Metabolites of Methyl 5(6)-Butyl-2-benzimidazolecarbamate (Parbendazole).[1] Structure and Synthesis

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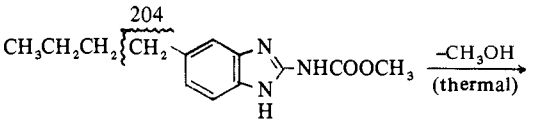
The structures of seven metabolites (II–VIII) of the potent anthelminthic methyl 5(6)-butyl-2-benzimidazolecarbamate (I) isolated from sheep and cattle and from two fungi were determined, largely by physical methods. Six were products of side-chain oxidation, and one was an aromatic-ring hydroxylation product. The two major metabolites isolated from both sheep and cattle were shown to be the carboxylic acid II and the 1,2-diol III. The structures of all metabolites were confirmed by synthesis, and the configuration of diol metabolite III was shown to be predominantly threo by synthesis *via* a stereospecific route.

Methyl 5(6)-butyl-2-benzimidazolecarbamate (parbendazole, I) is a potent anthelminthic agent which was discovered in our laboratories in 1966.[2] Since the compound was designed for agricultural use, it was necessary to establish the absence of possible toxic metabolites from the meat of treated animals intended for human consumption. As a preliminary step, the metabolic patterns in several species were investigated by isolation and identification of the urinary metabolites excreted after oral administration of the drug. Since the isolation procedures were time-consuming and frequently produced only small quantities of materials, concurrent studies of the microbial fermentation of the drug were undertaken; it was hoped that microorganisms would be found to duplicate some of the mammalian metabolites and provide a more convenient source for them. The isolation of both the mammalian[3,4] and the microbial[5] metabolites has been described in previous publications. The present paper deals with the identification of the metabolites, which was accomplished largely by physical methods, and the confirmation of their structures by chemical synthesis.

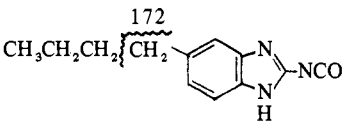
Identification of Metabolites. A total of seven different metabolites were characterized (see Table I). Four of them (III–V and VII) came from mammalian sources only, two (II and VI) from both mammalian and microbial sources, and one (VIII) from microbial sources only. All the metabolites were initially investigated by uv and mass spectrometry; the data are summarized in Table I. In several cases these two techniques alone were adequate to define the structures fully.

All uv measurements were carried out in an acid medium to avoid possible complications due to tautomerism. The spectrum of I in acidified EtOH shows two strong maxima at 282 and 288 nm. With the single exception of VII, all the metabolites had uv spectra closely matching that of I; this correspondence was taken as evidence that the aromatic ring system had not been substituted or otherwise modified.

The mass spectrum of I was complicated by the formation of varying amounts (depending on the probe temperature) of a thermal decomposition product arising from the loss of MeOH. Thus, I gave two molecular ions, one at *m/e* 247 (intact I) and one at *m/e* 215, to which we assign the isocyanate structure IX.[6] Both I and IX underwent cleavage at the benzylic position (loss of propyl) to give major fragments (possibly rearranged)[7] at *m/e* 204 and 172, respectively. All the metabolites showed similar dual fragmentation pathways,



I
(molecular ion at *m/e* 247)

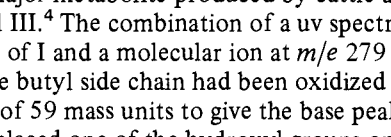


IX
(molecular ion at *m/e* 215)

but only the fragments derived from the intact carbamate molecular ions will be discussed; corresponding ions in the isocyanate series were observed 32 mass units lower.†

One of the major metabolites in both cattle and sheep was the acid II[4] which was also produced by the fungus *Cunninghamella bainieri* ATCC No. 9244.[5] The compound was characterized by the similarity of its uv spectrum to that of I and by its mass spectrum. The latter showed a molecular ion at *m/e* 277 with fragments at *m/e* 217 (loss of the elements of AcOH, with rearrangement)[8] and 204 (benzylic cleavage).

The other major metabolite produced by cattle and sheep was the glycol III.[4] The combination of a uv spectrum matching that of I and a molecular ion at *m/e* 279 suggested that the butyl side chain had been oxidized to a diol. The loss of 59 mass units to give the base peak at *m/e* 220 securely placed one of the hydroxyl groups on the α carbon of the butyl chain. The small peak at *m/e* 204 may arise from dehydration of the diol to the β ketone, followed by benzylic cleavage. The position of the second hydroxyl was established as vicinal to the first by carrying out

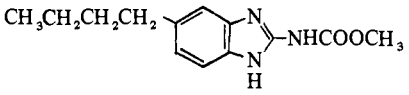
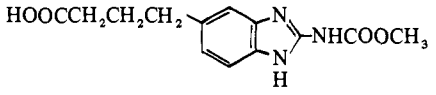
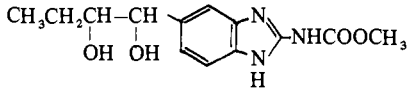
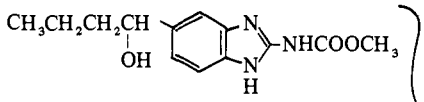
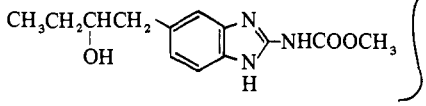
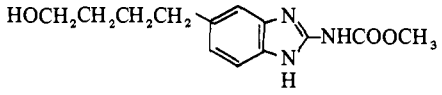
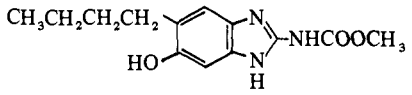
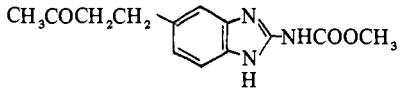


X

a periodate oxidation of III which proceeded cleanly to give aldehyde X, identified by its molecular ion at *m/e* 219.

† Examination of the metastable peaks showed that some of the fragment ions in the carbamate series lost methanol and so crossed over into the isocyanate series. This observation does not affect the validity of the structural arguments.

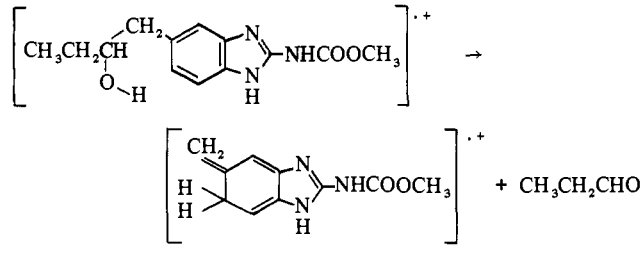
Table I. Parbendazole and Its Metabolites. Ultraviolet and Mass Spectra[a]

Structure	Uv maxima, nm[b]	Mass spectrum, *m/e* (rel abundance)[c]
 I	230, 282, 288	247 (20), 204 (50), 215 (17), 172 (100)
 II	227, 281, 287	277 (6), 245 (18), 217 (3), 204 (14), 198 (4), 185 (40), 172 (100)
 *threo*-III	223, 279, 285	279 (7), 261 (5), 247 (7), 234 (10), 229 (4), 220 (77), 204 (13), 203 (10), 192 (7), 188 (60), 172 (32), 160 (100)
 IV[d]	228, 281, 287	263 (40),[e] 245 (4), 231 (17),[e] 220 (36), 192 (7), 188 (19), 160 (38)
 V		263 (40),[e] 234 (6), 231 (17),[e] 205 (74), 204 (72), 173 (86), 172 (100)
 VI	227, 276, 287	263 (31), 231 (29), 204 (95), 172 (100)
 VII	239, 296, 304	263 (7), 231 (22), 220 (21), 188 (100)
 VIII	228, 279, 285	261 (76), 229 (26), 218 (34), 204 (84), 186 (82), 172 (100)

[a]The uv and mass spectral values reported were obtained on the natural metabolites. Due to the crude state of these metabolite preparations, accurate measurement of uv absorption intensities was not carried out. Qualitatively, however, the two long wavelength absorptions were strong and of essentially equal intensity in each case. The short wavelength absorption varied in intensity from one-half to twice that of the longer wavelength ones. [b]Run in 95% EtOH–1 *N* HCl. [c]Ionizing voltage 70 eV; source temperature ranged between 130 and 190° depending on the compound. [d]IV and V were obtained as an unresolved mixture. [e]Peaks common to IV and V.

Both the diol III and the alcohol IV showed a loss of carbon monoxide from the fragment ion at *m/e* 220, a decomposition (supported by a metastable peak) which is clearly open only to the α alcohols. The structure of III was further confirmed by the eventual isolation of sufficient material for an nmr examination. The threo stereochemistry of the glycol portion of the molecule was established by comparison with synthetic materials prepared by stereospecific routes (*vide infra*).

The two isomeric alcohols IV and V, metabolic products from sheep, were obtained as an unresolved mixture.[4] The uv spectrum and the molecular ion peak at *m/e* 263 were consistent only with monohydroxylation of the butyl side chain. The major fragment at *m/e* 220, which lost carbon monoxide, indicated that one of the components was the α alcohol IV. The abundant benzylic fragment at *m/e* 204 from the other alcohol was accompanied by a very substantial rearrangement peak at *m/e* 205. This type of rearrangement is characteristic of β-aryl alcohols which cleave with transfer of the hydroxylic hydrogen to the aromatic system.[9] Confirmation that the metabolite was indeed the β alcohol V was obtained by a deuterium exchange experiment. After brief exposure of the compound to deuteriomethanol the molecular ion was converted to a cluster (since deuteration was incomplete) at *m/e* 263, 264, 265, and 266 and the rearrangement peak at *m/e* 205 to a cluster at 205, 206, 207, and 208. The presence of the trideuterated peak at *m/e* 208 requires that the hydroxyl hydrogen (deuterium) be transferred in the fragmentation process, and this is entirely consistent with the β-alcohol structure rearranging through a six-membered cyclic transisiton state.



A third alcohol (VI) was obtained as a metabolite both from sheep and from *C. bainieri*.[5] The uv spectrum, the molecular ion at *m/e* 263, and the base peak at *m/e* 204 (ben-

zylic cleavage) with no substantial rearrangement peak at *m/e* 205 pointed to either the γ- or δ-alcohol structure. In this case sufficient material was available for an nmr spectrum which resolved the ambiguity in favor of the primary δ alcohol [two proton triplet at δ 4.45 (J = 5 Hz) in TFA, probably trifluoroacetate ester]. Presumably, VI is a precursor of the acid II.

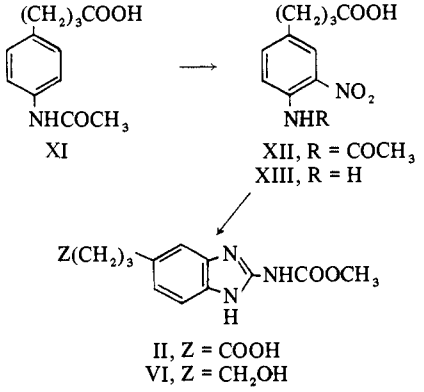
The phenol VII was a minor metabolite obtained from cattle.[4] It was clearly recognizable as a product of aromatic ring modification by the marked shift of its uv maxima to longer wavelengths than I. The molecular ion at *m/e* 263 and the base peak at *m/e* 220 (loss of propyl) were consistent with any of the three possible phenolic oxidation products of I. The uv spectrum of the metabolite (239, 296, and 304 nm) was compared with the spectra of the 4(7)- and 5(6)-methoxy derivatives of methyl 2-benzimidazolecarbamate (XXIX, 228, 270, and 278 nm; XXX, 234, 292, and 300 nm, respectively). The close correspondence of the uv spectrum of the metabolite to that of the 5(6) isomer established its structure as VII. Further proof was obtained from the nmr specturm (TFA) which showed two sharp singlets [$W_{1/2}$ = 1.5 Hz, $W_{1/2}$ (TMS) = 1 Hz] in the aromatic region. This was consistent only with structure VII which has the two remaining aromatic protons para to one another.

The ketone VIII was a metabolite from the fungus *Paecilomyces* species grown in potato dextrose broth; the product was isolated by extraction with $CHCl_3$ and chromatography on silica gel in 1:1 EtOAc-C_6H_6.‡ It was characterized by a uv spectrum closely matching that of I, a molecular ion at *m/e* 261, and fragments at *m/e* 246 (loss of methyl), 218 (loss of acetyl), and 204 (benzylic cleavage).

Synthesis of Metabolites. The structure of each metabolite was confirmed by synthesis. All natural and synthetic materials were compared by uv and mass spectrometry, by tlc mobility, and, where quantity permitted (II, III, VI-VIII), by nmr spectrometry. The carboxylic acid metabolite and the four metabolites resulting from hydroxylation of the butyl side chain were synthesized *via* ring closure on the appropriately substituted *o*-phenylenediamines. The ring-hydroxylated metabolite VII and the ketone VIII were synthesized from parbendazole (I).

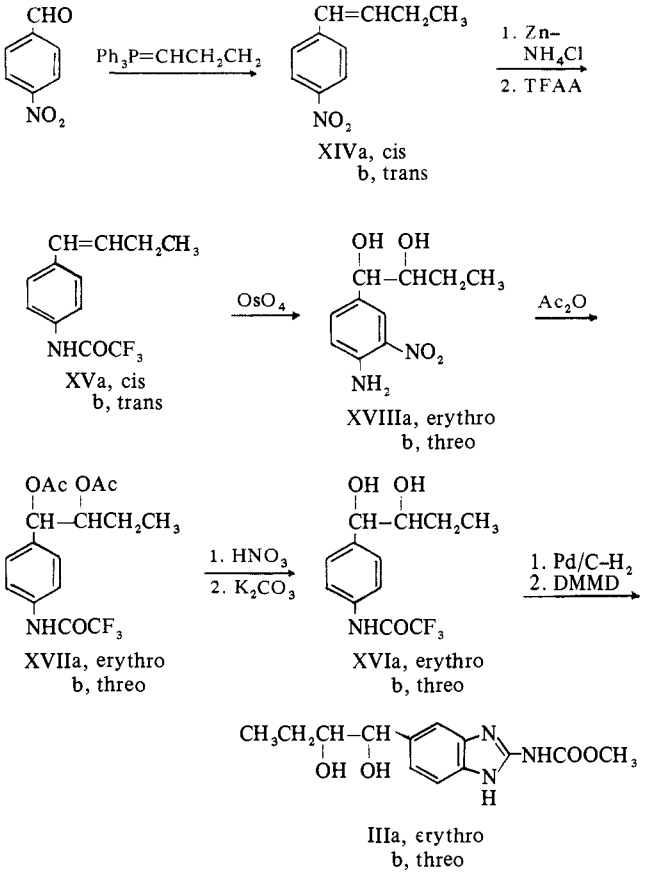
The carboxylic acid metabolite II was prepared as outlined in Scheme I. Thus, the acetanilide XI, obtained by reduction and acetylation of 4-(*p*-nitrophenyl)butyric acid, was successively nitrated and hydrolyzed to give the nitroamine XIII. Catalytic hydrogenation of XIII to the *o*-phenylenediamine followed by condensation with dimethyl [(methylthio)methylidyne]dicarbamate (DMMD)[10] afforded metabolite II. This served as the intermediate for the synthesis of metabolite VI through anhydride formation with ethyl chloroformate and $NaBH_4$ reduction (Scheme I).

Scheme I



Since the configuration of the glycol metabolite III was unknown, both the erythro and threo isomers were prepared by stereospecific routes (Scheme II). The first step in both sequences was a Wittig reaction between *p*-nitrobenzaldehyde and the phosphorane derived from *n*-propyltriphenylphosphonium bromide. Though as a general rule the trans isomer is usually favored, the resulting olefin XIV was shown by glc to be a 60:40 mixture of the cis and trans isomers with the cis isomer prodeominating.[11] The isomers were separated by fractional distillation and the component having the longer glc retention time was assigned the trans configuration on the basis of a strong ir absorption at 10.30 μ[12] and nmr data (*vide infra*). The cis isomer exhibited no significant ir absorption in the 10-11-μ region. The nitro group of the trans olefin XIVb was reduced with zinc and the resulting amine was converted to the *trans*-trifluoroacetamido olefin XVb. Hydroxylation of XVb with osmium tetroxide proceeded by stereospecific cis addition to yield the *threo*-diol XVIb. Besides ample literature precedents[13] for exclusive cis hydroxylation with osmium tetroxide, assignment of the threo configuration to XIVb was supported by comparing the nmr spectra of the cyclic carbonates of this diol and of the *erythro*-diol XVIa derived from osmium tetroxide oxidation of the cis olefin XVa (*vide infra*). Diol XVIb was acetylated, nitrated, and finally hydrolyzed under mildly alkaline conditions (K_2CO_3) to give the aminonitrodiol XVIIIb in good yield. Catalytic reduction of the nitro group followed by reaction of the re-

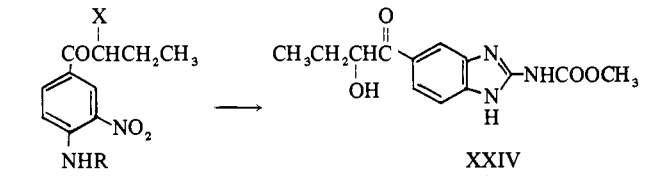
Scheme II



‡ The microbial fermentation experiment was performed by Mr. L. Fare at Smith Kline & French Laboratories.

sulting diamine with DMMD gave the benzimidazole IIIb (threo) in low yield. Repetition of this entire sequence starting with *cis*-1-(*p*-nitrophenyl)-1-butene (XIVa) gave the stereoisomeric benzimidazole IIIa (erythro). IIIa was also obtained by the alternate synthetic route illustrated in Scheme III. Nitration of *p*-acetamidobutyrophenone gave

Scheme III



XIX, R = $COCH_3$; X = H
XX, R = X = H
XXI, R = H; X = Br
XXII, R = H; X = OAc
XXIII, R = H; X = OH

XXIV

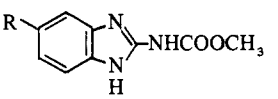
IIIa

XIX which was hydrolyzed with aqueous alkali to the aminonitro ketone XX. Monobromination of XX with cupric bromide[14] gave the α-bromo ketone XXI. Displacement of the bromine with NaOAc followed by hydrolysis of the intermediate acetoxy ketone XXII produced the hydroxy ketone XXIII. Hydrogenation and reaction with DMMD gave the benzimidazole XXIV which was reduced with $NaBH_4$ to give IIIa, identical with the erythro isomer prepared by the osmium tetroxide route. No threo isomer was evident in this product on tlc after work-up. The apparent exclusive production of the erythro isomer is consistent with Cram's rule of steric control of asymmetric induction.[15] Applying Cram's model for compounds having an OH group adjacent to the carbonyl function to XXIV dictates that hydride attacks the carbonyl from the least hindered (H) side producing the erythro isomer. Analogously, Zuman, *et al.*,[16] have reported obtaining the *erythro*-diol by $LiAlH_4$ reduction of 2-hydroxy-4′-methoxypropiophenone.

The spectral properties and melting points of the synthetic diols IIIa,b were too similar to allow unequivocal assignment of configuration to the natural metabolite. The nmr spectra of the erythro and threo isomers (DMSO-d_6) were virtually identical except that in the threo isomer the center of the multiplet due to the side chain methylene group was at δ ~1.1 while in the erythro isomer it was at δ ~1.4. However, the erythro (IIIa) and threo (IIIb) isomers could be differentiated by tlc on silica gel G impregnated with boric acid giving R_f's of 0.19 and 0.39, respectively, the complexed threo isomer migrating faster than the relatively uncomplexed *erythro*-diol.[17] The natural metabolite from sheep in the same system showed a major component at R_f 0.39 indicating that its configuration is predominantly threo. A very small quantity of a second component with R_f 0.19 also was present and may be the erythro isomer.

The synthesis of the α-alcohol metabolite IV was accomplished by catalytic hydrogenation of the nitroamino ketone XX (from Scheme III) to the corresponding diamine followed by ring closure to the ketobenzimidazole XXV with DMMD. $NaBH_4$ reduction of XXV gave IV. The β-alcohol metabolite V was obtained by $NaBH_4$ reduction of the ketone XXVI, which in turn had been prepared in good yield by rearrangement of *erythro*-diol IIIa in hot aqueous H_2SO_4 (the erythro isomer was used because of its availability; similar reaction with the threo isomer was not investigated).

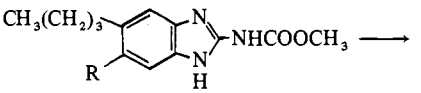
The remaining animal metabolite, phenol VII, was synthesized by the route outlined in Scheme IV; the reaction



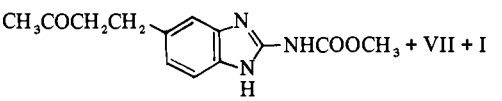
XXV, R = $CH_3CH_2CH_2CO$
XXVI, R = $CH_3CH_2COCH_2$

sequence also encompassed the serendipitous synthesis of the fungal metabolite VIII. Parbendazole (I) was nitrated under mild conditions to give the mononitro derivative XXVII. Catalytic hydrogenation of XXVII gave the amine XXVIII which was converted to the phenol VII by diazotization and hydrolysis.

Scheme IV



XXVII, R = NO_2
XXVIII, R = NH_2



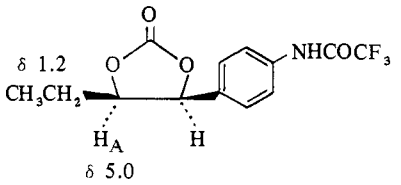
VIII

Ketone VIII was an unexpected by-product from the conversion of amino compound XXVIII to phenol VII. During chromatographic purification of VII, both VIII and I were found to be present in substantial amounts, the latter in much greater quantity than could have been carried through from the beginning of the reaction sequence. The mode of formation of VIII is not altogether clear, but we believe that the phenyl cation, presumably formed during the decomposition of the diazonium salt, must abstract a hydride ion from the γ position of the butyl side chain. A related reaction was observed by Lewin, *et al.*,[18] in the hydrolysis of diazotized *o*-amino-*N*,*N*-dialkylbenzamides.§ Reaction of the resulting alkyl carbonium ion with water would yield the γ alcohol derived from I. Alcohols are known to reduce diazonium salts[20] and we are forced to postulate that the alcohol resulting from hydride transfer reacts with diazotized XXVIII to yield VIII and I. This explanation, however, requires that the oxidation–reduction process takes place with high efficiency in quite dilute solution (none of the alcohol being found) and, on that account, is not wholly satisfactory.

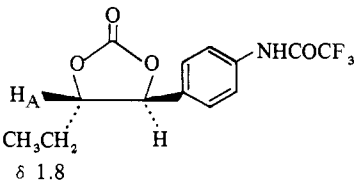
Nmr Spectra. In addition to the ir spectral evidence cited earlier for assigning cis and trans geometries to XIVa and XIVb, respectively, their nmr spectra also supported the structures. Thus, XIVa in CCl_4 showed a moderately broad doublet at δ 6.40 (J ~ 11 Hz) which we attribute to the benzylic vinyl proton. The vicinal coupling constant of 11 Hz is consistent with the proposed cis geometry. In the nmr spectrum of XIVb the two vinyl protons have very similar chemical shifts. The resulting complex multiplet at δ ~6.60 (Me_2CO-d_6) can be interpreted as the AB part of an ABX_2 system and comprises three overlapping AB quartets of relative intensities 1:2:1 all with J_{AB} = 16 Hz. This value is consistent with trans geometry.

§ Martinson[19] has reported that a number of diazotized *o*-alkylanilines undergo cyclization to indans during hydrolysis; this reaction may have as its first step the transfer of a hydride ion. In the present work, some of the crude products contained material giving a molecular ion at *m/e* 245; this may be the cyclized indan derivative.

Confirmation of the erythro and threo configurations of diols XVIa,b, respectively, is provided by the nmr spectra of their cyclic carbonates, prepared by treatment in pyridine (3 hr, 25°) with excess phosgene. The nmr spectrum of the cyclic carbonate of the *threo*-diol XVIb shows the signal for the methylene protons of the ethyl group as a multiplet at δ ~1.8, while the corresponding protons in the carbonate derived from the erythro isomer appear at higher field (δ ~1.2, m). Conversely, proton H_A of the *threo*-carbonate appears at higher field (δ ~4.65, m) that that of the *erythro*-carbonate (δ ~5.0, m). These observations can be explained after examination of molecular models of each of the carbonates. In the *erythro*-carbonate the ethyl group and the phenyl ring are cis to each other and the phenyl ring is probably turned so that the methylene protons lie in its shielding zone, in accord with observation. Analogously, proton H_A of the *threo*-carbonate is cis to the phenyl substituent and is probably in the shielding zone.[21]



erythro



threo

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Unimelt apparatus and are corrected. The decomposition points of the benzimidazoles were very dependent on the rate of heating. Uv spectra were determined in 95% EtOH using a Cary Model 11 recording spectrophotometer. Ir spectra were obtained in Nujol mull or as neat liquid using a Perkin-Elmer Infracord. Nmr spectra were obtained in a variety of solvents on a Varian T-60 or a Varian A-60 spectrophotometer using TMS as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer at 70 eV. Glc were performed on an F & M Model 700 gas chromatograph equipped with a thermal conductivity detector and using He as the carrier gas at 60 ml/min. Tlc was carried out using glass plates coated either with silica gel G or Al_2O_3 (Analtech, Inc.). All solvents used in anhydrous reactions were dried over Linde 4A molecular sieves. $MgSO_4$ was used as the drying agent for organic extracts. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

General Procedure for Preparing Methyl Benzimidazolecarbamates from Nitroamines. A solution of the appropriate nitroamine in an organic solvent was hydrogenated at 4.2 kg/cm² over 10% Pd/C on a Parr apparatus for 2 hr. The solution was filtered and evaporated *in vacuo* to give the crude diamine which was dissolved in 30% EtOH. A 10% molar excess of dimethyl [(methylthio)methylidyne)]-dicarbamate (DMMD)[10] was added and the mixture was heated at reflux for 2 hr (foaming and mercaptan evolution). After cooling to room temperature the solid was collected and then redissolved in 30% EtOH with dilute HCl. Neutralization with 10% NaOH yielded the benzimidazole which was collected and recrystallized as necessary.

Methyl 5(6)-Butyl-2-benzimidazolecarbamate (I). Following the general procedure using 4-butyl-*o*-phenylenediamine[22] (8.2 g, 0.05 mol) and DMMD (11.4 g, 0.055 mol) (in this experiment generated *in situ*[10] from 2-methyl-2-thiopseudourea sulfate and methyl chloroformate) yielded 9 g of crude product which was recrystallized twice from aqueous EtOH to give 6.6 g (54%) of I: mp 225–227° dec; uv (95% EtOH–1 *N* HCl) 282 nm (ε 16,200), 288 (20,000). *Anal.* ($C_{13}H_{17}N_3O_2$) C, H, N.

Reaction of **Metabolite III** with $NaIO_4$. A sample (1.0 mg) of the natural metabolite III was dissolved in 0.25 ml of MeOH and treated with 0.08 ml of $NaIO_4$ solution (6.3% w/v). After standing overnight at room temperature two types of crystals had precipitated, one of which dissolved readily upon adding a few drops of H_2O. The remaining slightly pink crystals were collected and dried: mass spectrum *m/e* 219 (80), 218 (20), 187 (95), 186 (100), 174 (28), 160 (20), 158 (45), which corresponds to aldehyde X ($C_{10}H_9N_3O_3$).

4-(*p*-Acetamidophenyl)butyric Acid (XI). A mixture consisting of 4-(*p*-nitrophenyl)butyric acid (15.7 g, 0.075 mol), glacial AcOH (270 ml), Ac_2O (19.1 g, 0.187 mol), and 10% Pd/C (1.57 g) was shaken under 4.2 kg/cm² of H_2 in a Parr apparatus at room temperature for 2 hr. After removal of the catalyst the solution was evaporated at 45° *in vacuo* to give 16.3 g of colorless solid, mp 169–173°. Recrystallization from 20% EtOH gave 15 g (90%) of X as colorless needles, mp 176–177° (lit.[23] 174–175°).

4-(4-Acetamido-3-nitrophenyl)butyric Acid (XII). Red fuming HNO_3 (15 ml) was added dropwise over 40 min to a cold stirred slurry of XI (15 g, 0.068 mol) in 40 ml of Ac_2O while the reaction temperature was kept between 0 and 4°. After the addition was complete the solution was allowed to stir at 2° for 2 hr and then poured onto 150 g of crushed ice. The yellow emulsion which formed was extracted with EtOAc and the dried organic layer was evaporated *in vacuo* to give an orange oil. The oil was triturated with 10 ml of Et_2O in a Dry Ice–*i*-PrOH bath to give 11.8 g of yellow solid. Recrystallization from 30% EtOH gave 9.9 g (55%) of XII as orange-yellow needles, mp 144–146°. *Anal.* ($C_{12}H_{14}N_2O_5$) C, H, N.

4-(4-Amino-3-nitrophenyl)butyric Acid (XIII). A solution of XII (12.2 g, 0.046 mol) in 85 ml of hot concentrated HCl was heated at reflux for 1 hr. The mixture was diluted with H_2O (250 ml) and cooled in ice. The solid was collected and washed with H_2O to give 9.4 g (91%) of XIII as orange crystals, mp 117–118°. *Anal.* ($C_{10}H_{12}N_2O_4$) C, H, N.

Methyl 5(6)-(3-Carboxypropyl)-2-benzimidazolecarbamate (II). Following the general procedure XIII (4.9 g, 0.022 mol) was hydrogenated in glacial AcOH and the resulting diamine allowed to react with DMMD (4.97 g, 0.024 mol) to give 2.7 g (44%) of II as a colorless solid, mp 300° dec. *Anal.* ($C_{13}H_{15}N_3O_4$) C, H, N.

Methyl 5(6)-(4-Hydroxybutyl)2-benzimidazolecarbamate (VI). Ethyl chloroformate (0.45 ml, 4.7 mmol) was added dropwise over 5 min to a cold (−5°) solution of acid II (1.30 g, 4.7 mmol) in 20 ml of DMF containing $(n\text{-Bu})_3N$ (1.12 ml, 4.7 mmol). After stirring at 0° for 1 hr $NaBH_4$ (0.36 g, 9.4 mmol) was added over 20 min and after stirring at room temperature for 2 hr, the mixture was adjusted to pH 7 with glacial AcOH. A second portion of $NaBH_4$ (0.36 g, 9.4 mmol) was added as before and after stirring at room temperature overnight the mixture was diluted with 100 ml of H_2O, adjusted to pH 7 with AcOH, and cooled in ice to give 1 g of product which was recrystallized from 5:1 Me_2CO-MeOH to give 175 mg of white solid. Chromatography on neutral Al_2O_3 in C_6H_5–EtOAc–MeOH (70:20:2) gave 45 mg of VI: mp 290° dec; mass spectrum *m/e* 263 (31), 231 (29), 204 (95), 172 (100). *Anal.* ($C_{13}H_{17}N_3O_3$) C, H; N: calcd. 15.96; found, 15.10.

***cis*- and *trans*-1-(*p*-Nitrophenyl)-1-butene (XIVa,b).** A solution of 1.9 *M* *n*-BuLi (108 ml, 0.205 mol) in C_6H_6-Et_2O (70:30) was added to a suspension of *n*-propyltriphenylphosphonium bromide (80.9 g, 0.21 mol) in dry Et_2O (700 ml) under N_2. After stirring overnight at room temperature the red-orange mixture was cooled to 5°, a solution of *p*-nitrobenzaldehyde (30.2 g, 0.20 mol) in dry Et_2O (300 ml) was added over 30 min, and the mixture allowed to stir overnight at room temperature. H_2O (800 ml) was added and the organic phase washed with H_2O and concentrated *in vacuo* to give a dark oil. This was extracted several times with warm hexane and the combined extracts were evaporated *in vacuo* to give 27.3 g of an orange oil. Distillation gave 18.8 g of a pale yellow liquid, bp 92–107° (0.15 mm). Glc on a 4-ft column of 10% SE-30 at 178° showed it to be a 60:40 mixture of two components with retention times of 2.2 and 3.4 min.

Fractional distillation at 0.04–0.08 mm on a 2-ft Podbielniak column packed with glass helices afforded 6.6 g with bp 130–138°, 2.0 g with bp 140°, and a further 3.3 g by flash distillation of the pot residue. The middle fraction (2.0 g) was homogeneous by glc (retention time 2.2 min) and was assigned the cis configuration XIVa on the basis of spectral evidence (see discussion). *Anal.* ($C_{10}H_{11}NO_2$) C, H, N.

The final 3.3-g fraction also was homogeneous by glc (retention time 3.4 min) and was assigned the trans configuration XIVb on the

basis of spectral evidence (see discussion). *Anal.* ($C_{10}H_{11}NO_2$) C, H, N. The initial fractions (6.6 g) contained a mixture of the cis olefin and *p*-nitrobenzaldehyde.

***trans*-1-(*p*-Trifluoroacetamidophenyl)-1-butene (XVb).** Zn dust (3.0 g, 0.046 mol) was added gradually during 15 min to a refluxing solution of trans olefin XIVb (2.62 g, 0.0148 mol) in a mixture of Me_2CO (25 ml) and H_2O (6 ml) containing 1.5 g of NH_4Cl. The Zn was added at a rate sufficient to maintain the solution at reflux without external heating. Another 1.5 g of Zn dust was added and the mixture was heated at reflux for 40 min. The hot solution was filtered and the filtrate was evaporated *in vacuo* to give an orange oil. The oil was dissolved in C_6H_6 and the solution evaporated *in vacuo* to give 1.53 g (70%) of crude amine.

A stirred solution of the amine (1.43 g, 0.01 mol) in 40 ml of Et_2O containing 12 g of suspended anhydrous Na_2CO_3 was treated dropwise over 7 min with 15.5 ml of $(F_3CCO)_2O$ with occasional cooling. The mixture was allowed to stir at room temperature for 1 hr and then was cautiously diluted with $CHCl_3$ (120 ml) and crushed ice. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic phases were washed with H_2O and evaporated *in vacuo* to give 1.7 g (70%) of yellow solid, mp 142-145°. Recrystallization from aqueous EtOH gave 1.24 g (51%) of XVb as yellow plates, mp 145-147°. *Anal.* ($C_{12}H_{12}F_3NO$) C, H, N.

***threo*-1-(*p*-Trifluoroacetamidophenyl)-1,2-butanediol (XVIb).** A solution of trans olefin XVb (5.30 g, 21.8 mmol) in 70 ml of dioxane was added in one portion to a solution of OsO_4 (6.25 g, 24.6 mmol) in 330 ml of dioxane at room temperature. The mixture was stirred overnight at room temperature, saturated with H_2S, and allowed to stir at room temperature for another hour. Excess H_2S was removed *in vacuo*. The mixture was filtered, the filter pad (Supercel) was washed well with EtOAc, and the combined filtrate and washings were evaporated *in vacuo* to give 5.38 g of off-white solid, mp 141-144°. Recrystallization from MeOH-$CHCl_3$ gave 3.90 g (65%) of XVIb as a colorless solid, mp 152-154°. A further recrystallization raised the melting point to 154-155°. *Anal.* ($C_{12}H_{14}F_3NO_3$) C, H, N.

***threo*-1-(*p*-Trifluoroacetamidophenyl)-1,2-butanediol 1,2-Diacetate (XVIIb).** Ac_2O (25 ml) was added gradually to a stirred solution of *threo*-diol XVIb (3.70 g, 13.3 mmol) in 40 ml of pyridine. Stirring was continued overnight, MeOH (12 ml) was added cautiously, and the mixture was concentrated to $^1/_2$ volume and poured into H_2O (350 ml) and $CHCl_3$ (150 ml). The organic phase was separated and the aqueous layer extracted with $CHCl_3$. Evaporation of the combined organic layers *in vacuo* gave an oil which was dissolved in $CHCl_3$ (75 ml) and washed with 1 *N* HCl and with H_2O. Evaporation of the solvent *in vacuo* gave 4.6 g (95%) of XVIIb as a viscous orange oil which was sufficiently pure for further reactions. Chromatography of a 200-mg sample on neutral alumina (Woelm) and elution with Et_2O gave 150 mg of XVIIb as a colorless solid, mp 90-92°. *Anal.* ($C_{16}H_{18}F_3NO_5$) C, H, N.

***threo*-1-(4-Amino-3-nitrophenyl)-1,2-butanediol (XVIIIb).** A cold solution of *threo*-diol XVIIb diacetate (4.41 g, 12.2 mmol) in 9 ml of Ac_2O was added dropwise over 10 min to an ice-cold solution of red fuming HNO_3 (3 ml) in 2 ml of glacial AcOH. After stirring in ice for 2 hr the mixture was allowed to warm to room temperature and then poured onto 200 ml of crushed ice. After 1 hr 100 ml of $CHCl_3$ was added, the layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined dried organic layers were evaporated *in vacuo* at 40° to yield 4.2 g (85%) of nitrated product as a viscous oil.

This oil (4.2 g, 10.3 mmol) was dissolved in 150 ml of a 7% solution of K_2CO_3 in 5:2 MeOH-H_2O and the solution was allowed to stand overnight at room temperature. Tlc ($CHCl_3$-MeOH, 9:1) showed incomplete hydrolysis, so the pH was raised from 8.0 to 9.5 by addition of solid K_2CO_3 and the mixture was stirred at room temperature for another 5 hr. The filtered solution was concentrated *in vacuo* and the aqueous residue was extracted with EtOAc. The combined organic layers were evaporated *in vacuo* to give a viscous oil which solidified after trituration with hexane-Et_2O. The crude solid (2.06 g) was recrystallized from H_2O to give 1.64 g (70%) of XVIIIb as orange-red needles, mp 143-144°. *Anal.* ($C_{10}H_{14}N_2O_4$) C, H, N.

Methyl *threo*-5(6)-(1,2-Dihydroxybutyl)-2-benzimidazolecarbamate (IIIb). Using the general procedure XVIIIb (1.2 g, 5.3 mmol) was hydrogenated in EtOAc and the resulting diamine allowed to react with DMMD (1.2 g, 5.8 mmol) to give 420 mg of IIIb. Recrystallization from MeOH gave 144 mg (10%) of IIIb as a colorless solid, mp >290° dec. *Anal.* ($C_{13}H_{17}N_3O_4$) C, H, N.

4'-Acetamido-3'-nitrobutyrophenone (XIX). *p*-Acetamidobutyrophenone[24] (10 g, 0.049 mol) was added over 15 min to 50 ml of cold (−10°) stirred red fuming HNO_3. The temperature was kept below 0° during addition. After stirring at −5° for another 15 min the solution was poured onto 300 g of crushed ice. The yellow precipitate was collected and washed successively with H_2O, 5% $NaHCO_3$, and again with H_2O to give 14.2 g of crude product. Recrystallization from 50% EtOH gave 9.3 g (74%) of XIX as bright yellow plates, mp 102-103° (lit.[24] 103-104°).

4'-Amino-3'-nitrobutyrophenone (XX). A mixture of XIX (6.8 g, 0.027 mol), 10% NaOH (6.8 ml), and 50% EtOH (70 ml) was heated at reflux for 1 hr during which time a precipitate formed. The mixture was allowed to stand in a refrigerator overnight and the yellow solid was collected (5.6 g). Recrystallization from 50% EtOH gave 5.3 g (94%) of XX as yellow crystals, mp 129.5-130.5°. *Anal.* ($C_{10}H_{12}N_2O_3$) C, H, N.

4'-Amino-2-bromo-3'-nitrobutyrophenone (XXI). A hot solution of ketone XX (73 g, 0.35 mol) in a mixture of EtOAc (300 ml) and $CHCl_3$ (100 ml) was added during 5 min to a refluxing mixture of EtOAc (100 ml) and $CHCl_3$ (200 ml) containing freshly ground $CuBr_2$ (131 g, 0.585 mol). After heating at reflux for 3.5 hr the mixture was cooled to 10°, filtered, and evaporated *in vacuo*. The resulting thick red oil solidified upon trituration with Et_2O to give 72.3 g of dark yellow solid, mp 100-101°. Recrystallization from aqueous MeOH afforded 52.8 g (52%) of bromo ketone XXI as bright yellow needles, mp 104-105°. *Anal.* ($C_{10}H_{11}BrN_2O_3$) C, H, N.

2-Acetoxy-4'-amino-3'-nitrobutyrophenone (XXII). A mixture of bromo ketone XXI (52.7 g, 0.183 mol) and NaOAc (50 g, 0.61 mol) in 1500 ml of DMF were heated with stirring at 67° under N_2 for 4 hr. The mixture was cooled to 10° and diluted to 10 l. with ice water. After standing for 2 hr in the cold, the precipitated yellow solid (45.1 g, 92%) was collected, mp 138.5-139.5°. Recrystallization from aqueous EtOH gave material with mp 139-140°. *Anal.* ($C_{12}H_{14}N_2O_5$) C, H, N.

4'-Amino-2-hydroxy-3'-nitrobutyrophenone (XXIII). A mixture of acetoxy ketone XXII (44 g, 0.166 mol), EtOH (880 ml), H_2O (1750 ml), and 3 *N* HCl (300 ml) was heated at 88° with stirring for 2 hr. The solution then was placed in a refrigerator for 3 days. The precipitated yellow solid was collected and washed sucessively with H_2O, 5% $NaHCO_3$, and H_2O to give 33.6 g (90%) of hydroxy ketone XXIII, mp 130-131.5°. Recrystallization from $CHCl_3$ and then from H_2O gave XXIII as pale yellow needles, mp 131-131.5°. *Anal.* ($C_{10}H_{12}N_2O_4$) C, H, N.

Methyl 5(6)-(2-Hydroxybutyryl)-2-benzimidazolecarbamate (XXIV). Following the general procedure XXIII (5.0 g, 0.023 mol) was hydrogenated in absolute EtOH and the resulting diamine allowed to react with DMMD (5.15 g, 0.025 mol) to give 4.0 g (62%) of XXIV as a colorless solid, mp 242° dec. *Anal.* ($C_{13}H_{15}N_3O_4$) C, H, N.

Methyl *erythro*-5(6)-(1,2-Dihydroxybutyl)-2-benzimidazolecarbamate (IIIa). Method A. A mixture of hydroxy ketone XXIV (3.0 g, 0.011 mol) and $NaBH_4$ (0.06 g, 0.016 mol) in 2 l. of *i*-PrOH was heated at 60° for 2 hr and cooled to 20° and the excess $NaBH_4$ decomposed by addition of glacial AcOH. The white solid obtained after evaporation of the solvent *in vacuo* was washed well with H_2O to give 2.4 g of crude diol IIIa. This was dissolved in H_2O (220 ml) by addition of 10% NaOH and reprecipitated by neutralization with 3 *N* HCl to pH 7. Recrystallization from 50% EtOH gave 1.64 g (53%) of diol IIIa as a colorless solid, mp 210° dec. *Anal.* ($C_{13}H_{17}N_3O_4$) C, H, N.

Method B. The sequence outlined above for the synthesis of the *threo*-diol IIIb was repeated using *cis*-1-(*p*-nitrophenyl)-1-butene (XIVa) as starting material. The cis olefin XVa and the *erythro*-diol XVIa were isolated and characterized but the remainder of the synthetic sequence was carried out without isolation of intermediates. XVa gave mp 91-92°. *Anal.* ($C_{12}H_{12}F_3NO$) C, H, N. XVIa gave mp 161-162°. *Anal.* ($C_{12}H_{14}F_3NO_3$) C, H, N. The *erythro*-diol IIIa obtained by this route was identical in every respect with that obtained by method A.

Methyl 5(6)-Butyryl-2-benzimidazolecarbamate (XXV). Using the general procedure XX (5.28 g, 0.025 mol) was hydrogenated in absolute EtOH and the resulting diamine allowed to react with DMMD (5.7 g, 0.027 mol) to give 5.0 g of XXV. Two recrystallizations from 95% EtOH-DMSO followed by slurrying the solid twice with boiling H_2O to remove residual DMSO gave 3.76 g (57%) of XXV as a colorless solid, mp 278-280° dec. *Anal.* ($C_{13}H_{15}N_3O_3$) C, H, N.

Methyl 5(6)-(1-Hydroxybutyl)-2-benzimidazolecarbamate (IV). A suspension of ketone XXV (0.50 g, 1.91 mmol) in 150 ml of *i*-PrOH was heated at 60° and treated portionwise with $NaBH_4$ (450 mg, 10.9 mmol) until tlc on silica gel G ($CHCl_3$-MeOH, 9:1) showed

the absence of starting material. After cooling the mixture to room temperature excess $NaBH_4$ was destroyed by adjustment to pH 7 with 3 *N* HCl. The residue obtained after evaporation of the solvent *in vacuo* was suspended in H_2O and adjusted to pH 7 and the solid (0.36 g) was collected. Recrystallization from aqueous EtOH followed by reprecipitation from aqueous acid gave 173 mg (35%) of IV as a colorless solid, mp 217° dec. *Anal.* ($C_{13}H_{17}N_3O_3$) C, H, N.

Methyl 5-(2-Oxobutyl)-2-benzimidazolecarbamate (XXVI). A solution of diol IIIa (1.50 g, 5.35 mmol) in 25 ml of 30% H_2SO_4 was heated on a steam bath for 30 min and allowed to cool to room temperature. The solution was diluted with 150 ml of H_2O and neutralized with solid Na_2CO_3, and the white solid (1.17 g) was collected and washed well with H_2O. Recrystallization from DMSO containing a small amount of H_2O followed by slurrying in hot H_2O to remove residual DMSO gave 0.75 g (54%) of colorless XXVI, mp 225–226°. *Anal.* ($C_{13}H_{15}N_3O_3$) C, H, N.

Methyl 5-(2-Hydroxybutyl)-2-benzimidazolecarbamate (V). A suspension of ketone XXVI (724 mg, 2.77 mmol) in 250 ml of *i*-PrOH containing $NaBH_4$ (400 mg, 10.6 mmol) was heated at 60–70° for 1.5 hr and allowed to stand overnight at room temperature. The mixture was acidified and evaporated *in vacuo*. The residue was dissolved in 50 ml of water and adjusted to pH 7 with 10% NaOH to give a solid (790 mg) which, after recrystallization from aqueous DMSO and slurrying in hot H_2O, afforded 430 mg (59%) of V, mp 261–262° dec. *Anal.* ($C_{13}H_{17}N_3O_3$) C, H, N.

Methyl 5(6)-Butyl-6(5)-nitro-2-benzimidazolecarbamate (XXVII). Parbendazole (I, 24.7 g, 0.10 mol) was added gradually to 150 ml of stirred red fuming HNO_3 keeping the temperature between 25 and 30° with ice cooling (vigorous nitrating conditions gave both di- and trinitro derivatives). After the addition was complete the solution was stirred for 40 min at room temperature, poured into 2 l. of crushed ice and H_2O, and basified to pH 7.5 with concentrated NH_4OH. The solid was collected, recrystallized from DMSO (450 ml), and slurried twice with boiling H_2O to remove DMSO to give 23.4 g (80%) of XXVII as a light yellow solid, mp 300° dec. *Anal.* ($C_{13}H_{16}N_4O_4$) C, H, N.

Methyl 6(5)-Amino-5(6)-butyl-2-benzimidazolecarbamate (XXVIII). A solution of the nitro derivative XXVII (8.0 g, 0.027 mol) in 250 ml of glacial AcOH containing 10% Pd/C (0.80 g) was hydrogenated at 4.2 kg/cm² on a Parr apparatus for 4 hr at room temperature. After removal of the catalyst the solution was evaporated *in vacuo* to a lavender-colored solid which was dissolved in 1 *N* HCl (250 ml). The solution was filtered and brought to pH 7.5 with concentrated NH_4OH, and the solid (6.5 g) was collected. Recrystallization from 95% EtOH gave 4.37 g (62%) of pale lavender XXVIII, mp 315° dec. *Anal.* ($C_{13}H_{18}N_4O_2$) C, H, N.

Methyl 5(6)-Butyl-6(5)-hydroxy-2-benzimidazolecarbamate (VII) and Methyl 5(6)-(3-Oxobutyl)-2-benzimidazolecarbamate (VIII). An aqueous solution of $NaNO_2$ (3.4 g, 0.049 mol) was added gradually over 45 min to an ice-cold stirred suspension of amine XXVIII (12.96 g, 0.0495 mol) in 325 ml of 2 *N* H_2SO_4. After the addition was complete the brown solution was allowed to stir for another 15 min and then was diluted with H_2O (2 l.). Excess $NaNO_2$ was decomposed with ammonium sulfamate and the resulting solution was heated on a steam bath for 1 hr, cooled to room temperature, and decolorized with charcoal. Neutralization of the light yellow solution to pH 7.5 with 25% NaOH precipitated a light brown solid (8.8 g). Chromatography of this product on neutral alumina (Woelm, grade III) gave two major solid fractions, A (1.47 g), eluted with C_6H_6, MEK, and CH_3OH (10:10:1), and B (2.75 g), eluted with C_6H_6, MEK, and CH_3OH (2:2:1).

Solid B was recrystallized from absolute EtOH (charcoal) to give 1.15 g of phenol VII which was identified from its physical and spectral properties, mp 283–285° dec. *Anal.* ($C_{13}H_{17}N_3O_3$) C, H, N.

Rechromatography of a 1.0-g sample of solid A on neutral alumina (Woelm, grade III) gave, upon elution with C_6H_6–MEK–CH_3OH (50:50:3), 190 mg of a white solid which, after recrystallization from absolute EtOH, was shown by comparison of tlc and spectral and physical properties to be identical with parbendazole (I). Elution with C_6H_6–MEK–MeOH (10:10:1) yielded 410 mg of another white solid which after recrystallization from absolute EtOH was identified as ketone VIII on the basis of analytical and spectral properties: mp 217–218.5° dec; ir (Nujol) 5.84 μ (C=O); nmr (TFA) δ 2.49 (s, 3, CH_3CO), 3.28 (s, 4, CH_2CH_2), 4.25 (s, 3, $COOCH_3$), and 7.60–8.05 ppm (m, 3). *Anal.* ($C_{13}H_{15}N_3O_3$) C, H, N.

Methyl 4(7)-Methoxy-2-benzimidazolecarbamate (XXIX). Following the general procedure using 3-methoxy-*o*-phenylenediamine[25] (10.0 g, 0.073 mol) and DMMD (15.1 g, 0.073 mol) yielded 15.5 g of crude product which was recrystallized twice from aqueous EtOH to give 10.5 g (65%) of XXIX as a colorless solid: mp 298–301° dec; uv (95% EtOH–1 *N* HCl) 228 nm (ϵ 29,000), 270 (8000), and 278 (8400). *Anal.* ($C_{10}H_{11}N_3O_3$) C, H, N.

Methyl 5(6)-Methoxy-2-benzimidazolecarbamate (XXX). Following the general procedure using 4-methoxy-*o*-phenylenediamine (10.0 g, 0.073 mol) and DMMD (15.1 g, 0.073 mol) yielded 12.4 g of crude product which was recrystallized twice from aqueous EtOH to give 8.5 g (53%) of XXX as a colorless solid: mp 235° dec; uv (95% EtOH–1 *N* HCl) 234 nm (ϵ 13,500), 292 (14,100), and 300 (14,100). *Anal.* ($C_{10}H_{11}N_3O_3$) C, H, N.

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