Kinsley and Plant: The Formation of

The Formation of Osazones during Attempted Fischer Indole 940. Syntheses.

By D. A. KINSLEY and (the late) S. G. P. PLANT.

Treatment of deoxybenzoin o-nitrophenylhydrazone with o-nitrophenylhydrazine in acid solution leads to benzil di-o-nitrophenylhydrazone. mechanism of this reaction is discussed. The behaviour of certain other o-nitrophenylhydrazones under the conditions of the Fischer indole synthesis has been investigated.

DURING attempts to prepare 7-nitro-2: 3-diphenylindole (I) by a Fischer synthesis. deoxybenzoin o-nitrophenylhydrazone (II; R = R' = Ph) was heated with acetic and hydrochloric acid. The product, however, was not the indole (I) but was identified as benzil di-o-nitrophenylhydrazone (III) which was synthesised from benzil and o-nitrophenylhydrazine.

It seemed likely that this osazone (III) was formed by reaction between the hydrazone (II; R = R' = Ph) and free o-nitrophenylhydrazine obtained from it by hydrolysis since, when o-nitrophenylhydrazine was added to the boiling mixture of the hydrazone (II; R =R' = Ph) and acetic and hydrochloric acids, the yield of the osazone was increased.



Further, o-nitroaniline was isolated from the mother-liquors of the reaction. This suggested that the oxidation of deoxybenzoin o-nitrophenylhydrazone to a derivative of benzil involved the corresponding reduction of o-nitrophenylhydrazine to o-nitroaniline, as occurs during the formation of the osazones of sugars.^{1,2} A probable mechanism (suggested to the authors by Dr. M. J. T. Robinson) is that the tautomeric form (IV) of the hydrazone (II; R = R' = Ph) is first converted into the vinylamine (V) by a rearrangement which is related to an o-semidine rearrangement ³ in the same way that the first stage

¹ Percival, "Advances in Carbohydrate Chemistry," Academic Press Inc., New York, 1948, Vol. III, p. 23.
² Braude and Forbes, J., 1951, 1762.
³ Cf. Hughes and Ingold, Quart. Reviews, 1952, 6, 34.

of the accepted mechanism of the Fischer indole synthesis 4,5 is related to an o-benzidine rearrangement. Hydrolysis of the vinylamine (V) would give the desylamine (VI) from which benzil di-o-nitrophenylhydrazone would be obtained by reaction with o-nitrophenylhydrazine,⁶ either directly or by the prior formation of benzoin by further hydrolysis. In these later reactions, o-nitrophenylhydrazine would be reduced to o-nitroaniline, possibly



by the mechanism for osazone formation suggested by Braude and Forbes.² Robinson and Robinson⁴ have previously pointed out that o-semidine rearrangements could occur during indole syntheses, and Dalgliesh and Mann 7 have observed the inhibiting effect of an ortho-substituent on certain Fischer indole reactions.

The experiments described above suggested that o-nitrophenylhydrazones resistant to the Fischer synthesis might give osazones under similar conditions. This was found to be the case with acenaphthenone o-nitrophenylhydrazone which was known not to undergo cyclisation to an indole 8 and, when acenaphthenone was heated with o-nitrophenylhydrazine and acetic and hydrochloric acid, acenaphthenequinone di-o-nitrophenylhydrazone was obtained.

Contrary to previous experience,⁹ coumaranone o-nitrophenylhydrazone was readily converted into the corresponding indole.

It was found that, while indan-2-one o-nitrophenylhydrazone cyclised to 7-nitroindeno-(2': 3'-2: 3) indole, the o-nitrophenylhydrazones of indan-1-one and propiophenone gave neither the indole nor the osazone. Further, Schofield and Theobald 10 have made 2-methyl-7-nitro-3-phenylindole from benzyl methyl ketone o-nitrophenylhydrazone. Now, since by the Fischer synthesis the o-nitrophenylhydrazones of simple aliphatic and alicyclic ketones readily provide 7-nitroindoles,¹¹ these results suggest that the indolisation of an o-nitrophenylhydrazone (II; R = alkyl or aryl) will occur if R' is aliphatic, but will not proceed if R' is aromatic. The example of coumaranone o-nitrophenylhydrazone shows, however, that this is not invariably the case.

In the reaction between 9-phenanthrol and o-nitrophenylhydrazine in acetic and hydrochloric acid, both indolisation and oxidation took place, leading to the formation of a mixture of 7'-nitroindolo(2': 3'-9: 10) phenanthrene and phenanthraquinone o-nitrophenylhydrazone, o-nitroaniline being obtained at the same time. Since 9-phenanthrol is known to undergo aerial oxidation to phenanthraquinone,¹² it is possible that some oxidation occurred in this way during this reaction with o-nitrophenylhydrazine.

EXPERIMENTAL

Benzil Di-o-nitrophenylhydrazone.--(a) Deoxybenzoin o-nitrophenylhydrazone 13 (1.1 g.), o-nitrophenylhydrazine (1.5 g.), acetic acid (20 c.c.), and concentrated hydrochloric acid (10 c.c.) were refluxed together for 11 hr., and the precipitate (0.7 g., 44%) of benzil di-o-nitrophenylhydrazone was collected and washed with acetic acid. It crystallised from anisole in red needles,

- ⁴ Robinson and Robinson, J., 1918, 113, 639.
 ⁵ Allen and Wilson, J. Amer. Chem. Soc., 1943, 65, 611.
 ⁶ Cf. Wolf, Chem. Ber., 1953, 86, 840.
- Dalgliesh and Mann, *J.*, 1947, 653. Bannister and Plant, *J.*, 1948, 1247. Cawley and Plant, *J.*, 1938, 1214.

- ¹⁰ Schofield and Theobald, J., 1950, 1255.
 ¹¹ Perkin and Riley, J., 1923, **123**, 2399; Plant, J., 1929, 2493; Bauer and Strauss, Ber., 1932, **65**, 308; Hughes, Lions, and Ritchie, J. Proc. Roy. Soc. New South Wales, 1938, 72, 209.
 ¹² Japp and Findlay, J., 1897, 71, 1115.
 ¹³ Fennell and Plant, J., 1932, 2872.

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m. p. 260—263°, not depressed by admixture with an authentic sample (see below) (Found : C, 65·1; H, 4·5. $C_{26}H_{20}O_4N_6$ requires C, 65·0; H, 4·2%). The acid filtrates from the Fischer reaction were diluted with water (150 c.c.), rendered alkaline with sodium hydroxide (40 g.), and, after addition of sodium sulphate (10 g.), were steam-distilled until the distillate, at first yellow, was colourless. From the latter (1200 c.c.) *o*-nitroaniline (0·4 g.), m. p. 71—73°, identified by mixed m. p., was isolated with ether.

(b) Benzil (0.7 g.) and o-nitrophenylhydrazine (1 g.) were heated together at 150° for $\frac{1}{2}$ hr. The solid was washed with acetic acid and crystallised first from benzene and then from anisole, to give red needles, m. p. 261-263°, of benzil di-o-nitrophenylhydrazone (Found : C, 65.0; H, 4.4; N, 17.3. C₂₆H₂₀O₄N₆ requires C, 65.0; H, 4.2; N, 17.5%), identical with the above.

The compound, m. p. 137°, reported by Guha and De¹⁴ as benzil di-o-nitrophenylhydrazone is possibly the mono-o-nitrophenylhydrazone, as it was formed by heating equimolecular proportions of benzil and o-nitrophenylhydrazine in acetic acid, but attempts to repeat the preparation led to crude material, m. p. 125—130°, which could not be purified.

Acenaphthenequinone Di-o-nitrophenylhydrazone.—(a) Acenaphthenone (1 g.), o-nitrophenylhydrazine (3 g.), acetic acid (100 c.c.), and concentrated hydrochloric acid (20 c.c.) were refluxed together for $3\frac{1}{2}$ hr. The precipitate crystallised from anisole, giving crimson microcrystalline acenaphthenequinone di-o-nitrophenylhydrazone (0.7 g.), m. p. 297—300° (decomp.), raised to 299—301° by further crystallisation from anisole, and not depressed by admixture with an authentic sample (see below) (Found: C, 63.9; H, 3.7. $C_{24}H_{16}O_4N_6$ requires C, 63.7; H, 3.5%).

(b) Acenaphthenequinone 15 (0.9 g.) and o-nitrophenylhydrazine (1.5 g.) were heated together for 50 min. at 140°. The solid crystallised from anisole as crimson, microcrystalline needles (0.9 g.), m. p. 299–301° (decomp.), of acenaphthenequinone di-o-nitrophenylhydrazone.

7-Nitrocoumarono(3': 2'-2: 3)indole.—Coumaranone o-nitrophenylhydrazone \circ (1 g.) was refluxed with acetic acid (9 c.c.) and concentrated hydrochloric acid (5 c.c.) for 40 min. The product (0.5 g.) was collected and crystallised from acetic acid, giving the *indole* as red needles, m. p. 248—251° (Found: C, 67.0; H, 3.3. C₁₄H₈O₃N₂ requires C, 66.7; H, 3.2%).

o-Nitrophenylhydrazones.—Indan-2-one (0.6 g.) and o-nitrophenylhydrazine (0.7 g.) were heated together for 15 min. at 120°. Crystallisation from benzene gave *indan-2-one* o-*nitrophenylhydrazone* (0.7 g.) as orange needles, m. p. 173—176°, which became brown in air (Found : C, 67.1; H, 4.8. $C_{15}H_{13}O_2N_3$ requires C, 67.4; H, 4.9%). Prepared in a similar way, *indan-1-one* o-*nitrophenylhydrazone* separated from benzene in red needles, m. p. 212—214° (Found : C, 67.8; H, 5.0%).

7-Nitroindeno(2': 3'-2: 3)indole.—After indan-2-one o-nitrophenylhydrazone (0.6 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (6 c.c.) had been refluxed together for $1\frac{1}{2}$ hr., the solid (0.2 g.) which crystallised was purified by passing it, in benzene, through a short column of alumina. The product, obtained by evaporation, separated first from anisole and then from benzene, giving the *indole* as red needles, m. p. 234—237° (Found : C, 71.5; H, 4.0. $C_{15}H_{10}O_2N_2$ requires C, 72.0; H, 4.0%).

7'-Nitroindolo(2': 3'-9: 10)phenanthrene.—9-Phenanthrol ¹⁶ (7 g.), o-nitrophenylhydrazine (15 g.), acetic acid (130 c.c.), and concentrated hydrochloric acid (100 c.c.) were boiled together under reflux for 3 hr. The precipitate was separated from the acid filtrates, washed with hot water, and dried. This crude mixture (8.5 g.; m. p. 205—213°) was crystallised twice from large quantities of ethyl acetate, and then from pyridine to give phenanthraquinone o-nitrophenylhydrazone (1.3 g.) as red needles, m. p. 247—249°, identical (mixed m. p.) with an authentic sample (see below). The mother-liquors from these crystallisations were evaporated and a portion (1.75 g.) of the residue, dissolved in benzene (1 l.), was passed through alumina (200 g.). Elution with benzene caused separation into an upper red band and a lower orange one. The latter was removed with benzene (6 l.), 7'-nitroindolo(2': 3'-9: 10)phenanthrene (0.9 g.), m. p. 255—257°, being obtained by evaporation. It separated from pyridine in orange needles, m. p. 258—260° (Found: C, 77·1; H, 3·9; N, 8·7. C₂₀H₁₂O₂N₂ requires C, 76·9; H, 3·8; N, 9·0%). Elution of the remaining red band with ethanol-benzene provided impure phenanthra-quinone o-nitro-

o-Nitroaniline (0.8 g.; m. p. $69-72^{\circ}$) was isolated from the acid filtrates in the manner described above.

Phenanthraquinone o-nitrophenylhydrazone¹⁴ was prepared by treating phenanthraquinone ¹⁴ Guha and De, J. Indian Chem. Soc., 1926, 3, 41.

- ¹⁵ Org. Synth., 1944, 24, 1.
- ¹⁶ Fieser, Jacobsen, and Price, J. Amer. Chem. Soc., 1936, 58, 2163.

(0.4 g.) in boiling acetic acid (10 c.c.) with o-nitrophenylhydrazine (0.3 g.). The product (0.5 g.) separated immediately and crystallised from pyridine in red needles, m. p. 246–249° (Found : C, 69.8; H, 4.0; N, 12.3. Calc. for $C_{20}H_{13}O_3N_3$: C, 70.0; H, 3.8; N, 12.3%).

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [Received, July 18th, 1956.]