

Synthesis of the Metabolites of Oxapadol, A New Non-Narcotic Analgesic Agent

Patrick Guerret, Jean-François Ancher and Michel Langlois*

Centre de Recherche Delalande, 10, rue des Carrières,
92500 - Rueil Malmaison, France
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Different metabolites (**2-7**) of oxapadol **1** were carried out from **3** by known methods. Their acidic hydrolysis provided compounds **4** in which the dioxolane moiety was opened. The reaction of glycerol with compounds **3** gave the dioxolane derivatives **5** which have a hydroxymethyl group and which (R = H) gave by oxidation the carboxylic acid **7**. From **3** (R = H), the hydroxy acid **6** has been also prepared.

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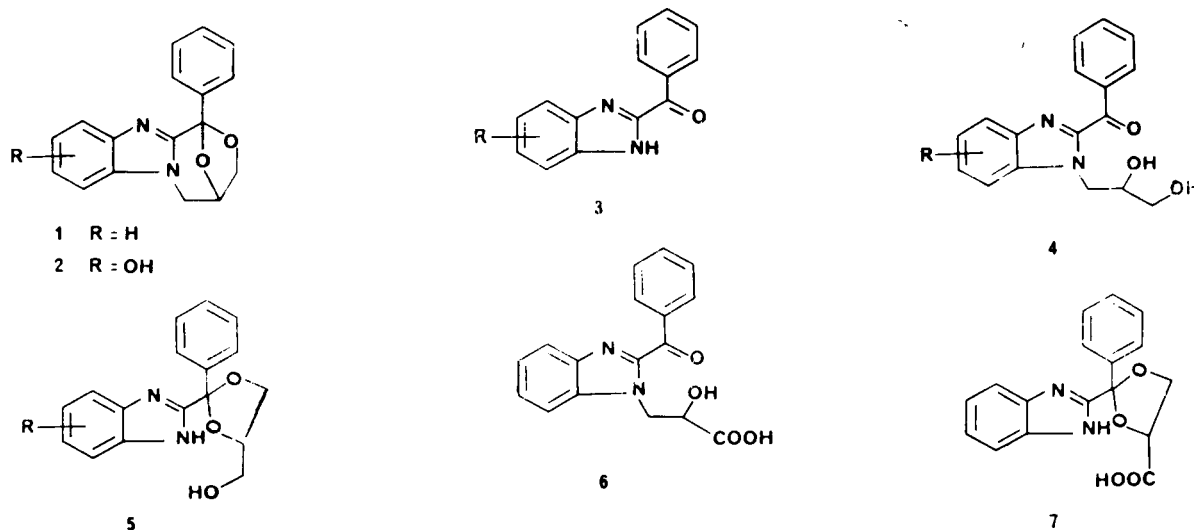
In a previous paper [1], we have described the analgesic properties of some derivatives of 1,4-epoxy-1*H*-[1,4]oxazepino[4,3-*a*]benzimidazole. One of them, oxapadol **1** [2], has been selected for clinical investigation [3] and its metabolism has been studied in rat, dog and man [4]. Mass spectrometry studies of its urinary metabolites have indicated that aromatic hydroxylation and opening of the bridged ring of **1** were the major pathways of metabolism. These reactions gave compounds of the types **2-7** (R = H, OH) listed in Scheme 1. A number of such compounds have been prepared for precise identification and pharmacological evaluation.

The hydroxylated derivatives of 2-benzoyl-1*H* benzimidazole, **3a** (R = 5(6)-OH) and **3b** (R = 4(7)-OH), were prepared according to the process described by Zellner [5]. Their synthesis is outlined in Scheme 2.

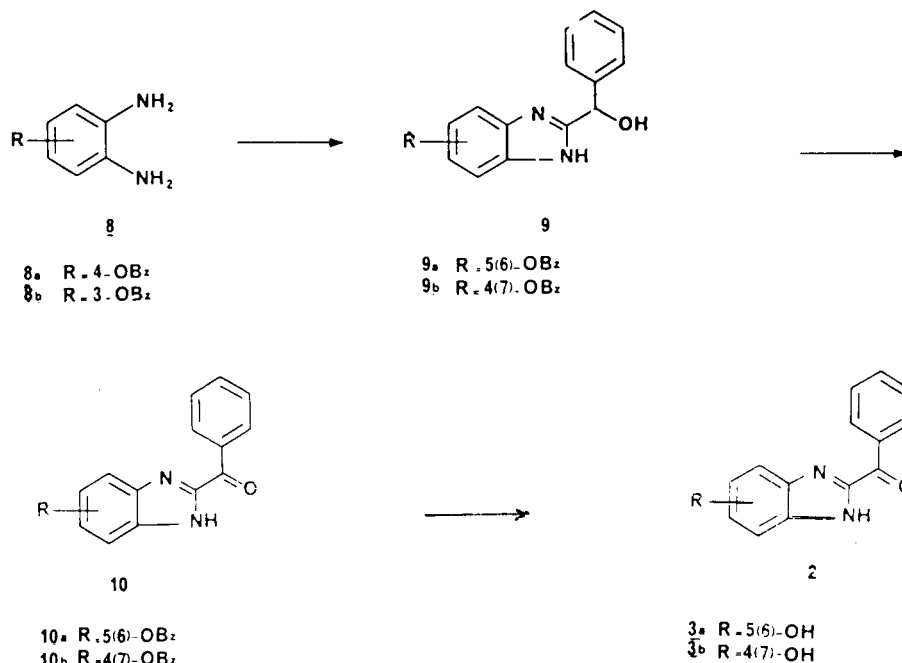
The reduction of 4-benzyloxy-2-nitroaniline [6] and 6-benzyloxy-2-nitroaniline (obtained by benzylation of 2-amino-3-nitrophenol [7]) by zinc in acetic acid, provided the correctly substituted ortho phenylenediamines **8a** and **8b**.

Their condensation with the methyl ester of mandelimidic acid hydrochloride in methanol or ethanol, as described by King [8] provided **9a** and **9b** which were subsequently oxidized with manganese dioxide to **10a** and **10b**. Debenzylation with aqueous hydrobromic acid then gave **3a** and **3b**.

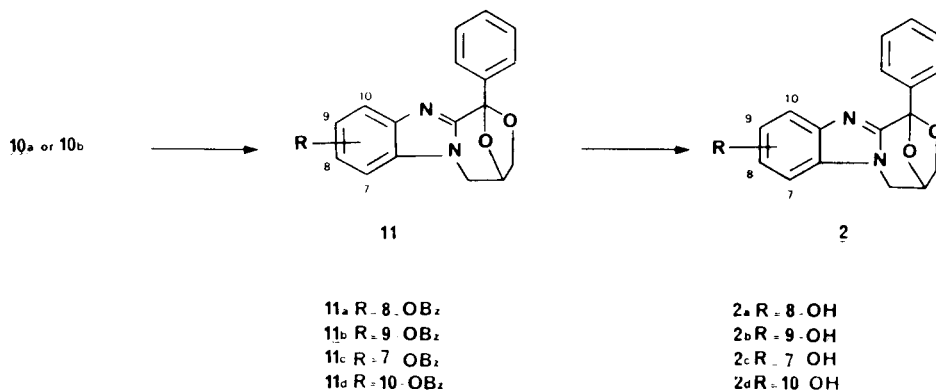
The derivatives **2** (R = OH) which are related to oxapadol, were obtained from **10a** and **10b** (Scheme 3). Thus, alkylation of **10a** with epibromohydrin gave two isomers, **11a** and **11b**, which were catalytically debenzylated with 10% palladium on charcoal to afford **2a** and **2b**, respectively. Compounds **2c** and **2d** were obtained in a similar way from **10b**. The position of the hydroxyl group in these four compounds has been elucidated through unequivocal synthesis of compounds **2b** and **2c** (Scheme 4). Reaction of 1-chloro-2,4-dinitrobenzene or of 1-chloro-2,6-dinitrobenzene with 4-aminomethyl-2,2-dimethyl-1,3-dioxolane [9], provided the corresponding dinitroanilines **13**. Selective reduction of one nitro group, according to Hungle and co-workers [10], gave the ortho phenylenediamines **14** which were condensed with methyl mandelimidate hydrochloride



Scheme 1



Scheme 2



Scheme 3

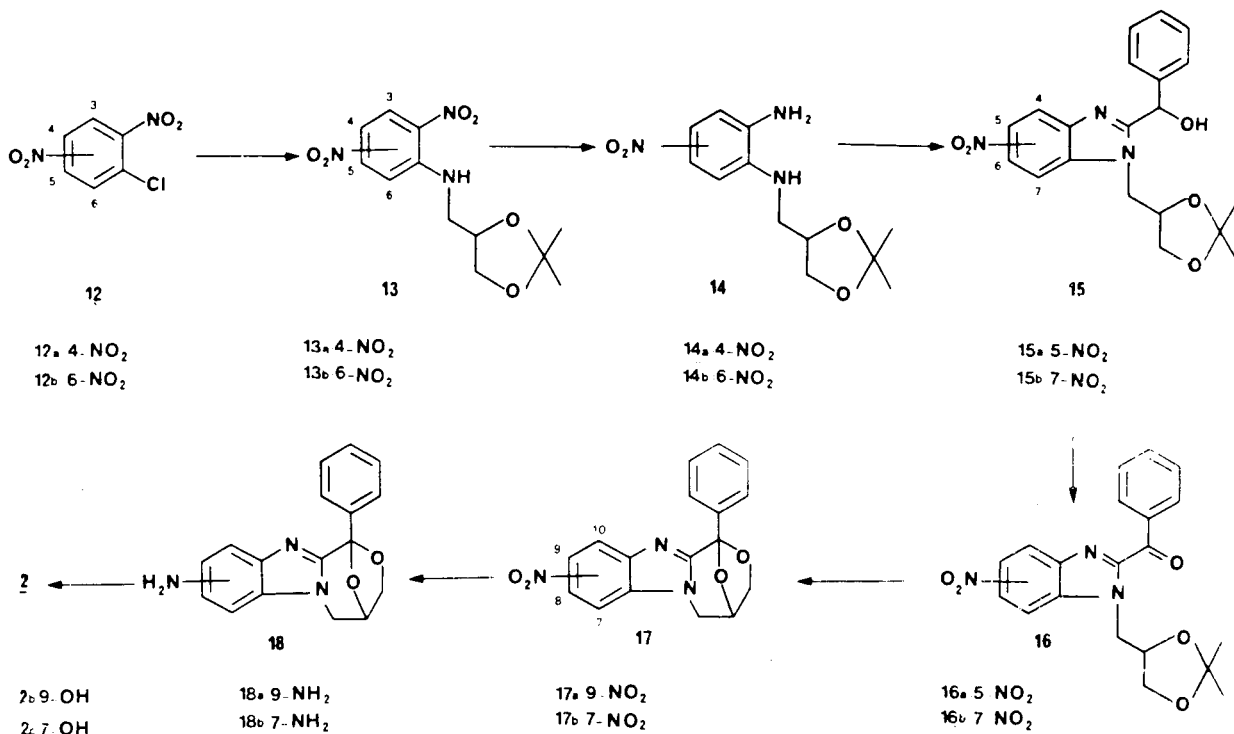
in methanol to give the corresponding benzimidazoles **15**. These compounds were oxidized with manganese dioxide to the 2-benzoyl-1*H*-benzimidazoles **16** which yielded the corresponding 4,5-dihydro-1,4-epoxy-1*H*-[1,4]oxazepino-[4,3-*a*]benzimidazoles **17** after acid hydrolysis. Reduction of the nitro group (10% palladium on charcoal) and final diazotization in the presence of cuprous oxide [11] provided **2b** or **2c**.

Compounds **4** could be obtained by acidic hydrolysis of oxapadol **1** or its derivatives **11**. Thus these compounds, when refluxed with 48% hydrobromic acid, provided **4** directly, although in very poor yields (Scheme 5).

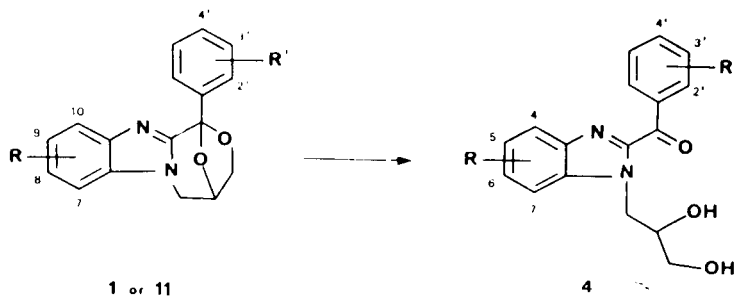
The compounds **5** produced by opening the oxazepino ring were obtained by condensation of glycerol with derivatives of 2-benzoyl-1*H*-benzimidazole **3** (R = H) or **10** (Scheme 6). Thus **3** (R = H) gave a mixture of two diaste-

reoisomers **5a**. The relative stereochemistry of these compounds was established in the following manner: one isomer (**5a trans** form) yielded, after treatment with tosyl chloride, only the corresponding tosylate, while the other (**5a cis** form) cyclized spontaneously to oxapadol; the cyclization being favoured by the *cis* disposition of the benzimidazole ring and hydroxymethyl group. This stereochemical assignment was also indicated by the presence in its

mass spectra of an M-18 ion which was more intense than that in the spectrum of the *trans* form. In the same way, when either **10a** or **10b** was heated with glycerol and *p*-toluenesulfonic acid, a mixture of the dioxolane diastereoisomers **5b** or **5c** were obtained which were separated by column chromatography. It is worth noting that debenzoylation also occurred during the course of the reaction. Compound **5a (cis form)** was oxidized by potassium per-



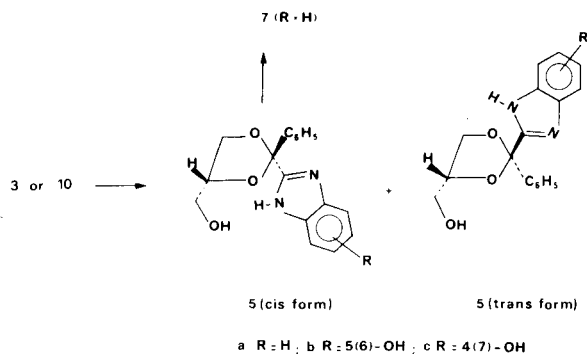
Scheme 4



R	R'
1 H	H
11a 8-OBz	H
11b 9-OBz	H
11c 7-OBz	H
11d 10-OBz	H
11e H	2'-OBz
11f H	3'-OBz
11g H	4'-OBz

R	R'
4a H	H
4b 6-OH	H
4c 5-OH	H
4d 7-OH	H
4e 4-OH	H
4f H	2'-OH
4g H	3'-OH
4h H	4'-OH

Scheme 5

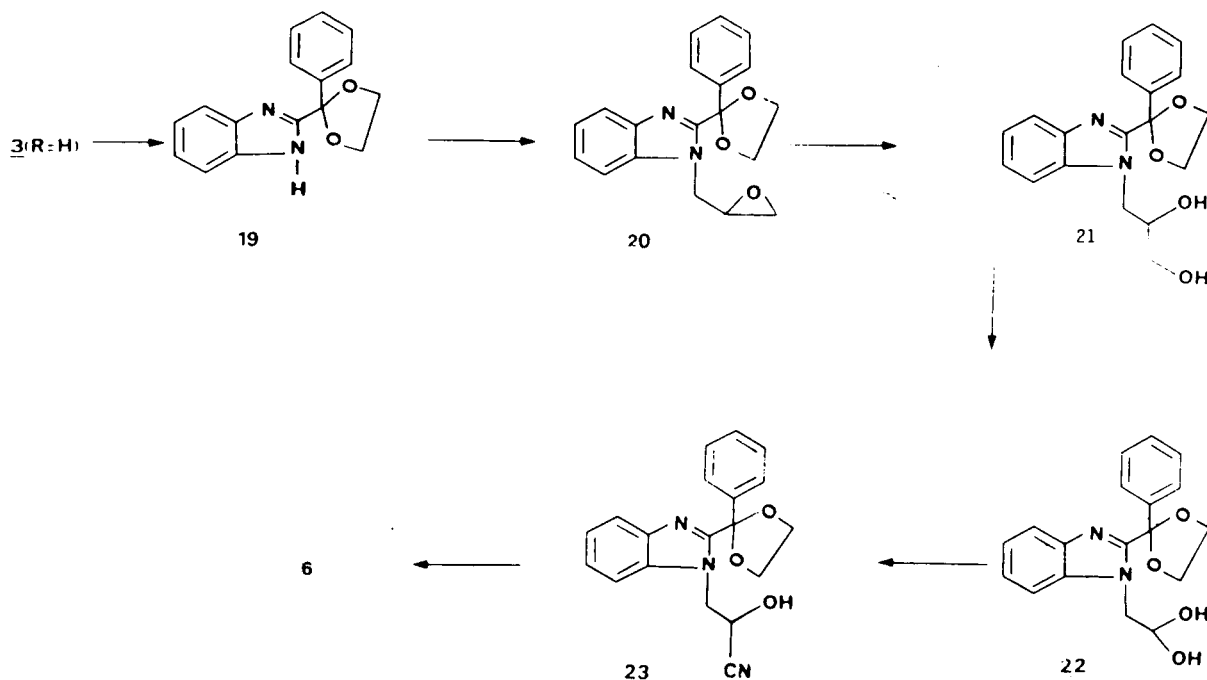


Scheme 6

manganate in basic solution to yield **7** in moderate yield.

Compound **6** which resulted from the opening and subsequent oxidation of the dioxolane moiety was synthesized by the process reported in Scheme 7.

2-Benzoyl-1*H*-benzimidazole **3** (R = H) was easily converted into the corresponding ethylene ketal **19** and alkylated with epibromhydrin in the presence of sodium hydride to give **20**. The hydrolysis with 10% sulfuric acid then yielded the diol **21**. The acid **6** was obtained from **21** by a previously described synthetic pathway [12]: oxidation with lead tetraacetate gave **22** which was transformed to the cyanohydrin **23** by treatment with an aqueous solution of potassium cyanide in the presence of sodium bisulfite. Hydrolysis of **23** with concentrated hydrochloric acid then gave **6**.



Scheme 7

Identification of urinary metabolites was performed by means of thin layer chromatographic comparison; the results have been reported elsewhere [4].

All the prepared compounds (except for **4b** and **4c**, which were obtained in very small amounts) have been screened for potential analgesic activity in mice using the phenylbenzoquinone writhing test [14]. In contrast to the results obtained with oxapadol, none of them showed significant effects at a dose of 50 mg/kg p.o. It thus seems probable that, in spite of its great susceptibility to enzymatic attack *in vivo*, oxapadol is active *per se* rather than after metabolic activation.

EXPERIMENTAL

All new compounds were characterized by ir, ¹H-nmr, mass spectrometry and/or elemental analysis. Melting points were determined on a Küfler hot-stage and are uncorrected. The ir spectra (potassium bromide) were obtained with a Perkin-Elmer 337 spectrophotometer; ¹H-nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are quoted in parts per million. Due to chemical exchange, the signals of some NH and OH protons were very broad and difficult to observe. Moreover some samples had to be treated with alumina before running the spectra in order to eliminate traces of paramagnetic impurities and some traces of water had been introduced. Mass spectra were measured with an AEI MS 30 instrument coupled to a DS 50 data system. The ionization potential was 70 eV, the trap current either 100 A or 333 μA and the source temperature ranged from 150 to 200°. Samples were introduced using a direct insertion probe. Thin layer chromatography experiments were performed on 0.25 mm E. Merck pre-coated silica gel plates (No. 60F254). Preparative separations were performed on Prep 100 Jobin Yvon using silica gel 40-60 μm. For brevity, many of the reactions were run once and purity rather than yield was the dominating factor.

2-Benzoyl-1H-benzimidazole (3).

Compound **3** was synthesized as reported [5].

2-Benzoyl-4(7)-benzyloxy-1H-benzimidazole (10b).

To a solution of 0.324 mole of 2-amino-3-nitrophenol [7] in 300 ml of ethanol were added 0.32 mole of potassium carbonate, 0.42 mole of benzylchloride and 2 g of sodium iodide. The reaction mixture was heated to reflux for 4 hours, then concentrated and poured into water. The aqueous layer was extracted with ethyl acetate and the organic extracts combined, dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was dissolved in aqueous acetic acid and zinc (90 g) was added portionwise over 90 minutes. As the reduction proceeded the temperature rose to 65°. The resulting aqueous solution was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude ortho phenylenediamine obtained was dissolved in ethanol (500 ml) with 0.35 mole of methyl mandelimidate hydrochloride and stirred at 25° for 20 hours. The mixture was concentrated and the residue was extracted with ethyl acetate. The organic solution was washed with water, dried over sodium sulfate and evaporated *in vacuo* to give **9b**. To a solution of **9b** (0.094 mole) in chloroform (350 ml) was added 93 g of manganese dioxide and this was then stirred for 3.5 hours. The mixture was filtered and the filtrate was evaporated *in vacuo* to give **10b**, (16%), mp 168°; ir: (ν cm⁻¹) 3295 (NH), 1640 (C=O); nmr (DMSO-d₆): δ 4.9 (s, 2, CH₂-O), 6.2-8.3 (m, 13, H arom).

Anal. Calcd. for C₂₁H₁₆N₂O₂: C, 76.31; H, 4.91; N, 8.53. Found: C, 76.56; H, 5.10; N, 8.49.

2-Benzoyl-6-benzyloxy-1H-benzimidazole (10a).

This derivative was prepared in the same way as **10b**, starting from 4-benzyloxy ortho phenylenediamine **8a**, (50%), mp 177°; ir: (ν cm⁻¹) 3300 (NH), 1630-1610 (C=O); nmr (DMSO-d₆): δ 5.2 (s, 2H, CH₂-O), 7-8.5 (m, 13H, H arom).

Anal. Calcd. for C₂₁H₁₆N₂O₂: C, 76.31; H, 4.91; N, 8.53. Found: C, 6.56; H, 5.10; N, 8.49.

2-Benzoyl-5(6)-hydroxy-1H-benzimidazole (3a).

Compound **10a** (0.051 mole) was added portionwise, over 30 minutes, to 350 ml of 48% hydrobromic acid. The reaction mixture was stirred at room temperature for 2 hours, then poured into cold water. The solid was separated and crystallized from acetonitrile to give the title compound (35%), mp 212°; ir: (ν cm⁻¹) 3400 (NH), 3050 (OH), 1640-1620 (C=O).

Anal. Calcd. for C₁₄H₁₀N₂O₂: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.62; H, 4.18; N, 11.87.

2-Benzoyl-4(7)-hydroxy-1H-benzimidazole (3b).

This compound was prepared from **10b** by the procedure described above, (30%), mp 211°; ir: (ν cm⁻¹) 3290 (NH), 3050 (OH), 1630 (C=O).

Anal. Calcd. for C₁₄H₁₀N₂O₂·1/8H₂O: C, 69.91; H, 4.19; N, 11.65. Found: C, 69.99; H, 4.15; N, 11.97.

8-Hydroxy-4,5-dihydro-1-phenyl-1,4-epoxy-1H,3H[1,4]oxazepino[4,3-a]benzimidazole (**2a**) and 9-Hydroxy-4,5-dihydro-1-phenyl-1,4-epoxy-1H,3H-1,4-oxazepino[4,3-a]benzimidazole (**2b**).

Sodium hydride (0.061 mole) was added to a solution of 0.061 mole of **10a** in 300 ml of dimethylformamide. The reaction mixture was stirred for 1 hour at room temperature and a solution of 0.083 mole of epibromohydrin in 50 ml of dimethylformamide was added over a period of 30 minutes. The mixture was stirred for a further 15 hours at 70°. The reaction mixture was then evaporated, poured into water and extracted with ethyl acetate. The organic extracts were washed with water and dried over anhydrous sodium sulfate. After concentration, the crude product was chromatographed on Prep 100 Jobin-Yvon (silica gel 15-20 μ m eluent: toluene) to separate the benzyloxy derivatives **11a** (yield, 30%) and **11b** (yield, 30%) which were debenzylated.

Thus, a solution containing 3.9 g (0.01 mole) of **11a** in 200 ml of ethanol and 0.7 g of 10% palladium on charcoal was hydrogenated at

room temperature under atmospheric pressure. The reaction mixture was filtered and concentrated. Recrystallization in ethanol left pure **2a** (61%), mp 250°, ir: (ν cm⁻¹) 3050 (OH); nmr (DMSO-d₆): δ 3.9-4.8 (m, 4H, CH₂-C-CH₂), 5.4 (m, 1H, C-CH-C), 6.6-8.0 (m, 8H, H arom), 9.5 (s, 1H, OH). Anal. Calcd. for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.80; N, 9.52. Found: C, 69.08; H, 5.18; N, 9.81.

Compound **11b** was debenzylated similarly to give 48% of **2b** which was shown to be identical (mp, ir, nmr) with the compound obtained according to the unequivocal synthesis of **2b**.

7-Hydroxy-4,5-dihydro-1-phenyl-1,4-epoxy-1H,3H[1,4]oxazepino[4,3-a]benzimidazole (**2c**) and 10-Hydroxy-4,5-dihydro-1-phenyl-1,4-epoxy[1H,3H]-1,4-oxazepino[4,3-a]benzimidazole (**2d**).

These compounds were prepared from **10b** according to the above procedure. Compound **2c** was obtained with a yield of 18% (based upon **10b**) after chromatography on silica gel (eluent: ethyl acetate) and was shown to be identical (mp, ir, nmr) with the compound obtained from the unequivocal synthesis of **2c**.

Compound **2d** was obtained with a yield of 22% after a recrystallization in ethyl acetate, mp 191°; ir: (ν cm⁻¹) 3300; nmr (DMSO-d₆): δ 3.8-4.7 (m, 4H, N-CH₂-C-CH₂), 5.4 (m, 1, C-CH-C), 6.5-7.9 (m, 8H, H arom).

Anal. Calcd. for C₁₇H₁₄N₂O₃·1/2H₂O: C, 67.32; H, 4.98; N, 9.23. Found: C, 67.54; H, 4.88; N, 9.44.

Unequivocal Synthesis of **2b** and **2c**.Synthesis of **2b**.

A solution of 0.445 mole of 1-chloro-2,4-dinitrobenzene in 1250 ml of ethanol and 0.562 mole of 4-(aminomethyl)2,2-dimethyl-1,3-dioxolane and 0.91 mole of triethylamine was refluxed for 2 hours. The mixture was concentrated and poured into water. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give **13a** which was used without further purification. A suspension of 0.1 mole of this compound in 250 ml of methanol was heated to 60° and a solution of 0.35 mole of sodium sulfide and 0.35 mole of sodium hydrogenocarbonate in 150 ml of water was added during a period of 10 minutes. The reaction mixture was stirred for 15 minutes at 60° and poured into cold water. The resulting aqueous phase was extracted with ethyl acetate. The organic extracts were washed with water, dried over anhydrous sodium sulfate and concentrated to leave **14a**. This compound (0.15 mole) was dissolved in 150 ml of methanol and added to a solution of 0.15 mole of ethyl mandelimidate hydrochloride in 150 ml of methanol. The resulting mixture was stirred for 15 hours at room temperature. After concentration, the residue was poured into water and extracted with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and concentrated to give **15a**, mp 183°. To a

solution of 0.044 mole of **15a** in 150 ml of chloroform was added 84 g of manganese dioxide and the reaction mixture was heated to reflux for 30 minutes. After filtration and concentration, the crude precipitate **16a** was added to 100 ml of 2 N hydrochloric acid and heated to 60° for 2.5 hours, the reaction mixture was cooled and neutralized with sodium carbonate to give the 4,5-dihydro-9-nitro-1-phenyl-1,4-epoxy-1H,3H[1,4]oxazepino[4,3-a]benzimidazole (**17a**) (56%), mp 206°; nmr (DMSO-d₆): δ 3.7-4.6 (m, 4H, N-CH₂-C-CH₂), 5.2 (m, 1H, C-CH-C), 7.0-8.3 (m, 8H, H arom).

Anal. Calcd. for C₁₇H₁₃N₃O₄: C, 63.16; H, 4.06; N, 13.00. Found: C, 63.16; H, 3.94; N, 13.03.

A suspension of 0.014 mole of **17a** and 0.8 g of 10% palladium on charcoal was hydrogenated at room temperature under atmospheric pressure. After removal of the catalyst and concentration, the precipitate **18a** (mp 239°) was dissolved in 18 ml of 3 N sulfuric acid at 0° and was added dropwise 0.0042 mole of sodium nitrite in 3 ml of water. The resulting mixture was neutralized by sulfanilic acid and 0.037 mole of cuprous oxide was added at room temperature. About 10 minutes after the addition of cuprous oxide, evolution of nitrogen ceased. The reaction mixture was poured into 100 ml of water and alkalized with 5 N sodium hydroxide. The solution was washed with ethyl acetate, neutralized with acetic

acid and extracted with ethyl acetate. The organic extracts were washed with water, dried over isolated by preparative chromatography on silica gel; mp 246°; ir: (ν cm⁻¹) 3126 (OH); nmr (DMSO-d₆): δ 3.2 (broad, 1H, OH), 3.8-4.8 (m, 5H, N-CH₂-CH-CH₂), 6.7-8.0 (m, 8H, H arom).

Anal. Calcd. for C₁₇H₁₄N₂O₃: C, 69.38; H, 4.80; N, 9.52. Found: C, 68.95; H, 4.68; N, 9.15.

Similarly prepared from 1-chloro-2,6-dinitro benzene was 7-hydroxy-4,5-dihydro-1-phenyl-1,4-epoxy-1*H*,3*H*-[1,4]oxazepino[4,3-*a*]benzimidazole (**2c**) in a yield of 0.5% based on 1-chloro-2,6-dinitro benzene, mp 260°; ir: (ν cm⁻¹) 3050 (OH); nmr (DMSO-d₆): δ 4.0-5.0 (m, 4H, N-CH₂-C-CH₂), 5.3 (m, 1H, C-CH-C), 6.6-7.0 (m, 8H, H arom).

Anal. Calcd. for C₁₇H₁₄N₂O₃·1/4H₂O: C, 68.32; H, 4.89; N, 9.37. Found: C, 68.42; H, 5.13; N, 9.55.

1-(3-Benzyloxyphenyl)-4,5-dihydro-1,4-epoxy-1*H*,3*H*-[1,4]oxazepino[4,3-*a*]benzimidazole (**11f**).

o-Phenylenediamine (0.048 mole) was dissolved in 2500 ml of absolute ethanol with 0.942 mole of methyl (3-benzyloxy)mandelimate hydrochloride [13] and stirred at room temperature for 24 hours. The mixture was concentrated and the residue was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give 2-(3-benzyloxy- α -hydroxybenzyl)-1*H*-benzimidazole, (72%), mp 172°. Manganese oxide (128 g) was added to a solution of 0.126 mole of the above compound in 500 ml of chloroform which was then heated to reflux for 2 hours. The reaction mixture was filtered and evaporated *in vacuo* to give 2-(3-benzyloxybenzyl)-1*H*-benzimidazole (85%), mp 148°; ir: (ν cm⁻¹) 3050 (OH), 1650 (C=O); nmr (DMSO-d₆): δ 5.2 (s, 2H, O-CH₂), 7.1-8.3 (m, 9H, H arom), 13.0 (broad, 1H, NH).

Anal. Calcd. for C₂₁H₁₆N₂O₂: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.61; H, 4.88; N, 8.42.

To a solution of 0.147 mole of this benzimidazole in 400 ml of dimethylformamide was added 0.121 mole of sodium hydride. After hydrogen evolution, a solution of 0.385 mole of epibromhydrin in 100 ml of dimethylformamide was added over a period of 45 minutes. The resultant mixture was stirred for 6 hours at 60°, then concentrated. The residue was crystallized in ethanol and recrystallized in acetone yielding 39% of **11f**, mp 169°; nmr (deuteriochloroform): δ 3.8-4.7 (m, 4H, N-CH₂-C-CH₂), 5.05 (m, 3H, C-CH-C and CH₂ phenyl), 6.8-8.0 (m, 12H, H arom).

Anal. Calcd. for C₂₄H₂₀N₂O₃: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.61; H, 5.24; N, 7.27.

1-(2-Benzyloxyphenyl)-4,5-dihydro-1,4-epoxy-1*H*,3*H*-[1,4]oxazepino[4,3-*a*]benzimidazole (**11e**).

This compound was obtained in a yield of 30% based on *o*-phenylenediamine, mp 178°; nmr (DMSO-d₆): δ 3.6-4.4 (m, 4H, N-CH₂-C-CH₂), 4.8 (q, 2H, OCH₂ phenyl), 6.2-8.0 (m, 12H, H arom).

Anal. Calcd. for C₂₄H₂₀N₂O₃: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.67; H, 5.29; N, 7.16.

1-(4-Benzyloxyphenyl)-4,5-dihydro-1,4-epoxy-1*H*,3*H*-[1,4]oxazepino[4,3-*a*]benzimidazole (**11g**).

This compound was obtained in a yield of 25% based on *o*-phenylenediamine, mp 220°; nmr (DMSO-d₆): δ 4.0-4.7 (m, 4H, N-CH₂-C-CH₂), 5.2 (s, 2H, OCH₂-phenyl), 5.4 (m, 1H, O-CH), 7.8 (m, 12H, H arom).

Anal. Calcd. for C₂₄H₂₀N₂O₃: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.89; H, 5.42; N, 7.05.

3-(2-Benzoyl-5-hydroxy-1*H*-benzimidazol-1-yl)-1,2-propanediol (**4c**).

Compound **11b** (1.59 mole) was added portionwise to a hot (80°) solution of 35 ml of 48% hydrobromic acid. The mixture was stirred for 5 minutes, poured into cold water, and neutralized with sodium hydroxide. The solution was extracted with ethyl acetate. The organic layer was chromatographed on silica gel, (chloroform/acetone, 85/15). The eluent was evaporated to yield **4c**, (10%), mp 169°; ir: (ν cm⁻¹) 3080 (OH), 1650 (C=O); nmr (DMSO-d₆): δ 3.5-5.3 (m, 7H, CH₂-CHOH-CH₂OH), 7.6-8.4 (m, 8H, H arom), 9.0 (broad s, 1H, OH).

Anal. Calcd. for C₁₇H₁₆N₂O₄·1/2H₂O: C, 63.54; H, 5.33; N, 8.72. Found:

C, 63.58; H, 5.20; N, 9.03.

In a similar manner, the derivative **4** was prepared from the appropriate compounds **11** and **1**.

3-(2-Benzoyl-1*H*-benzimidazol-1-yl)-1,2-propanediol (**4a**).

Compound **4a** was obtained in a yield of 8%, mp 135°; ir: (ν cm⁻¹) 3350-3150 (OH), 1660 (C=O); nmr (DMSO-d₆): δ 3.3 (m, 2H, CH₂-O), 3.8 (m, 1H, CH-O), 5.7 (m, 2H, N-CH₂), 5.0 (m, 2H, 2OH), 7.2-8.4 (m, 9H, H arom).

Anal. Calcd. for C₁₇H₁₆N₂O₃: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.95; H, 5.69; N, 9.61.

3-(2-Benzoyl-6-hydroxy-1*H*-benzimidazol-1-yl)-1,2-propanediol (**4b**).

Compound **4b** was obtained in a yield of 9%, mp 170°; ir: (ν cm⁻¹) 3500-3100 (OH), 1610 (C=O); nmr (DMSO-d₆): δ 3.3 (m, 2H, CH₂-O), 3.8 (m, 1H, CH-O), 4.6 (m, 2H, N-CH₂), 5.4-4.8 (m, 2H, OH), 6.8-8.3 (m, 9H, H arom).

Anal. Calcd. for C₁₇H₁₆N₂O₄·1/2H₂O: C, 63.54; H, 5.33; N, 8.72. Found: C, 63.48; H, 5.01; N, 8.79.

3-(2-Benzoyl-7-hydroxy-1*H*-benzimidazol-1-yl)-1,2-propanediol (**4d**).

Compound **4d** was obtained in a yield of 8%, mp 187°; nmr (DMSO-d₆): δ 3.0-4.1 (m, 3H, CH-CH₂), 5.4-4.2 (m, 4H, N-CH₂, 2OH), 6.6-8.4 (m, 9H, H arom).

Anal. Calcd. for C₁₇H₁₆N₂O₄·H₂O: C, 64.14; H, 5.28; N, 8.80. Found: C, 63.91; H, 5.16; N, 8.72.

3-(2-Benzoyl-4-hydroxy-1*H*-benzimidazol-1-yl)-1,2-propanediol (**4e**).

This compound was obtained in a yield of 8% (oil); ir: (ν cm⁻¹) 3550-3100 (OH broad), 1850 (C=O); nmr (DMSO-d₆): δ 3.6-4.0 (m, 3H, CH-CH₂), 4.4-5.2 (m, 4H, N-CH₂, 2OH), 6.5-8.4 (m, 9H, H arom). All attempts to obtain C, H, N agreeing with the theoretical value to within 0.4% failed. The compound was too hygroscopic.

3-[2-(2-Hydroxy)benzoyl-1*H*-benzimidazol-1-yl]-1,2-propanediol (**4f**).

Compound **4f** was obtained in a yield of 27%, mp 113°; ir: (ν cm⁻¹) 3350-3150 (OH), 1620-1600 (C=O); nmr (DMSO-d₆): δ 3.2 (m, 2H, CH{-O}), 3.8 (m, 1H, CH-O), 4.6-5.0 (m, 4H, N-CH{, 2OH), 6.7-8.3 (m, 8H, H arom), 11.5 (s, 1H, OH).

Anal. Calcd. for C₁₇H₁₆N₂O₄: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.15; H, 5.12; N, 8.83.

3-[2-(3-Hydroxy)benzoyl-1*H*-benzimidazol-1-yl]-1,2-propanediol (**4g**).

Compound **4g** was obtained in a yield of 2% after three crystallizations in ethanol, mp 193°; ir: (ν cm⁻¹) 3520-3150 (OH), 1645 (C=O); nmr (DMSO-d₆): δ 3.3 (m, 2H, CH₂-O), 3.7 (m, 1H, CH-O), 5.4 (m, 4H, N-CH₂, 2OH), 6.8-8.0 (m, 8H, H arom).

Anal. Calcd. for C₁₇H₁₆N₂O₄: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.37; H, 5.05; N, 8.68.

3-[2-(4-Hydroxy)benzoyl-1*H*-benzimidazol-1-yl]-1,2-propanediol (**4h**).

Compound **4h** was obtained in a yield of 22%, mp 202°; ir: (ν cm⁻¹) 3450-3100 (OH), 1620-1680 (C=O); nmr (DMSO-d₆): δ 3.4 (m, 2H, CH₂-O), 3.8 (m, 1H, CH-O), 4.6 (m, 2H, N-CH₂), 4.3-6.0 (broad, 2H, 2OH), 6.8-8.4 (m, 3H, H arom).

Anal. Calcd. for C₁₇H₁₆N₂O₄: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.08; H, 5.12; N, 9.02.

2-(1*H*-Benzimidazol-2-yl)-2-phenyl-1,3-dioxolan-4(5)-ylmethanol (**5a**) (*cis*) and 2-(1*H*-Benzimidazol-2-yl)-2-phenyl-1,3-dioxolan-5(4)-ylmethanol (**5a**) (*trans*). General Procedure.

A solution of 0.6 mole of 2-benzoyl-1*H*-benzimidazole (**3**, R = H) and 0.66 mole of anhydrous *p*-toluenesulfonic acid in 840 ml of glycerin was heated to 120° for 3 hours and poured into an aqueous solution of sodium carbonate. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent evaporated *in vacuo*. The products were chromatographed on silica gel (chloroform/methanol, 85/15) to give **5a**

(*cis*) (33%), mp 208°; ir: (ν cm⁻¹) 3550-3050 (NH, OH); nmr (DMSO-d₆): δ 3.3-4.7 (m, 5H, OCH₂-CH-CH₂-O), 5.0 (t, 1H, OH), 7.0-7.8 (m, 9H, H arom), 12.5 (broad, 1H, NH).

Anal. Calcd. for C₁₇H₁₆N₂O₃: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.73; H, 5.50; N, 9.62.

Compound **5a** (*trans*) was obtained in a yield of 33%, mp 211°; ir: (ν cm⁻¹) 3100 (NH, OH); nmr (DMSO-d₆): δ 3.5-4.4 (m, 6H, OCH₂-CH-CH₂-OH), 7.0-7.8 (m, 9H, H arom), 12.5 (broad, 1H, NH).

Anal. Calcd. for C₁₇H₁₆N₂O₃: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.01; H, 5.37; N, 9.68.

2-(5(6)-Hydroxy-1*H*-benzimidazol-2-yl)-2-phenyl-1,3-dioxolan-4(5)-ylmethanol (**5b**).

Compound **5b** (*cis*) was obtained in a yield of 30% based on **3a**, mp 140°; ir: (ν cm⁻¹) 3200 (NH, OH); nmr (DMSO-d₆): δ 3.4-5.6 (m, 5H, CH₂-CH-CH₂), 6.8-7.8 (m, 8H, H arom), 8.0 (broad, OH).

Anal. Calcd. for C₁₇H₁₆N₂O₄·0.5H₂O: C, 63.50; H, 5.32; N, 8.71. Found: C, 63.43; H, 5.03; N, 8.77.

Compound **5b** (*trans*) was obtained in a yield of 30% based on **3a**, mp 140°; ir: (ν cm⁻¹) 3300 (NH, OH, broad); nmr (DMSO-d₆): δ 3.3-4.3 (m, 5H, CH₂-CH-CH₂), 5.0 (broad, OH), 6.6-7.7 (m, 8H, H arom), 9.0 (broad, 1H, NH).

Anal. Calcd. for C₁₇H₁₆N₂O₄·H₂O: C, 63.19; H, 5.37; N, 8.67. Found: C, 63.06; H, 5.36; N, 8.69.

2-(4(7)-Hydroxy-1*H*-benzimidazol-2-yl)-2-phenyl-1,3-dioxolan-4(5)-ylmethanol (**5c**).

Compound **5c** (*cis* or *trans*) were obtained in 50% yield in equal ratio of *cis* and *trans* form determined by tlc on silica gel (eluent: chloroform).

Compound **5c** (*cis* or *trans*) had mp 243°; ir: (ν cm⁻¹) 3300 (NH, OH, broad); nmr (DMSO-d₆): δ 3.6-5.5 (m, 5H, CH₂-CH-CH₂), 6.8-8.0 (m, 8H, H arom).

Compound **5c** (*trans* or *cis*), mp 251°; ir: (ν cm⁻¹) 3300 (NH, OH, broad); nmr (DMSO-d₆): δ 3.7-5.6 (m, 5H, CH₂-CH-CH₂), 6.8-8.0 (m, 8H, H arom). All attempts to obtain C, H, N, agreeing with the theoretical value to within 0.4% failed. Compounds **5c** were hydrated.

In order to prove the stereochemistry, a sample of **5a** (*cis*) was cyclized to **1**, as follows: a solution of 0.046 mole of **5a** in 230 ml of pyridine was cooled to 5°, then treated with 0.05 mole of *p*-toluenesulfonyl chloride and warmed to 40° for 2 hours. The reaction mixture was poured into water and extracted with ether. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo* to give **1** [1]. Under the same conditions **5a** (*trans*) gave only a tosylate and no cyclization to **1** was detected.

2-(1*H*-Benzimidazol-2-yl)-2-phenyl-1,3-dioxolan-4-yl Carboxylic Acid (**7**) (*cis*).

To a solution of 5 mmole of **5a** (*cis*) in 60 ml of 0.1*N* sodium hydroxide were added 13 mmole of potassium permanganate over a period of 45 minutes at 10°. The reaction mixture was stirred for 5 hours at ambient temperature, then after addition of 10 ml of a solution of 1*N* sodium bisulfite an 10 ml of a solution of 1*N* sodium hydroxide, the mixture was washed with ether and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and evaporated to give **7** (17%), mp 250°; ir: (ν cm⁻¹) 1700 (C=O); nmr (DMSO-d₆): δ 4.0-4.6 (m, 2H, O-CH₂), 4.7-5.1 (m, 1H, O-CH), 7.0-8.0 (m, 9H, H arom), 12.0 (broad, 2H, NH, OH).

Anal. Calcd. for C₁₇H₁₄N₂O₄: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.59; H, 4.29; N, 8.72.

2-(2-Phenyl-1,3-dioxolan-2-yl)-1*H*-benzimidazole (**19**).

This product was prepared in the same way as **5** from ethylene glycol and 2-benzoyl-1*H*-benzimidazole (85%), mp 248° (ethanol); nmr (deuteriochloroform): δ 4.0 (m, 4H, CH₂-CH₂), 7.0-8.0 (m, 9H, H arom), 11.8 (s, 1H, NH).

Anal. Calcd. for C₁₆H₁₄N₂O₂: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.41; H, 5.34; N, 10.71.

2-(2-Phenyl-1,3-dioxolan-2-yl)-1-(oxiran-1-yl-methyl)-1*H*-benzimidazole (**20**).

To a solution of 0.735 mole of **19** in 200 ml of dimethylformamide 0.0735 mole of sodium hydride was added. About 30 minutes after the addition of sodium hydride, the evolution of hydrogen ceased and a solution of 0.12 mole of epibromhydrin in 20 ml of dimethylformamide was added dropwise. The reaction mixture was stirred for 15 hours at room temperature, poured into water, and the product was filtered and dried (59%), mp 132° (ethylacetate); nmr (deuteriochloroform): δ 2.2-3.0 (m, 3H, N-C-CH-CH₂O), 3.7-4.7 (m, 6H, N-CH₂, OCH-CH₂), 7.0-8.0 (m, 9H, H arom).

Anal. Calcd. for C₁₉H₁₈N₂O₃: C, 70.79; H, 5.63; N, 8.69. Found: C, 71.00; H, 5.53; N, 8.44.

3-[2-(2-Phenyl-1,3-dioxolan-2-yl)-1*H*-benzimidazol-1-yl]-1,2-propanediol (**21**).

To 200 ml of 10% sulfuric acid, 0.061 mole of **20** was added and stirred at room temperature for 3 hours. The mixture was neutralized with sodium hydroxide and extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and concentrated to give **21** (65%), mp 156°; ir: (ν cm⁻¹) 3400-3200 (OH); nmr (deuteriochloroform): δ 3.4-4.3 (m, 11H, OCH₂-CH₂O, CH₂-CHOH-CH₂OH), 7.0-8.0 (m, 9H, H arom).

Anal. Calcd. for C₁₉H₂₀N₂O₄: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.79; H, 5.98; N, 8.42.

2-[2-(2-Phenyl-1,3-dioxolan-2-yl)-1*H*-benzimidazol-1-yl]acetaldehyde Hydrate (**22**).

To a solution of 3 mmole of **21** in 50 ml of anhydrous benzene, 3.5 mmole of lead tetracetate were added in a period of 10 minutes. The reaction mixture was stirred during 30 minutes and poured into cold water. The two layers were filtered on celite. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to leave **22** (50%), mp 135°; ir: (ν cm⁻¹) 3300 (OH); nmr (DMSO-d₆): δ 3.9-4.3 (m, 4H, OCH₂-CH₂O), 5.0 (m, 1H, OCHO), 6.0 (broad, 2H, 20H), 7.0-8.0 (m, 9H, H arom).

Anal. Calcd. for C₁₈H₁₈N₂O₄: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.28; H, 5.46; N, 8.63.

3-(2-Benzoyl-1*H*-benzimidazol-1-yl)lactic Acid (**6**).

To a suspension of 24 mmole of **22** in 200 ml of water, 30 mmole of potassium cyanide in 20 ml of water and 30 mmole of sodium bisulfite were added. After stirring 12 hours at room temperature, the solid precipitate was filtered and dissolved in 100 ml of concentrated hydrochloric acid. After stirring for a period of 12 hours at room temperature, the cold solution was neutralized with concentrated aqueous ammonia and the hydroxy acid **6** was removed by filtration and dried (30%), mp 204° (ethanol); ir: (ν cm⁻¹) 3490 (OH), 1710 (C=O); nmr (DMSO-d₆): δ 4.4 (m, 2H, N-CH₂), 4.9 (m, 2H, OCHOH), 7.2-8.4 (m, 10H, H arom, OH).

Anal. Calcd. for C₁₇H₁₄N₂O₄: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.49; H, 4.40; N, 8.95.

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