SYNTHESIS OF THIAZOLE DERIVATIVES

XXIII*. 2-Methylbenzimidazoles with Thiazole, Benzothiazole, and Quinoline Groups as Substituents

V. M. Zubarovskii and M. P. Bachurina

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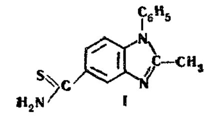
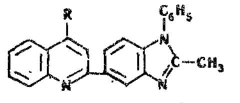
Derivatives of 1-phenyl-2-methylbenzimidazole, with nitrogen heterocycle groups thiazole, 4-substituted thiazole, benzothiazole, and quinoline, at position 5, are synthesized. The ethiodides of the new bases are used to prepare cyanine dyes: imidadimethinemero-, imidacarbo-, and, imidadicarbocyanines.

The literature describes [2–4] some derivatives of 2-methylbenzimidazole with alkyl or aryl groups at position 1, and heterocyclic nitrogen groups at position 5. We have now synthesized new compounds of that type, and used them to prepare imidacyanines. Thioamide I was prepared by adding hydrogen sulfide to the nitrile of 1-phenyl-2-methylbenzimidazole-5-carboxylic acid.

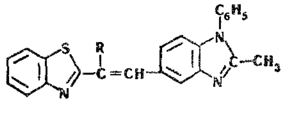


I reacts with α-halogenocarbonyl compounds in high boiling solvents and this reaction has now been used to prepare from tribromoparaldehyde, monobromoacetone, and ω-monobromo derivatives of acetophenone, acetothienone, and methyl(benzothiazolyl-2)ketone [5], 1-phenyl-2-methylbenzimidazoles with thiazole groups II–IV (Table 1).

Condensation of 1-phenyl-2-methyl-5-acetylbenzimidazole [1] with isatin under the conditions of the known Pfitzinger synthesis gives 2-(1'-phenyl-2' methylbenzimidazolyl-5') cinchoninic acid (VII), whose decarboxylation gave 1-phenyl-2-methyl-5-(quinolyl-2')benzimidazole (VIII).



VII, R = COOH; VIII, R = H



IX, R = CN; X, R = H

Our previously described [6] 1-phenyl-2-methyl-5-formylbenzimidazole is brought to react with 2-cyanomethylbenzothiazole in the presence of picoline, to give nitrile IX, forming on heating with hydrochloric acid the salt of base X. The base itself is isolated from the salt as a hydrate which loses water on melting.

In accordance with our observations [2, 7], the new bases II–VIII and X give quaternary salts when treated with excess ethyl iodide, only the benzimidazole group being involved. All the bases mentioned give ethiodides (Table 2), and the latter give imidadimethinemerocyanines with 3-ethylrhodanine and 3-ethyloxazolidine-2-thione-4-one groups (Table 3) and symmetrical imidacarbo- and imidadicarbocyanines (Table 4). The principal light absorption maxima of the dyes were determined.

EXPERIMENTAL

Thioamide of 1-phenyl-2-methylbenzimidazole-5-carboxylic acid (I). 35 ml Et_3N was added to a warm solution of 4.7 g(0.02 mole) 1-phenyl-2-methyl-5-cyanobenzimidazole [8] in 140 ml dry EtOH, and a moderate stream of H_2S passed in for 3 hr, during the first 10 min without cooling, thereafter at –10°. The solution was then left for 60 hr at room temperature, 85 ml mixed solvent distilled off, and the residue cooled for 1 hr in ice-water. The solid was washed with water and MeOH, dried, heated for 15 min at 100° with 25 ml toluene, cooled to +40°, filtered, and washed with ether. Yield of I 4.6–5.0 g (86–92%). Pale-yellow crystals mp 229–230° (ex toluene). Found: S 11.78; 11.72%. Calculated for $C_{15}H_{13}N_3S$: S 11.98%.

1-Phenyl-2-methyl-5-thiazolyl(or 4-substituted thiazolyl)benzimidazoles (II–VI) (Table 1). Hot solutions of 0.012 mole thioamide I in 30 ml nitrobenzene and 0.012 mole (in the case of tribromoparaldehyde 0.006 mole) of the appropriate halogenocarbonyl compound in 10–25 ml of the same solvent were mixed, and the mixture held at 140–145° for 1 hr, then left for 24–48 hr, and the HBr salt of the base synthesized filtered off. In the case of base III, the salt was obtained by adding, with stirring, 0.012 mole monobromoacetone in 20 ml toluene to a boiling solution of 0.004 mole thioamide in 400 ml dry toluene. From the HBr salts, after washing with ether or petrol ether, the base was liberated by adding 25% aqueous ammonia to a hot suspension of the salt in water. When recrystallizing bases II–VI, the mother liquor was decolorized by boiling with charcoal. The pure bases were colorless or yellowish crystalline compounds.

2-(1'-Phenyl-2'-methylbenzimidazolyl-5')cinchoninic acid (VII). A mixture of 2.94 g (0.02 mole) isatin, a solution of 6.0 g (0.15 mole) NaOH in 60 ml 60% aqueous MeOH, and 5.26 g (0.021 mole) 4-phenyl-2-methyl-5-acetylbenzimidazole [1] was stirred and heated for 12 hr on a boiling water bath. 50 ml water

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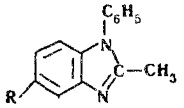
* For part XXII see [1].

Table 1

1-Phenyl-2-methyl-5-(R)-benzimidazoles



Compound	R	Mp,* C	Solvent for recrystallizing	Formula	Element	Found, %	Calculated, %	Yield, %
II	Thiazolyl-2	158	Ligroin	$C_{17}H_{13}N_3S$	S	10.61; 10.56	10.99	41
III	4-Methylthiazolyl-2	128	Ligroin	$C_{18}H_{15}N_3S$	S	10.57; 10.55	10.49	30
IV	4-Phenylthiazolyl-2	194	Glycol-ethanol (3:2)	$C_{23}H_{17}N_3S$	N	11.23; 11.32	11.44	70
V	4-(Thienyl-2)thiazolyl-2	204	Pyridine	$C_{21}H_{15}N_3S_2$	N S	11.20; 11.31 17.10; 17.07	11.26 17.15	50
VI	4-(Benzothiazolyl-2)-thiazolyl-2	257	Pyridine	$C_{24}H_{16}N_4S_2$	N S	13.17; 13.29 15.15; 15.22	13.20 15.09	80

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*All compounds first synthesized and described here have corrected melting points.

Table 2

Ethiodides of Bases

Base	Ethiodide					
	Mp, °C	Solvent for recrystallizing	Formula	I, %		Yield, %
				Found	Calculated	
II	260	Water	$C_{19}H_{18}IN_3S$	27.96; 28.12	28.41	94
III	265*	Water	$C_{20}H_{20}IN_3S$	27.26; 27.24	27.54	74
IV	266	Water	$C_{25}H_{22}IN_3S$	24.03	24.28	57
V	284*	Water	$C_{23}H_{20}IN_3S$	24.30; 24.32	24.00	86
VI	305*	Nitrobenzene	$C_{26}H_{21}IN_4S_2$	21.78; 21.86	21.89	91
VII	267*	Water	$C_{26}H_{22}IN_3O_2$	23.52	23.73	77
VIII	261*	Water	$C_{25}H_{22}IN_3$	26.13; 25.64	25.87	56
X	290	Dry EtOH	$C_{25}H_{22}IN_3S$	23.93; 24.16	24.28	92

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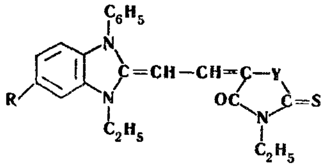
*Melts with decomposition.

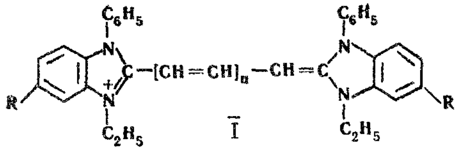
Table 3



3-Ethyl-5-([1'-phenyl-3'-ethyl-5'-(R)benzimidazolinylide-en-2'] ethylidene) rhodanines (or oxazolidinethione-4-ones)

Dye	R	Y	Starting quaternary salt	Mp, °C	Recrystallizing solvent	λmax, mμ	Formula	S, %		Yield, %
								Found	Calculated	
XI	Thiazolyl-2	S	A	255	EtOH	529	$C_{25}H_{22}N_4OS_3$	19.70; 19.73	19.59	20
XII	4-Methylthiazolyl-2	S	B	275	Pyridine-EtOH (1:1)	529	$C_{26}H_{24}N_4OS_3$	18.76; 18.68	19.04	40
XIII	4-Phenylthiazolyl-2	S	C	230	Pyridine-EtOH (1:6)	530	$C_{31}H_{26}N_4OS_4$	16.85; 16.91	16.96	50
XIV	4-(Thienyl-2)thiazolyl-2	S	D	228—229	EtOH	530	$C_{29}H_{24}N_4OS_4$	22.28; 22.15	22.37	23
XV	4-(Benzothiazolyl-2)thiazolyl-2	S	E	274—275	Pyridine-EtOH (1:1)	531	$C_{32}H_{25}N_5OS_4$	20.30; 20.25	20.54	50
XVI	β-(Benzothiazolyl-2)vinyl	S	H	180	Pyridine-EtOH (1:6)	538	$C_{31}H_{26}N_4OS_3$	16.49; 16.40	16.96	62
XVII	4-Carboxyquinolyl-2	S	F	232—233	EtOH	531	$C_{32}H_{26}N_4O_3S_2$	10.73; 10.85	11.07	7
XVIII	Quinolyl-2	S	G	213	EtOH	527	$C_{31}H_{26}N_4OS_2$	11.74; 11.68	11.98	92
XIX	Benzoxazolyl-2	0	I	311	Pyridine	509	$C_{29}H_{24}N_4O_3S$	6.26; 6.29	6.29	30
XX	Benzothiazolyl-2	0	K	273—274	Pyridine-5% water	511	$C_{29}H_{24}N_4O_2S_2$	12.07; 12.20	12.21	29
XXI	Quinolyl-2	0	G	262	Pyridine-15% water	507	$C_{31}H_{26}N_4O_2S$	5.94; 5.92	6.17	34

Table 4



1, 1'-Diphenyl-3, 3'-diethyl-5, 5'-di[R]imidacarbo- (or dicarbo) cyanineiodides

Dye	R	*n*	Starting quaternary salt	Mp, °C	Recrystallizing solvent	λ_{max}, mμ	Formula	I, %.		Yield %
								Found	Calculated	
XXII	Thiazolyl-2	1	A	194—196	Pyridine-water (1:2)	533	$C_{39}H_{33}IN_6S_2$	16.62; 16.81	16.37	12
XXIII	4-Methylthiazolyl-2	1	B	195	EtOH	535	$C_{41}H_{37}IN_6S_2$	15.97; 15.82	15.79	20
XXIV	4-Phenylthiazolyl-2	1	C	286*	Pyridine	536	$C_{51}H_{41}IN_6S_2$	13.76; 13.81	13.68	10
XXV	4-(Thienyl-2)thiazolyl-2	1	D	279—280*	Pyridine-water (1:1)	537	$C_{47}H_{37}IN_6S_4$	S 13.27; 13.21	S 13.61	10
XXVI	4-(Benzothiazolyl-2)thiazolyl-2	1	E	233—234	Pyridine-water (4:1)	538	$C_{53}H_{39}IN_8S_4$	12.20; 12.22	12.18	15
XXVII	β-(Benzothiazolyl-2)vinyl	1	H	274—276*	EtOH	551	$C_{51}H_{41}IN_6S_2$	13.37; 13.33	13.68	15
XXVIII	4-Carboxyquinolyl-2	1	F	176—179	EtOH	537	$C_{53}H_{41}IN_6O_4$	13.02; 12.90	13.34	11
XXIX	Quinolyl-2	1	G	211	Glycol-EtOH (1:4)	533	$C_{51}H_{41}IN_6$	N 9.31; 9.26	N 9.48	19
XXX	Benzoxazolyl-2	2	I	260—261	EtOH	634	$C_{49}H_{39}IN_6O_2$	14.50; 14.25	14.59	23
XXXI	Benzothiazolyl-2	2	K	276—278	Pyridine-water (4:3)	637	$C_{49}H_{39}IN_6S_2$	14.40; 14.44	14.07	6

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*Prior to recrystallization the crude dye was purified by chromatography (absorbent Al_2O_3, solvent $CHCl_3$).

was added, the pasty precipitate filtered off, washed with water, dissolved wet in 50 ml MeOH, the solution decolorized with charcoal (1.0 g), and after adding 2 ml glacial AcOH, cooled in ice. The precipitate was washed with MeOH, and recrystallized from 125 ml nitrobenzene. Yield of VII 6.0 g (79.2%). Colorless crystals mp 322°. Found: N 10.96; 11.07%. Calculated for $C_{24}H_{17}O_2N_3$: N 11.08%.

1-Phenyl-2-methyl-5-(quinolyl-2')benzimidazole (VIII). 2.65 g (0.007 mole) acid VII was quickly raised to 320–330°, the melt stirred, and in 9–11 min its temperature was brought to 360°, when heating was stopped. The melt was cooled, dissolved in 25 ml EtOH, decolorized with 0.4 g charcoal, and then left in ice for 20 hr. The precipitate was washed with cold MeOH. Concentration of the mother liquors gave a further quantity of VIII. Yield 1.5 g (68%). Yellowish crystals, mp 199–201°. Found: N 12.58; 12.56%. Calculated for $C_{23}H_{17}N_3$: N 12.53%.

1-Phenyl-2-methyl-5-[β-(benzothiazolyl-2')-β-cyanovinyl] benzimidazole (IX). 1.77 g (0.0075 mole) 1-phenyl-2-methyl-5-formylbenzimidazole [6], 1.3 g (0.0075 mole) 2-cyanomethylbenzothiazole [9], and 5 ml α-picoline were heated together at 100° for 2 hr. Then 20 ml ether was added, and after 30 min the solid filtered off and washed with ether. Yield of IX 2.6 g (89%), yellow crystals, mp 242° (ex EtOH). Found S 7.92; 7.09%. Calculated for $C_{24}H_{17}N_4S$: S 8.16%.

1-Phenyl-2-methyl-5-[β-(benzothiazolyl-2') vinyl] benzimidazole (X). 2.35 g (0.006 mole) nitrile IX and 6.6 ml HCl (d 1.19) were heated together for 3 hr at 145–155° in a sealed glass tube. After 20 hr the tube was opened, the precipitate filtered off, mixed with 20 g ice, and a 10% aqueous solution of NaOAc added till the reaction was alkaline. The precipitate was washed with water, recrystallized from ethanol, using charcoal, and dried, yield 1.25 g (50.7% calculated on the dihydrate of base X). Pale yellow needle-shaped crystals, melting over the range 110–126° with evolution of steam. Found: S 7.85; 7.90; N 10.66; 10.64%. Calculated for $C_{23}H_{17}N_3S \cdot 2H_2O$: S 7.94; N 10.42%.

1.6 g dihydrate was heated in a stream of N, and the temperature of the melt raised to 205°. It was then dissolved in 8 ml dry pyridine and the filtrate obtained after treatment with charcoal mixed with 16 ml hot petrol ether (bp 100–120°). After 20 hr the mixture was cooled, yield of base X 1.0 g, pale yellow crystals, mp 152°. Found: S 8.36; 8.35%; N 11.49; 11.39%. Calculated for $C_{23}H_{17}N_3S$: S 8.72%; N 11.44%.

Ethiodides of bases II-VIII and X (Table 2). 5–10 mole EtI was added to a warm solution of 1 mole of one of the bases II–VI, X, in 3–20 times its weight of nitrobenzene, and the mixture heated for 1 hr at 140–150° C. After 15–20 hr excess EtI was removed, and the residue washed with ether or acetone. The ethiodides were suitable without further purification for preparing the dyes. They were recrystallized, however, for analysis. The ethiodides of bases VII, VIII were made by heating the bases with excess (10 mole) EtI in sealed tubes at 150° (for VII) and 100° (for VIII). Base X can be used to prepare its ethiodide as a dihydrate.

Cyanine dyes XI–XXXI (Tables 3, 4). Imidadimethinemerocyanines, imidacarbo- and imidadicarbocyanines were prepared by known standard methods. The following arbitrary symbols are used to denote the ethiodides of the bases: II-A, III-B, IV-C, V-D, VI-E, VII-F, VIII-G, X-H, 1-phenyl-2-methyl-5 [benzoxazolyl(2')] benzimidazole-I, 1-phenyl-2-methyl-5-[benzothiazolyl-(2')] benzimidazole-J.

Merocyanines XI–XVIII were synthesized by boiling together for 1–2 hr equimolecular (1.5–3.0 mmole) amounts of the appropriate starting materials in dry EtOH or dry pyridine plus triethylamine, while merocyanines XIX–XXI were synthesized by boiling the starting materials together in a 10-fold amount of dry pyridine with 10% Ac_2O, and triethylamine. Carbocyanines XXII–XXIX were prepared by heating the starting materials together in nitrobenzene for 25–60 min at 190–200°, then the dye was separated by treating the products with excess ether.* To synthesize dicarbocyanines XXX and XXXI, a mixture of equimolecular amounts of the appropriate ethiodide and tetraethoxypropane were refluxed together in a 10-fold quantity of nitrobenzene for 10–40 min, the dye then precipiated with ether, unreacted starting salt extracted with hot water, and the dye recrystallized. Crude dyes XXII–XXXI were purified by recrystallizing in the presence of KI. For melting point determination, the capillary containing the compound was introduced into a bath heated to approximately 20° under the dye's melting point. The positions of the main light absorption maxima of the dyes were determined in alcoholic solution using a SF-10 spectrophotometer.

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*Dye XXVI was prepared from ethiodide E and chloral, similarly to [10].

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Institute of Organic Chemistry,
AS UkrSSR, Kiev