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The Reaction between Thiohydrazides and Ethyl Benzoylchloroacetate Part II *. Formation of Ethoxycarbonylmethyl Thiolcarboxylate Benzoylhydrazones

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The reaction between thiohydrazides and ethyl benzoylchloroacetate in alkaline medium has been shown to lead to benzoylhydrazones of S-ethoxycarbonylmethyl thiolcarboxylates. The benzoylhydrazones, which are derived from thiohydrazides with a free amino group, are readily cyclized to 1,3,4-oxadiazoles. This reaction has been shown to be subject to specific hydrogen ion catalysis. The derivatives of N-benzyl substituted thiohydrazides are more stable but can undergo hydrolysis in hot acid medium to 1,2-diacyl-1-benzylhydrazines. The ultraviolet spectra of the benzoylhydrazones are discussed in relation to a steric inhibition of resonance.

In Part I of this series it has been shown that thiohydrazides and ethyl benzoylchloroacetate react in the presence of slightly less than one equivalent of sodium ethoxide to form ultimately pyrazoles and sulphur. If, however, reactions were performed in the presence of more than one equivalent of base, a quite different course was observed. Thus, when thiobenzhydrazide and ethyl benzoylchloroacetate reacted in the presence of a little more than one equivalent of sodium ethoxide, a good yield was obtained of a product that had the empirical formula $C_{18}H_{18}N_2O_3S$ and was therefore isomeric with the compound (II b) described in Part I. However, the new compound could not be made to split off water and sulphur and form a pyrazole. Its infrared spectrum showed a strong band at 1736 cm^{-1}, corresponding to an ester carbonyl group, and another at 1669 cm^{-1}, corresponding to an amide carbonyl group. Furthermore, the compound split off ethyl mercaptoacetate and gave 2,5-diphenyl-1,3,4-oxadiazole (III b) when it was heated above its melting point. This reaction was also accomplished in solution. These observations can all be explained by the reactions A and B:

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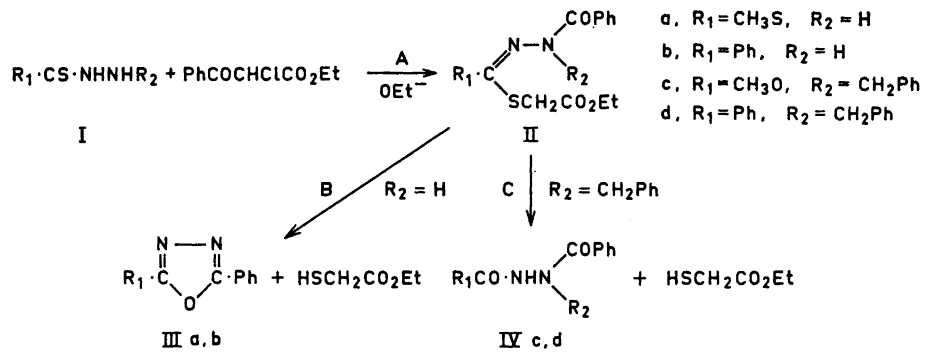


I II III a, b IV c, d

An unambiguous synthesis of the compound (II b) was achieved by reaction between 2-benzoylthiobenzhydrazide and ethyl chloroacetate in the presence of one equivalent of alkali:

$$\mathrm{Ph{\cdot}CS{\cdot}NHNH{\cdot}COPh} + \mathrm{ClCH_2CO_2Et} \xrightarrow{\mathrm{OH^-}} \text{(II b)}$$

The product of this reaction was found to be identical with the one obtained in reaction A.

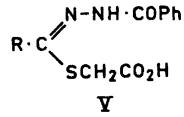
The formation of the benzoylhydrazones (II), involving cleavage of the benzoylacetate moiety, probably proceeds with hydroxy-dihydrothiadiazines (see Part I) as intermediates, because when ethyl 2,5-diphenyl-5-hydroxy-Δ^2-dihydro-1,3,4-thiadiazine-6-carboxylate was treated with sodium ethoxide or triethylamine, high yields of (IIb) were obtained. It may be worth mentioning that van Alpen [1] has observed that ethyl benzoylchloroacetate reacts with an excess of phenylhydrazine in ether to form 1-phenylbenzhydrazide. In reaction A sodium ethoxide, sodium hydroxide, and triethylamine were found equally efficient.

The reaction was also carried out with methyl dithiocarbazate (I b), methyl 3-benzylthioncarbazate (I c), and 2-benzylthiobenzhydrazide (for numbering see Ref.[2] p. 794) (I d). With the thioncarbazate (I c) reaction A occurred also when less than one equivalent of alkali had been added. This difference in behaviour can probably be explained by the low acid strength of the thioncarbazates as compared with the other thiohydrazides used in this investigation [2]. Reaction A seems to require a critical concentration of base, and with a weak acid this concentration is reached before one equivalent of the base has been added. In the absence of alkali no reaction occurred, and consequently no pyrazole could be obtained from this thiohydrazide.

On the other hand, 2-phenylthiobenzhydrazide did not react according to path A even in the presence of a substantial excess of base. Only ethyl 1,3,5-triphenylpyrazole-4-carboxylate was obtained in good yield (see Part I), and this is probably due to the low nucleophilic reactivity of the 2-nitrogen atom in this thiohydrazide.

The formation of oxadiazoles (reaction B) is restricted to benzoylhydrazones (II) with a free NH group. Thus methyl dithiocarbazate (I a) gave a non-crystalline product with ethyl benzoylchloroacetate and excess base. On heating, this product gave ethyl mercaptoacetate and 2-methythio-5-phenyl-

1,3,4-oxadiazole (III a), identical with a product prepared according to Hoggarth [3]. The non-crystalline product is probably S-methyl S'-ethoxycarbonylmethyl dithiolcarbonate benzoylhydrazone (II a). The corresponding carboxylic acid (V a) was obtained by reaction between sodium chloroacetate



V

a. R = CH_3S

b. R = Ph

and methyl 3-benzoyldithiocarbazate. It was crystalline and was shown to react in an analogous way, by formation of methyithio-phenyloxadiazole and mercaptoacetic acid. The acid (V b) was prepared in a similar way. Generally, the acids were more easily decomposed than the esters.

In the preliminary investigations, reaction B was found to be more rapid in acid than in neutral solution, and since the ultra-violet spectrum of (II b) was sufficiently different from that of (III b) (Fig. 1), a kinetic investigation was undertaken by following the change of absorption at 3100 Å. The spectra of the reaction mixture at different times passed through two isosbestic points, which showed that only two absorbing species were present. The rate of reaction was determined at 25° in water containing 1 % of ethanol and hydrochloric acid in the concentrations 0.05, 0.2, 0.3, 0.4, and 0.5. The initial concentration of (II b) was 5×10^{-5}. The rate was found to be first order in (II b) (Fig. 2), and the rate constants were proportional to the hydrogen ion concentrations (Fig. 3). Acetic acid and monochloroacetic acid in 0.5 M concen-

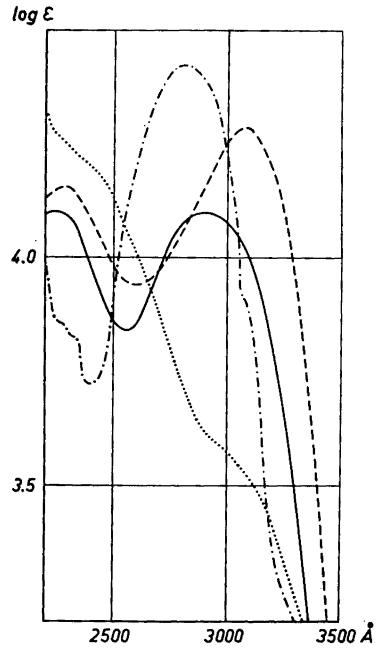


Fig. 1. Ultraviolet absorption spectra of the compounds (V a, ———), (II b, - - - -), (II d, ...), and (III b, —·—·—·—·—·—) in absolute ethanol.

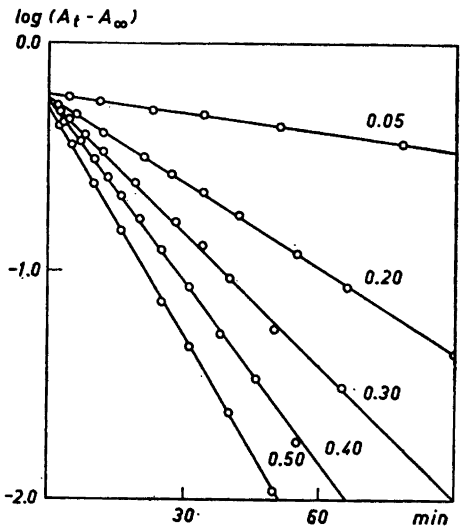


Fig. 2. Plots of the logarithm of the absorbance of remaining (II b) *versus* time at different concentrations of hydrochloric acid.

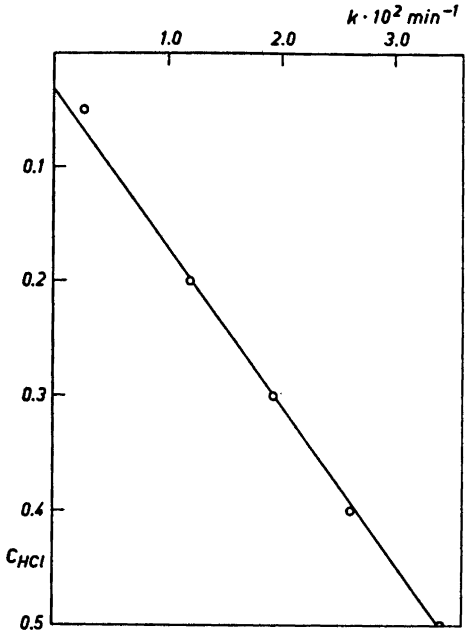


Fig. 3. Plot of rate constants *versus* concentration of hydrochloric acid.

tration were without noticeable catalytic effect, which indicates a case of specific hydrogen ion catalysis.

It can safely be assumed that the reactive species is a conjugate acid of (II b). Application of the law of mass action gives:

$$C_{\text{acid}} = \frac{f \cdot C \cdot a_{H^+}}{K_a \cdot f^+ + f \cdot a_{H^+}}$$

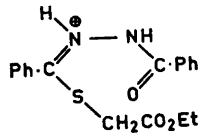
and therefore

$$k = k_o \frac{f \cdot a_{H^+}}{K_a \cdot f^+ + f \cdot a_{H^+}}$$

C_{acid} = concentration of the conjugate acid of (II b)
f = activity coefficient of (II b)
f^+ = activity coefficient of the conjugate acid
C = concentration of (II b) + conjugate acid
K_a = ionization constant of the conjugate acid of (II b)
k = the overall rate constant
k_o = the rate constant for the conjugate acid transformation

Since the activity coefficients cannot depart considerably from unity, proportionality between the rate constants and the hydrogen ion concentrations

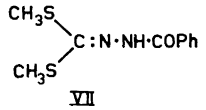
implies that K_a is considerably greater than a_{H^+}. Therefore, the activating protonation must occur at a very weakly basic site. Since the spectrum of (II b) is not very much changed by acidification, it is quite possible that the activating protonation is also the dominating one, as has been tacitly assumed in the above treatment. It can be assumed that the structure of the conjugate acid is (VI). The reaction B probably proceeds *via* a nucleophilic attack of the carbonyl oxygen atom on the carbon atom carrying the ethoxycarbonylmethylthio group, and this attack will be facilitated by the polarization of the C=N bond caused by the protonation.



VI

The reaction B is also accelerated by bases, but the effect is much smaller and has not been subjected to a kinetic analysis. Probably the effect is due to ionization of the NH—CO group with enhancement of the nucleophilic activity of the carbonyl oxygen atom.

The reaction B is analogous to a reaction, which has been described by Hoggarth [4], where 1-benzoyl-S-methyl-isothiosemicarbazide is decomposed on heating with formation of amino-phenyloxadiazole and methanethiol. However, the rather similar S,S′-dimethyl dithiolcarbonate benzoylhydrazone (VII) did not show the same reactivity. It could be heated to 270° without significant decomposition. In hot acid solution it was slowly hydrolyzed with formation of benzhydrazide. The oxadiazole formation seems to depend on the presence of a labile group on the carbon atom which is attacked by the carbonyl oxygen atom. The facile elimination of the mercaptoacetic acid group has been widely recognized and employed in reactions which involve nucleophilic attacks on thiocarboxylic ester derivatives.



VII

The reaction B cannot be performed with the benzoylhydrazones (II c) and (II d). When they are heated in acid solution, they split off ethyl mercaptoacetate more slowly than the unsubstituted analogues (II a) and (II b) and form 1,2-diacylbenzylhydrazines (IV), reaction C. The structure of these compounds is demonstrated by the appearance of two strong carbonyl bands in their infrared spectra and by the identity of (IV d) with the dibenzoylbenzylhydrazine described by Stollé and Benrath [5].

The ultraviolet spectrum of (II b) has a maximum at 3080 Å with log ε: 4.28, and (V a) has one at 2910 Å with log ε: 4.09 (Fig. 1). These maxima are probably to be ascribed to $\pi \rightarrow \pi^*$ transitions involving the whole conjugated system. The bathochromic and hyperchromic shifts when a methylthio group is replaced by a phenyl group are in harmony with this assignation.

The benzyl analogue (II d) shows only an inflexion with much reduced intensity in the near ultraviolet region. This must be ascribed to a steric inhibition of resonance, since an inspection of a molecular model reveals that the two halves of the molecule, joined by the N—N bond, cannot be coplanar but must be considerably twisted. For (V a) and (II b) coplanarity is possible.

EXPERIMENTAL

S-Ethoxycarbonylmethyl thiolbenzoate benzoylhydrazone (II b). Thiobenzhydrazide (I b, 4.5 g) was dissolved in N sodium ethoxide (31 ml), and ethyl benzoylchloroacetate (6.9 g) in absolute ethanol (20 ml) was added. Sodium chloride started to separate at once, and on the following day water (100 ml) was added. A solid, pale yellow product was obtained (9.0 g, 87 % yield), which crystallized from a mixture of chloroform and light petroleum (b.p. 40—60°) as colourless plates, m.p. 104—104.5°. (Found: C 63.1; H 5.36; N 8.29; S 9.31. $C_{18}H_{18}N_2O_3S$ (342.40) requires C 63.1; H 5.30; N 8.18; S 9.36).

Carboxymethyl dithiobenzoate [6] (10.5 g) in N NaOH (50 ml) was added to a solution of benzhydrazide (7.0 g) in ethanol (30 ml). The red colour faded rapidly, and on the following day pale yellow, rhombic plates had separated (11.0 g, 86 % yield), m.p. 141—142° (decomp.). Holmberg [7] reports m.p. 142—144° (decomp.) for 1-benzoylthiobenzhydrazide.

This compound (2.6 g) was dissolved in N NaOH (10 ml), and ethyl chloroacetate (1.4 g) in ethanol (20 ml) was added. An oil was deposited, which solidified to a colourless crystalline product (3.2 g, 94 % yield), which crystallized from chloroform-light petroleum (b.p. 40—60°) as colourless plates, m.p. 104—104.5°, identical with the benzoylhydrazone (II b) described above.

Ethyl 2,5-diphenyl-5-hydroxy-Δ^2-dihydro-1,3,4-thiadiazine-6-carboxylate (Part 1), 0.68 g) dissolved rapidly in 0.2 N sodium ethoxide (5 ml). After one hour 0.1 N aqueous acetic acid (10 ml) was added, and a precipitate of colourless plates was formed (0.63 g, 92 % yield), m.p. 102—103°, consisting of the benzoylhydrazone (IIb). When the experiment was repeated with a solution of triethylamine (1 ml) in absolute ethanol (5 ml) the starting material dissolved slowly, and when the solution was evaporated, a quantitative yield of (IIb) was obtained, m.p. 103—104°.

This hydrazone (6.8 g) was kept at 150° for 10 min. The resulting semi-solid mass was extracted with light petroleum (40—60°) and filtered. The solution was distilled, and after the petroleum had been driven off a fraction was obtained at 158—162°, consisting of ethyl mercaptoacetate according to its infrared spectrum and equivalent weight. (Found: equiv.wt. 122 (iodine) and 122 (hydrolysis). $C_4H_8O_2S$ requires equiv.wt. 120).

The undissolved solid material (3.8 g, 86 % yield) crystallized from ethanol as colourless plates, m.p. 139—140°, consisting of 2,5-diphenyl-1,3,4-oxadiazole (III b) according to analysis. (Found: C 75.4; H 4.54; N 12.7; M 233 (Rast).
$C_{14}H_{10}N_2O$ (222.24) requires C 75.7; H 4.54; N 12.6).

The identity of the product was demonstrated by comparison with an authentic specimen, prepared by oxidation of benzaldehyde benzoylhydrazone with chlorine in carbon tetrachloride solution [8]. The two products had identical infrared spectra.

S-Carboxymethyl thiolbenzoate benzoylhydrazone (V b). 2-Benzoylthiobenzhydrazide (2.6 g) was dissolved in N NaOH (10 ml), and a solution of bromoacetic acid (2.0 g) in N NaOH (14.4 ml) was added. On the following day the solution was cooled to —5°, and 5 N HCl (4 ml) was carefully added. Colourless prisms separated (2.5 g, 75 % yield), m.p. 63—64° (in a sealed tube). Attempts to recrystallize the product led to decomposition, and the same result was achieved when the product was dissolved in N NaOH and acidified at room temperature. According to analysis, the crude product was a fairly pure monohydrate of the hydrazone (V b). (Found: C 57.6; H 5.03; N 8.51; S 9.49. $C_{16}H_{14}N_2O_3S$, H_2O (332.37) requires C 57.8; H 4.85; N 8.43; S 9.65). Working up of the decomposed material gave a high yield of oxadiazole.

S-Ethoxycarbonylmethyl S'-methyl dithiolcarbonate benzoylhydrazone (II a). Methyl dithiocarbazate (I a, 2.5 g) was dissolved in N sodium ethoxide (21 ml) and ethyl benzoylchloroacetate (4.6 g) in absolute ethanol (20 ml) was added. On the following day the sodium chloride was filtered off, and the solution was evaporated *in vacuo* at 20°. The

remaining oil could not be induced to crystallize. It was therefore refluxed for 10 min in ethanol (20 ml) with 5 N HCl (5 ml). A paper chromatogram indicated that all starting material had been consumed. Ethanol was distilled off (15 ml), and water (20 ml) was added. The separated oil was taken up in 15 ml of chloroform, and the solution was extracted with N NaOH (20 ml) followed by water, and was then dried. The chloroform was distilled off, and the residue was distilled at 2 mm from a semimicro Claisen flask. A colourless liquid distilled at 156—158° (1.3 g, 34 % yield), which crystallized when seeded with an authentic specimen of 2-methylthio-5-phenyl-1,3,4-oxadiazole (III a) [3]. Both preparations had identical infrared spectra, and the same m.p. 36—37°, undepressed on admixture.

Methyl 3-benzoyldithiocarbazate [3] (2.3 g) in N NaOH (10 ml) was added to a solution of ethyl chloroacetate (1.6 g) in ethanol (20 ml). On the following day water (50 ml) was added to precipitate the product, and as in the preceding experiment it could not be obtained crystalline. It was then decomposed as above with much the same result.

S-Carboxymethyl S'-methyl dithiolcarbonate benzoylhydrazone (V a). Methyl 3-benzoyldithiocarbazate (2.3 g) was dissolved in N NaOH (10 ml), and bromoacetic acid (2.0 g) in N NaOH (14.5 ml) was added. On the following day 5 N HCl (4 ml) was added, and a solid product was obtained (2.6 g, 92 % yield), which crystallized from 50 % aqueous ethanol as colourless rods, m.p. 119—120°. (Found: C 46.4; H 4.37; N 9.78; S 22.5; equiv.wt. 287. $C_{11}H_{12}N_2O_3S_2$ (284.35) requires C 46.5; H 4.26; N 9.85; S 22.5; equiv.wt. 284).

The formation of oxadiazole from this compound was far slower than from the phenyl analogue (Vb b). Thirty minutes at 70° in 0.02 N HCl in ethanol were required for complete decomposition. When the acid (2.8 g) was refluxed in N HCl in 70 % aqueous ethanol for 10 min and the ethanol was distilled off, an oil was obtained, which was extracted with N NaOH (15 ml) to remove the mercaptoacetic acid. It was then seeded with methylthio-phenyloxadiazole and crystallized (1.8 g, 94 % yield), m.p. and mixed m.p. 35—36°. The infrared spectra of the two compounds were identical.

In another experiment 2.8 g of the acid (Vb a) was heated to 150° for 10 min in a semimicro Claisen flask. The residue was then distilled, and a fraction was obtained at 100° and 16 mm (0.44 g) which consisted of mercaptoacetic acid, according to its infrared spectrum and equivalent weight. (Found: 92.5 (iodine) and 93.2 (NaOH). $C_2H_4O_2S$ requires equiv.wt. 92.1). The residue in the flask would not give a pure fraction of the oxadiazole, but the distillate obtained at 2 mm and between 130° and 170° was extracted with N NaOH (10 ml) and then gave a crystalline product (1.5 g, 78 % yield), identified as methylthio-phenyloxadiazole.

Methyl S-ethoxycarbonylmethyl thiolcarbonate N-benzyl-N-benzoylhydrazone (II c) and 1-benzyl-1-benzoyl-2-methoxycarbonylhydrazine (IV c). Methyl 3-benzylthioncarbazate [2] (I c, 2.0 g) was dissolved in N sodium ethoxide (9.5 ml, 0.95 equiv.), and ethyl benzoylchloroacetate (2.3 g) in absolute ethanol (20 ml) was added. Sodium chloride separated at once, and on the following day the filtered solution was evaporated to dryness. The residue could not be induced to crystallize. It was then dissolved in ethanol (10 ml) and 5 N HCl (3 ml) and refluxed for 5 h. The ethanol was distilled off, and the aqueous solution, on cooling, deposited colourless prisms (2.0 g, 70 % yield), which crystallized from ethanol as colourless hairs, m.p. 135—136°, consisting of 1-benzyl-1-benzoyl-2-methoxycarbonylhydrazine (IV c) according to analysis. (Found: C 67.5; H 5.61; N 9.80. $C_{16}H_{16}N_2O_3$ (284.31) requires C 67.6; H 5.67; N 9.86). ν_{CO}: 1733 cm^{-1} and 1634 cm^{-1} in KBr.

S-Ethoxycarbonylmethyl thiolbenzoate N-benzyl-N-benzoylhydrazone (II d) and 1,2-dibenzoyl-benzylhydrazine (IV d). 2-Benzylthiobenzhydrazide [2] (I d, 4.9 g) was dissolved in N sodium ethoxide (21 ml), and ethyl benzoylchloroacetate (4.6 g) in absolute ethanol (20 ml) was added. Sodium chloride separated at once, and on the following day water (50 ml) was added to the filtered solution. A colourless oil was formed, which crystallized on standing. The product (7.5 g, 87 % yield) crystallized from methanol as colourless rods, m.p. 86—87°. (Found: C 69.1; H 5.66; N 6.68; S 7.42. $C_{25}H_{24}N_2O_3S$ (432.52) requires C 69.4; H 5.59; N 6.48; S 7.41). ν_{CO}: 1732 cm^{-1} and 1645 cm^{-1} in KBr.

This product (4.3 g) was refluxed for 48 h in ethanol (20 ml) and 5 N HCl (5 ml). The progress of the reaction could be followed by paper chromatography [9], and after 24 h an appreciable quantity of the starting material remained. After 48 h only one spot corresponding to the product could be observed. The spots were developed by photography in UV light, so ethyl mercaptoacetate did not appear. After cooling, the reaction mixture deposited colourless prisms (2.6 g, 79 % yield), which crystallized from ethanol

as colourless rods, m.p. 150–151°. (Found: C 76.1; H 5.42; N 8.61. $C_{21}H_{18}N_2O_2$ (330.37) requires C 76.3; H 5.49; N 8.48). For this compound Stollé and Benrath [5] report m.p. 152°. Their preparation was repeated, and the two products gave identical melting points and an undepressed mixed melting point.

Acid hydrolysis of S,S'-dimethyl dithiolcarbonate benzoylhydrazone [10] *(VII).* The benzoylhydrazone (VII, 2.4 g) was refluxed for 24 h with ethanol (15 ml) and 5 N HCl (5 ml). A smell of methanethiol could be noticed, and when the reaction mixture was diluted with water (10 ml), only an insignificant cloudiness appeared. Benzaldehyde (1.2 g) in ethanol (5 ml) was added, and a precipitate of colourless rods was formed (2.0 g), m.p. 209–210°, not depressed on admixture with pure benzaldehyde benzoylhydrazone [8].

The ultraviolet spectra were recorded with a Beckman DU spectrophotometer in absolute ethanol solution. The infrared spectra for identification were recorded on a Perkin-Elmer "Infracord" spectrophotometer. Where wave numbers have been given, the spectra have been recorded with a Perkin-Elmer model 221 instrument.

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REFERENCES

1. van Alpen, J. *Rec. Trav. Chim.* **65** (1946) 105.
2. Forsgren, B. and Sandström, J. *Acta Chem. Scand.* **14** (1960) 789.
3. Hoggarth, E. *J. Chem. Soc.* **1952** 4811.
4. Hoggarth, E. *J. Chem. Soc.* **1949** 1918.
5. Stollé, R. and Benrath, A. *J. prakt. Chem.* [2] **70** (1904) 278.
6. Holmberg, B. *Arkiv Kemi, Mineral. Geol.* **17 A** (1944) No. 23.
7. Holmberg, B. *Arkiv Kemi, Mineral. Geol.* **25 A** (1947) No. 18.
8. Stollé, R. *J. prakt. Chem.* [2] **85** (1912) 386.
9. Wickberg, B. *Acta Chem. Scand.* **12** (1958) 615.
10. Busch, M. and Starke, M. *J. prakt. Chem.* [2] **93** (1916) 49.

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