# Practicable Syntheses of 2-Hydroxymethyl-substituted Benzimidazoles and 2-Formylbenzimidazole

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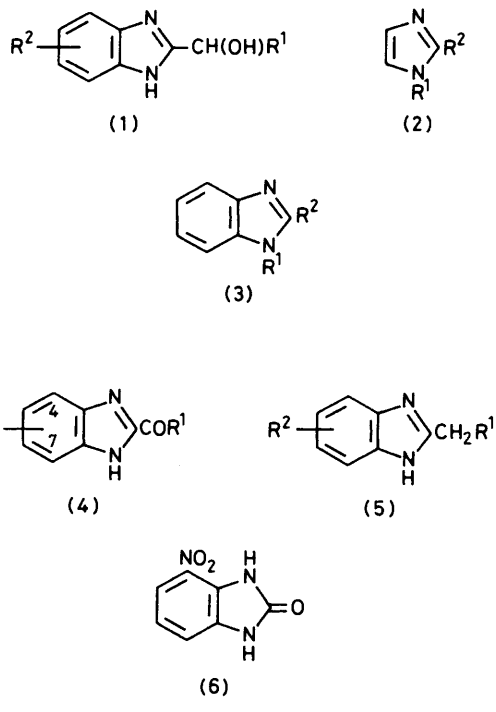
*N*-Protection of benzimidazole by a diethoxymethyl group, as in [3; $R^2$ = H, $R^1$ = $CH(OEt)_2$], allows exclusive lithiation at the 2-position. This protected anion can be made to react with various electrophiles (*e.g.* ketones, aldehydes) to yield the corresponding 2-hydroxymethylbenzimidazoles (1). Facile deprotection occurs with acid. Two practicable syntheses of 2-formylbenzimidazole are also described and an indirect route to benzimidazole-2-alcohols is discussed.

A collaboration to study the potential antiviral action in plants of 2-(α-hydroxybenzyl)benzimidazole (HBB) (1; $R^1$ = Ph, $R^2$ = H) and its analogues [1] has resulted in some new and practicable methods for the synthesis of these compounds. While the antiviral activity of benzimidazole derivatives, including that of HBB, has been widely explored [2] in man and animals, scant attention has so far been paid to their potential antiviral action in plants.[3]

For our part of the programme we required a series of HBB analogues such as (1; R = heterocyclic) which are often not accessible by the classical Phillips' method,[4] since the substituted glycolic acids required for the condensation with *o*-phenylenediamine are unstable under the reaction conditions. Also, our attempts to produce HBB (1; R = Ph), a test experiment, *via* a mono- or di-lithiated benzimidazole by treatment with n-butyl-lithium followed by benzaldehyde failed. Curtis and Brown [5] have recently reported the preparation of 2-substituted imidazoles by protection of the imidazole at the nitrogen with diethoxymethyl [2; $R^1$ = $CH(OEt)_2$, $R^2$ = H]; the protected imidazole was lithiated by n-butyl-lithium at −40 °C in tetrahydrofuran (THF) and converted into 2-substituted imidazoles [*e.g.* (2; $R^1$ = H, $R^2$ = $Bu^n$)] by reaction with various electrophiles. The authors were not able to apply the method to benzimidazole since the analogous compound [3; $R^1$ = $CH(OEt)_2$, $R^2$ = H] could not be isolated under the reaction conditions. However, we found that heating benzimidazole (3; $R^1$ = $R^2$ = H) in a large excess of triethyl orthoformate at 125—130 °C for 24 h in the presence of a catalytic amount of toluene-*p*-sulphonic acid gave a good yield (77%) of 1-diethoxymethylbenzimidazole [3; $R^1$ = $CH(OEt)_2$, $R^2$ = H]. Reduction of the reaction time to less than 16 h gave only traces of the product. The lithio-derivative was readily obtained by treatment with n-butyl-lithium at −70 °C in dry ether and reacted with various aldehydes to give the corresponding alcohol, often in good yield. It was also allowed to react with other electrophiles such as $CO_2$, ketones (see Table), and DMF (see Experimental section) in order to assess the scope of this method (*cf.* Table). The protecting group was rapidly removed during extraction with dilute acid. Condensation of the protected benzimidazole with pyridine-2- or -4-carbaldehyde gave only the corresponding stable ketones (*cf.* Table) in low yields; these were presumably formed by oxidation of the corresponding alcohols under the reaction conditions. The fair yield (56%) and the convenience of the method for obtaining 2-formylbenzimidazole (3; $R^1$ = H, $R^2$ = CHO) are noteworthy, since we found that the literature preparations [6] involve insoluble precursors and give generally low yields of a very impure aldehyde. Another practicable and novel synthesis of the aldehyde (3; $R^1$ = H, $R^2$ = CHO) was by oxidation ($MnO_2$) of 2-hydroxymethylbenzimidazole (3; $R^1$ = H, $R^2$ = $CH_2OH$) which is readily obtained from *o*-phenylenediamine and glycolic acid.



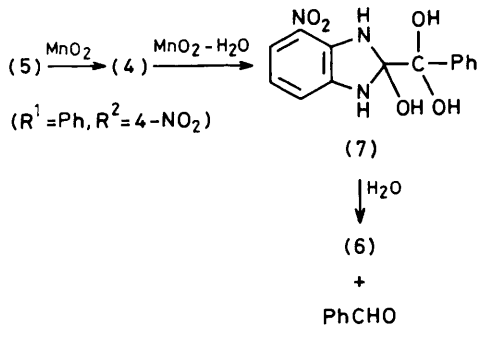

Some of the alcohols (1; $R^1$ = Ph, 2-thienyl, 2-furyl, $R^2$ = H) were also made by condensing the aldehyde (3; $R^1$ = H, $R^2$ = CHO) with the appropriate organolithium compound. This method gave, in some cases, a mixture of the alcohol (1) and the ketone (4), in proportions which depended on the reaction temperatures; it was not as productive as the route based on the protected benzimidazole.

We also studied an indirect route to some alcohols of the type (1; $R^1$ = heterocycle) which are inaccessible by the Phillips method because of the instability of the required heteroaromatic glycolic acids. This involved formation of the benzyl analogue (5; $R^1$ = heterocycle or Ph) followed by its oxidation to the ketone (4) and subsequent reduction to the alcohol (1) with sodium borohydride. The method did not work for the 2-furyl (1; $R^1$ = furyl) or 2-thienyl (1; $R^1$ = thienyl) derivatives as the appropriate acetic acids required for the condensation with phenylenediamine to give the intermediates (5; $R^1$ = 2-thienyl or 2-furyl) were unstable at elevated temperatures. Oxidation of the 2-(2-pyridylmethyl)- and the 2-(4)-pyridylmethyl)-benzimidazoles (5; $R^1$ = 2- or 4-

**Table.** Products from the reaction of 1-diethoxymethyl-2-lithiobenzimidazole [3; $R^1 = CH(OEt)_2$, $R^2 = Li$] with carbonyl compounds

| Carbonyl compound | Product [a] | Yield (%) | M.p. (°C) | Lit., M.p. (°C) [Lit., yield (%)] | Found (%) C | H | N | Formula | Required (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Benzaldehyde | (1; $R^1$ = Ph, $R^2$ = H) | 80 | 208 | 203[4] [50] | | | | | | | |
| *p*-Chlorobenzaldehyde | (1; $R^1$ = $C_6H_4Cl$-*p*, $R^2$ = H) | 67.3 | 145 | 144—145[7] [47] | | | | | | | |
| *m*-Chlorobenzaldehyde | (1; $R^1$ = $C_6H_4Cl$-*m*, $R^2$ = H) | 74.3 | 159 | | 64.8 | 4.4 | 10.9 | $C_{14}H_{11}ClH_2O$ | 65.0 | 4.3 | 10.8 |
| *o*-Fluorobenzaldehyde | (1; $R^1$ = $C_6H_4F$-*o*, $R^2$ = H) | 47.5 | 237 | | 69.6 | 4.6 | 11.6 | $C_{14}H_{11}FN_2O$ | 69.4 | 4.6 | 11.6 |
| *p*-Methylbenzaldehyde | (1; $R^1$ = $C_6H_4Me$-*p*, $R^2$ = H) | 71 | 135 | Not given [b] | | | | | | | |
| *o*-Methylbenzaldehyde | (1; $R^1$ = $C_6H_4Me$-*o*, $R^2$ = H) | 77 | 192 | | 75.6 | 5.8 | 11.65 | $C_{15}H_{14}N_2O$ | 75.6 | 5.9 | 11.8 |
| *m*-Methoxybenzaldehyde | (1; $R^1$ = $C_6H_4OMe$-*m*, $R^2$ = H) | 79.1 | 154 | | 70.7 | 5.5 | 11.1 | $C_{15}H_{14}N_2O_2$ | 70.8 | 5.55 | 11.0 |
| *o*-Piperidinobenzaldehyde | (1; R = $C_6H_4$·$NC_5H_{10}$-*o*, $R^2$ = H) | 72 | 206 | | 74.3 | 6.9 | 13.7 | $C_{19}H_{21}N_3O$ | 74.2 | 6.9 | 13.7 |
| *o*-Pyrrolidinylbenzaldehyde | (1; $R^1$ = $C_6H_4$·$NC_4H_8$-*o*, $R^2$ = H) | 74.4 | 175 | | 73.6 | 6.7 | 14.3 | $C_{18}H_{19}N_3O$ | 73.7 | 6.5 | 14.3 |
| 2-Formylfuran | (1; $R^1$ = 2-furyl, $R^2$ = H) | 65.8 | 185 | 182—184[7] [59] | | | | | | | |
| Thiophen-2-carbaldehyde | (1; $R^1$ = 2-thienyl, $R^2$ = H) | 82.6 | 202 | 196[7] [64.3] | | | | | | | |
| Pyridine-2-carbaldehyde | (4; $R^1$ = 2-pyridyl, $R^2$ = H) | 3.6 | 174 | 173—175[7] | | | | | | | |
| Pyridine-3-carbaldehyde | (1; $R^1$ = 3-pyridyl, $R^2$ = H) | 59.4 | 223 | | 69.2 | 4.9 | 18.6 | $C_{13}H_{11}N_3O$ | 69.3 | 4.9 | 18.7 |
| Pyridine-4-carbaldehyde | (4; $R^1$ = 4-pyridyl, $R^2$ = H) | 38.1 | 218—219 | | 70.0 | 4.0 | 18.8 | $C_{13}H_9N_3O$ | 70.0 | 4.1 | 18.8 |
| Cyclohexanecarbaldehyde | (1; $R^1$ = $C_6H_{11}$, $R^2$ = H) | 76 | 256—258 | 242—243[7] [75] | | | | | | | |
| Acetaldehyde | (1; $R^1$ = Me, $R^2$ = H) | 52 | 179 | 179.5[4] [70] | | | | | | | |
| Phenylacetaldehyde | (1; $R^1$ = $PhCH_2$, $R^2$ = H) | 61.3 | 263 | 260—261 [c] [43] | | | | | | | |
| Benzophenone | [3; $R^1$ = H, $R^2$ = $(Ph)_2COH$] | 80.7 | 218 | 220—222[7] [8.2] | | | | | | | |
| Butan-2-one | [3; $R^1$ = H, $R^2$ = MeC(OH)·Et] | 50.5 | 198 | 196 [d] [72] | | | | | | | |
| Cyclopentanone | (3; $R^1$ = H, $R^2$ = *cyclo*-$C_5H_8OH$) | 63.4 | 250 | | 71.2 | 7.0 | 14.0 | $C_{12}H_{14}N_2O$ | 71.3 | 7.0 | 13.85 |
| Cyclohexanone | (3; $R^1$ = H, $R^2$ = *cyclo*-$C_6H_{10}OH$) | 71.3 | 263 | | 72.0 | 7.5 | 13.0 | $C_{13}H_{16}N_2O$ | 72.2 | 7.5 | 12.95 |
| Adamantanone | (3; $R^1$ = H, $R^2$ = 1-hydroxy-adamantyl) | 77 | 256—257 | | 76.0 | 7.5 | 10.5 | $C_{17}H_{20}N_2O$ | 76.1 | 7.5 | 10.4 |
| 9-Fluorenone | (3; $R^1$ = H, $R^2$ = 9-hydroxy-fluorenyl) | 57.7 | 187—188 | | 80.6 | 4.9 | 9.2 | $C_{20}H_{14}N_2O$ | 80.5 | 4.7 | 9.4 |
| $CO_2$ | (3; $R^1$ = H, $R^2$ = $CO_2H$) | 65.0 | 171 | 169—171 [e] | | | | | | | |

[a] The i.r., $^1H$ n.m.r., and mass spectra of all products were in agreement with their proposed structure. [b] C. Fauran, J. Eberle, M. Turin, and G. Raynaud, G.P. 2,444,194/1975 (*Chem. Abstr.*, 1975, **83**, P114426n). [c] H. Zellner, G. Zellner, F. Köppl, and J. Dirnberger, *Monatsh. Chem.*, 1967, **98**, 643. [d] M. I. Ali, A. E. M. Abd-Elfattah, and H. A. Hammouda, *Z. Naturforsch., Teil B*, 1976, **31**, 254. [e] R. A. B. Copeland and A. R. Day, *J. Am. Chem. Soc.*, 1943, **65**, 1072.




**Scheme**

pyridylmethyl) with activated manganese dioxide gave the corresponding ketones in good yields (75 and 61%, respectively). Although reduction of these ketones with sodium borohydride in isopropyl alcohol gave high yields of the impure alcohols, recrystallisation caused reoxidation to the stable ketones, a complication noticed previously.[7] This indirect method [*i.e.* (5) ⟶ (4) ⟶ (1)] proved advantageous for the preparation of the 2-(α-hydroxybenzyl)-5(6)- (1; $R^1$ = Ph, $R^2$ = 5-$NO_2$) and the -4(7)-nitrobenzimidazole (1; $R^1$ = Ph, $R^2$ = 4-$NO_2$). The oxidation of compound (5; $R^1$ = Ph, $R^2$ = 4-$NO_2$) with manganese dioxide, if carried out in boiling benzene, gives unexpectedly 1,3-dihydro-4-nitrobenzimidazol-2-one (6) as the sole product. This unprecedented formation of a benzimidazolone [8] probably involves hydroxylation of the intermediate ketone (4; $R^1$ = Ph, $R^2$ = 4-$NO_2$) by manganese dioxide with hydrolytic cleavage of the 2-substituent to give carbonyl fragments, a route which is reminiscent of the oxidative cleavage of *vic*-diols by manganese dioxide [9] (see Scheme). This was partly borne out by the observation that treatment of the 2-benzoyl derivative (4; $R^1$ = Ph, $R^2$ = 4-$NO_2$) with manganese dioxide under the reaction conditions gave the benzimidazolone [Scheme, (4) ⟶ (7) ⟶ (6)]. The conventional synthesis, by condensing, for instance, 4-nitro-*o*-phenylenediamine with mandelic acid in 4M-hydrochloric acid, gave in contrast a very low yield (8.6%) of the required compound (1; $R^1$ = Ph, $R^2$ = 5-$NO_2$); on prolonged refluxing a mixture of the 2-benzoyl-5(6)-nitrobenzimidazole (4; $R^1$ = Ph, $R^2$ = 5-$NO_2$) (12%) and an unidentified orange solid (m.p. 194 °C; $M^+$ = 273) were obtained. The attempted preparation of 4(7)-nitrobenzimidazole (1; $R^1$ = Ph, $R^2$ = 4-$NO_2$) from 3-nitro-*o*-phenylenediamine and mandelic acid produced, somewhat unexpectedly, 4-nitro-2-phenylbenzimidazole. Oxidation of the mandelic acid by the nitro-group, followed by decarboxylation of the benzoylformic acid giving benzaldehyde, which then gives rise to the above observed phenylbenzimidazole, appears to be a valid interpretation.

## Experimental

$^1$H N.m.r. spectra were recorded on a Perkin-Elmer R32 instrument at 90 MHz with tetramethylsilane as internal standard, and mass spectra were obtained on a Kratos MS 30 instrument.

*Protection of Benzimidazole; 1-Diethoxymethylbenzimidazole* [3; $R^1$ = $CH(OEt)_2$, $R^2$ = H].—A mixture of benzimidazole (0.02 mol), triethyl orthoformate (0.08 mol), and toluene-*p*-sulphonic acid (*p*-TSA) (0.1 g) was heated at 125—130 °C for 24 h with exclusion of moisture. After cooling, the excess of orthoformate was removed under reduced pressure (102 °C at 60 mmHg). Solid sodium carbonate (0.1 g) was then added and 1-*diethoxymethylbenzimidazole* [3; $R^1$ = $CH(OEt)_2$, $R^2$ = H] (76.9%) was distilled off as a colourless oil, b.p. 132 °C at $10^{-4}$ mmHg, *m/e* 220 ($M^+$); τ ($CDCl_3$) 1.85 (1 H, s, Ar), 2.10—2.85 (4 H, m, Ar), 3.70 (1 H, s, CH), 6.40 (4 H, q, 2-$CH_2$, *J* 7 Hz), and 8.80 (6 H, t, 2Me, *J* 7 Hz). Owing to the instability of the product its microanalysis was unsatisfactory. It can, however, be kept at −5 °C for several days.

*Condensations of 1-Diethoxymethylbenzimidazole* [3; $R^1$ = $CH(OEt)_2$, $R^2$ = H]. *General Method.*—To a solution of the protected benzimidazole (0.01 mol) in dry diethyl ether (50 ml) at −70 °C was added dropwise a solution of n-butyllithium in hexane (0.011 mol) with stirring under nitrogen, and stirring was continued after the addition for 2 h at −20 °C. A solution of the required carbonyl compound (0.010 mol) in dry diethyl ether (20 ml) was then added dropwise with stirring at −60 °C to the orange solution of the lithio-compound. After completion of the addition the reaction mixture was stirred at 0 °C for a further 2 h and then set aside at room temperature overnight. After dilution with diethyl ether (80 ml) the mixture was extracted with 0.1M-hydrochloric acid (4 × 50 ml portions) and the combined extracts were stirred at room temperature for 0.5 h to ensure hydrolysis of the protecting group. Addition of ammonia produced a precipitate which was filtered off to yield the product after recrystallisation from the appropriate solvent, as shown in the Table.

*Preparation of 2-Formylbenzimidazole* (3; $R^1$ = H, $R^2$ = CHO).—(*a*) A mixture of dry dimethylformamide (DMF) (0.02 mol) in diethyl ether (40 ml) was added dropwise to an ethereal solution of 1-diethoxymethyl-2-lithiobenzimidazole (0.01 mol) at −60 °C (*cf.* above) and the mixture was stirred for 2 h at 0 °C and then left at room temperature overnight. The yellow reaction mixture was poured, with stirring, into 0.1M-hydrochloric acid (300 ml) and agitation continued for 0.5 h. The aqueous layer was separated and neutralised with ammonia (*d* 0.880) and the precipitate washed (ethanol–water) to give pure 2-formylbenzimidazole as an off-white powder (56%), m.p. 234–235 °C (decomp.) (lit.,[6a] m.p. 232 °C).

(*b*) Activated manganese dioxide (30 g), prepared by heating manganese oxalate,[10] was carefully suspended in ethanol (90 ml) by slow addition with stirring (**CAUTION**: addition of ethanol onto this activated manganese dioxide may cause ignition) and 2-hydroxymethylbenzimidazole (6 g) was then added. The suspension was set aside at room temperature for 48 h and stirred. The reaction mixture was evaporated to dryness and boiling DMF (200 ml) was added to the grey residue. The hot suspension was filtered through Kieselguhr and the filtrate was taken down to dryness under reduced pressure on a water-bath. The residue was washed repeatedly by decantation from boiling ethanol to give 2-formylbenzimidazole (4.87 g, 82.3%), m.p. 233 °C (decomp.).

*Condensation of 2-Formylbenzimidazole with Aromatic Lithium Compounds.*—(*a*) A solution of phenyl-lithium in tetrahydrofuran (THF) (40 ml), made from bromobenzene (0.05 mol) in the usual way, was added dropwise with stirring to a suspension of 2-formylbenzimidazole (0.02 mol) in dry THF (50 ml) at −20 °C. The mixture was then stirred for an hour, poured onto ice–water (50 ml) and neutralised with 4M-hydrochloric acid. The THF layer was separated, combined with ether washings (3 × 100 ml) of the aqueous layer and evaporated to give a yellow slurry. On addition of ethyl acetate, starting material (40%) separated and was removed. The filtrate was concentrated under reduced pressure to give 2-(α-hydroxybenzyl)benzimidazole (1; $R^1$ = Ph, $R^2$ = H) (16.1%), m.p. 208 °C (from ethyl acetate) (lit.,[4] m.p. 203 °C).

(*b*) A solution of n-butyl-lithium (0.05 mol) in hexane was added dropwise to thiophen (0.04 mol) in dry THF (20 ml) at −25 °C under nitrogen and the resulting mixture was stirred for 2 h at −15 °C. 2-Formylbenzimidazole (0.02 mol) suspended in dry THF (30 ml) was then added slowly at − 20 °C and the reaction mixture was stirred overnight at room temperature. Finally, the slurry was poured onto crushed ice (100 g) and neutralised with 4M-hydrochloric acid. The insoluble aldehyde was filtered off and the reaction mixture was worked-up as in (*a*) to give 2-(2-thienylhydroxymethyl)benzimidazole (1; $R^1$ = 2-thienyl, $R^2$ = H) (46.5%), m.p. 202 °C (from ethyl acetate–light petroleum, b.p. 80—100 °C) (lit.,[7] m.p. 196 °C; 64.3%). When the aldehyde was added at 0 °C to the reaction mixture (*cf.* above) a mixture of the hydroxymethylbenzimidazole (1; $R^1$ = 2-thienyl, $R^2$ = H) (7.8%) and *benzimidazol-2-yl 2-thienyl ketone* (4; $R^1$ = 2-thienyl, $R^2$ = H) (19.7%) was obtained, separable on silica with ethyl acetate–light petroleum (b.p. 80—100 °C), m.p. 198—90 °C (ethyl acetate–light petroleum, b.p. 80—100 °C) (Found: C, 62.4; H, 3.5; N, 12.0. $C_{12}H_8N_2OS$ requires C, 63.1; H, 3.5; N, 12.3%); τ [$CDCl_3$–$(CD_3)_2SO$] 3.0 (1 H, s, NH), 1.15 (1 H, d, Ar, *J* 4 Hz), and 2.17—2.70 (6 H, m, Ar).

(*c*) Similar conditions to those described in (*b*) were used for the reaction with furan, except that the ratio of 2-furyllithium to 2-formylbenzimidazole was 1 : 1 and the aldehyde was added at 0 °C. The mixture was allowed to stand at 0°C for 4 h and then worked up as in (*b*) to give 2-(2-furylhydroxymethyl)benzimidazole (1; $R^1$ = 2-furyl, $R^2$ = H) (21.3%), m.p. 185 °C (diethyl ether–light petroleum, b.p. 40—60 °C) (lit.,[7] m.p. 184 °C; 59%). When the reaction mixture was allowed to stand overnight at room temperature, work-up gave a mixture of the hydroxymethyl compound (1; $R^1$ = 2-furyl, $R^2$ = H; 9.1%) and *benzimidazol-2-yl (2-furyl) ketone* (4; $R^1$ = 2-furyl, $R^2$ = H) (8.7%) m.p. 181 °C (ethyl acetate–light petroleum, b.p. 80—100 °C) (Found: C, 68.15; H, 3.9; N, 13.3. $C_{12}H_8N_2O_2$ requires C, 67.9; H, 3.8; N, 13.2%); τ [$CDCl_3$–$(CD_3)_2SO$] −2.95 (1 H, s, NH), 1.42 (1 H, d, Ar, *J* 4 Hz), 2.05—2.75 (5 H, m, Ar), and 3.3 (1 H, m, Ar).

*Preparation of* 2-(*Pyridylhydroxymethyl*)*benzimidazoles* (1; $R^1$ = $NC_5H_4$, $R^2$ = H).—(*a*) The *2-(2-pyridylmethyl)-benzimidazole* (5; $R^1$ = 2-$NC_5H_4$, $R^2$ = H (26.8%) was prepared by heating ethyl 2-pyridylacetate[11] (0.022 mol) and *o*-phenylenediamine (0.02 mol) in the presence of a crystal of *p*-TSA at 210 °C for 4 h. It had m.p. 169—171 °C (Found: C, 74.2; H, 5.2; N, 20.0. $C_{13}H_{11}N_3$ requires C, 74.6; H, 5.3; N, 20.1%); τ ($CDCl_3$) 1.52 (1 H, d, Ar), 2.48 (3 H, m, Ar), 2.78 (4 H, m, Ar), and 5.55 (2 H, s, $CH_2$) (NH was not observed probably because of strong H-bonding). By an analogous method 2-(*4-pyridylmethyl*)*benzimidazole* (5; $R^1$ = 4-$NC_5H_4$, $R^2$ = H) (10%) was prepared from ethyl 4-pyridylacetate.[12] It had m.p. 181—183 °C (Found: C, 74.9; H, 5.4; N, 20.3. $C_{13}H_{11}N_3$ requires C, 74.6; H, 5.3; N, 20.1%); τ ($CDCl_3$) −2.65 (s, NH), 1.67 (2 H, d, Ar), 2.50 (2 H, dd, Ar), 2.70—3.00 (4 H, m, Ar), and 2.94 (2 H, s, $CH_2$).

(*b*) Benzimidazol-2-ylpyridyl ketones (4; $R^1$ = 2-$C_6H_4N$ or 4-$C_5H_4N$, $R^2$ = H) were prepared as follows. Activated manganese dioxide (1 g) was added to a solution of the 2-(2- and 4-pyridylmethyl)benzimidazole (0.2 g) in dioxan (10 ml) and the suspension was stirred for 48 h at room temperature. The mixture was filtered and the residue washed several times with hot dioxan. The combined filtrate and washings were evaporated to dryness and the residue purified by crystallisation (ethyl acetate). The benzimidazol-2-yl 2-pyridyl ketone (75.0%) had m.p. 174 °C (lit.,[7] m.p. 173—175 °C) while the *4-pyridyl isomer* had m.p. 218—219 °C (Found: C, 70.0; H, 4.0; N, 18.8. $C_{13}H_9N_3O$ requires C, 70.0; H, 4.1; N, 18.8%); τ [$CDCl_3$–$(CD_3)_2SO$] −3.45 (1 H, br, NH), 1.15 (2 H, dd, Ar), 1.60 (2 H, dd, Ar), 2.20 (2 H, m, Ar), and 2.70 (2 H, m, Ar).

(*c*) The 2-(pyridylhydroxymethyl)benzimidazoles (1; $R^1$ = $NC_5H_4$, $R^2$ = H) were prepared as follows. To a suspension of the 2-benzimidazolyl 2- or 4-pyridyl ketone (0.45 g) in isopropyl alcohol (50 ml), sodium borohydride (0.50 g) was added at room temperature and stirring continued for 20 min. The reaction mixture was treated with a saturated solution of sodium chloride (100 ml) and the resultant mixture extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered, and finally evaporated to dryness *in vacuo*. Purification was achieved by triturating the crude residue repeatedly in diethyl ether. Attempts at recrystallisation caused reconversion of the alcohol into the ketone. 2-(2-Pyridylhydroxymethyl)benzimidazole[7] had m.p. 134—136 °C (100% crude yield) (Found: $M^+$, 225.0900. $C_{13}H_{11}N_3O$ requires *M*, 225.0901). The 2-(4-pyridylhydroxymethyl)benzimidazole had m.p. 183—185 °C (91.1% crude yield) (Found: C, 69.5; H, 4.8; N, 18.4%; $M^+$, 225.0900. $C_{13}H_{11}N_3O$ requires C, 69.3; H, 4.9; N, 18.7%; *M*, 225.0901).

*Preparation of* 2-(*Hydroxymethyl*)*nitrobenzimidazoles* [1; $R^1$ = Ph, $R^2$ = 5(6)-$NO_2$ or 4(7)-$NO_2$].—The 2-benzyl-5(6)- and the -4(7)-nitrobenzimidazoles[13] were made from the appropriate nitro-*o*-phenylenediamines and phenylacetic acid in the usual way. A mixture of the 2-benzylnitrobenzimidazole (1 g), activated manganese dioxide (5 g), and dry dioxan (30 ml) was stirred at 50 °C for 2 days (when starting material disappeared on t.l.c.). The suspension was filtered and the residue washed with hot dioxan. The filtrate and washings were combined and evaporated to dryness under reduced pressure and the product was purified by recrystallisation (ethyl acetate). 2-Benzoyl-5(6)-nitrobenzimidazole (95.7%) had m.p. 254 °C (lit.,[14] m.p. 255 °C). 2-Benzoyl-4(7)-nitrobenzimidazole (85.3%) had m.p. 189—190 °C (Found: C, 63.0; H, 3.4; N, 15.8. $C_{14}H_9N_3O_3$ requires C, 62.9; H, 3.4; N, 15.7%). τ [$(CD_3)_2SO$] −3.75 (1 H, b, NH), 1.45 (2 H, d, Ar), 1.75 (2 H, m, Ar), and 2.35 (4 H, m, Ar).

When the oxidation of the 2-benzyl-4(7)-nitrobenzimidazole was carried out in boiling benzene for 72 h the product was 1,3-dihydro-4-nitrobenzimidazol-2-one (6) (34%), m.p. 340 °C (decomp.) (lit.,[15] m.p. 342 °C or [8] 349—350 °C).

Reduction of the appropriate 2-benzoylnitrobenzimidazoles (4; $R^1$ = Ph, $R^2$ = 5-$NO_2$ or 4-$NO_2$) with sodium borohydride as described for the preparation of the 2-(pyridylhydroxymethyl)benzimidazoles gave 2-(α-hydroxybenzyl)-5(6)-nitrobenzimidazole (1; $R^1$ = Ph, $R^2$ = 5-$NO_2$) (95.6%), m.p. 170—171 °C (lit.,[7] m.p. 169—171 °C) or 2-(*α-hydroxybenzyl*)-*4(7)-nitrobenzimidazole* (1; $R^1$ = Ph, $R^2$ = 4-$NO_2$) (92%), m.p. 168 °C (Found: C, 62.3; H, 4.2; N, 15.7. $C_{14}H_{11}N_3O_3$ requires C, 62.45; H, 4.1; N, 15.6%); τ [$(CD_3)_2SO$] −3.30 to −2.20 (br, NH), 1.95 (2 H, d, Ar), 2.45—2.75 (7 H, m, Ar and OH), and 3.85 (1 H, s, CH).

## Acknowledgements

We thank Professor A. C. Cassels, Department of Botany, University College, Cork, Ireland, for useful discussions and collaboration.

## References

1 A. C. Cassels and F. M. Cocker, *Z. Naturforsch., Teil C*, 1982, **37**, 390.

2 H. J. Eggers and I. Tamm, *Virology*, 1961, **13**, 545; D. G. O'Sullivan and P. W. Sadler, *Nature*, 1961, **192**, 341; D. G. O'Sullivan, D. Pantic, and A. K. Wallis, *Nature*, 1964, **201**, 378; I. Tamm

and P. B. Seghal, *Adv. Virus Res.*, 1978, **22**, 187; P. B. Seghal, *Antibiot. Chemother.*, 1980, **27**, 93.
3 H. Lapierre, C. Kusiak, J. Alboug, G. Macquaire, A. C. Farault, and T. Staron, *Ann. Phytopathology*, 1971, **3**, 3 (*Chem. Abstr.*, 1972, **76**, 54748n).
4 M. A. Phillips, *J. Chem. Soc.*, 1928, 2393; *ibid.*, 1929, 2820; *ibid.*, 1930, 1409.
5 N. J. Curtis and R. S. Brown, *J. Org. Chem.*, 1980, **45**, 4038.
6 (*a*) H. Baganz, *Angew. Chem., Int. Ed. Engl.*, 1956, **68**, 151; (*b*) C. F. Huebner, K. Lohman, R. J. Dimler, S. Moore, and K. P. Link, *J. Biol. Chem.*, 1945, **159**, 503; (*c*) Y. A. Zhdanov and G. N. Dorofeenko, *J. Gen. Chem.* (*U.S.S.R.*), 1959, **29**, 2643.
7 A. F. Wagner, P. E. Wittreich, A. Lusi, and K. Folkers, *J. Org. Chem.*, 1962, **27**, 3236.
8 'Benzimidazoles and Congeneric Tricyclic Compounds,' ed. P. N. Preston, Interscience, John Wiley, 1981, p. 348.
9 G. Ohloff and W. Giersch, *Angew. Chem. Int. Ed. Engl.*, 1973, **12**, 401.
10 R. Gritter and T. Wallace, *J. Org. Chem.*, 1959, **24**, 1051.
11 R. B. Woodward and E. C. Kornfeld, *Org. Syn. Coll.*, 1955, vol. III, p. 413.
12 R. L. Malan and P. M. Dean, *J. Am. Chem. Soc.*, 1947, **69**, 1797.
13 A. F. Casy and J. Wright, *J. Pharm. Pharmacol.*, 1966, **18**, 677.
14 P. Bouchet, C. Coquelet, J. Elguero, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1976, 192.
15 L. S. Efros and A. V. El'tsov, *Zh. Obshch. Khim.*, 1957, **27**, 127 (*Chem. Abstr.*, 1957, **51**, 12882g).

*Received* 24*th March* 1982; *Paper* 2/510