750 ml.) were refluxed for 2 days. Colourless crystals were obtained on cooling the concentrated mixture. These were dissolved in water, basified with sodium hydroxide, and extracted with ether. After removal of the dried ethereal extract the residue was distilled under reduced pressure, and the above *base* obtained, b. p. 124°/0·5 mm., m. p. 47—48° (Found : C, 63·0; H, 8·65; N, 13·2. $C_{11}H_{18}O_2N_2$ requires C, 62·9; H, 8·6; N, 13·3%). The *dihydrochloride* had m. p. 122° (from ethanol) (Found : N, 8·6; Cl, 21·7. $C_{11}H_{20}O_2N_2Cl_2,C_2H_5{\cdot}OH$ requires N, 8·5; Cl, 21·6%), and the *hydriodide* m. p. 163—165° (decomp.) (Found : C, 39·4; H, 5·5; N, 8·2; I, 57·4. $C_{11}H_{19}O_2N_2I$ requires C, 39·0; H, 5·6; N, 8·3; I, 37·5%).

TABLE 1. *Benziminazole perchlorates.*

Substituents in position :					Found (%)		Reqd. (%)	
1	2	4	M. p.*	Formula	N	Cl	N	Cl
H	H	OMe	195—200°	$C_8H_9O_5N_2Cl$	11·2	14·3	11·3	14·3
H	Me	OMe	255—256	$C_9H_{11}O_5N_2Cl$	11·3	13·0	10·7	13·5
H	Et	OMe	217—218	$C_{10}H_{13}O_5N_2Cl$	9·7	13·05	10·1	12·85
H	Pr^i	OMe	153—155	$C_{11}H_{15}O_5N_2Cl$	9·8	13·15	9·65	12·2
H	Bu^t	OMe	232—233	$C_{12}H_{17}O_5N_2Cl$	9·1	11·95	9·2	11·7
H	H	OH	203—204	$C_7H_7O_5N_2Cl$	11·8	15·7	11·95	15·15
H	Me	OH	177—178	$C_8H_9O_5N_2Cl$	11·3	14·7	11·3	14·3
H	Pr^i	OH	80—85	$C_{10}H_{13}O_5N_2Cl$	—	13·6	—	12·8
H	Bu^t	OH	227—230	$C_{11}H_{15}O_5N_2Cl$	9·7	11·35	9·6	12·2

* All with decomposition.

TABLE 2. *Miscellaneous substituted benziminazole hydrohalides.*

Substituent in position :						Found (%)		Reqd. (%)	
1	2	4	7	M. p.	Formula	N	Cl (or Br)	N	Cl (or Br)
H	H	OH	H [a]	282—283°	$C_7H_7ON_2Cl$	15·9	20·2	16·4	20·8
H	Et	OH	H	212—214	$C_9H_{11}ON_2Cl$	14·3	18·1	14·1	17·9
H	Pr^i	OH	H	215·5	$C_{10}H_{13}ON_2Cl$	13·3	16·2	13·2	16·7
H	Bu^t	OH	H	241·5	$C_{11}H_{15}ON_2Cl$	11·9	15·1	12·3	15·7
Me	H	OH	OH	256—259	$C_8H_9O_2N_2Cl,H_2O$	12·5	15·9	12·8	16·2
H	C_3F_7	OH	H [b]	97—99	$C_{10}H_6ON_2F_7Br,H_2O$	6·9	19·5	7·0	19·9
Me	CF_3	OH	OH [c]	224·5	$C_9H_8O_2N_2F_3Br$	9·25	—	8·95	—

[a] Sorkin, Roth, and Erlenmeyer [1] give m. p. 275—278°. [b] Found : C, 29·4; H, 2·4. Reqd.: C, 29·9; H, 2·0%. [c] Found : C, 35·3; H, 3·7. Reqd.: C, 34·5; H, 2·6%.

Note added in Proof.—Similar details for the preparation of some of these compounds are given in U.S.P. 2,663,712 (General Aniline and Film Corp.) but without m. p.s or analytical data.

Preparation of 2-Substituted Benziminazoles.—Equimolecular mixtures of the *o*-diamines (2 : 3-diaminoanisole, 2 : 3-diaminoquinol diethyl ether, and 2-amino-3-methylaminoquinol diethyl ether) and the appropriate acid were refluxed for 12 hr. in aqueous 4N-hydrochloric acid. The mixture was filtered and neutralised with sodium hydrogen carbonate, and the precipitated bases filtered off, washed, dried, purified by vacuum distillation, and crystallised from aqueous ethanol. When perfluoro-acids were used the vacuum distillation was omitted. Results are given in Tables 2, 3, and 5.

TABLE 3. *4-Methoxy-2-substituted benziminazoles.*

Substituent in position 2	M. p.	Equiv. Found	Equiv. Reqd.	Method	Formula	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
H	169—170°	147	148	(*a*) (i)	$C_8H_8ON_2$	64·7	5·3	18·8	64·9	5·45	18·9
Me	193	162	162	,,	$C_9H_{10}ON_2$	66·7	6·2	17·0	66·6	6·2	17·3
Et	136—139	177	176	,,	$C_{10}H_{12}ON_2$	68·1	6·9	15·9	68·1	6·9	15·9
Pr^i	203·5	189	190	,,	$C_{11}H_{14}ON_2$	69·1	7·3	14·8	69·4	7·4	14·8
Bu^t	233·5	204	205	,,	$C_{12}H_{16}ON_2$	70·4	8·0	15·2	80·6	7·9	13·7
CF_3	169—172	220	216	(*b*)	$C_9H_7ON_2F_3$	50·6	2·8	13·2	50·0	3·3	13·0
C_3F_7	189—190	320	316	(*b*)	$C_{11}H_7ON_2F_7$	41·8	2·2	9·15	41·8	2·2	8·9

TABLE 4. *4-Hydroxy-2-substituted benziminazoles.*

Substituent in position 2	M. p.	Equiv. Found	Equiv. Reqd.	Method	Formula	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
H [a]	200° (decomp.)	134	134	(*a*) (i)	$C_7H_6ON_2$	62·8	4·4	20·8	62·7	4·5	20·9
Me	216·5	149	148	(*b*)	$C_8H_8ON_2$	—	5·3	18·7	—	5·4	18·9
Et	157—159	163	162	(*a*) (ii)	$C_9H_{10}ON_2$	—	6·15	17·8	—	6·2	17·3
Pr^i [b]	191—193	88	88	(*b*)	$C_{10}H_{12}ON_2$	67·9	6·8	15·7	68·2	6·8	15·9
Bu^t	273·5	190	190	(*a*) (i)	$C_{11}H_{14}ON_2$	69·7	7·5	14·7	69·5	7·4	14·7
CF_3 [c]	173—174	207 104	202 101	(*b*)	$C_8H_5ON_2F_3{\cdot}H_2O$	44·1	3·5	12·5	43·6	3·2	12·7

[a] Sorkin, Roth, and Erlenmeyer [1] give m. p. 151—152°. [b] Titration in dimethylformamide. [c] Titration in dimethylformamide; two inflexion points are obtained, due to the separate neutralisation of the phenolic OH group and the 1-H atom.

TABLE 5. *1-Methyl-2 : 4 : 7-trisubstituted benziminazoles.*

Substituent in position: 2	4	7	M. p.	Formula	Found (%) C	Found (%) H	Found (%) N	Reqd. (%) C	Reqd. (%) H	Reqd. (%) N
CF_3	OEt	OEt	111—113°	$C_{13}H_{15}O_2N_2F_3$	54·1	5·2	9·55	54·1	5·25	9·7
CF_3	OH	OH	241—242	$C_9H_7O_2N_2F_3$	46·7	3·3	11·9	46·5	3·0	12·0
CF_3	OAc	OAc	128—129	$C_{13}H_{11}O_4N_2F_3$	49·3	3·8	9·6	49·3	3·5	8·9
H	OEt	OEt [a]	107—108	$C_{12}H_{16}O_2N_2$	65·2	6·8	12·9	65·45	7·3	12·7
H	AcO	OAc	218—129	$C_{12}H_{12}O_4N_2,\frac{1}{2}H_2O$	56·0	5·1	10·9	56·3	5·3	11·0
Me	OEt	OEt	98—99	$C_{13}H_{18}O_2N_2$	67·1	7·7	11·7	66·7	7·7	12·0

[a] Found: equiv. (*a*, i), 222. Reqd.: equiv., 220. [b] Found: equiv. (*a*, i), 233. Reqd.: equiv., 234.

Dealkylation.—The appropriate benziminazole was refluxed in benzene for 6 hr. with 2·1 mol. of anhydrous aluminium chloride. The benzene was then distilled off, the residual solid triturated with water, and the hydroxybenziminazole, isolated as its hydrochloride by addition of concentrated hydrochloric acid, was purified by repeated treatment of the aqueous solutions of the hydrochloride with charcoal, followed by addition of concentrated hydrochloric acid until the salt crystallised. Free bases were prepared by addition of a slight excess of sodium hydrogen carbonate solution to an aqueous solution of the corresponding hydrochloride, followed by repeated crystallisation (aqueous ethanol) of the precipitated base.

When the 2-substituent was a perfluoroalkyl group, dealkylation was effected by 6 hours' refluxing with concentrated hydrobromic acid. The hydrobromide which crystallised on cooling was hydrolysed by addition of water, and the free base recovered and crystallised (ethanol). Results are given in Tables 2, 4, and 5.

Reaction of 4-Hydroxy- and 4 : 7-Dihydroxy-benziminazole with Pyridine and Acetic Anhydride.—4 : 7-Dihydroxybenziminazoles were characterised by acetylation of the corresponding hydroxy-compound with pyridine and acetic anhydride; in the 4-hydroxybenziminazole series the only compounds giving the expected products were those containing a 2-perfluoroalkyl group.

4-Acetoxy-2-trifluoromethylbenziminazole, m. p. 130° (decomp.) (Found: C, 49·4; H, 2·9; N, 11·3. $C_{10}H_7O_2N_2F_3$ requires C, 49·2; H, 2·9; N, 11·5%), and *4-acetoxy-2-heptafluoropropylbenziminazole*, m. p. 160° (Found: C, 41·1; H, 2·7; N, 8·3. $C_{12}H_7O_2N_2F_7$ requires C, 41·9; H, 2·0; N, 8·1%), were obtained by this route. 4-Hydroxybenziminazole similarly treated gave *4(7)-acetoxy-1-acetylbenziminazole*, m. p. 106° (Found: C, 60·6; H, 4·4; N, 13·4. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·9%). With higher homologues in the 2-position products of unknown constitution were obtained which evolved acetic acid on drying and storage.

4-Methoxybenzotriazole.—2 : 3-Diaminoanisole (27·6 g.) was dissolved in glacial acetic acid (24 g.) and water (60 ml.) at 5°, and a cold solution of sodium nitrite (15 g.) in water (25 ml.) added in one portion. The temperature rose to 80° and after 1 hr. the dark red-brown, oily layer formed was removed, dried, and distilled under reduced pressure. The *base* was obtained as a yellow solid, b. p. 206—208°/0·5 mm. (19·5 g.), and after several recrystallisations (benzene) had m. p. 133·5—135° [Found: N, 28·2%; equiv. (*b*), 146. $C_7H_7ON_3$ requires N, 28·2%; equiv., 149].

4-Hydroxybenzotriazole.—4-Methoxybenzotriazole (5·9 g.) was refluxed for 8 hr. with anhydrous aluminium chloride (10 g.) in benzene (1 l.), water (200 ml.) was added, with stirring, and the aqueous layer evaporated to dryness, leaving a yellow solid. After recrystallisation

(water) the *hydroxy-base* had m. p. 215·5—217·5° [Found : N, 31·0%; equiv. (*b*), 69. $C_6H_5ON_3$ requires N, 31·1%; equiv., 67·5]. With acetic anhydride and pyridine 4-*acetoxybenzotriazole* was obtained, m. p. 170—171° [Found : N, 23·8%; equiv. (*b*), 90. $C_8H_7O_2N_3$ requires N, 23·8%; equiv., 88·5].

4-*Hydroxybenzoxazole*.—2-Aminoresorcinol hydrochloride (4 g.) and formamide (1·2 g.) were refluxed for 15 min. The mixture was extracted with ethanol, and colourless crystals were obtained on concentration of the extract. These were purified by dissolving them in aqueous sodium hydroxide followed by neutralisation with dilute hydrochloric acid. After crystallisation (ethanol) the base melted at 183° (Found : N, 10·0. Calc. for $C_7H_5O_2N$: N, 10·4%). Sorkin, Roth, and Erlenmeyer [1] record m. p. 180—181°. 4-*Hydroxy*-2-*methylbenzoxazole*, obtained similarly from acetamide and 2-aminoresorcinol hydrochloride, had m. p. 143° [Found : C, 64·4; H, 4·8; N, 9·75%; equiv.(*b*), 148. $C_8H_7O_2N$ requires C, 64·4; H, 4·7; N, 9·4%; equiv., 149].

4-*Hydroxybenzo*-2 : 1 : 3-*selenadiazole*.—4-Methoxybenzo-2 : 1 : 3-selenadiazole [7] (21 g.) was refluxed in benzene (150 ml.) with anhydrous aluminium chloride (28 g.) for 6 hr. Water was added, and the mixture boiled for a further 15 min. The benzene layer was concentrated, and the solid which separated filtered off. After several recrystallisations (ethylene glycol or diethyl oxalate) the above *hydroxy-base* formed red-brown plates, m. p. 187—188° [Found : C, 36·0; H, 2·0; N, 14·4%; equiv.(*b*), 204. $C_6H_4ON_2Se$ requires C, 36·2; H, 2·0; N, 14·1%; equiv., 209]. The corresponding *acetoxy-compound*, prepared by use of pyridine and acetic anhydride, formed felted yellow needles, m. p. 66—60° (decomp.) (Found : C, 39·7; H, 2·6; N, 12·1. $C_8H_6O_2N_2Se$ requires C, 39·8; H, 2·5; N, 11·6%).

Dealkylation of 4 : 7-*Diethoxybenzo*-2 : 1 : 3-*selenadiazole*.—This base [8] was recovered unchanged after 6 hours' refluxing in benzene with 1 mol. of anhydrous aluminium chloride. With 2 mols., 4-*ethoxy*-7-*hydroxybenzo*-2 : 1 : 3-*selenadiazole* was obtained by the above procedure as scarlet needles from ethanol, m. p. 187—187·5° [Found : C, 39·2; H, 3·4; N, 11·8%; equiv. (*b*), 238. $C_8H_8O_2N_2Se$ requires C, 39·5; H, 3·3; N, 11·5%; equiv., 243]. The corresponding *acetoxy-compound* (pyridine and acetic anhydride) formed yellow needles, m. p. 154·5—155° (with sublimation; from ethanol) (Found : C, 42·3; H, 3·3; N, 9·5. $C_{10}H_{10}O_3N_2Se$ requires C, 42·1; H, 3·5; N, 9·8%). With 3 mols. of aluminium chloride further dealkylation occurred but the product was oxidised rapidly on attempted isolation.

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[*Received, June 30th*, 1955.]

[7] Lane and Williams, *J.*, 1954, 2971.
[8] *Idem*, *J.*, 1955, 1469.