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Heterocyclic Tautomerisms. I.

An Investigation of the 2-Arylbenzothiazoline-2-(Benzylideneamino)thiophenol Tautomerism. Part 1.

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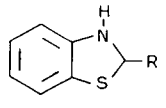
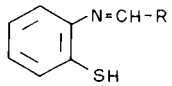
A definite tautomeric relationship has been found between 2-arylbenzothiazolines (I) and 2-(benzylideneamino)thiophenols (II). In a reaction characteristic of the closed ring structure (I), 2-arylbenzothiazolines were oxidized in high yield with benzoyl peroxide to the corresponding 2-arylbenzothiazoles (III). Reactions characteristic of the open ring structure (II) include the formation of the potassium salt of the open ring structure (IV) by reaction of 2-arylbenzothiazolines with potassium *t*-butoxide in toluene and oxidation of 2-arylbenzothiazolines to bis-[2-(benzylideneamino)phenyl] disulfides (V) by hydrogen peroxide in methanol.

Although tautomerism between 2-arylbenzothiazolines (I) and 2-(benzylideneamino)thiophenols (II) has been discussed (1-3), no significant work has been done to show its existence. Indeed, few reactions characteristic of 2-arylbenzothiazolines are known. These include, for example, substitution at the 3-position (4) and oxidation to benzothiazoles (3,5).

The infrared spectrum of 2-arylbenzothiazolines in the solid state (potassium bromide) or in solution (carbon tetrachloride) exhibit a sharp, strong absorption near 3 μ characteristic of a secondary amine N-H stretching frequency and no absorption in the region characteristic of the S-H stretching frequency. These compounds behave, under these conditions, as the closed ring tautomer (I). A reaction characteristic of this closed ring structure is the oxidation of 2-arylbenzothiazolines to 2-arylbenzothiazoles. Since the existing methods of preparation of 2-arylbenzothiazoles involve rather harsh conditions (3,5), a method requiring milder conditions for the preparation of oxidation-sensitive benzothiazoles, for example hydroxybenzothiazoles, would be useful. A procedure involving low temperature oxidation with benzoyl peroxide was found to be useful for this purpose (Table I).



I



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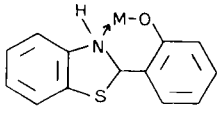
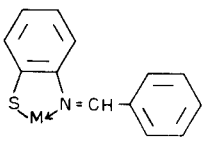
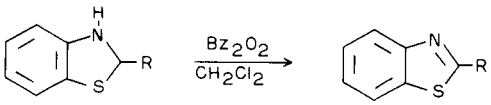


VI



VII

TABLE I



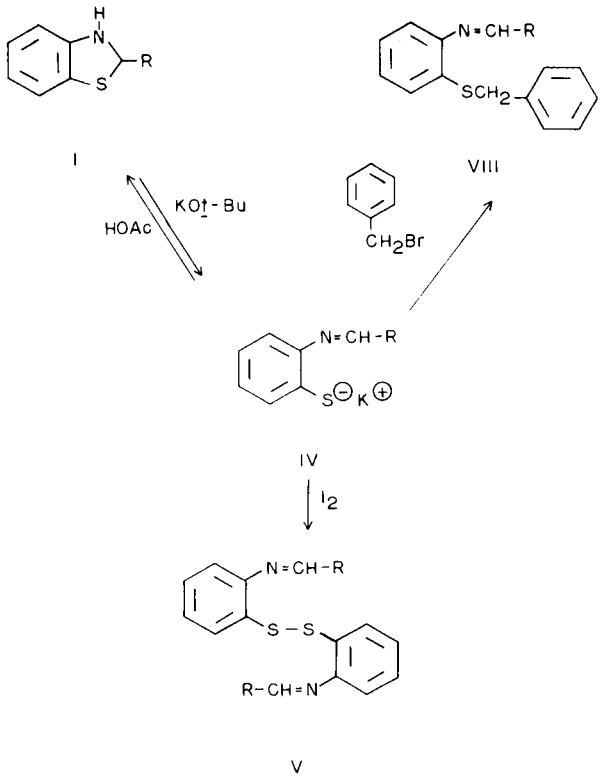
I III

R in III	Yield, %	Melting Point, °C Found	Literature
2-Chlorophenyl	60	81-82	82 (a)
2-Hydroxyphenyl	73	130-131	129 (b)
p-Phenylene-bis (c)	80	262-264	263 (d)

(a) D. S. Deshpande and N. W. Subbarao, *J. Sci. Ind. Research*, **16B**, 136 (1957). (b) A. W. Hofmann, *Ber.*, **13**, 1223 (1880). (c) The compound formed was *p*-phenylene-bis-(2-benzothiazole). The reaction was conducted in chloroform. (d) M. T. Bogart and A. Stull, *J. Am. Chem. Soc.*, 48, 248 (1926).

Apparently, no reactions of 2-arylbenzothiazolines involving the open ring tautomer (II) have been described as such. One might easily be led to suspect, however, that such compounds as the chelates derived from 2-(2-hydroxyphenyl)benzothiazoline described by Charles and Freiser (6) may well be derivatives of 2-(benzylideneamino)thiophenol (VII) even though these authors appear to consider these compounds to be derivatives of the closed ring structure (VI). Several years before, Bogart and Naiman (3) prepared zinc salts by allowing various aldehydes to react with the zinc salt of 2-aminothiophenol. Not only did the latter authors prepare a zinc salt by the reaction of salicylaldehyde with the zinc salt of 2-aminothiophenol but an analogous compound was obtained with benzaldehyde. This latter compound has, most probably, a structure of type VII. Further, the infrared spectrum of the zinc chelate prepared from 2-(2-hydroxyphenyl)-benzothiazoline by the method of Charles and Freiser and the zinc salt prepared from salicylaldehyde and the zinc salt of 2-aminothiophenol by the method of Bogart and Naiman were identical and very similar to that of bis-[2-(2-hydroxybenzylideneamino)phenyl] disulfide (V). In addition, none of these two former spectra possessed a band near 3 μ characteristic of N-H stretch.

In an effort to obtain a more easily characterized metallic salt of the 2-(benzylideneamino)thiophenol tautomer, potassium *t*-butoxide was allowed to react with substituted 2-arylbenzothiazolines in toluene solution. By this method, strongly colored potassium salts (7) were obtained as precipitates. The constitution and structure of these salts (IV) were proven by conversion to the parent benzothiazolines by solution in alcoholic acetic acid, by reaction with iodine in toluene to give bis-[2-(benzylidene-amino)phenyl] disulfides (V), and by reaction with benzyl bromide in toluene to give 2-(benzylidene-amino)phenyl benzyl sulfides (VIII, Table II).



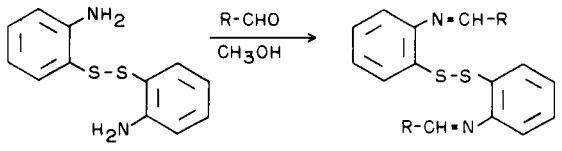
In order to offer proof of structure, the disulfides (V) were prepared by reaction of the respective aldehydes with bis-(2-aminophenyl) disulfide, the benzyl sulfides (VIII) by allowing the respective aldehydes to react with 2-aminophenyl benzyl sulfide (Tables III and IV).

TABLE II

R in I	Recovered I		V		VIII	
	Yield, %	Melting Point, °C	Yield, %	Melting Point, °C	Yield, %	Melting Point, °C
2-Chlorophenyl	50	83-85	50	174-179 (a)	71	109-111 (b)
2,4-Dichlorophenyl	40	94-96	40	184-186 (c)	50	107-110 (d)

(a) *Anal.* Calcd. for $C_{26}H_{18}Cl_2N_2S_2$: C, 63.29; H, 3.65. Found: C, 63.55; H, 3.90. (b) *Anal.* Calcd. for $C_{20}H_{16}ClNS$: C, 71.32; H, 4.75. Found: C, 71.13; H, 4.95. (c) *Anal.* Calcd. for $C_{26}H_{16}Cl_4N_2S_2$: C, 55.52; H, 2.85. Found: C, 55.80; H, 3.05. (d) *Anal.* Calcd. for $C_{20}H_{15}Cl_2NS$: C, 64.69; H, 4.40. Found: C, 64.72; H, 4.20.

TABLE III

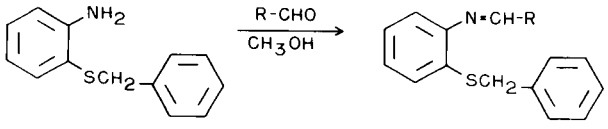


V

R	Yield, %	Melting Point, °C
2-Chlorophenyl	95	174-179 (a)
2,4-Dichlorophenyl	91	184-187 (a)
2-Hydroxyphenyl	95	171-172 (b)

(a) The infrared spectra of these disulfides were identical to those of the disulfides obtained from the potassium salts by iodine oxidation. No depression was noted on "mixed melting" the compound prepared by each procedure. (b) The literature melting point (3) is 171°.

TABLE IV



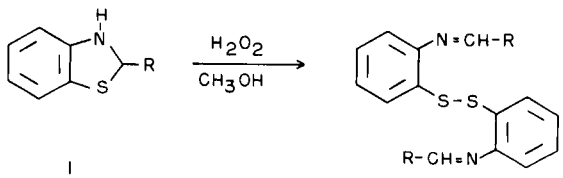
VIII

R	Yield, %	Melting Point, °C (a)
2-Chlorophenyl	86	109-112
2,4-Dichlorophenyl	87	106-109

(a) The infrared spectra of these sulfides were identical to those of the sulfides obtained from the potassium salts by reaction with benzyl bromide. No depression was noted on "mixed melting" the compounds prepared by each procedure.

In another series of reactions characteristic of the 2-(benzylideneaminophenyl)thiophenol tautomer, 2-arylbenzothiazolines were found to give good yields of bis-[2-(benzylideneamino)phenyl] disulfides (Table V) by oxidation with hydrogen peroxide in methanol.

TABLE V



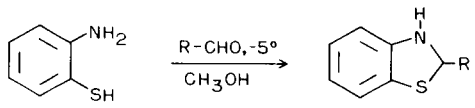
I V

R	Yield, %	Melting Point, °C
2-Chlorophenyl	80	172-177 (a)
2,4-Dichlorophenyl	85	184-186 (a)
2-Hydroxyphenyl	67	171-172 (a, b)
3-Methoxy-4-hydroxyphenyl	63	173-176 (c)

(a) These disulfides were shown by "mixed melting point" and infrared spectra to be identical to those noted in Tables II and III. (b) The literature melting point (3) is 171°. (c) *Anal.* Calcd. for $C_{28}H_{24}N_2O_4S_2$: C, 65.12; H, 4.65. Found: C, 65.37; H, 4.80.

In the course of this work, a more refined procedure for preparing 2-arylbenzothiazolines of high purity and yield with minimum possibility of side reactions was effected by reaction of 2-aminothiophenol with the desired aldehyde in methanol at -5°. Under these conditions the benzothiazoline gradually crystallized in almost analytical purity (Table VI).

TABLE VI



I

R	Yield, %	Melting Point, °C
2-Chlorophenyl	75	82-84 (a)
2,4-Dichlorophenyl	83	94-96 (b)
2-Hydroxyphenyl	80	140-141 (c, d)
3-Methoxy-4-hydroxyphenyl	84	100-102 (e, f)
p-Phenylene-bis (g)	86	133-135 (g)

(a) *Anal.* Calcd. for $C_{13}H_{10}ClNS$: C, 63.03; H, 4.04. Found: C, 63.16; H, 4.24. (b) *Anal.* Calcd. for $C_{13}H_9Cl_2NS$: C, 55.32; H, 3.19. Found: C, 55.37; H, 3.33. (c) The literature melting point is 163-165° [M. Claasz, *Ber.*, 49, 1141 (1916)]. (d) *Anal.* Calcd. for $C_{13}H_{11}NOS$: C, 68.12; H, 4.80. Found:

C, 67.96; H, 5.06. (e) The literature melting point [see (c) above] is 130°. (f) *Anal.* Calcd. for $C_{14}H_{14}NO_2S$: C, 64.62; H, 5.39. Found: C, 64.76; H, 5.23. (g) The compound formed was *p*-phenylene-bis-(2-benzothiazoline). *Anal.* Calcd. for $C_{20}H_{16}N_2S_2$: C, 68.93; H, 4.59. Found: C, 68.68; H, 4.85.

The conclusion that there exists a definite tautomeric relationship between 2-arylbenzothiazolines and 2-(benzylideneaminophenyl)thiophenols becomes, upon consideration of the data described herein, inescapable. The further observation that certain, substituted 2-arylbenzothiazolines exhibit reversible thermochromism in nonpolar solvents give grounds for the suspection that, for certain derivatives, the tautomerism is mobile. This matter is now being investigated for a future publication.

EXPERIMENTAL

Dibenzoyl Peroxide Oxidation of Benzothiazolines (Table I). A. Procedure for 2-(2-Hydroxyphenyl) and 2-(2-Chlorophenyl)benzothiazolines.

To a solution of 2.7 g. (0.011 mole) dibenzoyl peroxide in 50 ml. of dichloromethane at 0° was added 0.01 mole of the 2-arylbenzothiazoline. The resulting mixture was stirred at 25° until a spontaneous rise in temperature occurred (If this did not occur, gentle heat was applied to just cause the solvent to boil.). At this point the reaction mixture was cooled to 0°. After the mixture was allowed to stand at 0° for 20 minutes, the temperature was allowed to rise to 25° and stand at that temperature for 2 hours. The solution was then extracted with two 25 ml. portions of 1*F* sodium carbonate and the organic layer was concentrated to 5 ml. The oxidation product from the chlorophenyl derivative was purified by addition of 20 ml. of heptane, concentration to 18 ml., subjected to charcoal purification, concentrated to 10 ml. and cooled to effect crystallization. The oxidation product from the hydroxyphenyl derivative was purified by addition of 15 ml. of ethanol, concentrated to 10 ml. and cooled to effect crystallization.

B. Procedure For 1,4-Bis-(2-benzothiazolinyl)benzene.

To 1.0 g. of 1,4-bis-(2-benzothiazolinyl)benzene (0.003 mole) in 20 ml. of chloroform at 0° was added 2.0 g. (0.008 mole) of dibenzoyl peroxide. The resulting mixture was stirred at 0° for 30 minutes, then at 25° for 1 hour. The solid which separated was removed and washed with 10 ml. of chloroform.

Preparation of 2-Arylbenzothiazolines (Table VI).

To a solution of 0.05 mole of aldehyde in 50 ml. of ethanol (For vanillin one-half of this amount of alcohol was used.) at 0° was added 10.0 g. (0.08 mole) of 2-aminothiophenol and the resulting solution was cooled for 1 to 4 hours at -5° to -10° (For the vanillin derivative scratching the walls of the vessel was necessary for crystallization.). The product was removed and washed with 10-30 ml. of ethanol at -5° to -10°. The analytical samples were recrystallized from ethanol.

Preparation of 2-(Benzylideneaminophenyl) Sulfides (IV).

A thin, gelatinous suspension of potassium *t*-butoxide (0.25 mole per liter) was prepared by addition of a solution of potassium in *t*-butanol to toluene and distillation of most of the *t*-butanol. To a solution of 0.0055 mole 2-arylbenzothiazoline in 5 ml. of toluene was added 20 ml. of the above suspension. The dark red, gelatinous potassium salt precipitated immediately. Since this salt rapidly decomposed in moist air, it must be used as quickly as possible.

Reconversion to Benzothiazolines (Table II).

The toluene suspension of the potassium salt from 0.0055 mole of 2-arylbenzothiazoline was filtered by suction, washed with 100 ml. of pentane and the sulfide, moist with pentane, was added to 10 ml. of ethanol containing 1 ml. of acetic acid and, finally, 20 ml. of water added. The resulting suspension was filtered and the solid material was recrystallized from ethanol.

Preparation of Bis-(2-benzylideneaminophenyl) Disulfides From Potassium Salts (Table II).

To the toluene suspension of the potassium salt from 0.0055 mole of 2-arylbenzothiazoline was added 0.70 g. (0.003 mole) of powdered iodine. The resulting suspension was heated at 100° with stirring for 15 minutes. The reaction mixture was centrifuged at 3000 r.p.m. and the supernatent liquid concentrated to 5 ml. The concentrate was cooled to -5° for several hours and the solid material which crystallized was washed with 3 ml. of toluene followed by 10 ml. of pentane. For analysis the product was recrystallized twice from toluene.

Preparation of Bis-[2-(benzylideneamino)phenyl] Disulfides From 2-Arylbenzothiazolines (Table V).

A solution of 2.0 ml. of pure 30% hydrogen peroxide and 0.01 mole of 2-arylbenzothiazoline in 15 ml. of methanol was refluxed for 5 to 15 minutes and cooled to 25°. The material which precipitated [In the case of the disulfide form 2-(3-methoxy-4-hydroxyphenyl)benzothiazoline, water was slowly added and the solution cooled to -5°. The crystalline material which separated was recrystallized from aqueous alcohol.] was dissolved in a few ml. of hot dimethylformamide to which 15 ml. of ethanol was added. On cooling to -5°, the crystalline material which separated was removed and was recrystallized from toluene. For analysis the sample was again recrystallized from toluene.

Preparation of Bis-(2-benzylideneaminophenyl) Disulfides From Bis-(2-aminophenyl) Disulfide (Table III).

A solution of 0.50 g. (0.002 mole) of bis-(2-aminophenyl) disulfide and 0.01 mole of the desired aldehyde in 15 ml. of methanol was heated under reflux for 5-15 minutes. The material which crystallized was purified as described above.

Bis-(2-aminophenyl) Disulfide.

To a solution of 2.5 g. (0.02 mole) of 2-aminothiophenol in 10 ml. of 70% ethanol was added very slowly 2.0 ml. of 30% hydrogen peroxide (The temperature was not allowed to rise above 60°.). On cooling to 25°, the product separated as bright yellow rhombic plates. The crystalline product was removed and washed with 5 ml. of 70% ethanol to yield 2.3 g. (92%) of product, m.p. 93°.

2-Aminophenyl Benzyl Sulfide.

Sodium, 2.5 g. (0.11 mole), was dissolved in 50 ml. of absolute ethanol. To this solution was added 12.5 g. (0.10 mole) of 2-aminothiophenol followed by 18.0 g. (0.12 mole) of benzyl bromide. After the reaction mixture was allowed to stand for 15 minutes, 200 ml. of diethyl ether was added and the sodium bromide which separated was discarded. The filtrate was concentrated to a volume of 60 ml. and cooled to -10°. The crystals which separated (dry weight 15.0 g. or 71% yield of crude product of melting point 38-41°) were removed and recrystallized from ethanol to give 11.0 g. (52%) of colorless plates, m.p. 42-45°. The literature (8) melting point was 45°.

Preparation of 2-(Benzylideneaminophenyl) Benzyl Sulfides (Table II) From the Potassium Salt.

To the toluene suspension of the potassium salt from 0.0055 mole of 2-arylbenzothiazoline was added 0.9 g. (0.006 mole) of benzyl bromide. The resulting suspension was heated at 100° with stirring for 15 minutes. The reaction mixture was centrifuged at 3000 r.p.m. and the supernatant liquid concentrated to 5 ml. and cooled to -5° for several hours. The solid which separated was removed and washed with 3 ml. of toluene followed by 10 ml. of pentane. For analysis the product was recrystallized from toluene-pentane.

Preparation of 2-(Benzylideneaminophenyl) Benzyl Sulfides From 2-(Aminophenyl) Benzyl Sulfide (Table IV).

To 0.40 g. (0.002 mole) of 2-aminophenyl benzyl sulfide in 4.0 ml. of methanol at 60° was added 0.003 mole of the desired aldehyde and the resulting solution was cooled at 25° for 6 hours and finally to -10°. The material which crystallized was removed and recrystallized from toluene-pentane for analysis.

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