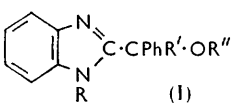
428. *Vibrational Frequency Correlations in Heterocyclic Molecules. Part VIII.*[1] *Infrared Spectra of Virus Inhibitors Related to Benzimidazole*

By D. G. O'Sullivan and A. K. Wallis

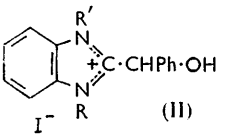
The picornavirus inhibitor, 2-(α-hydroxybenzyl)benzimidazole, whilst monomeric in dilute chloroform, is associated in the solid, the NH group being involved in relatively weak and the OH group in strong intermolecular hydrogen-bonding. Infrared spectra and molecular models show that any intramolecular OH · · · N= interaction can only be extremely weak. 1-Alkyl derivatives of 2-(α-hydroxybenzyl)benzimidazole, of importance because they protect growing cells against the three types of poliomyelitis virus, can form dimers with intermolecular OH · · · N= or OH · · · O links, both being present in chloroform and in the solid. Infrared spectra of potassium chloride discs show that the proportion of dimers of the first type decreases with increase in size of the alkyl substituent. Dimer-molecules of the 1-methyl derivative, possessing two OH · · · N= bridges, can be almost planar, but steric hindrance makes this configuration less likely with larger *N*-substituents. However, pairs of OH · · · N= bridges can still form between molecules lying in roughly parallel planes.

Infrared spectral features of 2-(α-hydroxybenzyl)benzimidazole, its 1-alkyl derivatives, and related quaternary iodides, ethers, and tertiary carbinols are discussed.

The successful stemming of a recent smallpox epidemic in Madras with an antiviral drug has awakened considerable interest in antiviral chemotherapy.[2,3] 2-(α-Hydroxybenzyl)-benzimidazole (I; R = R′ = R″ = H) and some of its derivatives are the most promising inhibitors of entero-viruses.[4,5] The parent compound, whilst very active against the poliomyelitis virus type 2, has only small activity against the types 1 and 3 viruses. However, the protection given to virus-infected tissue-culture cells increases with the introduction of *N*-alkyl substituents, a maximum being reached with the 1-propyl derivative (I; R = Pr, R′ = R″ = H) which offers cells outstanding protection against all three



(I)



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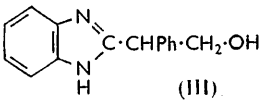


(III)

poliovirus types.[5] High protective action is also shown by the D-isomers of these compounds,[6] and by the 1-benzyl[7] and 1-methoxyethyl[8] derivatives. The methyl ether (I; R = R′ = H, R″ = Me)[8] has similar activity to 2-(α-hydroxybenzyl)benzimidazole, whilst quaternary salts,[9] tertiary carbinols,[5] and *o*-hydroxybenzyl compounds[10] related

[1] Part VII, D. G. O'Sullivan, *J.*, 1960, 3653.
[2] D. J. Bauer, L. St. Vincent, C. H. Kempe, and A. W. Downie, *Lancet*, 1963, II, 494.
[3] P. W. Sadler, D. G. O'Sullivan, and D. J. Bauer, *Antibiot. Chemotherapia*, 1963, **2**, 403.
[4] I. Tamm, R. Bablanian, M. M. Nemes, C. H. Shunk, F. M. Robinson, and K. Folkers, *J. Exp. Med.*, 1961, **113**, 625.
[5] D. G. O'Sullivan and A. K. Wallis, *Nature*, 1963, **198**, 1270.
[6] D. G. O'Sullivan, D. Pantic, and A. K. Wallis, *Nature*, 1964, **201**, 378; S. B. Kadin, H. J. Eggers, and I. Tamm, *ibid.*, p. 639.
[7] D. G. O'Sullivan, D Pantic, and A. K. Wallis, *Nature*, 1964, **203**, 433.
[8] D. G. O'Sullivan, D. Pantic, and A. K. Wallis, *Nature*, 1965, **205**, 262.
[9] D. G. O'Sullivan and A. K. Wallis, *Nature*, 1963, **200**, 1101.
[10] D. G. O'Sullivan and P. W. Sadler, *Nature*, 1961, **192**, 341.

to 2-(α-hydroxybenzyl)benzimidazole also show protective action. Knowledge, obtainable from spectra, of hydrogen-bonding propensities, shapes, and reactivities of these molecules can help to shed light on the mechanism of their action.

Results and Discussion

Frequencies between 4000 *and* 2000 *cm.*$^{-1}$.—In solid 2-(α-hydroxybenzyl)benzimidazole (I; R = R′ = R″ = H), the broad absorption with peaks between 3250 and 2650 cm.$^{-1}$ (Table) and the absence of marked absorption at higher frequencies indicate that both OH and NH groups are involved in hydrogen-bonding. The band at 3250 cm.$^{-1}$ is not present in the spectra of the *N*-alkyl derivatives (Table), suggesting that this frequency in 2-(α-hydroxybenzyl)benzimidazole is produced by NH groups which are engaged in hydrogen-bonding of only moderate strength. For comparison, the hydrogen-bonded NH stretching frequency of benzotriazole [1] is at 3200 cm.$^{-1}$, but in simple benz-

Infrared bands (cm.$^{-1}$) * between 4000 and 1500 cm.$^{-1}$

R	M. p.	Frequencies of benzimidazoles (I; R′ = R″ = H)							
H	206—207°	3250s	3060m		2800m	2650s	1625w	1590w	1530w
H †	98—99	3280s	3100s		2810s	2700m	1635w	1605w	1550w
Me	158—159		3050s		2820s	2700s	1610w	1580w	
Me †	190—191		3050s		2800s	2730m	1610w	1600w	
Et	170—171		3100s	3000s	2860s		1620w	1610w	
Pr^{n}	141—142		3150s	3000s 2930m	2870m	2710w	1620w	1610w	
Bu^{n}	134—135		3050s	2900s	2825m		1610w	1580w	
Pentyl	117—118		3100m	2920s	2840m		1610w	1600w	
Benzyl	166—167		3100s		2880s		1620w	1590w	
Methoxyethyl	135—136		3100s		2860s			1590w	

R	R′	M. p.	Frequencies of tertiary carbinols (I; R″ = H)					
H	Me	216—217°	3400m	3100s	2950s		1680s	1600m
Me	Me	194—195		3100s	2850m		1650w	1590w
H	Ph	220—221	3400s	3320s	3100m		1675s	1610m
Me	Ph	255—256		3350s	3070m		1640s	1600m

R	R′	M. p.	Frequencies of quaternary iodides (II)					
Me	Me	189—190°	3200s	3050m	2820w		1610w	1585w	1530s
Me	Et	137—139	3270s	3090m 3020m			1625w	1580w	1530s
Et	Et	155—156	3250s	3060m 3000m			1610w	1570w	1520m
Me	Pr^{n}	170—171	3220s	3050s 2990m	2900m		1610w	1570w	1525s
Et	Pr^{n}	186—187	3170s	3050s 2990s	2900m		1600w	1560m	1520m

* Measured in potassium chloride discs. † D-Isomer.

imidazoles [11,12] the NH groups are involved in strong intermolecular bonding forming resonance-stabilised linear polymers with broad bands between 3200 and 2400 cm.$^{-1}$.

α-Methyl (I; R = R″ = H, R′ = Me) and α-phenyl (I; R = R″ = H, R′ = Ph) derivatives of 2-(α-hydroxybenzyl)benzimidazole have NH stretching frequencies at 3400 cm.$^{-1}$ (Table) showing that steric hindrance either prevents this group from participating in hydrogen-bonding or makes such bonding extremely weak. The band at 3350 cm.$^{-1}$ in the 1-methyl-α-phenyl derivative (I; R = Me, R′ = Ph, R″ = H) can only be an OH stretching frequency and this band appears at 3320 cm.$^{-1}$ in the α-phenyl compound (I; R = R″ = H, R′ = Ph) (Table). Steric hindrance produced by the three rings attached to the carbinol group permits only weak hydrogen-bonding. In the

[11] D. G. O'Sullivan, *J.*, 1960, 3278.
[12] K. J. Morgan, *J.*, 1961, 2343.

α-methyl tertiary carbinols (Table), hydrogen-bonding is stronger and the OH frequencies drop to 3100 cm.$^{-1}$.

Dialkylbenzimidazolium salts give *NN'*-dialkyl-*o*-phenylenediamines on treatment with hot alkali [13] and thus possess a symmetrical structure with the positive charge shared between the two N-atoms. 1,3-Dialkyl-2-(α-hydroxybenzyl)benzimidazolium iodides (II) [9] in potassium chloride discs all have strong absorptions near 3200 cm.$^{-1}$ (Table), these frequencies necessarily arising from OH groups involved in intermolecular OH • • • OH bonds.

2-(α-Hydroxymethylbenzyl)benzimidazole (III), m. p. 150—151°, has a strong broad band at 3100 cm.$^{-1}$ containing both hydrogen-bonded OH and NH stretching modes. 2-(α-Methoxybenzyl)benzimidazole (I; R = R' = H, R'' = Me), m. p. 160—161°, possesses broad bands between 3100 and 2600 cm.$^{-1}$, resembling those of benzimidazole,[11,12] which are due to strong intermolecular NH • • • N bonds. These spectra contain at least

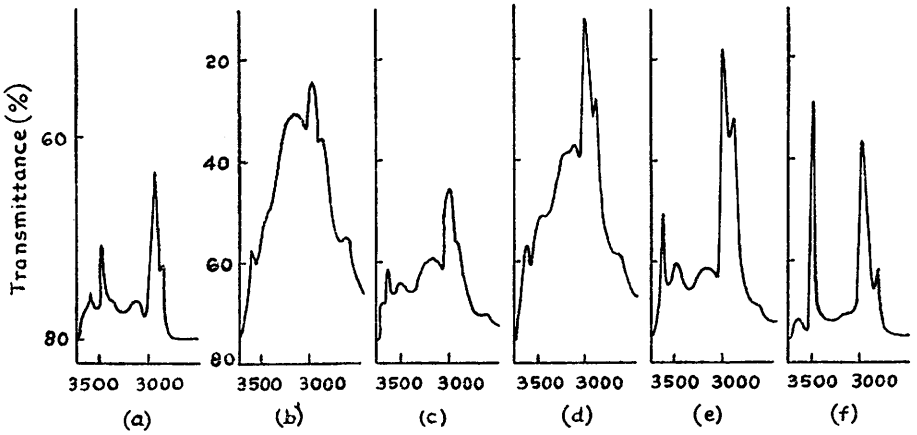


FIGURE 1. Infrared spectra (3800—2600 cm.$^{-1}$) in chloroform of the racemates: (a) 2-(α-hydroxybenzyl)benzimidazole (saturated solution); (b) 1-methyl-2-(α-hydroxybenzyl)benzimidazole (3·0%); (c) 1-methyl-2-(α-hydroxybenzyl)benzimidazole (0·75%); (d) 1-propyl-2-(α-hydroxybenzyl)benzimidazole (3·0%); (e) 1-propyl-2-(α-hydroxybenzyl)benzimidazole (0·75%); (f) 2-(α-methoxybenzyl)-benzimidazole (0·75%). For the 3% solutions 0·5-mm. cells were used, and for the 2-(α-hydroxybenzyl)benzimidazole and 0·75% solutions 1·0-mm. cells were used

one CH stretching absorption in the neighbourhood of 3000 cm.$^{-1}$, which frequently cannot be separated from the broad hydrogen-bonded OH stretching frequency (Table).

In spite of very low solubility, a saturated solution of 2-(α-hydroxybenzyl)benzimidazole in chloroform shows free OH and NH stretching frequencies at 3600 and 3490 cm.$^{-1}$, a CH stretching vibration at 2950 cm.$^{-1}$ and weaker absorptions at 3100 and 2880 cm.$^{-1}$ (Figure 1a). Quaternary iodides (II) in this solvent have free OH stretching frequencies near 3650 cm.$^{-1}$ as very weak bands in dilute solutions. A broad band at 3250 cm.$^{-1}$, similar to that shown by these compounds as solids, is due to intermolecular OH • • • O bonds. In addition to possessing CH and free OH stretching frequencies near 3000 and 3640 cm.$^{-1}$, respectively, the 1-methyl derivative (I; R = Me, R' = R'' = H) in chloroform (Figure 1b) has peaks near 2900 and 2700 cm.$^{-1}$, which tend to disappear on dilution (Figure 1c). These absorptions are less pronounced in the homologues. The 1-propyl derivative has only one shoulder near 2700 cm.$^{-1}$ (Figure 1d) which diminishes in relative intensity on dilution (Figure 1e); bands at 3000 and 2910 cm.$^{-1}$, which preserve their relative intensities on dilution, are both CH stretching frequencies. Both bands are also

[13] K. Hofmann, " Imidazole and its Derivatives," Interscience, New York, 1953, p. 280.

present in the spectrum (Figure 1f) of the α-methoxy-derivative (I; R = R′ = H, R″ = Me) in chloroform and the broader maximum at 2890 cm.$^{-1}$ in the 1-methyl derivative (Figure 1b) probably contains a second CH frequency as one component. Stronger absorption between 3200 and 3100 cm.$^{-1}$ in the spectra of the 1-alkyl derivatives (Figure 1b—e), similar to the corresponding bands of the quaternary salts, diminishes in relative intensity on dilution and clearly arises from intermolecular OH • • • O bonds. Bands near 2700 cm.$^{-1}$, also shown by 2-(α-hydroxybenzyl)benzimidazole and its 1-alkyl derivatives in discs, but absent from the solid and solution spectra of the quaternary salts, are probably due to OH • • • N bonds. In chloroform, 2-(α-methoxybenzyl)benzimidazole (I; R = R′ = H, R″ = Me), which can only form hydrogen-bonds through the imino-hydrogen, shows no bands near 3200 or 2700 cm.$^{-1}$ (Figure 1f).

With increase in chain length, a change occurs in the spectra of the 1-alkyl derivatives of 2-(α-hydroxybenzyl)benzimidazole in potassium chloride discs (Figure 2b—f). Bands

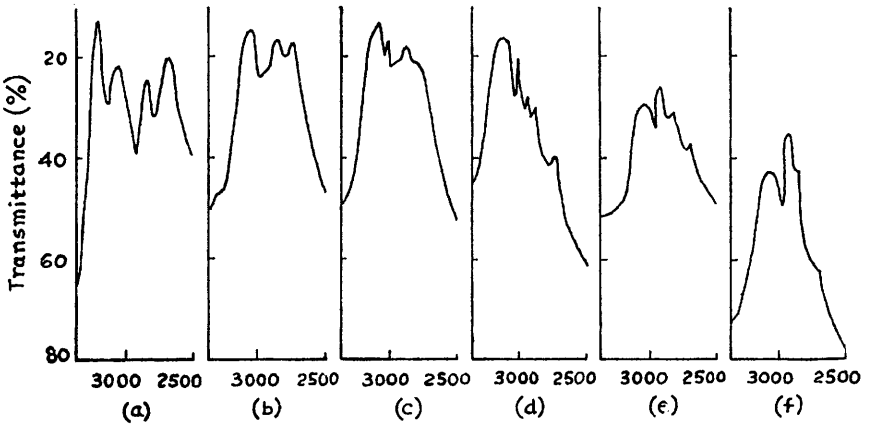
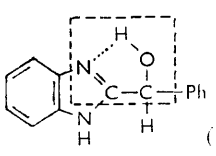
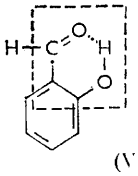


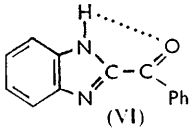
FIGURE 2. Infrared spectra (3500—2500 cm.$^{-1}$ region) in potassium chloride discs of the racemates: (a) 2-(α-hydroxybenzyl)benzimidazole (1·5%); (b) 1-methyl-2-(α-hydroxybenzyl)benzimidazole (1·5%); (c) 1-ethyl-2-(α-hydroxybenzyl)benzimidazole (1·5%); (d) 1-propyl-2-(α-hydroxybenzyl)benzimidazole (1·5%); (e) 1-butyl-2-(α-hydroxybenzyl)benzimidazole (1·3%); (f) 1-pentyl-2-(α-hydroxybenzyl)benzimidazole (1·3%)

between 2900 and 2700 cm.$^{-1}$ diminish in intensity, whilst the band near 3100 cm.$^{-1}$ broadens. This change in character of the hydrogen-bonding can be interpreted as a reduction in the share of OH • • • $\underset{|}{\text{N}}$= bonds to the total hydrogen-bonding on passing from the 1-methyl to the 1-pentyl derivative.

Inter- and Intra-molecular Hydrogen-bonding.—Any hydrogen-bonding between hydroxyl groups of the present compounds must necessarily be intermolecular, but OH • • • $\underset{|}{\text{N}}$= bonding can conceivably be inter- or intra-molecular [*e.g.*, (IV) or (IX)].


(IV)


(V)


(VI)

However, Figure 1b—e indicates that there is an increase in intensity of free OH absorption

(near 3650 cm.$^{-1}$), accompanied by a decrease in intensity of bands due to hydrogen-bonded OH groups, when solutions of the 1-alkyl derivatives of 2-(α-hydroxybenzyl)-benzimidazole in chloroform are diluted (and path-lengths increased). Thus hydrogen-bonding is largely intermolecular. Figure 3a is a scale plan of a portion of the 2-(α-hydroxybenzyl)benzimidazole molecule as indicated in (IV), assuming planarity. For comparison, an example of intramolecular hydrogen-bonding is given in Figure 3b, which portrays part of the salicylaldehyde molecule (V). Although the distance between the electronegative atoms, being less than 2·9 Å, is suitable for hydrogen-bonding in both cases, the position of the proton (Figure 3a) ensures that its interaction with the nitrogen atom in 2-(α-hydroxybenzyl)benzimidazole is very weak. Replacement of the hydroxyl hydrogen by a much larger atom, however, might produce internal bonding with the nitrogen atom. We find that 2-(α-hydroxybenzyl)benzimidazole and its 1-alkyl derivatives readily form copper(II) chelates.

In 2-benzoylbenzimidazole (VI) the C=O bond makes an angle of about 120° with the other two α-carbon valencies and the geometry is such that intramolecular hydrogen-bonding as shown (VI) is very unlikely. A saturated solution of this compound in chloroform has a strong free NH stretching frequency at 3400 cm.$^{-1}$ indicating that if any intramolecular interaction occurs, it can only be extremely weak.

Intramolecular hydrogen-bonding can occur in the 1-2′-methoxyethyl derivative of 2-(α-hydroxybenzyl)benzimidazole (VII). Dilution produces little change in the spectrum

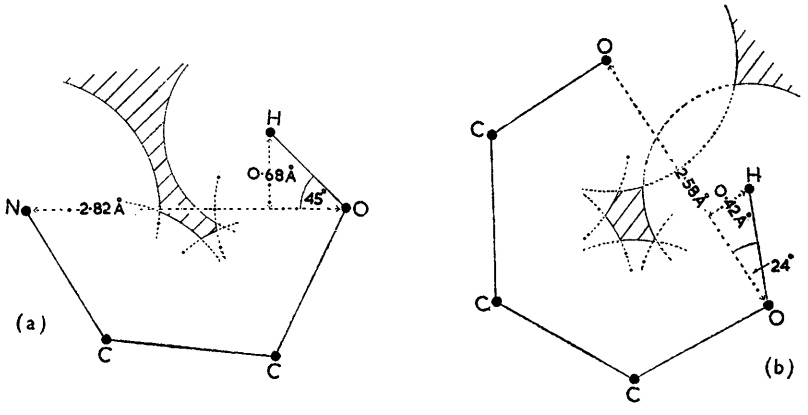
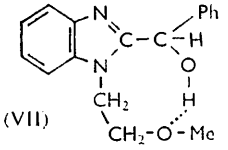


FIGURE 3. Configurations of portions of: (a) 2-(α-hydroxybenzyl)benzimidazole [shown in formula (IV)], and (b) salicylaldehyde [shown in formula (V)]. Arcs represent atomic dimensions

of this compound, confirming the presence of this type of bonding. The OH stretching frequency at 3400 cm.$^{-1}$ shows that the hydrogen-bonds are weak, as would be expected in an association involving an ether oxygen. Attempts to demethylate this compound



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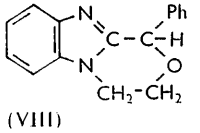
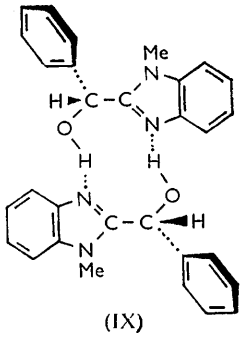


(VIII)

with hydrobromic acid to produce the 1-2′-hydroxyethyl derivative of 2-(α-hydroxybenzyl)benzimidazole gave the cyclic ether (VIII) (m. p. 161—162°). The structure of the product followed from its analysis and from the absence of an OH stretching frequency either in chloroform or in potassium chloride discs.

Dimeric Structures.—In 2-(α-hydroxybenzyl)benzimidazole, the presence of NH in addition to OH and tertiary nitrogen can produce extended hydrogen-bonded polymers in the solid. In solid *N*-alkyl derivatives, steric hindrance makes polymeric association unlikely, but dimers, linked by OH • • • N or OH • • • O bonds are possible. Scale molecular models show that OH • • •N linked dimers with almost coplanar heterocyclic rings and with the two phenyl groups in parallel planes (IX; D-configurations [6] illustrated) can form with the 1-methyl compound, but increase in the size of the 1-alkyl group makes this geometrical arrangement less likely. This structure, with two OH • • • N= links, can be achieved (*e.g.*, with models of the 1-propyl derivative) by placing two similarly oriented molecules on a flat surface, turning one upside-down and placing it on top of the other so that the two heterocyclic rings are in roughly parallel planes. Models also show that dimers with OH • • • O linkages readily form, supporting spectral evidence that this type of bonding may predominate in derivatives containing larger *N*-substituents



(IX)

Lower Frequencies.—The C=N stretching frequency occurs as a well-defined band between 1680 and 1640 cm.$^{-1}$ in the tertiary carbinols (Table). The weak band between 1635 and 1600 cm.$^{-1}$ in the other compounds may also have this origin but, as it is present at a similar frequency in the quaternary iodides, it is possibly a C=C stretching mode. The strong—or medium—intensity band near 1525 cm.$^{-1}$ in the quaternary salts (II) is absent from the spectra of the other compounds. Full spectra (prism spectrometer) are available elsewhere [14] and the lower-frequency bands of simple benzimidazoles have been discussed previously.[11,15]

Experimental

Substituted 2-Benzylbenzimidazoles.—These were prepared by heating, under reflux for 8 hr., the appropriate phenylacetic acid (1 mole) and the diamine (1 mole) in M-hydrochloric acid (2·5 moles).[5,6] 2-(α-*Methoxybenzyl*)*benzimidazole* (from α-methoxyphenylacetic acid) was obtained, in 80% yield, as white needles from aqueous methanol after charcoal treatment (Found: C, 75·5; H, 6·0; N, 11·6. $C_{15}H_{14}N_2O$ requires C, 75·6; H, 5·9; N, 11·8%). 2-(α-*Hydroxymethylbenzyl*)*benzimidazole* (from tropic acid) was obtained, in 3% yield, as white needles from aqueous ethanol after charcoal treatment (Found: C, 75·3; H, 6·1; N, 11·5. $C_{15}H_{14}N_2O$ requires C, 75·6; H, 5·9; N, 11·8%).

1-(2-*Methoxyethyl*)-2-(α-*hydroxybenzyl*)*benzimidazole* (VII).—*o*-Chloronitrobenzene (9·45 g., 0·06 mole) in 65% w/v aqueous 2-methoxyethylamine (21 ml., 0·18 mole) was heated at 100° for 10 hr. After cooling, an oil separated, which was extracted into ether, washed, and dried (Na_2SO_4). Removal of the ether gave 1-(2-methoxyethyl)-*o*-nitroaniline as a red oil (11 g., 94%). The nitroaniline (3·27 g., 0·017 mole) in methanol (50 ml.) was shaken in hydrogen at 1 atm. with Adams platinum oxide catalyst until hydrogen uptake ceased. After filtering, the methanol was removed under reduced pressure in nitrogen. The oil was heated, under reflux for 8 hr., with mandelic acid (2·54 g., 0·017 mole) in M-hydrochloric acid (45 ml.). Saturated sodium hydrogen carbonate solution was added, after cooling, and the precipitate was crystallised from aqueous methanol after treatment with charcoal. *The disubstituted benzimidazole* was obtained as white prisms (2·32 g., 49% from the nitroaniline) (Found: C, 72·4; H, 6·4; N, 9·8. $C_{17}H_{18}N_2O_2$ requires C, 72·4; H, 6·4; N, 9·9%).

3,4-*Dihydro*-1-*phenylbenzimidazo*[2,3-*c*][1,4]*oxazine* (VIII).—1-(2-Methoxyethyl)-2-(α-hydroxybenzyl)benzimidazole (0·7 g.) in hydrobromic acid (47% w/v; 3 ml.) was heated under reflux for 2½ hr. After dilution, 4M-ammonium hydroxide was added. The separated gum slowly crystallised and was then recrystallised from aqueous methanol after charcoal treatment. The *ether* (0·22 g., 35%) was obtained as white needles (Found: C, 76·4; H, 5·6; N, 11·2. $C_{16}H_{14}N_2O$ requires C, 76·8; H, 5·6; N, 11·2%).

1,3-*Dialkyl*-2-(α-*hydroxybenzyl*)*benzimidazolium Iodides* (II).—The iodides were obtained by

[14] A. K. Wallis, M.Sc. Thesis, London, 1964.
[15] D. J. Robiges and M. M. Joullie, *J. Org. Chem.*, 1964, **29**, 476.

heating at 100° for 24 hr. the 1-alkyl-2-(α-hydroxybenzyl)benzimidazole (0·002 mole) and the alkyl iodide (0·003 mole) in methanol (1 ml.) in a sealed tube.[9] The 1-ethyl-3-propyl compound (II; R = Et, R′ = Pr) was obtained in higher yield by quaternising the 1-ethyl rather than the 1-propyl derivative.

M. p.s are given in the Discussion section and in the Table.

Note.—Wagner *et al.*[16] treated 2-benzoylbenzimidazole with methylmagnesium iodide to give a product, m. p. 180—181° [we find m. p. 216—217° for 2-(α-methyl-α-hydroxylbenzyl)-benzimidazole] which on treatment with methyl iodide gave the 1-methyl derivative, identical in m. p. with the 1-methyl derivative (I; R = R′ = Me, R″ = H) we obtained by the different route.

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[16] A. F. Wagner, P. E. Wittreich, A. Lusi, and K. Folkers, *J. Org. Chem.*, 1962, **27**, 3236.