Department of Chemistry, Michigan State University

The Synthesis of 1-(2-Dialkylaminoethyl)-5 (and 6)-methoxy-2-methyl (and *H*)-benzimidazoles (1)

Homer A. Burch and Robert M. Herbst

The syntheses of twenty 1-(2-dialkylaminoethyl)-5 (and 6)-methoxy-2-methyl (and *H*)-benzimidazoles in which the dialkylamino groups are dimethylamino, diethylamino, pyrrolidino, piperidino and morpholino, are presented. These compounds failed to show any significant biological activity.

During the past few years several aza-analogs of physiologically active indole compounds have been reported (2). Two noteworthy indole derivatives similar in structure to the naturally occurring vasoconstrictor serotonin are the toad poison and pressor agent bufotenine, and the hallucinogen psilocine. The benzimidazole derivatives described herein represent aza-analogs of these biologically active indole compounds.

By modifications of the synthetic methods described by Simonov (3) and by King, *et al.* (4), it was possible to prepare all of the 5 (and 6)-methoxybenzimidazole derivatives from 4-methoxy-2-nitroaniline (I). These reactions are summarized in Figure I. In order to prepare the 6-methoxybenzimidazoles from I it was necessary to protect the amino group of I by acylation with formic acid or acetic anhydride to give IIa and IIb, respectively. Then reduction of the nitro group by chemical or catalytic methods gave the mono-acylated diamines IIIa and IIIb, respectively. Alkylation with several *N*-β-chloroethyldialkylamines at 110° took place on the primary amino groups of IIIa and IIIb, respectively, to give the intermediates shown by general formula IV. Usually intermediates IV were not isolated. After completing the alkylation step, the solvents were removed by distillation and the residue was heated at about 135° to effect cyclization to benzimidazoles V and VI. To establish the structure of IV as a general intermediate in this series, diamine IIIb was alkylated with *N*-β-chloroethylpiperidine to give a 51% yield of 2-acetamido-5-methoxy-*N*-(2-piperidinoethyl)aniline (IV, R = CH_3, R' = piperidino) which showed the correct analysis. A sample was then heated under reflux in xylene solution to give benzimidazole VId.

The 5-methoxybenzimidazoles were prepared as follows. The amino group of I was tosylated (5) to give sulfonamide VII in 87% yield. Alkylation of the sodium salt of VII in benzene with several *N*-β-chloroethyldialkylamines gave intermediates VIII in yields of 86-98%. Removal of the tosyl group from VIII by means of cold concentrated sulfuric acid gave the monoalkylated derivatives of I (IX) in yields of 87-95%. The physical and analytical data for intermediates VIII and IX are summarized in Table I. The nitro group of compounds IX was then hydrogenated over Raney nickel in glacial acetic acid solution to give the diamines X. After removal of the catalyst, the reduction mixture was heated at 120-125° to give the 2-methylbenzimidazoles XII. Since acetic acid proved to be a much better solvent than formic acid for the reduction of compounds IX, partial isolation of diamines X was necessary prior to cyclization of X in formic acid to give the 2*H*-benzimidazoles XI.

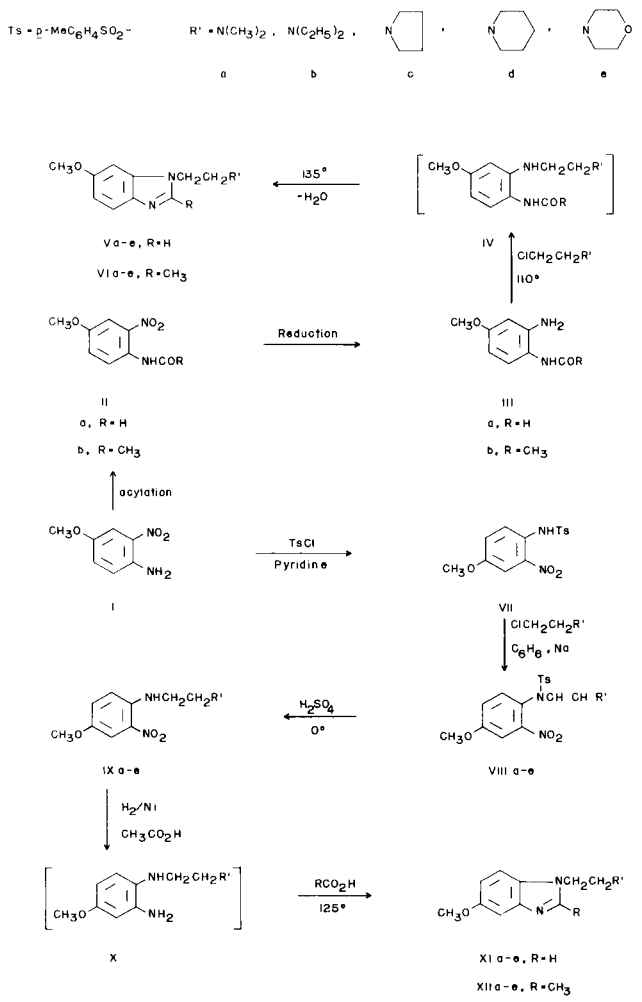
All but one (XIIa) of the benzimidazoles prepared were isolated by distillation under reduced pressure. These yellow viscous oils, which crystallized in some cases after long standing, were characterized as dipicrates or dimethiodides. All compounds were converted to dihydrochlorides for biological evaluation.

An examination of the infrared absorption spectra of the benzimidazole free bases in carbon tetrachloride solution revealed two characteristic bands of medium to strong intensity in the ranges of 1501-1529 and 1634-1652 cm^{-1}. These bands were attributed to the C=N absorption of the benzimidazole ring. Similar bands were observed in the spectra of the model compounds, 1-methyl- and 1,2-dimethylbenzimidazole, and were reported by Hunger, *et al.*, (6) to be in the spectrum of 1-(2-diethylaminoethyl)-2-benzylbenzimidazole. A single broad band was observed at 287-290 mμ in the ultraviolet absorption spectra of the benzimidazole dihydrochlorides in 0.01 *N* hydrochloric acid solution. A similar single broad band at 228 mμ was observed in the spectrum of the model compound, 5 (or 6)-methoxybenzimidazole hydrochloride (7). The physical and analytical data for all benzimidazoles are summarized in Table II.

Selected benzimidazoles from Table II were tested at Parke, Davis and Company for general antimicrobial and pharmacological activities. The compounds failed to show hypotensive activity. Tests for antibacterial activity *in vitro* against both gram-positive

and gram - negative organisms, schistosomiasis activity in mice, atherosclerosis activity in rats, antimalarial activity, anthelmintic activity in mice against several helminths, and antiviral activity using the measles plaque test were negative. No anti-inflammatory, diuretic or hypoglycemic activity was observed. All compounds were tested by the Southern Research Institute for antitumor activity against L-1210, CA-755 and S-180 and were found to be inactive.

FIGURE I



EXPERIMENTAL

All microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois. All melting points were taken in open capillaries using an oil bath and are uncorrected. The infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were obtained using a Beckman DU spectrophotometer.

4-Methoxy-2-nitroformanilide (IIa).

This compound was prepared in 80% yield by refluxing 4-methoxy-2-nitroaniline (I, Eastman) in anhydrous formic acid for 24 hours. Recrystallization from 70% aqueous ethanol (charcoal) gave IIa as golden yellow platelets melting at 149-150° [lit. (8) m.p. 150-151°].

4-Methoxy-2-nitroacetanilide (IIb).

This compound was prepared in 67% yield from I and acetic anhydride at reflux temperature for a few hours. Recrystallization from 95% ethanol (charcoal) gave IIb as yellow needles melting at 115-116° [lit. (9) m.p. 116.5-117°].

2-Amino-4-methoxyformanilide (IIIa).

To a vigorously stirred mixture of 110 g. of 40-mesh iron filings, 15 g. of sodium chloride and 300 ml. of water at 90° was added 36 g. (0.18 mole) of IIa in small portions during 0.5 hour. The mixture was stirred for an additional 2 hours at 90°, filtered hot by suction, and the residue washed with 150 ml. of boiling water. The combined filtrates were chilled and filtered to yield 18.2 g. (60%) of IIIa. Two recrystallizations of a sample from water (charcoal) gave IIIa as colorless needles melting at 139.5-140.5°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.81; H, 6.20; N, 16.61.

2-Amino-4-methoxyacetanilide (IIIb).

A similar procedure was followed to prepare IIIb in 69.5% yield, m.p. 148-149.5° [lit. (3) m.p. 150-150.5°].

The five dialkylaminoethyl chloride hydrochlorides used in this project were prepared according to procedures in the literature (10).

2-Acetamido-5-methoxy-*N*-(β-piperidinoethyl)aniline (IV).

A solution of 20.2 g. (0.11 mole) of *N*-β-chloroethylpiperidine hydrochloride in 50 ml. of 4 *N* sodium hydroxide solution was extracted with four 50-ml. portions of ether. The extracts were dried (sodium sulfate) and the ether was evaporated. To the residue was added 18.0 g. (0.10 mole) of IIIb and 5 ml. of absolute ethanol. The mixture was refluxed in an oil bath at 110-112° for 40 hours with vigorous stirring. The cooled mixture was dissolved in 60 ml. of water and extracted with ether to remove unreacted alkylating agent. The aqueous layer was added to 150 g. of 50% sodium hydroxide solution and the product was isolated by extraction with 400 ml. of benzene in several portions. The extracts were washed with water and dried (sodium sulfate). Evaporation of the solvent left 14.0 g. (51%) of crude product melting at 117-118°. Three recrystallizations of a sample from 50% aqueous ethanol (charcoal) raised the melting point to 125-125.5°.

Anal. Calcd. for $C_{16}H_{25}N_3O_2$: C, 65.95; H, 8.65; N, 14.42. Found: C, 65.78; H, 8.74; N, 14.28.

A solution of 1.4 g. of this compound in 50 ml. of xylene was refluxed for 7 days. The xylene was evaporated *in vacuo* and the residue was heated on a steam bath with 15 ml. of methyl iodide until the excess methyl iodide had evaporated. The solid residue was recrystallized from absolute ethanol (charcoal) to give colorless needles decomposing at 247-249°. This compound was shown to be identical, by melting point and mixture melting point, with the dimethiodide of benzimidazole (VId) prepared by the following general method.

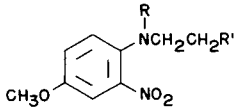
General Method for Preparing 6-Methoxybenzimidazoles (V) and (VI).

A solution of 0.24 mole of IIa or IIb in 250 ml. of warm dioxane was hydrogenated in a Parr apparatus over Raney nickel catalyst at an initial hydrogen pressure of 50-55 p.s.i. and at 25°. Meanwhile, 5.5 g. (0.24 g. atom) of metallic sodium was dissolved in 150 ml. of absolute ethanol. To this solution was added 0.24 mole of an *N*-β-chloroethyldialkylamine hydrochloride. The sodium chloride which formed was removed by suction filtration and washed with 20 ml. of ethanol. The ethanolic filtrate of the alkylating agent was added to the dioxane suspension of IIIa or IIIb. The resulting mixture was concentrated by distillation to a volume of about 250 ml. This mixture was then refluxed with stirring in an oil bath at 105-110° for 10 hours. While the temperature of the oil bath was being raised to 135-140°, all but about 50 ml. of the solvent was removed by distillation. Refluxing with stirring was then continued at 135-140° for 8 hours. The hot reaction mixture was dissolved partially in 250 ml. of warm water and then cooled. After removal of the Raney nickel catalyst by filtration, the filtrate was extracted with two 100-ml. portions of ether to remove unreacted alkylating agent. The aqueous solution was then made distinctly alkaline with 10 *N* potassium hydroxide solution and extracted with 450 ml. of benzene in several portions. The extracts were dried (sodium sulfate) and the benzene evaporated *in vacuo*. Distillation of the residue under reduced pressure gave the benzimidazoles as yellow viscous oils.

A cold solution of 0.1 mole of each benzimidazole in 700 ml. of anhydrous ether was saturated with dry hydrogen chloride. The salt was filtered rapidly by suction and was immediately dissolved in about 500 ml. of boiling absolute ethanol or absolute 2-propanol. Dilution of the alcoholic solution with anhydrous ether until turbid, followed by chilling, gave the dihydrochloride as short needles.

TABLE I

4-Methoxy-2-nitroaniline Intermediates



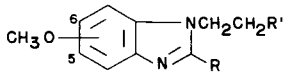
Ts p-$MeC_6H_4SO_2$-

			Free base (a)		Picrate salt									
			Yield				C, %		H, %		N, %		S, %	
Number	R	R'	%	m.p., °C	m.p., °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
VIIIa	Ts	$N(CH_3)_2$	86.5	98.5-99.5	183-184	$C_{24}H_{26}N_6O_{12}S$					13.50	13.31	5.15	5.03
b	Ts	$N(C_2H_5)_2$	95	(b)	153-155	$C_{26}N_{30}N_6O_{12}S$	(c)							
c	Ts	pyrrolidino	97.3	82-83.5	193.5-194.5	$C_{26}H_{28}N_6O_{12}S$	48.12	48.28	4.35	4.52	12.96	13.01	4.94	4.92
d	Ts	piperidino	98	89.5-91	150-152	$C_{27}H_{30}N_6O_{12}S$					12.68	12.91	4.84	4.91
e	Ts	morpholino	95	116-117	189.5-191	$C_{26}H_{28}N_6O_{13}S$	46.98	46.96	4.25	4.22	12.65	12.83	4.82	4.68
IXa	H	$N(CH_3)_2$	94.8	(b)	191.5-193	$C_{17}H_{20}N_6O_{10}$	43.59	43.75	4.30	4.40	17.95	17.84		
b	H	$N(C_2H_5)_2$	90.5	38-41	179-181	$C_{19}H_{24}N_6O_{10}$	(c)							
c	H	pyrrolidino	87	51-51.5	184-184.5	$C_{19}H_{22}N_6O_{10}$	46.17	45.94	4.49	4.63	17.00	16.71		
d	H	piperidino	87	73.5-75	193.5-194	$C_{20}H_{24}N_6O_{10}$					16.53	16.68		
e	H	morpholino	93.5	86-86.5	218.5-219.5	$C_{19}H_{22}N_6O_{11}$	44.71	44.61	4.34	4.03	16.48	16.55		

(a) All unknown free bases showed correct analyses. (b) Failed to crystallize. (c) See reference 4.

TABLE II

1-(2-Dialkylaminoethyl)-5 (and 6)-methoxy-2-methyl (and *H*)-benzimidazoles



				Free Base (a)			Dipicrate (a)	Dihydrochloride									
			CH_3O	Yield		Press.	(Dimethiodide)	Yield			C, %		H, %		Cl, %		N, %	
Number	R	R'	position	%	b.p., °C	mm. Hg	m.p., °C	%	m.p., °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Va	H	$N(CH_3)_2$	6	33.2	140-160	0.05	217-219	46.7	222-223	$C_{12}H_{19}Cl_2N_3O$	49.32	49.16	6.55	6.81	24.27	24.32	14.38	14.18
b	H	$N(C_2H_5)_2$	6	24.1	150-170	0.05	200-201.5	91.5	218.5-220	$C_{14}H_{23}Cl_2N_3O$	52.50	52.52	7.24	7.16	22.14	22.22	13.12	13.17
c	H	pyrrolidino	6	38.3	171-190	0.05	216-217	60	224-225.5	$C_{14}H_{21}Cl_2N_3O$	52.53	52.64	6.65	6.61	22.28	22.40	13.20	13.22
d	H	piperidino	6	29.6	168-184	0.03	200-201	81.5	242.5-243.5	$C_{15}H_{23}Cl_2N_3O$	54.22	54.19	6.98	6.94	21.34	21.43	12.65	12.75
e	H	morpholino	6	50.3	215-230	0.3	203.5-205	57.8	256.5-257.5	$C_{14}H_{21}Cl_2N_3O_2$	50.30	50.11	6.33	6.51	21.22	21.06	12.57	12.63
VIa	CH_3	$N(CH_3)_2$	6	35.5	170-180	0.06	(238.5-240)	57.1	226-227	$C_{13}H_{21}Cl_2N_3O$	50.98	51.00	6.91	7.17	23.16	23.04	13.72	13.64
b	CH_3	$N(C_2H_5)_2$	6	28.9	185-200	0.07	(236.5-237)	51	227-228	$C_{15}H_{25}Cl_2N_3O$	53.89	53.66	7.54	7.63	21.21	21.00	12.57	12.51
c	CH_3	pyrrolidino	6	41	190-195	0.08	(246-247)	57	240.5-241	$C_{15}H_{23}Cl_2N_3O$	54.22	54.02	6.98	7.13	21.34	21.13	12.65	12.59
d	CH_3	piperidino	6	17.5	196-216	0.4	(248.5-250)	57.5	235.5-236.5	$C_{16}H_{25}Cl_2N_3O$	55.49	53.74	7.28	7.09	20.48	20.64	12.13	11.91
e	CH_3	morpholino	6	25.2	185-210	0.07	(215-216)	65.7	236.5-237.5	$C_{15}H_{23}Cl_2N_3O_2$	51.73	51.53	6.66	6.95	20.36	20.05	12.07	12.18
XIa	H	$N(CH_3)_2$	5	47.6	140-153	0.03	204-205.5	69.4	237-238	$C_{12}H_{19}Cl_2N_3O$	49.32	49.20	6.55	6.45	24.27	24.41	14.38	14.39
b	H	$N(C_2H_5)_2$	5	63.8	160-165	0.15	215-216.5	77.5	202-203	$C_{14}H_{23}Cl_2N_3O$	(b)							
c	H	pyrrolidino	5	69.4	165-180	0.15	206-207.5	86.2	227-228.5	$C_{14}H_{21}Cl_2N_3O$	52.83	52.85	6.65	6.63	22.28	22.18	13.20	13.39
d	H	piperidino	5	55.2	170-187	0.05	212-212.5	81.5	237.5-239	$C_{15}H_{23}Cl_2N_3O$	54.22	53.98	6.98	7.16	21.34	21.24	12.65	12.38
e	H	morpholino	5	34.5	190-208	0.05	230-231.5	60	245-246	$C_{14}H_{21}Cl_2N_3O_2$	50.31	50.12	6.33	6.11	21.22	21.22	12.57	12.76
XIIa	CH_3	$N(CH_3)_2$	5	81.8	70-71.5 (c)	-	221.5-223	43	246.5-248	$C_{13}H_{21}Cl_2N_3O$	50.98	50.71	6.91	7.08	23.16	22.95	13.72	13.62
b	CH_3	$N(C_2H_5)_2$	5	69.3	161-181	0.05	227-228	83.5	233.5-235	$C_{15}H_{25}Cl_2N_3O$	53.89	53.65	7.54	7.74	21.21	21.08	12.57	12.44
c	CH_3	pyrrolidino	5	74.6	180-190	0.5	241-242	72.7	244-245	$C_{15}H_{23}Cl_2N_3O$	54.22	54.00	6.98	6.99	21.34	21.02	12.65	12.68
d	CH_3	piperidino	5	81.3	182-192	0.01	227-228	76.8	245-246.5	$C_{16}H_{25}Cl_2N_3O$	55.49	55.27	7.28	7.37	20.48	20.58	12.13	12.07
e	CH_3	morpholino	5	64.3	183-203	0.05	222.5-223	87.4	247.5-248	$C_{15}H_{23}Cl_2N_3O_2$	51.73	51.56	6.66	6.84	20.36	20.19	12.07	12.00

(a) These derivatives showed correct analysis. (b) See reference 4. (c) m.p., recrystallized from hexane.

The dipicrates of benzimidazoles (V) were prepared in hot absolute ethanol and were recrystallized from glacial acetic acid or 70% aqueous acetone.

The dimethiodides of benzimidazoles (VIb-e) were prepared as described previously.

3-Nitro-4-*p*-toluenesulfonamidoanisole (VII).

This compound, m.p. 100-103°, was prepared in 87.5% yield from I [lit. (5) m.p. 102-103°].

General Procedure for Preparing 3-Nitro-4-*p*-toluenesulfon(β-dialkylaminoethyl)amidoanisoles (VIII).

To a solution of 100 g. (0.31 mole) of VII in 2 l. of warm dry benzene was added 7.2 g. (0.31 g. atom) of freshly prepared sodium sand. The mixture was refluxed with stirring for 2 hours to complete salt formation. Meanwhile, 0.4 mole of *N*-β-chloroethyldialkylamine hydrochloride was dissolved in 300 ml. of 10% aqueous sodium hydroxide solution. The free base of the alkylating agent was extracted with benzene and the extracts dried (sodium sulfate). After adding the amine solution to the above benzene salt suspension, the mixture was refluxed with stirring for 48 hours. The chilled mixture was filtered to remove sodium chloride, and the filtrate evaporated *in vacuo* on a steam bath. To the residue was added 400 ml. of 2 *N* sodium hydroxide solution. Extraction of this solution with ether until the extracts were colorless followed by drying (sodium sulfate) of the extracts, and evaporation of the ether gave the crude product. Recrystallization from aqueous ethanol (charcoal) gave compounds VIII as yellow needles.

The dipicrates were prepared in hot absolute ethanol and recrystallized from aqueous ethanol (charcoal).

General Procedure for Preparing 4-β-Dialkylaminoethylamino-3-nitroanisoles (IX).

To 250 ml. of 90% aqueous sulfuric acid chilled to 0-5° was added in small portions, as it dissolved, 0.26 mole of the respective intermediate VIII. The mixture was allowed to stand overnight at 0-5° and then was heated on a steam bath for 30 minutes to complete the hydrolysis. The mixture was poured over 500 g. of ice and the resulting solution made basic by the cautious addition of cold concentrated aqueous ammonia. The product was obtained by extracting the solution with ether in several portions until the extracts were colorless. The extracts were dried (sodium sulfate) and the ether evaporated to give the product as a bright red oil which crystallized in some cases. The solid products were recrystallized from aqueous ethanol (charcoal).

The picrates were formed in hot absolute ethanol and were recrystallized from galcial acetic acid (charcoal).

General Procedure for Preparing 1-(β-Dialkylaminoethyl)-5-methoxy-2-methylbenzimidazoles (XII).

A solution of 0.15 mole of the respective intermediate IX in 200 ml. of glacial acetic acid was hydrogenated over Raney nickel at 25° and at an initial hydrogen pressure of 50 p.s.i. After removal of the catalyst by filtration, the green filtrate was refluxed with stirring in an oil bath at 125-130° for 17 hours. The cooled mixture was diluted with 100 ml. of water, made distinctly alkaline with 4 *N* sodium hydroxide solution, and extracted with 900 ml. of benzene in several portions. After drying the extracts (sodium hydroxide), the benzene was evaporated *in vacuo* on a steam bath. Products XIIb-e were distilled under reduced pressure. Product XIIa, a solid, was mixed intimately with charcoal and subjected to an extraction with hexane in a Soxhlet apparatus. Evaporation of the hexane gave XIIa as pale yellow needles.

General Procedure for Preparing 1-(β-Dialkylaminoethyl)-5-methoxybenzimidazoles (XI).

The respective intermediates (IX) (0.15 mole) were hydrogenated as described in the preceding preparation. The catalyst was removed by filtration. The chilled filtrate was diluted with 250 ml. of water, made alkaline with concentrated aqueous ammonia, and extracted with 400 ml. of ether in several portions. The extracts were dried briefly (Drierite), and the ether evaporated leaving a red syrupy residue (X) which was taken up in 150 ml. of 90% formic acid. The resulting solution was refluxed with stirring in an oil bath at 120-125° for 11 hours. The products (XI) were isolated as described in the previous preparation.

The dipicrates and dihydrochlorides of compounds XI and XII were prepared as described under compounds V and VI.

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