mero*Cyanines Derived from Thio-oxindole. Part IV.* The Isomerism of the Diazadimethin*mero*cyanines.*

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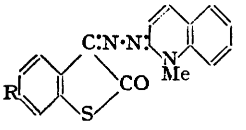
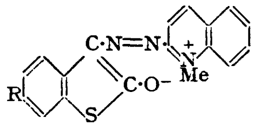
It is shown that the isomerisation of these diazadimethin*mero*cyanines, briefly recorded in Part II, is a common property of the four members of the series which have been prepared, but it has not been detected in the analogous dimethin*mero*cyanines. The conditions of the isomerisation and the probable nature of the isomerism are discussed.

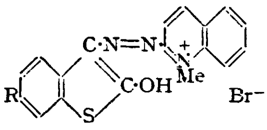
WE have previously recorded (*J.*, 1952, 5012) that the reddish-brown [3-(2 : 3-dihydro-2-oxothionaphthen)][2-(1 : 2-dihydro-1-methylquinoline)]diazadimethin*mero*cyanine (I; R = H), when treated in warm acetone solution with hydrobromic acid, forms an orange-yellow hydrobromide, which, in view of its marked colour, was considered to be a true cyanine of structure (II). Analogous dimethin*mero*cyanines show a similar salt formation (Glauert and Mann, *J.*, 1952, 2135). The orange [3-(2 : 3-dihydro-2-oxothionaphthen)][2-(3-ethylbenzothiazoline)]diazadimethin*mero*cyanine (III; R = H), m. p. 175—176°, however, when either treated in cold acetone with hydrobromic acid or boiled in acetic acid, was converted into a bright orange isomer, m. p. 259—260°. We have now investigated these reactions more fully, and find that both salt formation and isomerisation occur in all the four diazadimethin*mero*cyanines of type (I) and (III) at present available.



(I)

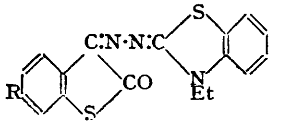


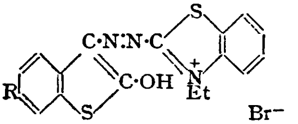
(I*A*)



(II)

(III)





(IV)

The *mero*cyanine (I; R = H), m. p. 225—226°, was unaffected when its ethanolic solution was boiled for 24 hours, but its solution in acetic acid, when boiled for 3 hours, gave an orange isomer, m. p. 236—237° : a mixture of the two forms melted slowly between 213° and 235°. A solution of each form in boiling hydrobromic acid gave the hydrobromide (II; R = H), m. p. 212°; this salt was sufficiently stable to allow recrystallisation from acetic acid, but addition of water to its cold ethanolic solution caused dissociation and deposition of the low-melting form of (I; R = H). The ultraviolet and visible spectra of the two forms in ethanol were almost identical, the low- and the high-melting form showing a main band at $\lambda_{max.}$ 470—472 mμ (ε 35,800) and 472 mμ (ε 37,500) respectively. On the other hand, the infrared spectra of the crystalline isomers were in general quite different (for example, that of the low-melting form showed a strong band at 9·98 μ which was absent in that of the isomer), but the two forms showed the CO band at 5·99 and 5·95 μ respectively (see Table).

We have investigated in greater detail the isomerism of the thiazoline *mero*cyanine (III; R = H), for the considerable difference in the m. p.s of the isomers facilitates their study : moreover the interconversion of the isomers apparently occurs more readily than in the quinoline series. In view of the fact that hydrobromic acid, when added to a cold acetone solution of the low-melting compound, causes such ready isomerisation, it is particularly noteworthy that both isomers when dissolved in hot hydrobromic acid give an unstable orange-yellow hydrobromide, presumably (IV; R = H), which on attempted recrystallisation from

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* Parts II and III, *J*, 1952, 5012; 1955, 28.

ethanol regenerates the low-melting form, but on slow heating gives the high-melting form. Although acids promote the isomerisation, they are not essential: a sample of the low-melting form, when kept at 200° for 15 min., underwent solidification with conversion into the high-melting form, m. p. 260°. Similarly a mixture of the two isomers when rapidly heated melted at 230—250°, but when slowly heated melted at 260°. Solutions of the low-melting form in benzene and in ethanol, when boiled for a short time and then set aside in closed flasks, deposited the high-melting form in 12 hours and 3—4 days respectively: chance inoculation of these solutions with the high-melting isomer was improbable. The latter isomer was unaffected when its solution in ethanol–triethylamine was boiled for 1 hour, so that bases do not apparently reverse the isomerisation. The two isomers resembled those of (I; R = H) in that their ultraviolet and visible absorption spectra were almost identical, whereas their infrared spectra were markedly different, except that they showed the CO band at 5·90 and 5·89 μ respectively: these values moreover were virtually unchanged in carbon disulphide solution (see Table).

	Visible spectra Main band, in mμ, followed by ε values ( )		Infrared spectra Bands in CO region and in 10-μ region [ ]	
	L.-m. isomer	H.-m. isomer	L.-m. isomer	H.-m. isomer
(I; R = H)	470—472 (35,800)	472 (37,500)	5·99 [9·98]	5·95
(I; R = OEt)	—	—	5·90 [9·97]	5·90
(III; R = H)	454—455 (26,400)	454—458 (25,300)	5·90 [10·00]	5·89
,, ...	—	—	5·87 * [10·07] *	5·85 *
(III; R = OEt)	—	—	5·89 [10·08]	5·87
Dimethin analogue of (I; R = H)	553		6·15	[9·91]
Dimethin analogue of (III; R = H)	531		6·10	
Thioindoxyl	—		5·85	
Thio-oxindole	—		5·80,	5·76 *

L.-m. = low-melting. H.-m. = high-melting.

The ultra-violet and visible spectra of compounds (I; R = H) and (III; R = H) were measured in ethanol, and those of their dimethin analogues in methanol.

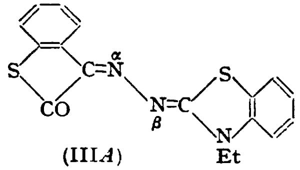
* Measured in CS_2 solution.

The 6-ethoxy-analogues, *i.e.*, (I and III; R = OEt), of the above compounds have been prepared. Each shows the same ready isomerisation in boiling acetic acid. Their hydrobromides (II and IV; R = OEt) are markedly more stable than the unsubstituted salts, and can be recrystallised unchanged from ethanol, but they undergo rapid hydrolysis in hot aqueous ethanol or ethanolic pyridine, liberating the low-melting isomer. The infrared spectra of each pair of isomers show the same relationship as those of (I and III; R = H).

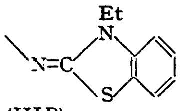
It is noteworthy that the infrared spectra of all four low-melting isomers show a strong band at *ca.* 10 μ (see Table), which is absent in those of the high-melting isomers. The significance of this band is uncertain, but it has been selected to exemplify the considerable difference between the spectra of each pair of isomers.

The above evidence leaves no doubt that each pair of the above four compounds represents true isomers, and that no question of dimorphism is involved. It is significant, moreover, that the dimethin analogues of (I and III; R = H), which are unaffected by boiling acetic acid and have given no evidence of isomerisation, show a carbonyl band at 6·15 and 6·10 μ respectively, whereas this band in the above four pairs of diazadimethin compounds falls between 5·87 and 5·99 μ. This indicates strongly that in the diazadimethin compounds the contribution of polar forms such as (I*A*) is much smaller than in the dimethin analogues. This deduction is supported (*a*) by the more intense colour of these analogues and (*b*) by the fact that thioindoxyl and thio-oxindole, which cannot show this marked charge separation, have their CO bands at 5·85 and 5·80 μ respectively (see Table).

The above data are insufficient to provide a decisive explanation of the isomerism of these diazadimethin compounds, and of the apparent absence of isomerism in their dimethin analogues. We would however tentatively put forward an explanation based on the following considerations. The diazadimethin compounds, for example (III), can theoretically exist (in their covalent state) in four geometrically isomeric forms, namely, (III*A* and *B*), in both of which the β-nitrogen atom is the *cis*-position to the CO group, but the NEt group is in the *cis*-position to this atom in (III*A*) and in the *trans*-position in (III*B*); and (III*C*) and (III*D*), in both of which the β-nitrogen is *trans* to the CO group, but which are otherwise analogous to (III*A*) and (III*B*) : four other conformations are precluded because they would entail overlapping of the two heterocyclic nuclei. The dimethin analogues could also show forms similar to (III*A*, *B*, *C*, and *D*). Each of the diazadimethin forms differs from its dimethin analogue, however, in that it has an extra polar form: for example, (III*A*) would receive contributions from the polar forms (III*A*i) and (III*A*ii). The contribution of (III*A*ii) must weaken that of (III*A*i), and may well be the reason why the infrared spectra show that the CO group is uniformly less strongly polar in the diazadimethin compounds than in the dimethin analogues. Furthermore, salt formation with (III*A*i) and (III*A*ii) would give the cations (IVi) and (IVii) respectively, which are in practice indistinguishable: in this cation, which would be markedly stabilised by the hydrogen-bonding, the benzothiazole group may have some rotational mobility about the βN–C link and will therefore adopt the most stable position, in which case the isomer (III*B*) would give the same cation. The *trans* isomers (III*C*) and (III*D*) could not form a cation of this type without intermediate conversion into the *cis*-analogues.



(III*A*)



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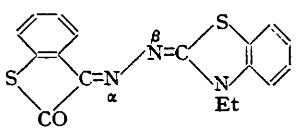
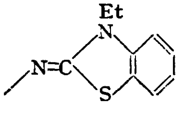


(III*C*)



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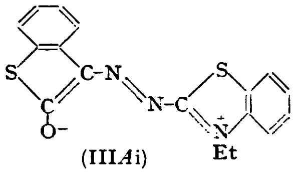
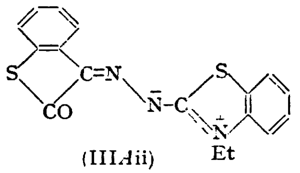
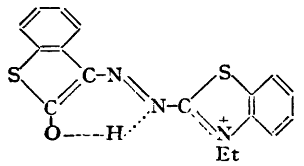


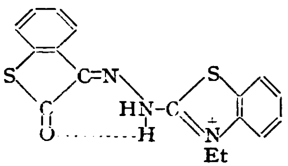
(III*A*i)



(III*A*ii)



(IVi)



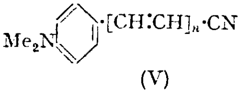
(IVii)

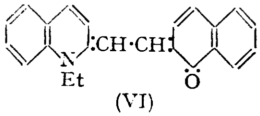
We suggest therefore that in all four diazadimethin compounds investigated, the low-melting isomer may have the *cis*-structure, being of type (III*A*) or (III*B*), and that the high-melting isomer has the *trans*-structure of type (III*C*) or (III*D*). The greater stability of the high-melting isomer, shown by the conversion low-melting ⟶ high-melting form, which may occur (with speed dependent on the particular compound) slowly in cold solvents, more rapidly in boiling solvents, and very readily on heating, is possibly due to the opposition of the dipoles on the negatively-charged oxygen and nitrogen atoms in (III*A*i) and (III*A*ii) respectively, which would become much weaker in the corresponding *trans*-forms. This interconversion is clearly not a difficult process; consequently a hot strong acid such as boiling 48% hydrobromic acid would convert each isomer into the most stable cation, *i.e.*, that of the *cis*-form (IVi ⟷ ii). This salt, on dissociation under mild conditions, would retain its essential conformation and hence hydrolysis gives the low-melting isomer throughout. It is probable moreover that in the preparation of the diazadimethin compounds of type (I) and (III) (cf. Part I), the initial reaction is the condensation of the thio-oxindole 3-hydrazone with 2-iodoquinoline methiodide and with 2-ethylthiobenzothiazole ethiodide, with liberation of hydrogen iodide and ethanethiol respectively, and with the formation in each case of the iodide of the cation (IV i $\longleftrightarrow$ ii) : the main function of the triethylamine is then to hydrolyse this salt, and thus the low-melting *cis*-isomer arises in all these preparations.

A very low hydrogen-ion concentration would appear to accelerate the normal *cis* → *trans* conversion, being unable to arrest this process at the intermediate cation stage: hence the low-melting isomer always in boiling acetic acid, and in the one case of (III; R = H) in warm acetone containing hydrobromic acid, is converted into the high-melting isomer.

The above considerations regarding the structural significance of salt formation will not apply to the dimethin analogues, in which however the >C:CH·CH:C< chain must for similar steric reasons also have the *trans*-form. The unlike terminal heterocyclic rings could again theoretically arrange themselves in *cis*- and *trans*-positions relative to one another. The fact that isomerism was never encountered in the numerous examples of these compounds studied (Glauert and Mann, *loc. cit.*) may indicate that these rings always adopt the most stable relative positions, and that similarly in the diazadimethin series only one member of each pair, (III*A*) or (III*B*), and (III*C*) or (III*D*), is actually formed.

There is evidence for similar isomerism in other types of *mero*cyanines, and possibly in true cyanines. Coenen and Pestemer (*Z. Elektrochem.*, 1953, **57**, 785) have described a number of *mero*cyanines of type (V; $n = 1$, 2, and 3), each of which has been isolated in two isomeric forms, which, like those of (I) and (III), have different m. p.s but almost identical ultraviolet spectra. Hirschberg and Fischer (*J. Chem. Phys.*, 1954, **22**, 572) record several *mero*cyanines, for example (VI), the colour of whose ethanolic solutions changes markedly at low temperature, possibly owing to isomeric interconversion (cf. also *J.*, 1954, 3129). Zechmeister and Pinckard (*Experientia*, 1953, **9**, 16) claim that the cyanine (VII), when passed in an acetone–ethylene dichloride solution down a calcium carbonate column, separates into three blue zones, but the dye in each zone, when removed and similarly treated, gives three zones apparently identical with the initial set. They suggest tentatively that the cyanine on dissolution at room temperature forms an equilibrium mixture of at least three isomeric forms, which can thus be separated, but each on elution spontaneously regenerates the original mixture.


(V)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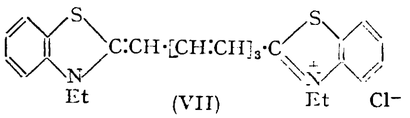
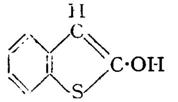

(VII)

Concrete evidence for isomerism, based on the actual isolation and investigation of the isomers, has been obtained apparently only for *mero*cyanines of type (I), (III), and (V).

The value for the CO group in the infrared spectrum of thio-oxindole, cited in the Table, raises a noteworthy point. Marschalk (*Ber.*, 1912, **45**, 1481; *J. prakt. Chem.*, 1913, **88**, 227) isolated thio-oxindole in two forms, m. p. 33—34° and 44—45°, which were very readily interconvertible : for example, steam-distillation gave the high-melting form, which when dried and distilled at atmospheric pressure gave the low-melting form. Komppa and Weckmann (*J. prakt. Chem.*, 1933, **138**, 109) decided that the low- and the high-melting product were probably the enol and the keto-form, (VIII) and (IX), respectively. Störmer (*Annalen*, 1900, **313**, 83) isolated *iso*coumaranone (X) in two forms, m. p. 28—28·5° and 49°, which were also very easily interconvertible.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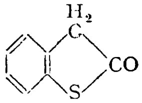
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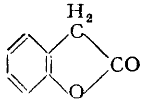
(X)

We have obtained thio-oxindole in two forms, m. p. 33—33·5° and 44—45°, and also 6-ethoxy(thio-oxindole) in two forms, m. p. 38—40° and 47—48° (*J.*, 1952, 2217). We find that a crude sample of the low-melting form of thio-oxindole, when confined in a desiccator at atmospheric pressure, changes to the high-melting form in *ca.* 7 days, but a pure sample remains unchanged for at least a month. The low-melting form can be recrystallised unchanged from aqueous ethanol, and its solutions in methanol and acetonitrile, when allowed to evaporate spontaneously, deposit the unchanged material, whereas those in carbon disulphide, chloroform, and carbon tetrachloride deposit the high-melting form. Each form, when dissolved in ice-cold aqueous potassium hydroxide which is then carefully acidified, is deposited unchanged. The infrared spectrum of the high-melting form in a Nujol mull, or as a solid film, showed CO absorption at 5·80 μ, with no indication of the presence of an OH group or of a double bond : the value for the CO absorption was virtually unchanged in carbon disulphide solution (see Table), so intermolecular hydrogen-bonding is absent. The spectrum of the low-melting form in the mull was unreliable owing to the possible onset of conversion, but in methanol solution it showed strong CO absorption at 5·78 μ, with absence of a double bond. Although in the enol form (VIII) the double bond in the " aromatic " thiophen ring would probably not give the normal ethylene band, the CO absorption in both forms gives a strong indication that they are dimorphic forms and not isomeric compounds. The earlier chemical evidence for isomerism must be treated with reserve, because their ready transformation might be strongly influenced by the nature of the reagent applied. The values for thio-oxindole quoted in the Table are those obtained with the high-melting form.

EXPERIMENTAL

[3-(2 : 3-*Dihydro*-2-*oxothionaphthen*)][2-(1 : 2-*dihydro*-1-*methylquinoline*)]*diazadimethin*mero*cyanine* (I; R = H).—A solution of this compound, m. p. 225—226°, in acetic acid, when boiled under reflux for 3 hr. and cooled, deposited the *isomer*, orange prisms, m. p. 236—237°, unchanged by recrystallisation from acetic acid (Found: C, 68·25; H, 4·6; N, 13·0. $C_{18}H_{13}ON_3S$ requires C, 67·7; H, 4·1; N, 13·14%).

A solution of this isomer in hot aqueous 48% hydrogen bromide gave, on cooling, an orange hydrobromide which, when collected and recrystallised (whilst damp) from ethanol, gave orange-brown crystals, m. p. 211—212° (decomp.) : a mixture of this salt and the hydrobromide, m. p. 210—211° (decomp.), derived from the low-melting isomer had m. p. 210—211° (decomp.).

Addition of water to an ethanolic solution of this hydrobromide precipitated the low-melting isomer, m. p. 225°, unchanged on admixture with an authentic sample but depressed to *ca.* 210° when mixed with the high-melting isomer.

The 6-*ethoxy*-analogue (I; R = OEt), prepared as (I; R = H) but with 6-ethoxythionaphthenquinone 3-hydrazone and recrystallised from ethanol, formed crimson needles (32%), m. p. 222—223° (Found: C, 65·6; H, 4·9; N, 12·0. $C_{20}H_{17}O_2N_3S$ requires C, 66·1; H, 4·7; N, 11·6%). Its solution in acetic acid, when boiled for 1·5 hr. and cooled, deposited the high-melting *isomer*, orange-red crystals, m. p. 233—234°, from acetic acid, depressed to 205—210° on admixture with the above compound (Found: C, 66·5; H, 5·05; N, 11·6%).

The addition of 48% hydrobromic acid to an acetone suspension of the low-melting isomer increased the temperature to *ca.* 40°, giving a clear orange-yellow solution which on cooling deposited the *hydrobromide trihydrate*, orange crystals, m. p. 209—210° inserted at 200° (Found: C, 48·6; H, 4·4; N, 8·7. $C_{20}H_{17}O_2N_3S,HBr,3H_2O$ requires C, 48·2; H, 4·85; N, 8·4%).

This hydrobromide recrystallised from ethanol as orange crystals of unchanged m. p. The addition of water to the ethanol solution precipitated the orange-red low-melting isomer (I; R = OEt) contaminated with the hydrobromide, the product after crystallisation from ethanol having m. p. 212—216° (preliminary softening), whereas the addition of a small quantity of pyridine to the original solution precipitated the pure red isomer, m. p. and mixed m. p. 220° after crystallisation from ethanol.

[3-(2:3-*Dihydro*-2-*oxothionaphthen*)][2-(3-*ethylbenzothiazoline*)]*diazadimethin*mero*cyanine* (III; R = H).—The conditions for the isomerisation of this compound have been described (Glauert and Mann, *loc. cit.*) : that caused by the addition of cold hydrobromic acid to an acetone solution of the low-melting form was erroneously stated to have been performed in acetic acid solution. The low-melting form, when kept at 200° for 10 min., remained as a clear liquid which when seeded with the high-melting form slowly solidified : when kept at 200° for 15 min., it spontaneously solidified. The product in each experiment, after crystallisation from ethanol, had m. p. 260° (alone and mixed). Each isomer gave, in boiling 48% aqueous hydrobromic acid, a yellow solution which on cooling deposited orange-yellow crystals of the *hydrobromide* (IV;

R = H), which, even when dried over calcium chloride in a vacuum, became red on the surface owing to slight dissociation (Found: C, 47·9; H, 4·3. $C_{17}H_{13}ON_3S_2$,HBr requires C, 48·6; H, 3·4%). Attempted recrystallisation of this salt from ethanol gave the low-melting isomer, m. p. and mixed m. p. 173—175°. The hydrobromide, when heated from room temperature or from 160°, had m. p. 249—251° with some previous shrinkage: when immersed and kept at 220° or 235° it shrank without melting. A mixture of this salt and the high-melting isomer (m. p. 259—260°), when immersed at 160° or 225°, had m. p. *ca.* 250°. It is clear therefore that this isomer is the ultimate product of thermal dissociation of the salt. A solution of the isomer, m. p. 259—260°, in ethanol–triethylamine (5 : 1 vol.) was boiled under reflux for 1 hr., and on cooling deposited the unchanged solute.

The 6-*ethoxy*-analogue (III; R = OEt), prepared as (III; R = H) but with 6-ethoxythionaphthenquinone 3-hydrazone, and recrystallised from ethanol formed the ***hemi-ethanolate*** (50%), orange-red needles, m. p. 197—198° (Found: C, 59·1; H, 4·7; N, 10·3. $C_{19}H_{17}O_2N_3S_2,0{\cdot}5C_2H_6O$ requires C, 59·1; H,· 5·0; N, 10·3%). Its solution in acetic acid, when boiled for 3 hr. and cooled, deposited the high-melting *isomer*, orange prisms, m. p. 207—208° (after recrystallisation from acetic acid), depressed to 173—177° by admixture with the above compound (Found: C, 59·2; H, 4·7; N, 11·0. $C_{19}H_{17}O_2N_3S_2$ requires C, 59·5; H, 4·5; N, 11·0%).

The addition of 48% hydrobromic acid (5 c.c.) to a solution of the low-melting isomer (0·1 g.) in hot acetone (10 c.c.), followed by cooling and stirring, deposited the ***hydrobromide*** (IV; R = OEt), orange crystals from acetic acid (Found: C, 48·3; H, 4·7; N, 8·1. $C_{19}H_{17}O_2N_3S_2$,HBr,$C_2H_4O_2$ requires C, 48·1; H, 4·2; N, 8·0%). This salt had m. p. 201—203° (softening from 198°) when heated from room temperature or from 150°: inserted at 180°, it melted with decomp. Mixtures of the salt with the low- and the high-melting isomer, heated from 150°, had m. p. 198—202° and 204—206° respectively. Attempted ethanolic recrystallisation of the hydrobromide gave the low-melting isomer, sparkling red crystals, m. p. and mixed m. p., 197—198°. It is noteworthy that the hydrobromide (II; R = H) also separated with acetic acid (1 mol.) of crystallisation.

Attempted Isomerisation of Dimethin Analogues.—An acetic acid solution of the analogue, m. p. 254°, of the compound (I; R = H) was boiled under reflux for 3 hr. and cooled. The deposited material, when recrystallised from ethanol, afforded the unchanged compound, m. p. 252—253°, mixed m. p. 253—254°. The analogue, m. p. 226°, of the compound (III; R = H), when similarly treated, was recovered unchanged, having m. p. 228—229°, mixed m. p. 226—228°.

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