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The Synthesis of Some 1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-substituted Benzimidazoles (1)

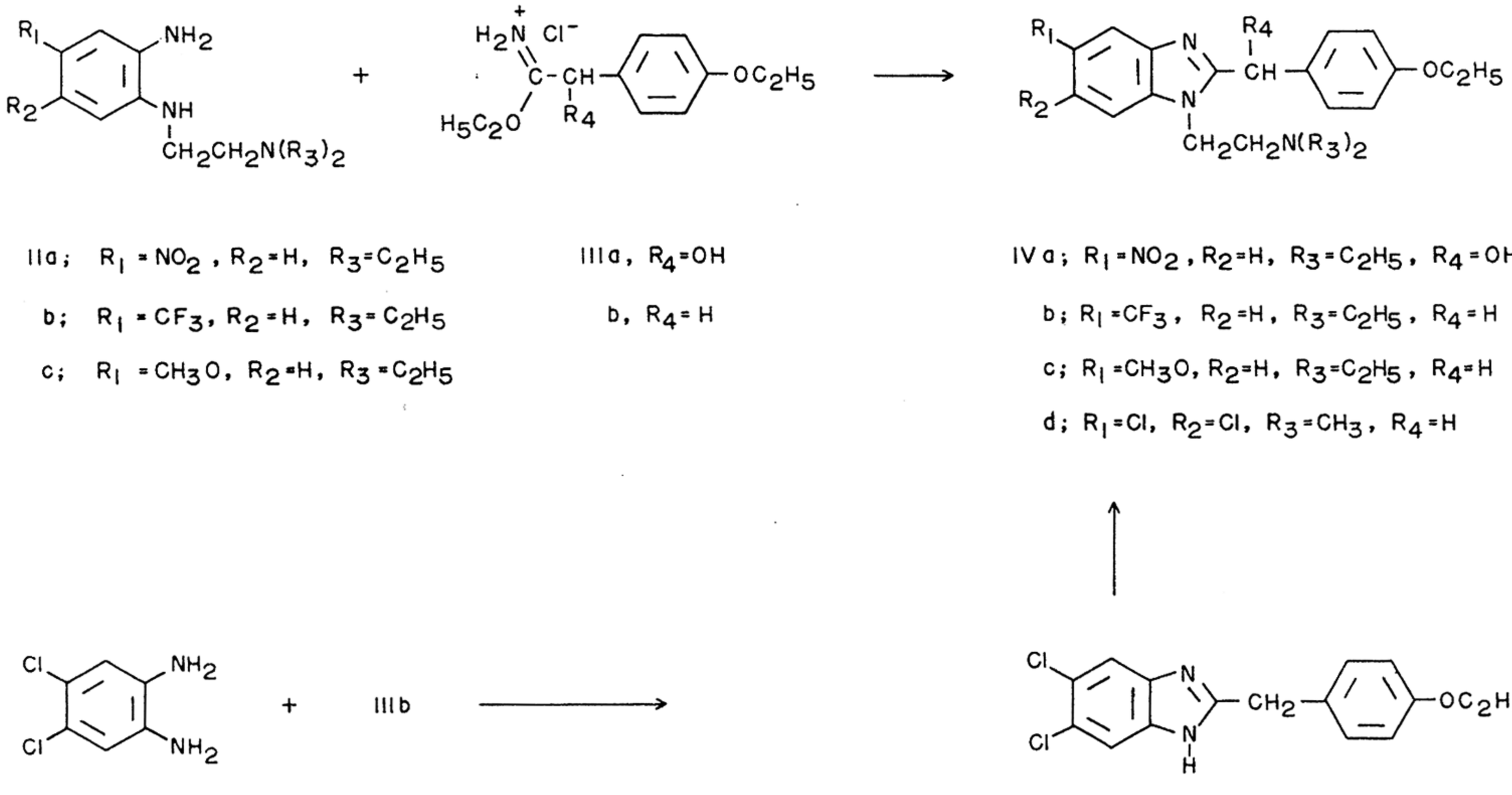
F. I. Carroll, R. W. Handy, J. A. Kepler, and Joan A. Gratz

The syntheses of several 5-substituted benzimidazoles structurally related to the highly active analgesic 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-nitrobenzimidazole are presented.

Hunger and his co-workers (2) have prepared some benzimidazole derivatives which show potent analgesic activity. 1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-nitrobenzimidazole (I) is 40-100 times more potent than morphine (3). This paper describes the synthesis and properties of several new benzimidazoles that are structurally related to I. These compounds were prepared by modification of the synthetic methods described by Hunger (2) and are outlined in Figures I and II. The condensation of 2-(β-diethylaminoethylamino)-5-nitroaniline monohydrochloride (IIa) with the acetimidate IIIa, prepared from *p*-ethoxybenzaldehyde cyanohydrin, gave a 56% yield of 1-(2-diethylaminoethyl)-2-(α-hydroxy-*p*-ethoxybenzyl)-5-nitrobenzimidazole (IVa). This compound contains all the functions present in the very active analgesic I and in addition has a hydroxyl group on the benzylic methylene at the 2-position of the benzimidazole ring.

1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-trifluoromethylbenzimidazole (IVb) and 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-methoxybenzimidazole (IVc) were prepared by the condensation of *p*-ethoxyphenylacetimidate hydrochloride (IIIb) with 2-(β-diethylaminoethylamino)-5-trifluoromethylaniline (IIb) and 2-(β-diethylaminoethylamino)-5-methoxyaniline (IIc) respectively. The starting aniline derivative (IIb) was obtained by nucleophilic displacement of chloride from 4-chloro-3-nitrobenzotrifluoride with *N,N*-diethylethylenediamine followed by catalytic reduction of the intermediate nitro compound, whereas, the methoxyaniline derivative (IIc) was prepared by the reduction of the product obtained from the alkylation of 4-methoxy-2-nitro-

Figure I



aniline with 2-diethylaminoethyl chloride in the presence of copper powder.

The reaction of 4,5-dichloro-*o*-phenylenediamine with ethyl *p*-ethoxyphenylacetimidate hydrochloride (IIIb) gave the symmetrical 2-*p*-ethoxybenzyl-4,5-dichlorobenzimidazole (V) which could be alkylated with β-dimethylaminoethyl chloride to give 1-(β-dimethylaminoethyl)-2-(*p*-ethoxybenzyl)-5,6-dichlorobenzimidazole (IV) in 62% yield.

In order to prepare 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carboxybenzimidazole (IVg) from 3-nitro-4-chlorobenzoic acid, it was necessary to protect the carboxylic acid group as its benzyl ester. The reaction of VIa with *N*,*N*-diethylethylenediamine gave 80% of 2-nitro-4-carbobenzoxy-*N*-(β-diethylaminoethyl)aniline (VIIa). Selective catalytic hydrogenation of the nitro group using Raney nickel as catalyst afforded 2-amino-4-carbobenzoxy-*N*-(β-diethylaminoethyl)aniline (VIIIa) which was converted directly to the amide (IXa) by treatment with *p*-ethoxyphenylacetic acid in the presence of *N*,*N*'-dicyclohexylcarbodiimide. The reaction of IXa with phosphorus pentachloride gave 32% of 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carbobenzoxybenzimidazole (IVe). Reductive debenzylation of IVe using a 10% palladium on carbon catalyst was extremely slow. After 24 hours, the reduction was still incomplete and only a small amount of impure IVg could be isolated from the reaction mixture. However, when a palladium hydroxide on carbon catalyst (4) was used in place of the 10% palladium on carbon catalyst, a quantitative uptake of hydrogen was obtained in 30 minutes and a 69% yield of the desired 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carboxybenzimidazole (IVg) was obtained.

Treatment of IVg with diazomethane afforded the

Figure 11

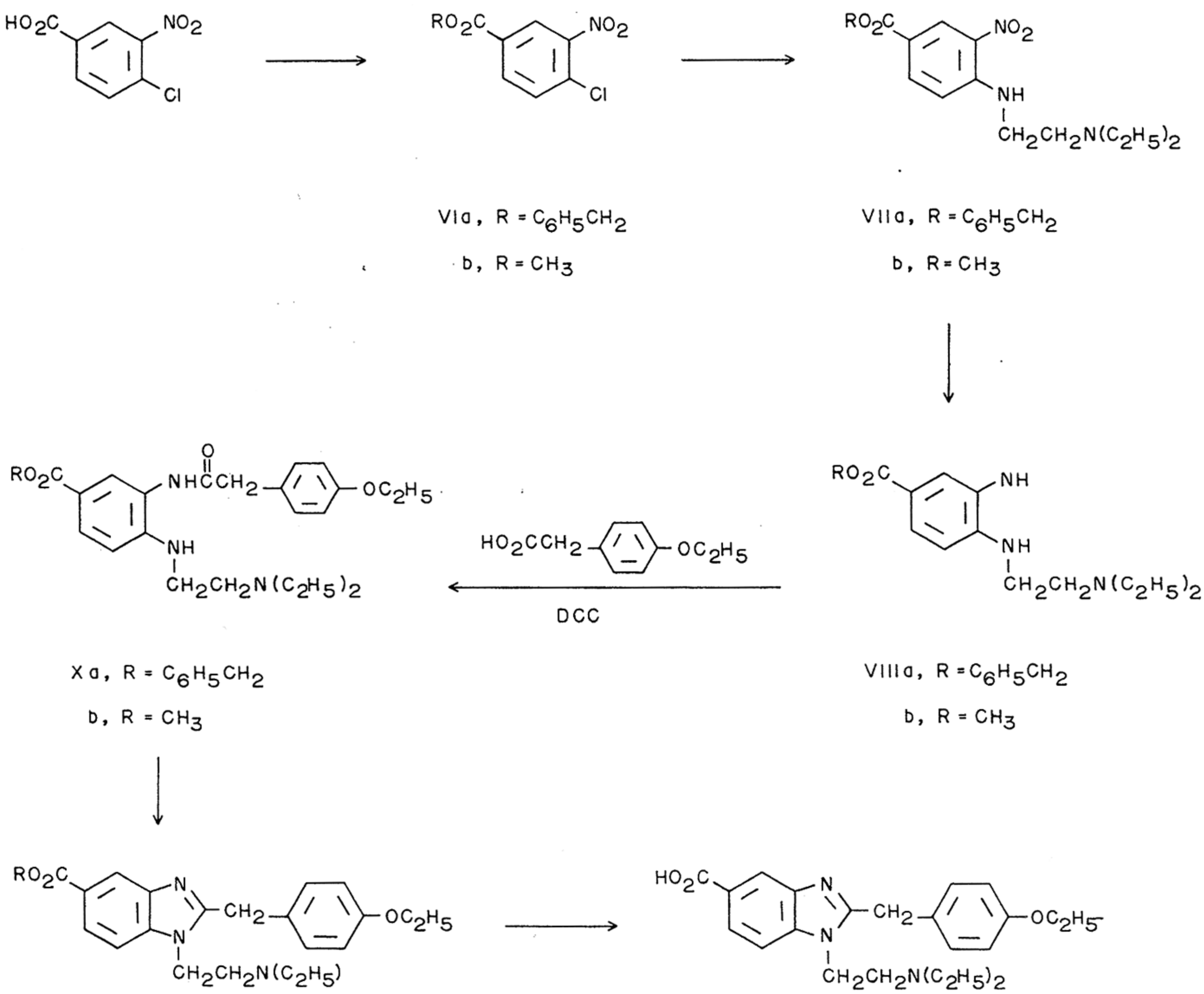


TABLE I

Nuclear Magnetic Resonance and Infrared Spectra of the Benzimidazoles (IV)

Compound	Chemical Shift, δ (a, b)				Coupling Constants J, cps	Infrared Bands, ν max (KBr) cm^{-1}	
	4-H	6-H	7-H	Other		C=C and C=N	Other
IVa	8.61d	8.18q	7.41d	6.22s (ArCHO)	$J_{6,7}$ = 8.5, $J_{4,6}$ = 2.5	1615 1510	1520 and 1330 (NO_2)
IVb	8.06s	7.19d	6.84d		$J_{6,7}$ = 9	1625 1520	
IVc	7.33	(c)	(c)	3.90 (OCH_3)		1615 1510	1705 (C=O)
IVd	7.90s		7.90s (d)			1610	
IVe	8.60d	8.05q	7.38d	7.4s ($C_6H_5CH_2$)	$J_{6,7}$ = 7, $J_{4,6}$ = 2	1620 1510	1700 (COOH)
IVf	8.50d	7.95q	7.25d	3.89 (OCH_3)	$J_{6,7}$ = 8.5, $J_{4,6}$ = 2	1622 1515	
IVg	8.75s	8.20d	7.48d	13.2 (-COOH)	$J_{6,7}$ = 8	1615 1510	1520 and 1330 (NO_2)
I (e)	8.96d	8.20q	7.40d		$J_{6,7}$ = 8.5, $J_{4,6}$ = 2.5	1615 1510	

(a) The spectra were determined in deuteriochloroform (internal standard tetramethylsilane). (b) s = single, d = doublet, q = quartet. (c) The resonances for the 6-H and 7-H were overlaped by the aromatic protons of the *p*-ethoxybenzyl group. (d) The resonances for the 4-H and 7-H appeared together as a singlet at 7.90 p.p.m. (e) Prepared by the procedure reported by Hunger, *et al.* (ref. 2).

methyl ester IVf. This ester could also be obtained from methyl 3-nitro-4-chlorobenzoate (VIb) via a scheme similar to the procedure used to prepare the benzyl ester IVe. Attempts to prepare the acid IVg by hydrolysis of IVf with aqueous sodium hydroxide in tetrahydrofuran or dioxane was unsatisfactory. The ester was somewhat resistant to hydrolysis and could be hydrolyzed only after heating at reflux for several hours. The infrared spectrum of the crude acid obtained by this procedure was very similar to the spectra of the acid IVg obtained by the debenzylation of IVe but all attempts to crystallize the acid obtained by the hydrolysis of the methyl ester failed.

The infrared spectra of all the benzimidazoles prepared show C=C and C=N absorption in the region between 1620 and 1510 cm^{-1}. These frequencies along with other group frequencies characteristic of the individual compounds are tabulated in Table I. The n.m.r. spectra of the benzimidazoles (IVa-IVg) were very simple allowing in most cases the assignment of every proton in the molecule. The aromatic ring protons showed *meta* coupling of 0 - 2.5 cps and *ortho* coupling of 7-9 cps depending on the substituent at the 5-position of the benzimidazole ring. The δ values of these aromatic protons as well as other pertinent resonances are listed in Table I.

EXPERIMENTAL

The melting points were obtained on a Kofler hot-stage and are corrected. The boiling points are uncorrected. The infrared spectra were obtained using a Perkin-Elmer Model 221 spectrophotometer. The n.m.r. spectra were obtained using a Varian A-60 spectrometer with samples dissolved in deuteriochloroform (internal standard tetramethylsilane). Microanalyses were by Micro-Tech Laboratories, Skokie, Illinois.

Preparation of *p*-Ethoxybenzaldehyde Cyanohydrin.

Ethyl iodide (200.0 g., 1.33 moles), *p*-hydroxybenzaldehyde (324 g., 2.65 moles) and potassium carbonate (366 g., 1.33 moles) were combined with 1700 ml. of acetone previously dried over anhydrous potassium carbonate. The reaction mixture was refluxed under nitrogen for 5 hours with stirring, then permitted to stand at room temperature for 24 hours. The mixture was diluted with water and extracted with chloroform. The chloroform extracts were washed with 10% sodium hydroxide solution and water, dried over anhydrous sodium sulfate and concentrated to give 166 g. of *p*-ethoxybenzaldehyde as a yellow liquid; ν max ($CHCl_3$), 2720 and 2820 (HCO) and 1700 cm^{-1} (C=O). The crude *p*-ethoxybenzaldehyde was used without further purification to prepare the cyanohydrin.

The *p*-ethoxybenzaldehyde was treated with a saturated solution of sodium hydrogen sulfite (192.3 g., 1.60 moles). The mixture was stirred vigorously until it was a solid mass. Then 160 g. (3.27 moles) of a saturated aqueous solution of sodium cyanide and 20 g. of sodium hydrogen sulfite were added. Ether was added to the mixture and the contents were stirred at room temperature for 18 hours. After this period of time, nearly all of the solids had reacted. The ether layer was separated and the remaining aqueous layer extracted with ether. The combined organic layers were washed with a saturated sodium hydrogen sulfite solution and water, dried over anhydrous sodium sulfate and concentrated to give a yellow oil. Crystallization from a benzene and petroleum ether mixture yielded 119.7 g. (70%) of the cyanohydrin, m.p. 42-46°. The n.m.r. spectrum ($CDCl_3$) showed a triplet at δ 1.38, J = 7.0 cps (methyl of CH_3CH_2O-), a quartet at 4.03, J = 7.0 cps (methylene of CH_3CH_2O-), a singlet at 3.87 (-O-H), a singlet at 5.4 ($ArCH\langle^{CN}_{O}$) and a typical A_2B_2 pattern for the aromatic protons centered at 7.14 ppm. This product was

used without further purification for the preparation of 1-(β-diethylaminoethyl)-2-(α-hydroxy-p-ethoxybenzyl)-5-nitrobenzimidazole.

The analytical sample was prepared by recrystallizing a portion of the solid from petroleum ether (b.p. 30-60°), m.p. 45-47°.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.71; H, 6.07; N, 7.73.

Preparation of 1-(β-Diethylaminoethyl)-2-(α-hydroxy-p-ethoxybenzyl)-5-nitrobenzimidazole (IVa).

Dry hydrogen chloride gas was passed into a stirred solution of 53.2 g. (0.30 mole) of p-ethoxybenzaldehyde cyanohydrin and 18.4 g. (0.40 mole) of ethanol in 200 ml. of anhydrous ether cooled in an ice bath. After 3/4 hour the reaction mixture turned deep red and then solidified to a solid mass. The solid acetimidate hydrochloride was filtered and washed well with anhydrous ether. The acetimidate hydrochloride was transferred to a one liter three-necked flask and 500 ml. of ethanol and 30 g. (0.104 mole) of 2-(β-diethylaminoethylamino)-5-nitroaniline monohydrochloride (2) was added. The stirred reaction mixture was maintained at 42-47° for 48 hours under a nitrogen atmosphere. The reaction mixture was concentrated to dryness, the residue dissolved in chloroform and made alkaline with 6 *N* ammonium hydroxide solution. The chloroform layer was then extracted with 6 *N* hydrochloric acid and the extracts again made alkaline with 6 *N* ammonium hydroxide solution. The aqueous layer was extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to give 40 g. of a brown solid. The solid was washed with hot ether which removed most of the colored impurities. Recrystallization from methanol gave 23.9 g. (56%) of 1-(β-diethylaminoethyl)-2-(α-hydroxy-p-ethoxybenzyl)-5-nitrobenzimidazole, m.p. 185-186.5°. The analytical sample was prepared by recrystallization from the same solvent, m.p. 185.5-186.5°; UV spectrum (CH_3OH) showed maxima at 244 mμ (ε = 29,500) and 311 mμ (ε = 10,300).

Anal. Calcd. for $C_{22}H_{28}N_4O_4$: C, 64.05; H, 6.84; N, 13.58. Found: C, 63.88; H, 6.74; N, 13.30 and 13.43.

Preparation of 2-Nitro-4-trifluoromethyl-*N*-(β-diethylaminoethyl)aniline.

To a solution of 4-chloro-3-nitrobenzotrifluoride (42.0 g., 0.187 mole) in 700 ml. of anhydrous dimethylformamide (DMF) was added *N,N*-diethylethylenediamine (45.8 g., 0.394 mole) in 300 ml. of DMF with stirring over a 2 hour period. The reaction mixture was allowed to stir overnight. The solvent was removed by distillation under reduced pressure. The remaining viscous liquid was partitioned between water and ether. The ether layer was dried and the solvent removed on the flash evaporator. The residual oil was vacuum distilled to give 39.52 g. (69%) of the desired product b.p. 148-151°/0.02 mm., n_D^{25} 1.5348. A picrate of the material melted at 165-168°. The analytical sample was prepared by recrystallization from ethanol.

Anal. Calcd. for $C_{19}H_{21}F_3N_6O_9$: C, 42.70; H, 3.96; N, 15.73. Found: C, 42.72; H, 4.08; N, 15.55.

Preparation of 1-(β-Diethylaminoethyl)-2-(p-ethoxybenzyl)-5-trifluoromethylbenzimidazole (IVb).

A solution of 18.30 g. (0.06 mole) of 2-nitro-4-trifluoromethyl-*N*-(β-diethylaminoethyl)aniline in 250 ml. of acetic acid containing 0.5 g. of platinum oxide was hydrogenated in a Parr Hydrogenator until no more hydrogen was absorbed. Removal of the catalyst by filtration afforded a light yellow solution which rapidly darkened upon exposure to air. Removal of the solvent by freeze drying left a dark brown oil. This oil was used in the next step without further purification.

The above oil was dissolved in 200 ml. of absolute ethanol and placed in a flask containing 18.5 g. (0.076 mole) of ethyl p-ethoxyphenylacetimidate hydrochloride (5). Nitrogen was passed through the solution which was maintained at 55-60° for 14 hours and then at reflux for 3 hours. The solution was treated with charcoal, filtered and the solvent removed on the flash evaporator. The residue was dissolved in 100 ml. of water and washed with 3 x 100 ml. of ether. The water layer was made basic with dilute ammonia with cooling. The aqueous layer was extracted with 5 x 150 ml. of ether. The ether solution was treated with charcoal and dried. The red ether solution was acidified with ethanolic hydrogen chloride until precipitation was complete and then extracted with 300 ml. of water. The water layer was extracted 5 x 200 ml. of methylene chloride. The combined methylene chloride solutions were dried and the solvent removed to give a light colored foam. The foam was recrystallized from a methylene chloride and ether solution to give needles, m.p. 76-115°. The needles were dissolved in water and neutralized with sodium bicarbonate solution. The basic layer was extracted with ether. Removal of the ether afforded a gum which crystallized upon trituration with hexane. Recrystallization from hexane gave 2.65 g. (10.5%) of needles, m.p. 79-80°.

Anal. Calcd. for $C_{23}H_{28}F_3N_3O$: C, 65.85; H, 6.72; N, 10.02. Found: C, 66.35; H, 6.77; N, 10.00.

Preparation of 4-Methoxy-2-nitro-*N*-(β-diethylaminoethyl)aniline.

The reaction was carried out using a procedure similar to that reported by Stahmann and Cope (6). A mixture of 50.2 g. (0.3 mole) of 4-methoxy-2-nitroaniline, 34.5 g. (0.2 mole) of 2-diethylaminoethyl chloride hydrochloride, 62.2 g. (0.45 mole) of anhydrous potassium carbonate, 1 g. of copper powder and 175 ml. of toluene was heated under reflux and stirred for 24 hours. The reaction mixture was then cooled, 250 ml. of 10% aqueous potassium hydroxide solution was added and the mixture was extracted several times with ether. The ether extracts were combined, washed with water and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Concentration of the ether solution afforded a red solid which was chromatographed on 2800 g. of silica gel. Elution with chloroform and chloroform:ether (95:5) afforded 26.8 g. of starting 4-methoxy-2-nitroaniline. Elution with ether afforded 25.0 g. (46.8%) of 4-methoxy-2-nitro-*N*-(β-diethylaminoethyl)aniline, m.p. 42-44°. Two recrystallizations from petroleum ether gave the analytical sample, m.p. 44-44.5°.

Anal. Calcd. for $C_{13}H_{21}N_3O_3$: C, 58.41; H, 7.92; N, 15.75. Found: C, 58.56; H, 8.10; N, 15.55.

A picrate was prepared and recrystallized from ethanol, m.p. 180-184°.

Anal. Calcd. for $C_{19}H_{24}N_6O_{10}$: C, 45.97; H, 4.87; N, 16.93. Found: C, 45.92; H, 4.86; N, 16.92.

Preparation of 1-(β-Diethylaminoethyl)-2-(p-ethoxybenzyl)-5-methoxybenzimidazole (IVc).

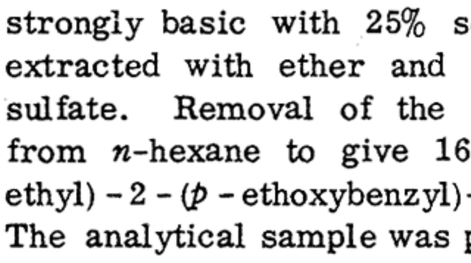
A solution of 4.62 g. (0.017 mole) of 4-methoxy-2-nitro-*N*-(β-diethylaminoethyl)aniline in 50 ml. of acetic acid containing 0.10 g. of 10% palladium on powdered charcoal was hydrogenated in a Parr Hydrogenator until hydrogen ceased to be absorbed. The catalyst was separated by filtration and the filtrate was concentrated by freeze-drying to afford a brown oil. This oil was used in the next step without further purification. The above oil was dissolved in a small amount of acetic acid and added to a solution of ethyl p-ethoxyphenylacetimidate hydrochloride (5) in 45 ml. of acetic acid. This solution was stirred for 24 hours at 47° and 20 hours at room temperature under a nitrogen atmosphere. The reaction mixture was treated with dilute ammonium hydroxide solution and extracted with ether. The combined ether layers were extracted with dilute hydrochloric acid. The acid extracts were made alkaline with concentrated ammonium hydroxide and extracted with ether. The combined ether layers were dried over anhydrous magnesium sulfate and concentrated to afford 5.17 g. of a dark oil. The oil was dissolved in chloroform and eluted through a short silica gel column to yield a light colored oil. The oil was dissolved in ether and treated with ethanolic hydrogen chloride to give a gummy solid. Recrystallization of the product from a methanol and ethyl acetate mixture afforded 4.94 g. (68.2%) of 1-(β-diethylaminoethyl)-2-(p-ethoxybenzyl)-5-methoxybenzimidazole hydrochloride. A portion of the hydrochloride was recrystallized several times, but still melted over a wide range. The remainder of the hydrochloride was dissolved in water, made alkaline with ammonium hydroxide solution and extracted with ether. The dried ether extracts were concentrated to give a crystalline solid. Recrystallization from petroleum ether (b.p. 30-60°) yielded 1.6 g. of 1-(β-diethylaminoethyl)-2-p-ethoxybenzyl-5-methoxybenzimidazole, m.p. 67-69°.

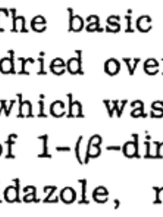
Anal. Calcd. for $C_{23}H_{31}N_3O_2$: C, 72.40; H, 8.19; N, 11.01. Found: C, 72.09; H, 8.05; N, 10.76.

Preparation of 2-(p-Ethoxybenzyl)-4,5-dichlorobenzimidazole (V).

A solution of 42.5 g. (0.24 mole) of purified 4,5-dichloro-o-phenylenediamine in 490 ml. of absolute ethanol was added in one portion to a solution of 58.3 g. (0.24 mole) of p-ethoxyphenylacetimidate (5) in 560 ml. portions of chloroform freshly distilled from phosphorus pentoxide. The resulting solution was refluxed overnight with stirring. The solution was filtered and the solvent removed on the rotary evaporator. The resulting solid was washed with 300 ml. of 3 *N* ammonium hydroxide and 300 ml. of water and dried in a vacuum desiccator. The solid was crystallized from chloroform and gave a total of 57.2 g. (75.5%) of V, m.p. 204.5-205.5°; ν max (KBr), 1610, 1450 (phenyl); 820 (2- adjacent hydrogens on the aromatic ring); 870 (isolated Ar-H); 1260 cm^{-1} (ArOR). The n.m.r. spectrum exhibited the following resonances: δ = 1.54, triplet, J = 7 cps (CH_3 of ethoxy group, 3.0 H); 4.35, quartet, J = 7 cps ($-CH_2-$ of ethoxy group); 4.12, singlet (-benzylic

$-CH_2-$) integration of the two methylene groups accounted for 3.8 H; δ = 7.29, quartet



, 4.0 H); 7.90, singlet ( , 2.1 H).

PPM

Anal. Calcd. for $C_{16}H_{14}Cl_2N_2O$: C, 59.82; H, 4.39; Cl, 22.08. Found: C, 59.81; H, 4.73; Cl, 22.54.

Very poor yields of pure product were obtained unless the 4,5-dichloro-*o*-phenylenediamine was carefully purified before use.

Preparation of 1-(β-Dimethylaminoethyl)-2-(*p*-ethoxybenzyl)-5,6-dichlorobenzimidazole (IVd).

To a solution of 21.4 g. (0.0667 mole) of V in 700 ml. of pure anhydrous dioxane was added 6.40 g. (0.133 mole) of a 50% suspension of sodium hydride in mineral oil. The solution was heated to 70° ±5° and maintained at this temperature for one hour. β-Dimethylaminoethyl chloride hydrochloride was added portionwise over a 0.5 hour period. The solution was maintained at 70° ±5° overnight. The precipitated sodium chloride was removed by filtration. The filtrate was concentrated, leaving an oil which was dissolved in ether. The ether solution was washed three times with 120 ml. of 1 *N* hydrochloric acid. The acid solution was decolorized with charcoal and made strongly basic with 25% sodium hydroxide. The basic solution was extracted with ether and the ether extracts dried over magnesium sulfate. Removal of the solvent left an oil which was crystallized from *n*-hexane to give 16.34 g. (62% yield) of 1-(β-dimethylaminoethyl)-2-(*p*-ethoxybenzyl)-5,6-dichlorobenzimidazole, m.p. 90-92°. The analytical sample was prepared by further recrystallization from hexane and had m.p. 91-93°.

Anal. Calcd. for $C_{20}H_{23}Cl_2N_3O$: C, 61.23; H, 5.91; N, 10.71. Found: C, 61.45; H, 5.98; N, 10.92.

Preparation of Benzyl 3-Nitro-4-chlorobenzoate (VIa).

A mixture of 110 g. (0.547 mole) of 3-nitro-4-chlorobenzoic acid, 86.5 g. (0.80 mole) of benzyl alcohol and 10 g. of *p*-toluenesulfonic acid in 1000 ml. of benzene was refluxed for 15 hours. The water of esterification was collected in a Dean-Stark trap. The reaction mixture was cooled, washed with a 5% aqueous potassium bicarbonate solution and dried over anhydrous magnesium sulfate. The resulting solution was evaporated *in vacuo* to yield a solid residue which on recrystallization from ether afforded 128 g. (87%) of benzyl 3-nitro-4-chlorobenzoate, m.p. 83-84.5°.

Two recrystallizations from the same solvent gave the analytical sample, m.p. 84.5-86°. The infrared spectrum (KBr) showed absorption maxima at 1690 (C=O), 1590 and 1550 (aromatic), 1520 and 1340 cm^{-1} ($-NO_2$). The n.m.r. spectrum ($CDCl_3$) contained signals at δ = 5.4 (CH_2, singlet), 7.4 (Ph, singlet), 7.55 (H_5, doublet, $J_{5,6}$ = 8.0 cps), 8.15 (H_6, quartet, $J_{6,2}$ = 2.0 cps) and 8.50 ppm (H_2, doublet).

Anal. Calcd. for $C_{14}H_{10}ClNO_4$: C, 57.64; H, 3.46. Found: C, 57.65; H, 3.53.

Preparation of 2-Nitro-4-carbobenzoxy-*N*-(β-diethylaminoethyl)aniline (VIIa).

A mixture of 19.6 g. (0.067 mole) of benzyl 3-nitro-4-chlorobenzoate, 8.13 g. (0.07 mole) of *N,N*-diethylethylenediamine and 5.65 g. (0.067 mole) of sodium bicarbonate was heated at 60° for 3 hours. The reaction mixture was cooled and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and treated with alcoholic hydrogen chloride. The insoluble yellow hydrochloride salt (27 g.) was removed by filtration, treated with aqueous ammonia and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated *in vacuo* to give a yellow oil. The product was isolated by means of column chromatography (500 g. of silica gel, eluting with chloroform). 2-Nitro-4-carbobenzoxy-*N*-(β-diethylaminoethyl)aniline (19.85 g., 80%) was recovered on evaporation of the eluent, m.p. 45-47°.

Recrystallization from an ether and hexane mixture gave the analytical sample, m.p. 46.5-47.5°. The infrared spectrum (KBr) contained absorption maxima at 3320-3360 (NH), 1690 (C=O), 1610 and 1550 (aromatic), 1515 and 1345 cm^{-1} (NO_2).

Anal. Calcd. for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.99; H, 7.05; N, 11.44.

Preparation of 4-Carbobenzoxy-2-(*p*-ethoxyphenylacetyl)amino-*N*-(β-diethylaminoethyl)aniline (IXa).

A solution of 28.1 g. (0.076 mole) of 2-nitro-4-carbobenzoxy-*N*-(β-diethylaminoethyl)aniline in 150 ml. of ethyl acetate containing Raney nickel was hydrogenated in a Parr Hydrogenator at room temperature until hydrogen ceased to be absorbed (hydrogen uptake was 80-90% of the theoretical amount). The catalyst was separated by filtration and the pale yellow solution of 2-amino-4-carbobenzoxy-*N*-(β-diethylaminoethyl)aniline was dried over anhydrous sodium sulfate and used directly in the next step.

This solution was treated with 13.8 g. (0.076 mole) of *p*-ethoxyphenylacetic acid and 15.8 g. (0.076 mole) of *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 3 days. The insolubles were removed by filtration and washed with hot ethyl acetate. The combined ethyl acetate phases were partially concentrated *in vacuo* to give on cooling, 20.5 g. (54%) of 4-carbobenzoxy-2-(*p*-ethoxyphenylacetyl)amino-*N*-(β-diethylaminoethyl)aniline, m.p. 126-128°.

Further recrystallization from the same solvent gave the analytical sample, m.p. 128-129°. The infrared spectrum (KBr) had absorption maxima at 3405 and 3250 (NH), 1700 (ester C=O), 1665 (amide C=O), 1610 and 1510 cm^{-1} (aromatic). The n.m.r. spectrum ($CDCl_3$) contained signals at δ = 0.99, (CH_3CH_2N-, triplet, J = 7 cps), 1.35 (CH_3CH_2O-, triplet, J = 7 cps), 2.5 (CH_3CH_2N-, quartet), 2.6 and 3.1 ($-NCH_2CH_2N-$, 2 broad signals), 3.62 ($-COCH_2-$, singlet), 3.99 (CH_3CH_2O-, quartet), 5.28 ($C_6H_5CH_2O-$, singlet), 6.59 (H_6, doublet, $J_{5,6}$ = 8 cps), 6.85 and 7.23 ($-CH_2C_6H_4O-$, 2 doublets, J = 8 cps), 7.36 ($C_6H_5CH_2O-$, singlet), 7.7 (H_3, doublet) and 7.86 ppm (H_5, quartet, $J_{3,5}$ = 2 cps).

Anal. Calcd. for $C_{30}H_{37}N_3O_4$: C, 71.54; H, 7.41; N, 8.34. Found: C, 71.32; H, 7.31; N, 8.65.

Preparation of 1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carbobenzoxybenzimidazole (IVe).

A mixture of 8.1 g. (0.016 mole) of 4-carbobenzoxy-2-(*p*-ethoxyphenylacetyl)amino-*N*-(β-diethylaminoethyl)aniline and 3.5 g. (0.0168 mole) of phosphorus pentachloride in 135 ml. of benzene was refluxed for 2 hours. The reaction mixture was cooled and treated with 27 ml. of a 14% aqueous ammonia solution. The benzene layer was separated, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was extracted with several portions of petroleum ether to give 2.5 g. (32%) of 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carbobenzoxybenzimidazole, m.p. 81-83°.

Anal. Calcd. for $C_{30}H_{35}N_3O_3$: C, 74.20; H, 7.27; N, 8.65. Found: C, 73.88; H, 7.17; N, 8.95.

Preparation of 1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carboxybenzimidazole (IVg).

A solution of 1.25 g. (0.0026 mole) of 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carbobenzoxybenzimidazole in 30 ml. of methanol containing 0.30 ml. of glacial acetic acid and 0.17 g. of palladium hydroxide on powdered charcoal (4) was hydrogenated at atmospheric pressure. The uptake of hydrogen was quantitative and complete in 30 minutes. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to a dry foam (1.2 g.) which on recrystallization from acetone and drying *in vacuo* at 55° afforded 0.7 g. (68.5%) of 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carboxybenzimidazole; m.p. 137-139°.

A TLC [*n*-butanol:water:glacial acetic acid - 4:1:1 (by volume)] showed a single spot, R_f 0.62.

Anal. Calcd. for $C_{23}H_{29}N_3O_3$: C, 69.85; H, 7.39; N, 10.63. Found: C, 69.60; H, 7.37; N, 10.46.

A 0.200 g. (0.506 mmole) sample of the acid was treated with an ethereal solution of diazomethane until diazomethane ceased to be taken up. At this point a small amount of a gummy solid was present. The ether solution was decanted from the solids and concentrated. The residue was taken up in benzene and placed on a 20 g. Florisil column. Elution with acetone followed by concentration and drying of the eluent afforded 0.120 g. of 1-(β-diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carbomethoxybenzimidazole (IVf) as an oil which could not be crystallized. The analytical sample was prepared by dissolving the oil in benzene, filtering and removing the solvent by freeze drying.

Anal. Calcd. for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.12; H, 7.44; N, 10.24.

Preparation of Methyl 3-Nitro-4-chlorobenzoate (VIb).

4-Chloro-3-nitrobenzoic acid (5 g., 0.025 mole) was dissolved in 50 ml. of methanol and dry hydrogen chloride was passed into the solution until saturated. The solution was then refluxed for 15 hours. Upon cooling, 5 g. (93%) of VIb precipitated, m.p. 66-67.5°. Further recrystallization from the same solvent gave the analytical sample, m.p. 82-82.5°.

Anal. Calcd. for $C_8H_6ClNO_4$: C, 44.57; H, 2.81. Found: C, 44.94; H, 2.91.

Preparation of 2-Nitro-4-carbomethoxy-*N*-(β-diethylaminoethyl)-aniline (VIIb).

A mixture of 48.4 g. (0.23 mole) of methyl 3-nitro-4-chlorobenzoate, 26 g. (0.23 mole) of *N,N*-diethylethylenediamine, 24 g. (0.23 mole) of sodium carbonate and 900 ml. of 2-propanol was stirred at 25° for 6 days. Dilution with water afforded a solid which was dissolved in ether and treated with a methanolic solution of hydrogen chloride. The hydrochloride which separated was dissolved in water and neutralized with aqueous ammonium hydroxide solution. A crystalline solid separated which was recrystallized from hexane to give 36.8 g. (55%) of VIIb, m.p. 83-85°. The analytical sample prepared by recrystallization from the same solvent had m.p. 86-86.5°.

Anal. Calcd. for $C_{14}H_{21}N_3O_4$: C, 56.93; H, 7.17. Found: C, 56.72; H, 7.04.

Preparation of 2-Amino-4-carbomethoxy-*N*-(β-diethylaminoethyl)aniline (VIIIb).

Reduction of 9.92 g. (0.034 mole) of VIIb under conditions used for the reduction of VIIa afforded 9.5 g. of an oil which crystallized to a solid mass. Recrystallization from an ether and hexane mixture gave 8.2 g. (93%) of VIIIb, m.p. 65-66°. Recrystallization from the same solvent gave the analytical sample, m.p. 65-66°.

Anal. Calcd. for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74. Found: C, 63.25; H, 8.78.

Preparation of 4-Carbomethoxy-2-(*p*-ethoxyphenylacetyl)amino-*N*-(β-diethylaminoethyl)aniline (IXb).

This compound was prepared by a procedure similar to that used for the preparation of IXa using 5.66 g. (0.022 mole) of VIIIb, 4.0 g. (0.022 mole) of *p*-ethoxyphenylacetic acid and 4.57 g. (0.022 mole) of dicyclohexylcarbodiimide. The residue obtained on concentration of the ethyl acetate was recrystallized from a mixture of ether and hexane to give 5.1 g. (54%) of IXb, m.p. 113-119°. The analytical sample prepared by recrystallization from hexane had m.p. 118.5-119.5°.

Anal. Calcd. for $C_{24}H_{33}N_3O_4$: C, 67.41; H, 7.77. Found: C, 67.69; H, 7.96.

Preparation of 1-(β-Diethylaminoethyl)-2-(*p*-ethoxybenzyl)-5-carbomethoxybenzimidazole (IVf) from IXb.

This compound was prepared by a procedure similar to that used for the preparation of IVe using 3.0 g. (0.007 mole) of IXb, 1.48 g. of phosphorus pentachloride and 75 ml. of benzene. The product obtained was chromatographed on 300 g. of Florisil using acetone as the eluent. Concentration of the eluent gave 1.07 g. (36%) of IVf as an oil. The infrared and n.m.r. spectra of this sample was identical to the spectra of IVf prepared from IVg.

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