330. *The Reaction of α-Bromobenzyl Cyanide with Ethyl Xanthamidate (Thioncarbamate).*

By W. Davies and J. A. Maclaren.

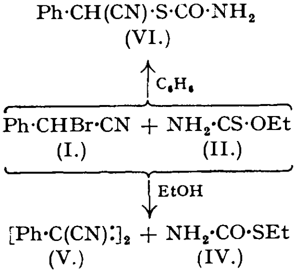
Reaction of α-bromobenzyl cyanide and ethyl xanthamidate, NH_2•CS•OEt, in benzene or without a solvent yields α-carbamylthiobenzyl cyanide (VI), whereas in alcohol the ethyl xanthamidate is isomerized to ethyl thiolcarbamate (IV). The reaction in benzene in the presence of sodium acetate gives 2 : 5-di-(2-ethoxy-5-phenyl-4-thiazolylimino)-3 : 4-diphenylpyrroline (VIII), a brilliant red pigment, of which the structure has been proved by hydrolysis. The synthesis of similar pigments also occurs when methyl and *n*-butyl xanthamidates are used.

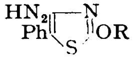
The interaction of α-bromobenzyl cyanide (I) and thiourea has been shown to yield the hydrobromide of 2 : 4-diamino-5-phenylthiazole (*A*) (Davies, Maclaren, and Wilkinson, *J.*, 1950, 3491). Attempts have now been made to extend this reaction by using ethyl xanthamidate (ethyl thioncarbamate) (II) instead of thiourea, and thus to obtain 4-amino-2-ethoxy-5-phenylthiazole (III; R = Et). However, the interaction of (I) and (II) was found to follow three different courses according to the experimental conditions.

In alcoholic solution, (I) and (II) afford ethyl thiolcarbamate (IV), diphenylmaleidinitrile (V), and some ammonium bromide. Various reagents are known to isomerize (II) to (IV); and, as Knorr (*Ber.*, 1917, **50**, 767) and Bettschart and Bystrzicki (*Helv. Chim. Acta*, 1919, **2**, 118) have shown, a trace of an alkyl halide can bring about rearrangements of this type. Hence (I) is probably the effective agent in this case. It is known that α-bromobenzyl cyanide gives (V) when treated with weak bases, when heated, or when kept for a long time (Kinnear, *J. Soc. Chem. Ind.*, 1948, **67**, 35), and the ammonium bromide must result from partial hydrolysis.

When ethyl xanthamidate and α-bromobenzyl cyanide are heated together alone, or in benzene solution, a compound $C_9H_8ON_2S$ (m. p. 105—106°) is formed. Since it cannot be desulphurized by the usual reagents, it might be regarded as either α-carbamylthiobenzyl cyanide (VI) or 2-hydroxy-4-amino-5-phenylthiazole (III; R = H). From the ready fissions which it undergoes, the acyclic structure (VI) seems to be correct. With mercuric chloride solution it gives the mercuric salt of α-mercaptobenzyl cyanide (VII). The derived free thiol has been described by Kretow and Pantschenko (*Chem. Zentr.*, 1930, I, 3551), but the details in the abstract are so vague that all our attempts to prepare this probably unstable compound have been unsuccessful. The above reaction of mercuric chloride, however, is now found to be general with thiolcarbamates and apparently proceeds thus :


(*A*.)


$$\begin{array}{c} Ph{\cdot}CH(CN){\cdot}S{\cdot}CO{\cdot}NH_2 \\ (VI.) \\ \uparrow C_6H_6 \\ Ph{\cdot}CHBr{\cdot}CN + NH_2{\cdot}CS{\cdot}OEt \\ (I.) \qquad (II.) \\ \downarrow EtOH \\ [Ph{\cdot}C(CN){:}]_2 + NH_2{\cdot}CO{\cdot}SEt \\ (V.) \qquad (IV.) \end{array}$$


(III.)

$Ph{\cdot}CH(SH){\cdot}CN$
(VII.)

$$2R{\cdot}S{\cdot}CO{\cdot}NH_2 + HgCl_2 \longrightarrow (R{\cdot}S)_2Hg + 2CO_2 + 2NH_4Cl$$

With aniline, the compound gives an unidentified thiol and *s*-diphenylurea; *p*-anisidine similarly gives *s*-di-(*p*-methoxyphenyl)urea. These are examples of a recognized general reaction (Blankenhorn, *J. pr. Chem.*, 1887, [ii], **16**, 375) :

$$R{\cdot}S{\cdot}CO{\cdot}NH_2 + 2R'{\cdot}NH_2 \longrightarrow (R'{\cdot}NH)_2CO + R{\cdot}SH + NH_3$$

Finally, the compound (m. p. 105—106°) is hydrolysed by alkaline solutions to the dinitrile (V), and this and the two previous reactions support the structure (VI) rather than (III). The observation that acid hydrolysis gives 2 : 4-dihydroxy-5-phenylthiazole (X) might seem to indicate structure (III; R = H), at least in acid solution. This assumption, however, is not essential since acid hydrolysis of α-thiocyano-esters and amides is known to give the corresponding 2 : 4-dihydroxythiazoles (*e.g.*, Wheeler and Barnes, *Amer. Chem. J.*, 1900, **24**, 80).

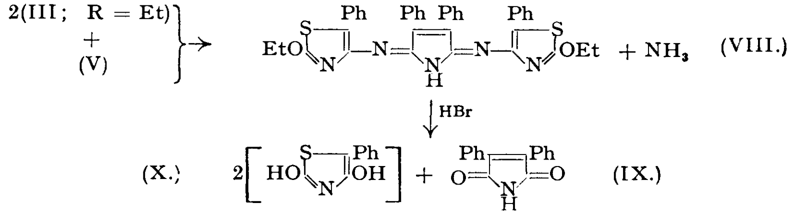
The formation of (V) on interaction of (VI) and alkali recalls its similar formation from α-bromobenzyl cyanide. There are other known instances where a potential anion (usually halogen) is removed as an alkali salt and an ethylenic compound formed; for example, ethyl α-bromophenylacetate with alkali gives diethyl diphenylmaleate (Ramart-Lucas and Hoch, *Ann. Chim.*, 1943, [x], **13**, 390), and similarly ethyl bromomalonate yields ethyl ethylenetetracarboxylate; also, in the benzyl chloride series, the nitro- and cyano-derivatives yield the corresponding disubstituted stilbenes (Weygand, " Organic Preparations ", Interscience Publ., New York, 1945, p. 417).

The absence of ring closure of the carbamylthiol (VI) is in contrast to the behaviour of the corresponding *iso*thiourea hydrobromide, which cannot be isolated since it is rapidly converted into the hydrobromide of 2 : 4-diamino-5-phenylthiazole (*A*) (Davies, Maclaren, and Wilkinson, *loc. cit.*). The weakly basic nature of the $S{\cdot}CO{\cdot}NH_2$ group in (VI) is in contrast to the strongly basic *iso*thiourea group and may be responsible for the lack of ring formation.

It seems likely that (VI) results by de-ethylation of the initially formed

$$Ph{\cdot}CH(CN){\cdot}S{\cdot}C({:}NH){\cdot}OEt$$

which, being a stronger base than (VI), might cyclize to form 4-amino-2-ethoxy-5-phenylthiazole (III; R = Et). Hantzsch (*Ber.*, 1927, **60**, 2537) has shown that, in the similar condensation of ethyl xanthamidate with chloroacetone, de-ethylation may be avoided by neutralizing the acid formed with potassium acetate. Accordingly ethyl xanthamidate and (I) have been condensed in the presence of sodium acetate, but instead of the expected primary reaction product (III; R = Et), much resinous matter and a bright red crystalline product $C_{34}H_{21}N_5S_2(OEt)_2$ were isolated. This compound is remarkably stable to heat and to the usual acid and alkaline reagents and hence probably has value as a pigment. It is, however, hydrolysed quantitatively by hydrobromic acid in acetic acid to yield ethyl and ammonium bromides, diphenylmaleinimide (IX), and 2 : 4-dihydroxy-5-phenylthiazole (X), the last two in the approximate molar ratio of 1 : 2. Hence 2 : 5-di-(2-ethoxy-5-phenyl-4-thiazolylimino)-3 : 4-diphenylpyrroline (VIII) is accepted as the structure of the pigment, in which the complete conjugation explains the intense colour. Methyl and *n*-butyl xanthamidates give the corresponding alkoxyhomologues of (VIII) as crystalline solids. The synthesis is probably due to the union of one molecule of (V) with two molecules of the intermediate (III; R = Et), thus:


(VIII.) (X.) (IX.)

The first step would be the addition of the amino- to the cyano-groups to form the diamidine derivative. This could then cyclize by loss of ammonia, just as succindiamidine is converted into succinimidine (Pinner, *Ber.*, 1883, **16**, 352). The mechanism, however, is obscure since no pigment is formed when (V) is heated with sodium acetate and salts of 2-amino- and 2 : 4-diamino-thiazole.

The scope of this synthesis has been shown by qualitative test-tube reactions. When samples of the reagents listed below are mixed with approximately equal amounts of α-bromobenzyl cyanide and sodium acetate and heated, the following colour changes (in parentheses) are observed: thiourea (red-brown); *N*-phenylthiourea (purple); benzamidine hydrochloride, 2-aminothiazole, 2-aminopyridine, and 2-4-diaminothiazole (red). Presumably the thioamide is first converted into the 4-aminothiazole derivative (Davies, Maclaren, Wilkinson, *loc. cit.*); it is seen that, with the exception of guanidine nitrate (which yields a brownish colour), all compounds containing the group ·C(:NH)·N: give an intensely coloured reaction mixture. Unfortunately in these cases the pigment has not been isolated, owing to the simultaneous formation of tar, which has defeated all attempts at recrystallization.

These polynuclear heterocyclic compounds (*e.g.*, VIII) are closely comparable with the tetra-arylazadipyrromethines (Rogers, *Nature*, 1943, **191**, 504; *J.*, 1943, 590). The structure of (VIII) also recalls that of the octaphenylporphyrazines, of which the metallic derivatives are made by heating (V) with various metals (Linstead and Cook, *J.*, 1937, 929).

EXPERIMENTAL.

Xanthamidates.—Ethyl xanthamidate was prepared by a method based on that of Holmberg (*Chem. Zentr.*, 1930, I, 1925): A solution of sodium hydroxide (20 g.) in water (300 ml.) was shaken with ethyl alcohol (100 ml.) and carbon disulphide (35 ml.), until dissolution was complete, and then left at room temperature for 1 hour. A solution of sodium hydroxide (20 g.) in water (200 ml.) was neutralized slowly with chloroacetic acid (47 g.) in an ice-bath, and the resulting solution was added to the sodium ethyl xanthate obtained above. After being kept overnight, this mixture was evaporated on the water-bath, at reduced pressure to 150 ml.; aqueous ammonia (30 ml.; *d* 0·88) was added and the mixture kept overnight. After neutralization with acetic acid, the mixture was extracted with ether (3 × 100 ml.), which after being dried (Na_2SO_4) and evaporated, yielded colourless plates (31 g., 58%), m. p. 38—40°, which were sufficiently pure for immediate use. This yield can be maintained even on five times this scale.

Methyl xanthamidate, prepared in the same manner, was obtained as plates, m. p. 42—45° (51%).

n-*Butyl xanthamidate*, obtained similarly, was distilled (b. p. 127—133°/15 mm.); it crystallized as plates, m. p. 16—19° (yield 45%) (Found: N, 10·6. $C_5H_{11}ONS$ requires N, 10·5%).

α-Bromobenzyl Cyanide.—The compound used was a redistilled approx. 60% solution of α-bromobenzyl cyanide in benzyl cyanide, prepared originally for chemical warfare purposes. That the benzyl cyanide took no part in the reactions was shown by repeating them on a small scale with pure α-chlorobenzyl cyanide, b. p. 117—118·5°/18 mm. (Hignett and Kay, *J. Soc. Chem. Ind.*, 1935, **54**, 98T, report b. p. 131·5°/13 mm.) (Found: N, 9·6. Calc. for C_8H_6NCl: N, 9·3%).

Interaction of α-Bromobenzyl Cyanide and Ethyl Xanthamidate.—Equimolar amounts of (I) and (II) in othyl alcohol were refluxed for 3 hours. The precipitate of ammonium bromide (0·05 mol.) was filtered off, and the filtrate on evaporation yielded a white crystalline solid and a brown oil. The solid, after being washed wth methyl alcohol and recrystallized from ethyl alcohol, melted at 162—163°, unchanged by mixing with authentic (V), prepared by Kinnear's method (*loc. cit.*). The brown oil solidified after being kept in a vacuum-desiccator and crystallized from benzene–light petroleum as plates, m. p. 102·5—103·5° (Found: N, 13·6. Calc. for C_3H_7ONS: N, 13·3%). This compound was identified as (IV) by a mixed m. p. with an authentic sample (Wheeler and Barnes, *Amer. Chem. J.*, 1899, **22**, 148). The reaction was the same when the above reaction mixture was kept at 40° for 5 days.

Equimolar amounts of (I) and (II) were refluxed in benzene for 3 hours, and the solvent was then removed on the water-bath; the reaction mixture, on cooling, deposited *α-carbamylthiobenzyl cyanide* as a crystalline solid, which recrystallized from benzene–light petroleum as needles (56%), m. p. 105—106° (Found: C, 56·6; H, 4·2; C, 17·1. $C_9H_8ON_2S$ requires C, 56·3; H, 4·2; S, 16·7%).

The same product was obtained by warming an equimolar mixture of the reactants until dissolution was complete and then storing them at 40° for 10 days.

This product was soluble in alcohol and aqueous alkali but insoluble in aqueous acid; it could not be diazotized or acetylated by the usual methods, and treatment with phenyl *iso*cyanate yielded only carbanilide, probably owing to presence of a trace of water.

Hydrolysis of α-*Carbamylthiobenzyl Cyanide.*—Acid hydrolysis resulted when the cyanide (0·5 g.) was refluxed in ethyl alcohol (5 ml.) and concentrated hydrochloric acid (5 ml.) for 2 hours. The mixture was evaporated to about half its volume, then diluted with water, and, on cooling, a precipitate formed which recrystallized from water as needles, m. p. 132—133° alone or mixed with an authentic sample of 2 : 4-dihydroxy-5-phenylthiazole (Davies, Maclaren, Wilkinson, *loc. cit.*).

Alkaline hydrolysis resulted when sodium (0·05 g.), dissolved in methyl alcohol (15 ml.), and the cyanide (VI) (0·5 g.) were kept at room temperature for 2 days. The pale brown solution was then filtered and the long needles were washed with a small volume of carbon disulphide and recrystallized from alcohol. The diphenylmaleidinitrile (0·2 g.) had m. p. 162—163°. The filtrate and wash-liquor contained sulphur and other unidentified products.

Hydrolytic fission occurred in a third manner in the presence of mercuric chloride. Solutions of the cyanide (VI) (0·5 g.) in ethyl alcohol (5 ml.) and of mercuric chloride (0·7 g.) in water (30 ml.) were mixed, and the mixture was heated to boiling, cooled, and filtered. The product which crystallized from aqueous alcohol as colourless plates, m. p. 159—160°, was the *mercuric* salt of α-mercaptobenzyl cyanide (Found: C, 38·7; H, 2·5; N, 5·5. $C_{16}H_{12}N_2S_2Hg$ requires C, 38·8; H, 2·4; N, 5·6%).

Methyl thiolcarbamate (0·2 g.) was dissolved in hot water and saturated mercuric chloride solution (20 ml.) was added. The resulting white precipitate was coagulated by boiling for 5 minutes; recrystallized from aqueous pyridine, *chloromercurithiomethane* melted above 300° (Found: C, 4·8; H, 1·4; S, 11·15. CH_3SClHg requires C, 4·2; H, 1·1; S, 11·3%).

Reaction of α-*Carbamylthiolbenzyl Cyanide with Amines.*—When equal weights of the cyanide and aniline were heated together, ammonia was evolved and the mixture became semisolid. After cooling, the mixture was filtered and the product washed with 50% acetic acid and crystallized from alcohol as needles, m. p. 237—238°, identical with *s*-diphenylurea. Under the same conditions, *p*-anisidine gave *s*-di-(*p*-methoxyphenyl)urea as needles (from alcohol), m. p. 236—237°, (Found: OMe, 22·9. Calc. for $C_{15}H_{16}O_3N_2$: OMe, 22·8%). Lossen (*Annalen*, 1875, **175**, 295) describes this substance as melting at 234—235°.

3 : 4-*Diphenyl*-2 : 5-*di*(*thiazolylimino*)*pyrroline Derivatives.*—In preliminary experiments, equimolar quantities of (I), (II), and sodium acetate were heated together on a water-bath for 5 hours. The mixture rapidly became deep red. The residue after steam-distillation was a black, brittle, thermoplastic resin which could not be crystallized, but in boiling alcoholic hydrochloric acid yielded some 2 : 4-dihydroxy-5-phenylthiazole, m. p. 130—132°. (II) (10·5 g.), (I) (40 ml. of 60%), and anhydrous sodium acetate (18 g.) were refluxed in benzene (60 ml.) for 5 hours. The reaction mixture was filtered and the precipitate was washed with hot benzene until colourless. The solvent was then evaporated from the filtrate and washings, and the last traces were removed on the water-bath at reduced pressure. The resulting red-black mixture was filtered and the precipitate was repeatedly crystallized from benzene as brilliantly red needles, m. p. 222·5—223°, of 2 : 5-*di*-(2-*ethoxy*-5-*phenyl*-4-*thiazolylimino*)-3 : 4-*diphenylpyrroline* (6 g., 10%) [Found: C, 69·2; H, 5·0; N, 10·6; S, 10·0; OEt, 13·95. $C_{34}H_{21}N_5S_2(OC_2H_5)_2$ requires C, 69·9; H, 4·8; N, 10·7; S, 9·8; OEt, 13·8%]. The product was soluble in hot chloroform, benzene, or dioxan, sparingly soluble in alcohol or acetone, and insoluble in water, light petroleum, aqueous acids or alkalis. It did not react with the usual acids and alkalis, but was hydrolysed by hydrobromic acid in acetic acid as follows.

The pyrroline (1 g.) in concentrated hydrobromic acid (1 ml.; *d* 1·70) and acetic acid (5 ml.) was heated to boiling, the solution being rapidly decolorized and finally becoming deep yellow. The solution was evaporated to dryness at reduced pressure, and the residue was treated with water (50 ml.). The resulting yellow precipitate was filtered off. Repeated extraction with boiling water separated the soluble 2 : 4-dihydroxy-5-phenylthiazole (0·40 g., 68%) from the insoluble diphenylmaleinimide (0·38 g., 99%). The former product crystallized from water as needles, m. p. and mixed m. p. 131—132°. The structure of the imide, which crystallized from alcohol as yellow needles, m. p. 217—218° (lit., 217°), was established by analyses (Found: C, 77·5; H, 4·7; N, 5·9. Calc. for $C_{16}H_{11}O_2N$: C, 77·1; H, 4·4; N, 5·6%) and by alkaline hydrolysis to diphenylmaleic anhydride.

2 : 5-*Di*-(2-*methoxy*-5-*phenyl*-4-*thiazolylimino*)-3 : 4-*diphenylpyrroline* was obtained in a similar manner by using methyl xanthamidate, and formed red needles (12%), m. p. 277—278°, from benzene [Found: C, 69·05; H, 4·2; N, 11·6; S, 10·2; OMe, 9·9. $C_{34}H_{21}N_5S_2(OCH_3)_2$ requires C, 69·2; H, 4·3; N, 11·2; S, 10·2; OMe, 9·9%].

2 : 5-*Di*-(2-n-*butoxy*-5-*phenyl*-4-*thiazolylimino*)-3 : 4-*diphenylpyrroline*, prepared from *n*-butyl xanthamidate, formed red needles (11%) (from acetic acid), m. p. 205—205·5° (Found: C, 71·2; H, 5·6; N, 9·8; S, 9·1. $C_{42}H_{39}O_2N_5S_2$ requires C, 71·1; H, 5·5; N, 9·9; S, 9·0%).

Molecular weight determinations. The Rast method was not applicable as the solutions obtained were too intensely coloured. However, the molecular weight of the ethoxy-derivative as determined by Clarke's isothermal distillation method (*Ind. Eng. Chem.*, 1941, **13**, 820), using chloroform as solvent and stilbene as standard, was 651 ± 6 ($C_{38}H_{31}O_2N_5S_2$ requires *M*, 653).

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