396. *Thio-oxindole, Thioindoxyl, and Certain Carbonyl Derivatives.*

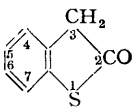
By R. H. Glauert and Frederick G. Mann.

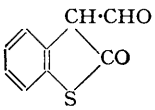
An improved preparation of thio-oxindole has been developed so that it can now be readily obtained in quantity. A critical examination of three methods for the preparation of thio-oxindole-3-aldehyde has been made, and for comparative purposes a number of thioindoxyl-2-aldehydes have also been isolated. 3-Acetyl(thio-oxindole) and 2-acetyl(thioindoxyl) can be readily prepared by the action of *NN'*-diphenylacetamidine on thio-oxindole and thioindoxyl respectively.

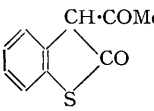
For the preparation of the *mero*cyanines described in the following paper, supplies of thio-oxindole (I), thio-oxindole-3-aldehyde (II), and 3-acetyl(thio-oxindole) (III), and of derivatives of these three compounds having substituents in the benzene ring, were required. We have therefore investigated in some detail the preparation of such

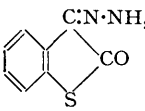
compounds, and also (less fully) that of analogous derivatives of thioindoxyl, which were required for comparative purposes.

Thio-oxindole (I) was first prepared by Marschalk (*Ber.*, 1912, **45**, 1481; *J. pr. Chem.*, 1913, **88**, 239), who converted oxindole into *o*-aminophenylacetic acid, which was transformed *via* its diazonium salt into *o*-mercaptophenylacetic acid: the latter when boiled in xylene with phosphoric anhydride underwent cyclisation to thio-oxindole. This method is tedious, however, and the over-all yield is low. Marschalk (*loc. cit.*) also showed that thionaphthen-


(I)


(II)


(III)


(IV)

quinone, when treated with hydrazine, gave a crude product which he presumed to be the 3-hydrazone (IV), since when heated above its m. p. it lost nitrogen and gave thio-oxindole. We have developed the preparation of the pure hydrazone (IV) so that it can be obtained in *ca.* 70% yield. Direct heating under Marschalk's conditions, unless performed with very small quantities, gave a violent and uncontrollable reaction, producing much tarry matter, from which the thio-oxindole was isolated in only 27% yield. Attempts to modify the violence of this reaction by working under reduced pressure—the method by which Curtius and Thun (*J. pr. Chem.*, 1891, **44**, 187) converted isatin-3-hydrazone into oxindole—failed, because the hydrazone (IV) volatilises unchanged under reduced pressure. A smooth decomposition was ultimately obtained by boiling a solution of the hydrazone (IV) in 25% aqueous potassium hydroxide under reflux for several hours, whereby a steady evolution of nitrogen occurred, and the red colour of the solution became straw-yellow: acidification of the cold solution precipitated *o*-mercaptophenylacetic acid in 84% yield. When this acid, mixed with hydrochloric acid, was distilled in steam, thio-oxindole was obtained in 90% yield: this method of cyclisation, originally due to Komppa and Weckman (*J. pr. Chem.*, 1933, **138**, 109), is far better than Marschalk's phosphoric anhydride method. By the above route we have now been able to prepare thio-oxindole readily in quantity with an over-all yield of 60%.

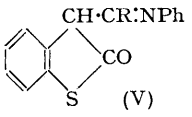
The use of 6-ethoxy(thionaphthen)quinone in this preparation similarly afforded 6-ethoxy(thio-oxindole), the first recorded substituted thio-oxindole.

It is noteworthy that Marschalk (*loc. cit.*) isolated thio-oxindole in two forms, (*a*) needles, m. p. 33—34°, and (*b*) prisms, m. p. 44—45°. He produced some evidence to show that the lower m. p. form was the enol and the higher m. p. form the keto-compound, a conclusion supported by Komppa and Weckman (*loc. cit.*). These authors showed that the lower m. p. form could be converted into the more stable, higher m. p. form by reprecipitation with acid from a solution in aqueous sodium hydroxide, or by confinement for one week in a desiccator: Marschalk, however, could not produce interconversion by seeding. We find that the hydrochloric acid distillation of *o*-mercaptophenylacetic acid always gave the lower m. p. form, which was unchanged after several months' exposure to the air. On one occasion, however, when the above acid was heated in a vacuum, the distilled thio-oxindole gave the higher m. p. form. Either form could be obtained by appropriate seeding of the molten lower m. p. form as it was cooling.

6-Ethoxy(thio-oxindole) when first prepared had m. p. 39—40°, and reprecipitation from an alkaline solution gave a product of the same m. p. When exposed to the air for one week, however, the m. p. had become 47—48°, and this form was then recovered again when reprecipitated from an alkaline solution.

Thio-oxindole-3-aldehyde (II) has been prepared by three methods. In the most convenient method, thio-oxindole was readily condensed in boiling ethanolic solution with diphenylformamidine (cf. Piggott and Rodd, B.P. 344,409; 1929) to form thio-oxindole-3-aldehyde anil (V; R = H) in 70% yield. Alkaline hydrolysis of this anil in aqueous ethanol furnished thio-oxindole-3-aldehyde in 72% yield. 6-Ethoxy(thio-oxindole) similarly gave 6-ethoxy(thio-oxindole)-3-aldehyde.

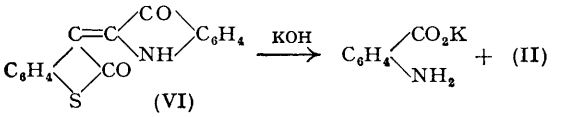
Thio-oxindole did not condense with diphenylacetamidine in boiling ethanolic solution : when, however, the two reagents were fused together at 140—150°, the 3-acetyl(thio-oxindole) anil (V; R = Me) was formed in 64% yield, and on alkaline hydrolysis furnished 3-acetyl(thio-oxindole) (III) in 88% yield. By the use of these two amidines, therefore, both the aldehyde (II) and the ketone (III) can readily be obtained.



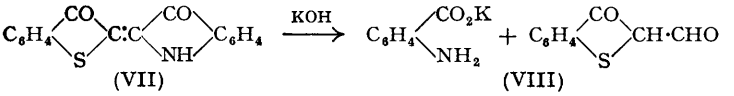
(V)

By the second synthetic method, thio-oxindole-3-aldehyde was obtained when thio-oxindole was treated with hydrogen chloride and hydrogen cyanide in chloroform solution; the yield of aldehyde was, however, only 5%, and so this method was not further investigated. The low yield obtained by this Gattermann reaction is in marked contrast to that of thioindoxyl-2-aldehyde similarly obtained from thioindoxyl (see below).

It is noteworthy that thio-oxindole appeared to be unaffected by ethyl formate in the presence of sodium ethoxide, although Julian, Pikl, and Boggess (*J. Amer. Chem. Soc.*, 1934, **56**, 1797) have shown that 1-methyloxindole is readily converted by these reagents into 1-methyloxindole-3-aldehyde.



(VI)



(VII) (VIII)

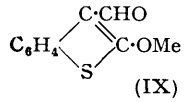
The third synthetic route does not require thio-oxindole as an intermediate, and we have therefore carefully investigated its utility. It has been shown (Friedländer, *Monatsh.*, 1908, **29**, 373, 375; Friedländer *et al.*, *Ber.*, 1910, **43**, 1971; 1911, **44**, 3098; cf. Marschalk, *J. pr. Chem.*, 1913, **88**, 227) that indoxyl condenses with thionaphthenquinone solely at the 3-position to give the compound (VI) of the indirubin type, which in turn can be hydrolysed by potassium hydroxide to anthranilic acid and the required aldehyde (II) : the latter can then be readily isolated as its potassium derivative and so purified. Harley-Mason and Mann (*J.*, 1942, 404) investigated the reaction of indoxyl with a number of thionaphthenquinones having substituents in the benzene ring, and concluded that condensation in all cases occurred at the 3-position (as above), and that alkali fission consequently always gave the corresponding substituted thio-oxindole-3-aldehyde. We find that certain of these conclusions require modification. The condensation of indoxyl with thionaphthenquinone certainly gives the pure compound (VI) and hence on hydrolysis the pure aldehyde (II). The product of the condensation of indoxyl with 6-ethoxy-, 6-chloro-4-methyl-, and 4 : 5-benzothionaphthenquinone is, however, a mixture of the corresponding compound of type (VI) and the isomeric compound (VII) of the indigo type. When this mixture is boiled with aqueous potassium hydroxide, only the compound (VI) undergoes hydrolysis and consequently only the thio-oxindole-3-aldehyde (as II) is obtained. When the residue, consisting of the compound (VII), is subsequently boiled with ethanolic potassium hydroxide, it undergoes hydrolysis to anthranilic acid and the corresponding thioindoxyl-2-aldehyde (as VIII). Consequently, if the hydrolysis is performed only with aqueous alkali, the presence of the component (VII) may escape detection. We find that the indoxyl condensation product with 6-ethoxy-, 6-chloro-4-methyl-, and 4 : 5-benzothionaphthenquinone gives on aqueous alkaline hydrolysis the corresponding 3-aldehyde (as II) in 30, 10, and 18% yields, respectively. There is little doubt therefore that the diphenylformamidine synthesis provides these aldehydes in greater yield and higher purity.

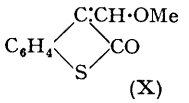
The identity of the various thioindoxyl-2-aldehydes (as VIII) formed by ethanolic alkaline hydrolysis of the products (as VII)—and hence of these products also—was established by an independent synthesis of the aldehydes from thioindoxyl by the Gattermann reaction with hydrogen chloride and hydrogen cyanide. This reaction proceeded smoothly and furnished the aldehyde (VIII) and also its 6-ethoxy-, 6-chloro-4-

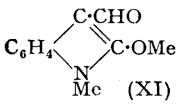
methyl-, and 4 : 5-benzo-derivatives in high yield: the first two of these substituted aldehydes have not previously been isolated (cf. Friedländer, *loc. cit.*; Krollpfeiffer *et al.*, *Ber.*, 1925, **58**, 1654; Harley-Mason and Mann, *loc. cit.*).

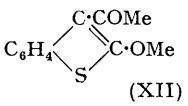
It is noteworthy that thioindoxyl also readily condensed with *NN'*-diphenylacetamidine, and the resulting anil on hydrolysis furnished 2-acetyl(thioindoxyl).

The possible methylation of the aldehyde (II) to the ketone (III) has also been investigated, although the obvious tautomeric potentialities of the aldehyde (II) made this route unpromising. No derivative could be isolated by the interaction of the aldehyde (II) or its potassium derivative with either methyl iodide or methyl sulphate. The aldehyde reacted, however, with diazomethane to give a monomethyl and a dimethyl derivative, both in low yield. The monomethyl derivative was not identical with the ketone (III), the structure of which is determined decisively by its synthesis. This derivative is there-


(IX)


(X)


(XI)


(XII)

fore either (IX) or (X). Julian *et al.* (*loc. cit.*) have shown that 1-methyloxindole-3-aldehyde gives a monomethyl derivative which is still an aldehyde and which therefore has structure (XI): by analogy our derivative is probably (IX). Our dimethyl derivative must be 3-acetyl-2-methoxy(thionaphthen) (XII): the yield was too small, however, to allow investigation of its possible hydrolysis to the ketone (III).

The phenylhydrazones of thio-oxindole-3-aldehyde, of its 6-ethoxy-derivative, and of 3-acetyl(thio-oxindole) show certain anomalous properties which will be fully described in a later communication.

Experimental

Thionaphthenquinone 3-Hydrazone (IV).—(*a*) Hydrazine hydrate (3·5 c.c., 1·2 mol.) was slowly added to a boiling solution of thionaphthenquinone (10 g.) in a minimum of ethanol. The solution was then boiled under reflux for 15 minutes (during which the initial orange-red colour became deep yellow) and hot water was then added to the boiling solution until crystals began to separate. On cooling, the almost pure hydrazone separated, and when collected, washed with aqueous ethanol, and dried had m. p. 135—136° (yield: 7·3 g., 67%). A sample, recrystallised from aqueous ethanol and then from *cyclo*hexane, formed yellow plates, m. p. 136° (Found: C, 54·1; H, 3·6; N, 16·0. Calc. for $C_8H_6ON_2S$: C, 53·9; H, 3·4; N, 15·7%): Marschalk (*loc. cit.*) gives m. p. 128°.

(*b*) A mixture of thionaphthenquinone (5 g.), hydrazine hydrochloride (3·2 g., 1 mol.), sodium acetate (13 g.), water (50 c.c.), and ethanol (105 c.c.) was boiled under reflux for 1·5 hours, and then diluted with hot water until it became cloudy. On cooling, the crude hydrazone (3·5 g., 64%), m. p. 123—128°, separated. Recrystallisation from *cyclo*hexane gave yellow crystals, m. p. 135—136°.

Thio-oxindole (I).—(*a*) A solution of the hydrazone (10 g.) in 25% aqueous potassium hydroxide (500 c.c.) was boiled gently under reflux for 16 hours; the evolution of nitrogen had then ceased and the initial orange-red colour had become pale straw-yellow. The solution, when cooled and acidified, deposited cream-coloured crystals of *o*-mercaptophenylacetic acid (8·0 g., 84%), m. p. 97°. Marschalk (*loc. cit.*) gives m. p. 96—97°.

A mixture of this acid (7·9 g.), concentrated hydrochloric acid (50 c.c.), and water (150 c.c.) was distilled in steam; the thio-oxindole readily crystallised in the distillate (*ca.* 500 c.c.), which was then saturated with sodium chloride and extracted with ether. Evaporation of the dried extract gave the thio-oxindole (I) as a pale yellow oil which readily formed fine, almost colourless, needles (6·1 g., 87%), m. p. 32·5—33°. A sample, purified by further steam-distillation, had m. p. 33—33·5° (Found: C, 63·9; H, 4·4. Calc. for C_8H_6OS: C, 64·0; H, 4·0%).

(*b*) The dry powdered hydrazone (3 g.) was heated in an oil-bath under a reflux air-condenser. Just above its m. p. a violent exothermic reaction occurred with vigorous effervescence and the production of a bluish-green vapour. The brown semi-solid residue on distillation gave an oil, b. p. 100—104°/0·15 mm., which solidified, and was then further distilled in steam. The

pale yellowish-brown oily thio-oxindole which distilled readily solidified: m. p. 41—43°. Repeated distillation in steam gave colourless slightly hygroscopic crystals, m. p. 44—45° (Found: C, 63·7; H, 4·3%).

(*c*) Expt. (*b*) was repeated, but the brown residue was now extracted with 10% aqueous potassium hydroxide solution. The extract, when acidified with hydrochloric acid and distilled in steam, gave thio-oxindole as colourless crystals, m. p. 31—33°, in low yield.

6-*Ethoxy*(*thionaphthen*)*quinone* 3-*Hydrazone*.—This was prepared precisely as was (IV), from the quinone (8 g.), hydrazine hydrate (2 c.c., 1·1 mol.), and boiling ethanol (*ca.* 400 c.c.). The crude *hydrazone* (7·0 g., 86%), m. p. 140—143°, when recrystallised from *cyclo*hexane gave orange-yellow crystals, m. p. 145° (Found: C, 54·1; H, 4·8. $C_{10}H_{10}O_2N_2S$ requires C, 54·0; H, 4·5%).

6-*Ethoxy*(*thio-oxindole*).—The hydrazone (3·1 g.) when boiled with 25% aqueous potassium hydroxide (155 c.c.) as before deposited 4-*ethoxy*-2-*mercaptophenylacetic acid* as colourless crystals (2·44 g., 82%), m. p. 80° unchanged by recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 56·9; H, 5·6. $C_{10}H_{12}O_3S$ requires C, 56·6; H, 5·7%).

The acid, when distilled in dilute hydrochloric acid as before, gave the *thio-oxindole* as colourless needles, m. p. 39—40° (Found: C, 62·4; H, 5·1. $C_{10}H_{10}O_2S$ requires C, 61·8; H, 5·2%): it has a characteristic odour resembling that of new rubber. A sample, when set aside for one week, had m. p. 47—48°, which did not further change. Both the low- and the high-melting form, when dissolved in 10% aqueous sodium hydroxide at 0°, were reprecipitated unchanged on acidification.

Synthesis of Thio-oxindole-3-aldehyde (II).—*First method.* A mixture of thio-oxindole (3 g.) and *NN'*-diphenylformamidine (3·9 g., 1 mol.) (Shoesmith and Haldane, *J.*, 1923, **123**, 2705) was warmed under reflux with ethanol (30 c.c.). The orange solution on boiling deposited yellow needles of thio-oxindole-3-aldehyde anil (V; R = H), which after 15 minutes' boiling were collected from the chilled mixture, washed with ethanol, and dried; the yield of material, m. p. 180—181°, was 3·75 g. (78%). The m. p. was unchanged when the product was mixed with an authentic sample prepared directly from the aldehyde.

The ethanolic mother-liquor when set aside deposited colourless crystals (0·53 g.) of *di*-(ω-*phenylcarbamyl*-o-*tolyl*) *disulphide* [·S·C_6H_4·CH_2·CO·NHPh]$_2$, m. p. 217° after recrystallisation from acetone [Found: C, 69·4; H, 5·3; N, 6·4%; *M* (Rast), 470. $C_{28}H_{24}O_2N_2S_2$ requires C, 69·4; H, 5·0; N, 5·8%; *M*, 484]. This compound was insoluble in aqueous sodium hydroxide and was unaffected in solution by iodine: it was sparingly soluble in cold acetone, whereas the anil was readily soluble. When a solution of thio-oxindole (0·5 g.) and aniline (0·31 g., 1 mol.) in ethanol (10 c.c.) was boiled under reflux for 2 hours and then set aside, this disulphide (0·225 g., 28%) separated slowly during a week, and when recrystallised from acetone had m. p. 217°, unchanged by admixture with the above sample.

A mixture of the anil (3·75 g.), water (60 c.c.), ethanol (30 c.c.), and potassium hydroxide (15 g.) was boiled under reflux for 1 hour, the initial orange-yellow becoming pale yellow. The solution was then diluted with water, filtered whilst hot, cooled, and acidified with hydrochloric acid. The crude aldehyde (II) (2·4 g.) thus precipitated had m. p. 123—128°; recrystallisation from *cyclo*hexane (charcoal) furnished colourless needles (2 g., 72%), m. p. 130° (Found: C, 60·7; H, 3·6. Calc. for $C_9H_6O_2S$: C, 60·7; H, 3·4%). Friedländer (*loc. cit.*) gives m. p. 130°.

The aldehyde gave the following derivatives: The *phenylhydrazone* was obtained when phenylhydrazine (0·4 g.) was added to a solution of the aldehyde (0·5 g.) in ethanol (10 c.c.), which was then boiled for 5 minutes, during which crystals separated; hot ethanol was then added to give a clear solution, which on cooling deposited the phenylhydrazone, yellow needles, m. p. 180—182° (decomp.) after further recrystallisation (Found: C, 67·1; H, 4·8; N, 10·7. $C_{15}H_{12}ON_2S$ requires C, 67·1; H, 4·5; N, 10·5%). The 2 : 4-*dinitrophenylhydrazone* was readily formed in the cold and after recrystallisation from acetic acid formed minute bright red crystals, m. p. 239—240° (decomp.) (Found: C, 50·5; H, 2·8; N, 15·5. $C_{15}H_{10}O_5N_4S$ requires C, 50·3; H, 2·8; N, 15·6%). The *anil* was readily prepared from the aldehyde and aniline in hot ethanolic solution: it formed yellow crystals, m. p. 184°, from ethanol (Found: C, 71·4; H, 3·9; N, 5·8. $C_{15}H_{11}ONS$ requires C, 71·1; H, 4·4; N, 5·5%). The *benzoyl* derivative was obtained when benzoyl chloride (2 c.c.) was added to a suspension of the aldehyde (1 g.) in 10% aqueous sodium hydroxide (15 c.c.), which was vigorously shaken. The sticky product which separated, was washed, dried, and recrystallised from benzene, and then gave straw-yellow needles, m. p. 178° (Found: C, 68·1; H, 3·9. $C_{16}H_{10}O_3S$ requires C, 68·1; H, 3·6%).

6-Ethoxy(thio-oxindole) (2 g.) and *NN'*-diphenylformamidine (2 g., 1 mol.), when similarly condensed, afforded 6-*ethoxy*(*thio-oxindole*)-3-*aldehyde anil* as yellow needles (2·1 g., 69%), m. p. 139°, from ethanol (Found: C, 68·6; H, 5·4. $C_{17}H_{15}O_2NS$ requires C, 68·6; H, 5·4%). Again, the initial mother-liquor deposited crystals (0·37 g.) which when recrystallised in turn from ethanol and acetone gave *di*-(4-*ethoxy*-ω-*phenylcarbamyl*-o-*tolyl*) *disulphide* as colourless needles, m. p. 205—206° (Found: C, 67·2; H, 5·8; N, 5·2. $C_{32}H_{32}O_4N_2S_2$ requires C, 67·1; H, 5·6; N, 4·9%), analogous to the disulphide similarly obtained from thio-oxindole.

The anil, when hydrolysed as before, furnished 6-ethoxy(thio-oxindole)-3-aldehyde as pale yellow crystals (87%), m. p. 156°, from *cyclo*hexane (Found: C, 59·5; H, 4·6. Calc. for $C_{11}H_{10}O_2S$: C, 59·5; H, 4·5%). Harley-Mason and Mann (*loc. cit.*) give m. p. 152—154°. The aldehyde formed a *phenylhydrazone* as bright yellow needles (from ethanol), m. p. 168—169° (decomp.), resolidifying when heated further and then melting again at *ca.* 272° (Found: C, 65·8; H, 5·0; N, 8·9. $C_{17}H_{16}O_2N_2S$ requires C, 65·3; H, 5·2; N, 9·0%), and a 2 : 4-*dinitrophenylhydrazone* as orange-red plates (from acetic acid), m. p. 216—217° (decomp.) (Found: C, 51·2; H, 3·5; N, 13·5. $C_{17}H_{14}O_6N_4S$ requires C, 50·75; H, 3·5; N, 13·9%).

Second method. Dry hydrogen chloride was passed into a solution of thio-oxindole (2·3 g.) and anhydrous hydrogen cyanide (3 c.c.) in chloroform (30 c.c.) at 0°. The solution became cloudy and crystals separated: after 1·5 hours, the passage of hydrogen chloride was stopped and the product set aside for 2 hours.

The crystalline precipitate was collected and triturated with water, whereupon much dissolved, leaving an oily residue. This was extracted with ether, and evaporation of the solvent then left an orange solid (0·29 g.) of the imino-hydrochloride, which was hydrolysed with boiling 20% aqueous sodium hydroxide. When evolution of ammonia ceased, cooling gave a crystalline deposit of the potassium derivative of the aldehyde, which was collected and acidified, giving the pure aldehyde (II), m. p. 129—129·5° unchanged by admixture of the specimen with an authentic sample: 0·14 g., 5%. Unchanged thio-oxindole (1·22 g., 53% of original material), m. p. 31—32°, was recovered from the chloroform mother-liquor.

Third method. Thioindoxyl and its substituted derivatives were condensed with dimethyl-*p*-nitrosoaniline to form the corresponding anils, and the latter then hydrolysed to the thionaphthenquinone, as described by Dalgliesh and Mann (*J.*, 1942, 404).

Thionaphthenquinone, and its substituted derivatives, were condensed with indoxyl by the following modification of Harley-Mason and Mann's method (*loc. cit.*): the product from thionaphthenquinone itself was solely (VI), whereas that from the substituted quinones was a mixture of the products corresponding to (VI) and (VII). Indoxyl (1·1 mol.) was added to a solution of the quinone in warm acetic acid (30 c.c./1 g. of quinone) containing concentrated hydrochloric acid (1 drop/1 g. of quinone), and the mixture was boiled for 10—15 minutes and cooled. The purple condensation product which separated was collected, washed with water, alcohol, and ether, and dried. The average yields from the various quinones were: unsubstituted quinone, 84; 6-ethoxy-, 73; 6-chloro-4-methyl-, 80; 4 : 5-benzo-, 82%. The average yield of the last three compounds was 57, 49, and 87%, respectively, when aluminium chloride (1 g./100 c.c. of acetic acid) replaced the hydrochloric acid.

Hydrolysis of the Condensation Product.—(i) *From thionaphthenquinone* (cf. Friedländer and Kielbasinski, *Ber.*, 1911, **44**, 3098). The condensation product (34 g.) was added to a solution of potassium hydroxide (102 g.) in water (400 c.c.) containing ethanol (35 c.c.), which was boiled under reflux for 15 minutes, the green colour becoming brown meanwhile. The solution was poured into a beaker and warmed until a crust of the crystalline grey potassium derivative of the aldehyde had formed. It was set aside overnight, and the crystals were then collected and washed with 20% aqueous potassium hydroxide. A solution of the crystals in hot water (300 c.c.) was filtered whilst hot directly on to ice, and the filtrate acidified with dilute hydrochloric acid. The precipitated aldehyde (II), when collected, washed, and dried, had m. p. 128—130° (13·1 g., 60%). In smaller-scale preparations yields up to 84% were obtained. The aldehyde was best purified by dissolution in a small quantity of hot water, and reprecipitation as the potassium derivative by addition of concentrated potassium hydroxide solution: the cream-coloured crystalline aldehyde, when regenerated as before, had m. p. 130—131° unchanged by recrystallisation from *cyclo*hexane, or from light petroleum (b. p. 60—80°) containing a small proportion of ethanol, from which it separated, however, as colourless crystals. The m. p. was also unaffected when the aldehyde was mixed with that obtained by the first method.

(ii) *From substituted thionaphthenquinones.* A mixture of the condensation product, 20% aqueous potassium hydroxide solution (12 parts), and ethanol (3 parts) was boiled under reflux

for 1 hour, by which time only a portion of the condensation product had dissolved in the brown solution. The mixture was diluted with hot water and immediately filtered, the undissolved residue being washed with hot water.

The combined filtrate and washings were evaporated until grey crystals of the potassium derivative formed, and were then set aside. Next day, the crystals were collected, and the substituted thio-oxindole-3-aldehyde (as II) then regenerated as described above. Purification was always best effected by one or more reprecipitations as the potassium derivative before recrystallisation from water or an organic solvent.

The undissolved residue was extracted as before for 1 hour to ensure elimination of all the component (as VI). The residue (as VII) was then boiled gently under reflux with 33% ethanolic potassium hydroxide (9 parts) : dissolution was rapid, and crystals of the potassium derivative of the corresponding thioindoxyl-2-aldehyde (as VIII) usually separated in 3—5 minutes. After 15 minutes' boiling, the solution was diluted with ethanol (6 parts) and set aside overnight. The greyish-blue crystals were then collected, washed with a small quantity of ethanol, and the 2-aldehyde regenerated as described above for the 3-aldehyde. The identity of the substituted thioindoxyl-2-aldehydes (as VIII) was confirmed by direct comparison with those prepared by the Gattermann reaction from the corresponding thioindoxyls (see below). The following aldehydes were thus obtained :

6-*Ethoxy*(*thio-oxindole*)-3-*aldehyde*. This crude aldehyde, m. p. 153—155°, was purified by reprecipitation as the potassium derivative, and when regenerated had m. p. 154—156° : subsequent recrystallisation from water gave cream-coloured needles, m. p. 155° alone and mixed with an authentic sample. The average yield, based on the condensation product used, was 30%.

6-*Chloro*-4-*methyl*(*thio-oxindole*)-3-*aldehyde*. The crude product, m. p. 151—153°, was thrice reprecipitated as the potassium derivative, and the *aldehyde* when then recrystallised from aqueous ethanol formed colourless needles, m. p. 154—155° (Found : C, 52·7; H, 3·4. $C_{10}H_7O_2ClS$ requires C, 53·0; H, 3·1%) : average yield, 10%. It formed a 2 : 4-*dinitrophenylhydrazone*, purple-brown needles, m. p. 262—263° (decomp.) after recrystallisation from acetic acid (Found : C, 46·8; H, 2·9; N, 14·3. $C_{16}H_{11}O_5N_4ClS$ requires C, 47·2; H, 2·7; N, 13·8%).

4 : 5-*Benzothio-oxindole*-3-*aldehyde*. The crude aldehyde, obtained in an average yield of 18%, consisted of 2 components. (*a*) Three recrystallisations from aqueous ethanol followed by one from *cyclo*hexane gave pale yellowish-brown crystals, m. p. 104—105° (Found : C, 70·4; H, 4·0%). These crystals, which formed the minor component and did not give a 2 : 4-dinitrophenylhydrazone, were not identified. (*b*) Direct recrystallisation from *cyclo*hexane gave fine pale yellow needles, m. p. 124°, apparently of the required *aldehyde*, although unsatisfactory analyses were obtained (Found : C, 67·7; H, 4·3. $C_{13}H_8O_2S$ requires C, 68·4; H, 3·5%) : these crystals, which formed the major component, readily gave a 2 : 4-dinitrophenylhydrazone.

The crude aldehyde gave the derivatives : 2 : 4-*dinitrophenylhydrazone*, orange-brown crystals from acetic acid, m. p. 240—241° (Found : C, 55·9; H, 3·8. $C_{19}H_{12}O_5N_4S$ requires C, 55·9; H, 3·0%) ; the *anil*, prepared in a hot ethanolic solution of aniline containing acetic acid, formed pale yellow crystals, m. p. 213—214°, from ethanol (Found : C, 74·95; H, 4·5; N, 4·6. $C_{19}H_{13}ONS$ requires C, 75·2; H, 4·3; N, 4·6%). The crude aldehyde was also successfully used in the preparation of certain *mero*cyanines (see following paper).

The Substituted Thioindoxyl-2-aldehydes (as VIII).—These compounds were thus obtained in two ways : (*a*) by the ethanolic-alkali hydrolysis of the undissolved residue described above, and (*b*) by the Gattermann synthesis for independent identification. This was carried out essentially by the method already described (p. 2132), but the orange-brown crystalline precipitate was collected, washed with water, and hydrolysed by boiling it with aqueous N-sodium hydroxide solution until evolution of ammonia ceased. The solution was filtered whilst hot from a small amount of undissolved material, and the filtrate cooled and acidified with hydrochloric acid. The precipitated aldehyde was collected and purified.

6-*Ethoxy*(*thioindoxyl*)-2-*aldehyde*. (*a*) The undissolved residue (53% of the condensation product) gave the *aldehyde* as pale yellow crystals from aqueous ethanol, m. p. 145—146° alone and mixed with following product. (*b*) The crude aldehyde (38% based on thioindoxyl) when similarly recrystallised had m. p. 147—149°, depressed to 130—135° by admixture of the sample with the isomeric 3-aldehyde (Found : C, 59·5; H, 4·5. $C_{11}H_{10}O_3S$ requires C, 59·5; H, 4·5%). It furnished a 2 : 4-*dinitrophenylhydrazone*, brown needles, m. p. 231—233° after recrystallisation from acetic acid and then xylene (Found : N, 13·5. $C_{17}H_{14}O_6N_4S$ requires N, 13·9%).

6-*Chloro*-4-*methyl*(*thioindoxyl*)-2-*aldehyde*. (*a*) The undissolved residue (50% of total product) furnished the *aldehyde* as pale yellowish-brown needles (from aqueous ethanol), m. p. 170—171°,

alone or mixed. (*b*) The crude aldehyde (48%), similarly recrystallised, gave pale pink needles, m. p. 170—172° (Found : C, 52·9; H, 3·1. $C_{10}H_7O_2ClS$ requires C, 53·0; H, 3·1%). The 2 : 4-*dinitrophenylhydrazone* formed brown needles, m. p. 263—264° (decomp.) from acetic acid (Found : N, 13·4. $C_{16}H_{11}O_5N_4ClS$ requires N, 13·8%).

4 : 5-*Benzothioindoxyl*-2-*aldehyde*. (*a*) The undissolved residue (66% of total product) gave the aldehyde as a pale fawn powder, m. p. 145—146°, which when recrystallised from ethanol formed pale straw-yellow needles, m. p. 147—148°, alone and mixed. (*b*) The crude aldehyde, twice recrystallised from aqueous ethanol, formed pale yellow needles, m. p. 146—147°. Krollpfeiffer *et al.* give m. p. 147°; Harley-Mason and Mann (*loc. cit.*) give m. p. 131—132°. It formed a 2 : 4-*dinitrophenylhydrazone*, orange-brown needles, m. p. 284° (decomp.), from acetic acid (Found : C, 55·9; H, 3·5; N, 14·1. $C_{19}H_{12}O_5N_4S$ requires C, 55·9; H, 3·0; N, 13·7%).

3-*Acetyl*(*thio-oxindole*) (III).—NN′-*Diphenylacetamidine*. A mixture of acetanilide (13·5 g.), aniline (9·3 g., 1 mol.), and phosphorus trichloride (50 g.) was heated under reflux at 110—120° for 40 minutes, a test portion then being completely soluble in water. The mixture was then poured into water, cooled, and basified : the precipitated amidine, when collected, washed with water, and recrystallised from ethanol, formed colourless needles (12·5 g., 60%), m. p. 128—129° (cf. Sen and Ray, *J.*, 1926, 646).

Thio-oxindole (3·14 g.; m. p. 33—33·5°) and the amidine (3·6 g., 1 mol.) were fused in a tube for 1·25 hours; the odour of thio-oxindole was then almost imperceptible, and drops of aniline had condensed on the upper and cooler portion of the tube. The reddish-brown melt was stirred with methanol (5 c.c.), and the crystals which separated on cooling were collected and recrystallised from ethanol. 3-*Acetyl*(*thio-oxindole*) *anil* (V; R = Me) was thus obtained as pale cream crystals, m. p. 129·5—130° (Found : C, 71·55; H, 4·65; N, 5·25. $C_{16}H_{13}ONS$ requires C, 71·9; H, 4·9; N, 5·2%) : 3·5 g., 58%.

The initial methanolic mother-liquor, when set aside for 2 days, furnished a crystalline deposit (0·58 g.), which after recrystallisation from acetone gave colourless needles, m. p. 217°, identical with those similarly obtained in the condensation with diphenylformamidine (p. 2131) and therefore di-(ω-phenylcarbamyl-*o*-tolyl) disulphide.

The anil (3·5 g.) was added to a solution of potassium hydroxide (14 g.) in ethanol (35 c.c.) containing water (70 c.c.), which was boiled under reflux for 30 minutes, cooled, and acidified with hydrochloric acid. The precipitate (2·42 g., 96%), when collected and recrystallised from 90% aqueous ethanol, gave 3-*acetyl*(*thio-oxindole*) (III) as colourless crystals, m. p. 105° (Found : C, 62·7; H, 4·2. $C_{10}H_8O_2S$ requires C, 62·5; H, 4·2%). The preparation and properties of the phenylhydrazone of this ketone will be discussed later.

2-*Acetyl*(*thioindoxyl*).—Thioindoxyl (1·5 g.) and *NN′*-diphenylacetamidine (2·1 g., 1 mol.) were fused under nitrogen at 145—150° for 45 minutes. The cold oily yellowish-brown residue, when stirred with methanol, deposited crystals of the *anil* (1·4 g., 53%) which after recrystallisation from *cyclo*hexane formed orange-yellow crystals, m. p. 111° (Found : C, 72·1; H, 4·8; N, 5·4. $C_{16}H_{13}ONS$ requires C, 71·9; H, 4·9; N, 5·2%).

The anil (0·6 g.) was added to a solution of potassium hydroxide (2·4 g.) in water (12 c.c.) and ethanol (6 c.c.), which was then boiled under reflux for 1 hour. The cold filtered solution, when acidified with hydrochloric acid, deposited the 2-acetyl(thioindoxyl) (0·43 g., 99%), which after recrystallisation from methanol (charcoal) formed colourless crystals, m. p. 79·5—80°. Smiles and McClelland (*J.*, 1921, **119**, 1810) give m. p. 81°.

Methylation of Thio-oxindole-3-*aldehyde*.—(*a*) The potassium derivative of the aldehyde was recovered unchanged after it had been boiled with methyl iodide for 3 hours, or vigorously shaken in aqueous potassium hydroxide suspension with methyl sulphate for 1 hour. (*b*) An ethereal diazomethane solution (36 c.c.; *ca.* 4·25 mol.) was added to a filtered solution of the aldehyde (1 g.) in ether (50 c.c.). After slight effervescence, the solution was again filtered and evaporated, leaving an orange-yellow gum which could not be recrystallised. It was dissolved in ether and shaken with 5% aqueous potassium hydroxide, which extracted some unchanged aldehyde. The residue from the evaporation of the ethereal solution was stirred with methanol, and the crystals which formed, when thrice recrystallised from aqueous ethanol, gave colourless crystals of the *monomethyl aldehyde* (probably IX), m. p. 67° (Found : C, 62·4; H, 4·5. $C_{10}H_8O_2S$ requires C, 62·5; H, 4·2%).

When, however, an ethereal solution of diazomethane (45 c.c.; *ca.* 1·25 g. of CH_2N_2) was added slowly with shaking to one of the aldehyde (1 g.) in methanol (25 c.c.), and the mixture, after cessation of the mild effervescence, was evaporated, an orange gum was obtained : after this had been stirred with methanol (3—4 c.c.), the small crop of crystals which separated furnished, after recrystallisation from methanol, pale straw-yellow needles of the *dimethyl*

derivative (XII), m. p. 125—126°, depressed to 79—82° by admixture of the sample with the original aldehyde (Found : C, 64·1; H, 5·1. $C_{11}H_{10}O_2S$ requires C, 64·0; H, 4·9%).

No satisfactory product could be isolated from the attempted interaction of diazomethane and the benzoyl derivative of the aldehyde.

We are greatly indebted to Imperial Chemical Industries Limited, Dyestuffs Division, for the gift of various intermediate compounds.

UNIVERSITY CHEMICAL LABORAOTY, CAMBRIDGE. [*Received, January* 16*th*, 1952.]