238. *The Comparative Reactivity of the Carbonyl Groups in the Thionaphthenquinones. Part III. The Influence of Solvents and Catalysts.*

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The condensation of thioindoxyl with thionaphthenquinone, with 6-chloro-4-methylthionaphthenquinone and with 6-ethoxythionaphthenquinone in a number of solvents, using various catalysts, has been studied, and the effect of these condensation media on the yield and composition of the dye has been determined.

Dichloro- and monochloro-acetic acids cause thioindoxyl to undergo self-condensation, with the formation of 2 : 3'-*dithioindoxylyl* (IV) and s-*tris*-2 : 3-*thiocoumaronobenzene* (V).

In the course of the work described in Part II (p. 893) it became clear that the nature of the product obtained by the condensation of a thioindoxyl and a thionaphthenquinone was markedly affected by the solvent and by catalysts, and hence the condensations recorded in Part II were performed throughout in our "standard medium," *i.e.*, acetic acid containing zinc chloride. To investigate this aspect more fully, we have examined the products formed by the condensation of thioindoxyl (I) with thionaphthenquinone (III),* with 6-chloro-4-methylthionaphthenquinone (III*b*), and with 6-ethoxythionaphthenquinone (III*d*) in a variety of media. The first and third of these condensations, when performed in our standard medium, give a mixture of a thioindigo and a thioindirubin (*i.e.*, $\alpha + \beta$-condensation), while the second gives solely a thioindigo (α-condensation); they were chosen to show in particular the effect of the medium on β-condensation in favourable and unfavourable circumstances respectively. The first condensation has been studied in greater detail, as no complication due to substituents can arise.

The condensation media with their catalysts are given in the Table approximately in order of decreasing acidity. Attempts to carry out the condensation in non-polar or weakly polar solvents, *e.g.*, chlorobenzene, gave only a very small yield of the dye and are omitted.

			Condensation of thioindoxyl (I) and thionaphthenquinone (III).			Condensation of thioindoxyl (I) and 6-chloro-4-methylthionaphthenquinone (III*b*).			Condensation of thioindoxyl (I) and 6-ethoxythionaphthenquinone (III*d*).		
Series.	Condensation medium.	Catalyst.	Time of boiling.	Yield,* %.	Condensation.	Time of boiling.	Yield,* %.	Condensation.	Time of boiling.	Yield,* %.	Condensation.
A	$Cl_2CH\cdot CO_2H$		5 mins.	95	$\alpha + \beta$						
B	$ClCH_2\cdot CO_2H$	H_2O	5 mins.	99	$\alpha + \beta$	5 mins.	67	α	10 mins.	98	$\alpha + \beta$
C	$MeCO_2H$	BCl_3	3 hrs.	93	$\alpha + \beta$						
D	$MeCO_2H$	$AlCl_3$	5 mins.	92	$\alpha + \beta$	3 hrs.	61	α	3 hrs.	93	$\alpha + \beta$
E	$MeCO_2H$	$AlCl_3$	3 hrs.	97	$\alpha + \beta$						
F	$MeCO_2H$	$ZnCl_2$	3 hrs.	95	$\alpha + \beta$	3 hrs.	58	α	3 hrs.	85	$\alpha + \beta$
G	$MeCO_2H$	HCl	3 hrs.	90	$\alpha + \beta$	3 hrs.	56	α	3 hrs.	61	$\alpha + \beta$
H	$MeCO_2H$		3 hrs.	39	α	3 hrs.	41	α	3 hrs.	53	$\alpha + \beta$
I	$MeCO_2H$	$MeCO_2Na$	3 hrs.	52	α	3 hrs.	48	α	3 hrs.	72	$\alpha(+\beta)$
J	$(Ac)_2O$		3 hrs.	27	α	—	—	—	3 hrs.	50	$\alpha + \beta$
K	EtOH	$ZnCl_2$	4 hrs.	43	α	3 hrs.	51	α	3 hrs.	70	α
L	EtOH		4 hrs.	20	α	3 hrs.	42	α	3 hrs.	64	α
M	EtOH	10% Aqueous NaOH	70 mins.	35	α †	3 hrs.	55	α	3 hrs.	67	α
N	C_5H_5N	10% Aqueous NaOH	4·5 hrs.	50	α	3 hrs.	27	α	3 hrs.	39	α

* Total yield of dye, calculated on the thionaphthenquinone taken. † The catalyst employed was NaOEt.

The following points arise: (1) *Time of heating.* The three condensations in monochloroacetic acid, and also the first condensation in dichloroacetic acid, were very rapid and 5—10 minutes' heating sufficed. These acids have a condensing action on thioindoxyl (I) itself (see later), but this action is markedly slower and in the presence of the thionaphthenquinone it can be ignored for the above periods. The first condensation in acetic acid catalysed by aluminium chloride was also very rapid and no significant difference in the product could be detected if the 5 minutes' heating was extended to 3 hours. In almost all the other media, however, the heating was continued for 3 hours irrespective of the speed of the reaction.

(2) *Yield of dye.* In all the three condensations studied, the yield of dye (*i.e.*, of condensation product, irrespective of its composition) tended to be highest in the most acidic medium. This factor is most marked in the first condensation. This tendency may, however, be reversed by an ionic catalyst; *e.g.*, in all three condensations the yield in acetic acid is less than that in acetic acid containing sodium acetate. It is noteworthy, however, that in the first condensation the amount of thioindigo present in the mixed ($\alpha + \beta$) product obtained in acetic acid containing aluminium chloride was approximately the same as that obtained in acetic acid without a catalyst. It is possible therefore that acidity of the medium does not appreciably affect the reactivity of the α-carbonyl group of the thionaphthenquinone, but greatly increases that of the β-carbonyl group.

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* For uniformity the numbers designating the thioindoxyls and the thionaphthenquinones are those used in Parts I and II.

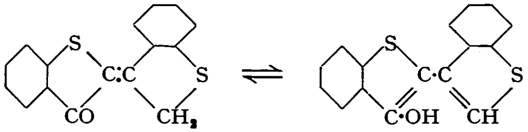
(3) *Composition of the dye.* The composition of the products obtained in the first condensation shows clearly that the more acidic media favour the β-condensation, *i.e.*, formation of the thioindirubin, and that weakly acidic, neutral or basic media allow only the α-condensation to occur. The same factor clearly controls the third condensation (with 6-ethoxythionaphthenquinone, III*d*). In the second condensation (with 6-chloro-4-methylthionaphthenquinone, III*b*), however, no detectable β-condensation occurs in any medium investigated. It should be remembered, however, that this thionaphthenquinone (III*b*) gives exclusively α-condensation with eleven of the twelve thioindioxyls studied in Part II (p. 896); the condensation must therefore be determined primarily by the structure of the thionaphthenquinone (III*b*), and this structural factor is evidently too strong to be affected by the nature of the condensation media employed.

Although, in the first and third condensations studied, an acidic medium favoured β-condensation, this influence was never sufficiently strong to suppress the α-condensation completely. An accurate analysis of the mixed (α + β) products obtained in the more acid media, had it been practicable, would have been useful since it would have shown whether the function of such media, as already suggested, is primarily to accelerate the β-condensation leaving the α-condensation virtually unaffected.

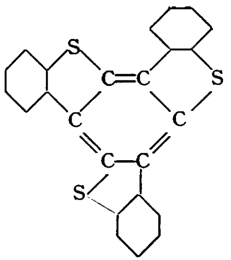
In Part II it was shown that 5-methylthionaphthenquinone (III*j*) in the standard medium gives solely α-condensation with eleven of the thioindoxyls but gives solely β-condensation with 4-chlorothioindoxyl (I*i*). It appeared probable, therefore, that the latter condensation might be readily affected by a change in the medium employed. We have consequently repeated this latter condensation in acetic acid containing sodium acetate and in ethyl alcohol containing 10% aqueous sodium hydroxide, but in these more basic media, only β-condensation again occurred. Here again, the structural factor appears to override the influence of the medium.

We have attempted to use trichloroacetic acid as a solvent in our condensations in order to employ a more strongly acidic medium than those mentioned above. Although the condensation of thioindoxyl and thionaphthenquinone (III) occurs rapidly in this solvent, the results are vitiated by the direct action of the acid on the thioindoxyl. We find that trichloroacetic acid gives a number of indefinite products with thioindoxyl alone, and the reaction is evidently very complex.

When thioindoxyl (I) was boiled with dichloroacetic acid, self-condensation occurred with the formation of two compounds, m. p. 225—226° and 422—425°, whose properties indicate that they are 2 : 3'-*dithioindoxylyl* (IV) and s-*tris*-2 : 3-*thiocoumaronobenzene* (V) respectively. The same condensation occurs, but more slowly, in monochloroacetic acid.

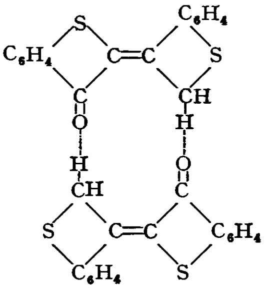


(IV.) (IVA.)

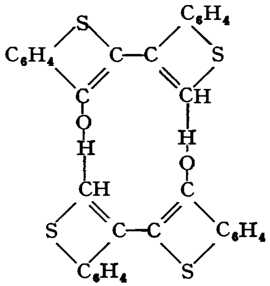


(V.)

The compound (IV) was unaffected by boiling monochloroacetic acid but, on the addition of thioindoxyl, underwent condensation to give the compound (V). This furnishes strong evidence for the structure of both compounds. The compound (IV), unlike thioindoxyl, was almost insoluble in cold aqueous sodium hydroxide solution; this was not unexpected, as enolisation to (IVA) may well take place to a much less extent than in the case of thioindoxyl. Molecular weight determinations indicated that in chloroform solution *ca.* 50% of (IV) existed as bimolecular associates, and that in *p*-xylene solution this association was virtually complete. Since the molecule of (IV) is flat, this association might readily occur through hydrogen-bond formation, the product being further stabilised as a resonance hybrid of the forms (IVB) and (IVC). It is significant that the compound (V) showed no association in *p*-xylene solution.



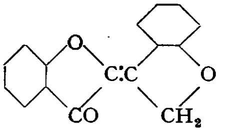
(IVB.)

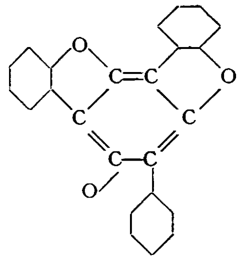


(IVC.)

The compounds (IV) and (V) are the thio-analogues of the 2 : 3′-dicoumaranyl (VI) and the *s*-tris-2 : 3-coumaronobenzene (VII) isolated by Fries and Pfaffendorf (*Ber.*, **1910**, **43**, 212; **1911**, **44**, 114) by the action of sodium on coumaranone in ether, although the true structure of these compounds was not known until Baker and Banks (*J.*, **1939**, 279) prepared and investigated the 5-methyl homologues of each.

(VI.)





(VII.)

No compounds analogous to (IV) and (V) were isolated by the action of mono- or di-chloroacetic acid on 4 : 5-benzthioindoxyl (I*e*) and 5 : 6-benzthioindoxyl (I*g*).

A mixture of acetic anhydride and zinc chloride also could not be used in our condensations, because, although it did not affect thioindoxyl, it readily converted thionaphthenquinone (III) into a brown amorphous product which could not be crystallised or purified. A similar but not identical product was obtained when a mixture of propionic anhydride and zinc chloride was used. Similar compounds were obtained from 5-chloro-7-methylthionaphthenquinone (III*c*). These compounds were not fully investigated owing to their intractable nature, but the ease of their formation appears to inhibit condensation of the original quinone with thioindoxyl. Preliminary experiments indicated that condensation of the thionaphthenquinone and the anhydride had occurred, probably with the formation of compounds of high molecular weight.

EXPERIMENTAL.

In each of the reactions given in the Table, pure freshly-prepared thioindoxyl (1 g.) was used; in the first condensation, thionaphthenquinone (III; 1 g.) was used, in the second, 6-chloro-4-methyl-thionaphthenquinone (III*b*; 1·3 g.) and in the third, 6-ethoxy-thionaphthenquinone (III*d*; 1·1 g.). In the series of reactions lettered in the Table the reaction media were: (A) dichloroacetic acid (15 c.c.); (B) monochloroacetic acid (25 g.) and water (1 g.); (C) acetic acid (25 c.c.) and boron trichloride (0·2 g.); (D) acetic acid (25 c.c.) and aluminium chloride (0·2 g.); (E) as (D); (F) acetic acid (25 c.c.) and zinc chloride (0·2 g.); (G) acetic acid (25 c.c.) and concentrated hydrochloric acid (0·1 c.c.); (H) acetic acid (25 c.c.); (I) acetic acid (25 c.c.) and anhydrous sodium acetate (0·3 g.); (J) acetic anhydride (15 c.c.); (K) alcohol (25 c.c.) and zinc chloride (0·2 g.); (L) alcohol (25 c.c.); (M) alcohol (25 c.c.) and 10% aqueous sodium hydroxide (0·1 c.c.), except in the first condensation when sodium (0·1 g.) was added to the alcohol in place of the hydroxide; (N) pyridine (20 c.c.) and 10% aqueous sodium hydroxide (0·1 c.c.).

Each reaction was carried out by refluxing for the time stated, the reaction mixture being then set aside until crystallisation of the product was complete. The pure dye was isolated as follows. Series (A) and (B): the crude reaction mixture was diluted with much water, warmed and filtered. The insoluble dye was then boiled with alcohol, and washed with ether to remove traces of unchanged material. Series (C)—(M): the crude product was collected, and washed with alcohol and ether. Series (N): the crude product was collected and washed with alcohol; the alcoholic washings when added to the mother-liquor precipitated a small second crop which was also collected. The final product in each case was weighed and its qualitative composition determined by reductive acetylation (see Part II). The mother-liquors from the recrystallisations of the diacetyl-dihydro-derivatives were set aside for several days to ensure that delayed crystallisation had not masked one of the components.

When the condensation of (I) and (III) was performed in chlorobenzene (25 c.c., 3 hrs.' boiling), the yield of the dye was 0·03 g. To ensure that the thioindigo obtained as a product of the condensation of (I) and (III) was not being formed partly by atmospheric oxidation of the thioindoxyl (I), a solution of the latter (1 g.) in alcohol (25 c.c.) was refluxed for 4 hours under conditions otherwise similar to those used in Series A—N; the total yield of thioindigo (0·015 g.) showed that such oxidation was negligible.

When a mixture of 4-chlorothioindoxyl (I*i*; 0·8 g.) and 5-methylthionaphthenquinone (III*j*; 0·7 g.) was refluxed for 3 hours with (*a*) alcohol (20 c.c.) containing 10% aqueous sodium hydroxide (0·1 c.c.), and (*b*) acetic acid (20 c.c.) containing sodium acetate (0·25 g.), the product in each case was solely 4-chloro-5′-methylthioindirubin (0·35 g., 0·5 g.).

Action of the di- and mono-chloroacetic acids on thioindoxyl. (i) A mixture of thioindoxyl (2 g.) and dichloroacetic acid (15 c.c.) was refluxed for 30 minutes; it rapidly darkened in colour and after 20 minutes' boiling a pale brown solid separated. The cold product was set aside overnight, and then diluted with much water. The insoluble product was collected, washed with water and boiled with alcohol to remove any unchanged thioindoxyl. The residue was extracted with boiling ether. The ethereal filtrate on evaporation deposited a brown powder (0·4 g.) which, when recrystallised from acetone and then from pyridine containing 20% of water, furnished 2 : 3′-*dithioindoxylyl* (IV), pale brown microcrystalline powder, m. p. 225—226° (Found: C, 68·0; H, 3·5; S, 22·9; *M*, ebullioscopic in 0·415% chloroform solution, 399, in 0·536% *p*-xylene solution, 519. $C_{16}H_{10}OS_2$ requires C, 68·1; H, 3·6; S, 22·7%; *M*, 282).

The residue insoluble in ether, when recrystallised from nitrobenzene and then *p*-xylene, furnished s-*tris*-2 : 3-*thiocoumaronobenzene* (V; 1·15 g., 65%), silvery needles, m. p. 422—425° (Found: C, 72·6; H, 3·3; S, 24·5; *M*, ebullioscopic in 0·465% *p*-xylene solution, 395. $C_{24}H_{12}S_3$ requires C, 72·7; H, 3·0; S, 24·3%; *M*, 396).

(ii) A mixture of thioindoxyl (3 g.) and monochloroacetic acid (30 g.) was refluxed for 2 hours; the boiling had then to be stopped owing to violent "bumping"; the mixture rapidly darkened and solid material separated after 50 minutes' boiling. Treatment of the product as in (i) gave a small quantity of (IV), the chief product (1·65 g.) being (V) (Found: C, 72·4; H, 2·8%). Longer boiling would almost certainly have increased the yield of (V).

(iii) Experiment (ii) was repeated but, to obtain a higher yield of the intermediate (IV), the refluxing was stopped after 1 hour and the mixture diluted with water. Two alternative methods of isolating (IV) were adopted in successive experiments. (*a*) The mixture was made alkaline with sodium hydroxide and unchanged thioindoxyl oxidised to thioindigo with potassium ferricyanide solution. The solid product was collected, washed with water, dried, and the compound (IV) extracted with boiling ether (500 c.c.). Evaporation of the ether, followed by recrystallisation of the product, furnished the pure compound (IV) (1·35 g.), m. p. 225—226° (Found : C, 68·3; H, 4·0%). (*b*) The mixture was made alkaline as before, boiled and filtered; the residue was washed with water, dried, and the compound (IV) extracted with boiling ether as in (*a*).

(iv) A solution of 2 : 3′-dithioindoxylyl (IV; 0·23 g.) in monochloroacetic acid (15 g.) when refluxed for 1·5 hours and cooled gave no crystalline deposit. The addition of thioindoxyl (I; 0·18 g., 1 mol.) followed by a further refluxing for 1 hr. gave on cooling a deposit of (V; 0·2 g.). The yield indicates that compound (V) arose from the condensation of the two components and not solely from the thioindoxyl.

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