[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetra- and Pentacyclic Benzimidazole Compounds as Analogs of Some Indole Alkaloids

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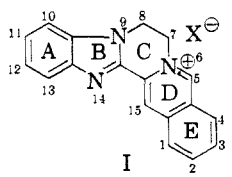
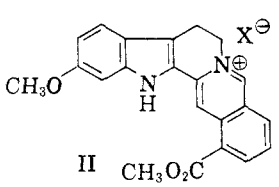
The preparation of the tetracyclic quaternary salt, 6,7-dihydrobenzimidazo[1,2-*a*]pyrido[2,1-*c*]pyrazinium bromide and its reduced form, 1,2,3,4,6,7-hexahydro-13*bH*-benzimidazo[1,2-*a*]pyrido[2,1-*c*]pyrazine is described. The synthesis of the corresponding pentacyclic quaternary salt, 7,8-dihydrobenzimidazo[1,2-*a*]isoquino[3,2-*c*]pyrazinium bromide and the form in which the D ring is reduced, 5,6,7,8-tetrahydro-14*bH*-benzimidazo[1,2-*a*]isoquino[3,2-*c*]pyrazine, is also described. The ultraviolet absorption curves are discussed.

Recent interest in benzimidazole analogs of physiologically active indole compounds, which has included the analogs of tryptophan[2] and serotonin[3,4] prompted us to report the synthesis of the benzimidazole analog (I) of the basic ring system of alstoniline[5,6] (II) as well as the corresponding tetracyclic quaternary salt (IV). It was hoped that such compounds or their reduced forms would possess hypotensive activity.



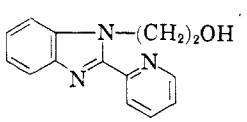
I



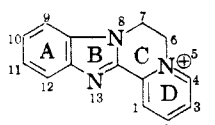
II

Attempts to benzoylate 2-phenylbenzimidazole have not been successful.[7] Furthermore, in our hands 2 - (2′ - pyridyl)benzimidazole[8] and 2 - (3′ - isoquinolyl)benzimidazole failed to alkylate in the 1 position with various active halides. In view of these findings it appeared necessary to introduce the substituent on the nitrogen of the 1 position prior to cyclization and introduction of an aryl group in the 2 position of the benzimidazole structure.

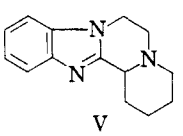
This approach was best achieved by treatment of *o*-nitrobromobenzene with ethanolamine forming *o*-nitro-*N*-(2-hydroxyethyl)aniline. Reduction of the nitro group provided *o*-amino-*N*-(2-hydroxyethyl)aniline which, in turn, was condensed with pyridine-2-carboxaldehyde in the presence of nitrobenzene to yield 1-(2′-hydroxyethyl)-2-(2′-pyridyl)benzimidazole (III). Treatment of III with refluxing hydrobromic acid effected ring closure to the quaternary salt, 6,7-dihydrobenzimidazo-[1,2-a]pyrido[2,1-*c*]pyrazinium bromide (IV). Reduction of the D ring of IV using hydrogen and platinum oxide gave the corresponding 1,2,3,4,6,7-hexahydro-13*bH*-benzimidazo[1,2-*a*]pyrido[2,1-*c*]-pyrazine (V).



III

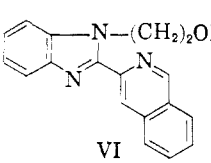


IV

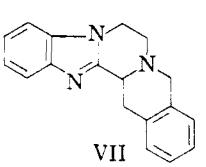


V

Isoquinoline-3-carboxaldehyde was similarly condensed with *o*-amino-*N*-(2-hydroxyethyl)aniline and gave 1-(2′-hydroxyethyl)-2-(3′-isoquinolyl)benzimidazole (VI). Also isolated from this reaction was a second product, a yellow solid melting at 246.5–247°. The identity of this material has not been established.



VI



VII

Treatment of VI with refluxing 48% hydrobromic acid effected ring closure to form 7,8-dihydrobenzimidazo[1,2-*a*]isoquino[3,2-*c*]pyrazium bromide (I). Reduction of the D ring using hydrogen and platinum oxide provided the 5,6,7,8-tetrahydro-14*bH* - benzimidazo[1,2 - *a*]isoquino[3,2 - *c*]pyrazine (VII).

Ultraviolet absorption spectra. Because of the interest in these compounds the ultraviolet absorption spectra of the 2-(2′-pyridyl)- and 2-(3′-isoquinolyl)benzimidazoles as well as the tetra- and pentacyclic quaternary salts and their reduced forms were examined.

The spectra of the benzimidazoles with a 2-pyridyl and 3-isoquinolyl group substituted in the

(1) Present address: Chas. Pfizer and Co., Inc., Brooklyn, N. Y.

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2 position of the benzimidazole were determined in ethanol and in 0.01*N* hydrochloric acid. The use of 0.01*N* hydrochloric acid as a solvent caused a broadening or smearing out in solution of the absorption peaks as well as a hyposochromic shift of the maxima and minima. 2-(3′-Isoquinolyl)benzimidazole shows some absorption above 340 mμ.

The spectra of the tetra- and pentacyclic quaternary salts, IV and I, in water, show absorption in the same general region as those of the pyridyl- and isoquinolyl- benzimidazoles in addition to absorption above 340 mμ. This absorption at longer wave lengths was anticipated because of the yellow color of the quaternary salts.

Reduction of the D ring of IV resulted in a compound (V) whose spectrum differed markedly from those thus far mentioned and was almost identical with those of 2-dialkylaminomethylbenzimidazoles.[3] The maxima and minima of the benzimidazole spectra are recorded in Table I.

TABLE I

ABSORPTION SPECTRA CHARACTERISTICS OF SOME BENZIMIDAZOLES

(Wave length in mμ)

Benzimidazole	Maxima	Minima	Shoulder
2-(2′-Pyridyl)[a]	240	237	245
	310	255	320
2-(3′-Isoquinolyl)[a]	235	265	
	280	288	
	322	334	
	339		
6,7-Dihydrobenzimidazo-[1,2-*a*]pyrido[2,1-*c*]-pyrazinium bromide[b]	245	233	
		265	
7,8-Dihydrobenzimidazo-[1,2-*a*]isoquino[3,2-*c*]-pyrazinium bromide[b]	247	261	286
	281	300	
	337		
1,2,3,4,6,7-Hexahydro-13*bH*-benzimidazo[1,2-*a*]-pyrido[2,1-*c*]pyrazine[a]	254	228	
	275	264	
	282	279	
2-Dialkylaminomethyl[c]	245	226	248
	277	260	
	283	278	

[a] In 95% ethanol. [b] In water. [c] Ref. 9.

EXPERIMENTAL[10,11]

Preparation of benzimidazoles. o-Nitro-N-(2-hydroxyethyl)-aniline. To 190 ml. of ethanolamine containing 27.5 g. (0.24 mole) of *o*-nitrobromobenzene was added 4.5 g. of anhydrous cupric chloride. The resulting mixture was heated on a steam bath for 90 min., care being taken that the temperature did not rise above 90°. The reaction mixture was then poured into ice and water. Filtration and drying of the solid which precipitated gave 39.7 g. (93%) of an orange colored product m.p. 71.5–73°. Recrystallization from aqueous ethanol raised the melting point to 72.5–73.5°. Ramage and Trappe report m.p. 74–75° for this compound.[12]

Anal. Calcd. for $C_8H_{10}O_3N_2$: C, 52.7; H, 5.5; N, 15.4. Found: C, 53.0; H, 5.6; N, 15.3.

o-Amino-N-(2-hydroxyethyl)aniline. Fifty-one and seven-tenths g. (0.28 mole) of *o*-nitro-*N*-(2-hydroxyethyl)aniline, 24 ml. of 20% sodium hydroxide, and 120 ml. of 95% ethanol were heated to reflux on a steam bath with constant stirring. The source of heat was removed and 78 g. of zinc dust gradually added over a period of 45 min. Heating on the steam bath was then resumed and continued until the solution was colorless. The mixture was filtered rapidly with suction and the filtrate evaporated to dryness *in vacuo*. Eighty ml. of cold water was added to the residue and the undissolved solid filtered and dried, m.p. 101–104°. Recrystallization from water (Norit) gave 17.5 g. (40.6%) of diamine, m.p. 104.5–106.5°.

Ramage and Trappe[12] and Kremer[13] report m.p. 105–106° and 106–106.5°, respectively, for this compound.

Anal. Calcd. for $C_8H_{12}ON_2$: C, 63.1; H, 8.0; N, 18.4. Found: C, 63.4; H, 8.0; N, 18.6.

1-(2′-Hydroxyethyl)-2-(2′-pyridyl)benzimidazole (III). To 120 ml. of nitrobenzene containing 21.7 g. (0.2 mole) of pyridine-2-carboxaldehyde was added 30.4 g. (0.2 mole) of *o*-amino-*N*-(2-hydroxyethyl)aniline. The mixture was heated slowly during 1 hr. to the boiling point of the solvent and maintained at this temperature for 10 min. After cooling the reaction mixture overnight in an ice box the tan solid which separated was filtered and washed with 25 ml. of ether, yield 22.2 g. (47%), m.p. 126–127.5°. Two recrystallizations of the product from toluene (Norit) gave 18.0 g. (38%) of III, m.p. 129–129.8°. Further concentration of the mother liquors gave an additional 1.2 g. of a less pure material.

Anal. Calcd. for $C_{14}H_{13}ON_3$: C, 70.3; H, 5.5; N, 17.6. Found: C, 70.6; H, 5.6; N, 17.6.

6,7-Dihydrobenzimidazo[1,2-a]pyrido[2,1-c]pyrazinium bromide (IV). Eighteen g. (0.075 mole) of III was added to 230 ml. of 48% hydrobromic acid and the mixture refluxed for 4 hr. Evaporation of the acid solution to dryness and trituration of the residue with acetone gave 32.7 g. of an orange-brown solid. Two recrystallizations from aqueous ethanol gave 15.8 g. (70%) of a yellow solid melting at 341° with decomposition.

Anal. Calcd. for $C_{14}H_{12}N_3Br$: C, 55.6; H, 4.0; N, 13.9; Br, 26.5. Found: C, 55.9; H, 4.1; N, 13.9; Br, 26.5.

1,2,3,4,6,7-Hexahydro-13bH-benzimidazo[1,2-a]pyrido[2,1-c]pyrazine (V). Eight g. (0.027 mole) of IV was dissolved in 100 ml. of water and hydrogenated over 100 mg. of platinum oxide at an initial pressure of 48 p.s.i. After 30 min. the theoretical amount of hydrogen had been taken up and the catalyst was filtered. The colorless solution, which had been orange prior to reduction, was made strongly basic with 10% sodium hydroxide. Cooling and scratching induced crystallization of a colorless solid which was filtered and dried, 5.1 g., m.p. 158.5–160°.

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 74.0; H, 7.5; N, 18.5. Found: C, 74.2; H, 7.3; N, 18.2.

1-(2′-Hydroxyethyl)-2-(3′-isoquinolyl)benzimidazole (VI). To 40 ml. of nitrobenzene containing 15.7 g. (0.1 mole) of isoquinoline-3-carboxaldehyde[14] was added 15.2 g. (0.1 mole) of *o*-amino-*N*-(2-hydroxyethyl)aniline and the mixture heated gradually during 1 hr. to the boiling point of the nitrobenzene. After maintaining the temperature at this point for 15 min., the solution was allowed to cool and was

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(10) All melting points were done in open capillaries and are not corrected.

(11) Analyses were done by Micro-Tech Laboratories, Skokie, Ill.

(12) G. R. Ramage and G. Trappe, *J. Chem. Soc.*, 4406 (1952).

(13) C. B. Kremer, *J. Am. Chem. Soc.*, **61**, 1321 (1939).

(14) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).

stored overnight in an ice box. The precipitate which formed was filtered and washed with ether to give 10.7 g. of crude product, m.p. 136.5–138°. Several recrystallizations from toluene gave 6.3 g. (21.8%) of VI, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{18}H_{15}ON_3$: C, 74.7; H, 5.2; N, 14.5. Found: C, 74.9; H, 5.3; N, 14.7.

Further cooling of the mother liquor from the reaction mixture gave a second crop of material which when recrystallized from toluene gave 4.1 g. of a yellow solid, m.p. 246.5–247°.

Refluxing this latter product with tetralin for 3 hr. left it unchanged. The product was not further characterized.

7,8-Dihydrobenzimidazo[1,2-a]isoquino[3,2-c]pyrazinium bromide (I). Two and nine-tenths g. (0.01 mole) of VI was added to 30 ml. of 48% hydrobromic acid and the mixture refluxed for 4 hr. The resulting dark red solution was evaporated to dryness. Trituration of the light tan residue with acetone gave 5.0 g. of crude product. Recrystallization from water gave 2.1 g. (60%) of the yellow quaternary salt, m.p. 347–348° with decomposition. The analytical sample was recrystallized again from water, m.p. 355–356° with decomposition.

Anal. Calcd. for $C_{18}H_{14}N_3Br$: C, 61.4; H, 4.0; N, 11.9; Br, 22.7. Found: C, 61.1; H, 4.1; N, 11.7; Br, 22.8.

5,6,7,8-Tetrahydro-14bH-benzimidazo[1,2-a]isoquino[3,2-c]pyrazine (VII). Three and seven-tenths g. (0.01 mole) of I was suspended in 200 ml. of water at 55°, and hydrogenated over 50 mg. of platinum oxide at an initial pressure of 47 p.s.i. After 2 hr. the hot solution was filtered and the filtrate made basic with ammonium hydroxide. The precipitate was filtered and dried, yield 1.9 g., m.p. 211–216°. Repeated recrystallizations from ethyl acetate gave the pure product, m.p. 221–223°.

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.5; H, 6.2; N, 15.3. Found: C, 78.6; H, 6.2; N, 15.5.

2-(3′-Isoquinolyl)benzimidazole. Thirty and nine-tenths g. (0.2 mole) of isoquinoline-3-carboxaldehyde[14] and 21.2 g. (0.2 mole) of *o*-phenylenediamine were added to 80 ml. of nitrobenzene and the mixture gradually heated during 40 min. to the boiling point of the nitrobenzene. This temperature was maintained for 10 min., then the reaction mixture was allowed to cool. After standing overnight in an ice box the tan solid which separated was filtered and washed with benzene, yield 28.7 g. Recrystallization of the crude product from toluene gave 20.7 g., m.p. 193–194°.

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.3; H, 4.5; N, 17.1. Found: C, 78.3; H, 4.6; N, 17.2.

Attempted alkylations of 2-arylbenzimidazoles. Attempts to alkylate 2-(2′-pyridyl)benzimidazole[8] with ethylene chlorohydrin in boiling toluene, with ethyl bromoacetate in absolute ethanolic potassium hydroxide at room temperature, or with allyl bromide in hot, absolute ethanolic sodium ethoxide were unsuccessful. The pyridylbenzimidazole was recovered from the reaction mixtures. 2-(3′-Isoquinolyl)-benzimidazole failed to give identifiable alkylation products with ethylene chlorohydrin in dioxane or with ethyl bromoacetate in hot, absolute ethanolic potassium hydroxide.

Absorption spectra. Ultraviolet absorption spectra were determined using a Beckman recording spectrophotometer, Model DK-2.

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Tetrazole Analogs of Aminobenzoic Acid Derivatives[1]

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The three isomeric 5-nitrophenyltetrazoles and 5-(2′-hydroxy-4′-nitrophenyl)tetrazole have been prepared from the corresponding benzonitriles. Reduction of the 5-nitrophenyltetrazoles resulted in the formation of the corresponding 5-aminophenyltetrazoles which included the tetrazole analogs of *p*-aminobenzoic acid, *m*-aminobenzoic acid, and 2-hydroxy-4-aminobenzoic acid.

In recent years two aminobenzoic acid derivatives have been prominent in chemotherapy. *p*-Aminobenzoic acid plays a unique role in metabolism as a portion of folic acid, an essential material for the synthesis of nucleic acids. Evidence that certain drugs structurally related to *p*-aminobenzoic acid can inhibit its incorporation into folic acid[4] resulted in the application of the antimetabolite concept in chemotherapy as a means of combating bacterial invasion of the body. Those drugs which have been most effective in interfering with the utilization of *p*-aminobenzoic acid have been shown to be related to sulfanilamide[5] and have been used widely in the therapy of staphylococcal and pneumococcal infections. The second aminobenzoic acid derivative, important for its tuberculostatic activity,[6] is 2-hydroxy-4-aminobenzoic acid commonly referred to as *p*-aminosalicylic acid.

Because of the acidic nature of 5-substituted tetrazoles[7–9] the replacement of the carboxyl group of the aminobenzoic acids by the 5-tetrazolyl group should result in compounds of similar acidity and solubility. The possibility that the tetrazolyl analogs of the aminobenzoic acids might

(1) Based on a thesis submitted to Michigan State University in 1958 by James M. McManus in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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