Synthesis of Very Pure Cyanine Dyes

Preparation of Vinylogous Series of Bis-Thiazolyl, Bis-Thiazolinyl, Bis-Benzothiazolyl and Bis-Benzoselenazolyl Cyanine Iodides

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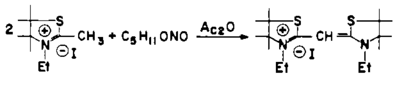
Vinylogous series of symmetrical cyanine dyes containing the benzothiazole, benzoselenazole, thiazole, and thiazoline nuclei were prepared. Very stringent conditions were placed on the acceptability of these dyes. The dyes had to be chromatographically pure, have a satisfactory elemental analysis and infrared spectrum, and be free of an electron spin resonance signal. Vinylogous series of the bis-thiazolinyl, bis-4-methyl thiazolyl, bis-4,5-diphenyl thiazolyl, bis-benzothiazolyl, and bis-benzoselenazolyl cyanine iodides were prepared. All attempts to synthesize the bis-thiazolyl heptamethines were unsuccessful.

SYSTEMATIC SERIES of these dyes were synthesized and their visible, infrared (*10*) and electron spin resonance spectra (*11*) were obtained. Additionally, charge transfer complexes were prepared from these dyes (*12*). The primary purpose was to correlate dye structure with their sensitizing properties on photographic film. Some of these dyes had been previously made and were reported in the patent literature frequently without melting points or other elementary physical data. Very stringent conditions were placed on the acceptability of our dyes. They had to be chromatographically pure, analyze correctly after chromatography for the required empirical formula, possess a satisfactory infrared spectrum, and be free of an electron spin resonance (free radical) signal.

SYNTHESIS

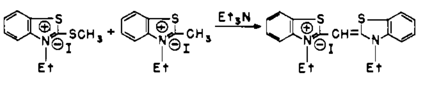
Monomethine Cyanines. These cyanines were prepared by the reaction of the quaternary salt with amyl nitrite and acetic anhydride (*4*).



(1)

Initially, difficulty was encountered in obtaining correct analyses for the monomethines. The problem was traced to the fact that in a number of cases under the reaction conditions, the iodide ion was converted to triodide ion. Reduction with sulfur dioxide converted the I_3^- to the I^- ion.

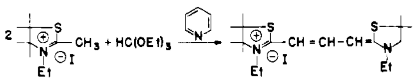
An alternative route employed was the reaction of the methyl mercapto quaternary salt with the 2-methyl quaternary salt (*7, 8*).



(2)

The physical data for the monomethine cyanines are given in Table I.

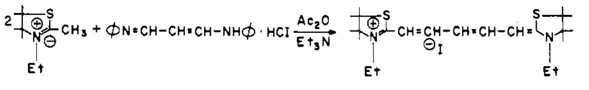
Trimethine Cyanines. These cyanines were prepared by reacting triethyl *o*-formate or triethyl *o*-acetate—where a methyl group on the bridge was desired—and the corresponding quaternary salt in the presence of pyridine as catalyst (*3*).



(3)

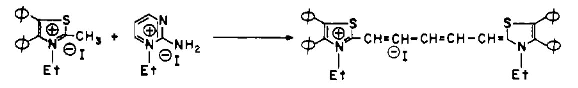
The physical data for the trimethine cyanines are supplied in Table I.

Pentamethine Cyanines. The thiazolinyl and thiazolyl pentamethine cyanines were prepared by utilizing β-anilinoacrolein-anil HCl (*5, 6*),



(4)

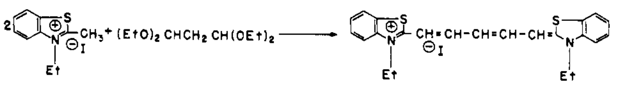
or aminopyrimidine ethiodide (*14*),



(5)

respectively, as the bridging agents.

The nonbridge-substituted benzothiazole and benzoselenazole cyanines were synthesized by reacting the quaternary salt and tetraethoxypropane in the presence of pyridine as catalyst (*13*).



(6)

To introduce a bromine atom on the bridge, mucobromic acid was reacted with aniline to give the mucobromic acid dianil hydrobromide which was then reacted with the quaternary salt (*5, 6*).

Table I. Melting Points, Chromatographic Data, and Elemental Analyses of the Thiazoline, Thiazole, Benzothiazole and Benzoselenazole Cyanines[a]

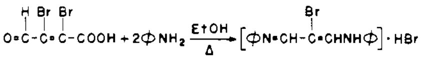
Compound	MP, °C.[b] Found	% C Found	% C Theory	% H Found	% H Theory	% N Found	% N Theory	%S/Se Found	%S/Se Theory	% I Found	% I Theory	Chromatography	
												Solvent	Eluent
2-Bis[3-ethylthiazolinyl] monomethine cyanine iodide	160	35.53	35.68	5.31	5.17		...	...	...	33.94	34.27	Chloroform	Chloroform
2-Bis[3-ethyl-4-methylthiazolyl] monomethine cyanine iodide	308	39.80	39.61	4.97	4.86	6.98	7.11	...	...	32.23	32.19	Chloroform	Acetone
2-Bis[3-ethyl-4,5-diphenylthiazolyl] monomethine cyanine iodide	265	62.34	62.68	4.94	4.66	4.15	4.18	...	...	19.01	18.92	Chloroform	Acetone
2-Bis[3-ethyl-4-methylthiazolyl] trimethine cyanine iodide	270	42.82	42.87	5.09	5.40	6.66	6.70	...	...	30.29	30.19	Chloroform	Acetone
2-Bis[3-ethylthiazolinyl] trimethine cyanine iodide[c]	248–50	39.50	39.39	5.39	5.34	7.07	7.05	...	...	31.45	32.02	Chloroform	Acetone
2-Bis[3-ethyl-4,5-diphenylthiazolyl] trimethine cyanine iodide	247–9	65.53	63.77	4.73	4.77	4.02	3.67	...	...	18.40	18.21	Chloroform	Acetone
2-Bis[3-ethylthiazolinyl] 7-methyl trimethine cyanine iodide	144	40.97	40.99	5.52	5.61	6.91	6.83	15.64	15.61	...	...	Chloroform	Acetone
2-Bis[3-ethylthiazolinyl] pentamethine cyanine iodide	209	42.60	42.60	5.60	5.49	6.63	6.45	...	...	29.51	30.04	Chloroform	Acetone-chloroform (9:1)
2-Bis[3-ethyl-4,5-diphenylthiazolyl] pentamethine cyanine iodide	196–7	65.56	64.81	5.09	4.88	3.69	3.88	8.53	8.87	16.91	17.56	Chloroform	Acetone
2-Bis[3-ethylthiazolinyl] 8-bromo pentamethine cyanine iodide	126–30	36.42	35.93	4.88	4.39	5.73	5.59	13.09	12.78	...	...	Acetone	Chloroform
2-Bis[3-ethyl-4-methylthiazolyl] pentamethine cyanine iodide	194	45.93	45.74	5.41	5.19	6.27	6.10	...	...	28.26	28.43	Chloroform	Chloroform
2-Bis[3-ethylthiazolinyl] heptamethine cyanine iodide	162–3	45.30	45.53	5.44	5.62	6.10	6.25	14.49	14.30	28.18	28.30	Acetone	Ethanol
2-Bis[3-ethylbenzothiazolyl] monomethine cyanine iodide	302	48.71	48.93	4.08	4.11	5.86	6.01	...	...	27.03	27.21	Chloroform	Acetone
2-Bis[3-methylbenzothiazolyl] monomethine cyanine iodide	289	46.25	46.58	3.74	3.45		...	14.89	14.63	29.76	28.95	Chloroform	Acetone
2-Bis[3-ethylbenzoselenazolyl] monomethine cyanine iodide	273	40.79	40.74	3.54	3.43	4.89	5.00	28.45	28.19	22.80	22.65	Methanol	Dimethyl formamide
2-Bis[3-ethylbenzothiazolyl] trimethine cyanine iodide	267–8	51.19	51.22	4.37	4.30	5.59	5.69	13.15	13.02	25.84	25.77	Chloroform	Acetone
2-Bis[3-ethylbenzothiazolyl] 9-methyl trimethine cyanine iodide	275–6	52.40	52.17	4.69	4.58	5.69	5.53	12.80	12.66	25.16	25.06	Chloroform	Acetone
2-Bis[3-ethylbenzoselenazolyl] trimethine iodide	264	42.74	43.03	3.59	3.61		...	26.76	26.94	21.45	21.65	Chloroform	Acetone
2-Bis[3-ethylbenzothiazolyl] pentamethine cyanine iodide	256–7	53.24	53.28	4.64	4.47	5.49	5.40	12.48	12.39	24.58	24.48	Chloroform	Acetone

2-Bis[3-ethylbenzothiazolyl]-10-bromo pentamethine cyanine iodide	194	46.24	46.24	3.80	3.71	4.69	4.74	10.93	10.73	24.58	24.48	Dimethyl formamide	Dimethyl formamide
2-Bis[3-ethylbenzothiazolyl]-9-[5-(1,3-diethyl-2-thiobarbiturenolide)] pentamethine cyanine	189-90.5	63.02	63.24	5.43	5.48	9.51	9.52	16.47	16.34	. . .	. . .	Chloroform	Acetone
2-Bis[3-ethylbenzothiazolyl]-9-[5-(1,3-dimethylbarbiturenolide)]pentamethine cyanine	191–4	. . .	. . .	. . .	. . .	10.44	10.29	11.53	11.77	. . .	. . .	Chloroform	Acetone
2-Bis[3-ethylbenzoselenazolyl]pentamethine cyanine iodide	225–	44.96	45.12	3.93	3.79	4.39	4.58	25.96	25.79	21.57	20.73	Chloroform	Acetone
2-Bis[3-ethylbenzothiazolyl] heptamethine cyanine iodide	201–2	55.15	55.35	4.66	4.27	5.32	5.16	11.81	11.82	23.24	23.39	Chloroform	Acetone
2-Bis[3-ethylbenzoselenazolyl] heptamethine cyanine iodide	211	46.85	47.04	3.82	3.95		. . .	24.69	24.74	20.14	19.88	Chloroform	Acetone

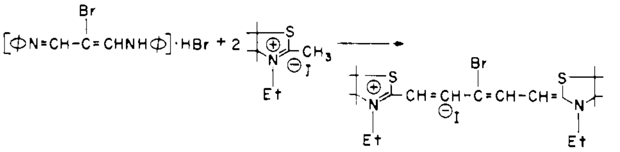
[a] Yields have not been included since after repeated recrystallization and chromatography they are extremely poor in most cases (< 10%).

[b] Melting point uncorrected.

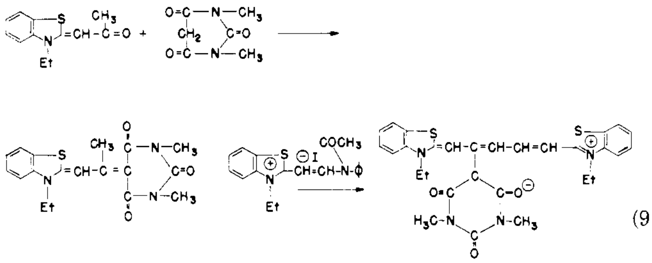
[c] This dye had a large ESR signal which could not be removed even after careful recrystallization. It should be emphasized that this dye analyzed for the correct empirical formula so that the impurities giving rise to the large ESR signal were exceedingly small.



$$O{=}C{-}C{-}C{-}COOH + 2\Phi NH_2 \xrightarrow[\Delta]{EtOH} [\Phi N{=}CH{-}C{=}CHNH\Phi]\cdot HBr \quad (7)$$

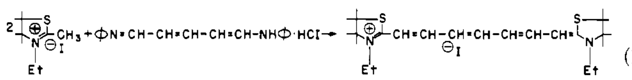

(8)

The trinuclear benzothiazole pentamethines were synthesized by reacting the barbituric or thiobarbituric acid derivative with 2-acetylmethylene-3-ethylbenzothiazolene to yield the 2-benzothiazolylidene-isopropylidene (thio) barbituric acid, then reacting this product with the acetanilido-vinyl benzothiazole ethiodide to yield the desired dye (*1*).


(9)

The physical data are given in Table I.

Heptamethine Cyanines. The heptamethines were prepared by reacting glutaconic dianil hydrochloride with the corresponding quaternary salt, utilizing sodium ethozide as catalyst (*2*).


(10)

The physical data for the heptamethine cyanines are supplied in Table I.

EXPERIMENTAL

Quaternary Salts. The quaternary salts were prepared by reacting the heterocyclic amine with ethyl iodide or ethyl *p*-toluene sulfonate. The experimental details are given in a previous paper (*9*).

Bridging Agents - β-ANILINOACROLEIN ANIL HYDROCHLORIDE. Into a 500-ml. ground glass flask plus attached condenser was charged 66 grams (0.5 mole) of 1, 3, 3-trimethoxypropene and 93 grams (1.0 mole) of aniline. The reaction mixture was refluxed for 1.5 hours, cooled, and 200 ml. of 20% HCl added with stirring and cooling. The product was filtered off and twice recrystallized from methanol, m. p. 205–206° C.

GLUTACONIC DIANIL HYDROCHLORIDE. Into a 500-ml. ground glass flask plus attached condenser was charged 47.1 grams (0.23 mole) of 2, 4-dinitrochlorobenzene and 37.6 ml. (0.4 mole, 37.0 grams) of pyridine. The reaction mixture was heated for 5 minutes at 60° C. and then for 15 minutes at 100° C. The reaction mixture was cooled, filtered, and recrystallized from ethanol to yield the 3, 4-dinitrophenyl pyridinium chloride, m. p. 189–190° C.

The above product, 42.8 grams (0.15 mole), 42.8 grams (0.53 mole) of aniline, and 60 ml. of absolute ethanol were heated on a steam bath for one hour, cooled, filtered, and washed with acetone to give the dianil hydrochloride, m. p. 142° C.

Preparation of Cyanine Iodides 2-ACETYLMETHYLENE-3-ETHYLBENZOTHIAZOLINE. 2-Methylbenzothiazole ethiodide [3.05 grams (.01 mole)] was suspended in 10 ml. of pyridine and cooled below 10° C. Then 0.98 gram (0.0125 mole) of acetyl chloride was added gradually with agitation. The reaction mixture was allowed to stand at 5° C. for 20 minutes, at room temperature for 30 minutes and finally heated at 100° C. for 20 minutes. The reaction mixture was cooled, pyridine removed under vacuum, diluted with water, fitered, and recrystallized from Skelly C, m. p. 111–113° C.

2-(β-Acetanilidovinyl) Benzothiazolium Iodide. 2-Methylbenzothiazole ethoidide [30 grams (0.1 mole)], 23.5 grams (0.12 mole) of diphenyl formamidine, and 170 grams (154 ml.) of acetic anhydride were refluxed for 20 minutes. The reaction mixture was then cooled, filtered, washed with ether, and twice recrystallized from methanol, m. p. 219–220° C.

2-Bis(3-Ethylthiazolinyl) Monomethine Cyanine Iodide. Amyl nitrite [3.45 grams (4.04 ml., 0.03 mole)], 10.2 grams (0.04 mole) of 2-methylthiazoline ethiodide, and 75 ml. of acetic anhydride were charged into the reaction pot and heated at 65 to 80° C. for 20 minutes. The reaction mixture was cooled, filtered, recrystallized from methanol, and chromatographed over alumina, m. p. 307–310° C.

2-Bis(3-Methylbenzothiazolyl) Monomethine Cyanine Iodide. 2-Methylbenzothiazole methiodide [2.4 grams (0.08 mole)], 2.7 grams (0.08 mole) of 2-methylthiobenzothiazole methiodide, 2.5 grams of triethylamine (0.025 mole), and 50 cc. of absolute ethanol were refluxed for 30 minutes. The reaction mixture was cooled, filtered, washed with acetone, recrystallized from methanol and chloroform, and chromatographed over alumina, m. p. 285–288° C.

2-Bis(3-Ethylthiazolinyl) Trimethine Cyanine Iodide. 2-Methylthiazoline ethiodide [8.4 grams (0.033 mole)] and 11 ml. of ethyl-*o*-formate were refluxed in 85 ml. of pyridine for 30 minutes. The reaction mixture was cooled, filtered and the product recrystallized from methanol and chromatographed over alumina, m. p. 248–250° C.

2-Bis(3-Ethylthiazolinyl) Pentamethine Cyanine Iodide. 2-Methylthiazoline ethiodide [4.2 grams (0.017 mole)], 2.2 grams (0.0085 mole) of β-anilinoacrolein anil HCl, 3.0 ml. of triethylamine, and 20 ml. of acetic anhydride were charged into a 100-ml. flask with attached condenser. The reaction mixture was refluxed for 10 minutes, cooled, filtered, washed with ether, and recrystallized from methanol, then chromatographed over alumina, m. p. 225° C.

2-Bis(3-Ethyl-4,5-Diphenylthiazolyl) Pentamethine Cyanine Iodide. 2-Methyl-4, 5-diphenylthiazolyl [25 grams (0.1 mole)] and 20 grams (0.1 mole) of ethyl *p*-toluene sulfonate were fused at 140° C. for 3 hours. After the mixture was cooled, 11.1 grams (0.044 mole) of 2-aminopyrimidine ethiodide and 150 ml. of absolute ethanol were added and refluxed for 1 hour. While still warm, the solution was poured into 180 ml. of 5% KI solution with agitation. The product was worked up and recrystallized from methanol, m. p. 196–197° C.

2-Bis(3-Ethylbenzoselenazolyl) Pentamethine Cyanine Iodide. 2-Methylbenzoselenazole ethiodide [25 grams (0.1 mole)] and 3.5 grams (0.01 mole) of tetraethoxypropane were charged into a flask with attached condenser. The reaction mixture was refluxed for 2 hours, cooled, filtered, washed with pyridine, 2-propanol, and water, and chromatographed over alumina, m. p. 225° C.

2-Bis(3-Ethylthiazolinyl) 9-Bromo Pentamethine Cyanine Iodide. Mucobromic acid [2.58 grams (0.01 mole)], 2.05 grams (0.022 mole) of aniline, and 50 ml. of absolute ethanol were heated for 1 hour on the steam bath. The mixture was cooled, filtered, and washed with acetone to afford the mucobromic dianil hydrobromide, m. p. 195–196° C.

2-Methylthiazoline ethiodide [10.2 grams (0.04 mole)], 8.02 grams (0.021 mole) of mucobromic dianil hydrobromide, 8.3 ml. of triethyl amine, and 100 ml. of absolute ethanol were refluxed for 30 minutes, cooled, filtered, washed with ether, chromatographed over alumina, and recrystallized from methanol, m. p. 126–130° C.

2-Bis(3-Ethylbenzothiazolyl) -9-[5-(1, 3-Diethyl-2-Thiobarbiturenolide)] Pentamethine Cyanine. 2-Acetylmethylene-3-ethylbenzothiazole [4.38 grams (0.02 mole)], 4.0 grams (0.02 mole) of *n,n*-diethylthiobarbituric acid, and 25 ml. of acetic anhydride were charged into a 100-ml. flask plus attached condenser. The reaction mixture was refluxed for 2 minutes, cooled, filtered, washed with ether, and dried, m. p. 222–3° C. The above intermediate product (2.68 grams), 5.8 grams (0.0129 mole) of 2-acetanilidovinyl benzothiazole ethiodide, 1.3 grams of triethylamine, and 40 ml. of pyridine were boiled for 30 seconds, transferred to a refrigerator overnight, and a small amount of solid was filtered off next morning. The filtrate was diluted with 1/2 liter of water and resultant precipitate filtered, washed with cold water, slurried with methanol and acetone, filtered off, and chromatographed over alumina, m. p. 189–190.5° C.

2-Bis(3-Ethylthiazolinyl) Heptamethine Cyanine Iodide. 2-Methylthiazoline ethiodide [5 grams (0.02 mole)] and 4.4 grams (0.015 mole) of glutaconic dianil HCl were dissolved in 40 ml. of boiling absolute ethanol. A solution of 0.72 gram of sodium in 40 ml. of absolute ethanol was dropped in with agitation and the heating continued for 2 minutes. The solution was cooled, the product filtered off, slurried with acetone, washed with ether and dried, and chromatographed over alumina, m. p. 162–163° C.

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