pler thiazolium salts. In this case the final equilibrium absorbancy was measured. Because of the slow reaction rates in the neighborhood of pK_{av}, and slow secondary reactions, these particular pK estimates have an uncertainty of as much as ± 0.2 unit.

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Metabolite Analogs. VII. Preparation of Some Benzimidazolyl Analogs of Ethyl Pteroylglutamate

BY W. RAYMOND SIEGART AND ALLAN R. DAY

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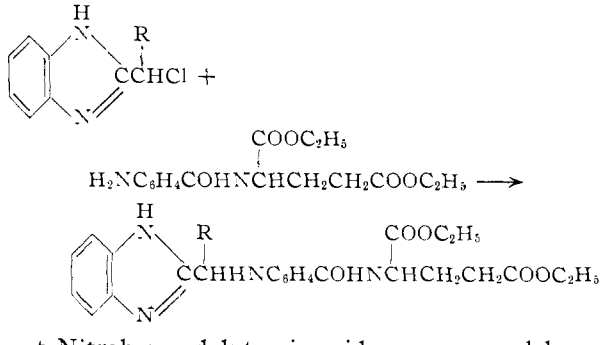
Some benzimidazolyl analogs of ethyl pteroylglutamate have been prepared. Substituents have been placed on the carbon atom of the methylene bridge and in the benzene ring of the benzimidazole.

Two benzimidazolyl analogs of pteroylglutamic acid have been reported previously, N-{4-[(2-benzimidazolyl)-methylamino]-benzoyl}-glutamic acid[1] and N{4-[(5-chloro-2-benzimidazolyl)-methylamino]-benzoyl}-glutamic acid. The first compound was reported to retain a certain degree of growth-promoting activity[1a] and also to be a weak growth antagonist.[1b] The 5-chloro compound was reported to be a stronger growth antagonist than the unsubstituted analog.[1b] It seemed to be desirable to extend this work, in several ways, in order to determine the possibility of obtaining strong anti-folic activity in this type of compound. In the present investigation, benzimidazolyl analogs of folic acid have been synthesized containing not only substituents in the benzene ring but also on the carbon atom of the methylene bridge. Substituents have been placed on the methylene bridge when there were no substituents on the ring and when there were substituents on the benzene ring. The choice of substituents in the benzene ring was influenced by the work of Hoover and Day.[2]

The syntheses of the benzimidazolyl analogs of pteroylglutamic acid involved four steps: (1) preparation of diethyl *p*-aminobenzoylglutamate; (2) preparation of 2-hydroxyalkylbenzimidazoles; (3) preparation of 2-chloroalkylbenzimidazoles; and (4) finally, the condensation of the chloroalkyl compound with the glutamate derivative.



p-Nitrobenzoylglutamic acid was prepared by a modified Schotten–Baumann procedure from *p*-nitrobenzoyl chloride and glutamic acid. The nitro group was reduced by catalytic hydrogenation over palladium and the corresponding aminobenzoylglutamic acid converted to its diethyl ester. Preliminary work had shown that the final products, the benzimidazolyl analogs of folic acid, were most readily isolated and purified in the form of their ethyl esters.

The 2-hydroxyalkylbenzimidazoles were prepared from the appropriate hydroxy acid and *o*-phenylenediamine by the Phillips method[3] or by fusing the reactants together. The hydroxy compounds were then converted to the corresponding chloro compounds by treatment with thionyl chloride.

In order to reduce side reactions to a minimum, the hydrochlorides of the chloro compounds were used for condensation with diethyl *p*-aminobenzoylglutamate. The condensations were carried out in dioxane solution in the presence of two equivalents of triethylamine. The main side-reaction which occurred to a greater or less extent, depending on the nature of the chloro compound, was self condensation. It had been shown earlier[4] that the 2α-chloroalkylbenzimidazoles do not always undergo normal anionic replacement reactions. They show a marked tendency to undergo self-condensation to form tetracyclic compounds. For example, 2-chloromethylbenzimidazole readily forms dibenzimidazo[1,2,-a,1′,2′,-d]piperazine. On several occasions during the course of the present work, high melting, crystalline compounds were isolated whose analyses indicated that they were tetracyclic. No attempt was made to purify these secondary products. Gummy materials also were separated from the reactions of the 2α-chloroalkylbenzimidazoles with ethyl *p*-aminobenzoylglutamate. They were assumed to be linear polymers formed from self-condensation of the chloro compounds.

For testing purposes, two benzimidazolyl analogs of the ethyl ester of pteroic acid were prepared also. They were prepared by condensing the chloroalkyl benzimidazoles with ethyl *p*-aminobenzoate.

All of the final products are being tested for physiological activity. The test results will be published elsewhere.

(1) (a) P. C. Edwards, D. Starling, A. M. Mattocks and H. E. Skipper, *Science*, **107**, 119 (1948); (b) F. E. King, R. M. Acheson, and P. C. Spensley, *Nature*, **162**, 153 (1948); *J. Chem. Soc.*, 1401 (1949).

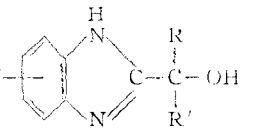
(2) J. R. E. Hoover and A. R. Day, THIS JOURNAL, **77**, 4324 (1955); **77**, 5652 (1955); Progress Report, July 1955–January 1956, U.S.P.H.S. Grant C-2189, University of Pennsylvania.

(3) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(4) H. Skolnik, J. G. Miller and A. R. Day, THIS JOURNAL, **65**, 1854 (1943).

TABLE I

2-HYDROXYALKYLBENZIMIDAZOLES



Compound	R	R′	Y	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
I[a]	CH_3	H	H	77	178.5–179.5								
II[b]	CH_3	CH_3	H	60	227.5–228.5								
III[c]	C_6H_5	H	H	30	202–203								
IV[c]	CH_3	H	5-Chloro	48	178–179	54.96	4.62	14.25	18.03	54.68	4.75	14.09	17.82
V[d]	CH_3	CH_3	5-Chloro	15	250–251	57.01	5.27	13.30	16.82	57.00	5.35	13.39	16.82
VI[f]	C_6H_5	H	5-Chloro	15	189–190.5	64.99	4.29	10.83	13.70	64.84	4.08	10.77	13.59
VII[c]	H	H	5-Nitro	52	196–198	49.74	3.63	21.75		49.70	3.86	21.69	
VIII[c]	CH_3	H	5-Nitro	33	204–205	52.17	4.39	20.29		52.35	4.57	20.35	
IX[c]	CH_3	CH_3	5-Nitro	21	219–221	54.29	5.02	18.99		54.27	4.95	18.89	
X[e]	H	H	4-Nitro 6-Chloro	20	213–215	42.21	2.65	18.47	15.57	42.27	2.47	18.29	15.42
XI[c]	CH_3	H	4-Nitro 6-Chloro	4	156–157	44.73	3.34	17.39	14.67	44.87	3.40	17.14	14.68
XII[d]	CH_3	CH_3	4-Nitro 6-Chloro	6	170–171.5	46.97	3.91	16.43	13.89	46.76	3.71	16.47	14.01
XIII[f]	H	H	5-Methyl	78	202–203								
XIV[c]	CH_3	H	5-Methyl	42	183–184	68.15	6.88	15.90		68.13	6.99	15.78	
XV[d]	CH_3	CH_3	5-Methyl	16	244–245	69.43	7.43	14.73		69.25	7.24	14.64	
XVI[d]	H	H	4-Amino 6-Chloro	53	224–225	48.61	4.09	21.27	17.94	48.45	4.29	21.15	17.76

[a] Ref. 3. [b] Ref. 4. [c] Recryst. from 33% ethanol. [d] Recryst. from 50% ethanol. [e] Recryst. from 95% ethanol. [f] P. Mamalis, V. Petrow and B. Sturgen, *J. Chem. Soc.*, 1600 (1950).

Experimental

p-**Nitrobenzoylglutamic Acid.**—A solution of 47 g. (0.25 mole) of *p*-nitrobenzoyl chloride in 170 ml. of benzene was added slowly, with stirring and cooling, to a solution of 29.4 g. (0.2 mole) of glutamic acid and 32 g. (0.8 mole) of sodium hydroxide in 170 ml. of water. After the completion of the reaction, the aqueous layer was separated and adjusted to a *p*H of 4 to 5 with concentrated hydrochloric acid and the *p*-nitrobenzoic acid removed by filtration. The filtrate was adjusted to a *p*H of 1 and cooled overnight. The precipitated *p*-nitrobenzoylglutamic acid was removed and recrystallized from hot water; yields 75–80%, m.p. 112.5–113.5°.

p-**Aminobenzoylglutamic Acid.**—The amino compound was obtained by hydrogenation of the nitro derivative over palladium-in-ethanol solution. The crude product was recrystallized from hot water with the aid of decolorizing carbon; yield 75%, m.p. 172–173°.

Diethyl *p*-Aminobenzoylglutamate.—This ester was prepared by the method of Waller, *et al.*[5]; yield 70%, m.p. 143–144°.

Preparation of 2-Hydroxyalkylbenzimidazoles.—These compounds were prepared from the corresponding *o*-phenylenediamines and α-hydroxy acids. The following were made by the Phillips method[3]: 2-(1-hydroxyethyl)-benzimidazole (I), 2-(1-hydroxyisopropyl)-benzimidazole (II), 2-(1-hydroxybenzyl)-benzimidazole (III), 2-(1-hydroxyethyl)-5-chlorobenzimidazole (IV), 2-(1-hydroxyisopropyl)-5-chlorobenzimidazole (V), 2-hydroxymethyl-5-nitrobenzimidazole (VII), 2-(1-hydroxyethyl)-5-nitrobenzimidazole (VIII), 2-(1-hydroxyisopropyl)-5-nitrobenzimidazole (IX), 2-hydroxymethyl-4-nitro-6-chlorobenzimidazole (X), 2-(1-hydroxyethyl)-4-nitro-6-chlorobenzimidazole (XI), 2-hydroxymethyl-5-methylbenzimidazole (XIII), 2-(1-hydroxyethyl)-5-methylbenzimidazole (XIV), 2-(1-hydroxyisopropyl)-5-methylbenzimidazole (XV), and 2-hydroxymethyl-4-amino-6-chlorobenzimidazole (XVI).

The Phillips method did not give good yields in all cases. In the preparation of IV and VIII, after the refluxing period was completed, the solution was adjusted to a *p*H of 5. The aqueous layer was decanted from a dark oil that had formed and the solution adjusted to *p*H 8 to precipitate the benzimidazole product. The procedure was least efficient for the preparation of X, XI and XII. In these cases, after the refluxing period, the mixture was cooled and the solid removed by filtration. After washing with water, the solid was treated with 2 *N* sodium hydroxide solution and filtered. The filtrate was acidified with hydrochloric acid, neutralized with ammonium hydroxide, cooled and the solid removed. The first filtrate was made 2 *N* with sodium hydroxide and filtered. The filtrate was acidified with hydrochloric acid, neutralized with ammonium hydroxide, cooled and the precipitate removed. The two precipitates were combined and recrystallized from alcohol.

The following compounds were prepared by fusing the diamine and hydroxy acid: 2-(1-hydroxybenzyl)-5-chlorobenzimidazole (VI) and 2-(1-hydroxyisopropyl)-4-nitro-6-chlorobenzimidazole (XII).

Preparation of VI.—4-Chloro-*o*-phenylenediamine (14.25 g., 0.1 mole) was added to 13.6 g. (0.1 mole) of molten mandelic acid (125°). The reaction mixture was maintained at 125° in an atmosphere of nitrogen for two hours. The dark gummy residue was dissolved in dry ethanol. Dry hydrogen chloride was passed into the solution and dry ether then added. The dark solid so obtained was dissolved in 2 *N* sodium hydroxide. After filtering, the solution was acidified with hydrochloric acid, neutralized with ammonium hydroxide and cooled to hasten the precipitation of the product. After recrystallization from 50% ethyl alcohol, with the aid of decolorizing carbon, the product melted at 189–190.5°.

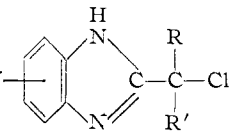
Preparation of Compound XII.—A mixture of 20.8 g. (0.2 mole) of-α-hydroxyisobutyric acid and 37.5 g. (0.2 mole) of 5-chloro-3-nitro-*o*-phenylenediamine was fused at 110° for six hours in an atmosphere of nitrogen. After cooling, 150 ml. of 4 *N* hydrochloric acid was added. The mixture was filtered and the filtrate neutralized with ammonium hydroxide and the product removed. The material that was insoluble in the hydrochloric acid was treated with 2 *N* sodium hydroxide and filtered. The filtrate was acidified with hydrochloric acid, neutralized with ammonium hydroxide, cooled and the product removed by filtration. The two products were combined and recrystallized from 50% ethyl alcohol with the aid of decolorizing carbon. Yellow needles were obtained.

Preparation of 2-Chloroalkylbenzimidazoles. Many difficulties were encountered in attempting to convert the hydroxy compounds to the corresponding chloro compounds.

(5) C. W. Waller, *et al.*, THIS JOURNAL, **70**, 19 (1948).

TABLE II

2-CHLOROALKYLBENZIMIDAZOLES



Compound	R	R′	Y	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
XVII[b]	CH_3	H	H	95[a]									
XVIII[b]	CH_3	CH_3	H	95[a]									
XIX	C_6H_5	H	H	28	164–168 d.	69.28	4.57	11.55	14.60	69.47	4.62	11.65	14.45
XX	CH_3	H	5-Chloro	12	128–130	50.23	3.72	13.02	33.02	50.47	3.75	12.87	32.84
XXI[b]	CH_3	CH_3	5-Chloro	47	123–125 d.	45.22	4.18	10.55	40.04	43.46	4.5–4.6	10–10.6	37–39
XXII	H	H	5-Nitro	23	184–185	45.40	2.86	19.86	16.75	45.39	3.08	19.87	16.55
XXIII[b]	CH_3	H	5-Nitro	25–40	[c]								
XXIV[b]	CH_3	CH_3	5-Nitro	35–40	[d]								
XXV[c]	CH_3	H	5-Methyl	50–60	[e]								
XXVI[b]	CH_3	CH_3	5-Methyl	76	[e]								

[a] Yield as hydrochloride. [b] This compound was not obtained analytically pure, but was used successfully to make the folic acid analog. [c] Gummy solid. [d] No definite m.p.; starts to decompose at 130°. [e] Starts to decompose at 45–50°.

The free bases of the 2-chloroalkylbenzimidazoles are very reactive and tend to self-condense. In four cases the pure free bases could not be obtained although the crude free bases were used successfully to make the folic acid analogs. In most cases the hydrochlorides of the 2-chloroalkyl compounds could be isolated in better yields than the free bases and they appeared to be considerably more stable.

2-(1-Chloroethyl)-benzimidazole (XVII) and 2-(1-chloroisopropyl)-benzimidazole (XVIII) were obtained as their hydrochlorides by heating the hydrochlorides of I and II, respectively, in chloroform solution for 2–3 hours with thionyl chloride.[4] After cooling, dry ether was added to precipitate the hydrochlorides. The products were thoroughly washed with ether and dried.

The hydrochloride of 2-(1-chlorobenzyl)-benzimidazole (XIX) was prepared in a similar way in 50–60% yields. The free base was obtained by dissolving the hydrochloride in the least amount of water. This solution was cooled and slowly neutralized with sodium bicarbonate solution. The crude free base was removed, washed with ice-water and dried *in vacuo*. It was recrystallized by dropping the compound into boiling acetone, decanting the acetone from a heavy red oil and cooling. White needles were obtained.

The hydrochloride of 2-(1-chloroethyl)-5-chlorobenzimidazole (XX) was prepared from 2-(1-hydroxyethyl)-5-chlorobenzimidazole hydrochloride as described above, yields 60–70%. The dry, crude free base obtained from the hydrochloride was recrystallized by adding it to boiling benzene. The benzene was decanted from a dark oil which formed and cooled. White needles were obtained.

Difficulties were encountered in preparing the hydrochloride of 2-(1-chloroisopropyl)-5-chlorobenzimidazole (XXI) from 2-(1-hydroxyisopropyl)-5-chlorobenzimidazole hydrochloride. When dry ether was added to precipitate the hydrochloride, a gummy material was obtained. It was converted to a solid by stirring it with several portions of dry ether. Attempts to recrystallize the solid from dry alcohol and ether gave a gummy material which once more was converted to a solid by treating several times with dry ether. Although it was not obtained analytically pure, it was used successfully for the preparation of the folic acid analog.

2-Chloromethyl-5-nitrobenzimidazole (XXII) was prepared by dissolving 0.1 mole of the corresponding hydroxymethyl compound in 250 ml. of boiling dioxane. The solution was cooled to 60° and 30 ml. of thionyl chloride was added with stirring. The reaction was exothermic and no further heat was applied. After the temperature dropped to room temperature, dry ether was added to complete the precipitation of the hydrochloride. After removing the hydrochloride, washing with dry ether and drying, it was dissolved in cold water. This solution was slowly neutralized with sodium bicarbonate solution. The product was removed by filtration, washed with water and dried. It was purified by dropping it into boiling benzene and filtering to remove insoluble material. On cooling slowly an oil first separated. The benzene was decanted and further cooled to give the product (white needles).

2-(1-Chloroethyl)-5-nitrobenzimidazole (XXIII) was prepared from 0.15 mole of the hydroxyethyl compound and 80 ml. of thionyl chloride. The solution was refluxed for 1.5 hours. The free base was obtained from this solution by the same procedure used for XXII. The product could not be obtained in pure form but it formed the expected analog with diethyl *p*-aminobenzoylglutamate. The following is a typical analysis. *Anal.* Calcd. for $C_9H_8O_2N_3Cl$: C, 47.90; H, 3.58; N, 18.63; Cl, 15.71. Found: C, 49.45; H, 3.64; N, 17.60; Cl, 14.44.

2-(1-Chloroisopropyl)-5-nitrobenzimidazole (XXIV) was prepared from 2-(1-hydroxyisopropyl)-5-nitrobenzimidazole in the same manner as XXIII. The final crystallization was made from a solution containing equal amounts of benzene and petroleum ether. The analytical data were similar to those noted above but the product was used successfully to prepare the desired analog.

2-(1-Chloroethyl)-5-methylbenzimidazole hydrochloride (XXV) was prepared from the corresponding hydroxyethyl compound by the method used for the preparation of XVII. The free base could not be obtained and even the hydrochloride could not be obtained analytically pure. The latter was obtained as an oil from dry ethanol and ether. The oil was extracted several times with dry ether and placed in a vacuum desiccator over calcium chloride until solidification was complete; yields 50–63%. A typical analysis: *Anal.* Calcd. for $C_{10}H_{12}N_2Cl_2$: C, 51.96; H, 5.24; N, 12.12; Cl, 30.67. Found: C, 50.19; H, 5.71; N, 11.99; Cl, 27.43.

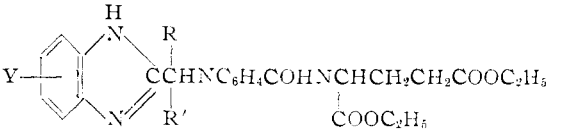
2-(1-Chloroisopropyl)-5-methylbenzimidazole (XXVI) was prepared from 2-(1-hydroxyisopropyl)-5-methylbenzimidazole by the same procedure used for XXV. Similar to XXV, it could not be obtained analytically pure, but was used successfully for the preparation of the corresponding folic acid analog.

Preparation of Benzimidazolyl Analogs of Diethyl *p*-Aminobenzoylglutamate. Diethyl N-{4-[1-(2-Benzimidazolyl)-ethylamino]-benzoyl}-glutamate (XXVII).—2-(1-Chloroethyl)-benzimidazole hydrochloride (54.25 g., 0.25 mole), 80 g. (0.25 mole) of diethyl *p*-aminobenzoylglutamate and 200 ml. of dry dioxane were placed in a flask. Triethylamine (50.5 g., 0.5 mole) was added and the solution refluxed for 10 hours. After standing overnight, the precipitated triethylamine hydrochloride was removed. It was washed with water and the water-insoluble residue was dried. The product was extracted with benzene and then recrystallized from alcohol–water.

Diethyl N-{4-[1-(2-Benzimidazolyl)-isopropylamino]-benzoyl}-glutamate (XXVIII).—The procedure for XXVII was used here also. In these preparations an additional small amount of product could be obtained by concentrating the original filtrate. The oil so obtained was extracted with hot benzene leaving a small amount of solid product.

TABLE III

DIETHYL BENZIMIDAZOLYL *p*-AMINOBENZOYLGLUTAMATES



Compound	Substituents R	R′	Y	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
XXVII	CH_3	*H*	H	23	197–198	64.35	6.49	12.01		64.45	6.45	12.03	
XXVIII	CH_3	CH_3	H	24	178–180	65.07	6.72	11.66		65.23	6.67	11.70	
XXIX	C_6H_5	H	H	41	168–170	68.17	6.11	10.60		68.38	6.02	10.51	
XXX	CH_3	H	5-Chloro	18	90–91	59.93	5.85	11.16	7.08	59.96	5.75	10.93	7.27
XXXI	CH_3	CH_3	5-Chloro	32	157–159	60.65	6.08	10.88	6.86	60.78	6.25	10.89	6.94
XXXII	H	H	5-Nitro	12	184–185	57.93	5.48	14.08		57.78	5.46	14.00	
XXXIII	CH_3	H	5-Nitro	11	107–110	58.69	5.73	13.69		58.50	5.54	13.87	
XXXIV	CH_3	CH_3	5-Nitro	14	195–197	59.46	5.96	13.33		59.45	5.91	13.47	
XXXV	CH_3	H	5-Methyl	11	161.5–162.5	64.97	6.72	11.66		64.91	6.61	11.73	
XXXVI	CH_3	CH_3	5-Methyl	15	108–110	65.55	6.94	11.33		65.39	6.93	11.38	

Diethyl N-{4-[1-(2-Benzimidazolyl)-benzylamino]-benzoyl}-glutamate (XXIX).—In this preparation the free base 2-(1-chlorobenzyl)-benzimidazole was used in place of the hydrochloride and only one equivalent of triethylamine was added. Otherwise the procedure for XXVII was followed.

Diethyl N-{4-[1-(5-Chloro-2-benzimidazolyl)-ethylamino]-benzoyl}-glutamate (XXX).—The procedure for the preparation of XXVII was used in this case. To obtain the product the filtrate from the triethylamine hydrochloride was evaporated under reduced pressure and the resulting oil allowed to stand overnight under benzene to produce a solid material which was recrystallized from benzene to give a product with one molecule of benzene; m.p. 103–105°.

Anal. Calcd. for $C_{31}H_{35}O_5N_4Cl$: C, 64.29; H, 6.10; N, 9.68; Cl, 6.12. Found: C, 63.98; H, 6.13; N, 9.69; Cl, 6.22.

Several recrystallizations from carbon tetrachloride gave a pure product free of benzene; yield 18%.

Diethyl N-{4-[1-(5-Chloro-2-benzimidazolyl)-isopropyl-amino]-benzoyl}-glutamate (XXXI).—The method used for preparing XXVII was employed here also. The product was obtained from the filtrate, after removing the triethylamine hydrochloride, in the same manner that XXIX was isolated. In this case the pure, unsolvated product was obtained by recrystallization from benzene.

Diethyl N-{4-[1-(5-Nitro-2-benzimidazolyl)-methyl-amino]-benzoyl}-glutamate (XXXII).—This compound was prepared by the method used for compound XXVII except that the product was isolated from the filtrate from the triethylamine hydrochloride by evaporation under reduced pressure. The oily product so obtained was extracted with hot benzene. On cooling to room temperature some diethyl *p*-aminobenzoylglutamate separated and was removed. The analog XXXII was obtained by evaporation of the benzene filtrate under reduced pressure. It was recrystallized from 50% alcohol–water.

Diethyl N-{4-[1-(5-Nitro-2-benzimidazolyl)-ethylamino]-benzoyl}-glutamate (XXXIII).—It was prepared by the method used for XXXI from 2-(1-chloroethyl)-5-nitrobenzimidazole hydrochloride and diethyl *p*-aminobenzoylglutamate with the following modifications: (a) the triethylamine in an equal volume of dioxane was added over a period of one hour to the reaction mixture at 60°; and (b) the resulting mixture was held at 60° for 8 hours with continual stirring.

Diethyl N-{4-[1-(5-Nitro-2-benzimidazolyl)-isopropyl-amino]-benzoyl}-glutamate (XXXIV) and diethyl N-{4-[1-(5-methyl-2-benzimidazoyl)-ethylamino]-benzoyl}-glutamate (XXXV) were prepared by the method used for XXX. In these cases, however, the products were recrystallized from alcohol–water.

Diethyl N-{4-[1-(5-Methyl-2-benzimidazolyl)-isopropyl-amino]-benzoyl}-glutamate (XXXVI).—The procedure used for the preparation of XXX was used here also. In this case the final purification was accomplished by recrystallization from carbon tetrachloride.

Preparation of Benzimidazolyl Analogs of the Ethyl Ester of Pteroic Acid. Ethyl 4-[1-(2-Benzimidazolyl)-ethylamino]-benzoate.—2-(1-Chloroethyl)-benzimidazole hydrochloride (39.4 g., 0.18 mole), 29.7 g. (0.18 mole) of ethyl *p*-aminobenzoate and 125 ml. of dry dioxane were placed in a flask and 36.36 g. (0.36 mole) of triethylamine added. The solution was refluxed for 8 hours, cooled and the precipitate removed. After thorough extraction with water, the residue was recrystallized from alcohol–water; yield 34%, m.p. 213–215°.

Anal. Calcd. for $C_{18}H_{19}O_2N_3$: C, 69.88; H, 6.20; N, 13.59. Found: C, 70.08; H, 6.34; N, 13.72.

Ethyl 4-[1-(5-Chloro-2-benzimidazolyl)-ethylamino]-benzoate.—This compound was prepared from 2-(1-chloroethyl)-5-chlorobenzimidazole by the above procedure. The product was purified by recrystallization from benzene; yield 14%, m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{18}O_2N_3Cl$: C, 62.87; H, 5.29; N, 12.22; Cl, 10.31. Found: C, 62.61; H, 5.37; N, 12.08; Cl, 10.27.