THE SYNTHESIS OF SUBSTITUTED BENZIMIDAZOLES AS POTENTIAL SEROTONIN ANTAGONISTS

Thesis for the Degree of Ph. D.
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Homer Albert Burch

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This is to certify that the

thesis entitled

THE SYNTHESIS OF SUBSTITUTED BENZIMIDAZOLES

AS POTENTIAL SEROTONIN ANTAGONISTS

presented by

Homer Albert Burch

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Robert M. Herbst
Major professor

Date March 1, 1960

THE SYNTHESIS OF SUBSTITUTED BENZIMIDAZOLES AS POTENTIAL SEROTONIN ANTAGONISTS

By

Homer Albert Burch

AN ABSTRACT

Submitted to the School for Advanced Graduate Studies of
Michigan State University of Agriculture and
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of the requirements for
the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

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Approved Robert M. Herbst

ABSTRACT

The potential value of a series of substituted benzimidazoles as potential antagonists toward serotonin (or 5-hydroxytryptamine), prompted the investigation in this laboratory of various modes for their synthesis.

The first part of this investigation was concerned with the synthesis of 1-(β-dialkylaminoethyl)-5-methoxy-2-methyl- and 1-(β-dialkylaminoethyl)-5-methoxybenzimidazoles in which the dialkylamino groups consisted of the following: dimethylamino, pyrrolidino, morpholino, diethylamino, and piperidino.

Using commercially available 4-methoxy-2-nitroaniline as the starting material and using synthetic procedures recorded in the literature (1,2), various 4-β-dialkylaminoethylamino-3-nitroanisoles were prepared as intermediates. 4-Methoxy-2-nitroaniline was converted to 3-nitro-4-p-toluenesulfonamidoanisole. Alkylation of this compound with various dialkylaminoethylchlorides followed by removal of the p-toluenesulfonyl group by hydrolysis gave the desired intermediates. Reduction of the 4-β-dialkylaminoethylamino-3-nitroanisoles gave the 3-amino-4-β-dialkylaminoethylaminoanisoles which, in turn, were converted into the desired 2-H- and 2-methylbenzimidazoles by heating with formic acid or acetic acid, respectively.

The second part of this investigation was concerned with the preparation of 1-(β-dialkylaminoethyl)-6-methoxy-2-methyl- and 1-(β-dialkylaminoethyl)-6-methoxybenzimidazoles. Acylation of 4-methoxy-2-nitroaniline followed by reduction of the nitro group gave 4-acylamido-3-aminoanisoles. Subsequent alkylation with various dialkylaminoethylchlorides followed by ring closure gave the desired benzimidazoles.

The benzimidazoles were characterized as dipicrates, dihydrochlorides, and, in some cases, dimethiodides. Infrared and ultraviolet absorption spectra were also obtained.

For evaluation of physiological and pharmacological actions, the benzimidazoles were converted into dihydrochlorides.

LITERATURE CITED

1. A. M. Simonov, J. Gen. Chem. (U.S.S.R.) 10, 1588(1940); C.A. 35, 2870(1941).

2. F. E. King, R. J. S. Beer, and S. G. Waley, J. Chem. Soc., 1946, 92.

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Sincere appreciation is expressed to Doctor Robert M. Herbst under whose direction this investigation was accomplished. His continued guidance, patience, and inspiration made this thesis possible.

* * * * * *

Appreciation is also extended to Michigan State University for their financial assistance in the form of Graduate Teaching Assistantships, and to Parke, Davis and Company for their fellowship during the academic year 1958-1959.

To my wife Janice

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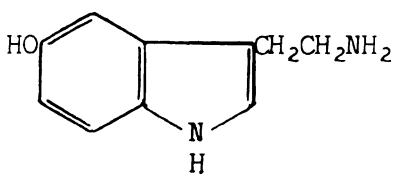
INTRODUCTION

During the past few years antimetabolites have been the subject of considerable investigation. Such compounds have two distinguishing features (1): (a) they resemble in chemical structure some naturally occurring compound which is essential in living processes, and (b) they specifically antagonize the biological action of such an essential compound. The net result of the interference by the antimetabolite with the utilization of the essential metabolite is to bring about a deficiency of the essential metabolite. Such results may be either detrimental or beneficial to the organism. An example of such an "essential metabolite" is serotonin (or 5-hydroxytryptamine).

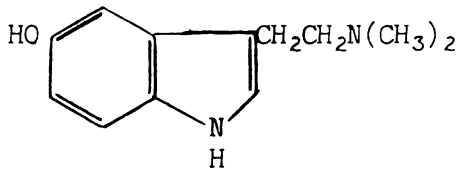


Since the isolation of serotonin from blood serum and its characterization by Page, et al., in 1947, the pharmacological effects of serotonin have been found to be most extensive, so much so that it is difficult to assess its true place in physiology (2,3,4). Of its many effects, vasoconstriction is, perhaps, the most noteworthy.

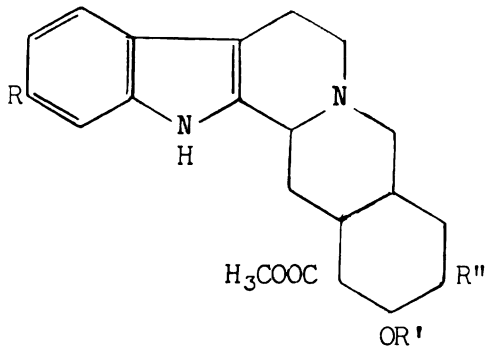
A wide variety of antagonists for serotonin have been found in the past few years. Most of them are competitive but there are also non-competitive antagonists that block one or more of the actions of serotonin. Such antagonists are of interest because they make possible the demonstration of the participation of serotonin in a variety of mechanisms.

Numerous examples of naturally occurring serotonin antagonists are described in the literature, all of which ellicit a variety of

responses, such as, behavioral changes and mental disturbances. The following compounds are examples of this class:



Bufotenin



Yohimbine: R = R' = R" = H

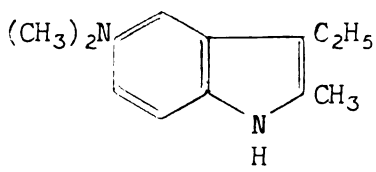
Reserpine: R = OCH_3,

R' = CH_3,

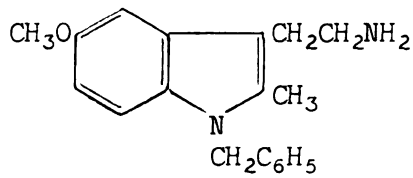
R" = $-OOC(C_6H_2)(OCH_3)_3$

The above examples bear certain structural similarities to serotonin, for example, they have the β-aminoethyl group in the 3-position of the indole ring.

A great number of synthetic serotonin antagonists have been prepared. Again the following compounds serve as examples of this class:

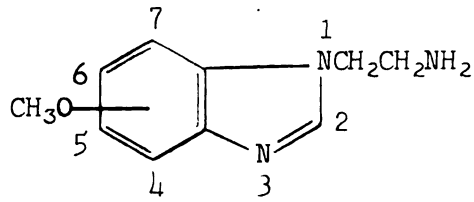


(Medmain)



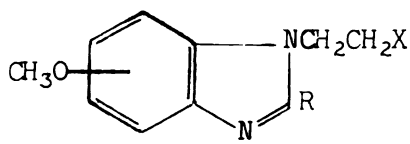
(BAS)

In 1957 Wheatley and Stiner (5) recorded the first example of a potential serotonin antagonist in the isosteric benzimidazole ring system. However, their synthesis of 1-(β-aminoethyl)-5(or 6)-methoxybenzimidazole was not unequivocal.



No mention was made of an attempt to separate the two isomers prepared in their investigation. This part of the problem was completed in 1957 when Ing, et al., (6) reported an unequivocal synthesis for 1-(β-aminoethyl)-6-methoxybenzimidazole.

These latter investigations prompted the synthesis in this laboratory of the following benzimidazole derivatives as potential serotonin antagonists:



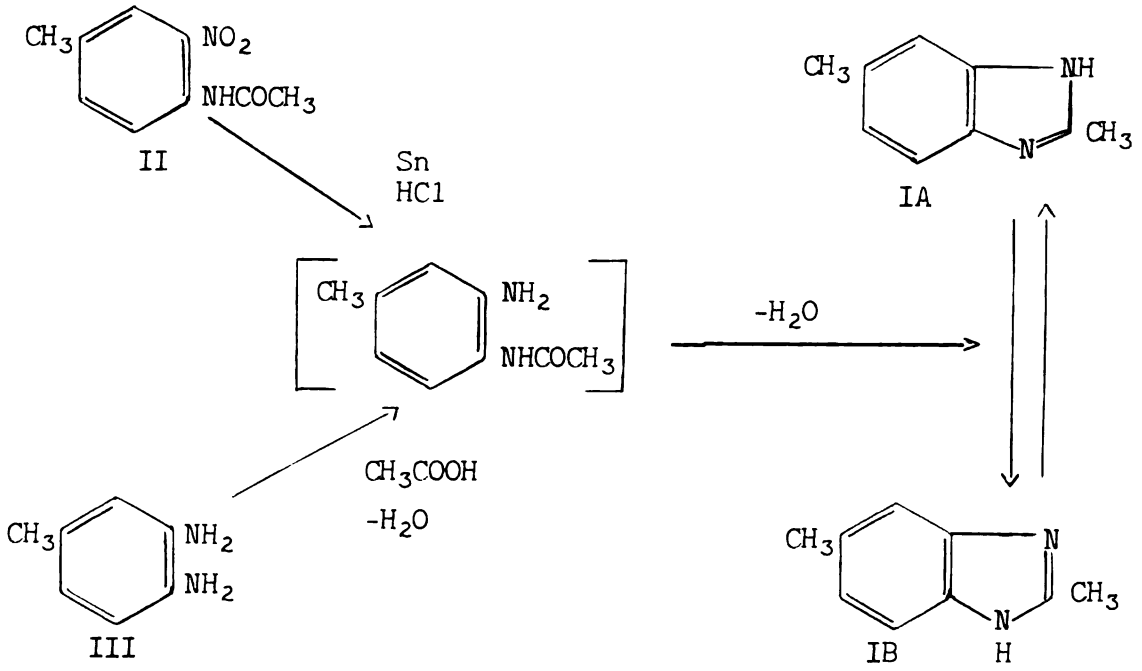
R = H, CH_3

X = $N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_4H_8)$, $N(C_4H_8)O$, $N(C_5H_{10})$

HISTORICAL

Since the synthesis of the first benzimidazole (also named benziminazole or benzoglyoxaline) in 1872 by Hoebrecker (7), the literature on this ring system has been quite extensive. Two review articles (8, 9) in 1951 and in 1953 have adequately discussed the known properties, methods of synthesis and reactions of benzimidazoles. The ensuing discussion includes only the historical developments pertaining to this investigation.

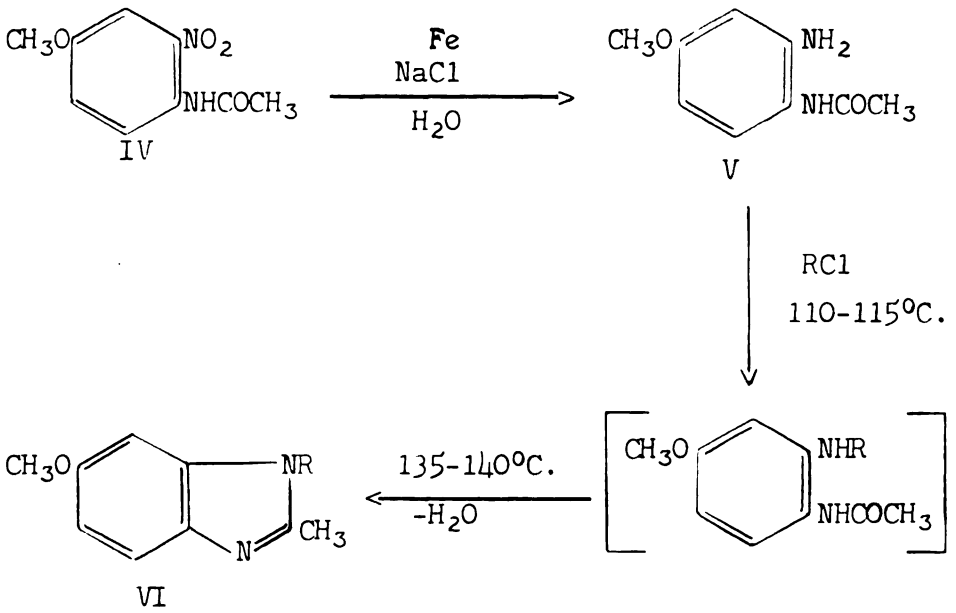
Hoebrecker obtained 2,5(or 2,6)-dimethylbenzimidazole, I, by the reduction of 4-methyl-2-nitroacetanilide, II. Further proof of the benzimidazole structure was supplied by the investigations of Ladenburg (10), in 1875, who obtained the same compound, I, by refluxing 3,4-diaminotoluene, III, with acetic acid.



As shown in the above formulas, the benzimidazole ring may be written in two tautomeric forms (IA and IB) when a hydrogen atom is attached to the nitrogen atom. Substitution of a group other than hydrogen on the nitrogen atom destroys the tautomerism and allows two isomeric structures to be written and synthesized when there is a substituent on the benzene portion of the molecule.

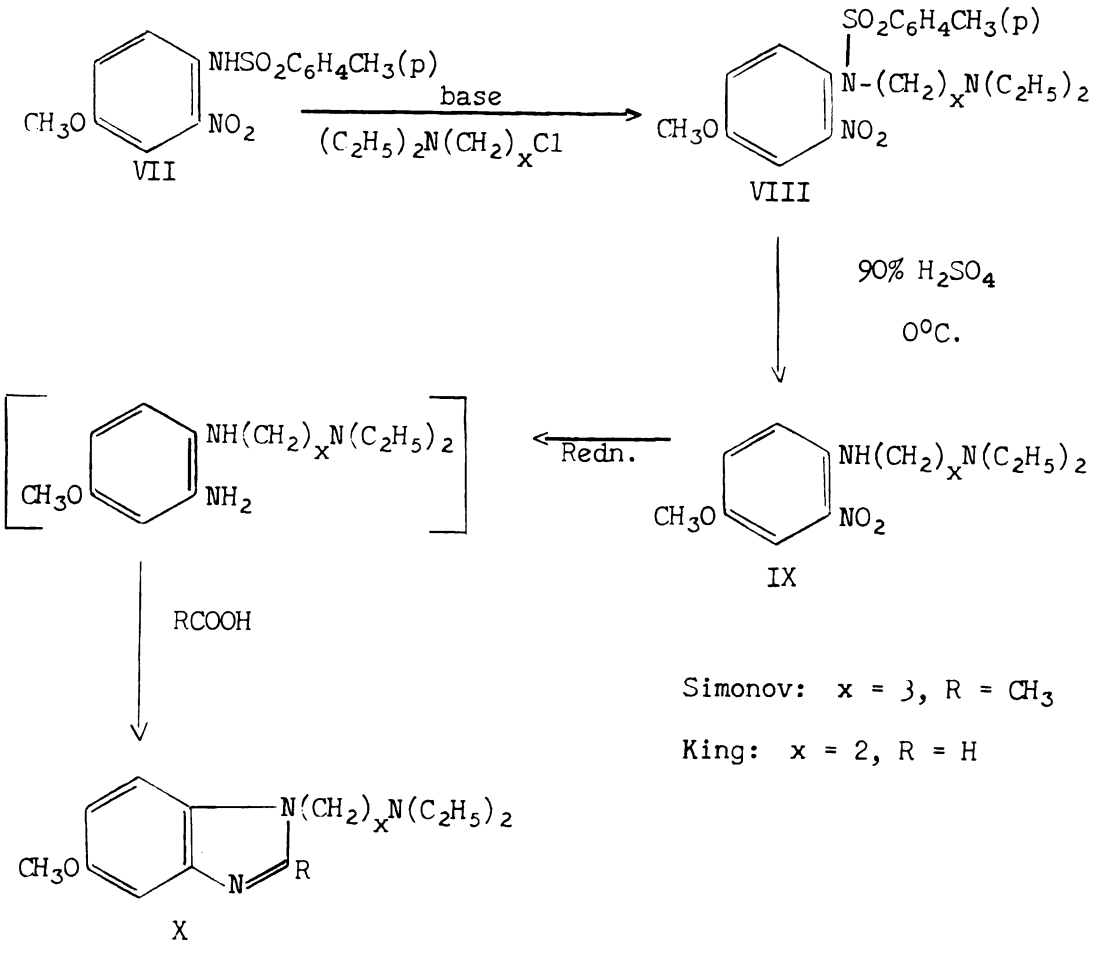
The synthetic schemes employed in this investigation for the preparation of 1,5- and 1,6-disubstituted and 1,2,5- and 1,2,6-trisubstituted benzimidazoles made use of the above methods of ring closure, and were modeled after the investigations of Simonov (11) (Schemes A and B), and of King, et al., (12) (Scheme B).

SCHEME A



R = $-CH_2CH_2CH_2N(C_2H_5^*)_2$

SCHEME B

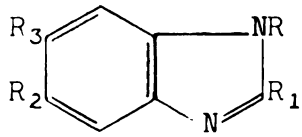


Benzimidazoles of the general structure shown in Schemes A and B have been tested for possible antimalarial properties but were found to be inactive. Benzimidazoles 1-4 in Table I were prepared by Clemo and Swan (13), in 1944, and were found to be without action on avian malaria. In 1946, McKee, et al., (14) prepared the compounds 5 and 6 in Table I and reported them also to be devoid of any antimalarial activity. Wright (15), in 1949, prepared the benzimidazoles 7-9 shown in Table I, which were reported to possess only slight antihistamine

activity. Finally, Ing, et al., (6) in 1957, investigated the benzimidazoles 10-17 shown in Table I as potential serotonin antagonists, but no results of physiological testing were reported.

TABLE I

SUBSTITUTED BENZIMIDAZOLES



No.	R_3	R_2	R_1	R
1	OCH_3	H	H	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
2	OCH_3	H	CH_3	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
3	H	OCH_3	H	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
4	H	OCH_3	CH_3	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
5	H	Cl	$C_6H_4OCH_3(p)$	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
6	H	Cl	SCH_3	$-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
7	H	H	H	$-CH_2CH_2N(CH_3)_2$
8	H	H	$CH(CH_3)_2$	$-CH_2CH_2N(CH_3)_2$
9	H	H	C_6H_5	$-CH_2CH_2N(CH_3)_2$
10	H	H	CH_3	$-CH_2CH_2N(CO)_2C_6H_4$
11	H	H	CH_3	$-CH_2CH_2NH_2$
12	H	H	C_6H_5	$-CH_2CH_2NH_2$
13	OCH_3	H	H	$-CH_2CH_2N(CO)_2C_6H_4$
14	OCH_3	H	H	$-CH_2CH_2NH_2$
15	OH	H	H	$-CH_2CH_2NH_2$
16	NH_2	H	CH_3	$-C_2H_5$
17	$NHCH_3$	H	CH_3	$-C_2H_5$

PART I. A.

1-(β-DIALKYLAMINOETHYL)-5-METHOXY-2-METHYLBENZIMIDAZOLES

Although the methods of synthesis used in this work have been reported previously in the literature, several useful modifications have been employed to circumvent the problems involved in adapting such procedures to larger scale preparations. For convenience, the problem will be discussed in two major parts, first, the preparation of 1,5-disubstituted and 1,2,5-trisubstituted benzimidazoles, and, second, 1,6-disubstituted and 1,2,6-trisubstituted benzimidazoles.

DISCUSSION

The procedures used for preparing this series of compounds are shown schematically in Scheme B on page 6.

In order to obtain only monoalkylation of the primary amino group in 4-methoxy-2-nitroaniline, the amino group was first protected by sulfonamide formation, thus making di- and trialkylation impossible. Following the alkylation of the sulfonamide, the protecting sulfonyl group was removed by hydrolysis.

Two satisfactory procedures for the preparation of 3-nitro-4-p-toluenesulfonamidoanisole have been reported in the literature. Barber, et al., (16) prepared this compound by sulfonating 4-methoxy-2-nitroaniline with p-toluenesulfonyl chloride in pyridine solution, while Simonov (11) obtained the same compound by nitrating 4-(p-toluenesulfonamido)anisole. Because of the commercial availability of 4-methoxy-2-nitroaniline the method of Barber, et al., was chosen. To prevent difficulties at later stages in the synthesis, it was necessary to

separate the monosulfonamide from the small amount of impurity, presumably the disulfonamide, produced during sulfonamide formation by taking advantage of the alkali solubility of the former compound.

Alkylation of the sulfonamide can also be achieved in a number of ways. Both Simonov (11) and King, et al., (12) used absolute ethanol as the solvent and sodium ethoxide as the base in the formation of the sodium salt of the sulfonamide. This method was satisfactory when 50 grams or less of the sulfonamide was alkylated. However, attempts to scale this reaction up to 100 grams caused a marked decrease in the yield and an increased recovery of apparently unalkylated sulfonamide. It was suspected, though not established, that salt formation was incomplete and that the sodium ethoxide was reacting instead with the dialkylaminoethylchloride in a Williamson type reaction to form the ether, 1-dialkylamino-2-ethoxyethane. Only a trace of material identifiable as an aliphatic ether by means of infrared analysis could be obtained. The small amount of ether that was isolated, however, did not account for the large decrease in the yield of alkylated sulfonamide that was observed.

Consistently good yields (85 per cent of the theoretical or better) could be obtained when the sodium salt of the sulfonamide was prepared in dry benzene using freshly prepared sodium sand. The sodium salt of the sulfonamide was obtained as a bright red solid. Interaction of the sodium salt in benzene suspension with various dialkylaminoethylchlorides was effected with ease. Alkylation of the sulfonamide was accompanied by a change in color from red to yellow.

Hydrolysis of the resulting 4-[N-(β-dialkylaminoethyl)-p-toluenesulfonamido]-3-nitroanisoles was effected easily in cold 90 per cent

sulfuric acid. The temperature of the reaction mixture during the addition of the sulfonamide to the acid was most critical; it was usually kept below 10°C. Once the sulfonamide had dissolved, the reaction could be hastened by gentle warming of the reaction mixture on a steam-bath. All of the 4-β-dialkylaminoethylamino-3-nitroanisoles prepared by this method were solids except the dimethylamino derivative. All were characterized as monopicrates.

Reduction of the nitro group leading to 3-amino-4-β-dialkylamino-ethylaminoanisoles could be brought about by either chemical or catalytic methods. For convenience, the latter method was chosen using Raney nickel as the catalyst. Platinum oxide was also an effective catalyst. The choice of solvent was important at this point. Although ethanol was the solvent used by King, et al., (12) it was found to be inadequate in this work when the reduction was scaled up from 0.007 mole to approximately 0.2 mole. Glacial acetic acid was the solvent of choice for two reasons. First, as an acid, it helped reduce the ease with which oxidation occurred during the subsequent exposure of the reaction mixture to air. Second, since the reaction of o-phenylenediamine derivatives with acetic acid produces 2-methylbenzimidazole derivatives the actual isolation of the unstable o-phenylenediamine derivatives was unnecessary. Substituted o-phenylenediamine derivatives of the type prepared here, have been isolated as red oils by distillation and have been characterized as dihydrochlorides. For example, Simonov (11) has reported that 3-amino-4-(γ-diethylamino-propylamino)anisole boils at 196-198°C./4 mm. Lott, et al., (17) have also reported in a patent that 3-amino-4-β-diethylaminoethylamino)-anisole dihydrochloride has a melting point of 160-162°C. However, because of their apparent unstability, the author did not attempt to

purify and to characterize the o-phenylenediamine derivatives as such. The characteristic behavior of the o-phenylenediamines during reduction and their subsequent conversion to benzimidazoles by interaction with carboxylic acids was considered sufficient proof of their formation.

The 2-methylbenzimidazoles prepared in this investigation were high boiling, golden-yellow, viscous oils which crystallized in some cases. The over all yields for the reduction and for the ring closure reactions ranged from 60 to 80 per cent of the theoretical.

The benzimidazoles were characterized as dipicrates and as dihydrochlorides. In addition, infrared and ultraviolet absorption spectra of the benzimidazoles were obtained. A brief discussion of these spectra appears in the appendix.

For evaluation of physiological and pharmacological actions the benzimidazoles were converted into dihydrochlorides, not, however, without some difficulties. The dihydrochlorides were found to be quite hygroscopic. They were best purified by using absolute ethanol and anhydrous diethyl ether as the solvent system. Normally, purification was effected by dissolving the dihydrochloride in the minimum amount of boiling ethanol, treating the solution with decolorizing charcoal, filtering, and then diluting the solution with anhydrous ether until turbid. When the solution was chilled, colorless needles precipitated in some cases. However, in the cases of 1-(β-morpholinoethyl)-, 1-(β-piperidinoethyl)-, and, to some extent, 1-(β-pyrrolidinoethyl)-5-methoxy-2-methylbenzimidazole dihydrochlorides, this treatment caused the material to turn pink or red. This happened frequently to all of the 2-methylbenzimidazole dihydrochlorides prepared in this investigation. Such coloring could be avoided, or at least minimized, by dissolving

the sample in ethanol at room temperature, filtering the solution, and diluting it with anhydrous ether.

EXPERIMENTAL*,**

N-β-Hydroxyethyldimethylamine

This compound was commercially available from Eastman Kodak Company.

N-β-Hydroxyethylpyrrolidine

A solution of 500 g. (7.03 moles) of pyrrolidine (Eastman Practical Grade) and 368 g. (4.58 moles) of ethylene chlorohydrin (Eastman Practical Grade) in 1.5 l. of dry benzene was allowed to stand at room temperature with slow stirring for two hours. By means of a steam-bath the temperature was gradually raised until refluxing began, after which the bath was removed. A vigorous, exothermic reaction continued for about one hour. After the initial reaction had subsided, external heating and refluxing with stirring were continued for ten hours. Upon cooling the solution two phases appeared. The lower layer which contained the product was separated, and the upper benzene layer was extracted repeatedly with 3N hydrochloric acid in small portions totaling 1 l. The combined product layer and acid extracts were made distinctly alkaline by the addition of 500 ml. of 10N sodium hydroxide solution causing two phases to appear again. The upper layer containing the product was separated, and the lower aqueous layer was extracted with diethyl ether in several portions totaling 1.5 l. After drying the

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*All analyses were done by Micro-Tech Laboratories, Skokie, Ill.

**All melting points were taken in open capillaries and are uncorrected.

extracts over anhydrous sodium sulfate, the ether was removed by distillation over a temperature range of 35-50°C. at atmospheric pressure. The next fraction, consisting of recovered pyrrolidine, distilled over the range 50-90°C. at atmospheric pressure. The product was obtained as a colorless oil boiling at 77-83°C./15 mm. in a yield of 301.3 g. (74.4% of the theoretical based on pyrrolidine). A boiling point of 78-81°C./15 mm. has been reported for this compound (18).

N-β-Hydroxyethylmorpholine

A solution of 308 g. (3.53 moles) of morpholine (Eastman Practical Grade) and 190 g. (2.30 moles) of ethylene chlorohydrin (Eastman Practical Grade) in 900 ml. of dry benzene was allowed to stand at room temperature for one hour with slow stirring. The resulting solution was then refluxed gently for eight hours with stirring on a steam-bath. After chilling the solution morpholine hydrochloride was filtered with suction and washed with 250 ml. of anhydrous diethyl ether in several portions. The combined filtrate and washings were then extracted with cold 3N hydrochloric acid in several portions totaling 1 l. The acid extracts were made distinctly alkaline by the addition of 1 l. of 10N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with diethyl ether in several portions until the aqueous solution was colorless. The extracts were dried over Drierite, and the ether was removed in vacuo on a warm water-bath. Distillation of the residue in a vacuum gave the product as a colorless oil boiling over the range 106-115°C./14 mm. in a yield of 124.8 g. (53.8% of the theoretical based on morpholine). A boiling point of 118-120°C/24 mm. has been reported for this compound (19).

N-β-Hydroxyethyldiethylamine

This compound was commercially available from Eastman Kodak Company.

N-β-Hydroxyethylpiperidine

This compound was prepared by the method used to prepare N-β-hydroxyethylmorpholine. The product was obtained as a clear, pale yellow oil boiling at 92-104°C./23 mm. in a yield of 87.2% of the theoretical based on piperidine. A boiling point of 196-199°C. at atmospheric pressure has been reported for this compound (20).

N-β-Chloroethyldimethylamine hydrochloride

This compound, prepared according to the procedure of Tilford, et al., (18) was obtained as long, colorless needles melting at 202-203.5°C. with decomposition in a yield of 80 per cent of the theoretical. Melting points of 194-196°C. (18) and of 201°C. (21) have been reported for this compound.

N-β-Chloroethylpyrrolidine hydrochloride

This compound, prepared according to the procedure of Tilford, et al., (18) was obtained as long, colorless needles melting at 171-172°C. with decomposition in a yield of 83.6 per cent of the theoretical. A melting point of 171-172°C. has been reported for this compound (18).

N-β-Chloroethylmorpholine hydrochloride

This compound, prepared according to the procedure of Tilford, et al., (18) was obtained as long, colorless needles melting at 180.5-182°C. with decomposition in a yield of 91.3 per cent of the theoretical. A melting point of 182-184°C. has been reported for this compound (18).

N-β-Chloroethyldiethylamine hydrochloride

This compound, prepared according to the procedure of Gough and King (22), was obtained as long, colorless needles melting at 209-210°C. with decomposition in a yield of 81 per cent of the theoretical. A melting point of 210-211°C. has been reported for this compound (22).

N-β-Chloroethylpiperidine hydrochloride

This compound, prepared according to the procedure of Tilford, et al., (18), was obtained as colorless needles melting at 228.5-229.5°C. with decomposition in a yield of 85.3 per cent of the theoretical. Melting points of 231-232°C. (18) and 229-231°C. (20) have been reported for this compound.

3-Nitro-4-p-toluenesulfonamidoanisole

The procedure of Barber, et al., (16) was followed on a smaller scale.

A mixture of 100 g. (0.60 mole) of 4-methoxy-2-nitroaniline (Eastman Practical Grade), 125 g. (0.72 mole) of p-toluenesulfonyl chloride, and 350 ml. of redistilled pyridine was gently heated on a steam-bath with stirring for 24 hours. The crude product was isolated by pouring the reaction mixture into 2.4 l. of ice-water and stirring vigorously with scratching until the gummy material crystallized. After filtering the mixture with suction and washing the filter cake with water to remove the pyridine, the product was purified by adding it to 300 ml. of warm 2N sodium hydroxide solution forming a red slurry. This was diluted with 2.7 l. of water and filtered with suction to remove any disulfonamide formed. Acidification of the filtrate with 6N hydrochloric acid precipitated the product. The product was obtained as yellow

crystals melting at 100-103°C. in an average yield of 168 g. (87.5% of the theoretical). Barber, et al., report a melting point of 102-103°C.

3-Nitro-4-p-toluenesulfon-(β-dimethylaminoethyl)amidoanisole

One hundred grams (0.31 mole) of 3-nitro-4-p-toluenesulfonamidoanisole was dissolved in 2 l. of warm, dry benzene. After solution was complete, 7.2 g. (0.31 gram-atom) of freshly prepared sodium sand was added. This mixture was refluxed with stirring on a steam-bath for two hours. Meanwhile, 57.6 g. (0.4 mole) of N-β-chloroethyldimethylamine hydrochloride was dissolved in a solution of 30 g. of sodium hydroxide in 300 ml. of water. After extracting the N-β-chloroethyldimethylamine with benzene, drying the extracts over anhydrous sodium sulfate and filtering, the solution was added to the above salt suspension. This reaction mixture was then refluxed with stirring on a steam-bath for 48 hours. The chilled solution was filtered with suction to remove sodium chloride, and the benzene removed in vacuo on a steam-bath. The residue was treated with 400 ml. of 2N sodium hydroxide solution, and the product extracted with diethyl ether in several portions until the extracts were colorless. Drying of the extracts over anhydrous sodium sulfate followed by evaporation of the ether gave 105.6 g. (86.5 % of the theoretical) of crude product as an orange-yellow solid. The melting point of the crude product was 92-95°C. Three recrystallizations of a sample from 50 per cent aqueous ethanol (Norite) gave the product as yellow needles melting at 98.5-99.5°C.

Analysis: Calculated for $C_{18}H_{23}N_3O_5S$: C, 54.95; H, 5.89; N, 10.68; S, 8.15. Found: C, 55.06; H, 5.95; N, 10.73; S, 8.01.

3-Nitro-4-p-toluenesulfon-(β-dimethylaminoethyl)amidoanisole picrate

The picrate was formed by dissolving 0.5 g. of the sulfonamide in 50 ml. of hot absolute ethanol and adding 50 ml. of a saturated alcoholic solution of picric acid. The precipitate which formed was filtered with suction and recrystallized three times from 95 per cent aqueous ethanol (Norite) to give the picrate as a pale yellow powder melting at 183-184°C. with decomposition.

Analysis: Calculated for $C_{24}H_{26}N_6O_{12}S$: N, 13.50; S, 5.15. Found: N, 13.31; S, 5.03.

4-β-Dimethylaminoethylamino-3-nitroanisole

To 250 ml. of 90 per cent aqueous sulfuric acid chilled to 0-5°C. was added, in small portions as it dissolved, 101.3 g. (0.26 mole) of 3-nitro-4-p-toluenesulfon-(β-dimethylaminoethyl)amidoanisole. The mixture was allowed to stand overnight at 0-5°C. and then was heated on a steam-bath for 30 minutes to complete the hydrolysis. After pouring the reaction mixture over 500 g. of ice and making it basic by the careful addition of cold concentrated aqueous ammonia, the product was obtained by extracting the basic solution with diethyl ether in several portions until the extracts were colorless. The ether extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent left the product as a bright red oil which failed to crystallize on chilling. The average yield was 58.5 g. (94.8% of the theoretical).

4-β-Dimethylaminoethylamino-3-nitroanisole picrate

The picrate was prepared in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Darco) from which it

separated as long orange needles melting at 191.5-193°C. with decomposition.

Analysis: Calculated for $C_{17}H_{20}N_6O_{10}$: C, 43.59; H, 4.30; N, 17.95. Found: C, 43.75; H, 4.44; N, 17.84.

1-(β-Dimethylaminoethyl)-5-methoxy-2-methylbenzimidazole

Thirty and eight-tenths grams (0.13 mole) of 4-β-dimethylaminoethylamino-3-nitroanisole was dissolved in 200 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture subjected to hydrogenation at room temperature at an initial hydrogen pressure of 50 p.s.i. After the theoretical amount of hydrogen had been taken up, the catalyst was removed by filtration with suction. The light green filtrate was then refluxed with stirring in an oil-bath at 125°C. for 17 hours. After cooling the reaction mixture, it was diluted with 100 ml. of water and was made distinctly basic with 4N sodium hydroxide solution. The product was obtained by extracting the basic mixture with benzene in several portions totaling 900 ml. After drying the extracts over Drierite, the benzene was evaporated *in vacuo* on a steam-bath. The solid residue was mixed intimately with Norite and was subjected to an extraction with n-hexane in a Soxhlet apparatus. Evaporation of the n-hexane yielded 24.5 g. (81.8% of the theoretical) of product as pale yellow needles melting at 69-71°C. Recrystallization of a small sample from n-hexane raised the melting point to 70-71.5°C.

This compound was not analyzed as the free base but was characterized by the following derivatives.

1-(β-Dimethylaminoethyl)-5-methoxy-2-methylbenzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was

recrystallized three times from glacial acetic acid (Darco). The dipicrate separated as short, yellow needles melting at 221.5-223°C. with decomposition.

Analysis: Calculated for $C_{25}H_{25}N_9O_{15}$: C, 43.42; H, 3.64; N, 18.23. Found: C, 43.47; H, 3.59; N, 18.12.

1-(β-Dimethylaminoethyl)-5-methoxy-2-methylbenzimidazole dihydrochloride

Twenty-three and nine-tenths grams (0.1 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether, and the cold ethereal solution was saturated with dry hydrogen chloride. The precipitate which formed was purified twice by dissolving it in the minimum amount of hot absolute methanol (Norite), diluting the solution with anhydrous diethyl ether until turbid and then chilling. The dihydrochloride was obtained as a pale pink powder melting at 245.5-247°C. with decomposition in a yield of 13.5 g. (43.1% of the theoretical). An analytical sample was purified again in the same manner. The melting point rose to 246.5-248°C. with decomposition.

Analysis: Calculated for $C_{13}H_{21}Cl_2N_3O$: C, 50.98; H, 6.91; Cl, 23.16; N, 13.72. Found: C, 50.71; H, 7.08; Cl, 22.95; N, 13.62.

3-Nitro-4-p-toluenesulfon-(β-pyrrolidinoethyl)amidoanisole

One hundred grams (0.31 mole) of 3-nitro-4-p-toluenesulfonamidoanisole was dissolved, with warming, in 1.5 l. of dry benzene. After solution was complete, 7.2 g. (0.31 gram-atom) of freshly prepared sodium sand was added, and the resulting mixture was refluxed with stirring on a steam-bath for two hours to complete salt formation. Meanwhile, N-β-chloroethylpyrrolidine was prepared by dissolving 68.0 g. (0.40 mole) of N-β-chloroethylpyrrolidine hydrochloride in a solution

of 40 g. of sodium hydroxide in 400 ml. of water. The free base was obtained by extracting the alkaline solution with benzene in eight 50 ml. portions. After drying the extracts over anhydrous sodium sulfate and filtering the solution, the benzene solution was added to the above salt suspension. Refluxing and stirring were then continued for 48 hours. After chilling and filtering the mixture with suction to remove sodium chloride, the benzene solution was extracted with 4N sodium hydroxide solution in several portions totaling 1 l. After washing the benzene solution with several portions of water to remove any base and any unchanged sulfonamide salt, the yellow benzene solution was dried over anhydrous sodium sulfate. About 1 l. of benzene was then recovered by distillation; the remaining solution was evaporated to dryness on a steam-bath. The yield of crude product as a yellow solid was 125.0 g. (97.3% of the theoretical). This material was used without further purification. A small sample was recrystallized three times from 70 per cent aqueous ethanol (Norite) from which it separated as a pale yellow powder melting at 82-83.5°C.

Analysis: Calculated for $C_{20}H_{25}N_3O_5S$: C, 57.26; H, 6.01; N, 10.02; S, 7.64. Found: C, 57.16; H, 5.98; N, 9.87; S, 7.42.

3-Nitro-4-p-toluenesulfon-(β-pyrrolidinoethyl)amidoanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized three times from 95 per cent aqueous ethanol (Norite). The picrate separated as yellow needles melting at 193.5-194.5°C. with decomposition.

Analysis: Calculated for $C_{26}H_{28}N_6O_{12}S$: C, 48.14; H, 4.35; N, 12.96; S, 4.94. Found: C, 48.28; H, 4.52; N, 13.01; S, 4.92.

3-Nitro-4-β-pyrrolidinoethylaminoanisole

One hundred and eighty grams (0.43 mole) of powdered 3-nitro-4-p-toluenesulfon-(β-pyrrolidinoethyl)amidoanisole was added in small portions as it dissolved to 600 ml. of 90 per cent aqueous sulfuric acid at 0-10°C. The reaction mixture was allowed to stand in an ice-box at 0-10°C. for 48 hours with occasional swirling. The mixture was then warmed on a steam-bath for 20 minutes to complete the hydrolysis, after which it was poured over 1 kg. of ice and was made distinctly basic by the careful addition of cold concentrated aqueous ammonia. External cooling in an ice-bath was necessary. The product was obtained by extracting the basic solution with 2 l. of diethyl ether in several portions. After drying the solution over anhydrous sodium sulfate, and filtering, the ether was evaporated. The yield of crude product was 99.1 g. (87.1% of the theoretical). This material was used without further purification. A small sample was recrystallized three times from 70 per cent aqueous ethanol (Norite) from which the free base separated as long, bright red needles melting at 51-51.5°C.

Analysis: Calculated for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 59.12; H, 6.96; N, 15.76.

3-Nitro-4-β-pyrrolidinoethylaminoanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized three times from 95 per cent aqueous ethanol (Norite) from which it separated as orange needles melting at 184-184.5°C. with decomposition.

Analysis: Calculated for $C_{19}H_{22}N_6O_{10}$: C, 46.17; H, 4.49; N,17.00. Found: C, 45.94; H, 4.63; N, 16.71.

5-Methoxy-2-methyl-1-(β-pyrrolidinoethyl)benzimidazole

Thirty and six-tenths grams (0.12 mole) of 3-nitro-4-β-pyrrolidinoethylaminoanisole was dissolved in 200 ml. of glacial acetic acid, 0.2 g. of platinum oxide catalyst was added, and the mixture was subjected to hydrogenation at an initial pressure of 50 p.s.i. at room temperature. After the theoretical amount of hydrogen had been taken up, the catalyst was recovered by filtration with suction. The resulting solution was then heated under reflux with stirring in an oil-bath at 140°C. for ten hours. The reaction mixture was chilled and was made distinctly alkaline by the addition of 4N sodium hydroxide solution. The product was obtained by extracting the basic solution with benzene in portions totaling 800 ml. After drying the extracts over anhydrous magnesium sulfate, the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a golden-yellow, viscous oil boiling at 180-190°C./0.5 mm. in a yield of 22.4 g. (74.6% of the theoretical). On long standing in the cold the oil solidified partially to a pale yellow, waxy material.

This compound was characterized by the following derivatives. The free benzimidazole was not analyzed.

5-Methoxy-2-methyl-1-(β-pyrrolidinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized five times from glacial acetic acid (Norite) from which it separated as bright yellow needles melting at 241-242°C. with decomposition.

Analysis: Calculated for $C_{27}H_{27}N_9O_{15}$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.19; H, 3.85; N, 17.53.

5-Methoxy-2-methyl-1-(β-pyrrolidinoethyl)benzimidazole dihydrochloride

Twenty-two grams (0.09 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. The chilled ethereal solution was saturated with dry hydrogen chloride. The colorless precipitate which formed was filtered with suction and was purified by dissolving it in the minimum amount of absolute ethanol at room temperature. After diluting the alcoholic solution with anhydrous diethyl ether until turbid and chilling the solution, the dihydrochloride separated as short, colorless needles melting at 242-244°C. with decomposition in a yield of 20.5 g. (72.7% of the theoretical). Six additional purifications of a small sample raised the melting point to 244-245°C. with decomposition.

Analysis: Calculated for $C_{15}H_{23}Cl_2N_3O$: C, 54.22; H, 6.98; Cl, 21.34; N, 12.65. Found: C, 54.00; H, 6.99; Cl, 21.02; N, 12.68.

3-Nitro-4-p-toluenesulfon-(β-morpholinoethyl)amidoanisole

One hundred grams (0.31 mole) of 3-nitro-4-p-toluenesulfonamidoanisole was dissolved with warming in 1.5 l. of dry benzene. After solution was complete, 7.2 g. (0.31 gram-atom) of freshly prepared sodium sand was added, and the resulting mixture was refluxed with stirring on a steam-bath for two hours to complete salt formation. Meanwhile, N-β-chloroethylmorpholine was prepared by dissolving 75.8 g. (0.4 mole) of N-β-chloroethylmorpholine hydrochloride in a solution of 40 g. of sodium hydroxide in 400 ml. of water. The free base was extracted with benzene in eight 50 ml. portions. After drying the extracts briefly over anhydrous sodium sulfate and filtering the mixture, the benzene solution was added to the above salt suspension. Refluxing and stirring were then continued for 48 hours. After chilling and

filtering the reaction mixture with suction to remove sodium chloride, the benzene solution was extracted with 4N sodium hydroxide solution in several portions totaling 1 l. After washing the benzene solution with several portions of water to remove any alkali and unchanged sulfonamide salt, the yellow solution was dried over anhydrous sodium sulfate. Approximately 1 l. of benzene was then recovered by distillation and the remaining solution evaporated to dryness on a steam-bath. The yield of crude product as a tan solid was 128.3 g. (95% of the theoretical). This material was used without further purification. A small sample was recrystallized three times from 50 per cent aqueous ethanol (Norite) from which the product separated as a pale yellow powder melting at 116-117°C.

Analysis: Calculated for $C_{20}H_{25}N_3O_6S$: C, 55.16; H, 5.79; N, 9.65; S, 7.36. Found: C, 55.12; H, 5.89; N, 9.56; S, 7.68.

3-Nitro-4-p-toluenesulfon-(β-morpholinoethyl)amidoanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized three times from 70 per cent aqueous acetic acid from which it separated as yellow needles melting at 189.5-191°C. with decomposition.

Analysis: Calculated for $C_{26}H_{28}N_6O_{13}S$: C, 46.98; H, 4.25; N, 12.65; S, 4.82. Found: C, 46.96; H, 4.22; N, 12.83; S, 4.68.

4-β-Morpholinoethylamino-3-nitroanisole

Sixty-six and five-tenths grams (0.15 mole) of powdered 3-nitro-4-p-toluenesulfon-(β-morpholinoethyl)amidoanisole was added in small portions as it dissolved to 300 ml. of 90 per cent aqueous sulfuric acid at 0-10°C. The reaction mixture was allowed to stand in an ice-box at 0-10°C. for 48 hours with occasional swirling. After warming on

a steam-bath for 20 minutes to complete the hydrolysis, the reaction mixture was poured over 500 g. of ice. The aqueous mixture was made distinctly basic by the careful addition of excess cold, concentrated aqueous ammonia. External cooling in an ice-bath was necessary. The product was obtained by extracting the basic suspension with 1.5 l. of diethyl ether in several portions. After drying the extracts over anhydrous sodium sulfate and filtering the solution, the ether was evaporated. The yield of solid, crude product was 40.0 g. (93.5% of the theoretical). This material was used without further purification. A small sample was recrystallized three times from 50 per cent aqueous ethanol (Norite) giving the product as long, bright red needles melting at 86-86.5°C.

Analysis: Calculated for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.84; H, 6.82; N, 14.80.

4-β-Morpholinoethylamino-3-nitroanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized three times from water (Darco) from which it separated as short, red-orange needles melting at 218.5-219.5°C. with decomposition.

Analysis: Calculated for $C_{19}H_{22}N_6O_{11}$: C, 44.71; H, 4.34; N, 16.48. Found: C, 44.61; H, 4.03; N, 16.55.

5-Methoxy-2-methyl-1-(β-morpholinoethyl)benzimidazole

Thirty grams (0.11 mole) of 4-β-morpholinoethylamino-3-nitroanisole was dissolved in 200 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at room temperature at an initial hydrogen pressure of 60 p.s.i. After the uptake of the theoretical amount of hydrogen, the catalyst was removed by

filtration with suction. The filtrate was then heated under reflux with stirring in an oil-bath at 140°C. for eight hours. The cooled reaction mixture was diluted with 200 ml. of hot water and was made distinctly alkaline by the addition of 4N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with 800 ml. of benzene in several portions. After drying the extracts over anhydrous sodium sulfate, the benzene was removed in vacuo on a steam-bath, and the residue was distilled in a vacuum. The yield of product as a pale yellow, viscous oil boiling over the range 183-203°C./0.05 mm. was 18.9 g. (64.3% of the theoretical). On standing the material crystallized to a pale yellow solid melting at 111-113°C.

This compound was characterized by the following derivatives; it was not analyzed as the free base.

5-Methoxy-2-methyl-1-(β-morpholinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized four times from glacial acetic acid (Norite). The dipicrate separated as short, yellow needles melting at 222.5-223°C. with decomposition.

Analysis: Calculated for $C_{27}H_{27}N_9O_{16}$: C, 44.21; H, 3.71; N, 17.19. Found: C, 44.50; H, 3.87; N, 17.07.

5-Methoxy-2-methyl-1-(β-morpholinoethyl)benzimidazole dihydrochloride

Sixteen and nine-tenths grams (0.06 mole) of free base was dissolved in 500 ml. of anhydrous diethyl ether. After saturating the cold ethereal solution with dry hydrogen chloride, the colorless precipitate which formed was filtered with suction and purified by dissolving it in the minimum amount of hot absolute ethanol, treating the

solution with Norite and filtering. The solution was diluted with anhydrous diethyl ether until turbid and then chilled. The product separated as long, slightly pink needles melting at 247.5-248°C. with decomposition. The yield was 18.7 g. (87.4% of the theoretical).

Analysis: Calculated for $C_{15}H_{23}Cl_2N_3O_2$: C, 51.73; H, 6.66; Cl, 20.36; N, 12.07. Found: C, 51.56; H, 6.84; Cl, 20.19; N, 12.00.

3-Nitro-4-p-toluenesulfon-(β-diethylaminoethyl)amidoanisole

The procedure of King, et al., (12) for the preparation of this compound was modified as follows:

One hundred grams (0.31 mole) of 3-nitro-4-p-toluenesulfonamidoanisole was dissolved with warming in 1.5 l. of dry benzene. After solution was complete, 7.2 g. (0.31 gram-atom) of freshly prepared sodium sand was added, and the resulting mixture stirred under reflux on a steam-bath for two hours. The N-β-chloroethyldiethylamine was prepared by dissolving 77.5 g. (0.45 mole) of N-β-chloroethyldiethylamine hydrochloride in a solution of 30 g. of sodium hydroxide in 300 ml. of water. After extracting the alkaline solution with benzene in five 50 ml. portions, drying the extracts over anhydrous sodium sulfate and filtering, the N-β-chloroethyldiethylamine solution was added to the above salt suspension. Refluxing and stirring were continued for 48 hours. The chilled solution was filtered with suction to remove sodium chloride, and the benzene was removed in vacuo on a steam-bath. The residue was treated with 400 ml. of 2N sodium hydroxide solution, and the product extracted with 1 l. of diethyl ether in several portions. Drying of the extracts over anhydrous sodium sulfate followed by evaporation of the ether gave an average yield of 124 g.

(95% of the theoretical) of product as a dark yellow, viscous oil which failed to crystallize.

3-Nitro-4-p-toluenesulfon-(β-diethylaminoethyl)amidoanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized twice from 95 per cent aqueous ethanol (Norite) from which it separated as yellow needles melting at 153-155°C. with decomposition. King, et al., (12) report a melting point of 154°C. for this compound.

4-β-Diethylaminoethylamino-3-nitroanisole

Thirty grams (0.07 mole) of 3-nitro-4-p-toluenesulfon-(β-diethylaminoethyl)amidoanisole was added in small portions as it dissolved to 150 ml. of 90 per cent aqueous sulfuric acid at 0-5°C. The mixture was allowed to stand over night at 0-5°C. and then was heated on a steam-bath for 20 minutes to complete the hydrolysis. After pouring the reaction mixture over 300 g. of ice and carefully making the aqueous solution alkaline with cold concentrated aqueous ammonia, the product was obtained by extracting the alkaline solution with diethyl ether in several portions until the extracts were colorless. The extracts were dried over anhydrous sodium sulfate followed by evaporation of the ether. The average yield of product as bright red needles was 17.2 g. (90.5% of the theoretical). The melting point of the crude product was 38-41°C. King, et al., (12) report a melting point of 42°C.

4-β-Diethylaminoethylamino-3-nitroanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized once from 95 per cent aqueous ethanol (Darco) from which it separated as orange-red needles melting at 179-181°C. with decomposition.

King, et al., (12) report a melting point of 181°C. with decomposition.

1-(β-Diethylaminoethyl)-5-methoxy-2-methylbenzimidazole

Twenty-five grams (0.09 mole) of 4-β-diethylaminoethylamino-3-nitroanisole was dissolved in 240 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at room temperature at an initial hydrogen pressure of 50 p.s.i. After the theoretical amount of hydrogen had been taken up, the light green mixture was filtered with suction to remove the catalyst. The filtrate was then refluxed with stirring in an oil-bath at 135°C. for eight hours. After cooling the solution, it was made distinctly alkaline by the addition of 4N sodium hydroxide solution, and was extracted with 1 l. of benzene in several portions. After drying the extracts over Drierite, the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a golden-yellow oil boiling over the range 161-181°C./0.05 mm. in a yield of 16.9 g. (69.3% of the theoretical).

This compound was characterized by the following derivatives; it was not analyzed as the free benzimidazole.

1-(β-Diethylaminoethyl)-5-methoxy-2-methylbenzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Darco) from which it separated as yellow needles melting at 227-228°C. with decomposition.

Analysis: Calculated for $C_{27}H_{29}N_9O_{15}$: C, 45.07; H, 4.06; N, 17.52. Found: C, 45.07; H, 4.18; N, 17.38.

1-(β-Diethylaminoethyl)-5-methoxy-2-methylbenzimidazole dihydrochloride

Sixteen and one-tenth grams (0.06 mole) of the free base was dissolved in 500 ml. of cold anhydrous diethyl ether and the solution saturated with dry hydrogen chloride. The colorless precipitate which formed was filtered with suction, dissolved in the minimum amount of hot absolute ethanol, treated with Norite, and again filtered. The filtrate was diluted with anhydrous diethyl ether until turbid and was then chilled thoroughly. The product separated as colorless needles melting at 233.5-235°C. with decomposition in a yield of 17.2 g. (83.5% of the theoretical).

Analysis: Calculated for $C_{15}H_{25}Cl_2N_3O$: C, 53.89; H, 7.54; Cl, 21.21; N, 12.57. Found: C, 53.65; H, 7.74; Cl, 21.08; N, 12.44.

3-Nitro-4-p-toluenesulfon-(β-piperidinoethyl)amidoanisole

One hundred grams (0.31 mole) of 3-nitro-4-p-toluenesulfonamidoanisole was dissolved with warming in 2 l. of anhydrous benzene. After solution was complete, 7.2 g. (0.31 gram-atom) of freshly prepared sodium sand was added, and the resulting mixture stirred under reflux on a steam-bath for two hours. The N-β-chloroethylpiperidine was prepared by dissolving 74.0 g. (0.4 mole) of N-β-chloroethylpiperidine hydrochloride in a solution of 30 g. of sodium hydroxide in 300 ml. of water. After extracting the free base with five 50 ml. portions of benzene, drying the benzene solution over anhydrous sodium sulfate and filtering, the N-β-chloroethylpiperidine solution was added to the above salt suspension. Refluxing and stirring were continued for 48 hours. The chilled mixture was filtered with suction to remove sodium chloride, and the benzene was removed *in vacuo* on a steam-bath. The residue was

treated with 400 ml. of 2N sodium hydroxide solution, and the product extracted with a 3:1 solution of diethyl ether and benzene. Drying of the extracts over anhydrous sodium sulfate followed by evaporation of the solvent gave 131.6 g. (98% of the theoretical) of crude product melting at 87-91°C. After three recrystallizations of a small portion from 70 per cent aqueous ethanol (Norite), the product was obtained as pale yellow needles melting at 89.5-91°C.

Analysis: Calculated for $C_{21}H_{27}N_3O_5S$: N, 9.69; S, 7.40. Found: N, 9.71; S, 7.36.

3-Nitro-4-p-toluenesulfon-(β-piperidinoethyl)amidoanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized three times from 95 per cent aqueous ethanol from which it separated as yellow needles melting at 150-152°C. with decomposition.

Analysis: Calculated for $C_{27}H_{30}N_6O_{12}S$: N, 12.68; S, 4.84. Found: N, 12.91; S, 4.91.

3-Nitro-4-β-piperidinoethylaminoanisole

Fifty grams (0.12 mole) of 3-nitro-4-p-toluenesulfon-(β-piperidinoethyl)amidoanisole was dissolved in 250 ml. of 90 per cent aqueous sulfuric acid at 0-10°C. and allowed to stand at this temperature overnight. After warming the solution for 20 minutes on a steam-bath to complete the hydrolysis, the solution was poured over 500 g. of ice and made distinctly alkaline by the addition of cold concentrated aqueous ammonia. The product was obtained by extracting the alkaline solution with diethyl ether in several portions until the extracts were nearly colorless. After drying the extracts over anhydrous potassium carbonate, the ether was evaporated. The average yield of product as a bright orange

solid was 28.1 g. (87% of the theoretical). Two recrystallizations of a small sample from 70 per cent aqueous ethanol gave the product as long orange needles melting at 73.5-75°C.

Analysis: Calculated for $C_{14}H_{21}N_3O_3$: C, 60.19; H, 7.58; N, 15.04. Found: C, 60.23; H, 7.46; N, 15.14.

3-Nitro-4-β-piperidinoethylaminoanisole picrate

The picrate was formed in hot absolute ethanol and was recrystallized three times from 95 per cent aqueous ethanol from which the picrate separated as long, orange needles melting at 193.5-194°C. with decomposition.

Analysis: Calculated for $C_{20}H_{24}N_6O_{10}$: N, 16.53. Found: N, 16.68.

5-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole

Thirty grams (0.11 mole) of 3-nitro-4-β-piperidinoethylaminoanisole was dissolved in 200 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at room temperature. After the theoretical amount of hydrogen had been taken up, the pale green solution was filtered rapidly with suction to remove the catalyst. The filtrate was heated in an oil-bath with stirring under reflux at 140°C. for 16 hours. Upon cooling, the solution was made distinctly alkaline by the addition of 2N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with 700 ml. of benzene in several portions. After drying the extracts over anhydrous sodium sulfate, the benzene was removed *in vacuo* on a steam-bath. Distillation of the residue in a vacuum gave the product as a light yellow, viscous oil boiling at 182-192°C./0.01 mm. Upon cooling and standing, the yellow

oil crystallized as colorless needles which melted at 110-112°C. The yield was 23.9 g. (81.3% of the theoretical).

This compound was characterized by the following derivatives; it was not analyzed as the free benzimidazole.

5-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Darco) from which it separated as yellow needles melting at 227-228°C. with decomposition.

Analysis: Calculated for $C_{28}H_{29}N_9O_{15}$: C, 45.97; H, 3.99; N, 17.23. Found: C, 45.99; H, 4.03; N, 17.41.

5-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole dihydrochloride

The dihydrochloride was prepared by dissolving 23.0 g. (0.08 mole) of the free base in 500 ml. of anhydrous diethyl ether. Saturation of the cold ethereal solution with dry hydrogen chloride gave a gummy precipitate which was filtered rapidly with suction and dissolved in the minimum amount of hot absolute ethanol. After treating the solution with Darco, filtering, and diluting with anhydrous diethyl ether until turbid, the solution was chilled thoroughly. Two similar purifications gave the dihydrochloride as a light pink powder melting at 245-246.5°C. with decomposition in a yield of 22.4 g. (76.8% of the theoretical).

Analysis: Calculated for $C_{16}H_{25}Cl_2N_3O$: C, 55.49; H, 7.28; Cl, 20.48; N, 12.13. Found: C, 55.27; H, 7.37; Cl, 20.58; N, 12.07.

PART I. B.

1-(β-DIALKYLAMINOETHYL)-5-METHOXYBENZIMIDAZOLES

DISCUSSION

Several attempts to hydrogenate the 4-(β-dialkylaminoethylamino)-3-nitroanisoles at low pressure over Raney nickel catalyst using formic acid as the solvent failed. Attempts to use the procedure of Ing, et al., (6) for the reduction and the ring closure also failed. By this latter method, reduction was brought about by adding a dilute aqueous solution of formic acid and hydrochloric acid to a hot aqueous mixture of iron powder and the nitro compound. Prolonged heating of the mixture after completion of the reduction brought about ring closure. Since reduction of the nitro group occurred with ease in glacial acetic acid over Raney nickel catalyst, this method was chosen for this series of compounds. It then became necessary, however, to isolate the intermediate o-phenylenediamines by making the acidic reduction mixture alkaline and separating the product by repeated ether extractions. After removal of the ether, ring closure was brought about by refluxing the o-phenylenediamines with formic acid. The average yields for the combined reduction and ring closure reactions ranged from 40 to 60 per cent of the theoretical. King, et al., (12) have reported 1-(β-diethylaminoethyl)-5-methoxybenzimidazole to be a red oil. Careful distillation, however, gave the compound as a golden-yellow oil. The red color was possibly due to residual material in the distillation pot which bumped over thus discoloring the distillate. Distillation of the other compounds in this series also resulted in yellow oils, some of which, namely, 1-(β-morpholinoethyl)- and 1-(β-piperidinoethyl)-5-methoxybenzimidazole, crystallized.

No difficulties were encountered in this series during either the preparation or the purification of these substituted benzimidazole dihydrochlorides. The benzimidazoles were further characterized as dipicrates.

For a discussion of the infrared and of the ultraviolet absorption spectra of the benzimidazoles see the appendix.

EXPERIMENTAL

1-(β-Dimethylaminoethyl)-5-methoxybenzimidazole

Thirty-six and four-tenths grams (0.15 mole) of 4-β-dimethylamino-ethylamino-3-nitroanisole was dissolved in 190 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at room temperature at an initial hydrogen pressure of 50 p.s.i. After the theoretical amount of hydrogen had been taken up, the catalyst was removed by filtration with suction; the chilled filtrate was diluted with 250 ml. of water and was made distinctly alkaline by the addition of concentrated aqueous ammonia. The diamine was obtained by extracting the alkaline solution with 400 ml. of diethyl ether in several portions. The extracts were dried over Drierite, and the ether evaporated *in vacuo*. To the red, syrupy residue was added 150 ml. of 90 per cent formic acid. This solution was refluxed with stirring in an oil-bath at 120°C. for eleven hours. After cooling and dissolving the reaction mixture in 250 ml. of warm water, it was made distinctly alkaline by the addition of 4N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with benzene in several portions totaling 500 ml. After drying the extracts over Drierite, the benzene was evaporated *in vacuo* on a steam bath, and the residue was distilled in a vacuum. The yield of product as a pale yellow, viscous oil boiling over the range 140-153°C./0.03 mm. was 15.6 g. (47.6% of the theoretical). Some decomposition occurred during the distillation. The material crystallized partially as colorless needles on standing in the cold.

This compound was characterized by the following derivatives. The free base was not analyzed.

1-(β-Dimethylaminoethyl)-5-methoxybenzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from 50 per cent aqueous acetic acid from which it separated as short, light yellow needles melting at 204-205.5°C. with decomposition.

Analysis: Calculated for $C_{24}H_{23}N_9O_{15}$: C, 42.54; H, 3.42; N, 18.62. Found: C, 42.78; H, 3.63; N, 18.60.

1-(β-Dimethylaminoethyl)-5-methoxybenzimidazole dihydrochloride

Eighteen and eight-tenths grams (0.09 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. After saturating the cold ethereal solution with dry hydrogen chloride, the colorless precipitate was filtered with suction and purified twice by dissolving it in the minimum amount of hot absolute methanol (Norite), filtering the solution, diluting the filtrate with anhydrous diethyl ether until turbid, and thoroughly chilling. The yield of product as a colorless powder melting at 236-237°C. with decomposition was 17.4 g. (69.4% of theoretical). A third purification of a small sample raised the melting point to 237-238°C. with decomposition.

Analysis: Calculated for $C_{12}H_{19}Cl_2N_3O$: C, 49.32; H, 6.55; Cl, 24.27; N, 14.38. Found: C, 49.20; H, 6.45; Cl, 24.41; N, 14.39.

5-Methoxy-1-(β-pyrrolidinoethyl)benzimidazole

A solution of 26.5 g. (0.1 mole) of 3-nitro-4-β-pyrrolidinoethylaminoanisole in 150 ml. of glacial acetic acid containing Raney nickel

catalyst was subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at room temperature. After the uptake of the theoretical amount of hydrogen, the catalyst was removed by filtration with suction. After diluting the solution with 500 ml. of cold water, it was made distinctly alkaline by the addition of cold concentrated aqueous ammonia. The diamine was obtained by extracting the alkaline solution with 600 ml. of diethyl ether in several portions. The extracts were dried over anhydrous sodium sulfate, and the ether was removed *in vacuo*. To the residue was added 100 ml. of 90 per cent formic acid. The resulting solution was refluxed with stirring in an oil-bath at 120°C. for 12 hours. Upon cooling, the reaction mixture was diluted with 100 ml. of water and was made distinctly alkaline with 4N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with benzene in several portions totaling 400 ml. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed *in vacuo* on a steam-bath. Distillation of the residue in a vacuum gave 17.0 g. (69.4% of the theoretical) of product as a light yellow, viscous oil boiling at 165-180°C./0.15 mm.

This compound was characterized by the following derivatives. It was not analyzed as the free base.

5-Methoxy-1-(β-pyrrolidinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Darco) from which it separated as short, yellow needles melting at 206-207.5°C. with decomposition.

Analysis: Calculated for $C_{26}H_{25}N_9O_{15}$: C, 44.38; H, 3.58; N, 17.92. Found: C, 44.21; H, 3.82; N, 17.71.

5-Methoxy-1-(β-pyrrolidinoethyl)benzimidazole dihydrochloride

A cold solution of 25.3 g. (0.1 mole) of the free base in 800 ml. of anhydrous diethyl ether was saturated with dry hydrogen chloride. The colorless precipitate was purified by dissolving it in the minimum amount of hot absolute ethanol (Darco), and filtering the solution. Dilution of the filtrate with anhydrous diethyl ether followed by chilling gave the dihydrochloride as a colorless powder melting at 226-228°C. with decomposition in a yield of 28.3 g. (86.2% of the theoretical). Three additional similar purifications of a small sample gave the dihydrochloride as fine, colorless needles melting at 227-228.5°C. with decomposition.

Analysis: Calculated for $C_{14}H_{21}Cl_2N_3O$: C, 52.83; H, 6.65; Cl, 22.28; N, 13.20. Found: C, 52.85; H, 6.63; Cl, 22.18; N, 13.39.

5-Methoxy-1-(β-morpholinoethyl)benzimidazole

Twenty-five grams (0.09 mole) of 4-β-morpholinoethylamino-3-nitroanisole was dissolved in 150 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at room temperature. The reduced solution was filtered with suction to remove the catalyst, and the green filtrate was diluted with 500 ml. of cold water. After making this solution distinctly alkaline by adding cold 4N sodium hydroxide solution, the diamine was extracted with 1 l. of diethyl ether in several portions. The extracts were dried over anhydrous sodium sulfate, and the ether was removed *in vacuo*. To the residue was added 100 ml. of 90 per cent formic acid, and the resulting solution was refluxed with stirring in an oil-bath at 135°C. for eight hours. After cooling

the solution, it was made distinctly alkaline by the addition of 4N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with benzene in several portions totaling 400 ml. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a light yellow, viscous oil boiling at 190-208°C./0.05 mm. The yield of product was 8.0 g. (34.5% of the theoretical). On standing in the cold the product crystallized as a pale yellow solid melting at 73-75°C.

This compound was characterized by the following derivatives; the free base was not analyzed.

5-Methoxy-1-(β-morpholinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from 50 per cent aqueous acetic acid (Darco) from which it separated as a yellow powder melting at 230-231.5°C. with decomposition.

Analysis: Calculated for $C_{26}H_{25}N_9O_{16}$: C, 43.40; H, 3.50; N, 17.52. Found: C, 43.55; H, 3.56; N, 17.42.

5-Methoxy-1-(β-morpholinoethyl)benzimidazole dihydrochloride

The dihydrochloride was formed by dissolving 17.8 g. (0.07 mole) of the free base in 500 ml. of anhydrous diethyl ether, and saturating the cold ethereal solution with dry hydrogen chloride. The colorless product was purified by dissolving it in the minimum amount of warm absolute ethanol, diluting the solution with anhydrous diethyl ether until turbid, and finally chilling the suspension. The dihydrochloride separated as slightly pink needles melting at 244-246°C. with decomposition

in a yield of 13.7 g. (60% of the theoretical). Three additional purifications of a small sample gave the dihydrochloride as colorless needles melting at 245-246°C. with decomposition.

Analysis: Calculated for $C_{14}H_{21}Cl_2N_3O_2$: C, 50.31; H, 6.33; Cl, 21.22; N, 12.57. Found: C, 50.12; H, 6.11; Cl, 21.22; N, 12.76.

1-(β-Diethylaminoethyl)-5-methoxybenzimidazole

Thirty-three grams (0.12 mole) of 4-β-diethylaminoethylamino-3-nitroanisole was dissolved in 200 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at room temperature at an initial hydrogen pressure of 50 p.s.i. After the uptake of the theoretical amount of hydrogen, the catalyst was removed by filtration with suction, and the colorless filtrate was made alkaline by adding an excess of 4N sodium hydroxide solution. The diamine was obtained by extracting the alkaline solution with diethyl ether in several portions totaling 1 l. After drying the ether solution over anhydrous sodium sulfate, the ether was removed in vacuo. To the dark red, oily residue was added 100 ml. of 88 per cent formic acid. The resulting solution was refluxed with stirring in an oil-bath at 120°C. for 18 hours. The reaction mixture was cooled and diluted with 250 ml. of water. After making the solution distinctly alkaline by the addition of concentrated aqueous ammonia, the product was obtained by extracting the alkaline solution with 400 ml. of benzene in several portions. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a light yellow oil boiling at 160-165°C./0.15 mm. in a yield of 19.5 g. (63.8% of the theoretical).

This compound was characterized by the following derivatives; the free base was not analyzed.

1-(β-Diethylaminoethyl)-5-methoxybenzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Darco) from which it separated as yellow needles melting at 215-216.5°C. with decomposition.

Analysis: Calculated for $C_{26}H_{27}N_9O_{15}$: C, 44.26; H, 3.86; N, 17.87. Found: C, 44.47; H, 4.01; N, 17.90.

1-(β-Diethylaminoethyl)-5-methoxybenzimidazole dihydrochloride

Eighteen and five-tenths grams (0.08 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. After saturating the cold ethereal solution with dry hydrogen chloride, the colorless precipitate was filtered with suction and was purified by dissolving it in hot absolute ethanol, treating the solution with Norite and filtering. The filtrate was diluted with anhydrous diethyl ether until turbid and then thoroughly chilled. The yield of dihydrochloride as short, colorless needles melting at 200-202°C. with decomposition was 18.6 g. (77.5% of the theoretical). Three additional purifications of a small sample raised the melting point to 202-203°C. with decomposition. King et al., (12) report a melting point of 203°C. for the dihydrochloride.

5-Methoxy-1-(β-piperidinoethyl)benzimidazole

Twenty-six and two-tenths grams (0.09 mole) of 3-nitro-4-β-piperidinoethylaminoanisole was dissolved in 200 ml. of glacial acetic acid, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at room temperature at an initial hydrogen pressure of 50 p.s.i.

After the uptake of the theoretical amount of hydrogen, the catalyst was removed by filtration with suction. The chilled solution was then made distinctly alkaline by the addition of cold, dilute aqueous ammonia. The red, oily diamine was obtained by extracting the alkaline solution with diethyl ether in several portions until the extracts were colorless. The extracts were dried over anhydrous sodium sulfate, and the ether removed *in vacuo*. To the red, solid residue was added 150 ml. of 98 per cent formic acid. The resulting solution was refluxed with stirring in an oil-bath at 120°C. for ten hours. The cooled reaction mixture was diluted with 100 ml. of water, and was then made distinctly alkaline with concentrated aqueous ammonia. The product was obtained by extracting the basic solution with 600 ml. of benzene in several portions. After drying the extracts over anhydrous sodium sulfate, the benzene was removed *in vacuo* on a steam-bath. Distillation of the residue in a vacuum gave 13.4 g. (55.2% of the theoretical) of product as a pale yellow, slightly viscous oil boiling at 170-187°C./0.05 mm. On standing in the cold this material crystallized as a pale yellow solid melting at 68-70°C.

This compound was characterized by the following derivatives; the free base was not analyzed.

5-Methoxy-1-(β-piperidinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from acetone (Norite) from which it separated as a yellow powder melting at 212-212.5°C. with decomposition.

Analysis: Calculated for $C_{27}H_{27}N_9O_{15}$: C, 45.19: H, 3.79; N, 17.57. Found: C, 45.25; H, 3.90; N, 17.35.

5-Methoxy-1-(β-piperidinoethyl)benzimidazole dihydrochloride

Twelve grams (0.05 mole) of free base was dissolved in 500 ml. of anhydrous diethyl ether. Saturation of the cold ethereal solution with dry hydrogen chloride caused a colorless precipitate to separate which, after filtration with suction, was purified by dissolving it in the minimum amount of warm absolute ethanol. Dilution of the alcoholic solution with anhydrous diethyl ether until turbid followed by chilling gave 13.7 g. (81.5% of the theoretical) of dihydrochloride as a white powder melting at 237.5-239°C. with decomposition.

Analysis: Calculated for $C_{15}H_{23}Cl_2N_3O$: C, 54.22; H, 6.98; Cl, 21.34; N, 12.65. Found: C, 53.98; H, 7.16; Cl, 21.24; N, 12.38.

PART II. A.

1-(β-DIALKYLAMINOETHYL)-6-METHOXY-2-METHYLBENZIMIDAZOLES

DISCUSSION

The synthetic sequence used by Simonov (11), as shown in Scheme A on page 5, for the preparation of 1,6-disubstituted and 1,2,6-trisubstitutedbenzimidazoles was modified to some extent as described below.

The starting material for this series, 4-acetamido-3-nitroanisole, was prepared by different methods.

Acetylation of 4-methoxy-2-nitroaniline with acetic anhydride gave a product which was extremely difficult to separate from unacetylated starting material. In all attempts, this reaction failed to go to completion. Separation of the product from the starting material was best achieved by repeated recrystallizations from dilute aqueous ethanol. However, this procedure caused a marked decrease in the yield of the amide due to the solubility of the amide in the solvent system chosen. The use of acetyl chloride as the acylating agent in dry pyridine solution failed to give better results.

Since 4-methoxy-2-nitroaniline was prepared commercially by acetylation and nitration of p-anisidine, followed by hydrolysis of the amide, the first step in this synthesis was utilized, with excellent results, to prepare the desired amide. The procedure for the acetylation of p-anisidine followed by nitration of the p-acetanisidide recommended by Fanta and Tarbell (23) was used without modification. This method gave 4-acetamido-3-nitroanisole in high yield and in high purity as long, yellow needles.

The reduction of the nitro group to form 4-acetamido-3-aminoanisole

was not achieved without some difficulties. Using the method of Simonov (11), reduction was brought about by means of iron filings in hot water as the reducing agent. Since this o-phenylenediamine derivative was slightly soluble in cold water and readily soluble in hot water, it was necessary to salt out the amine from solution with sodium chloride. The yield of product was only fair, possibly due to decomposition on exposure to air and to light.

Subsequent alkylation of the primary amino group of 4-acetamide-3-aminoanisole with various dialkylaminoethylchlorides resulted in at least two other products in addition to the desired 4-acetamido-3-(β-dialkylaminoethylamino)anisoles. Dialkylation of the 3-amino group followed by quaternary salt formation could account for some of these by-products.

The temperature of the oil-bath during the alkylation reaction was most important. Normally this reaction was carried out at an oil-bath temperature of 100-115°C. If the oil-bath temperature was much above 120°C., ring closure would have taken place prior to alkylation with the formation of 5-methoxy-2-methylbenzimidazole. Subsequent alkylation of this compound could result in a mixture of 1-(β-dialkylaminoethyl)-6-methoxy-2-methyl- and 1-(β-dialkylaminoethyl)-5-methoxy-2-methylbenzimidazole. Thus, it was necessary to maintain a lower temperature until alkylation had taken place, before the temperature was raised to bring about ring closure. This reaction was further complicated by the formation of quaternary salts resulting from the reaction of the 1-β-dialkylaminoethylbenzimidazoles with any dialkylaminoethylchloride still present.

One final complication, which must be taken into consideration, involved the reaction of the hydrogen chloride, produced during the alkylation step, with any or all of the above mentioned amino derivatives forming salts. Thus, one might expect some of the starting material, 4-acetamido-3-aminoanisole, to undergo hydrochloride formation. Alkylation of this salt would then be unlikely to occur, but, upon raising the temperature of the oil-bath, ring closure would take place resulting in the formation of some 5-methoxy-2-methylbenzimidazole. This, in turn, could then undergo alkylation and salt formation as discussed above.

Though a complicated mixture of products could and, undoubtedly, did occur in the above two-step reaction, the isolation of the desired 1,2,6-trisubstituted benzimidazoles was accomplished with ease. An ether extraction of an aqueous solution of the reaction mixture removed any excess dialkylaminoethylchloride. After making the aqueous solution distinctly alkaline, the product was obtained by extraction with benzene. A considerable amount of intractable tar remained which was soluble in ethanol, and was assumed to be a mixture of quaternary salts. Evaporation of the benzene from the extract followed by distillation of the residue in a vacuum gave the desired benzimidazole. Yields were seldom above 35 per cent of the theoretical based on 4-acetamido-3-aminoanisole.

In an attempt to establish the course of the above alkylation and ring closure reactions, the following experiments were performed. 4-Acetamido-3-aminoanisole was alkylated with N-β-chloroethylpiperidine at an oil-bath temperature of 110-115°C. 2-Acetamido-5-methoxy-N-(β-piperidinoethyl)aniline was obtained as a colorless powder melting at 125-125.5°C. in a yield of 51 per cent of the theoretical. Subsequently

this material was heated under reflux in xylene solution at an oil-bath temperature of 135-140°C. to produce 6-methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole, identical with the product obtained by the combined alkylation and ring closure reactions.

Since the course of this reaction sequence was known, these benzimidazoles were normally prepared without purification of intermediates in the three-step sequence of reactions in an attempt to obtain as high a yield as possible. The reduction of the nitro group in 4-acetamido-3-nitroanisole was carried out by hydrogenation over Raney nickel. When ethanol was used as the solvent, it was not necessary to isolate the 4-acetamido-3-aminoanisole prior to alkylation. The reduced reaction mixture was immediately subjected to alkylation and ring closure procedures. Ethanol, however, was not a good solvent for the reduction because of the low solubility of both the starting material and the product in it. Glacial acetic acid was an excellent solvent for the reduction, but, when it was used, it was necessary to isolate the 4-acetamido-3-aminoanisole prior to alkylation. This was accomplished by first concentrating the acid solution, then making it distinctly alkaline, and, finally, extracting the alkaline solution with diethyl ether. After evaporation of the solvent, the o-phenylenediamine derivative was alkylated in ethanol as described previously. The yield of benzimidazole from this procedure, however, was quite poor. During the later stages of this investigation it was observed that dioxane was a better solvent for the reduction than either ethanol or glacial acetic acid. After completion of the reduction the 4-acetamido-3-aminoanisole could be isolated by removing the dioxane in vacuo, or the reduction mixture could be subjected directly to the alkylation and ring closure reactions. Satisfactory yields of benzimidazoles were obtained when dioxane was used.

The benzimidazoles prepared in this series were found to be yellow

viscous oils boiling at higher temperatures than the corresponding 1,2,5-trisubstituted isomers. On standing in the cold crystallization could be induced in some cases.

These benzimidazoles were characterized as dimethiodides and as dihydrochlorides. While the dipicrates could be prepared, no suitable solvent could be found for purifying them.

All of the dihydrochlorides in this series developed deep colors when dissolved in hot ethanol. By using cold ethanol to dissolve the sample and then diluting the cold solution with diethyl ether, the dihydrochlorides were usually obtained as colorless needles.

EXPERIMENTAL

4-Methoxy-2-nitroacetanilide

The preparation of this compound according to the procedure of Fanta and Tarbell (23) resulted in a yield of 67 per cent of the theoretical of product as long, yellow needles melting at 115-116°C. Fanta and Tarbell report a melting point of 116.5-117°C.

4-Acetamido-3-aminoanisole

The procedure of Simonov (11) was followed on a larger scale.

Two hundred and thirty-seven grams (1.12 mole) of 4-acetamido-3-nitroanisole was added in small portions over a period of one hour to a well stirred mixture of 600 g. of 40 mesh iron filings and 50 g. of sodium chloride in 2.1 l. of water maintained at a temperature of 90°C. for two hours. The hot reaction mixture was filtered rapidly with suction through a preheated 21 cm. Büchner funnel. The filter cake was washed with two 300 ml. portions of boiling water. The hot filtrate was saturated with sodium chloride and chilled. The precipitate was filtered with suction and dried in a vacuum desiccator over Drierite. The yield of crude product as colorless needles melting at 142-146°C. was 140.4 g. (69.5% of the theoretical). Repeated recrystallizations of a small sample from hot water raised the melting point to 148-149.5°C. Simonov has reported the melting point of this compound as 150-150.5°C.

2-Acetamido-5-methoxy-N-(β-piperidinoethyl)aniline

Twenty and two-tenths grams (0.11 mole) of N-β-chloroethylpiperidine hydrochloride was dissolved in 50 ml. of 4N sodium hydroxide

solution. The N-β-chloroethylpiperidine was extracted with four 50 ml. portions of diethyl ether. After drying the extracts over anhydrous sodium sulfate, the ether was evaporated in vacuo. To the residue was added 18.0 g. (0.10 mole) of 4-acetamido-3-aminoanisole and 5 ml. of absolute ethanol. This mixture was refluxed in an oil-bath at 110-112°C. for 40 hours with vigorous stirring. The cooled reaction mixture was dissolved in 60 ml. of hot water, and extracted with two 50 ml. portions of diethyl ether to remove any unchanged N-β-chloroethylpiperidine. The aqueous layer was added to 150 g. of 50 per cent aqueous sodium hydroxide solution. The product was obtained by extracting this alkaline solution with 400 ml. of benzene in several portions. The extracts were washed once with 150 ml. of water and dried over anhydrous sodium sulfate. Evaporation of the benzene left 14.0 g. (51% of the theoretical) of crude product as a brown solid melting at 117-118°C. Three recrystallizations of a small sample from 50 per cent aqueous ethanol raised the melting point to 125-125.5°C.

Analysis: Calculated 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.

6-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole dimethiodide

One and four-tenths grams of 2-acetamido-5-methoxy-N-(β-piperidinoethyl)aniline was heated under reflux in 50 ml. of xylene for seven days. Evaporation of the xylene left a small amount of residue consisting of a dark yellow oil. This oil was dissolved in 15 ml. of methyl iodide, and the solution was heated on a steam-bath until the excess methyl iodide had evaporated. The gray, crystalline residue was recrystallized twice from absolute ethanol (Norite). The

dimethiodide separated as colorless needles melting at 247-249°C. with decomposition. A mixture melting point of this material and a sample of the same compound prepared for analysis by a different method showed no depression.

1-(β-Dimethylaminoethyl)-6-methoxy-2-methylbenzimidazole

Fifty grams (0.24 mole) of 4-acetamido-3-nitroanisole was dissolved in 250 ml. of warm dioxane, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at an initial hydrogen pressure of 55 p.s.i. at room temperature. Meanwhile, 5.5 g. (0.24 gram-atom) of sodium was dissolved in 150 ml. of absolute ethanol. To this solution was added 34.3 g. (0.24 mole) of N-β-chloroethyldimethylamine hydrochloride. The sodium chloride which formed was removed by filtering the solution with suction. The filter cake was washed with 20 ml. of ethanol. To the dioxane suspension of 4-acetamido-3-aminoanisole was added the ethanolic solution of N-β-chloroethyldimethylamine. 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°C. for ten hours. While the temperature of the oil-bath was raised to 135-140°C., all but about 50 ml. of the solvent was removed by distillation. Refluxing with stirring was then continued at this temperature for eight hours. The hot reaction mixture was dissolved in 250 ml. of warm water and then cooled. The Raney nickel catalyst was removed by filtering the solution with suction. The aqueous solution was extracted with diethyl ether in two 100 ml. portions to remove any unchanged N-β-chloroethyldimethylamine. The aqueous solution was then made distinctly alkaline by the addition of 10N potassium hydroxide solution. The product was obtained by extracting the alkaline solution with 450 ml. of benzene in several portions. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed *in vacuo* on a steam-bath. Distillation of the residue in a vacuum gave the product as a yellow, viscous oil boiling at 170-180°C./0.06 mm. in a yield of 19.7 g. (35.5% of the theoretical).

Since this compound was characterized by the following derivatives, it was not analyzed as the free base.

1-(β-Dimethylaminoethyl)-6-methoxy-2-methylbenzimidazole dimethiodide

Five-tenths gram of the free base was dissolved in 10 ml. of methyl iodide. The solution was warmed on a steam-bath until the excess methyl iodide had evaporated. The colorless residue was dissolved in the minimum amount of boiling absolute ethanol (Norite). The filtered solution was diluted with anhydrous diethyl ether until turbid and then chilled thoroughly. A second purification gave the dimethiodide as colorless needles melting at 238.5-240°C. with decomposition.

Analysis: Calculated for $C_{15}H_{25}I_2N_3O$: C, 34.83; H, 4.87; I, 49.08; N, 8.13. Found: C, 34.65; H, 5.07; I, 48.91; N, 8.26.

1-(β-Dimethylaminoethyl)-6-methoxy-2-methylbenzimidazole dihydrochloride

Twenty-two grams (0.09 mole) of the free base was dissolved in 700 ml. of anhydrous diethyl ether. The cold ethereal solution was saturated with dry hydrogen chloride. The colorless precipitate was filtered rapidly with suction, and was dissolved in about 1 l. of warm absolute isopropyl alcohol. Dilution of the alcoholic solution with anhydrous diethyl ether until turbid followed by chilling gave the dihydrochloride as short, faintly pink needles melting at 225-227°C. with decomposition in a yield of 16.5 g. (57.1% of the theoretical). Two additional purifications of a small sample gave the product as short, pink needles melting at 226-227°C. with decomposition.

Analysis: Calculated for $C_{13}H_{21}Cl_2N_3O$: C, 50.98; H, 6.91; Cl, 23.16; N, 13.72. Found: C, 51.00; H, 7.17; Cl, 23.04; N, 13.64.

6-Methoxy-2-methyl-1-(β-pyrrolidinoethyl)benzimidazole

Forty grams (0.19 mole) of 4-acetamido-3-nitroanisole was dissolved in 250 ml. of dioxane, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at room temperature. After the theoretical amount of hydrogen had been taken up, the catalyst was removed by filtration with suction. Meanwhile, 4.4 g. (0.19 gram-atom) of sodium was dissolved in 150 ml. of absolute ethanol. To this solution was added 32.3 g. (0.19 mole) of N-β-chloroethylpyrrolidine hydrochloride. The sodium chloride which formed was removed by filtration with suction, and the filter cake was washed with 20 ml. of ethanol. The N-β-chloroethylpyrrolidine solution was added to the above dioxane solution of 4-acetamido-3-aminoanisole. The resulting solution was refluxed with stirring in an oil-bath at 105-110°C. for ten hours. While the temperature of the oil-bath was being raised to 135-140°C., all but about 50 ml. of the solvent was removed by distillation. The resulting solution was refluxed with stirring at this temperature for ten hours. The solution was then diluted with 150 ml. of hot water and cooled. Extraction of the aqueous solution with diethyl ether in two 50 ml. portions removed any unchanged N-β-chloroethylpyrrolidine. After making the aqueous solution distinctly alkaline with 4N sodium hydroxide solution, the product was obtained by extracting the alkaline solution with 400 ml. of benzene in several portions. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a pale yellow, viscous oil boiling at 190-195°C./0.08 mm. in a yield of 20.2 g. (41% of the theoretical). On standing in the cold this material crystallized partially.

Since this compound was characterized by the following derivatives, it was not analyzed as the free base.

6-Methoxy-2-methyl-1-(β-pyrrolidinoethyl)benzimidazole dimethiodide

The dimethiodide, which was prepared and purified as described on page 55, was obtained as colorless needles melting at 246-247°C. with decomposition.

Analysis: Calculated for $C_{17}H_{27}I_2N_3O$: I, 46.72; N, 7.73. Found: I, 46.73; N, 7.86.

6-Methoxy-2-methyl-1-(β-pyrrolidinoethyl)benzimidazole dihydrochloride

Twenty and two-tenths grams (0.08 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. The cold ethereal solution was saturated with dry hydrogen chloride. The colorless precipitate was filtered rapidly with suction and was dissolved in the minimum amount of isopropyl alcohol. The alcoholic solution was diluted with anhydrous diethyl ether until turbid and then was chilled thoroughly. The dihydrochloride separated as a faintly tan powder melting at 238-239°C. with decomposition in a yield of 14.8 g. (57% of the theoretical). Two additional purifications of a small sample gave the dihydrochloride as short, colorless needles melting at 240.5-241°C. with decomposition.

Analysis: Calculated for $C_{15}H_{23}Cl_2N_3O$: C, 54.22; H, 6.98; Cl, 21.34; N, 12.65. Found: C, 54.02; H, 7.13; Cl, 21.13; N, 12.59.

6-Methoxy-2-methyl-1-(β-morpholinoethyl)benzimidazole

Sixty-three and one-tenth grams (0.30 mole) of 4-acetamido-3-nitroanisole was partially dissolved in 250 ml. of absolute ethanol, Raney nickel catalyst was added, and the mixture was subjected to

hydrogenation at an initial hydrogen pressure of 60 p.s.i. at 60°C. After the uptake of the theoretical amount of hydrogen, the 4-acetamido-3-aminoanisole was dissolved in 1 l. of hot absolute ethanol, and the solution was filtered to remove the catalyst. The ethanol solution was then concentrated in vacuo on a warm water bath to a volume of about 100 ml. Meanwhile, 7.4 g. (0.32 gram-atom) of sodium was dissolved in 200 ml. of absolute ethanol. To this solution was added 58.9 g. (0.32 mole) of N-β-chloroethylmorpholine hydrochloride. The mixture was filtered with suction to remove sodium chloride, and the filter cake was washed with 50 ml. of ethanol. The combined filtrate and washing containing N-β-chloroethylmorpholine was added to the 4-acetamido-3-aminoanisole, and the resulting mixture refluxed with stirring in an oil-bath at 100°C. for 15 hours. All but about 50 ml. of the ethanol was then removed by distillation, and the remaining mixture was heated under reflux with stirring for eight hours at an oil-bath temperature of 135-140°C. After cooling the mixture, it was dissolved in 200 ml. of warm water, and extracted with two 50 ml. portions of diethyl ether to remove any unchanged N-β-chloroethylmorpholine. The aqueous solution was then made distinctly alkaline with 10N sodium hydroxide solution. The product was obtained by extracting the alkaline solution with benzene in several portions totaling 900 ml. After drying the extracts over anhydrous sodium sulfate, the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a viscous, yellow oil boiling at 185-210°C./0.07mm. in a yield of 20.8 g. (25.2% of the theoretical). On standing in the cold this material solidified to a pale yellow, waxy solid.

Since this compound was characterized by the following derivatives, it was not analyzed as the free base.

6-Methoxy-2-methyl-1-(β-morpholinoethyl)benzimidazole dimethiodide

The dimethiodide, which was prepared and purified according to the procedure described on page 55, was obtained as colorless needles melting at 215-216°C. with decomposition.

Analysis: Calculated for $C_{17}H_{27}I_2N_3O_2$: C, 36.51; H, 4.87; I, 45.39: N, 7.51. Found: C, 36.31; H, 5.16; I, 45.31; N, 7.39.

6-Methoxy-2-methyl-1-(β-morpholinoethyl)benzimidazole dihydrochloride

Fourteen and five-tenths grams (0.05 mole) of the free base was dissolved in 700 ml. of anhydrous diethyl ether. The cold ethereal solution was saturated with dry hydrogen chloride. The colorless precipitate which formed was filtered rapidly with suction and was dissolved in the minimum amount of absolute ethanol at room temperature. The alcoholic solution was diluted with anhydrous diethyl ether until turbid and then chilled thoroughly. The dihydrochloride separated as pink needles melting at 232-234°C. with decomposition in a yield of 12.1 g. (65.7% of the theoretical). Three additional purifications of a small sample raised the melting point to 236.5-237.5°C. with decomposition.

Analysis: Calculated for $C_{15}H_{23}Cl_2N_3O_2$: C, 51.73; H, 6.66; Cl, 20.36; N, 12.07. Found: C, 51.53; H, 6.95; Cl, 20.05; N, 12.18.

1-(β-Diethylaminoethyl)-6-methoxy-2-methylbenzimidazole

Sixty-three and one-tenth grams (0.30 mole) of 4-acetamido-3-nitroanisole was partially dissolved in 250 ml. of absolute ethanol, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation

at an initial hydrogen pressure of 60 p.s.i. at 60°C. After the theoretical amount of hydrogen had been taken up, the reaction mixture was diluted to 1 l. with boiling absolute ethanol and filtered to remove the catalyst. The alcoholic solution of 4-acetamido-3-aminoanisole was then concentrated in vacuo on a warm water bath to a volume of about 100 ml. Meanwhile, 7.6 g. (0.33 gram-atom) of sodium was dissolved in 250 ml. of absolute ethanol. To this solution was added 47.5 g. (0.33 mole) of N-β-chloroethyldiethylamine hydrochloride. The sodium chloride that formed was removed by filtration with suction and the filter cake washed with 50 ml. of cold ethanol. The alcoholic filtrate and washing containing N-β-chloroethyldiethylamine were added to the alcoholic suspension of 4-acetamido-3-aminoanisole. The resulting mixture was heated under reflux with stirring in an oil-bath at 100°C. for 15 hours. All but about 50 ml. of the solvent was removed by distillation after which heating under reflux with stirring was continued for ten hours at an oil-bath temperature of 140-145°C. The cooled reaction mixture was diluted with 250 ml. of warm water. Extraction of the aqueous solution with diethyl ether in two 100 ml. portions removed the unchanged N-β-chloroethyldiethylamine. The aqueous solution was made distinctly alkaline by the addition of 10N sodium hydroxide solution. The product was separated by extracting the alkaline solution with 700 ml. of benzene in several portions. After drying the extracts over anhydrous sodium sulfate, the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a viscous, golden oil boiling at 185-200°C./0.07 mm. in a yield of 22.6 g. (28.9% of the theoretical).

Since this compound was characterized by the following derivatives, it was not analyzed as the free base.

1-(β-Diethylaminoethyl)-6-methoxy-2-methylbenzimidazole dimethiodide

The dimethiodide, which was prepared according to the procedure described on page 55, was obtained as short, colorless needles melting at 236.5-237°C. with decomposition.

Analysis: Calculated for $C_{17}H_{29}I_2N_3O$: C, 37.45; H, 5.36; I, 46.55; N, 7.71. Found: C, 37.49; H, 5.65; I, 46.23; N, 7.93.

1-(β-Diethylaminoethyl)-6-methoxy-2-methylbenzimidazole dihydrochloride

Twenty-one and five-tenths grams (0.08 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. The cold ethereal solution was saturated with dry hydrogen chloride. The colorless precipitate was isolated by filtering the mixture rapidly with suction. The filter cake was dissolved in the minimum amount of absolute ethanol at room temperature. The alcoholic solution was diluted with anhydrous diethyl ether until turbid, and then chilled thoroughly. The dihydrochloride separated as colorless needles melting at 225-227°C. with decomposition in a yield of 14.0 g. (51% of the theoretical). Three additional purifications of a small sample in a similar manner gave the dihydrochloride as short, pink needles melting at 227-228°C. with decomposition.

Analysis: Calculated for $C_{15}H_{25}Cl_2N_3O$: C, 53.89; H, 7.54; Cl, 21.21; N, 12.57. Found: C, 53.66; H, 7.63; Cl, 21.00; N, 12.51.

6-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole

Thirty-two and two-tenths grams (0.18 mole) of N-β-chloroethylpiperidine hydrochloride was added to 9.5 g. (0.18 gram-atom) of sodium methylate in 200 ml. of absolute ethanol. The mixture was filtered with suction to remove sodium chloride and the filter cake was washed

with 50 ml. of ethanol. To the combined filtrate and washing was added 30.0 g. (0.17 mole) of 4-acetamido-3-aminoanisole. The resulting mixture was refluxed with stirring in an oil-bath at 110-115°C. for ten hours. All but approximately 50 ml. of the solvent was then removed by distillation while the temperature of the oil-bath was raised to 135-140°C. Refluxing with stirring was continued at this temperature for eight hours. After cooling the reaction mixture and diluting with 250 ml. of hot water to dissolve all solids, the unchanged N-β-chloroethylpiperidine was removed by extraction with two 50 ml. portions of diethyl ether. After making the aqueous solution distinctly alkaline with 4N sodium hydroxide solution, the product was obtained by extracting the alkaline solution with benzene in several portions totaling 800 ml. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed *in vacuo* on a steam-bath. Distillation of the residue in a vacuum gave the product as a viscous, yellow oil boiling at 196-216°C./0.4 mm. in a yield of 8.0 g. (17.5% of the theoretical). On standing in the cold this material crystallized partially.

This compound was characterized by the following derivatives; it was not analyzed as the free base.

6-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole dimethiodide

The dimethiodide, which was prepared according to the procedure described on page 55, was obtained as colorless needles melting at 248.5-250°C. with decomposition after three recrystallizations from absolute ethanol.

Analysis: Calculated for $C_{18}H_{29}I_2N_3O$: C, 38.80; H, 5.24; I, 45.55; N, 7.54. Found: C, 38.51; H, 5.36; I, 45.27; N, 7.34.

6-Methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole dihydrochloride

Nineteen grams (0.07 mole) of the free base was dissolved in 500 ml. of anhydrous diether ether and the chilled solution saturated with dry hydrogen chloride. The colorless precipitate was purified three times by dissolving in the minimum amount of hot absolute ethanol (Norite). After filtering, the solution was diluted with anhydrous diethyl ether until turbid and then chilled thoroughly. The yield of dihydrochloride as short, pink needles melting at 235.5-236.5°C. with decomposition was 13.9 g. (57.5% of the theoretical).

Analysis: Calculated for $C_{16}H_{25}Cl_2N_3O$: C, 55.49; H, 7.28; Cl, 20.48; N, 12.13. Found: C, 53.74, 53.48; H, 7.02, 7.09; Cl, 20.64; N, 11.91.

The analysis of two additional samples failed to improve the carbon value although the chlorine and nitrogen values were in agreement with the calculated values.

PART II. B.

1-(β-DIALKYLAMINOETHYL)-6-METHOXYBENZIMIDAZOLES

DISCUSSION

The preparation of 4-formamide-3-nitroanisole, required as an intermediate for the synthesis of this group of benzimidazoles, was best achieved by direct formylation of 4-methoxy-2-nitroaniline with anhydrous formic acid. The yields obtained by this method were 80 per cent of the theoretical or better. All attempts to obtain the desired amide from p-anisidine by successive formylation and nitration were unsuccessful.

Subsequent reactions of 4-formamido-3-nitroanisole leading to the preparation of the benzimidazoles in this series were achieved in much the same manner as described in the previous section for the preparation of 1-(β-dialkylaminoethyl)-6-methoxy-2-methylbenzimidazoles.

The 1-(β-dialkylaminoethyl)-6-methoxybenzimidazoles were obtained by distillation in a vacuum as golden-yellow, viscous oils boiling at slightly higher temperatures than the corresponding 1,5-disubstituted isomers.

The benzimidazoles were characterized as dipicrates and as dihydrochlorides.

The dihydrochlorides were prepared for evaluation of physiological and pharmacological actions of the compounds. Little difficulty was encountered during their preparation and purification. A brief discussion of their infrared and of their ultraviolet absorption spectra is given in the appendix.

EXPERIMENTAL

4-Formamido-3-nitroanisole

Seventy-five grams (0.45 mole) of 4-amino-3-nitroanisole was dissolved in 300 ml. of anhydrous formic acid (boiling point 101-103°C.). The resulting solution was boiled under reflux with stirring for 24 hours. The mixture was poured over 300 g. of ice, diluted to approximately 1.5 l. with water, and allowed to stand in an ice-bath for three hours to complete the precipitation of the amide. The product was filtered with suction and washed with 300 ml. of cold water to remove traces of formic acid. After air drying, an average yield of 85.8 g. of crude product was obtained as a light tan powder. This material was recrystallized from 2 l. of boiling 70 per cent aqueous ethanol (Norite) giving an average of 69.9 g. (80% of the theoretical) of product as golden-yellow platelets melting at 145-148°C. Repeated recrystallizations of a small sample raised the melting point to 149-150°C. Knunyants and Benevelenskaya (24) report this compound to melt at 150-151°C.

3-Amino-4-formamidoanisole

Thirty-six grams (0.18 mole) of 4-formamido-3-nitroanisole was added in small portions, over a period of one-half hour, 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°C. After completing the addition, the mixture was stirred for an additional two hours at 90°C. The hot reaction mixture was filtered rapidly with suction through a preheated 21 cm. Büchner funnel, and the filter cake was washed with 150 ml. of boiling water. On chilling the solution to 0°C. and filtering with

suction, an average yield of 18.2 g. (60% of the theoretical) of product was obtained as a gray solid melting at 136-138°C. Two recrystallizations of a small sample from hot water (Norite) gave the product as colorless needles melting at 139.5-140.5°C.

Analysis: Calculated 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.

1-(β-Dimethylaminoethyl)-6-methoxybenzimidazole

Fifteen grams of 4-formamido-3-nitroanisole was dissolved in 250 ml. of dioxane, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at room temperature. After the theoretical amount of hydrogen had been taken up, the catalyst was removed by filtration with suction. The resulting solution was evaporated to dryness in vacuo on a warm water-bath. A total of 45.0 g. (0.23 mole) of 4-formamido-3-nitroanisole was reduced in this manner. Meanwhile, 5.5 g. (0.24 gram-atom) of sodium was dissolved in 150 ml. of absolute ethanol. After adding 34.3 g. (0.24 mole) of N-β-chloroethyldimethylamine hydrochloride, the sodium chloride which formed was removed by filtration with suction and washed with 50 ml. of ethanol. The alcoholic solution of N-β-chloroethyldimethylamine was added to the combined 3-amino-4-formamidoanisole solution, and the resulting mixture was refluxed with stirring in an oil-bath at 105-110°C. for ten hours. After removing all but about 50 ml. of the solvent by distillation, the mixture was refluxed with stirring in an oil-bath at 135-140°C. for eleven hours. The reaction mixture was dissolved in 250 ml. of warm water and cooled. Extraction with two 100 ml. portions of diethyl ether removed any unchanged

N-β-chloroethyldimethylamine. After making the solution distinctly alkaline by the addition of 10N sodium hydroxide solution, the product was obtained by extracting the alkaline solution with benzene in several protions totaling 700 ml. The extracts were dried over anhydrous sodium sulfate, and the benzene was removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave the product as a yellow, viscous oil boiling over the range 140-160°C./0.05 mm. in a yield of 17.2 g. (33.2% of the theoretical).

Since this compound was characterized by the following derivatives, it was not analyzed as the free base.

1-(β-Dimethylaminoethyl)-6-methoxybenzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Norite) from which it separated as long, yellow needles melting at 217-219°C. with decomposition.

Analysis: Calculated for $C_{24}H_{23}N_9O_{15}$: C, 42.54; H, 3.42; N, 18.62. Found: C, 42.75; H, 3.68; N, 18.38.

1-(β-Dimethylaminoethyl)-6-methoxybenzimidazole dihydrochloride

Twenty-one and seven-tenths grams (0.1 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. The cold ethereal solution was saturated with dry hydrogen chloride. The colorless precipitate was filtered rapidly with suction and dissolved in the minimum amount of warm absolute ethanol. The alcoholic solution was diluted with anhydrous diethyl ether until turbid and then chilled thoroughly. The dihydrochloride separated as a colorless powder melting at 221-223°C. with decomposition in a yield of 13.5 g. (46.7% of the theoretical).

Two similar additional purifications of a small sample raised the melting point to 222-223°C. with decomposition.

Analysis: Calculated for $C_{12}H_{19}Cl_2N_3O$: C, 49.32; H, 6.55; Cl, 24.27; N, 14.38. Found: C, 49.16; H, 6.81; Cl, 24.32; N, 14.18.

6-Methoxy-1-(β-pyrrolidinoethyl)benzimidazole

Twenty-nine and four-tenths grams (0.15 mole) of 4-formamido-3-nitroanisole was dissolved in 200 ml. of hot absolute ethanol, Raney nickel catalyst was added and the mixture subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at 60°C. After the theoretical uptake of hydrogen, the hot reaction mixture was filtered with suction to remove the catalyst, and the filter cake was washed with 100 ml. of boiling absolute ethanol. To this filtrate was added an alcoholic solution of N-β-chloroethylpyrrolidine, which was prepared by adding 30.6 g. (0.18 mole) of N-β-chloroethylpyrrolidine hydrochloride to a solution of 4.1 g. (0.18 gram-atom) of sodium in 100 ml. of absolute ethanol and filtering to remove the precipitated sodium chloride. The reaction mixture was then refluxed with stirring in an oil-bath at 100°C. for 12 hours. After distilling all but 50 ml. of the ethanol, the temperature of the oil-bath was raised to 135-140°C. and maintained at this point for eight hours. The cooled reaction mixture was dissolved in 250 ml. of hot water and extracted with two 100 ml. portions of diethyl ether to remove any unchanged N-β-chloroethylpyrrolidine. The aqueous solution was made alkaline by the addition of 200 ml. of 4N sodium hydroxide solution, and the product was obtained by extracting the alkaline solution with 400 ml. of benzene in several portions. The extracts were dried over Drierite, and the benzene removed in vacuo

on a steam-bath. Distillation of the residue in a vacuum gave 14.1 g. (38.3% of the theoretical) of product as a pale yellow, slightly viscous oil boiling over the range 171-190°C./0.05 mm.

This compound was characterized by the following derivatives; it was not analyzed as the free base.

6-Methoxy-1-(β-pyrrolidinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized five times from glacial acetic acid (Darco) from which it separated as bright yellow platelets melting at 216-217°C. with decomposition.

Analysis: Calculated for $C_{26}H_{25}N_9O_{15}$: C, 44.38; H, 3.58; N, 17.92. Found: C, 44.55; H, 3.84; N, 17.91.

6-Methoxy-1-(β-pyrrolidinoethyl)benzimidazole dihydrochloride

Fourteen and five-tenths grams (0.06 mole) of the free base was dissolved in 600 ml. of anhydrous diethyl ether. Saturation of the cold ethereal solution with dry hydrogen chloride precipitated the colorless product which was purified twice by dissolving in the minimum amount of hot absolute ethanol (Darco), filtering the solution, and diluting the filtrate with anhydrous diethyl ether until turbid. After thoroughly chilling the suspension, the product was obtained as a colorless powder melting at 224-225.5°C. with decomposition in a yield of 11.3 g. (60% of the theoretical).

Analysis: Calculated for $C_{14}H_{21}Cl_2N_3O$: C, 52.53; H, 6.65; Cl, 22.28; N, 13.20. Found: C, 52.64; H, 6.61; Cl, 22.40; N, 13.22.

6-Methoxy-1-(β-morpholinoethyl)benzimidazole

To 26.8 g. (0.16 mole) of 3-amino-4-formamidoanisole was added 26.0 g. (0.17 mole) of N-β-chloroethylmorpholine, the latter obtained by liberation of the free base from its hydrochloride, and 5 ml. of absolute ethanol. The mixture was heated under reflux with stirring in an oil-bath at 112-115°C. for four hours, and for 17.5 hours at 135-140°C. After cooling, 100 ml. of hot water was added, and the solution extracted with three 100 ml. portions of diethyl ether to remove any unchanged N-β-chloroethylmorpholine. After making the aqueous solution alkaline by the addition of 200 ml. of 4N sodium hydroxide solution, the product was obtained by extracting the alkaline solution with benzene in several portions totaling 600 ml. Drying of the extracts over Drierite followed by removal of the benzene *in vacuo* on a steam-bath left a residue which was distilled in a vacuum. The product was obtained as a light yellow, viscous oil, which solidified partially, boiling over the range 215-230°C./0.3 mm. in a yield of 21.0 g. (50.3% of the theoretical).

This compound was characterized by the following derivatives; it was not analyzed as the free base.

6-Methoxy-1-(β-morpholinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from glacial acetic acid (Norite) from which it separated as a yellow powder melting at 203.5-205°C. with decomposition.

Analysis: Calculated for $C_{26}H_{25}N_9O_{16}$: C, 43.40; H, 3.50; N, 17.52. Found: C, 43.62; H, 3.62; N, 17.48.

6-Methoxy-1-(β-morpholinoethyl)benzimidazole dihydrochloride

The dihydrochloride was prepared by dissolving 20.0 g. (0.08 mole) of the free base in cold anhydrous diethyl ether and saturating the ethereal solution with dry hydrogen chloride. The colorless precipitate was purified by dissolving in the minimum amount of hot absolute ethanol (Norite), filtering the solution, and diluting the filtrate with anhydrous diethyl ether until turbid followed by thorough chilling. Two similar purifications gave 14.8 g. (57.8% of the theoretical) of product as colorless needles melting at 256.5-257.5°C. with decomposition.

Analysis: Calculated for $C_{14}H_{21}Cl_2N_3O_2$: C, 50.30; H, 6.33; Cl, 21.22; N, 12.57. Found: C, 50.11; H, 6.51; Cl, 21.06; N, 12.63.

1-(β-Diethylaminoethyl)-6-methoxybenzimidazole

Fifteen grams of 4-formamido-3-nitroanisole was dissolved in 250 ml. of dioxane, Raney nickel catalyst was added, and the mixture was subjected to hydrogenation at an initial hydrogen pressure of 50 p.s.i. at room temperature. After the uptake of the theoretical amount of hydrogen, the catalyst was removed by filtration with suction. The dioxane was removed *in vacuo* on a warm water bath. A total of 45 g. (0.30 mole) of 4-formamido-3-nitroanisole was reduced in this manner. Meanwhile, 7.4 g. (0.32 gram-atom) of sodium was dissolved in 200 ml. of absolute ethanol. To this solution was added 55.0 g. (0.32 mole) of N-β-chloroethyldiethylamine hydrochloride. This mixture was filtered with suction to remove sodium chloride, and the filter cake was washed with 50 ml. of cold absolute ethanol. The alcoholic solution of N-β-chloroethyldiethylamine was added to the above 3-amino-4-formamidoanisole. The resulting mixture was refluxed with stirring in an oil-bath at

105-110°C. for ten hours. All but about 50 ml. of the solvent was removed by distillation. Refluxing with stirring of the residual material was then continued for ten hours at an oil-bath temperature of 130-135°C. The cooled reaction mixture was diluted with 250 ml. of warm water. Extraction with two 50 ml. portions of diethyl ether removed the unchanged N-β-chloroethyldiethylamine. The aqueous solution was made distinctly alkaline by the addition of 4N potassium hydroxide solution. The product was obtained by extracting the alkaline solution with benzene in several portions totaling 600 ml. After drying the extracts over anhydrous sodium sulfate, the benzene was removed *in vacuo* on a steam-bath. Distillation of the residue in a vacuum gave the product as a golden-yellow oil boiling at 150-170°C./0.05 mm. in a yield of 13.6 g. (24.1% of the theoretical).

Since this compound was characterized by the following derivatives, it was not analyzed as the free base.

1-(β-Diethylaminoethyl)-6-methoxybenzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from 70 per cent aqueous acetone (Norite) from which it separated as a yellow powder melting at 200-201.5°C. with decomposition.

Analysis: Calculated for $C_{26}H_{27}N_9O_{15}$: C, 44.26; H, 3.86; N, 17.87. Found: C, 44.30; H, 4.05; N, 17.67.

1-(β-Diethylaminoethyl)-6-methoxybenzimidazole dihydrochloride

Thirteen and six-tenths grams (0.06 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. The cold ethereal solution was saturated with dry hydrogen chloride. The colorless

precipitate which formed was removed by a rapid filtration with suction, and dissolved in the minimum amount of hot absolute ethanol. Dilution of the alcoholic solution with anhydrous diethyl ether until turbid, followed by thorough chilling, gave the dihydrochloride as pale pink needles melting at 217.5-219°C. with decomposition in a yield of 16.1 g. (91.5% of the theoretical). Three similar additional purifications of a small sample gave the dihydrochloride as long, colorless needles melting at 218.5-220°C. with decomposition.

Analysis: Calculated for $C_{14}H_{23}Cl_2N_3O$: C, 52.50; H, 7.24; Cl, 22.14; N, 13.12. Found: C, 52.52; H, 7.16; Cl, 22.22; N, 13.17.

6-Methoxy-1-(β-piperidinoethyl)benzimidazole

Fifty grams (0.26 mole) of 4-formamido-3-nitroanisole was partially dissolved in 250 ml. of absolute ethanol, Raney nickel catalyst was added, and the mixture was hydrogenated at an initial hydrogen pressure of 50 p.s.i. at 60°C. After the uptake of the theoretical amount of hydrogen, the reaction mixture was concentrated in vacuo to about 100 ml. Meanwhile, to a solution of 6.9 g. (0.30 gram-atom) of sodium in 150 ml. of absolute ethanol was added 55.2 g. (0.30 mole) of N-β-chloroethylpiperidine hydrochloride. The sodium chloride which formed was filtered with suction and washed with 50 ml. of cold absolute ethanol. The alcoholic solution of N-β-chloroethyl piperidine was then added to the 3-amino-4-formamidoanisole mixture. The resulting mixture was refluxed with stirring in an oil-bath at 100-105°C. for 12 hours. All but about 50 ml. of the solvent was removed by distillation and the residual mixture heated under reflux with stirring for seven hours at an oil-bath temperature of 140-145°C. After cooling, the reaction mixture was

dissolved in 250 ml. of hot water and filtered with suction to remove the nickel catalyst. Extraction of the aqueous solution with two 50 ml. portions of diethyl ether removed any unchanged N-β-chloroethylpiperidine. The aqueous solution was then made distinctly alkaline by the addition of 4N sodium hydroxide solution, and extracted with 1.2 l. of benzene in several portions. A large amount of black tar which was insoluble in water and in benzene but soluble in ethanol was discarded. The extracts were dried over anhydrous sodium sulfate and the benzene removed in vacuo on a steam-bath. Distillation of the residue in a vacuum gave 19.5 g. (29.6% of the theoretical) of product as a golden-yellow, viscous oil boiling over the range 168-184°C./0.03 mm. On standing in the cold partial crystallization of the product occurred.

This compound was characterized by the following derivatives; it was not analyzed as the free base.

6-Methoxy-1-(β-piperidinoethyl)benzimidazole dipicrate

The dipicrate was formed in hot absolute ethanol and was recrystallized three times from acetone (Norite) from which it separated as a yellow powder melting at 200-201°C. with decomposition.

Analysis: Calculated for $C_{27}H_{27}N_9O_{15}$: C, 45.19; H, 3.79; N, 17.57. Found: C, 45.46; H, 3.98; N, 17.64.

6-Methoxy-1-(β-piperidinoethyl)benzimidazole dihydrochloride

Nineteen and five-tenths grams (0.08 mole) of the free base was dissolved in 500 ml. of anhydrous diethyl ether. Saturation of the cold ethereal solution with dry hydrogen chloride produced a colorless precipitate which was filtered rapidly with suction and dissolved in 1.5 l. of absolute ethanol at room temperature. Dilution of the alcoholic

solution with anhydrous diethyl ether until turbid followed by thorough chilling gave the dihydrochloride as short, colorless needles melting at 242.5-243.5°C. with decomposition in a yield of 20.2 g. (81.5% of the theoretical).

Analysis: Calculated for $C_{15}H_{23}Cl_2N_3O$: C, 54.22; H, 6.98; Cl, 21.34; N, 12.65. Found: C, 54.19; H, 6.94; Cl, 21.43; N, 12.75.

SUMMARY

1. By means of a four step sequence of reactions the following benzimidazoles have been prepared from 4-methoxy-2-nitroaniline: 1-(β-dimethylaminoethyl)-5-methoxy-, 1-(β-dimethylaminoethyl)-5-methoxy-2-methyl-, 5-methoxy-1-(β-pyrrolidinoethyl)-, 5-methoxy-2-methyl-1-(β-pyrrolidinoethyl)-, 5-methoxy-1-(β-morpholinoethyl)-, 5-methoxy-2-methyl-1-(β-morpholinoethyl)-, 1-(β-diethylaminoethyl)-5-methoxy-, 1-(β-diethylaminoethyl)-5-methoxy-2-methyl-, 5-methoxy-1-(β-piperidinoethyl)-, and 5-methoxy-2-methyl-1-(β-piperidinoethyl)benzimidazole.

2. In addition, the corresponding 6-methoxy- isomers of the above benzimidazoles have been prepared by means of a four or five step sequence of reactions starting with 4-methoxy-2-nitroaniline or p-anisidine, respectively.

3. All the benzimidazoles were characterized as dipicrates and as dihydrochlorides. In each case sufficient dihydrochloride was prepared to permit evaluation of the physiological and pharmacological actions of these compounds.

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APPENDIX

PART I.

INFRARED ABSORPTION SPECTRA

An examination of the infrared absorption spectra of the twenty benzimidazoles prepared in this investigation showed them to be quite similar as would be expected. Because of their similarities, the spectra have not been reproduced in this thesis. They were used primarily as an indication that ring closure had taken place prior to the analysis of the benzimidazole dipicrates, dimethiodides, and dihydrochlorides. All of the spectra were determined in carbon tetrachloride solution on a Perkin-Elmer Recording Spectrophotometer, Model 21.

The presence of two bands in the spectra in the range 6.05-6.12 microns and 6.54-6.66 microns was taken as evidence for ring closure. According to Bellamy (25), a band falling in the range 6.02-6.13 microns may be attributed to the stretching vibrations of a structure containing an aromatic ring in conjugation with C=N. Such a structural unit appears in the benzimidazole ring. Bellamy further states that benzothiazoles usually give two bands in the range 6.07-6.61 microns and 6.54-6.79 microns. Because of structural similarities between benzothiazoles and 1-substituted benzimidazoles, one could expect them to show similar characteristic absorption bands. Since no discussion of the infrared absorption spectra of benzimidazoles was found in the literature, two previously characterized compounds of simple structure were prepared for comparative purposes, namely, 1-methyl- and 1,2-dimethylbenzimidazole. In both cases two bands were present in the ranges 6.05 microns and 6.55-6.65 microns, respectively.

Several other bands of interest were noted. Of the benzimidazoles

examined only the 2-methylbenzimidazoles contain the structural unit C-CH_3 for which a band in the range 7.03-7.10 microns was present. This band was absent in the spectra of the 2-H-benzimidazoles.

The location of bands which could be ascribed to the ether function was quite difficult. Bellamy states that a strong band is usually found in the range 8.70-9.43 microns for alkyl ethers. The benzimidazoles containing the morpholine ring showed a strong band at 8.95 microns which was absent in the spectra of the other benzimidazoles. Assignment of bands to the aromatic methoxy group was more difficult. In all of the spectra a sharp band in the range 9.57-9.70 microns was present. Bellamy states that a band of medium intensity in the range 9.35-10.0 microns could possible be connected with vibration of the CH_2-O- residue of the molecule. Such a band was not present in the model compounds, but was present in 4-methoxy-2-nitroaniline at 9.57 microns. Bellamy further assigns a strong band in the range 7.87-8.13 microns to the CH_3-O-Ar group. In all of the spectra strong bands were present in the range 7.83-8.35 microns, but it was not possible to assign a band to this functional group. Both of the model compounds had strong bands in this range, and 4-methoxy-2-nitroaniline had a strong doublet in the range 7.95-8.05 microns.

PART II.

ULTRAVIOLET ABSORPTION SPECTRA

The ultraviolet absorption spectra of the benzimidazole dihydrochlorides were determined in 0.01N hydrochloric acid solution using the Beckman DK-2 Recording Spectrophotometer to locate the approximate wavelength at which maximum absorption occurred. By means of the Beckman DU Spectrophotometer, the molar extinction coefficients (ϵ) at maximum wavelengths were determined. For convenience log ϵ, along with other pertinent data, have been summarized in Tables II and III. The molar extinction coefficients were calculated according to the following equation:

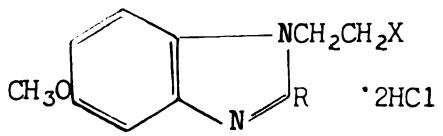
$$\epsilon = \frac{AM}{bc}$$

A=Absorbance; M = molecular weight; b = cell thickness in cm., and c = concentration in g./l.

A comparison of these spectra with the spectrum of benzimidazole showed two interesting features. Benzimidazole has two characteristic sharp bands, one at 2670Å (c = 0.0272 g./l., log ϵ = 3.55) and 2735Å (log ϵ = 3.54). Substitution of a methoxy group in position 5 or 6 of the benzimidazole ring causes a characteristic bathochromic shift to about 2880Å, and a loss of fine structure. Only one broad band was present.

TABLE II

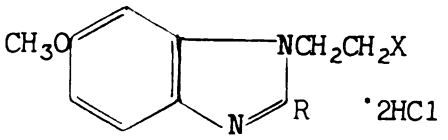
ULTRAVIOLET ABSORPTION MAXIMA OF SUBSTITUTED BENZIMIDAZOLES



X	R	c, g./l.	λ max, Å	log ∈
$N(CH_3)_2$	H	0.0254	2890	3.82
$N(CH_3)_2$	CH_3	0.0271	2880	3.90
NC_4H_8	H	0.0329	2890	3.82
NC_4H_8	CH_3	0.0248	2880	3.88
NC_4H_8O	H	0.0289	2880	3.83
NC_4H_8O	CH_3	0.0239	2880	3.89
$N(C_2H_5)_2$	H	0.0243	2900	3.83
$N(C_2H_5)_2$	CH_3	0.0242	2890	3.86
NC_5H_{10}	H	0.0242	2890	3.81
NC_5H_{10}	CH_3	0.0272	2875	3.90

TABLE III

ULTRAVIOLET ABSORPTION MAXIMA OF SUBSTITUTED BENZIMIDAZOLES



X	R	c, g./l.	λ max, Å	log ∈
$N(CH_3)_2$	H	0.0272	2890	3.82
$N(CH_3)_2$	CH_3	0.0240	2865	3.94
NC_4H_8	H	0.0288	2880	3.88
NC_4H_8	CH_3	0.0241	2870	3.96
NC_4H_8O	H	0.0270	2880	3.88
NC_4H_8O	CH_3	0.0238	2870	3.91
$N(C_2H_5)_2$	H	0.0239	2875	3.88
$N(C_2H_5)_2$	CH_3	0.0238	2865	3.94
NC_5H_{10}	H	0.0288	2870	3.86
NC_5H_{10}	CH_3	0.0258	2875	3.90