Lead tetraacetate oxidation of the above gave 3-chloro-2-pentanone (38%), b.p. 123–125° (730 mm.) (lit. b.p. 130°[18]), n_D^{20} 1.4280, which formed a 2,4-DNP melting at 106–107°.

Anal. Calcd. for $C_{11}H_{13}O_4N_4Cl$: C, 43.8; H, 4.3; Cl, 11.8; N, 18.7. Found: C, 43.9; H, 4.3; Cl, 11.5; N, 18.6.

Acknowledgments. This work was supported in part by a research grant from the National Science Foundation. We are greatly indebted to Dr. Calvin L. Stevens for his kind encouragement and helpful discussions.

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[18] M. Conrad, *Ann.*, **186**, 241 (1877).

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

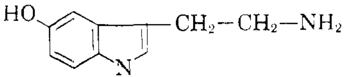
1-(β-Aminoalkyl)benzimidazoles[1a]

WILLIAM B. WHEATLEY AND GERALD F. STINER[1b]

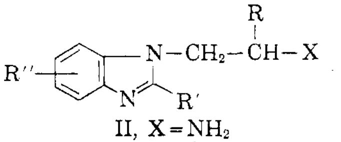
Received February 6, 1957

A series of 1-(β-aminoalkyl)benzimidazoles has been synthesized by a reaction sequence involving the base-catalyzed addition of acrylamide or methacrylamide to benzimidazoles and subsequent Hofmann rearrangement of the amides thus obtained.

During the past few years, the role of serotonin (I), 5-hydroxytryptamine, in certain physiological functions has been the subject of much investigation. Of particular interest have been its effect on the cardiovascular system and its place in mental processes, neither of which is completely understood as yet. It does indeed have a powerful vasoconstrictor action, and the hypothesis that an excess of serotonin is a significant factor in essential hypertension has been proposed.[2] This hypothesis has prompted the synthesis of a number of indoles related to serotonin which might be antagonists.[3] The authors became interested in this problem and decided to attack it by replacing the indole nucleus of serotonin with the isosteric benzimidazole nucleus. At this time the authors wish to report the synthesis of a series of compounds, the simplest of which is 1-(β-aminoethyl)benzimidazole (II, R, R′, R″ = H).

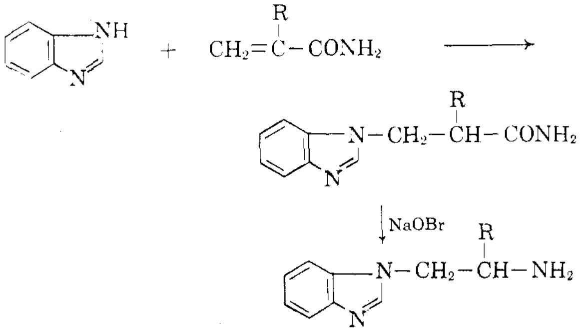


I



II, X = NH_2
III, X = $CONH_2$

Since benzimidazoles are readily obtained from *o*-phenylenediamine and organic acids,[4] it was felt that introduction of the β-aminoethyl group into a preformed benzimidazole would be the best synthetic approach. A sequence involving cyanomethylation of benzimidazole, followed by reduction to the primary amine, was attempted first, with quite unpromising results. Recalling that acrylonitrile adds to benzimidazole,[5] we tried the addition of acrylamide, to be followed if successful by a Hofmann rearrangement.



This synthesis proved to be acceptable, and could be adapted to the preparation of β-aminopropyl (R = CH_3) benzimidazoles by the use of methacrylamide. The synthesis of β-aminopropyl compounds had been contemplated, since it is known that the methyl group adjacent to the amine function is effective in inhibiting *in vitro* enzymatic degradation of many primary amines.[6]

Acrylamide and methacrylamide add to benzimidazoles, on boiling several hours in pyridine solution with Triton B as catalyst, to yield β-(1-benzimidazole)propionamides and β-(1-benzimidazole)-isobutyramides in reasonably good yields. In Table I are summarized a number of such amides; benzimidazoles substituted in the 2 and 5 positions were used. In the case of those benzimidazoles having a substituent in the benzene ring, the expected

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[1] (a) Presented before the Division of Medicinal Chemistry, AMERICAN CHEMICAL SOCIETY, Atlantic City, September, 1956. (b) Present address: State University of New York, College of Medicine, Syracuse, N. Y.

[2] D. W. Woolley and E. N. Shaw, *J. Am. Chem. Soc.*, **74**, 2948 (1952).

[3] D. W. Woolley and E. N. Shaw, *Science*, **124**, 34 (1956).

[4] J. B. Wright, *Chem. Revs.*, **48**, 397 (1951).

[5] (a) British patent **457,621** [*Chem. Abstr.*, **31**, 3068 (1937)]; (b) L. S. Efros and B. A. Poraĭ-Koshits, *Zhur. Obshchei Khim.*, **23**, 697 (1953)[*Chem. Abstr.*, **48**, 7603 (1954)].

[6] W. H. Hartung, *Ann. Rev. Biochem.*, **15**, 593 (1946).

TABLE I

SUBSTITUTED β-(1-BENZIMIDAZOLE)PROPIONAMIDES (III)

						Analyses			
						Carbon		Hydrogen	
R	R′	R″	Yield, %	M.P., °C.[a]	Formula	Calcd.	Found	Calcd.	Found
H	H	H	78	173.5–175.0	$C_{10}H_{11}N_3O$	63.5	63.6	5.9	6.1
	CH_3		67	195.5–197.0	$C_{11}H_{13}N_3O$	65.0	64.7	6.4	6.5
	C_3H_7		50	198.5–200.0	$C_{13}H_{17}N_3O$	67.5	67.8	7.4	7.4
	i-C_3H_7		61	213.5–215.0	$C_{13}H_{17}N_3O$	67.5	67.3	7.4	7.4
	$C_6H_5CH_2$		57[b]	192.5–194.5	$C_{17}H_{17}N_3O$	73.1	73.8	6.1	6.1
	H	CH_3	60	162–186	$C_{11}H_{13}N_3O$	65.0	65.1	6.4	6.4
		CH_3O	57	159–164	$C_{11}H_{13}N_3O_2$	60.3	60.1	6.0	6.2
		Cl	44	159–200	$C_{10}H_{10}ClN_3O$	53.7	54.0	4.5	4.5
CH_3		H	59	183.0–185.5	$C_{11}H_{13}N_3O$	65.0	65.1	6.4	6.4
	CH_3		48	227.5–231.0	$C_{12}H_{15}N_3O$	66.3	66.6	7.0	7.1

[a] All amides were recrystallized from water, except when R′ = $C_6H_5CH_2$ which was recrystallized from isopropyl alcohol. [b] It is reported that 2-benzylbenzimidazole does not add acrylonitrile.[5b]

TABLE II

SUBSTITUTED 1-(β-AMINOALKYL)BENZIMIDAZOLES II

						Analyses			
						Carbon		Hydrogen	
R	R′	R″	Yield, %	M.P., °C.[a]	Formula	Calcd.	Found	Calcd.	Found
H	H	H	27	271–277[b]	$C_9H_{11}N_3 \cdot 2HCl$	46.2	46.2	5.6	5.6
	CH_3		59	286–289	$C_{10}H_{13}N_3 \cdot 2HCl$	48.4	48.2	6.1	6.3
	i-C_3H_7		22	140–143	$C_{12}H_{17}N_3 \cdot 2HCl \cdot H_2O$	49.0	48.5	7.2	7.5
	$C_6H_5CH_2$		31	251.5–254	$C_{16}H_{17}N_3 \cdot 2HCl$	59.2	59.3	5.9	6.1
	H	CH_3	57	210–218	$C_{10}H_{13}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	46.7	47.0	6.4	6.3
		CH_3O	47	230–240	$C_{10}H_{13}N_3O \cdot 2HCl$	45.4	44.7	5.7	5.8
		Cl	44	243–247	$C_9H_{10}ClN_3 \cdot 2HCl$	40.3	40.2	4.5	4.6
CH_3		H	44	71.5–74.5[c]	$C_{10}H_{13}N_3$	68.5	68.1	7.5	7.2
	CH_3		64	268.5–275	$C_{11}H_{15}N_3 \cdot 2HCl$	50.3	50.1	6.5	6.9

[a] The dihydrochlorides were recrystallized from methanol-ether. [b] See ref. 9. [c] Recrystallized from benzene-cyclohexane.

mixtures of 5- and 6-isomeric amides were obtained. The Hofmann rearrangement proceeds in fair yields with the amides, giving the amines which are described in Table II.

It is probable that this sequence of reactions could be applied to other compounds, provided of course that a sufficiently activated position is available for addition of the unsaturated amide, and that other portions of the molecule are inert towards hypobromite. This might prove more satisfactory than methods hitherto used for introduction of the β-aminoalkyl group, many of which are quite lengthy.

EXPERIMENTAL[7]

β-(1-Benzimidazole)propionamide. Method A. Benzimidazole (59.0 g., 0.5 mole) and acrylamide (35.6 g., 0.5 mole) were suspended in 150 ml. of pyridine and 4.0 ml. of Triton B[8] was added. Heat was gradually applied to the stirred reaction mixture, bringing it to reflux, where it was maintained for 7 hr. On cooling, crystals separated and were collected by filtration. Recrystallization of the crude solid from water afforded 74.0 g. of β-(1-benzimidazole)propionamide, m.p. 173.5–175.0°.

Method B. A solution of 1.71 g. (0.01 mole) of β-(1-benzimidazole)propionitrile[5] in 5 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 24 hr. The reaction mixture was poured onto ice and made basic with ammonium hydroxide. Chilling and scratching induced crystallization, giving on filtration 1.67 g. (88%) of β-(1-benzimidazole)propionamide, m.p. 174.0–175.5°. A mixture of the amides prepared by the two different routes showed no depression in melting point.

The reaction of substituted benzimidazoles with acrylamide or methacrylamide yielded, as described in Method A, the amides listed in Table I. Those benzimidazoles containing substituents in the benzene ring gave mixtures of isomeric 5- and 6-substituted amides, as indicated by the wide melting ranges. These mixtures could not be separated reasily by crystallization and were not investigated further.

1-(β-Aminoethyl)benzimidazole. To an ice-cold, stirred solution of 24.0 g. (0.6 mole) of sodium hydroxide in 200 ml. of water was added 6.0 ml. (0.12 mole) of bromine. When all of the bromine had dissolved, 18.9 g. (0.10 mole) of β-(1-benzimidazole)propionamide was added all at once. The ice bath was removed and external heat applied, causing the amide to dissolve rapidly. The clear yellow solution was refluxed for 6 hr., then cooled and extracted with four 50-ml. portions of methylene chloride. Evaporation of the solvent from the combined extracts left a residual oil of 11.5 g., which could be crystallized with difficulty on scratching under ether. The oil was dissolved in 100 ml. of methanol, treated with an excess of dry hydrogen chloride and the acidic solution was diluted with 300 ml. of ether. There was thus obtained 12.7 g. of crude solid, which after several recrystallizations from methanol-ether afforded 6.3

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(7) Melting points are uncorrected.

(8) A 2.5*N* aqueous solution of benzyltrimethylammonium hydroxide supplied by Rohm & Haas was used.

g. of 1-(β-aminoethyl)benzimidazole dihydrochloride, m.p. 271–277° dec.[9]

In a similar manner the β-aminoalkylbenzimidazoles in Table II were prepared. One was isolated as the free base, the others as the dihydrochlorides. Even after several recrystallizations, these salts decomposed over a rather wide range at the melting point. In order to obtain material for preliminary pharmacological testing, the mixtures of isomeric 5- and 6-substituted amides (Table I, $R'' \neq H$) were treated as above with hypobromite. No attempt other than ordinary recrystallization was made to separate the mixtures of products.

Acknowledgment. The authors wish to acknowledge the continued interest of Dr. Lee C. Cheney throughout this work. Microanalyses were performed by Richard M. Downing.

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[9] This compound has also been prepared by a different synthesis, starting with *N*-(2-phthalimidoethyl)-*o*-phenylenediamine [P. Mamalis, V. Petrow, and B. Sturgeon, *J. Chem. Soc.*, 1600 (1950).

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

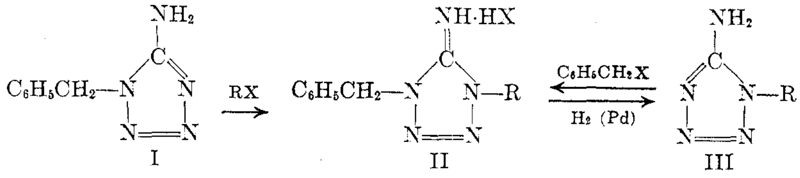
Alkylated 5-Aminotetrazoles, Their Preparation and Properties[1]

DOUGLAS F. PERCIVAL[2] AND ROBERT M. HERBST

Received February 13, 1957

A group of 1,4-benzylalkyl-5-iminotetrazolines was prepared both by alkylation of 1-benzyl-5-aminotetrazole and by benzylation of 1-alkyl-5-aminotetrazoles. In each instance both processes gave identical pairs of compounds. Furthermore, catalytic hydrogenolysis removed the benzyl group from both products and in each case a 1-alkyl-5-aminotetrazole was recovered. These observations confirm the conclusion that the alkylation of 1-alkyl-5-aminotetrazoles takes place in the 4-position. A group of 1,4-dialkyl-5-iminotetrazolines in which both alkyl groups were the same was prepared by similar procedures. A comparable group of 1-alkyl-5-alkylaminotetrazoles was prepared both by addition of hydrazoic acid to the appropriate carbodiimides and from suitable aminoguanidines. The marked differences between comparably substituted 1,4-dialkyl-5-iminotetrazolines and 1-alkyl-5-alkylaminotetrazoles further substantiates the conclusion that alkylation of 1-alkyl-5-aminotetrazoles leads primarily to the 1,4-dialkyl-5-iminotetrazolines with the alkylating agents and conditions employed. An attempt has been made to correlate the physical and chemical properties of the alkylated 5-aminotetrazoles with the tautomeric and resonance possibilities inherent in the several groups.

Many years ago Thiele and Ingle[3] showed that benzylation of 5-aminotetrazole led to several mono- and dibenzylated products whose structures were not established at that time. More recently the alkylation of a number of 1-alkyl-5-aminotetrazoles was studied[4] and it was noted that the introduction of a second alkyl group caused marked changes in the physical and chemical properties of the compounds. Although structures were assigned to the dialkylated aminotetrazoles, it was recognized that further work was required to establish the true structure of these compounds. Subsequently, based on a comparison of the physical properties of several dialkylated aminotetrazoles and their derivatives in which the same pair of alkyl groups had been introduced in different order, it was suggested that the compounds were actually 1,4 - dialkyl - 5 - iminotetrazolines.[5] This conclusion was supported by the ethylation of 1-benzyl-5-aminotetrazole (I) with ethyl sulfate followed by removal of the benzyl group by hydrogenolysis and isolation of 1-ethyl-5-aminotetrazole (III, R = ethyl).[5] A similar conclusion was reached by Henry *et al.*, as the result of methylation of I and isolation of 1-methyl-5-aminotetrazole (III, R = methyl) after hydrogenolytic removal of the benzyl group.[6] In both cases the conclusions were further supported by the fact that the benzylethyl(or methyl-) iminotetrazolines (II, R = ethyl or methyl, were identical whether prepared by ethylation (or methylation) of I or by benzylation of III (R = ethyl or methyl).



In this report further studies of the alkylation of 1-substituted 5-aminotetrazoles with a variety of alkylating agents are described from which it may

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[1] Based on a thesis submitted to the School for Advanced Graduate Studies at Michigan State University in 1955 by Douglas F. Percival in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Present address: California Research Corp., Richmond, Calif.

[3] J. Thiele and H. Ingle, *Ann.*, **287**, 233 (1895).

[4] R. M. Herbst, C. W. Roberts, and E. J. Harvill, *J. Org. Chem.*, **16**, 139 (1951).

[5] R. M. Herbst and D. F. Percival, *J. Org. Chem.*, **19**, 439 (1954).

[6] R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).