THE CHEMISTRY OF ANTI-PERNICIOUS ANÆMIA FACTORS

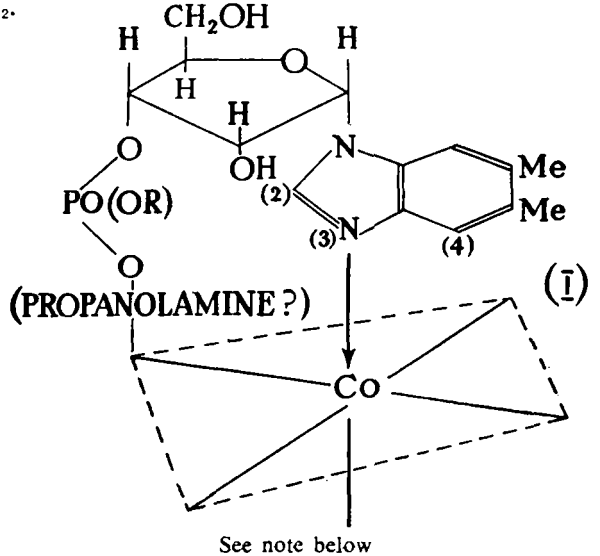
PART VIII. THE BASICITY OF SOME BENZIMINAZOLES AND BENZIMINAZOLE GLYCOSIDES

BY M. T. DAVIES, P. MAMALIS, V. PETROW AND B. STURGEON

From The Research Laboratories, The British Drug Houses, Ltd., London, N.1

Received May 4, 1951

SPECTROSCOPIC studies outlined in Part VI[1] of this series led Beaven, Holiday, Johnson, Ellis and Petrow to propose formula (I) for vitamin B_{12}.



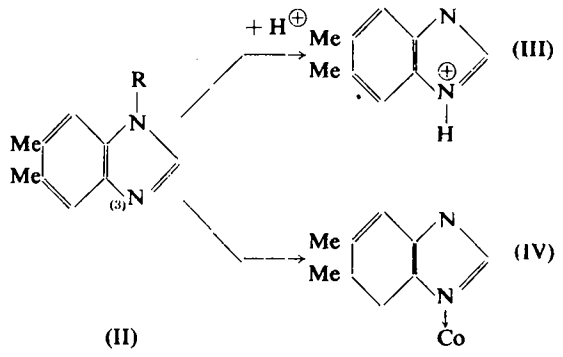
See note below

Such a formulation implies the existence of a stable co-ordinate link between a benziminazole glycosidic residue and a planar cobaltic complex of a character never previously recorded in the literature. We have, therefore, initiated studies on the co-ordinating properties of the benziminazoles, hoping thereby to obtain additional evidence in support of structure (I), and at the same time to pave the way for the synthesis of analogues.

The formation of a co-ordinate bond by a benziminazole (II) is exemplified in its simplest form by addition of a proton with formation of a benziminazolinium ion (III). The stability of such a species is directly related to the basicity of the proton-acceptor, i.e., to its pK_a. The latter function thus gives a measure of the co-ordinating power of (II) with a hydrogen ion. Somewhat similar considerations apply to the co-ordination of (II) with a metallic ion to give (IV), although in this instance the position is complicated by effects exerted by structural and stereochemical factors. Such factors may, indeed, play an overriding

Note: The structure shown in Part VII (*This Journal*, 1951, **3**, 271) contains a printing error. The structure shown above is as intended.

part in determining the stability of a metallic complex and thus invalidate conclusions drawn solely from measurements of basicity[2,3]. At the same time, the formation of both types of linkage (III and IV) involves the



same fundamental factor, the electron availability at N^3. Approximate correlation between pK_a and co-ordinating power should, therefore, exist in groups of structurally and spatially related compounds. We have, therefore, sought to determine the relationship between chemical constitution and basicity in the benziminazole and benziminazole glycoside series as a preliminary to co-ordination studies, an account of which will form the subject of a later communication.

The pK_a values of the benziminazoles examined were measured by potentiometric titration of their solutions in water using 0·1 N hydrochloric acid. In some cases, however, solution in water proved unsatisfactory owing to low solubility, when 50 per cent. aqueous ethanol was employed as solvent. In addition, certain compounds yielding well-defined salts were examined by titrating their hydrochlorides with 0·1N sodium hydroxide and a cross-check of the basicities obtained. The pK_a values determined in this way for benziminazole itself (see Table I), and for some of its 1-substituted derivatives, proved, in general, to be greater than the values obtained by forward titration by approximately 0·1 pK_a unit in water, and 0·06 pK_a unit in aqueous alcohol as solvent, respectively. These somewhat higher values for the pK_a cannot be attributed to the sodium ion error of the glass electrode, as forward titration of benziminazoles in either solvent was completely unaffected by the presence of sodium chloride of appropriate concentration.

A number of benziminazoles were examined in both aqueous and aqueous-ethanolic solutions. All showed weaker basicity in the latter solvent, the depression, ΔpK_a, varying qualitatively with the solubility of the base in accordance with the equation deduced thermodynamically by Kolthoff, Lingane and Larson[4].

$pK_{a(m)} - pK_{a(n)} = \Delta pK_a = \log D_B + \log D_{H^\oplus} - \log D_{BH^\oplus}$ where D is the distribution coefficent $\frac{a_{i(n)}}{a_{i(m)}}$ of species i between solvents n and m.

The present work has shown that the ΔpK_a factor is very markedly affected by the nature of the substituents within the benziminazole mole-

cule. The utmost caution must, therefore, be exercised in the interpretation of data based solely upon determinations carried out in aqueous-ethanolic solution. The basicities of some 60 benziminazoles were determined in the present investigation, the results obtained being recorded in Tables I, II, III and IV.

The classical pK_a values for benziminazole itself in aqueous solution at 18° and 25°C. obtained in the present investigation (see Table I)

TABLE I

THE CLASSICAL pK_a VALUE OF BENZIMINAZOLE

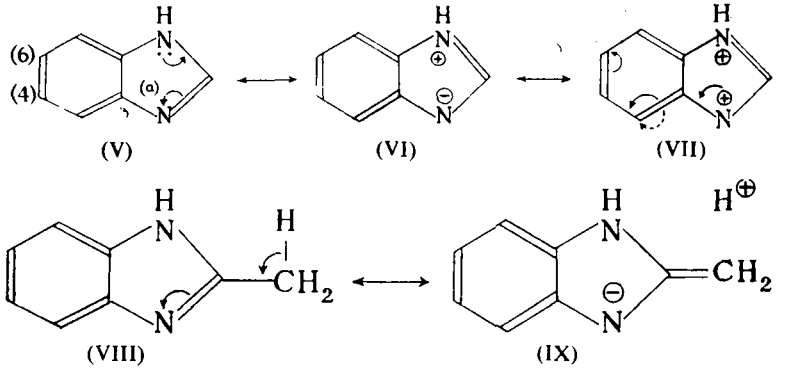
Solvent	Dilution $(\frac{1}{n})$	Temp. C.	pK_a	
Water	100	18 ± 1°	5·56	Present work
Water	40	20°	5·53	Albert *et al.*[4]
Water	200	20°	5·532	Schwarzenbach and Lutz[5]
Water	100	25 ± 1°	5·48	Present work
Water	100	25 ± 1°	5·57	A
Water	100	25 ± 1°	5·50	B
Aq. ethanol	200	25 ± 1°	4·98	Present work
Aq. „	200	25 ± 1°	4·96	A
Aq. „	200	25 ± 1°	4·98	C

A. By titration of the hydrochloride with 0·1 N sodium hydroxide.
B. In the presence of 0·005 M sodium chloride.
C. In the presence of 0·0025 M sodium chloride.

agree closely with those recorded in the literature[5,6]. The pK_a value falls by 0·08 units in passing from the lower to the higher temperature, a change which corresponds to a temperature coefficient of −0·0114 units per degree C. This figure agrees well with the temperature coefficient of −0·0125 previously obtained by Hall and Sprinkle[7] for compounds of similar basicity. Before attempting the interpretation of the pK_a values obtained for benziminazole and for its derivatives, however, it is perhaps relevant to consider in detail the electronic pattern existing within the molecule.

The conventional Kekulé type structure (V) for benziminazole fails to provide an interpretation for the extraordinary stability towards acidic and basic reagents of a molecule which is, *prima facie*, a substituted amidine (cf. diphenylformamidine). The enhanced stability resulting from the closure of the iminazole ring can accrue only from resonance between a number of perturbed structures. Of these, the major canonical structure (VI) derives from (V) by the primary electromeric shift (a), and is further stabilised by conjugation of the negative charge at N^3 with the benzenoid ring as indicated in (VII). This conjugation results in benziminazole being a weaker base than iminazole itself (*cf.* Albert, *loc cit.*; Kirby and Neuberger[8]).

Structure (VI)←→(VII) for benziminazole provides a ready interpretation of the chemical and physical properties of the molecule. Thus the chemical reactivity of positions 4(7) and 6(5) towards cationic reagents (cf. nitration, bromination, and chlorination of benziminazole) derives

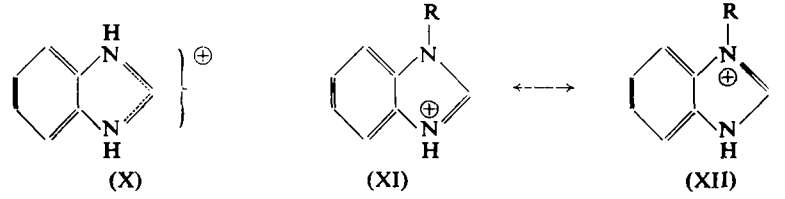


(V) (VI) (VII)

(VIII) (IX)

from the contribution of structure (VII). Again, the compound is highly associated in solution and is sparingly soluble in hydrocarbon solvents[9].

The introduction of an alkyl substituent into position 2 leads to an increase in basicity, the effect being probably enhanced by first order hyperconjugation as indicated in formulæ (VIII) and (IX). Hammett's generalisation[10], however, in which the +E effects of the alkyl grouping (hyperconjugative effects) fall in the order Me > Et > *iso*Pr > *tert.* - Bu, does not appear to apply in this instance (cf. nos. 6,7,9,10 : Table II). The Bz-methyl benziminazoles nos. 2 to 5 are likewise stronger bases than benziminazole itself (no. 1). 4-Methylbenziminazole is less basic than the 5-methyl isomer, and the same relationship holds with the corresponding methoxy-compounds nos. 27 and 28 and dichloro-compounds nos. 37 and 38. Introduction of an alkyl-grouping into position 1, however, leads to a more complicated electronic picture which no longer permits the facile prediction of resulting changes in the pK_a.



(X) (XI) (XII)

Addition of a proton to benziminazole leads to the formation of the benziminazolinium ion (X) which has a maximum resonance stability on account of the complete equivalence of the main canonical structures (XI and XII; R = H). Introduction of a 1-substituent, however, leads to destruction of this symmetry (cf. XI ⟷ XII) with consequent reduction in the resonance stability and hence in the basicity. The +I effect of the 1-alkyl group is thus opposed by the decrease in resonance energy consequent upon the decrease in symmetry. The relative importance of these two opposing effects, however, appears to vary with the structure of the compound.

The influence of structure upon ΔpK_a is well illustrated by the 1-substituted benziminazoles. In the series 1-methyl-, 1-ethyl-, and 1-*iso*propyl-benziminazole, the basicity in aqueous solution shows a steady increase;

whereas in aqueous ethanolic solution the pK_a values lie closer together. The explanation of these results lies in the marked diminution in water solubility with increasing size of the 1-alkyl substituent, an effect not

TABLE II

	Substance	pK_a values at 25 ± 1°C.				ΔpK_a
		Water	Dilution (litres/M)	50 per cent. Ethanol	Dilution (litres/M)	
1.	Benziminazole	5·48	100	4·98	200	0·50
2.	4-Methyl-	5·67	520	5·16	210	0·51
3.	5-Methyl-	5·81	200	5·32	210	0·49
4.	4 : 6-Dimethyl-	—	—	5·46	200	—
5.	5 : 6-Dimethyl-	5·98	510	5·48	200	0·50
6.	2-Methyl-	6·19	500	5·77	200	0·42
7.	2-Ethyl-	6·20	500	5·69	200	0·51
8.	2-*n*-Propyl-	(*a*)	—	5·66	220	—
9.	2-*iso*-Propyl-	6·23	500	5·79	200	0·44
10.	2-*tert.*-Butyl-	(*a*)	—	5·76	210	—
11.	1-Methyl-	5·57	100	4·88	200	0·69
		5·70 (*b*)	110	4·95 (*b*)	220	0·75
12.	1-Ethyl-	5·62	100	4·88	200	0·74
		5·71 (*b*)	120	4·97 (*b*)	240	0·74
13.	1-*n*-Propyl-	5·46	200	4·83	170	0·63
14.	1-*iso*-Propyl-	5·74	100	4·97	200	0·77
15.	1-*n*-Butyl-	5·31	230	4·75	200	0·56
16.	1-Allyl-	—	—	4·58 (*b*)	210	—
17.	1-Hydroxymethyl-	5·44	100	4·99	210	0·45
18.	1-β-Hydroxyethyl-	5·29	100	4·82	210	0·47
19.	1 : 5-Dimethyl-	—	—	5·22	190	—
20.	1 : 6-Dimethyl-	—	—	5·17	190	—
21.	2 : 5-Dimethyl-	—	—	6·03 (*c*)	190	—
22.	1 : 2 : 5-Trimethyl-... ...	—	—	6·07	200	—
23.	1 : 5 : 6-Trimethyl-... ...	—	—	5·45	180	—
24.	2 : 5 : 6-Trimethyl-... ...	—	—	6·29	180	—
25.	2-Phenyl-	—	—	4·51	210	—
26.	2-Phenyl-5 : 6-dimethyl- ...	—	—	5·10	200	—

(*a*) Too insoluble for determination at dilution 500/M.
(*b*) Determined by titration of the hydrochloride with 0·1N sodium hydroxide.
(*c*) This value is probably rather low.

paralleled by equivalent decrease in the solubility in ethanol. In accordance with Kolthoff's relationship the ΔpK_a values should, therefore, increase and the basicities of the benziminazoles in aqueous ethanol be depressed to an increasingly greater degree. The ΔpK_a values for 1-hydroxymethyl- and 1-β-hydroxyethyl-benziminazole are smaller than those of the corresponding alkylbenziminazoles owing to the hydrophilic

properties of the ω-hydroxyl group; the same effect is still more evident in the case of 1-β-D-glucopyranosylbenziminazole (No. 46).

TABLE III

	Substituted benziminazole	pK_a values at 25 ± 1° C.			
		Water	Dilution (litres/M)	50 per cent. Ethanol	Dilution (litres/M)
27.	4-Methoxy-	—	—	4·98	200
28.	5-Methoxy-	—	—	5·07	200
29.	5-Methoxy-1-methyl-	—	—	5·07	190
30.	5-Methoxy-2-methyl-	—	—	5·93	180
31.	5-Methoxy-1 : 2-dimethyl-	—	—	5·86	200
32.	5-Chloro-	—	—	3·92 (*a*)	270
33.	5-Chloro-1-methyl-	—	—	3·88 (*a*)	190
34.	6-Chloro-1-methyl-	—	—	3·88	190
35.	5-Chloro-2-methyl-	—	—	4·71	190
36.	5-Chloro-1 : 2-dimethyl-	—	—	4·75	200
37.	4 : 6-Dichloro-	—	—	2·76	200
38.	5 : 6-Dichloro-	—	—	3·26	200
39.	5-Nitro-	—	—	2·68	220
40.	5-Nitro-1-methyl-	—	—	2·67	200
41.	5-Nitro-2-methyl-	—	—	3·37	200
42.	2-Amino-	—	—	7·39 (*b*)	180
43.	5-Amino-	6·11, 3·07(*a*)	210	—	—
44.	5-Amino-1-methyl-	6·37, 2·90(*a*)	100	5·95, 2·75(*a*)	200
45.	5-Amino-2-methyl-	6·81, 3·45(*a*)	200	—	—

(*a*) Determined by titration of the (di)-hydrochloride with 0·1N sodium hydroxide.
(*b*) Albert *et al.*[6] found pK_a 7·54 in water (dilution 160/M) at 20° C.

A number of benziminazoles containing methoxyl (nos. 27 to 31), chloro- (nos. 32 to 38) and nitro-substituents (nos. 39 to 41) were also examined in the course of the present studies. The basicities are seen to vary with the known inductive effects of the substituents. Further introduction of methyl groups into positions 1 and 2 produces a decrease or increase, respectively, in the basicities of the benziminazoles in the manner previously established for the simpler compounds (see page 423). The increase in pK_a caused by introduction of an amino-grouping into position 5 is markedly lower than that observed by Albert *et al.*[6] in passing from acridine to 2-aminoacridine. The base-strengthening ionic resonance of the type postulated for 2-aminoacridine by the latter authors does not, therefore, appear to operate in this instance, or is, alternatively, of secondary importance to the base-strengthening effects associated with the conversion of benziminazole into the benziminazolinium ion (p. 423).

The pK_a values of the benziminazole glycosides (Table IV) are of particular interest. The compounds are considerably less basic than the corresponding benziminazoles, the glycosidic residues exerting a base-weakening influence by virtue of their – I effects. In general the basicity

appears to fall in the series of 1-β-D-ribo- > 1-α-D-arabo- > 1-α-L-arabo- > 1-β-D-gluco- > 1-β-D-xylopyranosyl. There is, however, no evident correlation between basicity and the spatial configuration of the hydroxyl-groups in the glycosidic side chain.

TABLE IV

Substance	pK_a values at 25 ± 1°C.				pK_a
	Water	Dilution (litres/M)	50 per cent. Ethanol	Dilution (litres/M)	
46. 1-β-D-Glucopyranosyl- ...	4·01 (*a*)	100	3·69 (*a*)	200	0·32
47. 1-β-D-Xylopyranosyl- ...	3·92	100	—	—	—
48. 1-α-D-Arabopyranosyl- ...	4·22	140	—	—	—
49. 1-α-L-Arabopyranosyl- ...	4·09	130	—	—	—
50. 1-β-D-Gluco.-5-methyl- ...	4·32	160	—	—	—
51. 1-β-D-Xylo.-5-methyl- ...	4·17	420	—	—	—
52. 1-α-D-Arabo.-5-methyl- ...	4·33	120	—	—	—
53. 1-β-D-Gluco.-5: 6-dimethyl-	4·63	150	—	—	—
54. 1-α-L-Arabo.-5 : 6-dimethyl-	4·58	430	—	—	—
55. 1-β-D-Ribo.-5 : 6-dimethyl-	4·70	490	—	—	—
56. 2-Pentahydroxyamyl-(D-Gluco.)	5·28	100	5·19	210	0·09

(*a*) Determined by titration of the hydrochloride with 0·1N sodium hydroxide.

Comparison of the basicity values in aqueous ethanol of a series of benziminazoles containing a common substituent with the pK_a values of the corresponding benziminazoles without that substituent, shows that the effect (δpK_a) of the substituent on the basicity of the benziminazole is essentially constant. Thus a 2-methyl group elevates the basicity of benziminazole itself by 0·79 units, of 5-methylbenziminazole by 0·81 units, and of 5-chlorobenziminazole by 0·79 units. A 5-chloro-substituent, on the other hand, decreases the basicity of both benziminazole and 2-methylbenziminazole by 1·06 units, etc.

Extensive comparisons of this kind lead to the following list of δpK_a values :

TABLE V

Substituent	δpK_a
1-Me ...	−0·04
2-Me ...	+0·79
5-Me ...	+0·31
5 : 6-Di-Me ...	+0·52
2-Ph ...	−0·42
5-OMe ...	−0·15
5-Cl ...	−1·04
5-NO_2 ...	−2·31

Employing these constants, the pK_a value (in aqueous ethanol) of a substituted benzimidazole may be readily calculated with impressive accuracy by adding the δpK_a values of the substituents to the value of pK_a for the parent base (4·98). Polar interaction between the substituents is thus of a very low order. Interaction between the electronic patterns of benzimidazole and its substituent groups is evident, however, as the δpK_a values of the latter vary markedly with their position within the benzimidazole framework.

Some of the benzimidazoles used in the present study have not previously been described in the literature, and their preparation is, therefore, recorded in the Experimental section.

Experimental

A Muirhead model D 303-C *p*H meter was employed throughout the investigation. The electrode assembly consisted of glass and calomel electrodes, of which the latter rested in a 3·5 M potassium chloride reservoir fitted with flexible capillary bridge, the tip of which, together with the glass electrode, was suspended in a thermostatically jacketed titration vessel equipped with thermometer and electrically-driven stirrer. The instrument was standardised at *p*H 4·00 and 9·00, and checked at *p*H 2·01, 2·99, 4·99, 6·01, 7·00 and 8·01, "B.D.H. electrometrically checked buffer solutions" being employed throughout. The titrants were 0·1 N aqueous hydrochloric acid or sodium hydroxide, which were added from a micro-burette to 25 ml. samples of the benzimidazole solutions.

Aqueous ethanol, when employed as solvent, was made up as 52 per cent. ethanol by volume at 25°C. The titrations were then carried out with aqueous titrants, thus ensuring that the ethanol concentration at the point of half neutralisation was 50 ± 1 per cent. ethanol. The absence of systematic error in this modified procedure[11] was confirmed by control experiments employing 50 per cent. aqueous ethanol as solvent for both base and titrant. Careful establishment of the liquid junction was essential for reproducibility of the determinations in aqueous alcohol.

A minimum of three titrations was performed with each base and the classical pK_a value obtained from a plot of the relationship $pK_a = pH + \log \frac{C_{BH^{\oplus}}}{C_B}$. Sets of titrations which showed a spread of more than 0·05 pK_a units were rejected and the experiments repeated with fresh samples of the base.

The foregoing simplified expression for calculating the pK_a does not allow for the effects of salt hydrolysis, which occur with weak bases ($pK_a < 4{\cdot}5$) or in very dilute solutions ($< \frac{1}{200}$ M). A calculated correction which compensates for this effect has, therefore, been made in the tabulated values.

The classical pK_a values are related to the thermodynamical values pK_a by the expression

$$pK_a = pK_a + \log_{10} f_{BH^{\oplus}}$$

where $f_{BH^{\oplus}}$ is the activity coefficient of species $BH^{\oplus}$. The latter has

been evaluated from the simplified Debye-Hückel expression for solutions of low ionic strength:

$$\log f\, i = -\mathrm{A}zi^2\sqrt{I}$$

where A is a constant equal to 0·509 (approx.) at 25°C. for aqueous solutions, zi is the valency of the ionic species i, and I is the ionic strength of the solution. Table VI records the activity correction factors which must be added to the classical $p\mathrm{K_a}$ values (in water) to convert them to the thermodynamical values. The corrections which must be applied to determinations in 50 per cent. aqueous ethanol are greater than these by a factor of approx. 1·8.

TABLE VI

ACTIVITY CORRECTION FACTORS

Titration Type	Dilution			
	0·01 M	0·005 M	0·3 M	0·002 M
Titration of base solution	−0·04	−0·03	−0·02	−0·02
Titration of hydrochloride soln.	−0·05	−0·04	−0·03	−0·02
Titration of dihydrochloride soln.(a)				
$p\mathrm{K_{a1}}$	−0·08	−0·07	—	—
$p\mathrm{K_{a2}}$	−0·07	−0·05	—	—

(a) $p\mathrm{K_{a1}}$ refers to the ionisation constant for the dissociation:

$$\mathrm{BH_2^{++}} \rightleftharpoons \mathrm{BH^+} + \mathrm{H^+}$$

and $p\mathrm{K_{a2}}$ to dissociation:

$$\mathrm{BH^+} \rightleftharpoons \mathrm{B} + \mathrm{H^+}$$

Synthetical Section

The following benziminazoles were prepared essentially by Phillips' method[12] (cf. Part III[13]) employing the appropriate *o*-dinitrobenzenes, *o*-nitroanilines, and *o*-nitromethylanilines.

Benziminazole hydrochloride hydrate crystallised from ethanol-light petroleum in long rods, m.pt. 110° to 112°C. Found: N, 16·1, 16·4; Cl, 20·6, 21·2. $\mathrm{C_7H_6N_2,HCl,H_2O}$ requires N, 16·2; Cl, 20·6 per cent.

1-*Ethylbenziminazole hydrochloride* separated from ethanol-ether in needles, m.pt. ⇌ 270°C. Found: C, 59·2; H, 6·3; N, 15·3; Cl, 19·3. $\mathrm{C_9H_{10}N_2,HCl}$ requires C, 59·2; H, 6·0; N, 15·3; Cl, 19·5 per cent.

2-tert.-*Butylbenziminazole* formed needles from aqueous ethanol, m.pt. 315°C. Found: C, 75·6; H, 8·1; N, 16·2. $\mathrm{C_{11}H_{14}N_2}$ requires C, 75·9; H, 8·0; N, 16·1 per cent.

5:6-*Dimethyl-2-phenylbenziminazole* was prepared by the method of Weidenhagen[14] and crystallised from aqueous ethanol in needles, m.pt. 251° to 252°C. Found: C, 81·0; H, 6·3; N, 12·6. $\mathrm{C_{15}H_{14}N_2}$ requires C, 81·0; H, 6·2; N, 13·0 per cent.

4-*Methoxybenziminazole* crystallised from ethanol-light petroleum in needles, m.pt. 169° to 170°C. Found: C, 65·3; H, 5·4; N, 18·8. $\mathrm{C_8H_8ON_2}$ requires C, 64·9; H, 5·4; N, 19·0 per cent.

5-*Methoxy*-1-*methylbenziminazole*, cream needles from ethyl acetate-light petroleum, m.pt. 113°C. Found: N, 17·1. $C_9H_{10}ON_2$ requires N, 17·3 per cent.

5-*Methoxy*-1:2-*dimethylbenziminazole* was obtained in prismatic needles from ethyl acetate-light petroleum, m.pt. 130°C. Found: N, 16·0. $C_{10}H_{12}ON_2$ requires N, 15·9 per cent.

5-*Chloro*-1-*methylbenziminazole hydrochloride* formed needles from alcohol-ether, m.pt. 242° to 243°C. Found: N, 13·4; Cl, 34·7. $C_8H_7N_2Cl$ requires N, 13·8; Cl, 34·9 per cent. The *picrate* separated from β-ethoxyethanol in yellow prismatic needles, m.pt. 261°C. (decomp.). Found: C, 42·8; H, 2·5; N, 17·7. $C_8H_7N_2Cl.C_6H_3O_7N_3$ requires C, 42·5; H, 2·6; N, 17·7 per cent.

6-*Chloro*-1-*methylbenziminazole* crystallised in long flat needles from ethyl acetate-light petroleum, m.pt. 123° to 124°C. Found: C, 57·7; H, 4·2; N, 17·2. $C_8H_7N_2Cl$ requires C, 57·7; H, 4·2; N, 16·8 per cent. The *picrate* formed soft yellow needles from β-ethoxyethanol, m.pt. 249°C. Found: N, 18·2. $C_8H_7N_2Cl.C_6H_3O_7N_3$ requires N, 17·7 per cent.

4:6-*Dichlorobenziminazole*, felted needles from aqueous ethanol, m.pt. 225° to 226°C. Found: N, 14·9. $C_7H_4N_2Cl_2$ requires N, 14·5 per cent. The *hydrochloride* formed silver leaflets from ethanol containing a little water, m.pt. 275° to 280°C. Found: N, 12·4; Cl, 46·8. $C_7H_4N_2Cl_2,HCl$ requires N, 12·5; Cl, 47·5 per cent.

5:6-*Dichlorobenziminazole*, colourless platelets from aqueous ethanol, m.pt. 204° to 205°C. Found: N, 14·1; Cl, 34·2. $C_7H_4N_2Cl_2.H_2O$ requires N, 13·7; Cl, 34·6 per cent. The *picrate* crystallised from β-ethoxyethanol in yellow needles, m.pt. 238°C. (decomp.). Found: N, 16·8. $C_7H_4N_2Cl_2.C_6H_3O_7N_3$ requires N, 16·7 per cent.

1-*Methyl*-5-*nitrobenziminazole*, prepared by treating 4-nitro-*N*(1)-methyl-*o*-phenylenediamine with formic acid, separated from benzene in flat yellow needles, m.pt. 209° to 210°C. Found: N, 24·0. $C_8H_7O_2N_3$ requires N, 23·7 per cent. The *picrate* formed yellow needles from β-ethoxyethanol, m.pt. 238°C. Found: N, 20·8. $C_8H_7O_2N_3.C_6H_3O_7N_3$ requires N, 20·7 per cent.

The 5-aminobenziminazole dihydrochlorides (nos. 43 to 45) were prepared by shaking alcoholic solutions of the corresponding nitro-compounds with hydrogen in the presence of palladised charcoal until hydrogen uptake was complete, followed by addition of concentrated hydrochloric acid until crystallisation commenced. 5-*Amino*-1-*methylbenziminazole dihydrochloride* crystallised from ethanol in colourless needles, m.pt. > 270°C. Found: N, 19·4; Cl, 31·8. $C_8H_9N_3,2HCl$ requires N, 19·1; Cl, 32·2 per cent.

1-*n*-*Propylbenziminazole*. A solution of 1-allylbenziminazole hydrochloride (12·5 g.) in ethanol (120 ml.) was shaken with hydrogen in the presence of palladised charcoal until 1 mole. had been taken up. The solution was then basified and the product extracted with chloroform. 1-*n*-Propylbenziminazole, purified by distillation (b.pt. 108°C./0·5 mm., 10 g.), formed crystals, m.pt. 30°C. The *picrate* separated from

β-ethoxyethanol in prismatic yellow needles, m.pt. 185°C. Found: C, 49·4; H, 3·7. Calc. for $C_{10}H_{12}N_2.C_6H_3O_7N_3$: C, 49·4; H, 3·9 per cent. Auwers and Mauss[15] give m.pt. 204° to 206° C., and Weidenhagen *et al.*[16] give m.pt. 180° to 181°C. for the picrate.

1-iso*Propylbenziminazole.* An ice-cold solution of benziminazole (20 g.) in *iso*propanolic sodium *iso*propoxide (prepared from 4 g. of sodium and 100 ml. of dry *iso*propanol) was treated with *iso*propyl bromide (25 g.). When the vigorous reaction had subsided the mixture was heated under reflux on the steam bath for 2 hours. Precipitated sodium chloride was removed and the filtrate evaporated to dryness. The residue was partitioned between ether and 2N sodium hydroxide solution and the ethereal layer removed and taken to dryness. 1-iso-*Propylbenziminazole* (10 g.) distilled as a colourless oil, b.pt. 98°C./0·1 mm. Found: C, 74·6; H, 8·0; N, 17·0. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·5; N, 17·5 per cent.

1-*Allylbenziminazole* was prepared essentially by the method of Buchanan, Johnson, Mills and Todd[17]. The *hydrochloride* crystallised from alcohol-ether in prismatic needles, m.pt. 155° to 156°C. Found: C, 61·4; H, 6·3; N, 13·8. $C_{10}H_{10}N_2.HCl$ requires C, 61·7; H, 5·7; N, 14·4 per cent. The *picrate* formed yellow needles from β-ethoxyethanol, m.pt. 180°C. Found: C, 49·5; H, 3·4; N, 18·4. $C_{10}H_{10}N_2.C_6H_3O_7N_3$ requires C, 49·6; H, 3·9; N, 18·1 per cent.

SUMMARY

1. The pK_a values of 56 substituted benziminazoles in water and/or aqueous ethanol have been determined.

2. The relationship between basicity and constitution in the benziminazole series is discussed.

The authors thank Dr. J. Forrest for the preparation of 1-*n*-butylbenziminazole, and the Directors of The British Drug Houses, Ltd., for permission to publish this work.

REFERENCES

1. Beaven, Holiday, Johnson, Ellis and Petrow, *J. Pharm. Pharmacol.*, 1950, **2**, 944.
2. Ablov, *Bull. Soc. chim.*, 1936, (5), **3**, 2270; ibid., 1937, (5), **4**, 1783.
3. Bailar and Clapp, *J. Amer. chem. Soc.*, 1945, **67**, 171.
4. Kolthoff, Lingane and Larson, *ibid.*, 1938, **60**, 2512.
5. Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.
6. Albert, Goldacre and Phillips, *J. chem. Soc.*, 1948, 2240.
7. Hall and Sprinkle, *J. Amer. chem. Soc.*, 1932, **54**, 3469.
8. Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146.
9. Hunter and Marriott, *J. chem. Soc.*, 1941, 777.
10. Hammett, *J. Amer. chem. Soc.*, 1937, **59**, 96.
11. *cf.* Albert and Goldacre, *J. chem. Soc.*, 1946, 706.
12. Phillips, *J. chem. Soc.*, 1928, 2393.
13. Beaven, Holiday, Johnson, Ellis, Mamalis, Petrow and Sturgeon, *J. Pharm. Pharmacol.*, 1949, **1**, 957.
14. Weidenhagen, *Ber. dtsch. chem. Ges.*, 1936, **69**, 2263.
15. Auwers and Mauss, *ibid.*, 1928, **61**, 2411.
16. Weidenhagen, Train, Wegner and Nordstrom, *ibid.*, 1942, **75**, 1936.
17. Buchanan, Johnson, Mills and Todd, *J. chem. Soc.*, 1950, 2485.