Derivatives of Thiazolo[5,4-*d*]thiazole.

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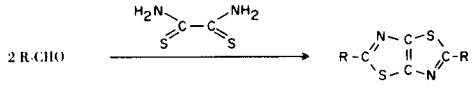
The condensation of dithio-oxamide with aromatic aldehydes was first described by Ephraim (1). More recently, Johnson and Ketcham (2) studied the reaction and established the structure of the resulting parent heterocycle as thiazolo[5,4-*d*]thiazole (I).



(I)

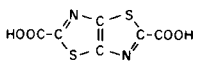
The reaction is comparable in scope with condensations such as those involved in the Perkin reaction and these authors (2) prepared a series of 2,5-disubstituted derivatives in moderate yeild from the corresponding substituted benzaldehydes. Similar derivatives were obtained from furfural and cinnamaldehyde, but condensation products were not obtained from aliphatic aldehydes (*e.g.* formaldehyde, *n*-butyl glyoxalate), although Moll (3) has recently described the preparation of the 2,5-dicyclohexyl derivative.

Subsequently, several papers (4,5) have described the preparation of other simple derivatives of 2,5-diphenylthiazolo[5,4-*d*]thiazole (I, R = Ph) and Fikrat and Oneto (6) have extended the applicability of the reaction to include some simple systems with heterocyclic substituents such as pyridyl, quinolyl and indolyl.

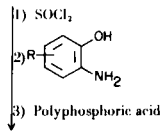
The purpose of our investigation has been to prepare a series of more highly conjugated derivatives for the comparison of their spectral characteristics with those (4) of the known 2,5-diphenylthiazolo[5,4-*d*]thiazoles which absorb strongly in the ultraviolet region. 2,5-Disubstituted thiazolo[5,4-*d*]thiazoles containing aromatic and heterocyclic functions were considered suitable for this investigation.

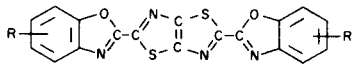
With regard to the general condensation of dithio-oxamide with the appropriate aldehyde (2), we have found that the use of *N*,*N*-dimethylformamide as solvent to be beneficial, as it gives a more controlled reaction resulting in improved yields (Table II) and also makes it possible to reduce the amount of aldehyde present from a great excess (2) to an equimolar quantity. For similar reasons, Preston (5) has recently recommended the use of *N*,*N*-dimethylacetamide. All compounds except 2,5-di(benzimidazol-2-yl)thiazolo[5,4-*d*]thiazole (I, R = benzimidazol-2-yl) were prepared from readily available intermediates. Benzimidazole-2-carboxaldehyde, which was required for this condensation, was prepared by hydrolysis of 2-dichloromethylbenzimidazole hydrochloride (7). Dimethyl sulphate treatment of the resulting thiazolo[5,4-*d*]thiazole caused 1-methylation of the benzimidazole substituents.

The availability of thiazolo[5,4-*d*]thiazole-2,5-dicarboxylic acid (II) (8) provided a route to 2,5-di(benzoxazol-2-yl)thiazolo[5,4-*d*]thiazole (III, R = H) and its derivatives.



(II)





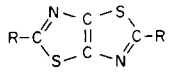
(III)

The compounds (Table III) were prepared by intermolecular condensation (9) of two moles of the appropriate *o*-aminophenol with one mole of thiazolo[5,4-*d*]thiazole-2,5-dicarbonylchloride (8) in polyphosphoric acid (10) at 200-250°. The compounds decomposed during the cyclisation step and the crude products were purified by vacuum sublimation and therefore the yields were low (< 35%).

The related 2,5-di[4-(benzoxazol-2-yl)phenyl]thiazolo-[5,4-*d*]thiazole (IV) has also been prepared from 4-ethoxycarbonylbenzaldehyde (11) and from 2-(4-methylphenyl)benzoxazole (*cf.* ref. 10) according to Scheme 1.

The derivatives listed in Tables II and III and compound IV are bright yellow or orange solids which are fluorescent in dilute solution with principal emission maxima in the range 440-470 mμ (Table I). The fluorescence masks the

TABLE I

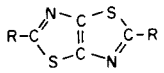


Ultraviolet and Fluorescence Spectra Data in Chloroform Solution

Compound R =	Ultraviolet Spectra λ max mμ, (log ε).										Fluorescence Spectra λ max, mμ (concentration ~10^{-4})			
Phenyl (a,b)	345	(4.53)	356*	(4.56)	375	(4.40)					410*	430 (i)		
p-Tolyl (c)	347 (i)	(4.57)	360*	(4.60)	375 (i)	(4.43)					418*	440 (i)		
1-Naphthyl			360*	(4.42)								440*	463	
2-Naphthyl			370 (i)	(4.65)	382*	(4.68)	398 (i)	(4.53)				442*	464 (i)	
9-Phenanthryl			360*	(4.48)								448*	475	
4-Biphenylyl			375*	(4.54)							430	448*		
2-Hydroxyl-1-naphthyl	335	(4.54)					419*	(4.70)	435 (i)	(4.60)			464	492*
2-Thienyl			375	(4.51)	388*	(4.56)	405	(4.41)				432	452*	
2-Styryl (a,b)					388 (i)	(4.59)	405*	(4.66)	422 (i)	(4.53)			458 (i)	476*
Benzimidazol-2-yl (b)					381 (i)	(4.63)	397*	(4.77)	421	(4.65)			462*	489 (i)
1-Methylbenzimidazol-2-yl (b)					381 (i)	(4.67)	400*	(4.79)	422	(4.66)		445	469*	495 (i)
Benzoxazol-2-yl					380	(4.59)	394*	(4.63)	418	(4.54)		432	453*	480 (i)
5-Chlorobenzoxazol-2-yl					380	(4.14)	397*	(4.26)	419	(4.13)		431	455*	480 (i)
5,7-Dichloro-6-methylbenzoxazol-2-yl					384	(4.69)	402*	(4.81)	424	(4.67)		440	464*	
4-Benzoxazol-2-yl-phenyl (d)					388	(4.59)	406*	(4.71)				438	465*	

(a) *cf.* reference 2. (b) measured in dioxane. (c) measured in methanol. (d) measured in acetone. (i) inflection. (*) principal maximum.

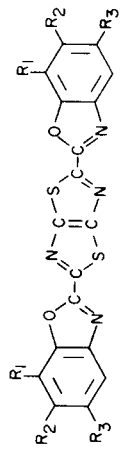
TABLE II



R	Method	Reaction Time (hours)	Yield (%)	M.p. °	Solvent	Found (%) C	H	N	S	Formula	Calcd. (%) C	H	N	S
Phenyl	A	0.75	57	217 (a)	C_6H_6	65.11	3.52	9.42	22.08	$C_{16}H_{10}N_2S_2$	65.30	3.43	9.52	21.75
p-Tolyl	A	1.5	54	294 (b,c)	$CHCl_3$	67.37	4.42	8.49	19.61	$C_{18}H_{14}N_2S_2$	67.07	4.38	8.69	19.86
1-Naphthyl	A	0.25	72	239	C_6H_6	73.23	3.75	7.14	16.82	$C_{24}H_{14}N_2S_2$	73.09	3.58	7.10	16.23
2-Naphthyl	B	0.75	44	288	C_6H_6	72.98	3.51	7.20	16.45	$C_{24}H_{14}N_2S_2$	73.09	3.58	7.10	16.23
9-Phenanthryl	B	2.5	64	>300	C_5H_5N	78.23	3.97	5.43	13.04	$C_{32}H_{18}N_2S_2$	77.72	3.67	5.67	12.94
4-Biphenylyl	B	0.5	50	>300	$CHCl_3$	75.36	4.31	6.20	14.41	$C_{28}H_{18}N_2S_2$	75.32	4.06	6.28	14.34
2-Hydroxy-1-naphthyl	B	0.5	70	339-342 (d)	C_5H_5N/EtOH	67.67	3.42	6.37	14.80	$C_{24}H_{14}N_2O_2S_2$	67.60	3.31	6.57	15.01
2-Thienyl	B	0.5	32	246 (e)	C_6H_6	47.31	2.03	8.88	41.63	$C_{12}H_6N_2S_4$	47.07	1.98	9.15	41.81
2-Styryl	A	0.5	8	245 (f)	C_6H_6	69.08	3.93	8.21	18.29	$C_{20}H_{14}N_2S_2$	69.36	4.07	8.09	18.48
2-Furyl	A	0.5	38	244 (g)	C_6H_6/petrol	52.70	2.15	10.13	23.16	$C_{12}H_6N_2O_2S_2$	52.56	2.21	10.22	23.34
Benzimidazol-2-yl	B	0.5	45	>400	C_5H_5N	58.01	2.83	22.68	17.11	$C_{18}H_{10}N_6S_2$	57.76	2.69	22.45	17.10

(a) lit. (2) m.p. 209-210°. (b) lit. (2) m.p. 292-293° with solid-liquid transition at 256-258°. (c) solid-liquid transition at 260-262°. (d) lit. (6) m.p. 338-342°. (e) lit. (6) m.p. 238-240°. (f) lit (2) m.p. 242-243°. (g) lit. (2) m.p. 238-240°.

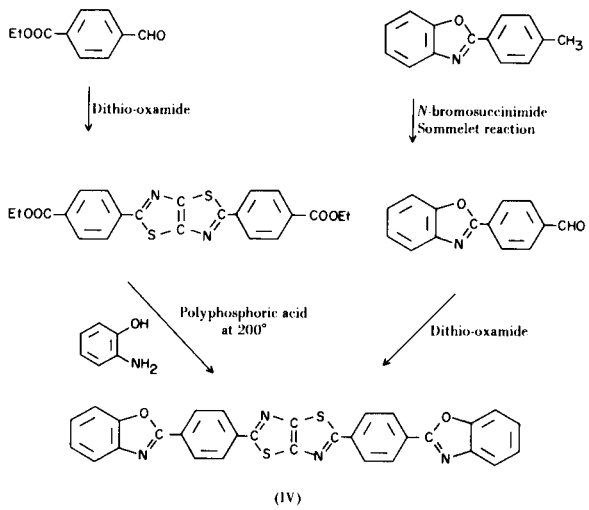
TABLE III



R_1	R_2	R_3	Yield (%)	Sublimation Temperature (°C) (at 0.1 mm.)	Found (%) C	H	Cl	N	S	Formula	Calcd. (%) C	H	Cl	N	S
H	H	H	35	250-270	57.36	2.04	---	14.90	16.82	$C_{18}H_8N_4O_2S_2$	57.45	2.14	---	14.89	17.01
H	H	Cl	20	280-320	48.60	1.52	16.05	12.51	14.68	$C_{18}H_6Cl_2N_4O_2S_2$	48.55	1.36	15.92	12.58	14.40
Cl	CH_3	Cl	10 (a)	300-320	44.09	1.68	26.00	10.36	11.55	$C_{20}H_8Cl_4N_4O_2S_2$	44.30	1.49	26.15	10.33	11.82

(a) The intermediate amide was prepared in benzene.

SCHEME 1



(IV)

intrinsic colour of the solution although quenching at high concentration imparts a yellow colour to the solution, which becomes progressively more blue on dilution.

The ultraviolet absorption spectra of the compounds exhibit three peaks in the 350-400 mμ region (Table I) although the exact positions of the maxima are dependent on the nature of the substituents at C_2 and C_5 positions. The spectra of some simple 2,5-disubstituted derivatives have been described previously (2) and we have found that with aromatic substituents *e.g.* (I, R = phenyl, 1- and 2-naphthyl, 4-biphenylyl, etc.), there is a bathochromic shift in the absorption maximum as the conjugation is extended. The shift in the absorption spectra is larger than that in the emission spectra. In the case of I (R = 2-hydroxy-1-naphthyl), there was a much greater bathochromic shift of about 50 mμ in both spectra. Also, the inclusion of a vinyl group (I, R = 2-styryl) produces a large bathochromic shift compared with the 2,5-diphenyl derivative (I, R = phenyl). The introduction of heterocyclic groups at positions C_2 and C_5 causes bathochromic shifts which are again greater than any observed with hydrocarbon substituents. The observed shifts are in the order: thienyl < benzoxazolyl < benzimidazolyl. Also, further substitution of these heterocyclic derivatives gives rise to small but definite successive shifts of a few mμ. A similar progression was observed with the fluorescence emission spectra. A further extension of the conjugation by the introduction of a phenyl ring as in IV gave rise to a bathochromic shift of about 10 mμ in both the absorption and emission spectra compared with III, (R = H).

EXPERIMENTAL

Melting points are corrected. Ultraviolet absorption spectra were measured in chloroform (0.02 g./litre) unless otherwise stated.

Fluorescence emission spectra were measured in chloroform (0.1 g./litre). The molecular weight of 2,5-di(1-methylbenzimidazol-2-yl)thiazolo[5,4-*d*]thiazole was confirmed by mass spectrometry.

2-(4-Bromomethylphenyl)benzoxazole.

A mixture of 2-(4-methylphenyl)benzoxazole (*cf.* ref. 10; 52.3 g.), recrystallized *N*-bromosuccinimide (50 g.) and benzoyl peroxide (2.5 g.) was suspended in carbon tetrachloride and heated under reflux with stirring for 5 hours. The solvent was removed *in vacuo* and the residue was washed thoroughly with boiling water, dried, and recrystallized from ethyl acetate to give 2-(4-bromomethylphenyl)benzoxazole, cream needles (51 g., 72%), m.p. 173-175°.

Anal. Calcd. for $C_{14}H_{10}BrNO$: C, 58.34; H, 3.55; Br, 27.73; N, 4.86. Found: C, 58.02; H, 3.43; Br, 27.51; N, 4.62.

2-(4-Formylphenyl)benzoxazole.

Hexamethylenetetramine (15 g.) was dissolved in boiling chloroform (200 ml.) and the solution was added to 2-(4-bromomethylphenyl)benzoxazole (28.8 g.) and the mixture heated under reflux for 16 hours. The salt was collected, dried and dissolved in 50% aqueous acetic acid (200 ml.) and heated under reflux for 1 hour. Hydrochloric acid (4*N*, 125 ml.) was added and the mixture boiled for 10 minutes, cooled and the precipitate of 2-(4-formylphenyl)-benzoxazole (15 g., 67%), m.p. 183-185°, ν max (potassium bromide), 1710 cm^{-1} (C=O) collected and dried.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.61; H, 4.10; N, 6.41.

Benzimidazole-2-carboxaldehyde.

This compound, m.p. 233° (lit. (7) m.p. 234°) was prepared by hydrolysis of 2-dichloromethylbenzimidazole hydrochloride according to the procedure of Hensel (7).

General Procedure for 2,5-Disubstituted Thiazolo[5,4-*d*]thiazoles (Table II).

Procedure A (2).

A mixture of dithio-oxamide (0.01 mole) and the appropriate aldehyde (0.1 mole) was heated in an oil bath to *ca.* 200° when a spontaneous reaction occurred. After the reaction subsided, the mixture was further heated at 200° (Table II), cooled to room temperature and diluted with acetone (150 ml.). The crude orange or yellow product was collected and recrystallized from a suitable solvent (Table II).

Procedure B.

A solution of the appropriate aldehyde (0.1 mole) and dithio-oxamide (0.05 mole) in *N,N*-dimethylformamide (100 ml.) was boiled under reflux (Table II), cooled, and the orange or yellow crystalline product collected, washed with ethanol and recrystallized from a suitable solvent (Table II).

2,5-Di(1-methylbenzimidazol-2-yl)thiazolo[5,4-*d*]thiazole.

A paste of 2,5-di(benzimidazol-2-yl)thiazolo[5,4-*d*]thiazole (1.87 g.) and dimethyl sulphate (5.04 g.) was heated on a steam-bath for 1.5 hours, cooled, diluted with water (25 ml.) and basified with dilute sodium hydroxide solution. The orange precipitate (1.6 g.) was collected, washed with ethanol and ether and dried. Vacuum sublimation at 260-300°/0.1 mm. gave 2,5-di(1-methylbenzimidazol-2-yl)thiazolo[5,4-*d*]thiazole as a bright yellow solid (1.2 g., 60%) m.p. > 300°.

Anal. Calcd. for $C_{20}H_{14}N_6S_2$: C, 59.70; H, 3.51; N, 20.89; S, 15.91; M, 402.36. Found: C, 59.60; H, 3.41; N, 21.31; S, 15.90; M, 402.

Thiazolo[5,4-*d*]thiazole-2,5-dicarbonylchloride (8).

Anhydrous thiazolo[5,4-*d*]thiazole-2,5-dicarboxylic acid (8), m.p. 212° (lit. (8), m.p. 211°) gave the 2,5-dicarbonylchloride on heating under reflux with thionyl chloride containing a few drops of *N,N*-dimethylformamide. The compound was not purified, but used directly in the next stage.

General Procedure for 2,5-Di(benzoxazol-2-yl)thiazolo[5,4-*d*]thiazole and Derivatives (Table III).

Thiazolo[5,4-*d*]thiazole-2,5-dicarbonylchloride (0.01 mole) was dissolved in hot chlorobenzene (60 ml.) and added to a stirred solution of the appropriate *o*-aminophenol (0.02 mole) in a minimum volume of hot chlorobenzene. An orange precipitate formed immediately and the mixture was cooled and the 2,5-dicarboxamide collected, washed with water, dried and added to polyphosphoric acid (100 ml.) with stirring at 70°. The temperature was gradually raised and maintained at 200-220° for 1 hour. The brown solution was cooled to 100°, poured onto crushed ice and the dark brown solid collected, washed with water, and dried *in vacuo*. Repeated vacuum sublimation gave the pure compound as a yellow solid (Table III).

2,5-Di(4-ethoxycarbonylphenyl)thiazolo[5,4-*d*]thiazole.

A solution of 4-ethoxycarbonylbenzaldehyde (11) (21.4 g., 0.12 mole) and dithio-oxamide (7.2 g., 0.06 mole) in *N,N*-dimethylformamide (50 ml.) was boiled under reflux for 1 hour, cooled, and the crystalline solid (2 g.) collected, washed with ethanol and dried. Recrystallization from chloroform gave 2,5-di(4-ethoxycarbonylphenyl)thiazolo[5,4-*d*]thiazole, yellow needles (1.5 g., 8%), m.p. 242-243°, ν max (potassium bromide), 1720 cm^{-1} (CO_2R).

Anal. Calcd. for $C_{22}H_{18}N_2O_4S_2$: C, 60.27; H, 4.14; N, 6.39; S, 14.60. Found: C, 60.53; H, 4.11; N, 6.22; S, 14.90.

2,5-Di[4-(benzoxazol-2-yl)phenyl]thiazolo[5,4-*d*]thiazole.

(a)

A mixture of 2,5-di(4-ethoxycarbonylphenyl)thiazolo[5,4-*d*]-thiazole (2.2 g., 5 millimoles) and *o*-aminophenol (1.09 g., 10 millimoles) was added to polyphosphoric acid (50 ml.) at 70° with stirring and the temperature raised to 200° and the mixture maintained at 200-210° for 1.5 hours. The dark solution was cooled to 100°, poured onto ice (200 g.) and the fine orange-brown precipitate (2.3 g., 87%) collected, washed with ethanol and dried. Repeated vacuum sublimation at 330-350°/0.04 mm. gave 2,5-di[4-(benzoxazol-2-yl)phenyl]thiazolo[5,4-*d*]thiazole, bright yellow needles, m.p. > 350°.

Anal. Calcd. for $C_{30}H_{16}N_4O_2S_2$: C, 68.18; H, 3.05; N, 10.60; S, 12.06. Found: C, 68.33; H, 3.27; N, 10.42; S, 12.04.

(b)

A solution of 2-(4-formylphenyl)benzoxazole (2.25 g., 10 millimoles) and dithio-oxamide (0.6 g., 5 millimoles) in *N,N*-dimethylformamide (50 ml.) was boiled under reflux for 1.5 hours, cooled and the yellow solid (1.9 g., 72%), m.p. > 350°, collected, washed with ethanol and dried. Vacuum sublimation at 330-360°/0.1 mm. gave 2,5-di[4-(benzoxazol-2-yl)phenyl]thiazolo[5,4-*d*]thiazole (1.2 g., 52%), m.p. > 350°. The infrared spectrum (potassium bromide) was identical with sample (a).

Anal. Calcd. for $C_{30}H_{16}N_4O_2S_2$: C, 68.18; H, 3.05; N, 10.60; S, 12.06. Found: C, 67.95; H, 2.96; N, 10.53; S, 12.10.

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