New Benzimidazoles and Novel Use of 2-Formylbenzimidazole in Syntheses

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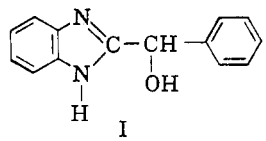
A series of analogs and derivatives of 2-(α-hydroxybenzyl)benzimidazole (HBB) was synthesized to establish the effect of structure on the antiviral activity of HBB. The compounds synthesized include HBB analogs with a substituent at the 4-, or 5-(6-) position of the benzo moiety, N^1 of the imidazole function, the α-carbon atom of the hydroxybenzyl group, or the *m*- or *p*-position of the phenyl moiety. An imidazole derivative corresponding to HBB and analogs of HBB in which the phenyl moiety is replaced by a 2-furyl or a 2-thienyl function are also described. A synthesis designed for the preparation of a 2-pyridyl analog of HBB yielded 2-pyridyl 2-benzimidazolyl ketone.

The selective inhibition of polio virus multiplication by 2-(α-hydroxybenzyl)benzimidazole (HBB) (I) has been described.[1,2] These initial observa-

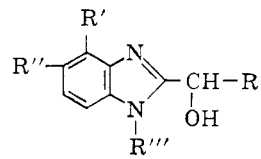


I

tions on the antiviral activity of HBB have been extended to include inhibition of cytopathic effects of enteroviruses in general, and the antiviral spectrum of HBB has been recorded.[3,4] As a part of the program leading to these observations, a series of HBB derivatives and analogs has been synthesized. Some of the new compounds were prepared by the novel use of 2-formylbenzimidazole; others were synthesized by the unexplored use of Grignard and organolithium reagents with 2-benzoylbenzimidazole. All of these compounds were tested to expand the data on the effect of structure on the viral inhibitory activity of HBB. The synthesis and chemical properties of such derivatives are recorded in this paper; the extensive data on structure-activity relationships will be described separately.[5]

The compounds described include HBB analogs with a substituent at the 4- or 5-(6) position of the benzo moiety, N^1 of the imidazole function, the α-carbon atom of the hydroxybenzyl group or the *m*- or *p*-position of the phenyl moiety. Certain derivatives with substituents at several positions are also described. In addition, synthesis of an imidazole derivative corresponding to HBB and analogs of HBB in which the phenyl moiety is replaced by an aromatic heterocyclic function are described.

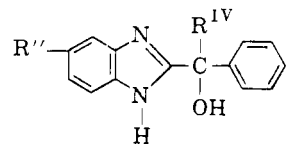
The N^1-methyl derivative and analogs of HBB with a substituent at the 4- or 5-(6-) position of the benzo moiety, or on the *m*- or *p*-position of the phenyl substituent were synthesized by condensing a suitably substituted phenylenediamine with an appropriate derivative of mandelic acid under acidic conditions (Phillips condensation).[6] These analogs are summarized by structures II–X.



Note: R's = H unless specified

II. R = C_6H_{11}
III. R = C_6H_5; R′ = C_2H_5
IV. R = *m*-$NO_2C_6H_4$
V. R = *p*-ClC_6H_4
VI. R = C_6H_5; R‴ = CH_3
VII. R = C_6H_5; R″ = CH_3
VIII. R = C_6H_5; R″ = CF_3
IX. R = C_6H_5; R″ = CH_3O
X. R = C_6H_5; R″ = NO_2

The derivatives XI–XVII with a substituent on the α-carbon atom of the hydroxybenzyl group were synthesized by condensing an appropriately substituted 2-benzoylbenzimidazole with either a Grignard reagent or an organolithium derivative of the desired substituent.

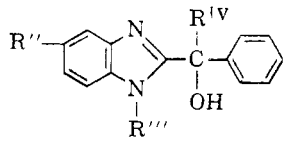


Note: R's = H unless specified.

XI. R^{IV} = CH_3
XII. R^{IV} = C_2H_5
XIII. R^{IV} = $(CH_3)_2CH$
XIV. R^{IV} = $CH_2{=}C(CH_3)CH_2$
XV. R^{IV} = CH_3; R″ = CF_3
XVI. R^{IV} = C_6H_5
XVII. R^{IV} = $CH_2CO_2C_2H_5$
XVII ⟶ XVIII. R^{IV} = $CH_2CO_2NH_4$

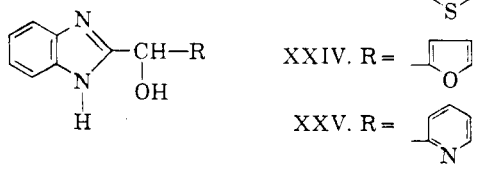
The N^1-substituted analogs XIX–XXI were prepared by the alkylation of the corresponding HBB derivatives with the appropriate alkyl halide in the presence of anhydrous potassium carbonate.

(1) A. C. Hollinshead and P. K. Smith, *J. Pharmacol. Exp. Therap.*, **123**, 54 (1958).
(2) I. Tamm and M. M. Nemes, *J. Clin. Invest.*, **38**, 1047 (1959).
(3) I. Tamm, R. Bablanian, M. M. Nemes, C. H. Shunk, F. M. Robinson, and K. Folkers, *J. Exp. Med.*, **113**, 625 (1961).
(4) H. J. Eggers and I. Tamm, *ibid.*, **113**, 657 (1961).
(5) I. Tamm, H. J. Eggers, R. Bablanian, A. F. Wagner, P. E. Wittreich, and K. Folkers, manuscript in preparation.
(6) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).



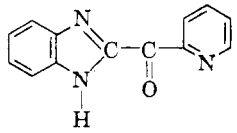
Note: R's = H unless specified.
XIX. R''' and R^{IV} = CH_3
XX. R''' and R^{IV} = CH_3; R'' = CF_3
XXI. R^{IV} = CH_3; R''' = $CH_2CO_2C_2H_5$
XXI ⟶ XXII. R^{IV} = CH_3; R''' = CH_2CO_2Na

Analogs of HBB in which the phenyl moiety is replaced by an aromatic heterocyclic moiety were synthesized by the condensation of 2-formylbenzimidazole[7] with a heterocyclic Grignard reagent. This method worked smoothly for the 2-thienyl (XXIII) and 2-furyl (XXIV) analogs, but not for the 2-pyridyl derivative (XXV).



XXIII. R = 
XXIV. R =
XXV. R =

The latter compound is apparently very susceptible to oxidation since 2-pyridyl 2-benzimidazolyl ketone (XXVI) was isolated from the reaction mixture in



XXVI

good yield. The ketone was reduced catalytically, and fractions were obtained which contained 2-(2-pyridyl-α-hydroxymethyl)benzimidazole. However, each purification step resulted in a further increase in the ketone content of the fraction.

2-(α-Hydroxybenzyl)imidazole[8] was synthesized from 2-lithio-N-benzylimidazole and benzaldehyde; selective cleavage of the N-benzyl group of the condensation product in the presence of the 2-(α-hydroxybenzyl) substituent was achieved using sodium in liquid ammonia.

Experimental[9]

General Method A. The Phillips Condensation.[6]—A mixture of 50 ml. of 4 *N* hydrochloric acid, 0.06 mole of a substituted mandelic acid and 0.04 mole of an appropriately substituted *o*-phenylenediamine was refluxed for 1–2 hr. The reaction mixture was cooled; in some instances, the product precipitated from the acid solution, and in others, the acid solution was neutralized with concentrated ammonium hydroxide to precipitate the product. The product was collected by filtration, washed with water, slurried with 6 *N* ammonium hydroxide, collected by filtration, and washed with water. The compound was purified by treating a hot ethanol solution of the product with Darco G-60. The ethanol solution was filtered, and the compound was precipitated by diluting the solution with water. The compound was usually recrystallized from aqueous ethanol. In some instances, ether–petroleum ether was used as a solvent for recrystallization.

2-(α-Hydroxycyclohexylmethyl)benzimidazole (II) was obtained from *o*-phenylenediamine and hexahydromandelic acid[10] (cyclohexylglycolic acid) in 75% yield, m.p. 242–243° (75% EtOH): λ_{max}^{EtOH} 245 mμ ($E_{1\,cm}^{1\%}$ 287), 274 mμ ($E_{1\,cm}^{1\%}$ 332), 281 mμ ($E_{1\,cm}^{1\%}$ 344).

Anal. Calcd. for $C_{14}H_{18}N_2O$ (230.30): C, 73.01; H, 7.88; N, 12.17. Found: C, 73.44; H, 7.40; N, 12.76.

2-(α-Hydroxybenzyl)-4-ethylbenzimidazole (III) was obtained from 3-ethyl-*o*-phenylenediamine[11] and mandelic acid in 55% yield; m.p. 189–190° (50% EtOH); λ_{max}^{EtOH} 254 mμ ($E_{1\,cm}^{1\%}$ 331), 274 mμ ($E_{1\,cm}^{1\%}$ 293), 282 mμ ($E_{1\,cm}^{1\%}$ 264).

Anal. Calcd. for $C_{16}H_{16}N_2O$ (252.30): C, 76.16; H, 6.39; N, 11.10. Found: C, 75.89; H, 6.13; N, 11.12.

2-(*m*-Nitro-α-hydroxybenzyl)benzimidazole (IV) was obtained from *o*-phenylenediamine and *m*-nitromandelic acid[12] in 39% yield; m.p. 201–202° dec. (50% EtOH); λ_{max}^{EtOH} 253 mμ ($E_{1\,cm}^{1\%}$ 479), 275 mμ ($E_{1\,cm}^{1\%}$ 496), 282 mμ ($E_{1\,cm}^{1\%}$ 442).

Anal. Calcd. for $C_{14}H_{11}N_3O_3$ (269.25): C, 62.45; H, 4.12; N, 15.61. Found: C, 62.25; H, 3.97; N, 15.82.

2-(*p*-Chloro-α-hydroxybenzyl)benzimidazole (V) was obtained from *o*-phenylenediamine and *p*-chloromandelic acid in 47% yield; m.p. 144–145° (ether–petroleum ether); λ_{max}^{EtOH} 246 mμ ($E_{1\,cm}^{1\%}$ 278), 275 mμ ($E_{1\,cm}^{1\%}$ 368), 282 mμ ($E_{1\,cm}^{1\%}$ 344).

Anal. Calcd. for $C_{14}H_{11}ClN_2O$ (258.70): C, 65.00; H, 4.29; N, 10.82; Cl, 13.71. Found: C, 65.41; H, 4.30; N, 10.34; Cl, 13.85.

1-Methyl-2-(α-hydroxybenzyl)benzimidazole (VI) was obtained from N-methyl-*o*-phenylenediamine[13] and mandelic acid in 56% yield; m.p. 158–160° (EtOH); λ_{max}^{EtOH} 254 mμ ($E_{1\,cm}^{1\%}$ 330), 270 mμ ($E_{1\,cm}^{1\%}$ 259), 277 mμ ($E_{1\,cm}^{1\%}$ 319), 284 mμ ($E_{1\,cm}^{1\%}$ 299).

Anal. Calcd. for $C_{15}H_{14}N_2O$ (238.28): C, 75.60; H, 5.92; N, 11.76. Found: C, 75.48; H, 5.65; N, 11.61.

2-(α-Hydroxybenzyl)-5-methylbenzimidazole (VII) was obtained from 4-methyl-*o*-phenylenediamine[14] and mandelic acid in 20% yield; m.p. 203–204° (50% EtOH); λ_{max}^{EtOH} 248 mμ ($E_{1\,cm}^{1\%}$ 289), 281 mμ ($E_{1\,cm}^{1\%}$ 370), 287 mμ ($E_{1\,cm}^{1\%}$ 363).

Anal. Calcd. for $C_{15}H_{14}N_2O$ (238.28): C, 75.60; H, 5.92; N, 11.76. Found: C, 75.69; H, 6.30; N, 11.28.

2-(α-Hydroxybenzyl)-5-trifluoromethylbenzimidazole (VIII) was obtained from 4-trifluoromethyl-*o*-phenylenediamine and mandelic acid in 38% yield; m.p. 197–198° (50% EtOH); λ_{max}^{EtOH} 251 mμ ($E_{1\,cm}^{1\%}$ 214), 275 mμ ($E_{1\,cm}^{1\%}$ 238), 282 mμ ($E_{1\,cm}^{1\%}$ 238).

Anal. Calcd. for $C_{15}H_{11}F_3N_2O$ (292.27): C, 61.66; H, 3.80; N, 9.59. Found: C, 61.75; H, 3.82; N, 9.88.

2-(α-Hydroxybenzyl)-5-methoxybenzimidazole (IX) was obtained from 4-methoxy-*o*-phenylenediamine[15] and mandelic acid in 21% yield; m.p. 165–166° (acetone–ether–petroleum ether); λ_{max}^{EtOH} 247 mμ ($E_{1\,cm}^{1\%}$ 252), 290 mμ ($E_{1\,cm}^{1\%}$ 390), 295 mμ ($E_{1\,cm}^{1\%}$ 354).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$ (254.28): C, 70.85; H, 5.55; N, 11.02. Found: C, 70.70; H, 5.38; N, 10.98.

2-(α-Hydroxybenzyl)-5-nitrobenzimidazole (X) was obtained from 4-nitro-*o*-phenylenediamine and mandelic acid

(7) A. Zhdanov and G. N. Dorofeyenko, *Zh. Obshch. Khim.*, **29**, 2677 (1959).

(8) This compound had been prepared previously from tartaric acid and phenacetaldehyde by A. Sonn and P. Greif, *Ber.*, **66**, 1900 (1933).

(9) Melting points were determined by the capillary method and are uncorrected.

(10) F. F. Blicke and W. K. Johnson, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 437 (1956).

(11) Prepared by catalytic reduction of 2-ethyl-6-nitroaniline [H. Paucksch, *Ber.*, **17**, 767 (1884)].

(12) Prepared according to the procedure for *o*-nitromandelic acid [G. Heller, *ibid.*, **37**, 938 (1904)].

(13) E. H. Usherwood and M. A. Whiteley, *J. Chem. Soc.*, **123**, 1069 (1923).

(14) Prepared by catalytic reduction of 4-methyl-2-nitroaniline.

(15) Prepared by catalytic reduction of 4-methoxy-2-nitroaniline.

in 43% yield; m.p. 169–171° dec. (ether–petroleum ether); λ_{max}^{EtOH} 238 mμ ($E_{1\,cm}^{1\%}$ 858); 308 mμ ($E_{1\,cm}^{1\%}$ 408).

Anal. Calcd. for $C_{14}H_{11}N_3O_3$ (269.25): C, 62.45; H, 4.12; N, 15.61. Found: C, 62.51; H, 4.22; N, 16.01.

General Method B. The Grignard Reaction.—The Grignard reagent was prepared from 3 g. (0.12 g.-atom) of magnesium turnings and 0.12 mole of the appropriate alkyl or aryl halide. When the preparation of the Grignard reagent was complete, the appropriate 2-benzoylbenzimidazole in ether solution was added rapidly. After about 1 hr., the reaction mixture was cooled, acidified with 25% sulfuric acid, and water was added. The product usually precipitated. If the product failed to precipitate, the aqueous phase was neutralized with concentrated ammonium hydroxide. The product was isolated by filtration and was recrystallized from aqueous ethanol.

2-(α-Methyl-α-hydroxybenzyl)benzimidazole (XI) was obtained from 2-benzoylbenzimidazole[16] and methylmagnesium iodide in 81% yield; m.p. 180–181° (50% EtOH); λ_{max}^{EtOH} 245 mμ ($E_{1\,cm}^{1\%}$ 273), 274 mμ ($E_{1\,cm}^{1\%}$ 357), 282 mμ ($E_{1\,cm}^{1\%}$ 342).

Anal. Calcd. for $C_{15}H_{14}N_2O$ (239.28): C, 75.60: H, 5.92; N, 11.10. Found: C, 75.67; H, 5.69; N, 11.50.

2-(α-Ethyl-α-hydroxybenzyl)benzimidazole (XII) was obtained from 2-benzoylbenzimidazole[16] and ethylmagnesium bromide in 62% yield; m.p. 168–170° (50% EtOH): λ_{max}^{EtOH} 245 mμ ($E_{1\,cm}^{1\%}$ 258), 275 mμ ($E_{1\,cm}^{1\%}$ 359); 282 mμ ($E_{1\,cm}^{1\%}$ 349).

Anal. Calcd. for $C_{16}H_{16}N_2O$ (252.30): C, 76.16; H, 6.39; N, 11.10. Found: C, 75.94; H, 5.95; N, 11.50.

2-(α-Isopropyl-α-hydroxybenzyl)benzimidazole (XIII) was obtained from 2-benzoylbenzimidazole[16] and isopropylmagnesium iodide in 75% yield; m.p. 187–188° (50% EtOH): λ_{max}^{EtOH} 246 mμ ($E_{1\,cm}^{1\%}$ 244); 275 mμ ($E_{1\,cm}^{1\%}$ 365), 282 mμ ($E_{1\,cm}^{1\%}$ 368).

Anal. Calcd. for $C_{17}H_{18}N_2O$ (266.33): C, 76.76; H, 6.81; N, 10.52. Found: C, 76.23; H, 7.13; N, 10.41.

2-(α-Methallyl-α-hydroxybenzyl)benzimidazole (XIV) was obtained from 2-benzoylbenzimidazole[16] and methallylmagnesium chloride in 24% yield; m.p. 181–182° (50% EtOH); λ_{max}^{EtOH} 246 mμ ($E_{1\,cm}^{1\%}$ 234), 275 mμ ($E_{1\,cm}^{1\%}$ 339), 282 mμ ($E_{1\,cm}^{1\%}$ 336).

Anal. Calcd. for $C_{18}H_{18}N_2O$ (278.34): C, 77.67; H, 6.52; N, 10.07. Found: C, 77.67; H, 6.52; N, 9.98.

2-(α-Methyl-α-hydroxybenzyl)-5-trifluoromethylbenzimidazole (XV).—A hot solution of 6.7 g. (0.02 mole) of 2-(α-hydroxybenzyl)-5-trifluoromethylbenzimidazole in 30 ml. of glacial acetic acid was added to a hot solution of 5.2 g. of sodium dichromate in 30 ml. of glacial acetic acid. The mixture was heated on a steam bath for 10 min., cooled, and diluted with 300 ml. of water. The product was isolated by filtration and washed thoroughly with water yielding 6.7 g. of 2-benzoyl-5-trifluoromethylbenzimidazole, m.p. 199–200° dec.; λ_{max}^{Nujol} 3.01 μ, 6.1 μ.

Anal. Calcd. for $C_{15}H_9F_3N_2O$: C, 62.07; H, 3.13: N, 9.66. Found: C, 62.26; H, 3.30; N, 9.63.

An ether solution of methylmagnesium iodide was prepared from 3 g. of magnesium turnings and 17.75 g. of methyl iodide in 150 ml. of anhydrous ether. A solution of 5.5 g. of 2-benzoyl-5-trifluoromethylbenzimidazole in 300 ml. of ether was added to the solution of the Grignard reagent in the course of 30 min. The reaction mixture was cooled, acidified with 30 ml. of 25% sulfuric acid, and diluted with 150 ml. of water. The ether phase was isolated and concentrated *in vacuo*, and the residue was slurried with 6 *N* ammonium hydroxide. The product was collected by filtration, washed with water, and recrystallized from chloroform and then benzene, yielding 3.87 g. of 2-(α-methyl-α-hydroxybenzyl)-5-trifluoromethylbenzimidazole, m.p. 179–181°; λ_{max}^{Nujol} 3.12 μ; λ_{max}^{EtOH} 252 mμ ($E_{1cm}^{1\%}$ 202), 276 mμ ($E_{1\,cm}^{1\%}$ 229), 282 mμ ($E_{1\,cm}^{1\%}$ 228).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O$ (306.28): C, 62.72; H, 4.28; N, 9.15. Found: C, 62.96; H, 4.38; N, 8.99.

(16) A. Bistrzycki and G. Przeworski, *Ber.*, **45**, 3483 (1912).

2-(α-Phenyl-α-hydroxybenzyl)benzimidazole (XVI).—A suspension of 0.37 g. (0.017 mole) of 2-benzoylbenzimidazole[16] in 10 ml. of ether was added to a solution of 0.05 mole of phenyllithium in 30 ml. of anhydrous ether. The reaction mixture was stirred at room temperature for about 2 hr. and then poured into a mixture of ice and water. The product was collected by filtration, washed with water, and crystallized from 50% aqueous ethanol yielding 0.42 g. of 2-(α-phenyl-α-hydroxybenzyl)benzimidazole, m.p. 220–222°; λ_{max}^{EtOH} 247 mμ ($E_{1\,cm}^{1\%}$ 224), 275 mμ ($E_{1\,cm}^{1\%}$ 328), 282 mμ ($E_{1\,cm}^{1\%}$ 334).

Anal. Calcd. for $C_{20}H_{16}N_2O$ (300.34): C, 79.98; H, 5.37: N, 9.33. Found: C, 79.55; H, 5.76; N, 9.16.

Other Methods. 2-(α-Carbethoxymethyl-α-hydroxybenzyl)benzimidazole (XVII).—Lithium (0.44 g.) was added in small portions to 100 ml. of liquid ammonia containing a few crystals of ferric nitrate. About 20 min. after the last portion of lithium was added, a gray suspension of lithium amide had formed, and a solution of 1.96 ml. of ethyl acetate in 5 ml. of ether was added slowly. The reaction mixture was stirred for about 20 min., and 4.45 g. (0.02 mole) of 2-benzoylbenzimidazole[16] was added in portions. The reaction mixture was stirred for 1 hr., neutralized with ammonium chloride, and allowed to evaporate. The product was extracted into ether, and the ether solution was washed with water. The product was extracted with 1 *N* sulfuric acid and precipitated from this solution by neutralization. Recrystallization of the product from 50% aqueous ethanol yielded 2.9 g. of 2-(α-carbethoxymethyl-α-hydroxybenzyl)-benzimidazole, m.p. 161–162°; λ_{max}^{EtOH} 252 mμ ($E_{1\,cm}^{1\%}$ 252), 277 mμ ($E_{1\,cm}^{1\%}$ 222), 285 mμ ($E_{1\,cm}^{1\%}$ 212).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$ (310.34): C, 69.66; H, 5.85; N, 9.03. Found: C, 69.63; H, 5.59; N, 9.40.

Ammonium Salt of 2-(α-Carboxymethyl-α-hydroxybenzyl)-benzimidazole (XVIII).—One gram of 2-(α-carbethoxymethyl-α-hydroxybenzyl)benzimidazole was hydrolyzed by treatment with 20 ml. of 2.5 *N* sodium hydroxide for 0.5 hr. on the steam bath. The reaction mixture was cooled, washed with ether, and passed through a column of Dowex 50 (H^+). The column was washed with water until the eluate was neutral, and the product was eluted with 0.5 *N* ammonium hydroxide. The eluate was concentrated under reduced pressure and the residue was dissolved in 2 ml. of ethanol. The ethanol solution was diluted with ether and the product crystallized to yield 0.2 g. of the ammonium salt of 2-(α-carboxymethyl-α-hydroxybenzyl)benzimidazole, λ_{max}^{EtOH} 246 mμ ($E_{1\,cm}^{1\%}$ 210), 275 mμ ($E_{1\,cm}^{1\%}$ 296), 282 mμ ($E_{1\,cm}^{1\%}$ 294).

Anal. Calcd. for $C_{16}H_{17}N_3O_3$ (299.32): C, 64.27; H, 5.98; N, 13.48. Found: C, 64.20; H, 5.78; N, 14.04.

1-Methyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole (XIX).—A mixture of 0.5 g. (0.002 mole) of 2-(α-methyl-α hydroxybenzyl)-benzimidazole, 2 g. of anhydrous potassium carbonate, 0.29 g. (0.002 mole) of methyl iodide, and 15 ml. of acetone was stirred in a stoppered flask overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was crystallized from 50 ml. of 50% aqueous methanol yielding 0.39 g. of 1-methyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole, m.p. 191–193°; λ_{max}^{EtOH} 254 mμ ($E_{1\,cm}^{1\%}$ 311,) 270 mμ ($E_{1\,cm}^{1\%}$ 241), 277 mμ ($E_{1\,cm}^{1\%}$ 292), 285 mμ ($E_{1\,cm}^{1\%}$ 283).

Anal. Calcd. for $C_{16}H_{16}N_2O$ (252.30): C, 76.16; H, 6.39; N, 11.10. Found: C, 75.96; H, 6.19; N, 11.10.

1-Methyl-2-(α-methyl-α-hydroxybenzyl)-5-trifluoromethylbenzimidazole (XX).—A mixture of 0.5 g. (0.0016 mole) of 2-(α-methyl-α-hydroxybenzyl)-5-trifluoromethylbenzimidazole, 2 g. of anhydrous potassium carbonate, 0.23 g. (0.0016 mole) of methyl iodide, and 15 ml. of acetone was stirred in a stoppered flask overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was crystallized from 25% aqueous ethanol yielding 0.19 g. of 1-methyl-(2-α-methyl-α-hydroxybenzyl)-5-trifluoromethylbenzimidazole, m.p. 163–165°; λ_{max}^{EtOH} 256 mμ ($E_{1\,cm}^{1\%}$ 179), 772 mμ ($E_{1\,cm}^{1\%}$ 189), 284 mμ ($E_{1\,cm}^{1\%}$ 202).

Anal. Calcd. for $C_{17}H_{15}N_2OF_3$ (320.33): C, 63.74; H, 4.71; N, 8.75. Found: C, 63.99; H, 4.29; N, 8.63.

1-Carbethoxymethyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole (XXI).—A mixture of 0.5 g. (0.002 mole) of 2-(α-methyl-α-hydroxybenzyl)benzimidazole, 2 g. of anhydrous potassium carbonate, 0.35 g. (0.002 mole) of ethyl bromoacetate, and 15 ml. of acetone was stirred in a stoppered flask overnight. The reaction mixture was filtered and concentrated, and the residue was crystallized from ether–petroleum ether yielding 0.3 g. of 1-carbethoxymethyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole, m.p. 145–147°; λ_{max}^{EtOH} 247 mμ ($E_{1\,cm}^{1\%}$ 207), 276 mμ ($E_{1\,cm}^{1\%}$ 294), 282 mμ ($E_{1\,cm}^{1\%}$ 296).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$ (324.37): C, 70.35; H, 6.22; N, 8.64. Found: C, 70.77; H, 6.26; N, 9.04.

Sodium Salt of 1-Carboxymethyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole (XXII).—A mixture of 8.1 ml. of 0.1 *N* sodium hydroxide and 0.27 g. of 1-carbethoxymethyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole was heated for 3 hr. The solution was concentrated, and the residue was dissolved in 2 ml. of ethanol. The ethanol solution was diluted with 12 ml. of ether, and the product crystallized yielding 0.23 g. of the sodium salt of 1-carboxymethyl-2-(α-methyl-α-hydroxybenzyl)benzimidazole, m.p. 190–192° dec.; λ_{max}^{EtOH} 257 ($E_{1\,cm}^{1\%}$ 239), 271 mμ ($E_{1\,cm}^{1\%}$ 181), 278 mμ ($E_{1\,cm}^{1\%}$ 213), 286 mμ ($E_{1\,cm}^{1\%}$ 200).

Anal. Calcd. for $C_{17}H_{15}N_2O_3Na$ (318.32): C, 64.14: H, 4.75; N, 8.80. Found: C, 64.02; H, 4.76; N, 8.90.

2-(2-Thienyl-α-hydroxymethyl)benzimidazole (XXIII).—2-Thienylmagnesium bromide was prepared in the usual manner from 1.09 g. (0.045 g.-atom) of magnesium turnings and 7.28 g. (0.045 mole) of 2-bromothiophene in 20 ml. of tetrahydrofuran. A suspension of 0.6 g. (0.005 mole) of 2-formylbenzimidazole[7] in 40 ml. of tetrahydrofuran was added rapidly to the solution of the Grignard reagent. The reaction mixture was warmed in a hot water bath and stirred for about 1.5 hr. The reaction mixture was neutralized with a cold ammonium chloride solution and the tetrahydrofuran phase was separated. The aqueous phase was washed with three portions of ether and the organic phases were combined and extracted three times with 2 *N* sulfuric acid. The combined acid extracts were neutralized with 6 *N* ammonium hydroxide and the product was extracted with ether. The ether solution was dried and concentrated, and the residue was crystallized from 50% aqueous ethanol yielding 0.74 g. of 2-(2-thienyl-α-hydroxymethyl)benzimidazole, m.p. 192–194° dec. Recrystallization of the compound from ethyl acetate raised the melting point to 194–196° dec. The ultraviolet absorption spectrum of the compound in ethanol solution was characterized by maxima at 238 mμ ($E_{1\,cm}^{1\%}$ 593), 275 mμ ($E_{1\,cm}^{1\%}$ 391), 281 mμ ($E_{1\,cm}^{1\%}$ 365).

Anal. Calcd. for $C_{12}H_{10}N_2OS$ (230.29): C, 62.59; H, 4.38; N, 12.16; S, 13.93. Found: C, 62.20; H, 4.31; N, 10.20; 10.32, 10.11; S, 14.14.

2-(2-Furyl-α-hydroxymethyl)benzimidazole (XXIV).—This compound was synthesized by the procedure used for the 2-(2-thienyl-α-hydroxymethyl)benzimidazole by substituting an equivalent amount of 2-furylmagnesium bromide in the place of 2-thienylmagnesium bromide. 2-(2-Furyl-α-hydroxymethyl)benzimidazole, m.p. 182–184° dec. (EtOAc) was obtained in 59% yield. The ultraviolet absorption spectrum of the compound in ethanol solution was characterized by the following absorption maxima: 245 mμ ($E_{1\,cm}^{1\%}$ 344), 274 mμ ($E_{1\,cm}^{1\%}$ 356), 281 mμ ($E_{1\,cm}^{1\%}$ 350).

Anal. Calcd. for $C_{12}H_{10}N_2O$ (214.23): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.21; H, 4.41; N, 11.22, 11.31.

2-Pyridyl 2-Benzimidazolyl Ketone (XXVI).—2-Pyridylmagnesium bromide was prepared by the entrainment method[17] and was treated with an equivalent amount of 2-formylbenzimidazole.[7] The reaction mixture was worked up in the usual manner, and 2-pyridyl 2-benzimidazolyl ketone, m.p. 173–175° (benzene), was obtained. The product was characterized by the following absorption bands in the infrared: λ_{max}^{Nujol} 3.05 μ, 6.0 μ; and by the following absorption maxima in the ultraviolet: λ_{max}^{EtOH} 271 mμ ($E_{1\,cm}^{1\%}$ 246), and 328 mμ ($E_{1\,cm}^{1\%}$ 676).

Anal. Calcd. for $C_{13}H_9N_3O$ (223.22): C, 69.94; H, 4.06; N, 18.83. Found: C, 69.67; H, 4.00; N, 19.05.

The ketone XXVI was reduced by catalytic hydrogenation. On one occasion the 2-pyridyl analog of HBB was isolated after several fractional crystallizations of the reduction product. In general, however, attempts to isolate the crystalline carbinol gave a mixture of the ketone XXVI and the carbinol XXV. In a given fraction, the ketone content increased with each purification operation thus reflecting a ready susceptibility of the carbinol to oxidation.

2-(α-Hydroxybenzyl)imidazole.[8]—A solution of 0.09 mole of butyllithium in 112 ml. of ether was added slowly in the course of 0.5 hr. to a suspension of 12.65 g. (0.08 mole) of N-benzylimidazole[18] in 60 ml. of ether. After the reaction mixture was stirred for about 1 hr., 9.3 g. (0.088 mole) of benzaldehyde was added dropwise. The reaction mixture was acidified with 2 *N* hydrochloric acid, and the product was isolated by filtration, washed with water, and washed with ether. The product was dissolved in 400 ml. of 2 *N* hydrochloric acid and a small amount of insoluble material was removed by filtration. The filtrate was neutralized with concentrated ammonium hydroxide, and the product was collected by filtration and washed with water. Recrystallization of the product from cyclohexane yielded 3.4 g. of 2-(α-hydroxybenzyl)-N-benzylimidazole, m.p. 112–114°.

Anal. Calcd. for $C_{17}H_{16}N_2O$ (264.33): C, 77.25; H, 6.10; N, 10.60. Found: C, 77.12; H, 6.00; N, 10.84.

A solution of 3.5 g. (0.013 mole) of 2-(α-hydroxybenzyl)-N-benzylimidazole in 100 ml. of liquid ammonia was treated with a solution of 0.95 g. (0.04 mole) of sodium in 50 ml. of liquid ammonia. The reaction mixture was acidified with 5 g. of ammonium chloride and then concentrated. The residue was triturated with water, and the product was collected by filtration and recrystallized from ethanol yielding 0.69 g. of 2-(α-hydroxybenzyl)imidazole, m.p. 193–195°; $\lambda_{max}^{pyridine}$ 3.2 μ.

Anal. Calcd. for $C_{10}H_{10}N_2O$ (174.21): C, 68.95; H, 5.79; N, 16.08. Found: C, 69.15; H, 5.48; N, 15.49.

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