[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

4-STYRYLTHIAZOLES. SYNTHESES AND RELATIONSHIPS AMONG ULTRAVIOLET ABSORPTION SPECTRA

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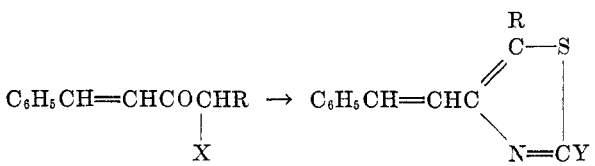
Recent work in this laboratory on the bromination of β-phenyl-α,β-unsaturated ketones has made available halomethyl and halobenzyl styryl ketones of



I II

a,	R = H,	X = I	a,	R = H,	Y = H	f,	R = H,	Y = SH
b,	R = C_6H_5,	X = Br	b,	R = H,	Y = CH_3	g,	R = C_6H_5,	Y = SH
c,	R = C_6H_5,	X = I	c,	R = C_6H_5,	Y = CH_3	h,	R = H,	Y = OH
			d,	R = H,	Y = NH_2	i,	R = C_6H_5,	Y = OH
			e,	R = C_6H_5,	Y = NH_2			

the type I (1). These halo ketones have been found to react with thioamides and related compounds, apparently without complication due to the conjugated unsaturation, to yield the 4-styrylthiazoles (II). The latter compounds may be regarded as analogs of stilbene derivatives. Stilbene derivatives and such stilbene analogs as styryl derivatives of pyridine, benzoquinoline, benzothiazole, and acridine have been studied as growth inhibitors and carcinogenic agents (2); the styrylthiazoles described here may be of interest in the same connection. Numerous 2-styrylthiazoles are known, but 4- or 5-styrylthiazoles, in which the carbon to carbon double bond of the thiazole ring is conjugated directly with the styryl group, have apparently not been reported previously. A report of the preparation of 5-styrylthiazole (3) was later found to be in error (4).

The ultraviolet absorption spectra of these compounds, most of which show two or more strong bands, afford an opportunity to compare effects produced by a variety of substituent groups (phenyl, methyl, amino, hydroxyl, mercapto) with effects due to corresponding groups in derivatives of aromatic hydrocarbons. It has been found that spectral effects in this 4-styrylthiazole series can often be predicted remarkably well from relationships which have been found to hold among derivatives of quite a different family of compounds, the polynuclear aromatic hydrocarbons, which have been chosen for comparison here

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because their thoroughly investigated spectra usually show several strong bands (5).

Three halogenated ketones, one derived from benzalacetone and two derived from benzyl styryl ketone, were used in the synthesis of the 4-styrylthiazoles (II). The conversion of benzalacetone into iodomethyl styryl ketone (Ia) and of benzyl styryl ketone into 1-bromo-1,4-diphenyl-3-buten-2-one (Ib) have been described previously (1). The third halo ketone, 1-iodo-1,4-diphenyl-3-buten-2-one (Ic), was prepared by treatment of a direct bromination product of benzyl styryl ketone, 1,3,4-tribromo-1,4-diphenyl-2-butanone, with excess sodium iodide in acetone solution. This iodo ketone was more easily crystallized than the corresponding bromo compound and was frequently used in place of the latter compound for that reason. The three different halo ketones were converted into thiazoles by suitable modification of procedures which have appeared in the literature (6).

The parent compound of this series of thiazole derivatives, 4-styrylthiazole (IIa), was prepared by treatment of iodomethyl styryl ketone (Ia) with thioformamide. The crude thiazole was a liquid from which a picrate was obtained. However, the yield of crystalline picrate was only 8%, based on the iodomethyl styryl ketone (Ia) used, and because of the low yield of this thiazole it has not been investigated further. The yield of 2-methyl-4-styrylthiazole (IIb) produced by the reaction of thioacetamide with iodomethyl styryl ketone was somewhat better (19%, isolated as the picrate). Although in the free form this thiazole has been obtained only as a liquid, a crystalline hydrochloride was also obtained.

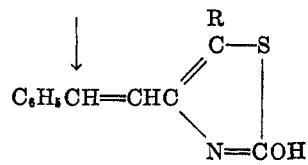
Treatment of the bromo ketone (Ib) with thioacetamide resulted in a 24% yield of 2-methyl-4-styryl-5-phenylthiazole (IIc), which was isolated and characterized in the form of the hydrochloride. As the free base this compound has also been obtained only in the form of an oil.

Reactions of the halo ketones Ia and Ic with thiourea gave 2-amino-4-styryl thiazole (IId) and 2-amino-4-styryl-5-phenylthiazole (IIe), respectively. These compounds were crystalline solids and were obtained in considerably better yields (49% for IId, 48% for IIe) than were the 2-methyl derivatives. The thiazole IIe was also obtained directly from benzyl styryl ketone in 38% yield by treatment of the ketone with iodine and thiourea, a procedure which has been used with other types of ketones (not α, β-unsaturated) for the preparation of 2-aminothiazoles (7). However, 2-amino-4-styrylthiazole (IId) was not successfully prepared from benzalacetone by this means.

Treatment of the halo ketones Ia and Ic with ammonium dithiocarbamate gave the crystalline 2-mercapto-4-styrylthiazole (IIf) (49% yield) and 2-mercapto-4-styryl-5-phenylthiazole (IIg) (28% yield), respectively. The crystalline 2-hydroxy-4-styrylthiazole (IIh) and 2-hydroxy-4-styryl-5-phenylthiazole (IIi) were obtained by treatment of the halo ketones Ia and Ic with barium thiocyanate, followed by cyclization of the resulting thiocyano ketones IIIa and IIIb:

$$\text{Ia or Ic} \xrightarrow{Ba(SCN)_2} C_6H_5CH{=}CHCOCHSCN \quad (R)$$

IIIa, R = H
IIIb, R = C_6H_5



IIh, R = H
IIi, R = C_6H_5

Thiocyanomethyl styryl ketone (IIIa) was obtained in crystalline form in 67% yield, then was purified and converted into the hydroxythiazole IIh in quantative yield by heating with 3 *N* hydrochloric acid. The thiocyano ketone IIIb, however, was obtained only as an oil and was cyclized without purification to give the thiazole IIi in a 20% over-all yield from the iodo ketone Ic.

The following significant relationships may be observed in the ultraviolet spectra of these compounds:

(a) The spectrum of 2-methyl-4-styrylthiazole (IIb) (Fig. 1, Curve A), obtained from the thiazole hydrochloride by addition of sodium hydroxide to the ethanol solution used in the measurement, shows a considerable resemblance to

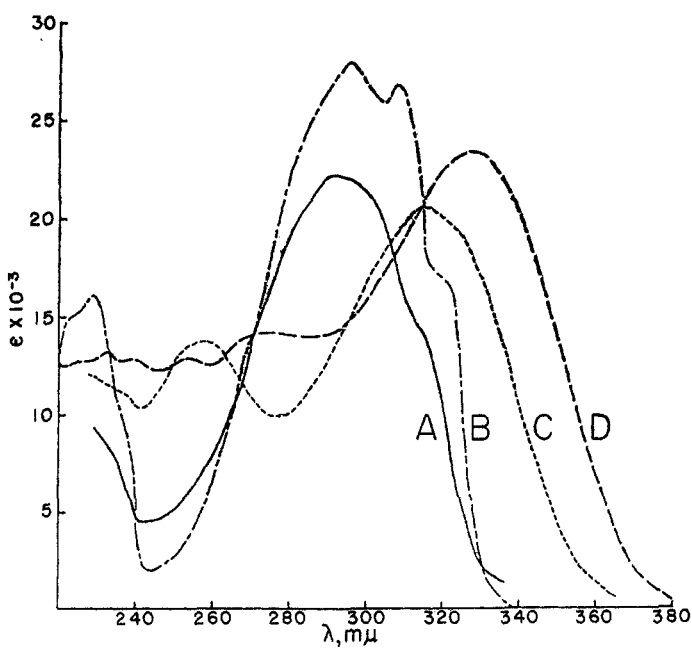


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA: A, 2-Methyl-4-styrylthiazole (IIb) in 0.1 *N* ethanolic potassium hydroxide; B, *trans*-Stilbene in 95% ethanol; C, 2-Methyl-4-styryl-5-phenylthiazole (IIc) in 0.1 *N* ethanolic potassium hydroxide; D, 2-Amino-4-styryl-5-phenylthiazole (IIe) in 0.1 *N* ethanolic hydrochloric acid.

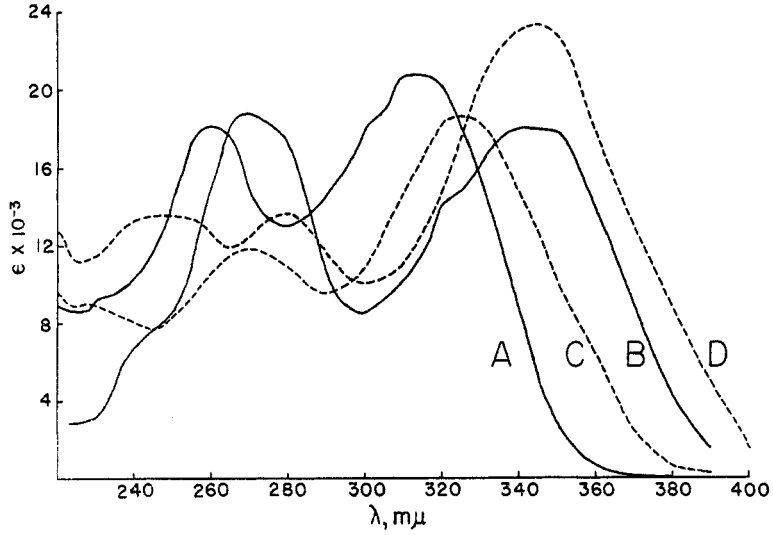


FIG. 2. ULTRAVIOLET ABSORPTION SPECTRA IN 95% ETHANOL: A, 2-Amino-4-styrylthiazole (IId); B, 2-Amino-4-styryl-5-phenylthiazole (IIe); C, 2-Mercapto-4-styrylthiazole (IIf); D, 2-Mercapto-4-styryl-5-phenylthiazole (IIg).

the spectrum of *trans*-stilbene (Fig. 1, Curve B),[2] although less fine structure is evident in the spectrum of the thiazole derivative. The spectra of the 2- and 4-styrylpyridines (stilbazoles), it may be mentioned, are also similar to the spectrum of *trans*-stilbene (9). All of the 4-styrylthiazoles described here are probably of the *trans*-configuration; degradations of the parent halo ketones Ia and Ic have yielded *trans*-cinnamic acid (1, 10). Since there is a strong band at 292 mμ in the spectrum of 2-methyl-4-styrylthiazole (IIb), whereas the principal maxima in styrene (λ 244 mμ; log ε 4.23) (11) or β-methylstyrene (λ 246 mμ; log ε 4.25) (11) and in 2-methylthiazole (λ 244 mμ; log ε 4.34) are at much shorter wave lengths, it is clear that in compound IIb there is effective conjugation between the styryl group and the thiazole ring.

(b) Comparison of the spectra of the four pairs of 4-styrylthiazoles having the same group in the 2-position of the thiazole ring shows that the spectrum of the member of each pair which contains the 5-phenyl group regularly shows bathochromic shifts affecting all of the bands. The longest wave length bands are shifted toward the visible to the extent of 20–29 mμ, whereas the band found in the 260–280 mμ region for most of the compounds is shifted by only 10–12 mμ. (In the case of the 2-mercaptothiazoles there is a third, rather poorly defined band at still shorter wave length which is shifted by 20 mμ.) In the cases of 2-amino-4-styryl-5-phenylthiazole (IIe) (compare Curves A and B, Fig. 2), of 2-mercapto-4-styryl-5-phenylthiazole (IIg) (compare Curves C and D, Fig.2)

[2] Curve B is the spectrum for *trans*-stilbene in 95% ethanol reported by Beale and Roe (8).

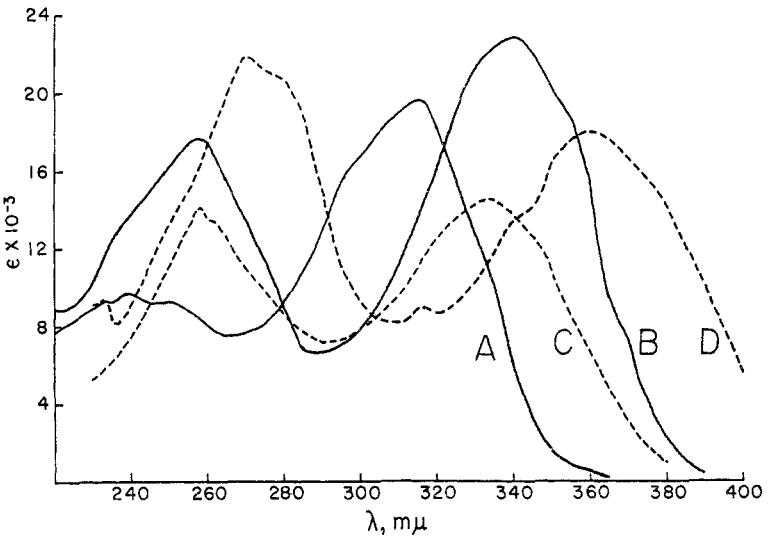


FIG. 3. ULTRAVIOLET ABSORPTION SPECTRA: A, 2-Hydroxy-4-styrylthiazole (IIh) in 95% ethanol; B, 2-Hydroxy-4-styryl-5-phenylthiazole (IIi) in 95% ethanol; C, 2-Hydroxy-4-styrylthiazole (IIh) in 0.1 *N* ethanolic sodium hydroxide; D, 2-Hydroxy-4-styryl-5-phenylthiazole (IIi) in 0.1 *N* ethanolic sodium hydroxide.

and of 2-hydroxy-4-styryl-5-phenylthiazole (IIi) in alkaline solution (compare Curves C and D, Fig. 3), the bathochromic shifts due to the 5-phenyl group are accompanied by remarkably little change in the shape of the curves. Relatively small bathochromic shifts without significant alteration of the shape or intensity of the curves, effects which are typically produced by alkyl side chains in polynuclear aromatic hydrocarbons, have been designated "B-effects" by Jones (5), who has pointed out a striking example of such effects caused by the phenyl groups of 9,10-diphenylanthracene. In that case the failure of the phenyl groups to produce the larger changes ("C-effects") (5) usually associated with addition of conjugated unsaturation was attributed to prevention by steric interference of coplanarity of the phenyl groups with the anthracene nucleus ("S-effect") (5). In the case of the 4-styrylthiazole derivatives under consideration here, examination of scale models[3] discloses that coplanarity of the thiazole ring simultaneously with the 4-styryl and 5-phenyl groups is difficult to accommodate because of steric interference. The observation in these cases of what should probably be considered nothing more than a B-effect due to the added 5-phenyl group is therefore understandable.

(c) Comparison of the spectra of 4-styrylthiazoles containing the functional groups NH_2, SH, or OH in the 2-position of the thiazole ring with spectra of the corresponding 2-methyl compounds reveals in every case a bathochromic shift of the longest wave length band by 21–33 mμ, with the mercapto group pro-

[3] The Fisher-Taylor-Hirschfelder models were used. With the sets available to us the thiazole ring could not quite be closed, but it was clear that this fact did not seriously alter the picture of steric interference between the phenyl and styryl groups.

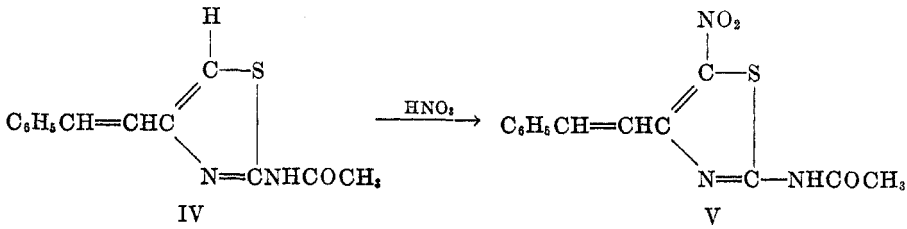
ducing the largest shifts. In magnitude and character these shifts are similar to those observed upon introduction of hydroxyl groups into polynuclear aromatic hydrocarbons (5). It should be noted that the relatively large C-effects due to the introduction of the amino group into polynuclear aromatic hydrocarbons [or into the 4-position of stilbene (8)] are not observed in this series, at least not with the amino group placed as found in these particular compounds.

(d) In alkaline solution (0.1 *N* ethanolic sodium hydroxide) where the compounds might be expected to exist in the form of their sodium salts, the spectra of both of the 2-hydroxythiazoles, IIh and IIi, (Curves C and D, Fig. 3) showed bathochromic shifts of the bands of the corresponding free hydroxy compounds very similar in magnitude to those found when phenols derived from polynuclear aromatic hydrocarbons are converted into their sodium or potassium salts (5). It is observed that the formation of the sodium salts of these hydroxy thiazoles increased the intensity of the shorter wave length bands, especially in the case of 2-hydroxy-4-styrylthiazole (IIh), and decreased somewhat the intensity of the longest wave length band. As is true in the case of salts of phenols derived from polynuclear aromatic hydrocarbons, the spectra of the salts of the hydroxythiazoles IIh and IIi resemble rather closely in shape the spectra of the corresponding amino compounds IId and IIe (Fig. 2, Curves A and B), with corresponding bands lying at slightly longer wave lengths in the case of the salts of the hydroxy compounds (5).

(e) The spectrum of 2-amino-4-styryl-5-phenylthiazole (IIe) in a 0.1 *N* alcoholic hydrochloric acid solution (Fig. 1, Curve D) shows a hypsochromic shift of the long wave-length band as compared to the spectrum of the same compound in neutral ethanol (Fig. 2, Curve B), and the spectrum becomes quite similar in general shape to that of the corresponding methyl derivative, 2-methyl-4-styryl-5-phenylthiazole (IIc) (compare Curves C and D, Fig. 1). This is the behavior commonly noted when amino derivatives of polynuclear aromatic hydrocarbons are converted into their salts (5). However, the spectrum of the aromatic amine salt is often a closer duplicate of the spectrum of the corresponding methyl derivative than is observed with these styrylthiazole derivatives. It should be mentioned that although 2-methyl-4-styryl-5-phenylthiazole (IIc) is sufficiently basic to form a hydrochloride readily in concentrated aqueous hydrochloric acid, its spectrum taken in 0.1 *N* ethanolic hydrochloric acid is nearly indistinguishable from Curve C, Fig. 1, which was taken in 0.1 *N* ethanolic sodium hydroxide.

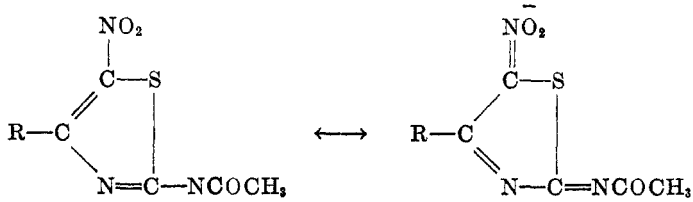
Reactions other than salt formation have been investigated for only one of the nine thiazoles described here, 2-amino-4-styrylthiazole (IId). This substance was readily acetylated with acetic anhydride to give 2-acetamido-4-styrylthiazole (IV). Compound IV underwent nitration with concentrated nitric acid to yield a bright-yellow mononitro derivative. The nitro group was shown not to have entered the benzene ring, since oxidation of the compound with chromic oxide in acetic acid yielded benzoic acid. Formula V is therefore written for the nitro compound on the assumption that the nitro group has entered the only open position on the thiazole nucleus. Compound V is soluble in aqueous sodium

hydroxide, giving orange-colored solutions. The same behavior has been observed in the case of 2-acetamido-5-nitrothiazole, the nitration product of 2-acet-



IV V

amidothiazole (12). The acidity of these compounds can be accounted for on the basis of a resonance stabilized anion:



EXPERIMENTAL[4, 5]

Benzyl styryl ketone. The following has been found to be a reliable procedure for the preparation of benzyl styryl ketone. Procedures previously described [see Ref. (1) and references cited therein] in which details were less completely specified, frequently gave mainly a different, higher-melting condensation product.

Purified benzaldehyde (10.2 g.; 0.096 mole) was added to a solution of 0.75 g. of sodium hydroxide in 400 ml. of distilled water contained in a 500-ml. Erlenmeyer flask. The flask was placed in a thermostatted oil-bath held at 58–60° and the mixture was stirred with a Hershberg (13) stirrer turning at the rate of 720 r.p.m. When the mixture reached the bath temperature, 12.5 g. (0.093 mole) of phenylacetone was added. Stirring and heating were maintained for 18 to 20 hours. The flask then was cooled under a stream of tap water and the aqueous solution was decanted from the solid cake of benzyl styryl ketone which separated in the bottom of the flask. The cake was washed once with water, and the material then was crystallized from methanol (used in large enough volume to keep the ketone from "oiling out") to yield 10–12 g. (50–60%) of light-yellow flakes, m.p. 69–73°, which were of a suitable purity for use as starting material in the bromination reactions performed next.

1,3,4-Tribromo-1,4-diphenyl-2-butanone. A compound of this structure, m.p. 143–144° was previously obtained by bromination of benzyl styryl ketone at room temperature or below (1). In the present work bromination was carried out at elevated temperatures in order to avoid premature separation of partially brominated products, but with the result that there was obtained a lower-melting tribromide which is evidently another diastereoisomer or a mixture of diastereoisomers, but is suitable for use in the preparation of 1-iodo-1,4-diphenyl-3-butene-2-one (Ic).

To a stirred solution of 15 g. (0.0675 mole) of benzyl styryl ketone in 30 ml. of hot carbon tetrachloride, 21.6 g. (0.135 mole) of bromine was added. The mixture was allowed to cool

[4] Microanalyses by Clark Microanalytical Laboratories, Urbana, Illinois, Drs. G. Weiler and F. B. Strauss, Oxford, England, and Micro Tech Laboratores, Skokie, Illinois.

[5] Melting points are corrected.

slowly to room temperature while large quantities of hydrogen bromide were evolved. As soon as crystals began to separate from the solution, an additional 30 ml. of carbon tetrachloride was added, and after crystallization seemed complete, the mixture was filtered to remove the product. The material was twice suspended in 30-ml. portions of ethanol and recovered by filtration, then was washed with water and dried over phosphorus pentoxide in a vacuum desiccator. Grinding was necessary during the drying procedure, and a final period of drying in air was needed to remove all of the carbon tetrachloride. The yield was 17 g. (54.5%) of material suitable for use in the preparation of the iodo ketone (Ic). Two crystallizations from aqueous ethanol gave white crystals, m.p. 126–128°, which showed a slightly high carbon content, presumably because of traces of the corresponding dibromide.

Anal. Calc'd for $C_{16}H_{13}Br_3O$: C, 41.65; H, 2.82.

Found: C, 42.33; H, 2.99.

1-Iodo-1,4-diphenyl-3-buten-2-one. A solution of 9.9 g. (0.066 mole) of sodium iodide in the minimum amount of warm acetone (*ca.* 60 ml.) was added to a solution of 10 g. (0.022 mole) of 1,3,4-tribromo-1,4-diphenyl-2-butanone in the minimum volume of acetone (*ca.* 40 ml.). A precipitate of sodium bromide formed immediately. The mixture was warmed to 50°, then allowed to stand for one hour as it cooled toward room temperature. The mixture was diluted with 150 ml. of water and 125 ml. of ether was added. Aqueous sodium sulfite solution was then added in portions and the mixture was shaken in a separatory funnel until the iodine color had disappeared in both layers. The ether layer was separated, washed with water, and dried over magnesium sulfate. The solid residue obtained after evaporation of the solution was recrystallized from ethanol to yield 4.1 g. (55%) of crude material, m.p. 73–77°. Further recrystallization from ethanol yielded light-yellow granules, m.p. 91.5–93°.

Anal. Calc'd for $C_{16}H_{13}IO$: C, 55.20; H, 3.75.

Found: C, 54.44; H, 3.77.

The slightly low analytical value for carbon has not been explained.

4-Styrylthiazole picrate. To a solution of 0.25 g. (0.003 mole) of thioformamide hydrate (14) in 4 ml. of ethanol was added a solution of 0.75 g. of iodomethyl styryl ketone in 4 ml. of ethanol. The mixture, which darkened immediately, became clear when heated for 1 hour on a steam cone. The mixture was made basic by addition of aqueous sodium hydroxide, additional water was added, and the mixture was extracted with two 25-ml. portions of ether. The ether extracts were washed once with water and then dried over calcium chloride. Evaporation of the ether left a brown oil. The oil was taken up in 5 ml. of ethanol and 10 ml. of a saturated solution of picric acid in ethanol was added. After a period of standing, the picrate, m.p. 160–162°, crystallized from the solution. The yield was *ca.* 0.10 g. (8%). Recrystallization from ethanol raised the m.p. to 163–166°, giving yellow prisms.

Anal. Calc'd for $C_{17}H_{12}N_4O_7S$: C, 49.05; H, 2.91.

Found: C, 49.15; H, 2.89.

Similar results were obtained in another experiment in which the reaction mixture was not heated, but was allowed to stand for 3 days in the refrigerator.

2-Methyl-4-styrylthiazole. A solution prepared from 2 g. (0.0074 mole) of iodomethyl styryl ketone, 0.55 g. (0.0074 mole) of thioacetamide, and 10 ml. of absolute ethanol was refluxed for 1 hour and then allowed to stand for 2 days at room temperature. The solution was made basic with concentrated ammonium hydroxide and diluted with 200 ml. of water. An oil separated. The mixture was extracted with two 50-ml. portions of ether, and the ether extracts, which contained the crude thiazole, were washed with water, dried over magnesium sulfate, and filtered.

(A) *The picrate.* The oil remaining after evaporation of the ether was dissolved in 15 ml. of ethanol and 15 ml. of a saturated ethanolic picric acid solution was added. The yellow crystals which separated after the flask was scratched were removed by filtration. The yield was 0.6 g. (19%); m.p. 177–180°. Recrystallization from ethanol did not change the melting point. The compound crystallized in yellow plates.

Anal. Calc'd for $C_{18}H_{14}N_4O_7S$: C, 50.23; H, 3.28.
Found: C, 50.10; H, 3.29.

(B) *The hydrochloride.* Dry hydrogen chloride was passed into the ether solution of the free thiazole. The supernatant ether was decanted from the oil which was precipitated and concentrated hydrochloric acid was added to the oil. The mixture was heated and the resulting solution was filtered free of undissolved material. After the solution had been kept for 3 days in the freezing compartment of a refrigerator, the light-tan needles which separated were collected by filtration, pulverized, and dried under reduced pressure for 6 hours. The dried crystals melted at 146–152°.

Anal. Calc'd for $C_{12}H_{12}ClNS$: C, 60.61; H, 5.09; N, 5.89.
Found: C, 60.19; H, 4.98; N, 5.81.

2-Methyl-4-styryl-5-phenylthiazole hydrochloride. A solution prepared from 3 g. (0.01 mole) of 1-bromo-1,4-diphenyl-3-butene-2-one, 0.75 g. (0.01 mole) of thioacetamide, and 10 ml. of absolute ethanol was refluxed for 2 hours. A solid product separated during the heating period. The mixture was cooled and diluted with ether and the product was removed by filtration. The yield was 1 g. of a material melting with decomposition at *ca.* 226°, which is presumed to consist mainly of the thiazole hydrobromide. It was dissolved in 15 ml. of warm ethanol, and dilute aqueous sodium hydroxide was added until the solution was basic to litmus. The solution was then diluted with a large volume of water. The oil which separated was taken up by 2 extractions of the mixture with ether. The ether solution was washed with water, dried over magnesium sulfate, and filtered. Hydrogen chloride was passed into the filtrate, and the resulting white crystalline precipitate was removed by filtration, washed with ether, and dried. The yield was 0.75 g. (24%) of material melting at 145–153°. Recrystallization from ethanol gave a sample melting with decomposition at 145–155°.

Anal. Calc'd for $C_{18}H_{16}ClNS$: C, 68.88; H, 5.14; N, 4.46.
Found: C, 68.45; H, 5.30; N, 4.38.

2-Amino-4-styrylthiazole. To a solution prepared by warming 2 g. (0.0074 mole) of iodomethyl styryl ketone with 14 ml. of ethanol was added a solution of 0.56 g. (0.0074 mole) of thiourea in 10 ml. of hot ethanol. The mixture was allowed to stand for 15 minutes, then was cooled and kept overnight at a temperature of −10°. The precipitated light-yellow product was removed by filtration, washed with a small amount of cold ethanol, and dried. The yield of crude product, m.p. 177–181°, was 1.6 g. (57.5%). Recrystallization from ethanol gave white cubes, m.p. 181–181.5°. Analytical results indicated that this product is 2-amino-4-styrylthiazole hydroiodide with one mole of ethanol of crystallization.

Anal. Calc'd for $C_{11}H_{11}IN_2S \cdot C_2H_5OH$: C, 41.49; H, 4.55; N, 7.44.
Found: C, 41.10; H, 4.36; N, 7.70.

The free aminothiazole was obtained from this salt by addition of aqueous ammonia. To a solution of 0.8 g. (0.0021 mole) of the salt in 10 ml. of ethanol, concentrated aqueous ammonia was added until the solution was alkaline to litmus. Dilution with water precipitated a pale-yellow product, which was removed by filtration and dried. The yield was 0.4 g. (49% over-all) of material melting at 157–161°. Recrystallization from ethanol gave pure 2-amino-4-styrylthiazole, m.p. 160–162°, as pale-yellow needles.

Anal. Calc'd for $C_{11}H_{10}N_2S$: C, 65.30; H, 4.98; N, 13.84.
Found: C, 65.20; H, 5.02; N, 13.5, 14.3.

2-Amino-4-styryl-5-phenylthiazole. (A) *From 1-iodo-1,4-diphenyl-3-buten-2-one.* To a solution prepared by warming a mixture of 3 g. (0.0086 mole) of 1-iodo-1,4-diphenyl-3-buten-2-one and 15 ml. of ethanol was added 0.66 g. (0.0087 mole) of thiourea. The mixture was heated on a steam-bath for 90 minutes and then cooled in a refrigerator overnight. The tan product which separated was removed by filtration, washed with small portions of cold ethanol, and dried to yield 2 g. of a product melting at 186–190°. This crude material evidently contained the desired aminothiazole in the form of a hydriodide. A 2.2-g. sample of it was dissolved in a hot solution prepared from 15 ml. of ethanol and 7 ml. of water, and a 5% sodium carbonate solution was added until the solution was basic to litmus.

During the addition 2 ml. of hot ethanol was added to clear the solution, and at the end of the addition the mixture was heated for 5 minutes on a steam-bath, then diluted with water until cloudy and kept in a refrigerator overnight. The yellow precipitate was removed by filtration, washed twice with water, and dried, to give 1.1 g. (48.2% yield from the iodo ketone) of material melting at 156–158.5°. Recrystallization from ethanol gave yellow plates, m.p. 160–161.5°.

Anal. Calc'd for $C_{17}H_{14}N_2S$: C, 73.35; H, 5.06; N, 10.06.
Found: C, 73.70; H, 5.04; N, 9.84.

(B) *Directly from benzyl styryl ketone.* A mixture prepared from 5 g. (0.0225 mole) of benzyl styryl ketone, 5.7 g. (0.0225 mole) of iodine, 6 g. (0.045 mole) of thiourea, and 20 ml. of ethanol was refluxed for 12 hours. A quantity of crystalline material separated during the heating period. The mixture was then kept at 0° overnight and the tan, crystalline precipitate was removed by filtration and washed twice with small amounts of cold water. The yield was 3.5 g. (38% calculated as the aminothiazole hydriodide) of material melting at 186–190°. Treatment of the substance with alkali yielded the free 2-amino-4-styryl-5-phenylthiazole, m.p. 160–161.5°. Recrystallization of the crude salt from ethanol gave white needles melting at 217–228° which are apparently the hydriodide.

Anal. Calc'd for $C_{17}H_{15}IN_2S$: C, 50.25; H, 3.72; N, 6.89.
Found: C, 49.96; H, 3.76; N, 6.41.

2-Mercapto-4-styryl-5-phenylthiazole. Ammonium dithiocarbamate (0.66 g. (0.006 mole), freshly prepared by adding carbon disulfide to a 2-molar proportion of ammonia dissolved in absolute ethanol) was suspended in 10 ml. of ethanol. The resulting suspension was stirred while 2 g. (0.0058 mole) of 1-iodo-1,4-diphenyl-3-buten-2-one was added over a period of 5 minutes. The mixture was kept at room temperature for 10 minutes, then was heated on a steam-bath for one hour. The white product, m.p. *ca.* 180° separated when the mixture was cooled. The yield was 0.5 g. (28%). Recrystallization from a chloroform-petroleum ether (b.p. 65–110°) mixture gave light-yellow needles, m.p. 224–225°.

Anal. Calc'd for $C_{17}H_{13}NS_2$: C, 69.15; H, 4.43; N, 4.74.
Found: C, 68.80; H, 4.58; N, 4.60.

2-Mercapto-4-styrylthiazole. A solution of 2 g. (0.0074 mole) of iodomethyl styryl ketone in 20 ml. of ethanol was added over a period of 30 minutes to a stirred suspension of 0.88 g. (0.008 mole) of ammonium dithiocarbamate, prepared as described above, in 10 ml. of ethanol which was cooled in an ice-bath. After completion of the addition the mixture was cooled for 30 minutes. Crystallization of the product was induced by scratching the flask, and the resulting white product was removed by filtration and dried. The yield was 0.8 g. (49%) of material melting at 210–212°. Recrystallization from ethanol gave pale-yellow prisms melting at 210–211.5°.

Anal. Calc'd for $C_{11}H_9NS_2$: C, 60.20; H, 4.14; N, 6.39.
Found: C, 60.12; H, 4.02; N, 6.25.

Thiocyanomethyl styryl ketone. Iodomethyl styryl ketone (2 g., 0.0074 mole) and barium thiocyanate dihydrate (2 g., 0.0067 mole) were dissolved in 15 ml. of ethanol. An immediate precipitation of white crystals occurred. The mixture was cooled in an ice-bath for 1 hour, then the product was removed by filtration and dried. The yield was 1.0 g. (67%) of material melting at 117–119°. Recrystallization from ethanol raised the m.p. to 118.5–119.5°, giving colorless plates.

Anal. Calc'd for $C_{11}H_9NOS$: C, 64.99; H, 4.46; N, 6.88.
Found: C, 64.60; H, 4.55; N, 7.11.

2-Hydroxy-4-styrylthiazole. A suspension of 0.6 g. of thiocyanomethyl styryl ketone in 12 ml. of 3 *N* hydrochloric acid was heated for approximately 5 hours on a steam-bath. The mixture was cooled, and the product was removed by filtration. The yield was 0.6 g. (quantitative) of a crude product melting at 194–206°. Recrystallization from ethanol gave light-tan prisms melting at 211–214°.

Anal. Calc'd for $C_{11}H_9NOS$: C, 64.99; H, 4.46; N, 6.88.
Found: C, 64.65; H, 4.81; N, 6.76.

2-Hydroxy-4-styryl-5-phenylthiazole. A solution of 2.5 g. (0.0072 mole) of 1,4-diphenyl-1-

iodo-3-buten-2-one and 1.2 g. (0.0041 mole) of barium thiocyanate dihydrate in ethanol was refluxed for 5 hours. The mixture then was diluted with water and extracted twice with ether. The combined ether solutions were washed with water, dried over calcium chloride, filtered, and concentrated by evaporation. The residual light-brown oil was dissolved in 10 ml. of glacial acetic acid and 1 ml. of concentrated hydrochloric acid was added. The mixture was heated for 90 minutes on a steam-bath, then neutralized and diluted with a large volume of water. The product was extracted into ether, and the ether extract was dried over calcium chloride, filtered, and concentrated to a volume of 7 ml. When this solution was cooled with Dry Ice, a light-tan solid separated and was removed by filtration. The yield was 0.4 g. (20%) of material melting at 216–225°. Crystallization from a mixture of chloroform and petroleum ether (b.p. 65–110°) gave pale-yellow needles, m.p. 227–229°.

Anal. Calc'd for $C_{17}H_{13}NOS$: C, 73.10; H, 4.69; N, 5.02.
Found: C, 72.70; H, 4.53; N, 4.91.

2-Acetamido-4-styrylthiazole. A mixture of 2.1 g. (0.011 mole) of 2-amino-4-styrylthiazole and 20 ml. of acetic anhydride was heated on a steam-bath for 30 minutes. Water then was added to the resulting solution to hydrolyze the excess acetic anhydride. The white solid which separated was removed by filtration. The yield was 2.3 g. (85%) of material melting at 204–206°. Recrystallization from ethanol gave colorless plates, m.p. 205.5–206.5°.

Anal. Calc'd for $C_{13}H_{12}N_2OS$: C, 63.90; H, 4.95; N, 11.46.
Found: C, 63.92; H, 4.82; N, 11.50.

2-Acetamido-4-styryl-5-nitrothiazole. To 0.9 g. (0.0037 mole) of 2-acetamido-4-styrylthiazole 10 ml. of concentrated nitric acid was added. The temperature of the resulting suspension rose to 40°. After several minutes bright-yellow crystals appeared in the reaction mixture. The product was collected by filtration through glass wool, washed with water, and dried. The yield was 0.4 g. (38%), m.p. 257–259°. Recrystallization gave deep-yellow needles, m.p. 261–262°.

Anal. Calc'd for $C_{14}H_{11}N_3O_3S$: C, 53.96; H, 3.83; N, 14.52.
Found: C, 54.38; H, 3.91; N, 14.45.

The compound dissolved in dilute aqueous sodium hydroxide to give an orange solution.

Oxidation of the compound with chromic anhydride in glacial acetic acid at the reflux temperature yielded a small amount of benzoic acid. There was evidence of the formation of another, higher-melting product, but not enough material was recovered to permit its purification.

Ultraviolet absorption spectra. The ultraviolet absorption spectra were determined with a Beckman Model DU spectrophotometer. For spectra determined in alkaline solution the solvents were prepared by dissolving 5.6 g. of potassium hydroxide in 100 ml. of 95% ethanol, or 4 g. of sodium hydroxide in 10 ml. of water, and diluting the resulting solutions to 1000 ml. with 95% ethanol to obtain 0.1 *N* alkaline solutions. The solvent for the determinations in acid solution was prepared by diluting 8.4 ml. of concentrated hydrochloric acid to 1000 ml. with 95% ethanol to obtain 0.1 *N* acid solutions.

SUMMARY

4-Styrylthiazole and ten related compounds have been prepared, and the ultraviolet absorption spectra of eight of the compounds have been investigated. The spectrum of 2-methyl-4-styrylthiazole shows a close resemblance to the spectra of *trans*-stilbene or of 2- or 4-stilbazole. Effects on the spectra of compounds in this 4-styrylthiazole series produced by the functional groups NH_2, SH, or OH in the 2-position of the thiazole ring and of the phenyl group in the 5-position of the thiazole ring have been found to parallel in many respects effects produced by corresponding groups in derivatives of aromatic hydrocarbons.

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