

Department of Chemistry, University of Pennsylvania

1,2,3-Benzotriazines. I.

The Synthesis of Some Benzimidazo[1,2-c][1,2,3]-benzotriazines and

Naphth[1',2'(2',1'):4,5]imidazo[1,2-c][1,2,3]benzotriazine (I)

Laura L. Zaika and Madeleine M. Joullie'

A number of substituted benzimidazo[1,2-c][1,2,3]benzotriazines were prepared by the diazotization of the appropriate 2-(*o*-aminophenyl)benzimidazoles. Diazotization of 2-(*o*-aminophenyl)naphth[1,2-d]imidazole yielded a new heterocyclic ring system. Various methods of preparation of 2-(*o*-aminophenyl)benzimidazoles were investigated. The condensation of *o*-phenylenediamines with anthranilic acids, in the presence of polyphosphoric acid, provided a convenient route to 2-(*o*-aminophenyl)benzimidazoles but in several cases the products were contaminated with considerable amounts of 6-(*o*-aminophenyl)benzimidazo[1,2-c]quinazolines. 2-(*o*-Aminophenyl)benzimidazoles were also obtained by the catalytic hydrogenation of 2-(*o*-nitrophenyl)benzimidazoles which resulted from the condensation of an *o*-phenylenediamine with an *o*-nitrobenzaldehyde in ethanol, nitrobenzene or acetic acid. When the condensation was carried out in nitrobenzene, small amounts of 2-(*o*-aminophenyl)benzimidazoles were also formed. The Weidenhagen synthesis, which involves the reaction of an aromatic diamine with an aldehyde in the presence of copper acetate and subsequent decomposition of the cuprous salt of the benzimidazole, yielded 2-(*o*-aminophenyl)benzimidazoles instead of the expected 2-(*o*-nitrophenyl)benzimidazoles when the decomposition was carried out in ethanol. When the cuprous salt was treated with hydrogen sulfide in dilute hydrochloric acid, a mixture of amino- and nitrobenzimidazoles resulted. The ultraviolet and infrared spectra of all the compounds prepared were examined.

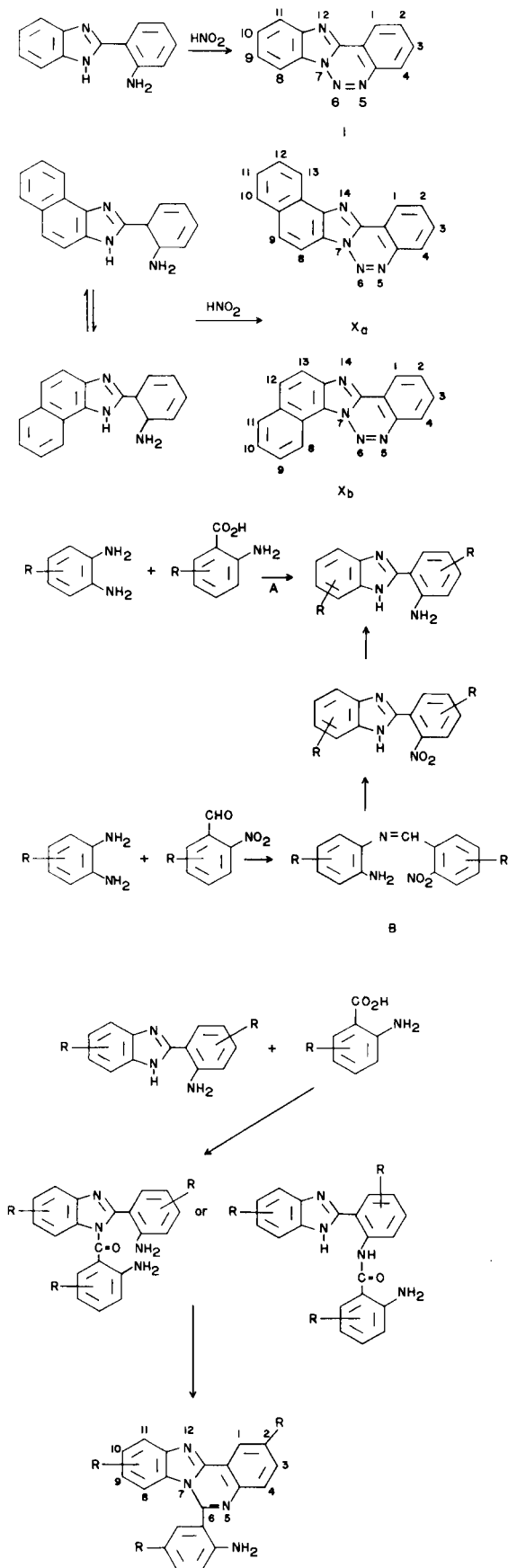
Although substituted 1,2,3-benzotriazines have been extensively studied (2a-e), systems in which the 1,2,3-benzotriazine nucleus is fused to another heterocyclic nucleus have not received wide attention. As part of a program investigating the physical and chemical properties of 1,2,3-benzotriazines fused to other heterocyclic rings and their potential pharmacological properties, we now report the synthesis of various benzimidazo[1,2-c][1,2,3]benzotriazines and a naphth[1',2'(2',1'):4,5]imidazo[1,2-c][1,2,3]benzotriazine.

The benzimidazo[1,2-c][1,2,3]benzotriazine system was first synthesized and studied by v. Niementowski in 1898 (3). All the triazines reported were prepared by the method described by this author which involved the diazotization of 2-(*o*-aminophenyl)benzimidazole to benzimidazo[1,2-c][1,2,3]benzotriazine (I). Substituents did not affect the ease of ring closure and all the triazines were obtained in excellent yields (Table I).

Benzimidazo[1,2-c][1,2,3]benzotriazines are yellow crystalline compounds. They are soluble in most organic solvents, acetic acid and mineral acids,

although some 2-substituted derivatives tend to form insoluble salts when treated with acids. Four- or 5-substituted 2-(*o*-aminophenyl)benzimidazoles may yield two isomeric benzimidazo[1,2-c][1,2,3]benzotriazines upon diazotization. The triazines obtained from 5(6)-methyl- and 5(6)-chloro-2-(*o*-aminophenyl)benzimidazoles exhibited a large melting point range indicating the presence of two isomers.

Attempts were made to separate these isomers by fractional recrystallizations but these were not successful. In the case of the chloro derivative a product was finally obtained which melted within a one degree range but the other isomer was not isolated. Although v. Niementowski reported a melting point of 187-188° for 9(10)-methylbenzimidazo[1,2-c][1,2,3]benzotriazine, the compound we obtained showed a melting range of 165-180°. Fractional recrystallization from ethanol finally yielded two fractions, one melting at 192-195° and the other at 167-168°. No significant differences could be detected in the infrared and ultraviolet spectra of these compounds. Because of our inability to establish the identity of the possible isomers, these



compounds are referred to as 9(10)-methyl- and 9(10)-chlorobenzimidazo[1,2-*c*][1,2,3]benzotriazines.

Diazotization of 2-(*o*-aminophenyl)naphth[1,2-*d*]-imidazole gave rise to a new ring system. In this case also isomeric compounds were formed and the product obtained exhibited a large melting point range, indicating a mixture of two isomers. Thus it is referred to as a naphth[1',2'(2',1'):4,5]imidazo[1,2-*c*][1,2,3]benzotriazine. Two methods were chosen for the preparation of the substituted 2-(*o*-aminophenyl)benzimidazoles which were to serve as starting materials for the preparation of the triazines. The first method (A) involved the condensation of an *o*-phenylenediamine with an anthranilic acid in polyphosphoric acid at 250°. The second method (B) consisted of the condensation of an *o*-phenylenediamine with an *o*-nitrobenzaldehyde followed by the cyclization of the resultant Schiff's base to yield a 2-(*o*-nitrophenyl)benzimidazole which was converted to the desired amino derivative by catalytic reduction.

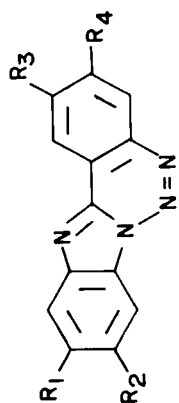
The condensation reaction in polyphosphoric acid was complicated by the formation of 6-(*o*-aminophenyl)benzimidazo[1,2-*c*]quinazolines. These compounds probably arise from the reaction of the 2-(*o*-aminophenyl)benzimidazole with anthranilic acid to give a *N*-*o*-aminobenzoyl derivative which cyclizes to a quinazoline. Davis and Mann (4) reported that 2-(*o*-aminophenyl)benzimidazole did not condense with anthranilic acid or acetylanthranilic acid in the presence of phosphorus trichloride, phosphoryl chloride, or other reagents. However, when they heated 2-[*o*-(*o*-aminobenzamido)phenyl]benzimidazole in polyphosphoric acid at 250°, they obtained 6-(*o*-aminophenyl)benzimidazo[1,2-*c*]quinazoline in 60% yield.

These conditions are comparable to the conditions used in this work. Hein and co-workers (5) studied the condensation of *o*-phenylenediamine with anthranilic acid and noted that 250° was the optimum temperature for the formation of 2-(*o*-aminophenyl)benzimidazole. They did not observe the formation of a quinazoline but at 175° they obtained a mixture containing unidentified products and only a 21% yield of the desired benzimidazole. In the present work, although the use of an excess of diamine did not suppress the formation of the quinazoline, it did produce a higher yield of benzimidazole.

It was expected that the Weidenhagen synthesis (6, 7) would provide a convenient route to 2-(*o*-nitrophenyl)benzimidazoles. This synthesis involves the reaction of an *o*-phenylenediamine with an *o*-nitrobenzaldehyde in the presence of copper (II) acetate, isolation of the insoluble copper salt, and its decomposition, in aqueous alcohol, with hydrogen sulfide to yield the free base. In the present investigation, the reaction of *o*-phenylenediamine and *o*-nitrobenzaldehyde under these conditions did not yield the expected product but its reduced derivative. Leandri and co-workers (8) noted that products obtained by the Weidenhagen synthesis consisted of approximately an equimolar mixture of 2-(*o*-nitrophenyl)- and 2-(*o*-aminophenyl)benzimidazoles. They

TABLE I

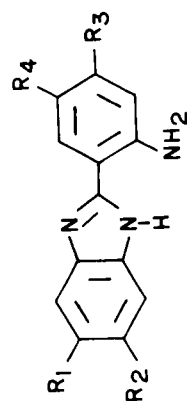
Benzimidazo[1,2-c][1,2,3]benzotriazines



Compound	R ₁	R ₂	R ₃	R ₄	Yield, %	M.p., °C	Formula	C, %		H, %		N, %		Cl or F, %	
								Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
I	H	H	H	H	92	210.5-211 (a)	C ₁₃ H ₆ N ₄	70.90	71.05	3.66	3.81	25.44	25.48	-----	-----
II (b)	Cl	H	H	H	92	178-184	C ₁₃ H ₇ N ₄ Cl	61.30	61.49	2.77	2.96	22.00	22.33	13.92	13.84
III (b)	CH ₃	H	H	H	93	165-180	C ₁₄ H ₁₀ N ₄	71.78	71.57	4.30	4.32	23.92	24.03	-----	-----
IV	Cl	Cl	H	H	97	272-274	C ₁₃ H ₆ N ₄ Cl ₂	54.00	53.99	2.09	1.86	19.38	19.58	24.53	24.51
V	CH ₃	CH ₃	H	H	94	222-224.5	C ₁₅ H ₁₂ N ₄	72.56	72.75	4.87	5.01	22.57	22.33	-----	-----
VI	H	H	Cl	H	97	211-212.5	C ₁₃ H ₇ N ₄ Cl (c)	61.31	61.48	2.77	2.88	22.00	21.94	13.92	13.95
VII	H	H	H	Cl	98	215-216.5	C ₁₃ H ₇ N ₄ Cl	61.31	61.54	2.77	2.95	22.00	21.84	13.92	13.73
VIII	H	H	H	CH ₃	94	178-179	C ₁₄ H ₁₀ N ₄	71.78	71.69	4.30	4.27	23.92	23.70	-----	-----
IX	H	H	H	F	94	158-159	C ₁₃ H ₇ N ₄ F (d)	65.54	65.69	2.96	3.03	23.52	23.71	7.98	7.78

(a) Lit. (3) m.p. 207-208°. (b) These compounds are mixtures of the 9- and 10-isomers. (c) Recrystallized from 1-pentanol. (d) Recrystallized from petroleum ether, b.p. 60-110°.

TABLE II

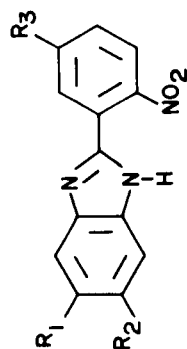
2-(*o*-Aminophenyl)benzimidazoles

Compound	R ₁	R ₂	R ₃	R ₄	Method (a)	Yield, %	M. p., °C	Formula	C, %		H, %		N, %		Cl or F, %	
									Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XI	H	H	H	H	A	46	213-214 (b, c)	C ₁₃ H ₁₁ N ₃	-----	-----	-----	-----	-----	-----	-----	-----
					B	75										
					C	98										
XII	Cl	H	H	H	A	30	181-182 (d, e)	C ₁₃ H ₁₀ N ₃ Cl	64.07	64.27	4.13	4.33	17.24	17.33	14.55	14.71
XIII	CH ₃	H	H	H	A	33	189.5-191 (b)	C ₁₃ H ₁₃ N ₃	-----	-----	-----	-----	-----	-----	-----	-----
					A (f)	54										
XIV	Cl	Cl	H	H	C	84	265.5-266.5 (d)	C ₁₃ H ₉ N ₃ Cl ₂	56.14	55.98	3.26	3.19	15.11	15.08	25.49	25.40
XV	CH ₃	CH ₃	H	H	C	59	211-213 (b)	C ₁₅ H ₁₅ N ₃	75.92	75.74	6.37	6.52	17.71	17.76	-----	-----
					B	72										
XVI	H	H	Cl	H	A	41	198-198.5 (d)	C ₁₃ H ₁₀ N ₃ Cl	64.07	63.99	4.13	4.01	17.24	17.17	14.55	14.52
XVII	H	H	H	Cl	A	22	244-245.5 (b)	C ₁₃ H ₁₀ N ₃ Cl	64.07	64.25	4.13	4.31	17.24	17.40	14.55	14.49
					B	34										
XVIII	H	H	H	CH ₃	A	17	229-230.5 (b)	C ₁₄ H ₁₃ N ₃	75.33	75.48	5.87	6.00	18.82	18.65	-----	-----
XIX	H	H	H	F	A (g)	--	225.5-227.5 (b)	C ₁₃ H ₁₀ N ₃ F	68.71	68.75	4.44	4.51	18.49	18.29	8.36	8.49
					B	61										

(a) A-condensation of *o*-phenylenediamine with anthranilic acid in polyphosphoric acid. B-Weidenhagen method. C-catalytic hydrogenation of 2-(*o*-nitrophenyl)benzimidazole. (b) Recrystallized from aqueous ethanol. (c) Lit. (5) m.p., 213.5-214.0°. (d) Recrystallized from chloroform. (e) A. L. L. Poot, J. F. Williams, and F. C. Hengebaert, [*Bull. Soc. Chim. Belges*, 72, 365 (1963)] report m.p. 178°. (f) Two equivalents of 3,4-toluenediamine were used. (g) The product contained a large amount of quinazoline.

TABLE III

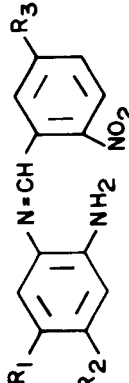
2-(*o*-Nitrophenyl)benzimidazoles



Compound	R ₁	R ₂	R ₃	Method (a)	Yield, %	M. p., °C	Formula	C, %		H, %		N, %		Cl or F, %	
								Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XXI	H	H	H	D	46	267-269.5 (b, c)	C ₁₃ H ₉ N ₃ O ₂	65.26	65.08	3.79	3.82	17.57	17.26	-----	-----
				E	54			-----	-----						
				F	40			-----	-----						
XXII	Cl	H	H	D	--	190-191.5 (d, e)	C ₁₃ H ₈ N ₃ O ₂ Cl	57.05	57.11	2.95	3.00	15.35	15.36	12.96	13.07
				E	38			-----	-----						
XXIII	CH ₃	H	H	E	30	225-227 (b, f)	C ₁₄ H ₁₁ N ₃ O ₂	66.39	66.27	4.38	4.38	16.59	16.46	-----	-----
				B	16			-----	-----						
XXIV	Cl	Cl	H	E	29	226-228 (d)	C ₁₃ H ₇ N ₃ O ₂ Cl ₂	50.67	50.73	2.29	2.37	13.64	13.39	23.02	23.10
				F	38			-----	-----						
XXV	CH ₃	CH ₃	H	E	84	217-218.5 (b)	C ₁₅ H ₁₃ N ₃ O ₂	67.40	67.32	4.90	4.85	15.72	15.72	-----	-----
				D	74			-----	-----						
XXVI	H	H	Cl	D	32	225.5-227 (b)	C ₁₃ H ₈ N ₃ O ₂ Cl	57.05	56.98	2.95	2.88	15.35	15.27	12.96	12.98
				B(g)	10			-----	-----						
XXVII	H	H	F	E	32	231-232.5 (d)	C ₁₃ H ₈ N ₃ O ₂ F	60.70	60.62	3.14	3.04	16.34	16.25	7.39	7.24
				E	32			-----	-----						
XXVIII	NO ₂	H	H	(h)	52	223.5-225 (b, i)	C ₁₃ H ₈ N ₃ O ₄	54.93	54.90	2.84	3.01	19.71	19.65	-----	-----

(a) B-Weidenhagen method. D-from the Schiff's base in ethanol. E-from the Schiff's base in nitrobenzene. F-from the Schiff's base in acetic acid. (b) Recrystallized from aqueous ethanol. (c) Lit. (8) m.p. 267-268°; lit. (17) m.p. 208° but this appears to be an error. (d) Recrystallized from toluene. (e) N. V. Subba Rao and C. Ratnam [*Proc. Indian Acad. Sci.*, 48A, 256 (1958)] report 187°. (f) N. V. Subba Rao and C. Ratnam [*Proc. Indian Acad. Sci.*, 45A, 253 (1957)] report 214°. (g) Decomposition of the copper salt was carried out in 4% HCl. (h) The Schiff's base was heated in diphenyl ether for 20 minutes. (i) N. V. Subba Rao and C. V. Ratnam [*Proc. Indian Acad. Sci.*, 49A, 193 (1959)] report 222°.

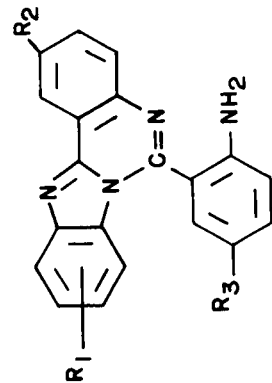
TABLE IV
N-*o*'-Nitrobenzylidene-*o*-phenylenediamines



Compound	R ₁	R ₂	R ₃	Yield, %	M.p., °C (a)	Formula	C, %		H, %		N, %		Cl or F, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XXX	H	H	H	82	79-81	C ₁₃ H ₁₁ N ₃ O ₂	64.72	64.81	4.60	4.70	17.42	17.49	-----	-----
XXXI	Cl	H	H	83	91-93 (b)	C ₁₃ H ₁₀ N ₃ O ₂ Cl	56.63	56.74	3.66	3.80	15.24	15.06	12.86	12.75
XXXII	CH ₃	H	H	78	85.5-88	C ₁₄ H ₁₃ N ₃ O ₂	65.87	65.77	5.13	5.19	16.46	16.29	-----	-----
XXXIII	Cl	Cl	H	91	140-145	C ₁₃ H ₉ N ₃ O ₂ Cl ₂	50.34	50.29	2.93	3.12	13.55	13.45	22.86	22.77
XXXIV	CH ₃	CH ₃	H	83	102-104	C ₁₅ H ₁₅ N ₃ O ₂	66.90	66.92	5.61	5.64	15.60	15.58	-----	-----
XXXV	H	H	F	84	122-124	C ₁₃ H ₁₀ N ₃ O ₂ F	60.23	60.20	3.89	4.01	16.21	16.15	7.33	7.46
XXXVI	NO ₂	H	H	75	231-233 (c, d)	C ₁₃ H ₁₀ N ₄ O ₄	54.54	54.31	3.52	3.71	19.57	19.29	-----	-----

(a) Analytical samples were obtained by washing the product with a small amount of ethanol, unless otherwise noted. (b) Recrystallized from ethanol.
 (c) Recrystallized from acetone. (d) N. V. Subba Rao and C. V. Ratnam [*Proc. Indian Acad. Sci.*, 49A, 193 (1959)] report 218°.

TABLE V
 6-(*o*-Aminophenyl)benzimidazo[1,2-*c*]quinazolines



Compound	R ₁	R ₂	R ₃	M.p., °C	Formula	C, %		H, %		N, %		Cl or F, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
XXXVII	H	F	F	277-278 (a)	C ₂₀ H ₁₂ N ₄ F ₂	69.36	69.27	3.49	3.41	16.18	16.30	10.97	10.85
XXXVIII	H	Cl	Cl	317-318.5 (b)	C ₂₀ H ₁₂ N ₄ Cl ₂	63.34	63.27	3.19	3.30	14.77	14.62	18.70	18.90
XXXIX	H	CH ₃	CH ₃	254-256 (a)	C ₂₂ H ₁₈ N ₄	78.08	77.99	5.36	5.46	16.56	16.39	-----	-----
XL	CH ₃	H	H	274-276 (b)	C ₂₁ H ₁₆ N ₄	77.76	77.69	4.97	4.99	17.27	17.26	-----	-----
XLI	Cl	H	H	264.5-267 (b)	C ₂₀ H ₁₃ N ₄ Cl	69.67	69.60	3.80	3.77	16.25	16.15	10.28	10.26

(a) Recrystallized from chloroform-petroleum ether (b.p. 30-60°). (b) Recrystallized from chloroform.

TABLE VI

Ultraviolet Spectra of Benzimidazoles (a)

2-(*o*-Aminophenyl)benzimidazoles (b)

Compound	λ max, $m\mu$ (log ϵ)
XI (c)	249 (4.26); 287 (4.16); 296 (4.11); 339 (4.08)
XII	251 (4.16); 277 (3.93); 292 (4.05); 301 (4.08); 344 (4.12)
XIII	251 (4.16); 292 (4.04); 299 (4.08); 339 (4.11)
XIV	248 (4.14); 278 (3.90); 296 (3.99); 307 (4.10); 350 (4.18)
XV	252 (4.09); 294 (4.05); 302 (4.07); 340 (4.17)
XVI	254 (4.15); 292 (4.08); 298 (4.12); 344 (4.16)
XVII	257 (4.20); 291 (4.07); 298 (4.06); 354 (4.02)
XVIII	250 (4.20); 290 (4.14); 298 (4.14); 344 (4.03)
XIX	247 (4.09); 290 (4.13); 349 (4.09)

2-(*o*-Nitrophenyl)benzimidazoles (d)

XXI (e)	(240)(4.06); 272(4.02); 280(4.02)
XXII	(243)(4.10); 286(4.03)
XXIII	(240)(4.05); 284(4.01)
XXIV	295(4.05)
XXV	244 (4.04); 288 (4.06)
XXVI	(240)(3.99); 273 (4.11); 278 (4.10)
XXVII	(243)(4.08); 272 (4.10); 279 (4.10)
XXVIII	243 (4.33); 309 (4.10)

(a) A shoulder is indicated by a λ max value in parentheses. (b) Solutions 1.7 to $2.4 \times 10^{-5}M$ in absolute ethanol. (c) Lit. (8) 225 (4.62); 256.7 (4.29); 289 (4.31); 300 (4.28); 347-348 (4.03); Lit. (19) 279-282 (4.29); 289 (4.31); 300 (4.28); 348.9 (4.02). (d) Solutions 1.8 to $2.5 \times 10^{-5}M$ in absolute ethanol. (e) Lit. (8) (240)(4.09); 274.5 (4.50); 330 (3.58).

TABLE VII

Ultraviolet Spectra of Benzotriazines and Quinazolines (a)

Benzimidazo[1,2-*c*][1,2,3]benzotriazines (b)

Compound	λ max, $m\mu$ (log ϵ)
I	227 (4.51); 281 (4.62); 287 (4.60); (320)(3.84)
II	228 (4.41); 283 (4.55); 290 (4.54); (320)(3.88)
III	227 (4.48); 286 (4.54); 292 (4.52); (326)(3.83)
IV	229 (4.54); 287 (4.61); 295 (4.58); (324)(3.99)
V	227 (4.36); 291-299 (4.50); (328)(3.82)
VI	233 (4.40); 287-293 (4.56); (326)(3.83)
VII	233 (4.45); 287 (4.58); 293 (4.58); (327)(3.90)
VIII	230 (4.42); 282 (4.64); 289 (4.61); (322)(3.90)
IX	230 (4.43); 284 (4.57); 289 (4.56); (324)(3.89)

6-(*o*-Aminophenyl)benzimidazo[1,2-*c*]quinazolines (c)

XXXVII	231 (4.42); (267)(4.57); 275 (4.62); 311 (4.04); 325 (4.05); 341 (3.93)
XXXVIII	233 (4.55); (271)(4.65); 280 (4.74); 310 (4.06); 324 (4.03); 342 (3.92)
XXXIX	230 (4.62); 267 (4.68); 276 (4.75); 304 (4.07); 320 (4.05); 339 (3.93)
XL	230 (4.50); (270)(4.61); 277 (4.68); 304 (4.06); 320 (4.04); (336)(3.86)
XLI	230 (4.46); 266 (4.59); 276 (4.64); 305 (4.01); 318 (4.02); (334)(3.80)

(a) A shoulder is indicated by a λ max value in parentheses. (b) Solutions 6.6×10^{-6} to $2.0 \times 10^{-5} M$ in absolute ethanol. (c) Solutions 1.2 to $1.4 \times 10^{-5} M$ in absolute ethanol.

suggested that the decomposition be carried out in 3% hydrochloric acid to yield a nitrobenzimidazole. In the present work mixtures were isolated using both conditions. Only in the case of *o*-phenylenediamine and *m*-nitrobenzaldehyde, the expected 2-(*m*-nitrophenyl)benzimidazole was isolated as the sole product. However, the yield obtained was lower than that reported by Weidenhagen (6). Although the Weidenhagen synthesis is not a useful method to prepare 2-(*o*-nitrophenyl)benzimidazoles, the corresponding 2-(*o*-aminophenyl)benzimidazoles may be obtained in good yields. It appears probable that the reduction of the nitro group takes place during the decomposition of the cuprous salt with hydrogen sulfide. The infrared spectra of the copper salts showed no bands which could be attributed to N-H vibrations but strong bands around 1520 cm^{-1} and 1340 cm^{-1} could be observed, indicating the presence of nitro groups. Sodium sulfide has been used to reduce nitro groups to amino groups (9). Alkaline hydrogen sulfide has been used as a selective reducing agent to convert *N*-formyl-2,4-dinitroaniline into 5-nitrobenzimidazole-3-oxide by the action of hydrogen sulfide and ammonia (10). It is possible that the pH of the reaction mixture during the decomposition of the copper salt plays an important role in determining the products obtained. Also the reduction of the nitro group may be facilitated by the proximity of this group to the oxidation site in the formation of 2-(*o*-nitrophenyl)benzimidazole as opposed to the *m*- or *p*-nitro isomer. It was noted that hydrogen sulfide in ethanol did not reduce 2-(*o*-nitrophenyl)benzimidazole.

Other conditions were investigated to obtain 2-(*o*-nitrophenyl)benzimidazoles from *o*-phenylenediamines and *o*-nitrobenzaldehydes. Schiff's bases were prepared by heating equimolar amounts of diamine and aldehyde in ethanol (11). The Schiff's bases precipitated from the solution in good yields. If the filtrates were allowed to stand in air for several days or heated for several hours, yields of 5-10% of the corresponding nitrobenzimidazoles were isolated. When a 3- or 4-substituted *o*-phenylenediamine was used, two possible Schiff's bases could result depending on which one of the two amino groups reacted with the aldehyde group. Since both isomers yielded the same benzimidazole no effort was made to establish the structure of the Schiff's bases. The wide melting point range of these products indicated that a mixture of isomers was formed.

A variety of solvents were tried to effect the conversion of the Schiff's bases into the corresponding nitrophenylbenzimidazoles. The use of nitrobenzene as the dehydrogenating agent and solvent was developed by Jerchel and co-workers (12a, b). Other authors have also used this method successfully (13). In the present study several 2-(*o*-nitrophenyl)benzimidazoles were prepared by this method. Although the nitrobenzimidazoles were the major products in all cases, significant amounts of the corresponding amino derivatives were shown to be present in the majority of the reactions tried. In

general, small amounts of the aminobenzimidazole could be removed by recrystallization from aqueous alcohol in which the nitrobenzimidazole was less soluble.

Dehydrogenation of the Schiff's bases in ethanol was the only method which lead to the formation of 2-(*o*-nitrophenyl)benzimidazoles without reducing the nitro group.

Ethylene glycol also converted the Schiff's bases into benzimidazoles but reduction of the nitro group was also found to occur in the *ortho* series of benzimidazoles.

Diphenyl ether was also used successfully to convert Schiff's bases into the desired benzimidazoles.

Acetic acid has often been used as a solvent for the reaction of aromatic diamines with aromatic aldehydes (14). The main products isolated in these studies were 2-substituted benzimidazoles and 1,2-disubstituted benzimidazoles. Occasionally dianils and 2,3,4-trisubstituted-1,5-3*H*-benzodiazepines were isolated. This method was also tried in this investigation. Towards the completion of this work, several new methods for the preparation of 2-arylbenzimidazoles have been reported (15-18) but could not be tried. The various intermediates prepared in the course of this work are listed in Tables II, III, IV and V.

Several investigators have studied the ultraviolet spectra of 2-phenylbenzimidazoles (8,19,20). The ultraviolet spectra of the benzimidazoles prepared in this investigation are listed in Table VI.

The ultraviolet spectra of 2-(*o*-aminophenyl)benzimidazoles show three characteristic regions of absorption: $250\text{ m}\mu$, $280\text{-}300\text{ m}\mu$, and $340\text{-}350\text{ m}\mu$. Substitution in the 5(6)-position causes a small shift of the $280\text{-}300\text{ m}\mu$ band to longer wavelengths. Substitution in the 2-phenyl ring has no effect on this band. The band in the $340\text{-}350\text{ m}\mu$ region undergoes a small bathochromic shift in substituted compounds. In the case of compound XIX there is a loss of fine structure and only one band appears in the $280\text{-}300\text{ m}\mu$ region. The ultraviolet spectra of 2-(*o*-nitrophenyl)benzimidazoles are easily distinguishable from those of 2-(*o*-aminophenyl)benzimidazoles. Two bands may be observed: a broad band with a maximum in the $278\text{-}295\text{ m}\mu$ region which is sometimes resolved into two closely overlapping bands of similar intensity and a shorter wavelength band near $240\text{ m}\mu$ which is generally quite diffuse. Substituents cause a small bathochromic shift of the long wavelength band. However, when the substituent is a nitro group in the 5(6)-position, the long wavelength band undergoes a bathochromic shift and the intensity of the shorter wavelength band increases.

There is no systematic data on either the infrared or ultraviolet absorption spectra of 1,2,3-benzotriazines. Grammaticakis (21) examined the ultraviolet spectra of 2-aryl-1,2,3-benzotriazin-4(3*H*)-ones and found that they resembled those of *N*-benzoylarylamines.

The ultraviolet spectra of benzimidazo[1,2-*c*]-

[1,2,3]benzotriazines (Table VII) show three characteristic regions of absorption: 230 μ , 280-300 μ , and 325 μ . Substituents do not affect the intensities of the bands to any large degree. The ultraviolet spectrum of I is very similar to that of 2-phenylbenzimidazole (8,19,20) and it is reasonable to suppose that absorptions in the triazines arise from the excitations of amidine, benzenoid, diazo, or benzylideneimine chromophores as well as a chromophore involving the entire conjugated system. The triazines have more intense absorption bands than the 2-aryl benzimidazoles probably because the formation of the triazine ring gives rise to a nearly coplanar molecule.

The ultraviolet spectra of 6-(*o*-aminophenyl)benzimidazo[1,2-*c*]quinazolines show three characteristic absorption regions: 230 μ , 260-280 μ , and 305-340 μ , and thus afforded an easy way to distinguish them from the corresponding benzimidazo[1,2-*c*]-[1,2,3]benzotriazines. Two very intense bands, sometimes poorly resolved, appear in the 260-280 μ region. The band in the 305-340 μ region shows fine structure consisting of three diffuse bands.

This band is of lower intensity than the other bands. The ultraviolet spectra of compounds XXXVII-XLI are similar to that of 6-methylbenzimidazo[1,2-*c*]quinazoline. Only a small bathochromic shift of the bands in the 260-280 μ region is noted in going from a 6-methyl- to a 6-(*o*-aminophenyl)quinazoline. The phenyl group must form a large angle with the plane of the molecule because of steric hindrance. Thus, there is little resonance interaction between the 6-phenyl group and the benzimidazo[1,2-*c*]quinazoline nucleus.

The infrared spectra of benzimidazoles are quite complex and have not been extensively investigated (22,23,24). The spectra of 2-(*o*-aminophenyl)benzimidazoles show two strong bands associated with NH stretching vibrations, a sharp band around 3385-3364 cm^{-1} and a broad band in the 3100-3250 cm^{-1} region. Characteristic infrared absorption bands are found in the 1630-1500 cm^{-1} region. These bands arise from aromatic C=C and C=N stretching modes and cannot be distinguished. The 1600 cm^{-1} band is rather strong and broad in the case of the amino-benzimidazoles. The N-H in-plane deformation of the primary amino group is associated with a strong band in the region and therefore the bands due to skeletal stretching cannot be distinguished from this band. A strong band is also present between 1250-1240 cm^{-1} which may be attributed to the C-N stretching mode. All benzimidazoles show characteristic bands in the 1450-1430 cm^{-1} region. The nitro substituted benzimidazoles show two strong bands around 1525-1515 cm^{-1} and 1345-1335 cm^{-1} due to the nitro group. Absorptions in the 1225-950 cm^{-1} region may be assigned to in-plane CH deformations and are generally weak. The out-of-plane CH deformations give rise to strong bands in the 900-650 cm^{-1} region. All benzimidazoles with four adjacent hydrogen atoms show strong absorption around 770-730 cm^{-1} .

The infrared spectra of benzimidazo[1,2-*c*][1,2,3]-benzotriazines have many absorption regions in common with 2-aryl benzimidazoles. All triazines absorb around 1620-1560 cm^{-1} . Many intense bands are found between 1160-1140 cm^{-1} while 2-aryl benzimidazoles show only weak absorption in this region.

The infrared spectra of 6-(*o*-aminophenyl)benzimidazo[1,2-*c*]quinazolines show similarities to the spectra of the triazines. Three bands are found in the 3480-3150 cm^{-1} region which may be attributed to the NH stretching vibrations.

EXPERIMENTAL (25)

Preparation of Benzimidazo[1,2-*c*][1,2,3]benzotriazines. Typical Procedure, Table I, Compounds I-IX.

This procedure is a modification of the one described by v. Niementowski (3) and is illustrated with the preparation of I. 2-(*o*-Aminophenyl)benzimidazole (15.0 g., 0.072 mole) was dissolved in 600 ml. of hot 95% aqueous ethanol and treated while still hot with 150 ml. of concentrated hydrochloric acid. The salt precipitated from the solution as it cooled. While the mixture was warm, a solution of sodium nitrite (7.2 g., 0.10 mole) in 27 ml. of water was added to it, dropwise, with stirring over a period of 35 minutes. The yellow precipitate which formed was collected, washed with water and dried.

Preparation of 2-(*o*-Aminophenyl)benzimidazoles. Typical Procedure, Table II, Compounds XI-XIII and XVI-XIX. Method A.

The reaction is illustrated with the preparation of XIII. A mixture of 3,4-toluenediamine (24.46 g., 0.20 mole), anthranilic acid (27.43 g., 0.20 mole), and 353 g. of polyphosphoric acid was heated with stirring for 2 hours at 250°, cooled and poured into 2 l. of cold water. The precipitate which formed was removed by filtration. The filtrate was decolorized with activated carbon and treated with a 50% aqueous sodium hydroxide solution. The solid which precipitated was collected and dried to yield 29.5 g. of a product (m.p. 168-190°) which was a mixture of XIII and XL. The benzimidazole was soluble in ethanol but slightly soluble in chloroform while the quinazoline was very soluble in chloroform but slightly soluble in ethanol. Thus, the mixture could be separated by fractional recrystallization from either chloroform or ethanol. Compounds XXXVII-XLI (Table V) were all obtained by this procedure. If the same reaction was carried out using two equivalent of diamine for one of acid, an increased yield of benzimidazole was obtained.

Typical Procedure, Table II, Compounds XI, XV, XVII, and XIX. Method B.

This procedure is illustrated with the synthesis of XIX. 5-Fluoro-2-nitrobenzaldehyde was prepared as described by Subba Rao and Ratnam (26). A solution of copper acetate monohydrate (21.0 g., 0.10 mole) in 300 ml. of water and a solution of 5-fluoro-2-nitrobenzaldehyde (8.45 g., 0.05 mole) in 50 ml. of methanol were added to a solution of *o*-phenylenediamine (5.40 g., 0.05 mole) in 150 ml. of methanol. The mixture was refluxed for 2 hours and left standing overnight. The brown solid which formed was collected and dried to yield 18.4 g. of a brown copper salt. This salt could be decomposed in two different ways.

Decomposition in Ethanol.

The copper salt (9.2 g.) was suspended in 200 ml. of 50% aqueous ethanol and decomposed by bubbling a slow stream of hydrogen sulfide into its suspension, with stirring, for 1 hour. The reaction mixture was heated to its boiling point, the copper sulfide removed by filtration and the solid extracted with 200 ml. of hot 95% aqueous ethanol. The ethanolic solution was treated with decolorizing carbon, the carbon was removed by filtration and the red filtrate was concentrated to yield XIX.

Decomposition in 4% Hydrochloric Acid.

The copper salt (9.2 g.) was suspended in 300 ml. of 4% hydrochloric acid and decomposed as previously described. The cooled reaction filtrate yielded a brown solid, which was dissolved in water, decolorized and neutralized with sodium bicarbonate to yield 0.6 g. of a cream-colored solid, m.p. 215-225° (fraction 1). The dark red acid filtrate was treated with decolorizing carbon, and the carbon removed by filtration. This filtrate was neutralized with sodium bicarbonate to yield a brown solid. This solid was collected by filtration, washed with water and dried to yield 3.2 g. of a solid, m.p. 155-195° (fraction 2). The copper sulfide previously isolated was extracted with 250 ml.

of hot water. The extracts were cooled and neutralized with sodium bicarbonate to yield 0.7 g. of a tan solid, m.p. 155–200° (fraction 3). Recrystallization of fractions 1 and 3 from aqueous ethanol yielded 2-(*o*-nitro-5-fluorophenyl)benzimidazole (XXVII), Table III. Recrystallization of fraction 2 from the same solvent yielded XIX.

Typical Procedure, Table II, Compounds XI, XIV and XV. Method C.

The method is illustrated with the preparation of XIV. Compound XXIV (3.09 g., 0.01 mole) was dissolved in 100 ml. of ethanol, 0.1 g. of 10% palladium on charcoal was added to this solution, and the mixture was hydrogenated in a Parr apparatus. The catalyst was removed by filtration and the filtrate reduced in volume to yield XIV.

Preparation of 2-(*o*-Nitrophenyl)benzimidazoles. Typical Procedure, Table III, Compounds XXI, XX, XXV, and XXVI. Method D.

The procedure is illustrated with the preparation of XXV. A solution of *o*-nitrobenzaldehyde (3.02 g., 0.02 mole) in 10 ml. of ethanol was added to a solution of 4,5-dimethyl-*o*-phenylenediamine (2.72 g., 0.02 mole) in 20 ml. of boiling ethanol and the mixture was heated for 5 minutes. The Schiff's base (XXXIV) precipitated when the reaction mixture was cooled. Compound XXXIV was collected by filtration, washed with cold ethanol and dried.

A solution of compound XXXIV (1.00 g., 0.004 mole) in ethanol was heated for 5 hours and allowed to stand for 12 days. The ethanol was removed by distillation to yield XXV.

Typical Procedure, Table III, Compounds XXI–XXV and XXVII. Method E.

This method is also illustrated with the preparation of XXV. The aldehyde and diamine were mixed as previously described and 10 ml. of nitrobenzene was added to the red solution. The ethanol and water were removed by distillation, and the mixture heated for 1 minute. The reaction mixture was poured into 10 ml. of ethanol saturated with anhydrous hydrogen chloride and 50 ml. of anhydrous ether were added. The hydrochloride (5.50 g.) was suspended in 100 ml. of water and neutralized with a solution of sodium carbonate to yield XXV in an impure form. Thin layer chromatography revealed that this product was contaminated by XV (Table II) which exhibited a bright blue fluorescent spot identical with that produced by an authentic sample of XV.

Typical Procedure, Table III, Compounds XXI and XXIV. Method F.

The procedure is illustrated with the preparation of XXIV. *o*-Nitrobenzaldehyde (1.51 g., 0.01 mole) was added to a solution of 4,5-dichloro-*o*-phenylenediamine (1.77 g., 0.01 mole) in 20 ml. of glacial acetic acid, and the resulting solution refluxed for 1.5 hours. The red Schiff's base, which separated initially, dissolved to yield a light brown solution at the end of the heating period. The solution was cooled, poured into 400 ml. of cold water and neutralized with 50% aqueous sodium hydroxide to yield XXIV.

Preparation of Schiff's Bases. Typical Procedure, Table IV, Compounds XXX–XXXVI.

The procedure is illustrated with the preparation of XXXIII. A solution of *o*-nitrobenzaldehyde (3.34 g., 0.022 mole) in 25 ml. of ethanol was added to a solution of 4,5-dichloro-*o*-phenylenediamine (3.91 g., 0.022 mole) in 25 ml. of boiling ethanol and the mixture heated for 5 minutes. Compound XXXIII separated from solution as red needles which were collected by filtration. When the ethanolic filtrate was allowed to stand in an open flask for a long period of time yellow brown crystals of XXIV (Table III) could be isolated. Naphth[1',2'(2',1'):4,5]imidazo[1,2-*c*][1,2,3]benzotriazine (Xa or Xb).

This compound was prepared by the same procedure described for the compounds in Table I. It was recrystallized from absolute ethanol. A yield of 98% of deep yellow plates was obtained, m.p. 211–213°. Ultraviolet bands λ max (Ethanol), $m\mu$ (log ϵ): 246 (4.42); 293 (4.57); 341 sh (3.96).

Anal. Calcd. for $C_{17}H_{10}N_4$: C, 75.54; H, 3.73; N, 20.73. Found: C, 75.49; H, 3.86; N, 20.53.

2-(*o*-Aminophenyl)naphth[1,2-*d*]imidazole (XX).

This compound was prepared by method A. It was recrystallized from toluene. A 42% yield of colorless needles was obtained, m.p.

210–211°. Ultraviolet bands, λ max (Ethanol), $m\mu$ (log ϵ): 241 (4.66); 268 sh (4.39); 275 (4.41); 352 (4.27).

Anal. Calcd. for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.21. Found: C, 78.91; H, 5.15; N, 16.08.

N-*o*'-Nitrobenzylidene-1,2-naphthalenediamine (XXIX).

This compound was prepared by the procedure described for the compounds in Table IV (XXX–XXXVI). It was recrystallized from ethanol to give a 74% yield of cherry red needles, m.p. 106–110°.

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.43. Found: C, 70.00; H, 4.62; N, 14.36.

Attempts to dehydrogenate this Schiff's base in ethanol yielded a yellow product but no satisfactory analytical data could be obtained for this compound. The infrared and ultraviolet spectra [λ max (Ethanol), $m\mu$ (log ϵ): 234 (4.57); 260 (4.19); 326 (3.80)] indicated that it could be a nitronaphthimidazole.

REFERENCES

- (1) Abstracted in part from the Ph.D. dissertation of Laura L. Zaika, University of Pennsylvania, 1964.
- (2a) M. Busch, *J. Prakt. Chem.*, **51**, 113, 257 (1895); (b) H. Finger, *ibid.*, **37**, 431 (1888); **48**, 92 (1893); (c) K. Kratz, *ibid.*, **53**, 210 (1896); (d) H. Mehner, *ibid.*, **63**, 241 (1901); (e) G. Heller, *ibid.*, **111**, 1 (1925); (f) H. Meyer, *Ann. Chem.*, **351**, 267 (1907).
- (3) S. v. Nientowski, *Ber.*, **31**, 314 (1898).
- (4) M. Davis and F. G. Mann, *J. Chem. Soc.*, 945 (1962).
- (5) D. W. Hein, R. J. Alheim, and J. J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).
- (6) R. Weidenhagen, *Chem. Ber.*, **69**, 2263 (1936).
- (7) R. C. DeSelms, *J. Org. Chem.*, **27**, 2163 (1962).
- (8) G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazz. Chim. Ital.*, **85**, 769 (1955).
- (9) W. Borsche, W. Doeller, and M. Wagner-Roemmich, *Chem. Ber.*, **76**, 1101 (1943).
- (10) S. Takahashi and H. Kano, *Chem. Pharm. Bull. Japan*, **12**, 289 (1964).
- (11) F. F. Stephens and J. D. Bower, *J. Chem. Soc.*, 2971 (1949).
- (12a) v. D. Jerchel, H. Fischer, and M. Kracht, *Ann. Chem.*, **575**, 162 (1952); (b) v. D. Jerchel, M. Kracht, and K. Krucher, *ibid.*, **590**, 232 (1954).
- (13) L. N. Pushkina, S. A. Mazalov, and I. Y. Postovskii, *Zh. Obshch. Khim.*, **32**, 2624 (1962).
- (14) N. V. Subba Rao and C. V. Ratnam, *J. Indian Chem. Soc.*, **38**, 631 (1961).
- (15) L. Krbeček and H. Takimoto, *J. Org. Chem.*, **29**, 3630 (1964).
- (16) V. J. Grenda, R. E. Jones, G. Gal, and M. Sletzing, *ibid.*, **30**, 259 (1965).
- (17) J. H. Hall and D. R. Kamm, *ibid.*, **30**, 2092 (1965).
- (18) H. F. Ridley, R. G. W. Spickett and G. M. Timmis, *J. Heterocyclic Chem.*, **2**, 453 (1965).
- (19) A. Mangini and F. Montanari, *Bull. Sci. Fac. Chim. Ind. Bologna*, **14**, 36 (1956).
- (20) P. Brocklehurst, *Tetrahedron*, **18**, 299 (1962).
- (21) P. Grammaticakis, *Compt. Rend.*, **243**, 2094 (1956).
- (22) K. J. Morgan, *J. Chem. Soc.*, 2343 (1961).
- (23) D. G. O'Sullivan, *Spectrochim. Acta*, **16**, 762 (1960).
- (24) D. J. Rabiger and M. M. Joullié, *J. Org. Chem.*, **29**, 476 (1964).
- (25) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tennessee, and Dr. A. Bernhardt, Max Planck Institut, 433 Mülheim (Ruhr), West Germany. Infrared spectra were determined as potassium bromide discs with a Perkin-Elmer model 421 recording spectrophotometer. Ultraviolet spectra were obtained on a Beckman DU Spectrophotometer modified by Process and Instruments with an attached Leeds and Northrup Speedomax Type G Recorder. The cells used were 1 cm. quartz cells.
- (26) N. V. Subba Rao and C. V. Ratnam, *Proc. Indian Acad. Sci.*, **43A**, 173 (1956).

Received June 23, 1966

Philadelphia, Pa. 19104