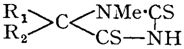
329. *The Reaction between Carbon Disulphide and Some α-Methylamino-nitriles.*

By H. C. Carrington.

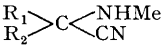
The α-methylamino-nitriles derived from aliphatic or alicyclic ketones react with carbon disulphide to give 4 : 4-disubstituted 5-imino-3-methylthiazolidine-2-thiones, which are readily hydrolysed by acid to the corresponding thiazolidone-2-thiones. A member of the latter series, 3 : 4 : 4-trimethylthiazolid-5-one-2-thione, has also been synthesised by treating an alkaline solution of α-methylamino*iso*butyric acid with carbon disulphide and acidifying the product.

During work on the synthesis of 5 : 5-disubstituted 1-methyl-2 : 4-dithiohydantoins (I) it appeared desirable to investigate the possibility of preparing these compounds by the action of carbon disulphide on the α-methylamino-nitriles (II) derived from ketones. Bucherer and Lieb (*J. pr. Chem.*, 1934, **141**, 5), in a study of the formation of hydantoins from ketones, found that 5 : 5-disubstituted 1-methylhydantoins were not produced when ketone cyanohydrins were treated with methylamine and carbon dioxide, but Jacobson, in a patent describing the formation of 2 : 4-dithiohydantoins by the action of carbon disulphide on α-amino-nitriles (U.S.P. 2,143,816, 1939), stated that 1 : 5 : 5-trimethyl-2 : 4-dithiohydantoin (I; $R_1 = R_2 =$ Me) could be prepared



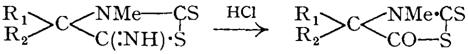
$$\begin{matrix}R_1\\R_2\end{matrix}{>}C{<}\begin{matrix}NMe{\cdot}CS\\CS{-}NH\end{matrix}$$

(I.)



$$\begin{matrix}R_1\\R_2\end{matrix}{>}C{<}\begin{matrix}NHMe\\CN\end{matrix}$$

(II.)



$$\begin{matrix}R_1\\R_2\end{matrix}{>}C{<}\begin{matrix}NMe{-\!-}CS\\C(:NH){\cdot}S\end{matrix} \xrightarrow{HCl} \begin{matrix}R_1\\R_2\end{matrix}{>}C{<}\begin{matrix}NMe{\cdot}CS\\CO{-}S\end{matrix}$$

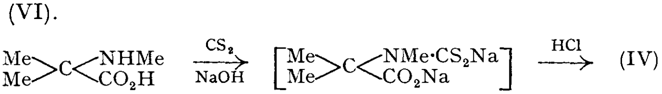
(III.) (IV.)

in this way from α-methylamino*iso*butyronitrile (II; $R_1 = R_2 =$ Me) as a colourless crystalline substance, m. p. 83·5—84·5°.

1 : 5 : 5-Trimethylhydantoin has been prepared by Biltz and Slotta (*J. pr. Chem.*, 1926, **113**, 233; see also Stuckey, *J.*, 1947, 331) by the action of cyanate on α-methylamino*iso*butyronitrile and treatment of the product with acid. On reaction with phosphorus pentasulphide and " liver of sulphur " in boiling xylene it gave a yellow crystalline compound, m. p. 146—147°, which was soluble in cold dilute aqueous sodium hydroxide, was reprecipitated by acid, and was, in fact, authentic 1 : 5 : 5-*trimethyl*-2 : 4-*dithiohydantoin*.

A reinvestigation of the reaction between α-methylamino*iso*butyronitrile and carbon disulphide showed the main product to be 5-*imino*-3 : 4 : 4-*trimethylthiazolidine*-2-*thione* (III; $R_1 = R_2 =$ Me), a bright yellow crystalline substance, m. p. 115°, isomeric with 1 : 5 : 5-trimethyl-2 : 4-dithiohydantoin, but with quite different properties. It was insoluble in cold dilute aqueous sodium hydroxide, but readily soluble in cold dilute hydrochloric acid. From the solution in acid there rapidly separated 3 : 4 : 4-*trimethylthiazolid*-5-*one*-2-*thione* (IV; $R_1 = R_2 =$ Me), a colourless crystalline compound, m. p. 85°, in which the original 5-imino-group was replaced by oxygen.

The constitution of the latter substance was confirmed by an alternative synthesis. An alkaline solution of α-methylamino*iso*butyric acid (V), shaken for several days with carbon disulphide, gave on acidifying, in small yield, 3 : 4 : 4-trimethylthiazolid-5-one-2-thione identical with that described above. This synthesis probably proceeds through the salt of the dithiocarbamic acid (VI).



$$\begin{matrix}Me\\Me\end{matrix}{>}C{<}\begin{matrix}NHMe\\CO_2H\end{matrix} \xrightarrow[NaOH]{CS_2} \left[\begin{matrix}Me\\Me\end{matrix}{>}C{<}\begin{matrix}NMe{\cdot}CS_2Na\\CO_2Na\end{matrix}\right] \xrightarrow{HCl} (IV)$$

(V.) (VI.)

It seems probable that the product obtained by Jacobson was 3 : 4 : 4-trimethylthiazolid-5-one-2-thione, although no intervention of acid was mentioned in the description of his process. The melting point and appearance are in agreement with this supposition. A nitrogen analysis would have clarified the situation, but none was reported, and the other analytical figures would not disclose the replacement of an imino-group by an oxygen atom.

α-Methylamino-α-methylbutyronitrile (II; $R_1 =$ Me, $R_2 =$ Et) with carbon disulphide similarly gave the yellow crystalline 5-*imino*-3 : 4-*dimethyl*-4-*ethylthiazolidine*-2-*thione* (III; $R_1 =$ Me, $R_2 =$ Et), which was readily hydrolysed by dilute acid to 3 : 4-*dimethyl*-4-*ethylthiazolid*-5-*one*-2-*thione* (IV; $R_1 =$ Me, $R_2 =$ Et).

The yellow 5-imino-compounds were readily converted by warm aqueous alcoholic sodium hydroxide into isomeric colourless forms, which with dilute acid readily gave the same thiazolid-5-ones as were obtained from the yellow forms. The relationship between the two forms of the 5-imino-compounds has not yet been elucidated, and no method of reconverting the colourless forms into the yellow ones has been discovered. In view of the facility with which both forms are hydrolysed to the same thiazolid-5-ones, it is difficult to postulate any structural difference between them. The yellow 5-imino-compounds were very readily acetylated by acetic anhydride in the cold, and the *acetyl* derivatives, on treatment with aqueous-alcoholic sodium hydroxide, were deacetylated to the colourless forms.

The 5-imino-group of 5-imino-3 : 4 : 4-trimethylthiazolidine-2-thione was readily replaced by other basic groups. For instance, on warming with aqueous 2-aminoethyl alcohol, ammonia was evolved, and the corresponding 5-(2′-*hydroxyethylimino*)-3 : 4 : 4-*trimethylthiazolidine*-2-*thione* was produced. This substance, like the parent 5-imino-compound, was readily soluble in dilute acid, and hydrolysed to the corresponding thiazolid-5-one on warming.

When the α-methylamino-nitriles from cyclic ketones reacted with carbon disulphide, the corresponding 5-iminothiazolidine-2-thiones were obtained as colourless crystalline solids. For example, 1-methylamino-1-cyano*cyclo*hexane (II; $R_1R_2 = CH_2{<}[CH_2]_4{>}$) gave 5-*imino*-4 : 4-cyclo*pentamethylene*-3-*methylthiazolidine*-2-*thione* (III; $R_1R_2 = CH_2{<}[CH_2]_4{>}$), and 1-methylamino-1-cyano-4-methyl*cyclo*hexane (II; $R_1R_2 = CH_3{\cdot}CH{<}[CH_2]_4{>}$) gave 5-*imino*-4 : 4-(3′-*methyl*cyclo*pentamethylene*)-3-*methylthiazolidine*-2-*thione* (III; $R_1R_2 = CH_3{\cdot}CH{<}[CH_2]_4{>}$).

No yellow forms of these substances were observed. They were readily hydrolysed by dilute acid to the corresponding 4 : 4-cyclo*pentamethylene-3-methyl-* (IV; $R_1R_2 = CH_2<[CH_2]_4>$) and 4 : 4-(3′-*methyl*cyclo*pentamethylene*)-3-*methyl-thiazolid-5-one-2-thione* (IV; $R_1R_2 = CH_3{\cdot}CH<[CH_2]_4>$), respectively.

EXPERIMENTAL.

Reaction of α-Methylamino-nitriles with Carbon Disulphide.—α-Methylamino*iso*butyronitrile (60 g.) and carbon disulphide (80 g.) were heated in a water-bath at 50° under reflux for 24 hours. The excess of carbon disulphide was removed under diminished pressure and the residual oil crystallised on standing. Benzene (50 c.c.) was added, and the crystalline solid was separated, washed with benzene, and recrystallised from aqueous methanol to give 5-*imino*-3 : 4 : 4-*trimethylthiazolidine-2-thione* as large yellow plates, m. p. 115—116°, in 48% yield (Found: C, 41·2; H, 5·5; N, 16·4; S, 36·9. $C_6H_{10}N_2S_2$ requires C, 41·35; H, 5·75, N, 16·1; S, 36·8%). In a similar manner α-methylamino-α-methylbutyronitrile gave in 40% yield the yellow crystalline 5-*imino*-3 : 4-*dimethyl-4-ethylthiazolidine-2-thione*, m. p. 117° (Found: N, 14·5; S, 34·3. $C_7H_{12}N_2S_2$ requires N, 14·9; S, 34·1%). 1-Methylamino-1-cyano*cyclo*hexane gave in 30% yield the colourless crystalline 5-*imino*-4 : 4-cyclo*pentamethylene-3-methylthiazolidine-2-thione*, m. p. 125° (Found: N, 13·1; S, 29·9. $C_9H_{14}N_2S_2$ requires N, 13·1; S, 29·9%). 1-Methylamino-1-cyano-4-methyl*cyclo*hexane gave in 30% yield the colourless crystalline 5-*imino*-4 : 4-(3′-*methyl*cyclo*pentamethylene*)-3-*methylthiazolidine-2-thione*, m. p. 146—147° (Found: N, 12·0; S, 27·8. $C_{10}H_{16}N_2S_2$ requires N, 12·3; S, 28·1%).

Acid Hydrolysis of the Imino-compounds.—The imino-group of the 3 : 4 : 4-trisubstituted 5-iminothiazolidine-2-thiones was readily replaced by oxygen by warming with dilute aqueous or aqueous-alcoholic hydrochloric acid. The trimethyl compound dissolved readily in cold 7% hydrochloric acid and the product of hydrolysis separated on standing at room temperature for a few minutes. The 3 : 4-dimethyl-4-ethyl homologue was soluble in cold dilute hydrochloric acid, and the solution was heated for 10 minutes on the steam-bath to complete the hydrolysis. The two compounds with cyclic substituents in the 4-position were not readily soluble in dilute aqueous hydrochloric acid. They were dissolved in aqueous-alcoholic hydrochloric acid, the hydrolysis was completed by heating on the steam-bath for ½ hour, and the colourless crystalline product separated on cooling. In all cases the yield was nearly quantitative, and the products were purified by crystallisation from aqueous methanol. There were thus obtained 3 : 4 : 4-*trimethyl-*, m. p. 85° (Found: N, 7·8; S, 36·8. $C_6H_9ONS_2$ requires N, 8·0; S, 36·6%); 3 : 4-*dimethyl-4-ethyl-*, m. p. 76° (Found: N, 7·0; S, 33·5. $C_7H_{11}ONS_2$ requires N, 7·4; S, 33·8%), 4 : 4-cyclo*pentamethylene-3-methyl-*, m. p. 85° (Found: N, 6·8; S, 29·7. $C_9H_{13}ONS_2$ requires N, 6·5; S, 29·8%), and 4 : 4-(3′-*methyl*cyclo*pentamethylene*)-3-*methylthiazolid-5-one-2-thione*, m. p. 110° (Found: N, 6·0; S, 28·4. $C_{10}H_{15}ONS_2$ requires N, 6·1; S, 28·0%).

The Two Forms of 3 : 4 : 4-Trisubstituted 5-Iminothiazolidine-2-thiones.—The yellow form of 5-imino-3 : 4 : 4-trimethylthiazolidine-2-thione (m. p. 115°), on warming with aqueous-alcoholic sodium hydroxide and cooling, gave colourless needles, which after recrystallising from aqueous methanol had m. p. 58°, rising to 70° with loss of solvent on drying in a vacuum (Found, on dried material: N, 15·9; S, 37·0. $C_6H_{10}N_2S_2$ requires N, 16·1; S, 36·8%). On warming for a few minutes with dilute hydrochloric acid this colourless *form* was hydrolysed to 3 : 4 : 4-trimethylthiazolid-5-one-2-thione, m. p. 85°, identical with that similarly obtained from the yellow form. The yellow form of 5-imino-3 : 4 dimethyl-4-ethylthiazolidine-2-thione (m. p. 117°) on treatment with warm aqueous-alcoholic sodium hydroxide was converted into a colourless *form*, crystallising from aqueous methanol with m. p. 85° (Found: N, 14·65; S, 34·1. $C_7H_{12}N_2S_2$ requires N, 14·9; S, 34·1%). With dilute hydrochloric acid this gave 3 : 4-dimethyl-4-ethylthiazolid-5-one-2-thione, m. p. 76°, identical with that obtained from the yellow form.

The 5-imino-3-methylthiazolidine-2-thiones with cyclic substituents in the 4-position, which were originally isolated in colourless form, were unchanged on treatment with warm aqueous-alcoholic sodium hydroxide, and no yellow forms of these compounds have been obtained.

Derivatives of 3 : 4 : 4-Trisubstituted 5-Iminothiazolidine-2-thiones.—(a) *Acetyl derivatives.* 5-Imino-3 : 4 : 4-trimethylthiazolidine-2-thione (yellow form, m. p. 115°, 2 g.) was mixed with acetic anhydride (1 c.c.); a vigorous reaction took place, and after being stirred with water the solid product was filtered off and crystallised from aqueous methanol to give the *acetyl* derivative as colourless crystals (1·5 g.), m. p. 147—148° (Found: C, 44·5; H, 5·6. $C_8H_{12}ON_2S_2$ requires C, 44·8; H, 5·7%). The acetyl derivative (1 g.) was warmed with 4% aqueous-alcoholic sodium hydroxide (8 c.c.) on the steam-bath for 10 minutes. On cooling there separated the colourless form of 5-imino-3 : 4 : 4-trimethylthiazolidine-2-thione, m. p. 58°, rising to 70° on drying in a vacuum, identical with that described above. In a similar way 5-imino-3 : 4-dimethyl-4-ethylthiazolidine-2-thione (yellow form, m. p. 117°) gave a colourless *acetyl* derivative, m. p. 112° (Found: N, 12·1; S, 28·0. $C_9H_{14}ON_2S_2$ requires N, 12·2; S, 27·8%). Deacetylation with aqueous-alcoholic sodium hydroxide gave the colourless form of the imino-compound, m. p. 85°, identical with that described above.

(b) 2-*Hydroxyethyl derivative.* 5-Imino-3 : 4 : 4-trimethylthiazolidine-2-thione (yellow form, m. p. 115°, 2 g.) was heated on the steam-bath for 10 minutes with 2-aminoethanol (4 c.c.) and water (4 c.c.). Ammonia was evolved, with traces of hydrogen sulphide. On cooling, a white crystalline solid separated. After crystallising from aqueous methanol 5-(2′-*hydroxyethylimino*)-3 : 4 : 4-*trimethylthiazolidine-2-thione* had m. p. 100° (Found: C, 43·85; H, 6·3. $C_8H_{14}ON_2S_2$ requires C, 44·0; H, 6·4%). This compound was readily soluble in cold dilute hydrochloric acid, and on warming the solution there was produced 3 : 4 : 4-trimethylthiazolid-5-one-2-thione, m. p. 85°, identical with that previously described.

*Reaction of α-Methylamino*iso*butyric Acid with Carbon Disulphide.*—α-Methylamino*iso*butyric acid (1 g.) in 8% aqueous sodium hydroxide (10 c.c.) was shaken with carbon disulphide (2 c.c.) for 3 days. The unchanged carbon disulphide was separated, and the yellow solution acidified with hydrochloric acid. The colourless solid was separated (0·1 g.), and after crystallisation from aqueous methanol it had m. p. 85°, and was identical with the 3 : 4 : 4-trimethylthiazolid-5-one-2-thione described above.

1 : 5 : 5-*Trimethyl*-2 : 4-*dithiohydantoin*.—A suspension of 1 : 5 : 5-trimethylhydantoin (5 g.), finely ground phosphorus pentasulphide (5 g.), and liver of sulphur (6 g.) in dry xylene (100 c.c.) was stirred and boiled under reflux for 18 hours. The hot mixture was filtered, and the product, which separated from the filtrate on cooling, was crystallised from aqueous methanol to give 1 : 5 : 5-*trimethyl*-2 : 4-*dithiohydantoin* as long pale yellow plates (1 g.), m. p. 146—147° (Found : N, 15·9; S, 37·2. $C_6H_{10}N_2S_2$ requires N, 16·1; S, 36·8%.

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