4-Aminoquinoline was formed when 4-chloroquinoline (from 4-quinolinol[90] by reaction with phosphorus oxychloride) was dissolved in phenol and treated with ammonia at about 170°.[91-93] After crystallization from benzene, the melting point was 155–155.5°.

The **5- and 8-aminoquinolines** were obtained by the reduction over Raney nickel in alcohol[94] of the mixed nitro compounds resulting from the nitration of quinoline.[51] The 5-amino compound was crystallized from alcohol, m. p. 110–111°; the 8-isomer melted at 65–66° after crystallization from octane.

7-Aminoquinoline was obtained through a Skraup reaction[95,96] followed by reduction[94]; the anhydrous form[97] was obtained, after crystallization from water, by thorough drying, m. p. 94–94.5°.

4-Dimethylaminoquinoline was prepared from 4-chloroquinoline in a manner similar to that used for the 2-isomer; it was isolated as the monohydrochloride, needles from alcohol–ether, m. p. 214.5–215°.

Anal. Calcd. for $C_{11}H_{12}N_2 \cdot HCl$: Cl, 17.10; N, 13.48. Found: Cl, 16.93; N, 13.45, 13.60.

6-Dimethylaminoquinoline was formed by a Skraup synthesis[95,96]; the compound oxidized very readily in the air, hence was recrystallized from pentane under dry nitrogen, pale yellow warts, m. p. 52–53°. This compound was used immediately, for it turned black within a day or two.

1-Aminoisoquinoline was formed by the amination of isoquinoline with sodamide,[4,86] and crystallized from water as white needles, m. p. 123–123.5°.

4-Aminoisoquinoline was obtained by bromination of isoquinoline and then reaction of the 4-bromo compound with cuprammonium sulfate–ammonia.[98] It crystallized from benzene, creamy white needles of m. p. 109–109.5°.

5-Aminoisoquinoline was prepared by catalytic reduction of the nitro compound in alcohol with palladium–charcoal.[99] The base recrystallized well from chloroform–hexane in the form of yellowish leaflets, m. p. 129.5–130°.

Dimethyl-α-naphthylamine was available commercially; it was redistilled immediately before use.

Dimethyl-β-naphthylamine was prepared essentially as described by Hodgson and Crook,[100] modified slightly on the basis of earlier work on the α-isomer.[101] The resublimed sample melted 46.5–47°.

Acknowledgments.—The authors are pleased to express their appreciation to Mrs. N. P. Gorman for preparative assistance and to Mrs. C. M. Grant and Mr. M. Priznar for aid in the spectrophotometric studies. The development of the present contribution was materially aided by discussions with Dr. F. C. Nachod. Dr. C. J. Cavallito was kind enough to furnish several intermediates used in this work. The analytical staff of the Institute, under the direction of Mr. M. E. Auerbach, carried out requisite analyses.

Summary

1. The ultraviolet absorption spectra have been determined for all of the isomeric amino derivatives of pyridine and quinoline and also for several aminoisoquinolines.

2. Spectrophotometric evidence is in essential agreement with other physical and chemical data in the assignment of an imine structure to the amino pyridines, quinolines and isoquinolines where the substituent is in the α- or γ-position relative to the ring nitrogen. The other isomers exhibit the characteristics of the naphthylamines, the amino group being aromatic in character.

(90) Cavallito and Haskell, THIS JOURNAL, **66**, 1166 (1944).
(91) Andersag, Breitner and Jung, U. S. Patent 2,233,970; *Chem. Abs.*, **35**, 3771 (1941).
(92) Steck, Hallock and Holland, THIS JOURNAL, **68**, 129 (1946).
(93) Elderfield, Gensler, Birstein, Kreysa, Maynard and Galbreath, *ibid.*, **68**, 1250 (1946).
(94) Winterbottom, *ibid.*, **62**, 160 (1940).
(95) Knueppel, *Ber.*, **29**, 706 (1896).
(96) Manske, Leger and Gallagher, *Can. J. Research*, **B19**, 318 (1941).
(97) Hamer, *J. Chem. Soc.*, **119**, 1436 (1921).
(98) Craig and Cass, THIS JOURNAL, **64**, 783 (1942).
(99) Misani and Bogert, *J. Org. Chem.*, **10**, 358 (1945); LeFèvre and LeFèvre, *J. Chem. Soc.*, 1475 (1935).
(100) Hodgson and Crook, *ibid.*, 1502 (1936).
(101) Gokhlé and Mason, *ibid.*, 1757 (1930).

RENSSELAER, NEW YORK RECEIVED NOVEMBER 3, 1947

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Absorption Spectra of Heterocyclic Compounds. III. Some Benzimidazole Derivatives

BY EDGAR A. STECK, FREDERICK C. NACHOD, GALEN W. EWING[1] AND NANCY H. GORMAN

Introduction

Interest in the absorption spectra of 2-dialkylaminomethylbenzimidazoles was aroused by the description of two compounds of this type as colored substances.[2,3] There was little reason to expect that the replacement of a methyl by a dialkylaminomethyl group would result in a bathochromic effect. In our hands, none of the compounds of either the 2-methyl or the 2-dialkylaminomethyl benzimidazole type were obtained in colored form when pure, but, nonetheless, the absorption spectra were studied. Matters relating to 2-dialkylaminomethylbenzimidazoles led to investigation of the spectral characteristics of two 2-aminobenzimidazoles.

Imidazoles have long been considered as cyclic amidines (*cf.* ref. 4) and are the most basic of the imide-containing azoles.[5-7] Because imidazole derivatives occupy a position of importance in matters relative to the constitution of heterocycles as well as in biochemistry, their physical proper-

(1) Present address: Department of Chemistry, Union College, Schenectady 8, New York.
(2) Bloom and Day, *J. Org. Chem.*, **4**, 14 (1939).
(3) Roeder and Day, *ibid.*, **6**, 25 (1941).
(4) Bamberger, *Ann.*, **273**, 300 (1893).
(5) Sen and Ray, *J. Chem. Soc.*, 646 (1926).
(6) Schwarzenbach and Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940).
(7) Wheland, The Theory of Resonance, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 180.

TABLE I

BENZIMIDAZOLE DERIVATIVES

Benzimidazole	Yield, %	Solvent[a]	Appearance	M. p., °C.[b]	N Analyses, % Calcd.	Found
2-Dimethylaminomethyl	87	BS	White needles	132.5–153	23.99	24.05
2-Diethylaminomethyl[c]	86	E	White needles	166.5–167	20.69	20.79
2-Dipropylaminomethyl	81	aAc	White needles	180.5–181	18.28	18.41
2-Diisopropylaminomethyl	84	aE	Felted white needles	178–178.5		18.57
5(6)-Chloro-2-chloromethyl	84	OS	Creamy needles	133.5–134	13.95	14.10
5(6)-Chloro-2-piperidinomethyl[d]	78	EO	White needles	>250	13.07	13.16
2-Amino-5(6)-chloro[e]	71	B	Creamy needles	164.5–165	25.10	25.33

[a] Ac, acetone; B, benzene; E, ethanol; O, ether; S, hexane; a, aqueous. [b] Uncorrected. [c] *Cf.* ref. 2. [d] Isolated as the dihydrochloride. [e] *Cf.* ref. 18.

ties have been investigated rather well,[6,8–13] including a mathematical treatment of resonance forms.[14] Although it has not been established unequivocally that the nucleus has true, conjugated double-bond character, imidazoles have been shown, as cyclic amidines, to have charges present on the nitrogen atoms in a system possessing some degree of hindered resonance. The imidazoles in which the imino hydrogen has not been replaced by some other group exhibit considerable association, as is evidenced by many properties. It is also apparent that the ring system possesses greater polarity than the related pyrazole, but not to such an extent as expected from the classical polar formula.

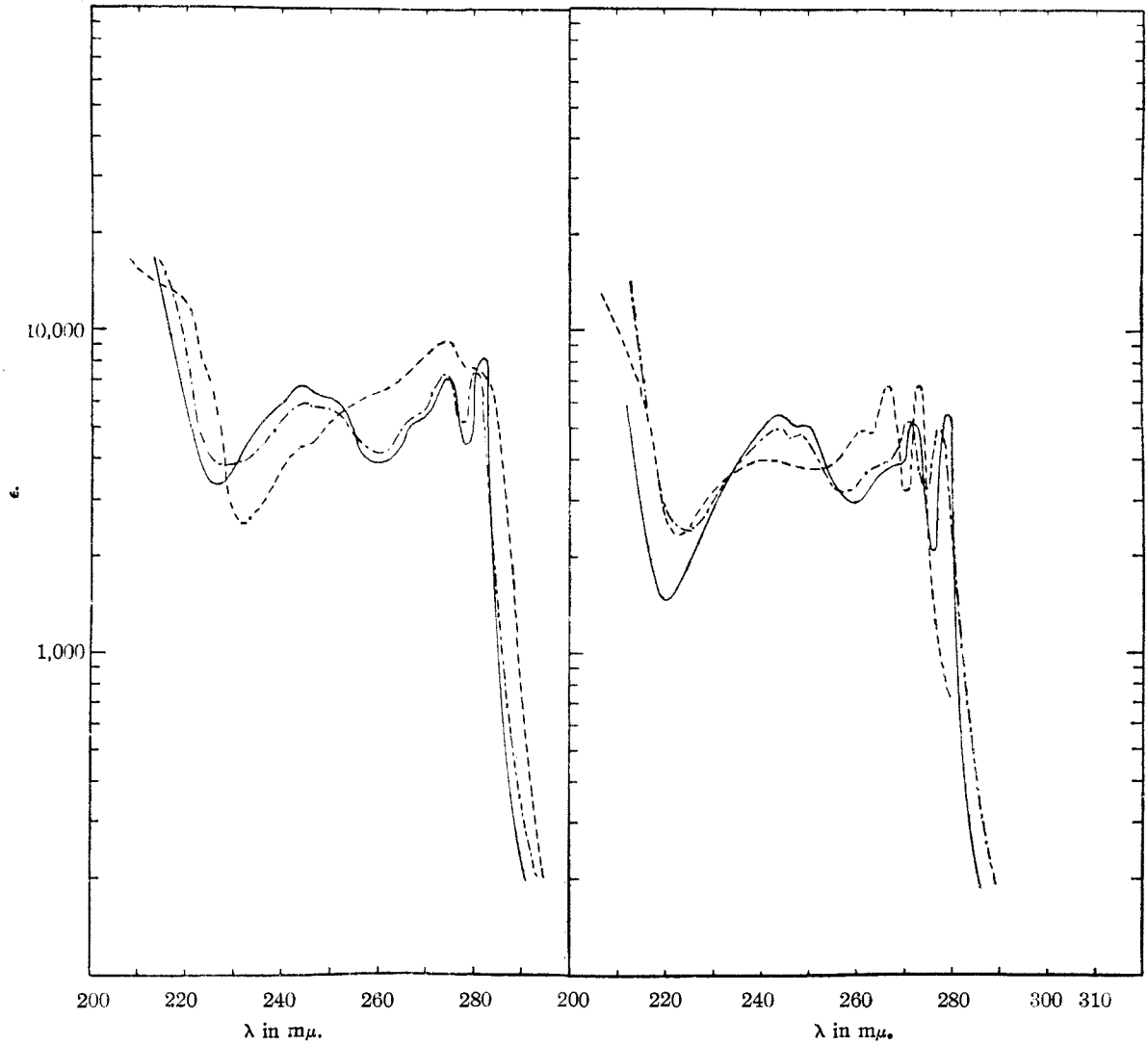
Preparation of Benzimidazoles

Benzimidazole, 2-chloromethylbenzimidazole, and their 5(6)-chloro analogs were prepared by the Phillips procedure.[2,15,16] The reaction of the 2-chloromethyl compounds with secondary amines was accomplished after the method of Bloom and Day.[2] 2-Dimethylaminomethylbenzimidazole, earlier reported[2] as yellow in color, was obtained as a white product by chromatographic adsorption on alumina. The 2-aminobenzimidazole and its 5(6)-chloro analog were synthesized as described by Pierron.[17,18] Table I summarizes data pertinent to the new compounds involved in this study.

Discussion

That the variation in the chain length of alkyl groups in the 2-dialkylaminomethyl benzimidazoles from methyl to *n*-butyl (the isopropyl was not studied) resulted in no apparent changes in the structure was evident in the spectra. The absorption spectra of all compounds studied followed the same pattern in any one solvent, were it ethanol, 0.01 *N* hydrochloric acid or 0.01 *N* sodium hydroxide. The curves shown in Fig. 1 represent the results obtained with dimethylaminomethyl-, diethylaminomethyl-, di-*n*-propylaminomethyl- and di-*n*-butylaminomethylbenzimidazole in the several media, all of which were the same within the limits of experimental accuracy. All compounds showed no absorption above 300 mμ, as expected. Earlier studies in the quinoline series[19] had indicated that the structure of these benzimidazole derivatives would probably resemble the parent heterocyclic type. Thus, these 2-dialkylaminomethylbenzimidazoles would probably be similar in nature to 2-methylbenzimidazole in alcohol and show corresponding spectral characteristics. This prediction was supported to an outstanding extent when the data of Behaghel and Schneider[8] on the absorption spectrum of 2-methylbenzimidazole in methanol were compared with our values on the 2-dialkylaminomethylbenzimidazoles in ethanol. Table II shows the striking similarities in maxima, and minima as well, of 2-methyl- and the 2-dialkylaminomethylbenzimidazoles. The spectrum of benzimidazole in ethanol also included in Table II (*cf.* also Fig. 2) is very closely similar to those given, even to a shoulder at 248 mμ. The spectra of the 2-dialkylaminomethylbenzimidazoles in acid do show a measure of similarity to that obtained in ethanol or alkali (Fig. 1), but most of the fine structure which was apparent in the last two solvents exists only to a minor degree. The shoulders observable are quite probably the results of shiftings in the active tautomerism in the imidazole moiety by the nucleophilic dialkylamino residue. That the dialkylamino group should cause enhanced basicity in compounds related to those here studied is well evidenced in the work of Roeder and Day.[3] The various 2-(α-dialkylaminoethyl)-benzimidazoles formed only dihydrochlorides, whereas 2-(α-alkylaminoethyl)-benzimidazoles yielded monohydrochlorides. The differences in the maxima of the spectra in acidic and basic media are indicative that the ease of cation and anion formation by the ring nitrogen in the 2-dialkylaminomethyl benzimidazoles is not the same as that of 2-methylbenzimidazole, as is expected.

(8) Behaghel and Schneider, *Ber.*, **69B**, 92 (1936).
(9) Kohlrausch and Seka, *ibid.*, **71B**, 985 (1938).
(10) Hückel, Datow, and Simmersbach, *Z. physik. Chem.*, **A186**, 129 (1940).
(11) Hunter and Marriott, *J. Chem. Soc.*, 777 (1941).
(12) Jensen and Friediger, *Chem. Zentr.*, I, 416 (1944).
(13) Syrkin and Shott-L'vova, *Acta Physicochem., U. R. S. S.*, **20**, 397 (1945).
(14) Hill and Branch, *Science*, **91**, 145 (1940).
(15) Phillips, *J. Chem. Soc.*, 2393 (1928).
(16) Skolnik, Miller and Day, THIS JOURNAL, **65**, 1854 (1943).
(17) Pierron, *Ann. chim.*, [8] **15**, 189 (1908).
(18) Since this work was completed, Leonard, Curtin and Beck [THIS JOURNAL, **69**, 2460 (1947)] reported the preparation of 2-amino-5(6)-chlorobenzimidazole.
(19) Steck and Ewing, THIS JOURNAL, **70**, 3397 (1948).



Figs. 1 and 2.—Absorption spectra of 2-dialkylaminomethyl benzimidazoles and of benzimidazole in — 95% ethanol, - - - - 0.01 *N* HCl, and —·—· 0.01 *N* NaOH.

TABLE II

SPECTRAL CHARACTERISTICS OF CERTAIN BENZIMIDAZOLES

Wave length in mμ in (log ε)

	2-Methyl[a]	2-Dialkyl-aminomethyl[b]	Benzimid-azole[b]
Maxima	245 (4.1)	245 (3.8)	244 (3.74)
	274 (4.06)	277 (3.9)	272 (3.71)
	280 (4.18)	283 (3.8)	279 (3.73)
Minima	225 (3.55)	226 (3.53)	220 (3.16)
	258 (3.6)	260 (3.6)	260 (3.46)
	277 (3.7)	278 (3.7)	278 (3.32)
Shoulder	[c]	248 (3.8)	248 (3.7)

[a] Data of Behaghel and Schneider[8] (in methanol). [b] In ethanol. [c] Insufficient detail from the curves obtained with quartz spectrograph to distinguish possible detail.

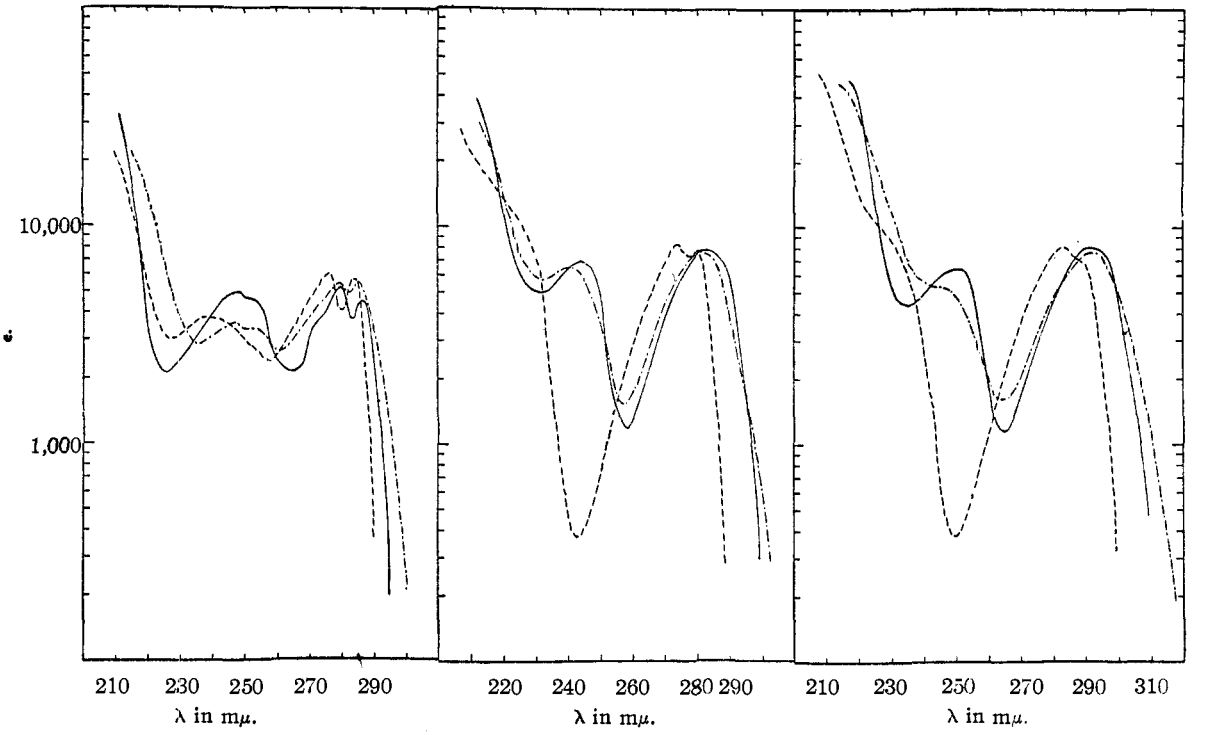
In the comparison of the spectral characteristics of benzimidazole, 5(6)-chlorobenzimidazole, and their related 2-amino derivatives, it appears to be necessary to integrate the discussion through grouping the compounds in pairs. Benzimidazole and the 5(6)-chloro analog will be first, next benzimidazole and 2-aminobenzimidazole will be treated, and, finally, 2-aminobenzimidazole and the related 5(6)-chloro compound (*cf.* Table III).

TABLE III

SPECTRAL CHARACTERISTICS OF BENZIMIDAZOLE AND ITS CHLORO- AND AMINO-SUBSTITUTION PRODUCTS IN ETHANOL

Wave length in mμ and (log ε)

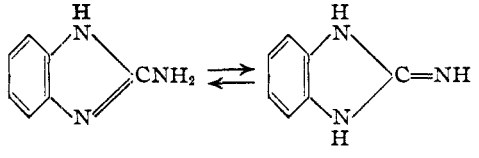
	Benzimidazole	5(6)-Chloro-	2-Amino-	5(6)-Chloro-2-amino-
Maxima	244 (3.74)	248 (3.69)	244 (3.83)	251 (3.80)
	272 (3.71)	280 (3.72)	283 (3.89)	292 (3.91)
	279 (3.73)	286 (3.65)		
Minima	220 (3.16)	225 (3.32)	231 (3.70)	235 (3.64)
	260 (3.46)	264 (3.33)	258 (3.08)	265 (3.06)
	278 (3.32)	284 (3.58)		
Shoulder	258 (3.7)	253 (3.40)		



Figs. 3, 4 and 5.—Absorption spectra of 5(6)-chlorobenzimidazole, 2-aminobenzimidazole, and 5(6)-chloro-2-aminobenzimidazole in — 95% ethanol, - - - - 0.01 *N* HCl and, —·— 0.01 *N* NaOH.

As will be seen in a comparison of Figs. 2 and 3, the introduction of a chlorine into position 5(6) of the benzimidazole nucleus causes several alterations in the spectra despite a retention of the fundamental character of the several curves. The mildly auxochromic nature of the halogen results in shifting a portion of the spectra, from *ca.* 250 mμ, in a bathochromic manner. There is also a diminished difference in the extinction coefficients of the related maxima and minima in the case of 5(6)-chlorobenzimidazole. In the region of 240–260 mμ, the extinction coefficients of the two compounds are most widely separated in alcohol and 0.01 *N* sodium hydroxide. These effects are, in all probability, results of the influence of the halogen substituent upon the tautomeric state within the benzimidazole system, but there appears to be little further conclusion possible at this time.

The relations of the spectral characteristics in the several solvents for benzimidazole and its 2-amino derivative are to be seen in Figs. 2 and 4. In 2-aminobenzimidazole the amino group renders possible an active guanidine type of tautomerism, thus



The extent of the prototropy seems to be sufficiently appreciable in alcohol to obliterate almost all of the fine structure of the parent compound as shown by an hyperchromic shift. In acid, a bare "memory" of the fine structure is retained, doubtlessly an indication of the formation of a cation of the guanidinium type (*cf.* refs. 11, 20). There is a bathochromic shift of *ca.* 10 mμ from *ca.* 250 mμ in the three solvents employed for the compounds. These observations are not in disharmony with investigations carried out on the structure of guanidine types.[11,21,22]

A comparison of the spectra of 2-aminobenzimidazole and its 5(6)-chloro derivative (Figs. 4 and 5) gives indication of a relationship rather akin to that noted above for the parent compounds (Figs. 2 and 3). The chloro group apparently continues to exert an auxochromic effect, and most of the curves are shifted toward longer wave lengths by *ca.* 10 mμ. In this case there is a diminished accentuation of the minima, while the heights of the maxima are essentially unchanged throughout. There may be some interplay of the influences of the 5(6)-chloro and the 2-amino groups upon the tautomeric state within the molecule (*cf.* ref. 11, wherein the presence of a 5(6)-substituent modified the tendency for association of a 2-substituted benzimidazole). An extension of our conclusions seems unwarranted at this time.

(20) Lecher and Graf, *Ann.*, **438**, 154 (1924); **445**, 61 (1925).
(21) Graubner, *Chem. Zentr.*, **100**, I, 2068 (1929).
(22) Kellner, *Proc. Royal Soc. (London)*, **A177**, 456 (1941).

Experimental[23]

I. **Preparation of Benzimidazoles.**—Benzimidazole was obtained by the method of Phillips,[15] m. p. 170.5–171° (lit. m. p. 170°); the 5(6)-chloro analog was made similarly, m. p. 121–121.5° (lit.[24] m. p. 125°).

Anal. Calcd. for $C_7H_5ClN_2$: N, 18.34. Found: N, 18.24.

2-Chloromethylbenzimidazole[2,15] and the related 5(6)-chloro compound were formed by the Phillips synthesis. The properties of the latter substance were closely akin to the parent, the chloro group attached to position 2 showing allylic character (*cf.* ref. 16). When 5(6)-chloro-2-chloromethylbenzimidazole was boiled in water, a titration of the resulting chloride ion indicated that *ca.* 98% of the halogen in position 2 had been liberated.

Anal. Calcd. for $C_8H_6Cl_2N_2$: Cl (one), 17.64. Found: Cl, 17.34.

The several 2-dialkylaminomethylbenzimidazoles which were required were prepared from the 2-chloromethyl compound and a secondary amine in ethereal alcoholic solution.[2] Purification of the products was markedly facilitated by passage of their solutions through a column of activated alumina.[25] 2-Dimethylaminomethylbenzimidazole was most tedious of purification and it seemed of interest to study it microscopically.[26] The compound crystallizes in the form of blades which show oblique extinction; it is dimorphic and both the stable and unstable forms show anomalous polarization colors; the refractive index varies considerably with the wave length of light used.

(23) The melting points reported are not corrected for stem emergence.

(24) O. Fischer, *Ber.*, **37**, 556 (1904).

(25) Purchased from Aluminum Ore Co., East St. Louis, Ill., Grade F20, −80 mesh.

(26) Dr. Robert L. Clarke of this Institute was kind enough to carry out the microscopic studies here reported.

2-Aminobenzimidazole and its 5(6)-chloro analog were synthesized by the method of Pierron.[17,18]

The data pertinent to the new compounds are summarized in Table I.

II. **Absorption Spectra.**—The absorption spectra were all determined with a Beckman Quartz Spectrophotometer, Model DV, Serial No. D-377, as described in the first paper of this series.[27] All solvents herein employed met the conditions earlier noted.

Acknowledgments.—The authors wish to express their appreciation to Mrs. M. Becker and Mr. M. Priznar for their aid in the spectrophotometric studies, and to Mrs. B. Beecher for the careful plotting of the results. Most of the analyses have been due to the efforts of the group under the direction of Mr. M. E. Auerbach of this Institute.

Summary

1. Several new 2-dialkylaminomethyl benzimidazole type compounds have been prepared. 2-Diethylaminomethylbenzimidazole, earlier reported as a colored substance, has been obtained white when pure.

2. The absorption spectra of a number of benzimidazoles have been determined in alcohol, 0.01 *N* hydrochloric acid and 0.01 *N* sodium hydroxide. Certain features of the results obtained were emphasized due to bearing upon the structures involved.

(27) Ewing and Steck, THIS JOURNAL, **68**, 2181 (1946).

RENSSELAER, N. Y. RECEIVED DECEMBER 30, 1947

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Absorption Spectra of Heterocyclic Compounds. IV. Some Bz-Halo-4-aminoquinoline Derivatives[1]

BY EDGAR A. STECK, GALEN W. EWING[2] AND FREDERICK C. NACHOD

Introduction

The interest in 4-aminoquinoline types was heightened markedly when tablets of an antimalarial drug, seized during the North African campaign of the World War II, were found to contain the methane bis-1,1′-(2-hydroxy-3-naphthoate) of 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-3-methylquinoline.[3] These laboratories participated in the program of the Office of Scientific Research and Development[4] in this field, which led to the production of Aralen[5] (Chloroquine,[6] 7-chloro-4-(4′-diethylamino-1′-methylbutylamino)-quinoline,[7] (SN 7618[8]). The present contribution commenced as an adjunct in the characterization of 7-halo-4-aminoquinolines and their congeners, and expanded with the scope of the program of research in this Institute to include some theoretical aspects. A portion of the investigation was co-extensive with that of Irvin and Irvin,[9] who employed some compounds submitted by us to the OSRD. All compounds herein discussed have one halogen attached to the benzenoid moiety of a 4-aminoquinoline derivative. In the instance of the 3-methyl series, the 5-iodo compound is the only missing member of

(1) This paper was presented before the 113th meeting of the A. C. S. in Chicago, April 19–23, 1948.

(2) Present address: Department of Chemistry, Union College, Schenectady 8, N. Y.

(3) The identification was made November 12, 1943, by Mr. Irwin S. Shupe, now Assistant Director of Control, Winthrop–Stearns, Inc. Each tablet contained 3.25 grains of the salt or 1.5 grains of base.

(4) *Cf.* Elderfield, *Chem. Eng. News*, **24**, 2598 (1946).

(5) Registered mark of Winthrop–Stearns, Inc., for its brand of Chloroquine.

(6) Loeb, *et al.*, *J. Am. Med. Assoc.*, **130**, 1069 (1946).

(7) (a) Andersag, Breitner and Jung, U. S. Patent, 2,233,970; (b) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(8) This code number was assigned by the OSRD, Survey of Antimalarial Drugs. Data relating to the testing of the compounds are tabulated in a monograph "Antimalarial Drugs, 1941–1946," edited by Wiselogle, Edwards Bros., Ann Arbor, Mich., 1946.

(9) Irvin and Irvin, THIS JOURNAL, **69**, 1091 (1947).