

The Electrophilic Reactivity of Alkoxyalkylidene Derivatives of Heterocyclic Keto-methylene Compounds.

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Certain cyclic keto-methylene compounds condense with orthoesters to give 1-alkoxyalkylidene derivatives. Some of these have been converted into dimethinmerocyanines substituted by alkyl in the chain. 5-1'-Alkoxyalkylidenerhodanines with ammonia or primary or secondary amines give 5-1'-aminoalkylidenerhodanines. The latter were quaternized by methyl toluene-*p*-sulphonate and then converted into complex merocyanines by condensation with heterocyclic keto-methylene compounds.

5-1'-Ethoxyethylidenerhodanines and 4-1'-ethoxyethylidene-2-ethylthiothiazol-5-one react with a number of thiols, to give the related alkyl(or aryl)-thioethylidene derivatives. The latter have, in many cases, been isolated in two forms believed to be the *cis*- and *trans*-isomers.

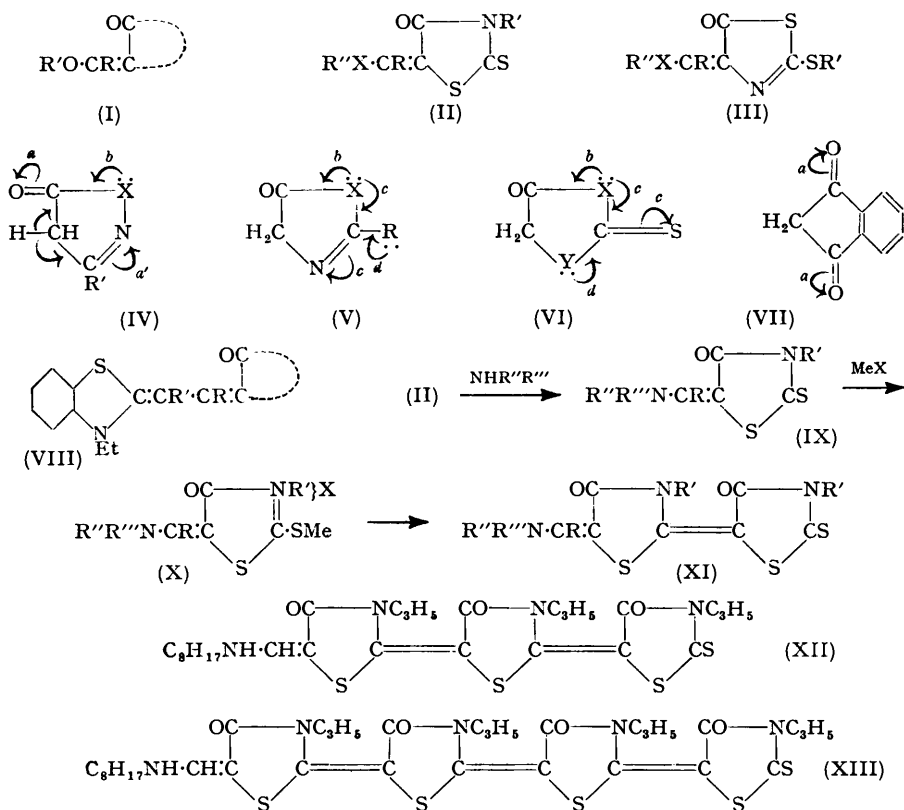
It is known that certain heterocyclic keto-methylene compounds behave in the same way as their open-chain analogues (Claisen, *Annalen*, 1897, **297**, 5, 16; Jones, *J. Amer. Chem. Soc.*, 1952, **74**, 4889) in forming alkoxyalkylidene derivatives (I) when refluxed with alkyl orthoesters with or without the addition of acetic anhydride. For instance, Kendall and Fry (B.P. 544,647/1940) found that pyrazolones condensed with orthoesters other than orthoformates when merely boiled together. Kendall and Duffin (B.P. 585,089, 633,736) obtained 4-alkoxyalkylidene-2-phenyloxazol-5-ones by cyclizing hippuric acid with acetic anhydride in the presence of an orthoester, and 2-alkylthio-4-ethoxymethylene- and -4-1'-ethoxyethylidene-thiazol-5-ones (III; X = O) were obtained similarly from *N*-dithioalkoxycarbonylglycines by Cook, Harris, Heilbron, and Shaw (*J.*, 1948, 1056), and by Aubert, Knott, and Williams (*J.*, 1951, 2185) respectively. Behringer and Weissauer (*Chem. Ber.*, 1952, **85**, 774) have also recently obtained 3-ethoxyalkylidene derivatives of oxindole and its *N*-acetyl derivative. These substances are useful as intermediates for merocyanines, and it was therefore of interest to extend this reaction to other keto-methylene compounds, as well as to examine their reactivities towards simple nucleophilic reagents.

The nucleophilic reactivity of the methylene carbon atom of these heterocyclic compounds towards orthoesters (or aldehydes) results from the +*M* effect of the adjacent carbonyl oxygen atom denoted in (IV) and (VII) by the curved arrow (*a*). This reactivity

is affected profoundly by the configuration of the rest of the molecule, and is enhanced by the presence of a second conjugated +M atom (effect *a'*) as in pyrazolones (IV; X = NR), isooxazolones (IV; X = O), and indanedione (VII). This is shown by the ability of all three of these compounds to react rapidly with boiling orthoester without the addition of acetic anhydride (cf. Kendall and Fry, *loc. cit.*).

On the other hand, in many compounds the +M effect is partially neutralized by the -M effect (arrow *b*) of an adjacent atom X in (IV), (V), and (VI). Whereas 3-alkyl-2-thiothiazolid-5-ones (VI; X = S, Y = NR) condense with ethyl orthoformate in acetic anhydride, the related 1:3-dialkyl-2-thiohydantoin (VI; X = Y = NR) are inert. The lower -M effect when X = S compared with that when X = NR indicated by this difference in reactivity is in agreement with the accepted relative values.

The deactivating effect (*b*) in many of these rings is itself opposed by the activating effect of a second +M atom, e.g., the imino-nitrogen atom of (V) or the thione-sulphur atom in (VI), as denoted by the curved arrows (*c*). Although this effect has not been noted



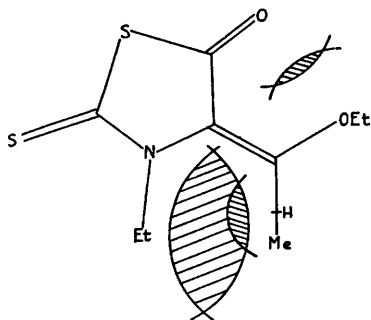
in this series it is clearly shown by the very much greater reactivity towards aldehydes of 2-thiohydantoin (VI; X = Y = NR) compared with that of the related hydantoin (Wheeler and Brautlecht, *Amer. Chem. J.*, 1911, 45, 446), corresponding with the much weaker +M effect of ketonic oxygen compared with that of thionic sulphur.

Finally there is usually a secondary deactivating process (*d*) resulting from the presence of a second -M atom, e.g., Y in (VI). This is shown by the fact that the replacement of Y = S by Y = O or Y = NR in (VI; X = NR), i.e., an increase in this -M effect, is sufficient to prevent reaction with orthoesters.

This resonance or electronic analysis of keto-methylene compounds has been described by Brooker *et al.* (*J. Amer. Chem. Soc.*, 1951, 73, 5332) in explaining the variations in +M effect (acidity) of a number of such nuclei. That an increase in the +M effect

increases the nucleophilic reactivity of the nucleus was also observed in certain cases by the above authors in their experiments on oxonol formation.

Steric effects are also of importance in reactions involving orthoesters other than orthoformates when the two atoms adjacent to the reactive methylene group carry substituents. In such molecules the groups OR' and R of the side chain which is introduced on reaction cannot lie in the same plane as the heterocyclic ring, as can be seen from scale drawings. This effect is shown by 3-ethyl-2-thiothiazolid-5-one (VI; X = S, Y = NEt) which condenses with ethyl orthoformate in acetic anhydride to give the planar



4-ethoxymethylene derivative (see Figure) but does not condense with ethyl orthoacetate. The 4-1'-ethoxyethylidene derivative which could be formed is non-planar, according to the Figure. Similar steric considerations apply to pyrazolones (IV; X = NR), isooxazolones (IV; X = O), indane-1:3-dione (VII), and 1:3-disubstituted 2-thiohydantoin (VI; X, Y = NR), and the fact that the first three of these compounds react easily with ethyl orthoacetate or orthopropionate is another indication of the activating influence of the second +M atom. However the distortion in the molecules is shown by their instability, decomposition occurring on repeated recrystallization or on keeping.

Attempts to condense ethyl orthobenzoate with 3-ethoxycarbonylmethylrhodanine in acetic anhydride gave traces of the required 5-1'-ethoxybenzylidenerhodanine after prolonged heating under reflux, but these were not isolated.

It is known that the C_(1')-atom of the 1-alkoxyalkylidene chain of examples of this type exhibits electrophilic reactivity. They have been condensed, with the elimination of the alkoxy-group as an alcohol, with heterocyclic quaternary salts containing a nucleophilic methyl group to give dimethinmerocyanines (VIII; R = H, R' = H, Me, or Et) (Kendall and Fry, *loc. cit.*; Cook, Harris, and Shaw, *J.*, 1949, 1435; Aubert *et al.*, *loc. cit.*) and with amines to give 4-aminomethyleneoxazol-5-ones (Barber and Slack, "The Chemistry of Penicillin," Oxford Univ. Press, p. 817), 4-aminomethylene-2-mercaptothiazol-5-ones (Cook Harris, Pollock, and Swan, *J.*, 1950, 1947), and 3-aminomethyleneoxindoles (Behringer *et al.*, *loc. cit.*). The present intermediates have also been converted into chain-substituted dimethinmerocyanines (VIII; R = alkyl, R' = H) by condensation with 2-methylbenzothiazole ethiodide, and also into (VIII; R = H, R' = Me) by condensation with 2-ethylbenzothiazole ethiodide. Analogous dyes were also obtained from 2-ethylthiazolinium salts. From the rhodanines (II; X = O) numerous 4-1'-aminoalkylidenerhodanines (IX) have been obtained. These are all pale yellow dyes, closely related to the merocyanines and sensitize silver chloride or chlorobromide emulsions moderately well. By analogy with the oxonols, these dyes may be termed oxamines. They are readily quaternized by methyl toluene-*p*-sulphonate or methyl sulphate to give (X), which contains an electrophilic C₍₂₎-atom as in the case of simpler 2-alkylthio-derivatives of heterocyclic quaternary salts. Treatment of (X) with keto-methylene heterocycles in alcoholic triethylamine leads to the more complex dyes (*e.g.*, XI). In one case the process of quaternization and condensation was repeated, to give dyes (XII) and (XIII), which are related to the complex merocyanines of Kendall and Fry (B.P. 489,335) and Brooker (Mees, "The Theory of the Photographic Process," Macmillan, New York, 1942, p. 1038-1040).

Attempts to quaternize the alkoxyalkylidene derivatives (II; X = O) of 3-substituted rhodanines themselves were unsuccessful. This observation, together with the fact that the aminoalkylidene derivatives quaternize much less rapidly than related merocyanines in which R''R'''N·CR: is part of a heterocyclic ring, agrees with the expectation that the rate of quaternization would increase with an increase in the electron density on the thionic sulphur atom, since this is the point of attack by the electrophilic methyl group of methyl toluene-*p*-sulphonate. The process denoted by arrow (a) in (VI) would thus be an activating process for quaternization. Deactivation, represented by the arrow (b), is a

result of the presence of the carbonyl-oxygen atom and will be decreased by any $-M$ effect from the group in the 5-position which will tend to satisfy the $+M$ effect of the carbonyl-oxygen atom. Such a $-M$ effect increases in the order: ethoxyalkylidene, aminoalkylidene, nitrogen-heterocyclidene, as is known from other data.

For certain reactions described in the following paper and involving the nucleophilic reactivity of the $C_{(2)}$ -atom of the ethylidene group (I; R = Me), 1'-alkyl(aryl)thioethylidene derivatives (e.g., II or III; X = S, R = Me) were required. Condensation of the keto-methylene compound with ethyl trithio-orthoformate did not proceed as expected. Croxall, Freimuller, and Shropshire (*J. Amer. Chem. Soc.*, 1950, **72**, 4275) obtained β -arylthioacrylates by heating β -ethoxyacrylates with thiophenol, etc., in the presence of sodium hydrogen sulphate; Cook *et al.* (*loc. cit.*, 1950) condensed toluene- ω -thiol with 4-ethoxymethylene-2-mercaptothiazol-5-one with triethylamine as catalyst; and Behringer *et al.* (*loc. cit.*) obtained alkylthio- and arylthio-methyleneoxindoles by fusion of ethoxymethyleneoxindole with the required thiol. A similar method which gave high yields of the required compounds was to treat 5-1'-ethoxyethylidenerhodanine (II; X = O) or 4-1'-ethoxyethylidene-2-ethylthiothiazol-5-one (III; X = O) at room temperature with the required thiol in the presence of zinc chloride and hydrogen chloride. In this way the ethylthio-, isopropylthio-, *n*-butylthio-, *n*-octylthio-, benzylthio-, and *p*-tolylthio-groups were introduced. [Attempts to bring about the reaction of two molecules of (I) with ethanedithiol and toluene-3 : 4-dithiol were unsuccessful.] In most cases the product was isolated in two forms differing considerably in melting point. These are believed to be *cis*- and *trans*-isomers. Related isomers were isolated by Cook *et al.* (*loc. cit.*, 1950). Similarly *cis*- and *trans*-arylthioacrylates were obtained by Croxall *et al.* (*loc. cit.*), but Behringer *et al.* (*loc. cit.*) could not isolate such isomers of 3-arylthiomethyleneoxindole. That no such geometrical isomers have been isolated in the case of 1'-ethoxyethylidene derivatives is possibly due to the stronger $-M$ effect of the OR compared with the SR group. The resultant decrease in the bond order of the double bond in the side chain would tend to make the existence or isolation of the form with higher energy less likely. Lur'e and Ravdel (*Doklady Akad. Nauk S.S.S.R.*, 1952, **83**, 97) have, however, isolated stereoisomers of 4-1'-ethoxyethylidene-2-phenyloxazol-5-one. Similar considerations apply to the strongly resonating dimethinmerocyanines prepared from these intermediates, both forms of the latter giving the same dye.

These arylthioethylidene or alkylthio-derivatives all exhibit the electrophilic reactivity characteristic of the alkoxyethylidene analogues.

EXPERIMENTAL

Determinations of λ_{\max} . are in MeOH unless otherwise stated.

4-1'-Ethoxyethylidene-2-ethylthiothiazol-5-one (III; R = Me, R', R'' = Et, X = O).—*N*-Dithioethoxycarbonylglycine (108 g.), ethyl orthoacetate (200 c.c.), and acetic anhydride (400 c.c.) were heated together on the steam-bath for 1 hr. (or at 125° in an oil-bath for 30 min.). The solvents were removed and the residual oil was distilled. The distillate (b. p. 124—140°/2 mm.) was redistilled and collected at 132—134°/2 mm. It (76.25 g., 55%) formed an orange oil which partly solidified to long needles at 4° (Found: C, 47.1; H, 5.5; N, 6.2; S, 27.5. $C_9H_{13}O_2NS_2$ requires C, 46.8; H, 5.6; N, 6.05; S, 27.7%).

2-Benzylthio-4-1'-ethoxyethylidenethiazol-5-one (III; R = Me, R'X = EtO, R' = CH_2Ph) was obtained similarly from *N*-dithiobenzoyloxycarbonylglycine in 32% yield. It distilled as an orange oil, b. p. 208°/1 mm. (Found: S, 21.95. $C_{14}H_{15}O_2NS_2$ requires S, 21.85%).

2-1'-Ethoxyethylideneindane-1 : 3-dione.—Indane-1 : 3-dione (2.9 g.) and ethyl orthoacetate (10 c.c.) were refluxed together for 3 min. The product separated as a crystalline mass. After chilling, the crystals were collected, and formed brown needles, m. p. 151—158°, from ethanol. It tended to decompose on recrystallization (Found: C, 72.1; H, 5.4. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.55%).

4-1'-Ethoxyethylidene-3-phenylisooxazol-5-one.—Obtained similarly in 63% yield after boiling the reactants for 5 min., this compound formed pale brown plates, m. p. 113°, from ethanol (Found: C, 67.4; H, 5.65; N, 6.35. $C_{13}H_{13}O_3N$ requires C, 67.6; H, 5.65; N, 6.15%). It decomposed during 24 hr. at room temperature.

3-Ethoxycarbonylmethyl-5-ethoxymethylene-2-thiothiazolid-4-one (II; R = H, R' =

$\text{CH}_2\cdot\text{CO}_2\text{Et}$, $\text{R}''\text{X} = \text{EtO}$).—3-Ethoxycarbonylmethylrhodanine (30 g.), ethyl orthoformate (75 c.c.), and acetic anhydride (120 c.c.) were cautiously heated together until reaction set in. When this slackened the whole was refluxed for 1 hr., the solvent was distilled off, and the residue dissolved in hot isopropanol (50 c.c.). The substance obtained on chilling of the isopropanol solution formed pale yellow needles, m. p. 100–101°, in 80.5% yield after a further recrystallization from the same solvent (Found: C, 43.65; H, 5.05; N, 5.0; S, 23.1. $\text{C}_{16}\text{H}_{13}\text{O}_4\text{NS}_2$ requires C, 43.65; H, 4.75; N, 5.1; S, 23.3%).

3-Ethoxycarbonylmethyl-5-1'-ethoxyethylidene-2-thiothiazolid-4-one (II; $\text{R} = \text{Me}$, $\text{R}' = \text{CH}_2\cdot\text{CO}_2\text{Et}$, $\text{R}''\text{X} = \text{EtO}$).—3-Ethoxycarbonylmethylrhodanine (87.6 g.), ethyl orthoacetate (150 c.c.), and acetic anhydride (500 c.c.), in a 1½-l. flask with a reflux condenser, were heated cautiously on a gauze. An exothermic reaction occurred and was controlled by cooling. After the initial reaction had slackened, the mixture was refluxed for 1 hr., the solvents were removed under reduced pressure, and the residual *product* recrystallized from ligroin. It (93.0 g., 80.5%) formed flat, buff needles, m. p. 105°, after a second recrystallization from isopropanol (Found: N, 4.9; S, 22.3. $\text{C}_{11}\text{H}_{15}\text{O}_4\text{NS}_2$ requires N, 4.85; S, 22.1%), λ_{max} , 352 m μ .

4-Ethoxymethylene-3-ethyl-2-thiothiazolid-5-one.—3-Ethyl-2-thiothiazolid-5-one (Jeffreys and Knott, *J.*, 1952, 4632) (1.0 g.), ethyl orthoformate (2 c.c.), and acetic anhydride (5 c.c.) were heated together on a steam-bath for 30 min. Removal of the solvents left a brown oil from which the required *product* was extracted with ligroin (b. p. 100–120°). It formed colourless needles, m. p. 76°, after a further recrystallization from ligroin (Found: S, 29.6. $\text{C}_8\text{H}_{11}\text{O}_2\text{NS}_2$ requires S, 29.5%).

Further examples of this type are given in Table I.

2-[1-(3-Ethylbenzothiazolin-2-ylidene)prop-2-ylidene]indane-1:3-dione (cf. VIII; $\text{R} = \text{Me}$, $\text{R}' = \text{H}$).—2-Methylbenzothiazole ethiodide (1.5 g.), 2-1'-ethoxyethylideneindane-1:3-dione (1.1 g.), ethanol (20 c.c.), and triethylamine (0.8 c.c.) were refluxed together for 5 min. The whole solidified rapidly and the dye was obtained in 82% yield as soft red needles, m. p. 270° (decomp.), from benzene-ethanol (Found: C, 72.35; H, 4.95. $\text{C}_{21}\text{H}_{17}\text{O}_2\text{NS}$ requires C, 72.6; H, 4.9%), λ_{max} , 496 m μ .

4-[1-(3-Ethylbenzothiazolin-2-ylidene)prop-2-ylidene]-3-phenylisooxazol-5-one (cf. VIII; $\text{R} = \text{Me}$, $\text{R}' = \text{H}$).—Obtained similarly from 4-1'-ethoxyethylidene-3-phenylisooxazol-5-one (1.15 g.) in 72% yield, the dye formed orange-red needles, m. p. 203°, from benzene-ethanol (Found: N, 8.0; S, 8.9. $\text{C}_{21}\text{H}_{18}\text{O}_2\text{N}_2\text{S}$ requires N, 7.75; S, 8.85%), λ_{max} , 477 m μ .

3-Ethoxycarbonylmethyl-5-[1-(3-ethylbenzothiazolin-2-ylidene)prop-2-ylidene]-2-thiothiazolid-4-one (cf. VIII; $\text{R} = \text{Me}$, $\text{R}' = \text{H}$).—Obtained similarly from 3-ethoxycarbonylmethyl-5-1'-ethoxyethylidenerhodanine (1.45 g.), the dye (67% yield) formed soft, brown needles, m. p. 176°, from pyridine-ethanol (Found: N, 6.5; S, 22.7. $\text{C}_{19}\text{H}_{20}\text{O}_3\text{N}_2\text{S}_3$ requires N, 6.65; S, 22.9%), λ_{max} , 530 m μ .

3-Ethoxycarbonylmethyl-5-[1-(3-ethylbenzothiazolin-2-ylidene)but-2-ylidene]-2-thiothiazolid-4-one (cf. VIII; $\text{R} = \text{Et}$, $\text{R}' = \text{H}$).—2-Methylbenzothiazole ethiodide (1.5 g.), 3-ethoxycarbonylmethyl-5-1'-ethoxypropylidenerhodanine (1.45 g.), ethanol (10 c.c.), and triethylamine (0.8 c.c.) were refluxed together for 15 min. When the mixture was chilled, the dye separated as an oil which crystallized on being scratched. It (1.7 g., 78.5%) formed a green crystalline powder, m. p. 182°, from benzene-ethanol (Found: N, 6.5; S, 21.95. $\text{C}_{20}\text{H}_{22}\text{O}_3\text{N}_2\text{S}_3$ requires N, 6.45; S, 22.15%), λ_{max} , 530 m μ .

3-Ethoxycarbonylmethyl-5-[2-(3-ethylbenzothiazolin-2-ylidene)prop-1-ylidene]-2-thiothiazolid-4-one (cf. VIII; $\text{R} = \text{H}$, $\text{R}' = \text{Me}$).—2-Ethylbenzothiazole ethiodide (1.6 g.), 3-ethoxycarbonylmethyl-4-ethoxymethylenetherhodanine (1.4 g.), ethanol (10 c.c.), and triethylamine (0.8 c.c.) were refluxed together for 15 min. The dye (0.8 g., 38%), collected after chilling of the mixture for 3 hr., formed fine, dark red needles, m. p. 159°, from benzene-ethanol (Found: N, 6.45; S, 23.0. $\text{C}_{19}\text{H}_{20}\text{O}_3\text{N}_2\text{S}_3$ requires N, 6.65; S, 22.9%), λ_{max} , 530 m μ .

3-Ethoxycarbonylmethyl-5-[2-(3-ethylthiazolidin-2-ylidene)prop-1-ylidene]-2-thiothiazolid-4-one was obtained similarly from 2-ethylthiazoline ethiodide (1.35 g.) in 50% yield and formed flat, magenta needles, m. p. 121°, from ethanol (Found: N, 7.75; S, 25.6. $\text{C}_{15}\text{H}_{20}\text{O}_3\text{N}_2\text{S}_3$ requires N, 7.55; S, 25.8%), λ_{max} , 490 m μ .

4-[2-(3-Ethylbenzothiazolin-2-ylidene)prop-1-ylidene]-2-ethylthiothiazol-5-one (cf. VIII; $\text{R} = \text{H}$, $\text{R}' = \text{Me}$).—2-Ethylbenzothiazole ethiodide (1.6 g.), 4-ethoxymethylene-2-ethylthiothiazol-5-one (1.1 g.), ethanol (10 c.c.), and triethylamine (0.8 c.c.) were refluxed together for 10 min. The dye (0.9 g., 50%) obtained on chilling formed red flakes with a blue reflex, m. p. 112°, from ethanol. The crystals lost ethanol in a vacuum-desiccator (Found: N, 7.7; S, 26.3. $\text{C}_{17}\text{H}_{18}\text{ON}_2\text{S}_3$ requires N, 7.75; S, 26.5%), λ_{max} , 540 m μ .

TABLE 1. 3-Substituted 4-1'-alkoxyalkylidene-2-thiothiazolid-4-ones (II; X = O).

R	R'	R''	Reaction time (min.)	Yield (%)	Appearance (solvent) †	M. p.	Formula	Found (%)			Required (%)				
								C	H	N	C	H	N	S	
Me	Et	Et	240	51	Orange needles (P)	80°	C ₉ H ₁₃ O ₃ NS ₂	—	—	5.95	27.8	—	—	6.05	27.7
Me	Ph	Et	45	93.5	Orange needles (M)	164—166	C ₁₃ H ₁₉ O ₂ NS ₂	55.2	4.9	—	23.25	55.5	4.65	—	22.9
H	Ph	Et	73	73	Cream needles (E)	150—151	C ₁₃ H ₁₉ O ₂ NS ₂	—	—	5.55	24.05	—	—	5.3	24.2
Et	Ph	Et	60	22	Orange plates (P)	180—182	C ₁₄ H ₁₉ O ₂ NS ₂	56.8	5.05	4.85	21.55	57.3	5.1	4.8	21.85
H	A *	Et	300	69.5	Red needles (A)	53—54	C ₉ H ₁₁ O ₄ NS ₂	47.7	5.15	6.25	27.9	47.2	4.8	6.1	27.95
Me	A *	Et	400	88.5	Brown plates (L)	63—64	C ₁₀ H ₁₃ O ₂ NS ₂	49.6	5.5	5.65	26.2	49.4	5.35	5.75	26.35
Et	A *	Et	480	55	Gold needles (P)	62—63	C ₁₁ H ₁₅ O ₂ NS ₂	—	—	5.35	—	—	—	5.45	—
Me	A *	Me	600	44.5	Brown needles (P)	83—84	C ₉ H ₁₁ O ₂ NS ₂	—	—	6.15	27.95	—	—	6.1	27.95
Me	C *	Me	60	97.5	Straw needles (P)	113—114	C ₁₀ H ₁₃ O ₂ NS ₂	43.85	4.85	—	22.95	43.6	4.7	—	23.3
H	B *	Et	300	74.5	Pink needles (P)	87	C ₁₃ H ₁₉ O ₂ NS ₂	—	—	4.95	—	—	—	5.0	—
Me	B *	Et	300	59	Flat needles (P)	109	C ₁₄ H ₁₉ O ₂ NS ₂	—	—	4.7	22.1	—	—	4.8	22.0
H	CH *	Et	150	50	Yellow needles (P)	139—140	C ₁₃ H ₁₉ O ₂ NS ₂	—	—	4.9	23.7	—	—	5.15	23.6
Me	CH *	Et	180	59	Orange flakes (P)	105	C ₁₃ H ₁₉ O ₂ NS ₂	—	—	4.7	22.1	—	—	4.9	22.45

* A = allyl, B = benzyl, C = ethoxycarbonylmethyl, CH = cyclohexyl.
 † E = ethanol; M = methanol; A = cyclohexane; P = isopropanol; L = light petroleum, b. p. 60—80°.

TABLE 2. 3-Substituted 5-1'-aminoalkylidene-2-thiothiazolid-4-ones.

R	R''R'''N	Yield (%)	Appearance	M. p.	Formula	Found (%)		Required (%)	
						N	S	N	S
Me	Anilino	79.5	Golden laths	173—175°	C ₁₃ H ₁₆ O ₃ N ₂ S ₂	8.15	19.1	8.35	19.05
H	Piperidyl	76.5	Pale yellow needles	146—147	C ₁₃ H ₁₆ O ₂ N ₂ S ₂	8.8	20.6	8.9	20.4
H	Morpholinyl	95.0	Flat yellow needles	172—173	C ₁₂ H ₁₆ O ₂ N ₂ S ₂	8.6	—	8.85	—
H	N-Methylanilino	41.5	Orange laths	146—149	C ₁₂ H ₁₆ O ₂ N ₂ S ₂	8.15	—	8.35	—
H	Benzylamino	62.5	Yellow needles	109	C ₁₆ H ₁₆ O ₂ N ₂ S ₂	8.3	—	8.35	—
H	β-Phenylhydrazino	65	Straw needles	184	C ₁₄ H ₁₅ O ₂ N ₂ S ₂ ^d	12.3	18.75	12.45	19.0
Me	cycloHexylamino	70	Yellow tablets	133—134	C ₁₄ H ₁₅ O ₂ N ₂ S ₂	8.3	—	8.55	—
H	Ethylamino	95	Cream plates	121	C ₁₄ H ₂₀ O ₂ N ₂ S ₂	9.7	—	9.7	—
H	Dibenzylamino	94	Yellow needles	103—104	C ₂₂ H ₂₂ O ₂ N ₂ S ₂	6.5	—	6.55	—
H	Dicyclohexylamino	73	Yellow tablets	159	C ₂₀ H ₃₀ O ₂ N ₂ S ₂	6.7	—	6.85	—
(IX; R' = CH ₂ ·CH(CH ₃))									
H	Amino	90	Orange needles ^a	104—109	C ₇ H ₈ ON ₂ S ₂	13.8	—	14.0	—
H	Carboxymethylamino ^b	90	Yellow needles	195—196	C ₉ H ₁₀ O ₂ N ₂ S ₂	10.65	—	10.85	—
Me	Ethylamino	93	Straw flakes	65	C ₁₀ H ₁₄ ON ₂ S ₂	11.7	26.3	11.55	26.45
H	Morpholinyl	85	Yellow needles ^c	180	C ₁₁ H ₁₄ ON ₂ S ₂	10.1	—	10.35	—
H	Diethylamino	67	Yellow needles	74	C ₁₁ H ₁₆ ON ₂ S ₂ ^d	10.75	—	10.95	—
Et	Ethylamino	70	Orange flakes	49—51	C ₁₁ H ₁₆ ON ₂ S ₂	10.8	—	10.95	—
H	n-Octylamino	92	Yellow threads	98—100	C ₁₇ H ₂₄ ON ₂ S ₂ ^f	9.0	20.4	9.0	20.5
H	Ethylamino	88	Yellow threads	132	C ₉ H ₁₂ ON ₂ S ₂	12.25	28.2	12.3	28.1

^a From aq. ethanol. ^b Obtained from the potassium salt of glycine. ^c From benzene. ^d Found: C, 50.25; H, 4.25. Req'd.: C, 49.8; H, 4.45%.
^e Found: C, 51.7; H, 6.05. Req'd.: C, 51.55; H, 6.25%. ^f Found: C, 57.4; H, 7.75. Req'd.: C, 57.7; H, 7.7%.

2-Ethylthio-4-[2-(3-methylthiazolidin-2-ylidene)prop-1-ylidene]thiazol-5-one, obtained (0.8 g., 52.5%) similarly from 2-ethylthiazoline methiodide (1.3 g.), formed orange rosettes, m. p. 119°, from ethanol (Found: N, 9.35. $C_{12}H_{16}ON_2S_3$ requires N, 9.35%), λ_{\max} 490 m μ .

3-Substituted 5-1'-aminoalkylidene-2-thiothiazolid-4-ones (IX) (Table 2) were all obtained by heating equimolecular amounts of (II; X = O) and the amine in ethanol on a steam-bath for 15–30 min. They usually crystallized when the liquid was chilled, and were recrystallized from ethanol unless otherwise stated.

1: 6-Di-(3-ethoxycarbonylmethyl-4-oxo-2-thiothiazolidin-5-ylidene)-2: 5-diazahehexane.—3-Ethoxycarbonylmethyl-5-ethoxymethylenerhodanine (5.5 g.), ethylenediamine hydrate (0.81 c.c.), and ethanol (25 c.c.) were refluxed together for 15 min. When the resulting solution was chilled a thick oil separated which solidified on being scratched. From ethanol (twice) it (3.6 g., 70%) formed pale yellow needle aggregates, m. p. 145° (Found: N, 10.75; S, 24.5. $C_{18}H_{22}O_6N_4S_4$ requires N, 10.8; S, 24.7%).

5-Benzothiazol-2'-ylaminomethylene-3-ethoxycarbonylmethyl-2-thiothiazolid-4-one.—3-Ethoxycarbonylmethyl-5-ethoxymethylenerhodanine (2.75 g.), 2-aminobenzothiazole (1.5 g.), and ethanol (10 c.c.) were refluxed together for 1 hr. The compound separated on chilling and formed yellow needles, (2.65 g., 70%), m. p. 190–191°, from ethanol (Found: N, 10.95. $C_{16}H_{18}O_3N_3S_3$ requires N, 11.1%).

3-Ethoxycarbonylmethyl-5-(3-ethylbenzothiazolin-2-ylideneaminomethylene)-2-thiothiazolid-4-one.—This dye was prepared as in the preceding preparation, with 2-aminobenzothiazole ethotoluene-*p*-sulphonate (3.5 g.) and triethylamine (1.5 c.c.). The product (3.2 g., 79%) was obtained as orange plates, m. p. 199°, from benzene (Found: N, 10.55. $C_{17}H_{17}O_3N_3S_3$ requires N, 10.35%).

3-Allyl-2-(2-ethylthio-5-oxothiazolin-4-ylidene)-5-n-octylaminomethylenethiazolid-4-one.—3-Allyl-5-n-octylaminomethylenerhodanine (0.8 g.) and methyl toluene-*p*-sulphonate (0.5 g.) were fused together at 150° for 2 hr. *N*-Dithioethoxycarbonylglycine (1.0 g.) was cyclized to 2-ethylthiothiazol-5-one by heating it with acetic anhydride (20 c.c.) for 1 hr. on a steam-bath. The solvent was removed and the residual oil washed into the above quaternary salt with ethanol (10 c.c.). Triethylamine (1.0 c.c.) was added and the whole heated for 5 min. on the steam-bath. The yellow needles (0.3 g., 27%) which separated on chilling formed soft yellow threads, m. p. 156°, from ethanol (Found: N, 9.75; S, 22.0. $C_{20}H_{29}O_2N_3S_3$ requires N, 9.95; S, 21.9%), λ_{\max} 450 m μ .

3-Ethoxycarbonylmethyl-2-(3-ethyl-4-oxo-2-thio-oxazolidin-5-ylidene)-5-morpholin-3'-ylmethylenerhodanine.—3-Ethoxycarbonylmethyl-5-morpholin-3'-ylmethylenerhodanine (1.0 g.) and methyl toluene-*p*-sulphonate (0.6 g.) were fused together at 125° for 1 hr. 3-Ethyl-2-thio-oxazolid-4-one (0.5 g.), ethanol (10 c.c.), and triethylamine (0.5 c.c.) were added and the mixture was refluxed for 10 min. The yellow grains (0.5 g., 37%) obtained when the resulting product was chilled formed yellow needles, m. p. 155–157°, from isopropanol (Found: N, 10.0. $C_{17}H_{21}O_6N_3S_2$ requires N, 9.85%), λ_{\max} 418 m μ .

[3-Allyl-4-oxo-5-n-octylaminomethylene-2-thiazoline][3-ethyl-2-benzothiazole]methincyanine Perchlorate.—3-Allyl-5-n-octylaminomethylenerhodanine (0.8 g.) and methyl toluene-*p*-sulphonate were fused for 2 hr. at 140°. 2-Methylbenzothiazole ethotoluene-*p*-sulphonate (0.9 g.), ethanol (10 c.c.), and triethylamine (0.4 c.c.) were added and the mixture was refluxed for 10 min. Saturated aqueous sodium perchlorate (0.5 c.c.) was added and the flask chilled overnight. The dye (0.9 g., 63.5%) formed light brown threads, m. p. 190°, from ethanol (Found: N, 7.65; S, 11.6. $C_{25}H_{34}O_5N_3ClS_2$ requires N, 7.55; S, 11.55%), λ_{\max} 465 m μ .

2-Dicyanomethylene-3-ethoxycarbonylmethyl-5-piperid-1'-ylmethylenerhodanine.—3-Ethoxycarbonylmethyl-5-piperid-1'-ylmethylenerhodanine (1.6 g.) was quaternized as above and refluxed for 15 min. with malononitrile (0.4 g.), ethanol (10 c.c.), and triethylamine (0.8 c.c.). The dye (0.6 g., 34%) formed pale yellow crystals, m. p. 164–166°, after three recrystallizations from ethanol (Found: N, 16.0. $C_{16}H_{18}O_3N_4S$ requires N, 16.2%), λ_{\max} 386 m μ .

3-Allyl-2-(3-allyl-4-oxo-2-thiothiazolidin-5-ylidene)-5-ethylaminomethylenethiazolid-4-one (XI; R, R' = H, R'' = allyl, R''' = Et).—3-Allyl-5-ethylaminomethylenerhodanine (2.3 g.) and methyl toluene-*p*-sulphonate were fused at 130° for 2 hr. 3-Allylrhodanine (1.8 g.), ethanol (10 c.c.), and triethylamine (1.5 c.c.) were added and heated for 5 min. on a steam-bath. The dye (2.65 g., 72%) formed orange flakes, m. p. 177°, from ethanol (Found: N, 11.5. $C_{15}H_{17}O_2N_3S_3$ requires N, 11.45%), λ_{\max} 459 m μ in EtOH.

5-N-Acetylethylamidomethylene-3-allyl-2-(3-allyl-4-oxo-2-thiothiazolidin-5-ylidene)thiazolid-4-one (XI; R = H, R' = allyl, R'' = Ac, R''' = Et).—The previous dye (1.0 g.) and acetic anhydride (25 c.c.) were refluxed together for 3 hr. and the solvents were removed. The residual product

formed long, orange-brown needles (0.8 g.), m. p. 160—161°, after two recrystallizations from ethanol (Found: C, 50.1; H, 4.75; N, 10.3; S, 23.2. $C_{17}H_{19}O_3N_3S_2$ requires C, 49.85; H, 4.65; N, 10.3; S, 23.45%), λ_{\max} . 441 m μ .

3-Ethoxycarbonylmethyl-2-(3-ethoxycarbonylmethyl-4-oxo-2-thiothiazolidin-5-ylidene)-5-piperid-1'-ylmethylenethiazolid-4-one (XI; $R' = CH_2 \cdot CO_2Et$, $R = H$, $R''R'''N =$ piperidyl).—3-Ethoxycarbonylmethyl-5-1'-piperidinomethylene-2-thiothiazolid-4-one (1.6 g.) and methyl toluene-*p*-sulphonate (0.95 g.) were fused together for 2 hr. at 120°. 3-Ethoxycarbonylmethylrhodanine (1.1 g.), ethanol (20 c.c.), and triethylamine were added and the whole was refluxed for 5 min. on a steam-bath. A solid yellow mass of crystals separated. They were washed with ethanol and formed soft, yellow needle rosettes (1.5 g., 59.0%), m. p. 234°, from benzene-ethanol (Found: N, 8.4; S, 19.2. $C_{20}H_{25}O_5N_3S_3$ requires N, 8.45; S, 19.2%), λ_{\max} . 458 m μ .

3-Allyl-2-(3-allyl-4-oxo-2-thiothiazolidin-5-ylidene)-5-n-octylaminomethylenethiazolid-4-one (XI; $R, R'' = H$, $R''' = n$ -octyl $R' =$ allyl).—Obtained similarly in 62% yield, this dye formed orange flakes, m. p. 127—128°, from methanol (Found: N, 9.3; S, 21.15. $C_{21}H_{29}O_2N_3S_3$ requires N, 9.3; S, 21.3%), λ_{\max} . 460 m μ .

3-Allyl-2-(3-allyl-4-oxo-2-thiothiazolidin-5-ylidene)-5-(3-allyl-4-oxo-5-n-octylaminomethylene-thiazolidin-2-ylidene)thiazolid-4-one (XII).—The preceding dye (XI) (1.5 g.) and methyl toluene-*p*-sulphonate (0.65 g.) were fused at 130° for 1 hr. 3-Allylrhodanine (0.6 g.), ethanol (15 c.c.), and triethylamine (0.5 c.c.) were added and the whole was refluxed for 5 min. The dye (1.25 g., 63.5%) which separated on chilling formed soft, red needles, m. p. 199—201°, from benzene-ethanol (Found: N, 9.3; S, 21.8. $C_{27}H_{34}O_3N_4S_4$ requires N, 9.5; S, 21.7%), λ_{\max} . 508 m μ in MeOH, 518 m μ in pyridine.

3-Allyl-2-[3-allyl-2-(3-allyl-4-oxo-2-thiothiazolidin-5-ylidene)-4-oxothiazolidin-5-ylidene]-5-(3-allyl-4-oxo-5-n-octylaminomethylenethiazolidin-2-ylidene)thiazolid-4-one (XIII).—The above dye (0.7 g.) and methyl toluene-*p*-sulphonate (0.5 g.) were fused at 140° for 30 min. To the solid quaternary salt were added 3-allylrhodanine (0.25 g.) and ethanol (20 c.c.), and the mixture was heated to give a red solution. Triethylamine (0.3 c.c.) was then added to give an immediate precipitation of the dye, which (0.6 g., 70%) formed a red crystalline powder, m. p. 263°, from pyridine (Found: C, 54.1; H, 5.3; N, 9.5; S, 22.1. $C_{33}H_{39}O_4N_5S_5$ requires C, 54.3; H, 5.35; N, 9.6; S, 21.95%), λ_{\max} . 548 m μ in pyridine.

3-Ethoxycarbonylmethyl-5-1'-ethylthioethylidene-2-thiothiazolid-4-one (II; $R = Me$, $R'X = EtS$, $R' = CH_2 \cdot CO_2Et$).—3-Ethoxycarbonylmethyl-5-1'-ethoxyethylidenerhodanine (2.9 g.), ethanethiol (1.5 c.c.), powdered anhydrous zinc chloride (2.7 g.), and dioxan (10 c.c.) were saturated with dry hydrogen chloride at 25° and set aside for 15 hr. Water (100 c.c.) was added to precipitate an orange oil which soon solidified. From ethanol this compound (2.8 g., 82%) formed yellow flakes, m. p. 67—68° (Found: C, 43.55; H, 5.15; N, 4.75; S, 31.2. $C_{11}H_{15}O_3NS_3$ requires C, 43.25; H, 4.9; N, 4.6; S, 31.5%), λ_{\max} . 370 m μ .

3-Ethoxycarbonylmethyl-5-1'-isopropylthioethylidene-2-thiothiazolid-4-one was obtained in 54.5% yield as pale yellow flakes, m. p. 107—108°, from light petroleum (b. p. 60—80°) (Found: C, 45.3; H, 5.45; N, 4.5; S, 29.9. $C_{12}H_{17}O_3NS_3$ requires C, 45.1; H, 5.35; N, 4.4; S, 30.3%).

5-1-n-Butylthioethylidene-3-ethoxycarbonylmethyl-2-thiothiazolid-4-one was obtained similarly from *n*-butanethiol in 82.5% yield and formed pale yellow tablets, m. p. 68—69° (Found: C, 47.05; H, 5.8; N, 4.15; S, 28.8. $C_{13}H_{19}O_3NS_3$ requires C, 46.85; H, 5.7; N, 4.2; S, 28.65%), and orange needles, m. p. 92—93°, from light petroleum (b. p. 60—80°) (Found: C, 46.9; H, 5.75; S, 29.0%). The solid with the higher m. p. crystallizes first from the solvent.

5-1'-Benzylthioethylidene-3-ethoxycarbonylmethyl-2-thiothiazolid-4-one was obtained similarly by using toluene- ω -thiol and formed pale yellow flakes, m. p. 99—100°, in 46.5% yield after three recrystallizations from ethanol (Found: S, 26.3. $C_{16}H_{17}O_3NS_3$ requires S, 26.15%), λ_{\max} . 375 m μ .

5-1'-Ethylthioethylidene-3-cyclohexyl-2-thiothiazolid-4-one.—5-1'-Ethoxyethylidene-3-cyclohexylrhodanine (14.25 g.), ethanethiol (7.5 c.c.), powdered zinc chloride (13.6 g.), and dioxan (50 c.c.) were saturated with dry hydrogen chloride at 25° and set aside for 20 hr. Water (200 c.c.) was added to precipitate a yellow oil which rapidly crystallized. The yield of crude air-dried product was 98.5% (14.75 g.). From light petroleum (b. p. 60—80°) yellow threads first separated (3.5 g.). After two further recrystallizations from the same solvent they had m. p. 148—149° (Found: S, 31.8. $C_{13}H_{19}ONS_3$ requires S, 31.9%), λ_{\max} . 374 m μ in MeOH. The filtrate from the first crystallization on concentration and chilling gave soft yellow needles (9.1 g.), m. p. 89—91°, from isopropanol (Found: S, 32.1), λ_{\max} . 374 m μ .

3-Benzyl-5-1'-ethylthioethylidene-2-thiothiazolid-4-one.—Obtained similarly from 3-benzyl-5-1'-ethoxyethylidenerhodanine, the product (81% yield) after one recrystallization from *iso*-

propanol was dissolved in the same solvent (30 c.c./g.) and allowed to cool. Fine orange needles (34.6%), m. p. 107—108°, after a second recrystallization, separated first (Found: C, 54.85; H, 4.65; N, 4.45; S, 30.9. $C_{14}H_{15}ONS_3$ requires C, 54.35; H, 4.85; N, 4.55; S, 31.1%); it had λ_{\max} 376 m μ in MeOH. The filtrate then deposited pale yellow threads (48.4%), m. p. 107—108° with softening at 92° (Found: C, 54.5; H, 4.7; N, 4.4; S, 31.3%), λ_{\max} 375 m μ .

3-Ethoxycarbonylmethyl-5-1'-p-tolylthioethylidene-2-thiothiazolid-4-one.—Obtained crude in 100% yield from *p*-thiocresol, the first crop from isopropanol (36.5% yield) formed orange flakes, m. p. 139—140°, after two recrystallizations from the same solvent (Found: C, 51.9; H, 4.8; N, 3.65; S, 25.95. $C_{16}H_{17}O_3NS_3$ requires C, 52.3; H, 4.65; N, 3.8; S, 26.2%). The second crop (43.5% yield) obtained on concentration of the first filtrate formed flat, yellow needles, m. p. 91.5°, from isopropanol (Found: C, 52.2; H, 4.75; N, 3.75; S, 26.35%). *3-Allyl-5-1'-p-tolylthioethylidene-2-thiothiazolid-4-one* was obtained in 35% yield and formed flat, cream needles, m. p. 90°, from isopropanol (Found: C, 55.95; H, 4.85; N, 4.2; S, 29.95. $C_{15}H_{15}ONS_3$ requires C, 56.05; H, 4.7; N, 4.35; S, 30.0%).

3-Ethoxycarbonylmethyl-5-1'-n-octylthioethylidene-2-thiothiazolid-4-one was obtained similarly from molar amounts of reactants. The mixture was set aside for 72 hr. before addition of water. The oil was distilled and collected (54% yield) at 232—240°/2.5 mm. It slowly crystallized and a sample formed soft, pale yellow needles, m. p. 38°, from isopropanol (Found: S, 26.5. $C_{17}H_{27}O_3NS_3$ requires S, 26.65%).

2-Ethylthio-4-1'-ethylthioethylidenethiazol-5-one (III; R = Me, R', R'' = Et, X = S).—*4-1'-Ethoxyethylidene-2-ethylthiothiazol-5-one* (23.1 g.) was dissolved in dioxan (30 c.c.) and ethanethiol (15 c.c.). Powdered anhydrous zinc chloride (27 g.) was added and the whole saturated at 25° with dry hydrogen chloride. The orange solution was shaken with water and ether, the ethereal layer dried (Na_2SO_4), and the ether removed. Distillation gave an orange oil, b. p. 120/3 mm. (5.45 g.), which was rejected and the required compound (16.15 g., 65%), b. p. 170°/3 mm., which solidified in the receiver. It formed pale yellow needles, m. p. 60—61°, from isopropanol (Found: C, 43.65; H, 5.65; N, 5.7; S, 38.75. $C_9H_{13}ONS_3$ requires C, 43.7; H, 5.25; N, 5.65; S, 38.9%), λ_{\max} 370 m μ .

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