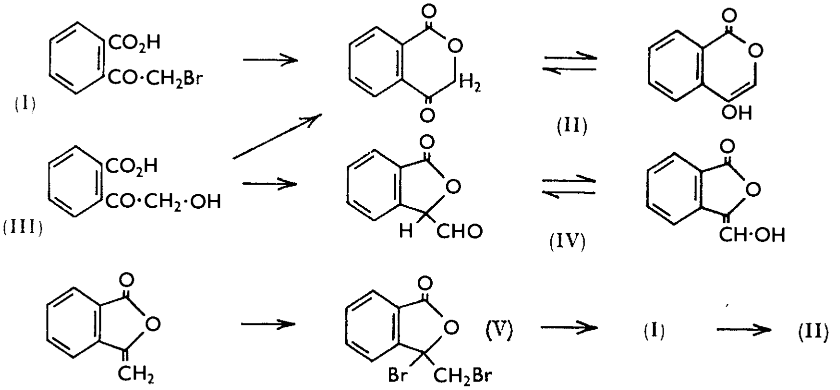
62. *Isochroman-*1,4-*dione and Some of its Reactions.*

By E. B. Knott.

The product obtained by the elimination of hydrogen bromide from *o*-bromoacetylbenzoic acid is shown to be isochroman-1,4-dione (II), and not 3-formylphthalide (IV) as formulated by Gabriel. It contains a nucleophilic methylene-carbon atom.

During an investigation of the potential use of *o*-bromoacetylbenzoic acid (I) in the Hantzsch thiazole synthesis, an attempted condensation with alcoholic isopropyl thioncarbamate in the presence of solid sodium hydrogen carbonate gave a crystalline product, m. p. 147—149°, containing no sulphur. The same product was obtained by treating *o*-bromoacetylbenzoic acid in ethanol with sodium hydrogen carbonate or, better, with anhydrous sodium acetate. Its empirical formula, $C_9H_6O_3$, and molecular weight indicated that its formation had resulted from the elimination of hydrogen bromide from the bromo-acid.

The same compound has been described by Gabriel[1] (with Michael[2]), who obtained it by refluxing the bromo-acid (I) in water or aqueous alkali and assigned it structure (IV), 3-formylphthalide. He obtained the same compound by treating methyl *o*-bromoacetylbenzoate with sodium methoxide,[3] and from methylenephthalide by bromination followed by heating of the resulting bromo-compound (V) with water.[4]



Its reactions, however (see below), show the presence of a nucleophilic centre, an α-keto-methylene group, not present in the phthalide (IV). Its infrared spectrum showed no aldehyde peak at 2700 cm.$^{-1}$, but strong peaks at 1689 and 1721 cm.$^{-1}$, indicative of ketonic and ester carbonyl groups, respectively, and a weak hydroxyl peak at 3448 cm.$^{-1}$.*

This evidence rules out structure (IV) and confirms the belief that the compound is isochroman-1,4-dione (II).† The weak hydroxyl peak would then be due to the presence of traces of its tautomer, 4-hydroxyisochromen-1-one. Its formation by intramolecular esterification of *o*-bromoacetylbenzoic acid (I) is rational, and at least as probable as hydrolysis of the bromo-acid (I) to *o*-hydroxyacetylbenzoic acid (III) followed by lactonization to 3-formylphthalide (IV).

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* Its nuclear magnetic resonance spectrum (see Experimental) favoured the isochromandione structure (II) and precluded its being 3-formylphthalide (IV).

† Since this paper was written, Bhati (*J. Org. Chem.*, 1962, **27**, 1183) has obtained 8-methoxy- and 8-nitro-isochroman-1,4-dione by treatment of the substituted methyl hydrogen phthalate with diazomethane followed by the decomposition of the resulting diazo-ketone with hydriodic acid.

[1] Gabriel, *Ber.*, 1907, **40**, 71.

[2] Gabriel and Michael, *Ber.*, 1878, **11**, 1007.

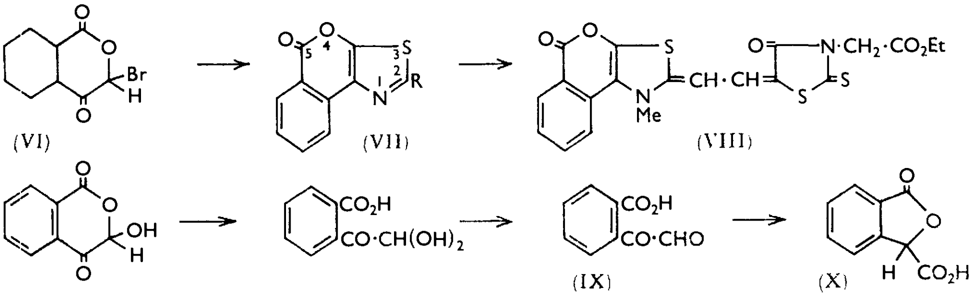
[3] Gabriel, *Ber.*, 1907, **40**, 4227.

[4] Gabriel, *Ber.*, 1884, **17**, 2521.

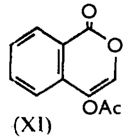
The presence of the 4-carbonyl group of isochromandione (II) is indicated by the formation of an oxime and phenylhydrazone.[1] The reducing properties in alkaline solution, also observed by Gabriel, may indicate hydrolysis to the acid (III) under such conditions, the α-hydroxy-ketonic group thus formed being a well-known reducing group.[5,6]

Bromination[1] yields 3-bromoisochroman-1,4-dione (VI), an α-bromo-ketone, which readily undergoes the Hantzsch thiazole condensation with thioacetamide or thiourea to give the isochromeno[4,3-*d*]thiazoles (VII; R = Me and NH_2, respectively). Quaternization of the thiazole (VII; R = Me) with methyl sulphate followed by condensation with 3-ethoxycarbonylmethyl-5-ethoxymethylenerhodanine affords the merocyanine (VIII). Treatment of the bromo-compound with barium hydroxide gives phthalide-3-carboxylic acid[1] (X), possibly by the route illustrated, the intermediate substituted glyoxal (IX) being that postulated by Gabriel in his scheme for the formation of phthalide-3-carboxylic acid from 3-bromo-3-formylphthalide.

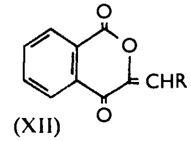
Isochromandione is acetylated to 4-acetoxyisochromen-1-one (XI) by acetic anhydride, and is converted into a mixture of the acetate (XI) and 3-ethoxymethyleneisochroman-1,4-dione (XII; R = OEt) by ethyl orthoformate in the presence of acetic anhydride.



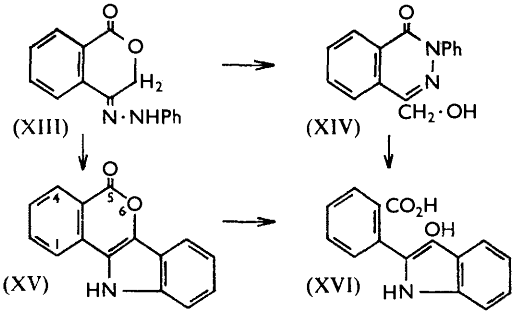
Treatment of the ether (XII; R = OEt) with dimethylamine affords 3-dimethylaminomethyleneisochroman-1,4-dione (XII; R = NMe_2), a yellow dye fluorescing intensely yellow in ultraviolet light. The related 3-anilinomethyleneisochroman-1,4-dione (XII; R = NHPh) is obtained directly from *o*-bromoacetylbenzoic acid by treatment with ethoxymethyleneaniline (ethylisoformanilide) in ethanol. The yellow phenylhydrazone (XIII) of isochromandione[1] undergoes two interesting transformations. Its solution in aqueous-alcoholic sodium hydroxide yields a colourless isomer on acidification, believed to be 1,2-dihydro-4-hydroxymethyl-2-phenylphthalazin-1-one (XIV), the ultraviolet absorption of which is almost identical with that of authentic 1,2-dihydro-4-methyl-2-phenylphthalazin-1-one. When the phenylhydrazone (XIII) is dissolved and boiled for a few minutes in acetic acid, a yellow crystalline product of empirical formula $C_{15}H_9NO_2$



(XI)



(XII)



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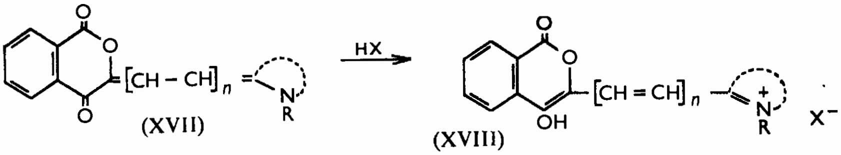
[5] Hunaeus and Zincke, *Ber.*, 1874, **10**, 1487.
[6] Perkin, *J.*, 1891, **59**, 793.

separates, a molecule of ammonia having been eliminated from the phenylhydrazone. A Fischer-type indole reaction thus appears to take place under these mild conditions, to give 5-oxoisochromeno[4,3-*b*]indole (XV). This product is hydrolysed by alkali to an acid, analysis of which agrees with its being the indole (XVI).

Isochroman-1,4-dione yields highly fluorescent merocyanines (XVII; $n = 0$, 1, or 2) with alkylthio, β-acetanilidovinyl, or δ-acetanilidobuta-1,3-dienyl derivatives of heterocyclic quaternary ammonium salts. Their strongly polar, and hence basic, nature is manifested by their deep absorption and the ease of formation of stable yellow salts (XVIII) with mineral acids. The hypsochromic effect of proton addition to the dyes (XVII) is striking, and is a function of the great increase in energetic asymmetry of the resonance system. This asymmetry of the base (XVII) will decrease, and of the salt (XVIII) will increase, with increasing $-M$ effect (basicity) of the nitrogen heterocycle. It would, consequently, be expected that the hypsochromic shift on proton addition would increase with increasing basicity of the nitrogen heterocycle. This is the case (see Experimental section), the shift increasing from 3-ethylbenzoxazoline (71 mμ), through 3-ethylbenzothiazoline (105 mμ) and 3-ethyl-4,5-diphenyloxazoline (137 mμ), to 1-ethyl-1,2-dihydropyridine (186 mμ).



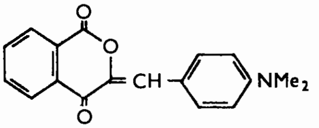
(XVII) (XVIII)

With *p*-dimethylaminobenzaldehyde and 1-ethyl-3-formyl-2,5-dimethylpyrrole, isochroman-1,4-dione condenses to give dyes (XIX) and (XX), respectively.

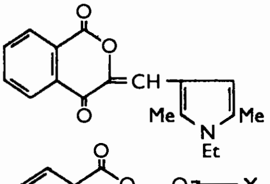
The oxonols derived from isochromandione are accessible by the interaction of the latter with the reactive ethoxymethylene derivatives of ketomethylene compounds, or from the ketomethylene compounds and 3-ethoxymethyleneisochroman-1,4-dione (XII; R = OEt). They are all yellow or orange, usually with a very highly coloured anion, thus exhibiting pH indicator properties.

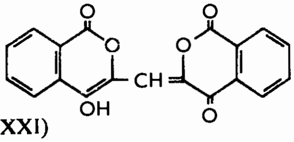
The symmetrical oxonol (XXI) affords a yellow solution in hot pyridine, the colour changing to blue, the colour of the anion, on freezing. It gives a blue adsorbate on alumina. Such deepening of colour at low temperatures of its solution in a weak base is analogous to that shown by certain fluorene derivatives prepared by Schönberg and Singer.[7] The rhodanine oxonol (XXII) behaves similarly and has a magenta anion and forms a magenta adsorbate on alumina. It affords a yellow acetate on treatment of its pyridine solution with acetic anhydride.

(XIX)

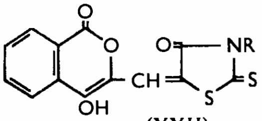


(XX)

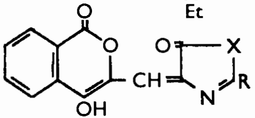




(XXI)



(XXII)



(XXIII)

The oxonols (XXIII; X = S, R = SEt; and X = O, R = Ph) are of interest in that they crystallize from alcohol in the presence of 1 mol. of triethylamine. They are pale yellow compounds yielding purple and orange anions, respectively. Benzene solutions of the oxonol (XXIII; X = O, R = Ph) fluoresce strongly blue in daylight.

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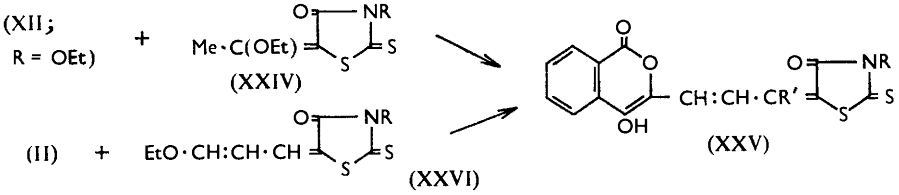
[7] Schönberg and Singer, *Chem. Ber.*, 1961, **94**, 248.

Unsymmetrical trimethineoxonols were obtained in two ways. Condensation of 3-ethoxymethyleneisochroman-1,4-dione (XII; R = OEt) with a 3-substituted 5-1′-ethoxyethylidenerhodanine (XXIV) gives the oxonol (XXV; R′ = OEt), and isochromandione condenses with a 3-substituted 5-(3-ethoxyprop-2-enylidene)rhodanine (XXVI) to give the oxonol (XXV; R′ = H). Both oxonols afford blue solutions of the anions, the free acids being orange. The intermediate ethoxypropenylidenerhodanine (XXVI) is obtained by the condensation of the 3-substituted rhodanine with 1,3,3-triethoxypropene in acetic anhydride.

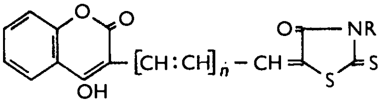
For a spectrographic comparison of the colour value of the isochroman-1,4-dione residue with those of the isomeric chroman-2,4-dione (4-hydroxycoumarin) and of a 3-substituted rhodanine, dyes (XXVII; *n* = 0, 1) and (XXVIII) were synthesized and compared with dyes (XXII) and (XXV; R′ = H). The absorption maxima of the anions of the dyes in ethanolic triethylamine were determined. In the monomethineoxonol series the isochromanone dye (XXII; R = $CH_2{\cdot}CO_2Et$) shows a maximum at 582 mμ compared with 458 mμ of the chromanone analogue (XXVII; *n* = 0, R = $CH_2{\cdot}CO_2Et$). In the trimethineoxonol series the values are 665 mμ for (XXV; R′ = H, R = $CH_2{\cdot}CO_2Et$) and 503 mμ for (XXVII; *n* = 1, R = $CH_2{\cdot}CO_2Et$), whilst the peak of the anion of the symmetrical rhodanine dye (XXVIII) lies at 608 mμ.



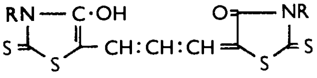
(XII; R = OEt) + (XXIV)

(II) + (XXVI)

(XXV)



(XXVII)



(XXVIII)

Powerful hypsochromic shifts (124 and 162 mμ) thus accompany the replacement of the isochromanone by the chromanone nucleus, and a smaller hypsochromic shift (57 mμ) occurs when the isochromanone is replaced by the rhodanine nucleus.

This comparison, together with the extremely long-wavelength absorption of the anion of the symmetrical isochromanone oxonol (XXI) ($\lambda_{max.}$ 626, 582 mμ), emphasizes the unusually high colour value of this nucleus.

EXPERIMENTAL

Isochroman-1,4-*dione* (4-*Hydroxyisochromen*-1-*one*) (II).—*o*-Bromoacetylbenzoic acid (2·43 g., 0·01 mole) and finely powdered anhydrous sodium acetate (0·82 g., 0·01 mole) were covered with ethanol (5 ml.) in a conical flask and warmed gently on a steam-bath. As the solids dissolved a thick, crystalline meal separated. Undissolved crystals of sodium acetate caused a local red colour and these were dispersed with a glass rod. Heating was discontinued after 2 min. The mixture was chilled, and the crystals were collected and washed free from sodium bromide with water. The compound (1·25 g., 77%) formed glassy needles, m. p. 147—149°, from benzene [Found: C, 66·5; H, 3·75; *M* (Rast), 157. Calc. for $C_9H_6O_3$: C, 66·7; H, 3·7%; *M*, 162].

4-*Acetoxyisochromen*-1-*one* (XI) was obtained as yellow needles, m. p. 82—83° (from benzene–light petroleum), by refluxing isochromandione in acetic anhydride for 2 hr. (Found: C, 64·5; H, 4·15. $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%).

2-*Amino*-5-*oxoisochromeno*[4,3-d]*thiazole* (VII; R = NH_2). Isochroman-1,4-dione (4·05 g., 0·025 mole) in chloroform (50 ml.) was treated with a solution of bromine (1·3 ml., 0·025 mole) in chloroform (10 ml.) with stirring. The reaction was initiated by adding a few drops of bromine solution and warming the mixture until it became colourless. No further application of heat was then necessary. The solvent and hydrogen bromide were removed at 45° under reduced pressure, to yield crystalline 3-bromoisochroman-1,4-dione (VI). Thiourea (2 g.) and ethanol (10 ml.) were added to the residue, and the whole was heated for 5 min. on a steam-bath. The solids dissolved and crystallization set in. The mixture was chilled and the crystals of the *hydrobromide* (6·05 g., 80%) of the base (VII; R = NH_2) were collected and washed with ethanol–ether (1 : 1). A sample from ethanol containing a drop of hydrobromic acid formed cream needles, m. p. 257° (decomp.) (Found: Br, 26·5. $C_{10}H_6N_2O_2S,HBr$ requires Br, 26·75%). The hydrobromide was dissolved in hot pyridine and the *base* (VII; R = NH_2) (97%) was precipitated with water as yellow grains. From pyridine–ethanol it formed bright yellow needles, m. p. 260° (decomp.) (Found: C, 55·1; H, 2·9; N, 12·6; S, 14·9. $C_{10}H_6N_2O_2S$ requires C, 55·05; H, 2·75; N, 12·85; S, 14·7%).

2-*Methyl*-5-*oxoisochromeno*[4,3-d]*thiazole* (VII; R = Me).—Isochroman-1,4-dione (4·05 g.) was brominated as in the preceding preparation. The resulting, crude 3-bromoisochroman-1,4-dione, thioacetamide (2·0 g.), and ethanol (10 ml.) were then heated together on a steam-bath. The solids dissolved and an exothermic reaction set in. Heating was interrupted as a solid separated. After chilling, the solid *base* (3·5 g., 78%) was collected. It formed pale cream needles, m. p. 161°, from ethanol containing a little triethylamine (Found: C, 60·75; H, 3·4; N, 6·25; S, 14·9. $C_{11}H_7NO_2S$ requires C, 60·8; H, 3·2; N, 6·45; S, 14·75%).

2-(3-*Ethoxycarbonylmethyl*-4-*oxo*-2-*thiothiazolidin*-5-*ylidene-ethylidene*)-2,3-*dihydro*-3-*methyl*-5-*oxoisochromeno*[4,3-d]*thiazole* (VIII).—The thiazole (VII; R = Me) (0·5 g.) and methyl sulphate (0·3 ml.) were heated together at 160° for 2 hr. The resulting quaternary salt was washed with ether and mixed with 3-ethoxycarbonylmethyl-5-ethoxymethylenerhodanine (0·65 g.), methanol (10 ml.), and triethylamine (0·5 ml.), and the whole was refluxed on a steam-bath for 5 min. On chilling, the *dye* (0·1 g., 9·5%) separated. It formed maroon crystals, m. p. 300—301°, from pyridine–ethanol (Found: C, 52·45; H, 3·8; N, 6·05; S, 20·75. $C_{20}H_{16}N_2O_5S_3$ requires C, 52·2; H, 3·5; N, 6·1; S, 20·9%).

3-*Ethoxymethyleneisochroman*-1,4-*dione* (XII; R = OEt).—Isochroman-1,4-dione (4·0 g.), acetic anhydride (10 ml.), and ethyl orthoformate (50 ml.) were refluxed on a gauze for 1 hr. The solvents were removed under reduced pressure, and the residue recrystallized from ethanol. It (2·0 g., 37%) formed straw-coloured needles, m. p. 152—153° (Found: C, 66·2; H, 4·6. $C_{12}H_{10}O_4$ requires C, 66·05; H, 4·6%). The ethanol filtrates yielded 4-acetoxyisochromen-1-one. The above *ether* (XII; R = OEt) (0·73 g.) was dissolved in warm dimethylformamide (5 ml.) and treated with 33% alcoholic dimethylamine (1 ml.). A yellow precipitate was given, and was collected after dilution of the mixture with ether (20 ml.). From ethanol the 3-*dimethylaminomethyleneisochroman*-1,4-*dione* (XII; R = NMe_2) (0·6 g., 82%) formed yellow needles, m. p. 212—213°, exhibiting a brilliant yellow fluorescence in ultraviolet light (Found: C, 66·1; H, 5·25; N, 6·55. $C_{12}H_{11}NO_3$ requires C, 66·3; H, 5·05; N, 6·45%), $\lambda_{max.}$ 407 mμ in chloroform.

3-*Anilinomethyleneisochromanone* (XII; R = NHPh).—*o*-Bromoacetylbenzoic acid (2·45 g.), ethylisoformanilide (3 ml.), and ethanol (10 ml.) were heated together on a steam-bath for 10 min. A deep yellow colour developed, crystals separated and then redissolved, and fine yellow needles filled the liquor. On chilling, the whole solidified. The *product* (0·85 g., 32%) formed orange threads, m. p. 224°, from ethanol (Found: C, 71·7; H, 4·6; N, 5·15. $C_{16}H_{11}NO_3$ requires C, 72·5; H, 4·2; N, 5·3%), $\lambda_{max.}$ 424 mμ in chloroform.

4-*Phenylhydrazonoisochroman*-1,4-*dione* (XIII).—Isochroman-1,4-dione (4·05 g.) was dissolved in a hot mixture of ethanol (75 ml.) and water (25 ml.). Addition of phenylhydrazine (2·5 ml.) in ethanol (5 c.c.) and acetic acid (5 c.c.) gave a clear solution from which pale yellow needles rapidly separated. After 15 min. the mixture was chilled and the crystals were collected. The *phenylhydrazone* (6·1 g., 97%) was obtained as pale yellow threads, m. p. 190—192°, by dissolving the crude material in pyridine and adding ¼ volume of water (Found: C, 71·9; H, 5·05; N, 11·3. $C_{15}H_{12}N_2O_2$ requires C, 71·4; H, 4·75; N, 11·1%). Gabriel gives m. p. 180° for the so-called derivative of the aldehyde (IV).

Dissolution of the phenylhydrazone (2·5 g.) in boiling acetic acid (30 c.c.) gave a clear solution which suddenly filled with yellow grains. From aqueous pyridine the product (2·1 g.), believed to be 5-*oxoisochromeno*[4,3-b]*indole* (XV) formed yellow crystals, m. p. 304—305° (Found: C, 77·1; H, 3·9; N, 5·95. $C_{15}H_9NO_2$ requires C, 76·6; H, 3·85; N, 5·95%). This product (1 g.), methanol (10 ml.), and aqueous 2N-sodium hydroxide (2 ml.) were heated together on a steam-bath, to give an orange, yellow-fluorescent solution that was filtered and acidified with hydrochloric acid. The precipitate (0·75 g.) recrystallized from ethanol, to yield a first crop of pale yellow crystals, m. p. 240—241°, and a second crop, m. p. *ca.* 290°. The first crop formed bright yellow crystals, m. p. 241—243°, from benzene (Found: C, 71·5; H, 4·25; N, 5·45. $C_{15}H_{11}NO_3$ requires C, 71·2; H, 4·35; N, 5·55%); it is believed to be 2-o-*carboxyphenyl*-3-*hydroxyindole* (XVI).

The phenylhydrazone (2 g.) with methanol (20 ml.) and aqueous 2N-sodium hydroxide (10 ml.) on a steam-bath gave a clear solution. Concentrated hydrochloric acid (2 ml.) was added and water was then run into the hot solution. Crystals separated (1·9 g., 95%), believed to be 1,2-*dihydro*-4-*hydroxymethyl*-2-*phenylphthalazin*-1-*one* (XIV), that formed cream needles, m. p 171°, from ethanol (Found: C, 71·1; H, 4·95; N, 11·15. $C_{15}H_{12}N_2O_2$ requires C, 71·4; H, 4·75; N, 11·1%). Its ultraviolet absorption spectrum shows a maximum at 293 mμ compared with one at 296 mμ for 1,2-dihydro-4-methyl-2-phenylphthalazin-1-one, the curves being almost identical.

Merocyanines Derived from Isochroman-1,4-*dione* (XVII).—These dyes were obtained by the reaction of the alkylthio, acetanilidovinyl, or acetanilidobutadienyl derivative of the quaternary salt in alcohol for a few minutes with the isochromandione in the presence of 1 mol. of triethylamine, or with *o*-bromoacetylbenzoic acid in the presence of 2 mol. of triethylamine. The dye usually crystallized during the refluxing period.

3-(3-*Ethylbenzothiazolin*-2-*ylidene*)*isochroman*-1,4-*dione* was obtained in 83% yield as orange needles, m. p. 232—233° (from pyridine–ethanol) (Found: C, 66·5; H, 4·3; N, 4·15; S, 10·15. $C_{18}H_{13}NO_3S$ requires C, 66·8; H, 4·05; N, 4·35; S, 10·0%), $\lambda_{max.}$ 450 mμ in chloroform. It fluoresces a brilliant yellow in ultraviolet light.

3-(3-*Ethylbenzothiazolin*-2-*ylidene-ethylidene*)*isochroman*-1,4-*dione* formed green needles, m. p. 285—286° (from pyridine–ethanol; 80% yield) (Found: C, 68·95; H, 4·6; N, 4·05; S, 9·05. $C_{20}H_{15}NO_3S$ requires C, 68·75; H, 4·3; N, 4·0; S, 9·15%), $\lambda_{max.}$ 571 (ε 5·1 × 10^4) and 550 (ε 5·0 × 10^4) in chloroform, and 466 mμ (ε 4·0 × 10^4) in ethanolic HCl.

3-(1-*Ethyl*-1,2-*dihydropyrid*-2-*ylidene-ethylidene*)*isochroman*-1,4-*dione* was obtained in 29% yield as green tablets, m. p. 257—258° (from ethanol) (Found: C, 73·8; H, 5·3; N, 4·7. $C_{18}H_{15}NO_3$ requires C, 73·8; H, 5·1; N, 4·8%), $\lambda_{max.}$ 561 (ε 3·9 × 10^4) and 603 mμ (ε 4·9 × 10^4) in chloroform, and 417 mμ (ε 3·3 × 10^4) in ethanolic HCl.

3-(3-*Ethyl*-4,5-*diphenyloxazolin*-2-*ylidene-ethylidene*)*isochroman*-1,4-*dione* formed dark-green aggregates, m. p. 268°, from benzene (Found: C, 77·3; H, 5·05; N, 3·15. $C_{28}H_{21}NO_4$ requires C, 77·25; H, 4·8; N, 3·2%). Its benzene solution fluoresced magenta in ultraviolet light. It had $\lambda_{max.}$ 542 (ε 5·05 × 10^4) and 575 mμ (ε 4·7 × 10^4) in chloroform. Its hydrochloride, 3-*ethyl*-2-(4-*hydroxy*-1-*oxoisochromen*-3-*ylvinyl*)-4,5-*diphenyloxazolium chloride*, formed yellow threads, m. p. 268° (from ethanol–ether) (Found: C, 71·2; H, 4·8; Cl, 7·6; N, 3·1. $C_{28}H_{22}ClNO_4$ requires C, 71·45; H, 4·65; Cl, 7·55; N, 2·95%), $\lambda_{max.}$ 438 mμ (ε 4·1 × 10^4) in ethanolic HCl.

3-(3-*Ethylbenzothiazolin*-2-*ylidenebut*-2′-*enylidene*)*isochroman*-1,4-*dione* was obtained in 43% yield as green needles, m. p. 267—268° (from pyridine–ethanol) (Found: C, 70·7; H, 4·75; N, 3·45; S, 8·45. $C_{22}H_{17}NO_3S$ requires C, 70·4; H, 4·55; N, 3·75; S, 8·55%), $\lambda_{max.}$ 635 mμ (ε 6·9 × 10^4) in chloroform, 489 mμ (ε 5·35 × 10^4) in ethanolic HCl.

3-p-*Dimethylaminobenzylideneisochroman*-1,4-*dione* (XIX).—Isochroman-1,4-dione (0·8 g.), *p*-dimethylaminobenzaldehyde (0·75 g.), ethanol (5 ml.), and piperidine (2 drops) were heated together on a steam-bath for 5 min. Crystals separated and were collected after chilling. The *product* (XIX) (0·65 g., 44·5%) formed green crystals, m. p. 261—262°, from pyridine–ethanol (Found: C, 73·6; H, 5·2; N, 4·9. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·1; N, 4·75%). It fluoresced in ultraviolet light, yellow in benzene and red in pyridine, and had $\lambda_{max.}$ 491 mμ (ε 3·2 × 10^4) in chloroform.

3-(1-*Ethyl*-2,5-*dimethyl*-3-*pyrrylmethylene*)*isochroman*-1,4-*dione* (XX).—Isochroman-1,4-dione (0·5 g.), 1-ethyl-2,5-dimethylpyrrole-3-aldehyde (0·45 g.), ethanol (5 ml.), and piperidine (2 drops) were heated together for 1 min. on a steam-bath to cause solidification. The *dye* formed orange threads, m. p. 217°, from ethanol (Found: C, 73·4; H, 5·9; N, 4·8. $C_{18}H_{17}NO_3$ requires C, 73·2; H, 5·75; N, 4·75%). Its benzene solution fluoresced yellow in ultraviolet light. It had $\lambda_{max.}$ 460 mμ (ε 2·2 × 10^4) in chloroform.

3-(4-*Hydroxy*-1-*oxoisochromen*-3-*ylmethylene*)*isochroman*-1,4-*dione* (*Triethylammonium Salt*) (XXI).—Isochroman-1,4-dione (0·4 g.) and 3-ethoxymethyleneisochroman-1,4-dione (0·55 g.)

were dissolved in hot dimethylformamide (10 ml.), and triethylamine (0·4 ml.) was added. The whole was heated on a steam-bath for 1 min. and the blue *dye salt* caused to crystallize by addition of ether (50 ml.). It (0·35 g., 33%) formed green crystals, m. p. 196° (decomp.) (Found: C, 68·5; H, 5·7; N, 3·25. $C_{25}H_{25}NO_6$ requires C, 68·95; H, 5·75; N, 3·2%), $\lambda_{max.}$ 626 (ε 3·0 × 10^4) and 582 mμ (ε 3·15 × 10^4) in ethanolic triethylamine, pK 5·0, colour change at pH 5·8—4·2.

The free *phenol*, liberated from a dimethylformamide solution of the triethylamine salt with acetic acid, crystallized as maroon needles, decomp. 230° (Found: C, 68·7; H, 3·2. $C_{19}H_{10}O_6$ requires C, 68·3; H, 3·0%).

3-*Ethoxycarbonylmethyl*-5-(4-*hydroxy*-1-*oxoisochromen*-3-*ylmethylene*)-2-*thio*-4-*thiazolidone* (XXII; R = $CH_2{\cdot}CO_2Et$).—*o*-Bromoacetylbenzoic acid (1·2 g.) and 3-ethoxycarbonylmethyl-5-ethoxymethylenerhodanine (1·4 g.) were dissolved in hot ethanol (10 ml.), and triethylamine (1·5 ml.) was added. The mixture was refluxed for 5 min. and concentrated hydrochloric acid was added until the purple colour changed to orange. The *dye* (1·6 g., 82%) crystallized and was purified by dissolution in hot alcoholic triethylamine followed by acidification with hydrochloric acid. It forms an ochre powder shrinking at *ca.* 260° and decomposing at *ca.* 280° (Found: C, 52·1; H, 3·5; N, 3·65; S, 16·6. $C_{17}H_{13}NO_6S_2$ requires C, 52·4; H, 3·35; N, 3·6; S, 16·45%). It gives a yellow solution in hot pyridine which changes to degraded red, then blue on cooling and freezing. In aqueous pyridine the solution is magenta, *i.e.*, the dye ionizes. It gives a purple adsorbate on alumina. It has $\lambda_{max.}$ 582 mμ (ε 3·05 × 10^4) in ethanolic triethylamine. The pK is 4·6; a colour change occurs at pH 5·6—3·6.

Its *acetate* was obtained by addition of acetic anhydride (1·1 mol.) to a solution of the dye (1 mol.) in hot pyridine (colour change from purple to yellow), and was precipitated by dilute acetic acid; it formed bright yellow threads, m. p. 200—202°, from benzene or propan-2-ol (Found: C, 52·95; H, 3·55; N, 3·2; S, 14·65. $C_{19}H_{15}NO_7S_2$ requires C, 52·7; H, 3·5; N, 3·2; S, 14·8%).

3-*Ethyl*-5-(4-*hydroxy*-1-*oxoisochromen*-3-*ylmethylene*)-2-*thio*-4-*thiazolidone* (XXII; R = Et) was obtained similarly in 73% yield and formed bright yellow crystals, decomp. 270°, after purification through its triethylamine salt (Found: C, 54·45; H, 3·4; N, 4·15; S, 19·35. $C_{15}H_{11}NO_4S_2$ requires C, 54·1; H, 3·3; N, 4·2; S, 19·2%). Its *acetate* was formed in pyridine and precipitated by ether; it formed yellow needles, m. p. 217—220° (3·5 g., 93%), from ethanol (Found: C, 54·5; H, 3·6; N, 3·6; S, 17·1. $C_{17}H_{13}NO_5S_2$ requires C, 54·4; H, 3·45; N, 3·75; S, 17·05%).

4-(4-*Hydroxy*-1-*oxoisochromen*-3-*ylmethylene*)-2-*phenyl*-5-*oxazolone* (XXIII; X = O, R = Ph).—Isochroman-1,4-dione (1·62 g.), 4-ethoxymethylene-2-phenyloxazol-5-one (2·17 g.), ethanol (20 ml.), and triethylamine (1·5 ml.) were heated together on a steam-bath for 2—3 min. The solid product was collected and washed with ethanol, giving 2·45 g. (73·5%) of the free *oxonol*. It was dissolved in hot chloroform and the solution diluted with hot methanol (2 vol.), thus giving pale yellow threads, m. p. 238° (Found: C, 68·2; H, 3·55; N, 4·3. $C_{19}H_{11}NO_5$ requires C, 68·4; H, 3·5; N, 4·2%). The crystals fluoresce green in ultraviolet light; the benzene solution fluoresces blue, even in daylight. The dye gives an orange solution in alcoholic sodium hydroxide; it has $\lambda_{max.}$ 380 (ε 3·9 × 10^4) and 400 mμ (ε 3·6 × 10^4) in ethanolic triethylamine.

2-*Ethylthio*-4-(4-*hydroxy*-1-*oxoisochromen*-3-*ylmethylene*)-5-*thiazolone* (XXII; X = S, R = SEt).—*N*-[(Ethylthio)thiocarbonyl]glycine (9·0 g.), acetic anhydride (50 ml.), and ethyl orthoformate (20 ml.) were heated at 140° for 30 min. and the solvent was then removed under reduced pressure. To the residual, crude 4-ethoxymethylene-2-ethylthio-5-thiazolone was added a slurry of isochroman-1,4-dione, obtained by treating *o*-bromoacetylbenzoic acid (12·2 g.) in ethanol (25 ml.) with sodium acetate (4·1 g.). Ethanol (25 ml.) and triethylamine (7·5 ml.) were added and the whole was heated for 1—2 min. on a steam-bath. The dye (6·95 g., 41·5%) which separated was washed with ethanol containing a few drops of hydrochloric acid; it forms yellow threads, m. p. 204—205° (decomp.), from acetic acid (Found: C, 54·4; H, 3·5; N, 4·25; S, 19·3. $C_{15}H_{11}NO_4S_2$ requires C, 54·05; H, 3·3; N, 4·2; S, 19·2%), gives a purple solution of its anion in alcoholic triethylamine, has $\lambda_{max.}$ 557 (ε 2·25 × 10^4) and 592 mμ (inflexion) (ε 1·55 × 10^4) and pK 5·0, and undergoes a colour change at pH 6·0—4·0.

3-*Ethyl*-5-(4-*hydroxy*-1-*oxoisochromen*-3-*ylmethylene*)-2-*thio*-4-*oxazolidone*.—3-Ethoxymethyleneisochroman-1,4-dione (1·05 g.), 3-ethyl-2-thio-4-oxazolidone (0·75 g.), ethanol (5 ml.), and triethylamine (0·8 ml.) were heated together on a steam-bath for 5 min. Ethanol (5 ml.) was added to the magenta solution, and concentrated hydrochloric acid was dropped in until the solution was yellow. The *dye* crystallized on chilling. On acidification of its solution in alcoholic triethylamine it (0·5 g., 33%) was obtained as flat, rust-coloured needles, decomp. 250—260° (Found: C, 56·9; H, 3·75; N, 4·2; S, 10·3. $C_{15}H_{11}NO_5S$ requires C, 56·75; H, 3·45; N, 4·4; S, 10·1%), $\lambda_{max.}$ 524 mμ in ethanolic triethylamine.

3-*Ethoxycarbonylmethyl*-5-[1-*ethoxy*-3-(4-*hydroxy*-1-*oxoisochromen*-3-*yl*)*prop*-2-*enylidene*]-2-*thio*-4-*thiazolidone* (XXV; R′ = OEt, R = $CH_2·CO_2Et$).—Ethoxymethyleneisochroman-1,4-dione (0·55 g.), 3-ethoxycarbonylmethyl-5-1′-ethoxyethylidenerhodanine (0·75 g.), propan-2-ol (5 ml.), and triethylamine (0·4 ml.) were heated on a steam-bath to give a pale green solution. Water (5 ml.) was then added; a deep blue colour developed rapidly. After being heated for 1 min. the solution was treated with hydrochloric acid until the colour changed to yellow and crystallization commenced. The crystals were collected after chilling. The *dye* (0·45 g., 39%) formed rust-coloured needles, m. p. 257° (previously darkening), from its acidified solution in alcoholic triethylamine (Found: C, 54·4; H, 4·1; N, 3·15; S, 13·9. $C_{21}H_{19}NO_7S_2$ requires C, 54·75; H, 4·1; N, 3·0; S, 13·9%). It had $\lambda_{max.}$ 660 (592) mμ in ethanolic triethylamine.

3-*Ethoxycarbonylmethyl*-5-[3-(4-*hydroxy*-1-*oxoisochromen*-3-*yl*)*prop*-2-*en*-1-*ylidene*]-2-*thio*-4-*thiazolidone* (XXV; R′ = H, R = $CH_2·CO_2Et$).—Isochroman-1,4-dione (0·8 g.), 3-ethoxycarbonylmethyl-5-(3-ethoxyprop-2-enylidene)-2-thio-4-thiazolidone (1·5 g.) (see below), ethanol (10 ml.), and triethylamine (0·8 ml.) were heated together on a steam-bath for 10 min. A 1 : 10 mixture of concentrated hydrochloric acid and ethanol was dropped into the blue solution until the colour changed to orange and a tar separated. After chilling, the liquor was decanted and the tar dissolved in hot ethanol (10 ml.). The *dye* (0·3 g., 14·5%) crystallized as rusty-gold flakes, m. p. 238—240° (Found: C, 55·05; H, 3·8; N, 3·15; S, 15·2. $C_{19}H_{15}NO_6S_2$ requires C, 54·7; H, 3·6; N, 3·55; S, 15·35%), $\lambda_{max.}$ 665 (623) mμ in ethanolic triethylamine. It gives a blue adsorbate on alumina.

3-*Ethoxycarbonylmethyl*-5-[3-(4-*hydroxy*-2-*oxochromen*-3-*yl*)*prop*-2-*en*-1-*ylidene*]-2-*thio*-4-*thiazolidone* (XXVII; R = $CH_2·CO_2Et$, *n* = 1). Procedure as in the previous preparation but with isochroman-1,4-dione replaced by 4-hydroxycoumarin (0·8 g.) gave the *dye* as a meal on acidification of the orange-red mixture. It (0·65 g., 31%) was obtained as rusty-red flakes, m. p. 148—150°, by acidifying its alcoholic triethylamine solution (Found: C, 54·9; H, 3·8; N, 3·4; S, 15·1. $C_{19}H_{15}NO_6S_2$ requires C, 54·7; H, 3·6; N, 3·35; S, 15·35%). It gives a pink adsorbate on alumina and has $\lambda_{max.}$ 503 mμ in ethanolic triethylamine.

3-*Ethoxycarbonylmethyl*-5-(3-*ethoxyprop*-2-*enylidene*)-2-*thio*-4-*thiazolidone* (XXVI; R = $CH_2·CO_2Et$).—3-Ethoxycarbonylmethylrhodanine (21·9 g.), 1,3,3-triethoxypropene (28 ml.), and acetic anhydride (50 ml.) were heated together for 2 hr. at 160°, the ethyl acetate formed in the reaction being allowed to distil through a short column. The solvents were then removed under reduced pressure and the residual orange tar was treated with propan-2-ol (25 ml.). The *product* crystallized on chilling and was collected and washed with propan-2-ol–water (2 : 1). It (9·9 g., 33% formed orange needles, m. p. 102°, from ethanol (Found: C, 48·1; H, 5·15; N, 4·55; S, 21·25. $C_{12}H_{15}NO_4S_2$ requires C, 47·85; H, 5·0; N, 4·65; S, 21·25%).

3-*Ethoxycarbonylmethyl*-5-(4-*hydroxy*-2-*oxochromen*-3-*ylmethylene*)-2-*thio*-4-*thiazolidone* (XXVII; R = $CH_2·CO_2Et$, *n* = 0). 4-Hydroxycoumarin (3·25 g.), 3-ethoxycarbonylmethyl-5-ethoxymethylenerhodanine (5·5 g.), ethanol (20 ml.), and triethylamine (3 ml.) were heated together on a steam-bath for 5 min. The solution was cooled and acidified with 2N-hydrochloric acid. The yellow flakes were washed with water to remove a red dye (the symmetrical rhodanine oxonol). The *product* (5·65 g., 72%) formed orange needles, m. p. 261° (from ethanol) (Found: C, 52·3; H, 3·5; N, 3·5; S, 16·3. $C_{17}H_{13}NO_6S_2$ requires C, 52·2; H, 3·3; N, 3·6; S, 16·35%), $\lambda_{max.}$ 458 mμ in ethanolic triethylamine.

3-*Ethoxycarbonylmethyl*-5-[3-(3-*ethoxycarbonylmethyl*-4-*hydroxy*-2-*thiothiazolin*-5-*yl*)*prop*-2-*en*-1-*ylidene*]-2-*thio*-4-*thiazolidone* (XXVIII; R = $CH_2·CO_2Et$).—3-Ethoxycarbonylmethyl-5-ethoxypropenylidenerhodanine (XXVI; R = $CH_2·CO_2Et$) (1·5 g.), 3-ethoxycarbonylmethylrhodanine (1·1 g.), ethanol (10 ml.), and triethylamine (0·8 ml.) were heated together on a steam-bath for 15 min. Concentrated hydrochloric acid (2 ml.) was added to the blue solution. A tar was precipitated which solidified on chilling. The liquor was decanted and the solid washed with ethanol. It was dissolved in a hot solution of triethylamine (1·5 ml.) in ethanol (75 ml.) and treated with concentrated hydrochloric acid (3 ml.) in ethanol (10 ml.). A brown powder separated which was washed with ethanolic hydrochloric acid. This *dye* (1·15 g., 49%) formed an orange-brown powder of indefinite m. p. (Found: C, 43·6; H, 4·1; N, 5·65; S, 27·3.

$C_{17}H_{18}N_2O_6S_4$ requires C, 43·1; H, 3·8; N, 5·9; S, 27·0%), $\lambda_{max.}$ 608 mμ in ethanolic triethylamine.

[*Added, November 7th,* 1962.] The nuclear magnetic resonance spectrum of the isochromandione was determined by Dr. T. Crawford through the good offices of Prof. R. H. Wiley (Louisville).

The sample was examined in a saturated solution of deuterochloroform (~5%) with tetramethylsilane as internal standard. There is a strong complex absorption band in the region 2·14 τ, which is assigned to the methylene peak and is in the approximate region for this type of proton. A small peak at 2·78 τ with a shoulder at 2·73 τ is not readily assigned, nor are two small peaks at 8·00 and 8·20. Two of these may be assigned perhaps to the enol form with 2·78 assigned to the olefinic proton and 8·20 to the OH proton. 8·20 τ is unusually high for an OH but the OH peak position depends largely on concentration and is known to shift strongly to high field on high dilution. A 5% solution, which probably corresponds to a much lower concentration of enol form, is a fairly dilute solution and may account for this assignment. Other than this possibility, these extraneous peaks may be impurites.

There is no indication in the spectrum of the presence of an aldehyde proton which would have given a band at very low field, 0·5—1τ, and would also have resulted in the peak of the methine proton [in structure (IV)] being split into a doublet.

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