

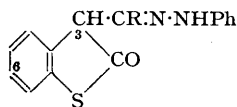
450. *The Molecular Rearrangement of the Phenylhydrazones of Thio-oxindole-3-aldehyde and of 3-Acetyl(thio-oxindole).*

By R. H. GLAUERT and FREDERICK G. MANN.

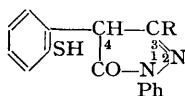
It is shown that the above phenylhydrazones readily undergo a molecular rearrangement to the 4-*o*-mercaptophenyl derivatives of the 1-phenylpyrazolones, which in turn undergo ready oxidation to the corresponding disulphides. The labile nature of these phenylhydrazones entails considerable care in their preparation and characterisation.

WE have already briefly drawn attention to the labile nature of the phenylhydrazones of thio-oxindole-3-aldehyde, its 6-ethoxy-derivative, and of 3-acetyl(thio-oxindole) (*J.*, 1952, 2127), and the properties of these compounds have now been more fully investigated. All show essentially the same behaviour under certain conditions, and that of the derivatives of thio-oxindole-3-aldehyde will therefore alone be cited in detail.

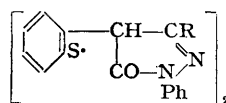
Thio-oxindole-3-aldehyde phenylhydrazone (I; R = H) is best prepared by the action of pure phenylhydrazine on a cold ethanolic solution of the aldehyde, and when recrystallised from ethanol is obtained as pale yellow crystals, m. p. 180—181°, which are only slowly soluble in 10% aqueous potassium hydroxide, and are unaffected by iodine. When a solution of this phenylhydrazone in ethanol containing hydrogen chloride is boiled, the



(I)



(II)

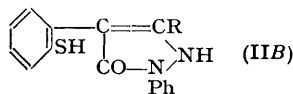
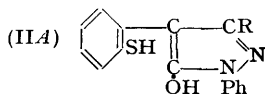


(III)

yellow solution becomes paler and on cooling deposits an isomeric compound as very pale yellow (almost colourless) crystals, m. p. 195°. These crystals are freely soluble in aqueous potassium hydroxide, and the presence of a mercapto-group is shown by the deep colour which the alkaline solution gives with sodium nitroprusside. The presence of this mercapto-group is further confirmed by the fact that an ethanolic solution of the isomer reacts readily with iodine to give a compound of composition $C_{30}H_{22}O_2N_4S_2$ as colourless crystals, m. p. 257—259°, which are also soluble in 10% aqueous potassium hydroxide but give no colour with sodium nitroprusside.

These facts leave little doubt that the phenylhydrazone (I; R = H) under the influence of the hydrogen chloride has undergone a molecular rearrangement which entails opening of the thiophen ring and formation of a pyrazole ring, the product being 4-*o*-mercapto-phenyl-1-phenylpyrazolone (II; R = H), and that it is this thiol which undergoes oxidation by iodine to furnish di-*[o*-(1-phenylpyrazol-5-on-4-yl)phenyl] disulphide (III; R = H). This explains why the isomer gives the nitroprusside and the iodine reaction, whilst the oxidation product of course does neither. The fact that the disulphide is freely soluble in cold aqueous potassium hydroxide provides additional evidence for its constitution, because, since 1:4-diphenylpyrazolone is soluble in aqueous alkalis (Wislicenus, *Ber.*, 1887, **20**, 2930), a compound of structure (III; R = H) would almost certainly have a similar solubility: the intermediate compound (II; R = H) owes its alkali-solubility both to the pyrazolone ring and to the thiol grouping.

The pyrazolone structure of our intermediate compounds has been independently confirmed by the infra-red spectra of the compounds (II; R = H and Me), on which Dr. R. N. Haszeldine reports: "The presence of a thiol group in both compounds is shown by the weak bands in the 3·7—3·95- μ region of the spectrum. Furthermore a strong band at 6·20 μ is ascribed to the ketone group, possibly hydrogen-bonded to the thiol group. In addition, the spectra of the compounds show no bands in the 2·5—3·25- μ region, and hydroxy- and imino-groups are therefore absent. These observations provide strong evidence, not only for the pyrazolone ring, but also for its presence in the form (II) as distinct from the tautomeric forms (IIA and B)."



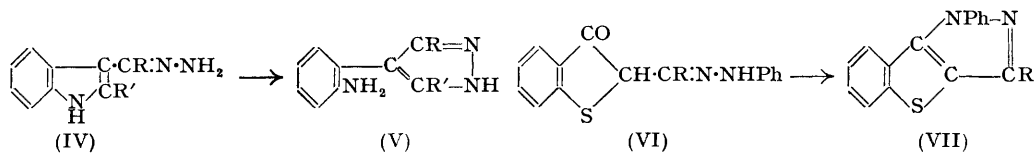
The changes (I \rightarrow II \rightarrow III) occur very readily, and there is some evidence that the over-all change may not necessarily require an external oxidising agent. Thus 6-ethoxy-thio-oxindole-3-aldehyde phenylhydrazone (as I) forms bright yellow crystals, m. p. 168—169°, which are transformed as before into the thiol (as II), very pale yellow crystals, m. p. 243°, which on oxidation give the disulphide (as III), colourless crystals, m. p. 270—272°. In determining the melting point of the phenylhydrazone in the usual capillary tube, however, considerable effervescence immediately follows the fusion at 168—169° and the material then resolidifies, and, if the heating is continued, then remelts at 270—272°, *i.e.*, conversion into the disulphide is now complete. It is unlikely that sufficient oxygen can be present in these circumstances to cause this complete oxidation, and the possibility that the effervescence may indicate loss of gaseous hydrogen from the intermediate thiol,

although improbable, cannot be entirely ignored. The phenylhydrazone of the unsubstituted aldehyde (I; R = H) also melts with effervescence and subsequent resolidification and formation of the crude disulphide (III; R = H), but the process in this series is much slower (and probably less complete) than in the 6-ethoxy-series.

3-Acetyl(thio-oxindole) phenylhydrazone (I; R = Me) forms very pale yellow crystals, m. p. 166°, which are converted by ethanolic hydrogen chloride into the thiol (II; R = Me), colourless plates, m. p. 225—227°, which on oxidation by iodine give the disulphide (III; R = Me), colourless crystals, m. p. 281—282°. In this series, however, it was found that a sample of the phenylhydrazone, when heated in the air at 170—175° for five minutes, was converted into the thiol. This confirms the fact that, although the presence of acid may accelerate the change (I) → (II), it is not essential for this purpose. Furthermore, when 3-acetyl(thio-oxindole) was boiled in ethanolic solution with an excess of phenylhydrazine containing a trace of acetic acid, the disulphide (III; R = Me) was the main product. In this case it is probable that the acetic acid initiated the change (I) → (II), and then the excess of phenylhydrazine may have oxidised the thiol to the disulphide. No similar change was detected, however, when thio-oxindole-3-aldehyde was similarly boiled with an excess of phenylhydrazine and acetic acid, only the normal phenylhydrazone being now isolated.

In view of the labile nature of the above phenylhydrazones it will be clear that both their preparation and the determination of their melting points must be performed with great care.

A reaction analogous to the above formation of the thiols apparently occurs in the indole series, for Alberti (*Gazzetta*, 1947, **77**, 398) has shown that the hydrazones (IV) of 3-acylindoles when heated with sodium ethoxide or hydrazine hydrate also undergo a molecular rearrangement, probably with the formation of the corresponding 4-*o*-aminopyrazoles (V).



It is of interest that the phenylhydrazones (VI) of 2-acylthioindoxyls when heated with acid lose water with the formation of the corresponding thionaphthenopyrazoles (VII) (Barry and McClelland, *J.*, 1935, 471). In this series, the opening of the thiophen ring to form a thiol, similar to that which we have recorded, is not possible.

EXPERIMENTAL

To determine the m. p. of a new phenylhydrazone or thiol described below, a series of tests had to be made in which a number of capillary tubes containing the material were plunged in turn into a heating-liquid at various temperatures, until a *short* range of temperature was found between failure to melt immediately and immediate fusion. A fresh sample was then immersed at the bottom of the range, and the temperature then raised fairly rapidly.

The Phenylhydrazones (I).—Phenylhydrazine (1 mol.) was added to a solution of the carbonyl compound in a minimum of cold ethanol, which was then set aside until crystallisation was complete. The phenylhydrazone was collected and rapidly recrystallised from ethanol. The preparation and m. p. of the first two of the following compounds, already described by Glauert and Mann (*loc. cit.*), were checked. Thio-oxindole-3-aldehyde phenylhydrazone, pale yellow needles, m. p. 180—181° (effervescence). 6-Ethoxythio-oxindole-3-aldehyde phenylhydrazone, bright yellow crystals, m. p. 168—169° (effervescence, followed by solidification and remelting at ca. 272°). 3-Acetyl(thio-oxindole) phenylhydrazone, very pale yellow crystals, m. p. 166° (Found: C, 68.0; H, 4.6; N, 10.1. C₁₆H₁₄ON₂S requires C, 68.1; H, 5.0; N, 9.9%).

When thio-oxindole-3-aldehyde (0.5 g.), phenylhydrazine (0.25 c.c., 2 mols.), and acetic acid (0.16 c.c., 1 mol.) had been dissolved in turn in ethanol (25 c.c.) and the whole boiled under reflux for 15 minutes, the clear yellow solution on cooling deposited the phenylhydrazone (I;

R = H), m. p. 178° (effervescence) (0.24 g., 64%). No indication of conversion into the disulphide, which occurs so readily with 3-acetyl(thio-oxindole) in these conditions (see below), could be detected.

All these phenylhydrazones were unaffected by iodine in cold ethanol; they dissolved slowly in cold 10% potassium hydroxide, the yellow solution ultimately becoming orange.

The 4-*o*-Mercaptophenyl-1-phenylpyrazolones (II).—A solution of the phenylhydrazone in boiling ethanol was diluted by one-third of its volume of ethanol previously saturated with hydrogen chloride, the yellow solution becoming rapidly paler. The solution was boiled under reflux for 5 minutes, and then just sufficient water was added to the boiling solution to start crystallisation. After cooling, the thiol was collected, washed with water, and recrystallised from ethanol (absolute or aqueous) or benzene. All the thiols were readily soluble in 10% aqueous potassium hydroxide, and the solutions gave an intense permanganate colour with aqueous sodium nitroprusside solution.

4-*o*-Mercaptophenyl-1-phenylpyrazolone (II; R = H) formed very pale yellow needles, m. p. 195°, from aqueous ethanol or benzene (Found: C, 67.3; H, 4.6; N, 10.4. $C_{15}H_{12}ON_2S$ requires C, 67.1; H, 4.5; N, 10.5%). 4-(4-Ethoxy-2-mercaptophenyl)-1-phenylpyrazolone formed very pale yellow crystals, m. p. 243°, from ethanol (Found: C, 65.0; H, 5.2; N, 8.65. $C_{17}H_{16}O_2N_2S$ requires C, 65.3; H, 5.2; N, 9.1%). 4-*o*-Mercaptophenyl-3-methyl-1-phenylpyrazolone (II; R = Me) formed colourless plates, m. p. 225–227°, from ethanol (Found: C, 68.0; H, 5.35; N, 10.0. $C_{16}H_{14}ON_2S$ requires C, 68.1; H, 5.0; N, 9.9%); this compound was also formed when the phenylhydrazone (I; R = Me) was heated at 170–175° for 5 minutes in the air.

The Di-[*o*-(1-phenylpyrazol-5-*on*-4-yl)phenyl] Disulphides (III).—These were prepared by adding ethereal iodine solution dropwise to a cold agitated ethanolic solution of the corresponding thiol (II) until a faint permanent iodine colour remained. The solution was then heated to the b. p., and water added (when necessary) to initiate crystallisation. The disulphide was collected, washed with ethanol, and recrystallised either from a considerable volume of ethanol or from aqueous pyridine. Molecular-weight determinations could be made only in camphor because the low solubility of the disulphides in other solvents (even when boiling) made such determinations unreliable.

Di-[*o*-(1-phenylpyrazol-5-*on*-4-yl)phenyl] disulphide (III; R = H) formed colourless crystals, m. p. 257–259°, from ethanol (Found: C, 67.9; H, 4.2; N, 10.9%; *M*, 505, 515. $C_{30}H_{22}O_2N_4S_2$ requires C, 67.4; H, 4.1; N, 10.5%; *M*, 534). Alternatively, the phenylhydrazone (I; R = H) (0.2 g.) was heated in a test-tube at 175–180° in an oil-bath. Gentle effervescence, which occurred just above the m. p., was complete in 5–6 minutes, and the melt then rapidly became semisolid and remained so during 12 minutes' total heating. The crude product, when recrystallised in turn from aqueous and glacial acetic acid (charcoal), gave the disulphide, m. p. 257–259° (alone and when mixed with above specimen) in low yield; the crystals persistently retained, however, a pale yellow colour.

Di-[5-ethoxy-2(1-phenylpyrazol-5-*on*-4-yl)phenyl] disulphide formed colourless crystals, m. p. 270–272°, from aqueous pyridine (Found: C, 65.9; H, 4.95; N, 9.25. $C_{34}H_{30}O_4N_4S_2$ requires C, 65.55; H, 4.9; N, 9.0%); this compound was also readily formed when the corresponding phenylhydrazone was heated in the air for 5 minutes at 170–175°.

Di-[*o*-(3-methyl-1-phenylpyrazol-5-*on*-4-yl)phenyl] disulphide (III; R = Me) formed colourless crystals, m. p. 281–282°, from ethanol (Found: C, 68.1; H, 4.8; N, 10.0. $C_{32}H_{26}O_2N_4S_2$ requires C, 68.3; H, 4.7; N, 10.0%). When a solution of the phenylhydrazone (III; R = Me) in ethanol was boiled with an excess of phenylhydrazine containing a few drops of acetic acid for 5 minutes, the product consisted almost entirely of this disulphide.

We are greatly indebted to Dr. R. N. Haszeldine for the spectroscopic investigation, and to Imperial Chemical Industries Limited, Dyestuffs Division, for the gift of various intermediate compounds.