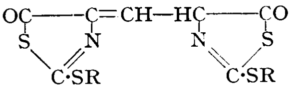
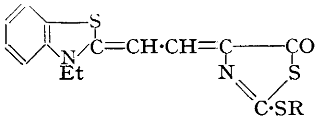
306. *Studies in the Azole Series. Part XV. The Reactivity of 4-Ethoxymethylene-5-thiazolones and -oxazolones.**

By A. H. Cook, G. Harris, and G. Shaw.

Various *S*-substituted 2-mercapto-4-ethoxymethylenethiazolones have been condensed with compounds containing reactive methyl or methylene groups to give stable pigments (*e.g.*, II, III, VII). Analogous 4-ethoxymethyleneoxazolones undergo similar condensations to give pigments such as (VIII) and (IX).

Part IV of this series (*J.*, 1948, 1056) included a description of the preparation of 2-ethylthio-5-thiazolone and thence of its 4-ethoxymethylene derivative. It has now been found that these two compounds easily interact to give *methinbis*-4-[2-(*ethylthio*-5-*thiazolone*)] (I; R = Et), a compound which is more conveniently prepared by condensing 2 moles of 2-ethylthio-5-thiazolone with one of ethyl orthoformate. The analogous *benzylthio*-compound (I; R = CH_2Ph) was prepared from 2-benzylthio-5-thiazolone and its 4-ethoxymethylene derivative.


(I.)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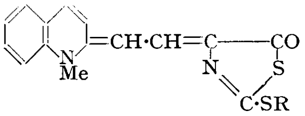
(III.)

The ethoxymethylene compounds mentioned above reacted rapidly with other compounds containing reactive methyl or methylene groups and the *dimethin dyes* (II and III; R = Et or CH_2Ph) were prepared from 2-methylbenzthiazole ethiodide and quinaldine methiodide, respectively; these preparations were notably facile when carried out in cold ethanol in presence of triethylamine, the products crystallising within a few minutes. Like the other dyes described below, these were surprisingly stable; for example, (II and III; R = CH_2Ph) could be boiled with concentrated sulphuric acid without suffering apparent change apart from being converted into water-soluble sulphonates. The dyes also gave water-soluble products when heated with methyl sulphate but the detailed chemistry of these reactions was not studied. This stability suggested the preparation of more readily substituted dyes, and α-chloromethylnaphthalene, glycine, and carbon disulphide were allowed to interact to give *α-naphthyl* N-*carboxymethyldithioacetate* (IV) which was cyclised in presence of ethyl orthoformate, and the ethoxymethylene compound condensed with the second components to give the *dyes* (II and III; R = $CH_2{\cdot}C_{10}H_7$-α). Quite similarly, glycine, carbon disulphide, and ethyl chloroformate gave *N*-carbethoxydithiocarboxyglycine (V) (CPS 583; Cook, Harris, and Heilbron, *J.*, 1948, 1056) and thence 2-*carbethoxythio*-4-*ethoxymethylene*-5-*thiazolone* (VI), which afforded the dyes (II and III; R = CO_2Et). Compound (VI) condensed also with facility with 1 : 3 : 3-trimethyl-2-methyleneindoline to give the *dye* (VII). The products (II and III; R = CO_2Et) have additional interest as dyes in that they are readily hydrolysed by cold alkali, the products suffering decarboxylation on acidification and being precipitated still in pigmented form.

These experiments suggested that ethoxymethyleneoxazolones might be similarly useful. 2-Phenyl-, 2-*n*-amyl-, and 2-benzyl-4-ethoxymethyleneoxazolones all condensed at once in cold methanol with quinaldine or 2-methylbenzthiazole quaternary salts and the dyes (VIII) and (IX) were isolated.

All these dyes were remarkable for their intense colour in spite of the simple nature of the thiazolone and oxazolone rings. That the bathochromic influence is due to these ring systems is shown by the fact that the absorption spectra were not markedly different in the two series of dyes, and in the thiazolone series were not noticeably dependent on the radical attached to the mercapto-residue. It is remarkable that the instability of the oxazolone or thiazolone ring seems to be almost completely suppressed in these dyes: the mercapto-thiazolone dyes, for example, reacted with bases (piperidine) to give water-soluble products which still retained dye character and presumably still contained the two terminal heterocyclic rings, though the chemistry of these modified dyes remains to be examined. The colour of all the dyes described in this paper was changed by alkali, but the original colour returned

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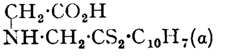
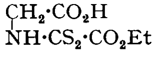
* This work was carried out in 1945 and an account of it was submitted as CPS 584 for the information of the Committee for Penicillin Syntheses, and for publication as soon as permissible.

on neutralisation or acidification. The dyes were reduced in alcoholic solution to colourless leuco-compounds (*e.g.*, by sodium dithionite) which were reoxidised by air to the original dyes.



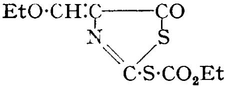
$$\begin{array}{l} CH_2{\cdot}CO_2H \\ NH{\cdot}CH_2{\cdot}CS_2{\cdot}C_{10}H_7(a) \end{array}$$

(IV.)

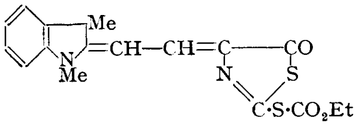


$$\begin{array}{l} CH_2{\cdot}CO_2H \\ NH{\cdot}CS_2{\cdot}CO_2Et \end{array}$$

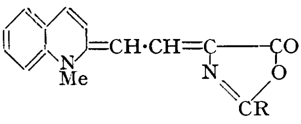
(V.)



(VI.)

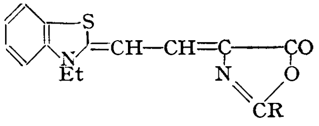


(VII.)



(R = Ph, C_5H_{11}, CH_2Ph.)

(VIII.)



(R = Ph, CH_2Ph.)

(IX.)

EXPERIMENTAL.

2-*Benzylthio*-5-*thiazolone Derivatives*.—Dithiocarbobenzoxyglycine (Cook, Harris, Heilbron, and Shaw, *loc. cit.*) (5 g.), ethyl orthoformate (5 g.), and acetic anhydride (25 c.c.) were warmed to 90° for 30 minutes. After removal of solvents the purple crystalline dye was washed with warm ether and recrystallised from acetone; *methinbis*-[4-(2-*benzylthio*-5-*thiazolone*)] (2·5 g.) separated in red-purple needles, m. p. 187° (decomp.) (Found: C, 55·2; H, 3·7; N, 6·2. $C_{21}H_{16}O_2N_2S_4$ requires C, 55·2; H, 3·5; N, 6·1%). 2-Benzylthio-4-ethoxymethylene-5-thiazolone (0·17 g.) and quinaldine methiodide (0·21 g.) in ethanol (10 c.c.) were treated with triethylamine (0·1 c.c.). The solution immediately became deep violet and on standing the dye (0·3 g.) crystallised. *Dimethin*[2-(1-*methylquinoline*)][4-(2-*benzylthio*-5-*thiazolone*)] recrystallised from ethanol in dark violet needles with a green sheen, m. p. 210° (decomp.) (Found: C, 67·7; H, 4·64; N, 7·6. $C_{22}H_{16}ON_2S_2$ requires C, 67·7; H, 4·65; N, 7·2%). 2-Benzyl-4-ethoxymethylene-5-thiazolone (0·65 g.) and 2-methylbenzthiazole ethiodide (0·77 g.) in warm methanol (20 c.c.) were treated with triethylamine (1 c.c.), and a mass of dark red needles was soon deposited. *Dimethin*[2-(1-*ethylbenzthiazole*][4-(2-*benzylthio*-5-*thiazolone*)] (yield, 1·15 g.) crystallised from aqueous acetone in needles, m. p. 175° (Found: C, 61·25; H, 4·6. $C_{21}H_{18}ON_2S_3$ requires C, 61·4; H, 4·4%).

2-*Ethylthio*-5-*thiazolone Derivatives*.—2-Ethylthio-4-ethoxymethylene-5-thiazolone was condensed with quinaldine methiodide and with 2-methylbenzthiazole ethiodide as in previous similar reactions in presence of triethylamine. *Dimethin*[2-(1-*methylquinoline*)][4-(2-*ethylthio*-5-*thiazolone*)] crystallised from ethanol–water in purple or almost black needles with a green lustre, m. p. 172° (decomp.) (Found: C, 62·2; H, 4·8; N, 8·9. $C_{17}H_{16}ON_2S_2$ requires C, 62·2; H, 4·9; N, 8·5%). *Dimethin*[2-(1-*methylbenzthiazole*)][4-(2-*ethylthio*-5-*thiazolone*)] separated from ethanol in needles, m. p. 173—174° (Found: C, 55·3; H, 4·5; N, 8·4. $C_{16}H_{16}ON_2S_3$ requires C, 55·2; H, 4·6; N, 8·0%). The ethoxymethylene compound (2·7 g.) and 2-ethylthio-5-thiazolone (2 g.) in methanol (5 c.c.) were treated with triethylamine (4 drops), and the solution boiled. On cooling the deep red solution, the dye crystallised. *Methinbis*[4-(2-*ethylthio*-5-*thiazolone*)] crystallised from ethanol in glistening violet laths, m. p. 150° (Found: C, 39·7; H, 3·8; N, 8·6. $C_{11}H_{12}O_2N_2S_4$ requires C, 39·8; H, 3·6; N, 8·4%). The same compound was obtained in small yield by boiling the ethoxymethylene compound with alcoholic hydrochloric acid (Found: C, 40·2; H, 3·7%).

2-Ethylthio-4-ethoxymethylene-5-thiazolone (0·22 g.) and 8-amino-6-methoxyquinoline (0·17 g.) were mixed in ethanol (3 c.c.). On scratching, the condensation product (0·35 g.) separated as an orange-yellow precipitate. 2-*Ethylthio*-4-(6′-*methoxy*-8′-*quinolylaminomethylene*)-5-*thiazolone* crystallised from ethanol in clusters of yellow needles, m. p. 167—168° (Found: C, 55·3; H, 4·4; N, 12·0. $C_{16}H_{15}O_2N_3S_2$ requires C, 55·6; H, 4·4; N, 12·15%). It was only slightly soluble in dilute mineral acids. The same quinoline was similarly condensed with 2-benzylthio-4-ethoxymethylene-5-thiazolone. 2-*Benzylthio*-4-(6′-*methoxy*-8′-*quinolylaminomethylene*)-5-*thiazolone* crystallised from much ethanol in yellow needles, m. p. 159° (Found: C, 61·5; H, 4·3; N, 10·4. $C_{21}H_{17}O_2N_3S_2$ requires C, 61·9; H, 4·2; N, 10·3%).

2-*Benzyl*-5-*oxazolone Derivative*.—2-Benzyl-4-ethoxymethyleneoxazolone (0·6 g.) and quinaldine methiodide (0·93 g.) in methanol (12 c.c.) were treated with triethylamine (0·1 g.). Diluting the magenta solution with a little water and keeping it at 0° gives the crystalline dye. It was soluble in most organic solvents but crystallised from aqueous pyridine in long needles with a green lustre. *Dimethin*-[2-(1-*methylquinoline*)][4-(2-*benzyl*-5-*oxazolone*)] had m. p. 184—185° (Found: N, 8·2. $C_{22}H_{18}O_2N_2$ requires N, 8·2%). Light absorption (ethanol): max. at λ = 5100 A., ε = 53,500. 2-Amyl-4-ethoxymethyleneoxazolone was condensed similarly. *Dimethin*[2-(1-*methylquinoline*)][4-(2-*amyl*-5-*oxazolone*)] separated from aqueous pyridine in clusters of fine purple needles, m. p. 109—110° (Found: C, 74·3; H, 6·9; N, 8·8. $C_{20}H_{22}O_2N_2$ requires C, 74·5; H, 6·8; N, 8·7%). Light absorption (ethanol): max. at λ = 5140 A., ε = 73,500.

2-*Phenyl*-5-*oxazolone Derivatives*.—2-Methylbenzthiazole ethiodide (0·22 g.) and 2-phenyl-4-ethoxymethyleneoxazolone (0·2 g.) in methanol (7 c.c.) were treated with triethylamine (3 drops). A deep red colour appeared within 10 seconds and the reaction mixture soon set to a mass of deep red needles (0·2 g.). *Dimethin*[2-(1-*ethylbenzthiazole*)][4-(2-*phenyl*-5-*oxazolone*)] separated from ethanol in red laths (occasionally in plates), m. p. 210° (Found: C, 68·7; H, 4·6; N, 6·1. $C_{20}H_{16}O_2N_2S$ requires C, 69·0; H, 4·6; N, 8·0%). Light absorption (acetone): max. at $\lambda\lambda$ = 5100, 4850 A. Quinaldine methiodide was used similarly, and *dimethin*[2-(1-*methylquinoline*)][4-(2-*phenyl*-5-*oxazolone*)] separated from ethanol, or better from pyridine containing a little water, in almost black permanganate-like needles, m. p. 222° (Found: C, 76·4; H, 4·8. $C_{21}H_{16}O_2N_2$ requires C, 76·8; H, 4·9%). Light absorption (acetone): max. at $\lambda\lambda$ = 5310, 4980 A.

2-α-*Naphthylmethylthio*-5-*thiazolone Derivatives*.—Glycine (10 g.) in water (15 c.c.) was treated with an ice-cold solution of potassium hydroxide (15·5 g.) in water (20 c.c.) and shaken for 3—4 hours with carbon disulphide (10·1 g.). The clear solution was then further shaken with 1-chloromethylnaphthalene (23·5 g.) for 40 hours. The solid was filtered off and shaken with 2N-hydrochloric acid (250 c.c.), and the liberated acid (31 g.) soon solidified. α-*Naphthyl* N-*carboxymethyldithioacetate* crystallised from chloroform–light petroleum or from chlorobenzene in needles, m. p. 196—198° (Found: C, 58·1; H, 4·2; N, 4·3. $C_{14}H_{13}O_2NS_2$ requires C, 57·7; H, 4·5; N, 4·8%). The acid (3·8 g.), ethyl orthoformate (7·0 g.), and acetic anhydride (6 c.c.) were heated together for 30 minutes on the steam-bath, the solution evaporated in a vacuum and the crude oil used directly. The crude ethoxymethylene compound (1·7 g.) was dissolved in boiling ethanol (70 c.c.), and quinaldine methiodide (1·5 g.) and triethylamine (1 c.c.) added. The dye commenced to crystallise immediately. It was practically insoluble in ethanol and was thoroughly extracted with that solvent and recrystallised from chloroform–ether. *Dimethin*[2-(1-*methylquinoline*)][4-(2-α-*naphthylmethylthio*-5-*thiazolone*)] separated in thin purple laths which had a green lustre, m. p. 216° (decomp.) (yield, 70%) (Found: C, 70·7; H, 4·5; N, 6·4. $C_{26}H_{20}ON_2S_2$ requires C, 70·9; H, 4·6; N, 6·4%). 2-Methylbenzthiazole ethiodide was similarly condensed with the ethoxymethylene compound; *dimethin*[2-(1-*ethylbenzthiazole*)][4-(2-α-*naphthylmethylthio*-5-*thiazolone*)] separated from glycol monomethyl ether in thin purple laths, m. p. 188—189° (Found: C, 65·3; H, 4·3; N, 5·9. $C_{25}H_{30}ON_2S_3$ requires C, 65·2; H, 4·4; N, 6·1%).

2-*Carbethoxythio*-5-*thiazolone Derivatives*.—Glycine (5 g.) in water (6 c.c.) was treated, with strong cooling, with potassium hydroxide (7·7 g.) in water (10 c.c.), and the solution shaken with carbon disulphide (5·1 g.) until a clear brown solution was obtained. Ethyl chloroformate (7·2 g.) was added, and the mixture again shaken, with cooling. A vigorous reaction set in and much solid separated. Ice and water were added to effect solution, and acidification then precipitated the product (yield, 59%). *N*-Carbethoxydithiocarboxyglycine crystallised from ether–light petroleum in rhombocidal prisms, m. p. 125° (Found: C, 32·6; H, 4·0; N, 6·3. Calc. for $C_6H_9O_4NS_2$: C, 32·3; H, 4·0; N, 6·5%). The preceding compound (5 g.), ethyl orthoformate (7 c.c.), and acetic anhydride (40 c.c.) were heated to 90° for 25 minutes, and the solution evaporated in a vacuum. 2-*Carbethoxythio*-4-*ethoxymethylene*-5-*thiazolone* crystallised from light petroleum in needles, m. p. 83° (Found: C, 41·1; H, 4·4. $C_9H_{11}O_4NS_2$ requires C, 41·4; H, 4·2%). The ethoxymethylene compound (0·15 g.) was condensed with 2-methylbenzthiazole ethiodide (0·13 g.) in methanol (5 c.c.) containing triethylamine (3 drops). The deep red solution soon deposited crystals of the pure dye (0·22 g.), m. p. 174—175°. *Dimethin*[2-(1-*ethylbenzthiazole*)][4-(2-*carbethoxythio*-5-*thiazolone*)] crystallised from methanol in red laths, m. p. 174—175° (Found: C, 52·0; H, 4·1; N, 7·3. $C_{17}H_{16}O_3N_2S_2$ requires C, 52·0; H, 4·1; N, 7·1%). Condensation with quinaldine methiodide was carried out similarly in excellent yield, *dimethin*[2-(1-*methylquinoline*]-[4-(2-*carbethoxythio*-5-*thiazolone*)] crystallising from methanol in deep violet needles or laths, m. p. 168—169° (decomp.) (Found: C, 57·9; H, 4·3. $C_{16}H_{16}O_3N_2S_2$ requires C, 58·0; H, 4·3%). The ethoxymethylene compound (0·13 g.) was mixed with 1 : 3 : 3-trimethyl-2-methyleneindoline (0·08 g.) in methanol (1 c.c.). The red crystalline condensation product (0·18 g.) began to separate almost immediately. *Dimethin*[2-(1 : 3 : 3-*trimethylindoline*][4-(2-*carbethoxythio*-5-*thiazolone*)] crystallised from methanol in red needles, m. p. 178° (decomp.) (Found: C, 58·4; H, 5·2; N, 7·1. $C_{19}H_{20}O_3N_2S_2$ requires C, 58·7; H, 5·2; N, 7·2%).

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