578. *The Structure of "isoThiohydantoin" and Related Compounds.*

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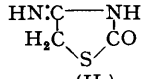
Thiocyanatoacetamide (I; R = H) is claimed by Miolati (*Gazzetta*, 1893, **23**, I, 90) to isomerise to "*iso*thiohydantoin" (II), for which a new formula, cyanomethyl thiolcarbamate (IV; R = H) is now proposed. This is supported by the fission products of the compound and by its infrared spectrum. A rearrangement similar to that of (I; R = H) to (IV; R = H) is also found with α-thiocyanatopropionamide (I; R = Me) which is converted into 1-cyanoethyl thiolcarbamate (IV; R = Me). A probable mechanism of the rearrangement is suggested.

The chemistry of 2 : 4-diaminothiazoles (Davies, Maclaren, and Wilkinson, *J.*, 1950, 3491) drew attention to the only other 4-aminothiazole (or 4-iminothiazoline) previously described, the so-called "*iso*thiohydantoin" or 4-imino-2-ketothiazolidine (II). Thiocyanatoacetamide (I; R = H) was prepared by Miolati (*loc. cit.*) from chloroacetamide and potassium thiocyanate, and this compound was isomerised in dilute sulphuric acid to (II). This preparation was confirmed by Ganapathi and Venkataraman (*Proc. Indian Acad. Sci.*, 1945, **22**, 359), who also converted their product into 2 : 4-diketothiazolidine (III; R = H) by acid hydrolysis.



(II.)

$NCS{\cdot}CHR{\cdot}CO{\cdot}NH_2$ (I.)

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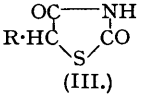
$H_2N{\cdot}CO{\cdot}S{\cdot}CHR{\cdot}CN$ (IV.)



(III.)

The structure of thiocyanatoacetamide itself has been queried by Frerichs and Beckurts (*Chem. Zent.*, 1900, **71**, I, 589), who suggested that it was an *iso*thiocyanato-compound. However, the work of Wheeler and Merriam (*J. Amer. Chem. Soc.*, 1901, **23**, 283) indicates that the above normal structure (I; R = H) is correct. On the other hand, the accepted structure (II) for "*iso*thiohydantoin" is surprising, since, by analogy with other 4-aminothiazoles (Davies, Maclaren, and Wilkinson, *loc. cit.*), (II) might be expected to darken rapidly in air, be easily acetylated, and be very unstable in acid solution. On the contrary, this compound is quite stable in air for many weeks, cannot be acetylated by the usual means, and is unaffected when dissolved at room temperature in 2N-sulphuric acid, in which it is obtained in 93% yield from (I).

It is found that "*iso*thiohydantoin" reacts with hot aniline to yield an unidentified thiol and *s*-diphenylurea, and that with a hot aqueous solution of mercuric chloride a crystalline mercury salt, $C_4H_4N_2S_2Hg$, is obtained. "*iso*Thiohydantoin" also reacts in alcoholic solution with an equimolar mixture of chloro-2 : 4-dinitrobenzene and sodium hydroxide to yield a yellow crystalline sulphide, $C_8H_5O_4N_3S$. These three reactions, which cannot be easily understood on the basis of structure (II), are readily explicable if we assume that "*iso*thiohydantoin" is cyanomethyl thiolcarbamate (IV; R = H). From the known general reactions of thiolcarbamates (Davies and Maclaren, *J.*, 1951, 1434), it is seen that the reaction with aniline has proceeded thus :

$$R{\cdot}CH(CN){\cdot}S{\cdot}CO{\cdot}NH_2 + 2NH_2Ph \longrightarrow CO(NHPh)_2 + R{\cdot}CH(CN){\cdot}SH + NH_3$$

Similarly, the product of the reaction with mercuric chloride is the mercuric salt of mercaptoacetonitrile (thioglycollonitrile) (V; R = H) :

$Hg(S{\cdot}CHR{\cdot}CN)_2$ (V.) $C_6H_3(NO_2)_2{\cdot}S{\cdot}CHR{\cdot}CN$ (VI.) $C_2H_5{\cdot}O{\cdot}CS{\cdot}NH_2$ (VII.) $R{\cdot}S{\cdot}CO{\cdot}NH_2$ (VIII.) $S(CH_2{\cdot}CN)_2$ (IX.)

Hydrolysis of the thiolcarbamate group to thiol has occurred also in the reaction with alkaline chloro-2 : 4-dinitrobenzene, since the product is undoubtedly 2 : 4-dinitrophenylthioacetonitrile (VI; R = H). This reaction with thiolcarbamates is found to be a general one; *e.g.*, methyl thiolcarbamate (VIII; R = Me) yields 2 : 4-dinitrophenyl methyl sulphide, fission again occurring between the sulphur atom and the carbamyl group.

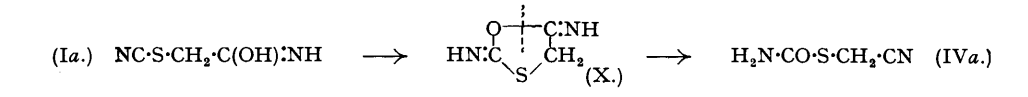
The accepted structure of "*iso*thiohydantoin" is chiefly based on its conversion by acid hydrolysis into 2 : 4-diketothiazolidine (III; R = H). However, this observation does not conflict with the structure now proposed (IV; R = H) since similar treatment of α-thiocyanatoamides and esters (Miolati, *loc. cit.*; also Wheeler and Barnes, *Amer. Chem. J.*, 1900, **24**, 80)

gives the corresponding 2 : 4-diketothiazolidine (III). Alternatively, the unknown thiazolidine (II) may well be a still-unisolated intermediate in the conversion of (IV; R = H) into (III; R = H). Finally an examination of the infra-red spectrum of "*iso*thiohydantoin" reveals bands which are quite compatible with the proposed structure (IV; R = H) but not with (II) or its amino- or enolic tautomers.

A rearrangement similar to that of (I; R = H) to (IV; R = H) is also found with α-thiocyanatopropionamide (I; R = Me) which forms 1-cyanoethyl thiolcarbamate (IV; R = Me). In exactly the same way as its lower homologue, this ester yields the mercuric salt of α-mercaptopropionitrile (V; R = Me), and α-(2 : 4-dinitrophenylthio)propionitrile (VI; R = Me); likewise, *s*-diphenylurea is formed when the compound is heated with aniline. On the other hand, all attempts to isomerize α-thiocyanatophenylacetamide (I; R = Ph) and α-selenocyanatoacetamide (I; R = H, Se for S) have been unsuccessful.

The most direct proof of the structures of "*iso*thiohydantoin" and its homologue would be to synthesise them by another means, and two methods have been tried unsuccessfully. Chloroacetonitrile does not react with ethyl thioncarbamate (VII) to form the desired product, but instead causes a rearrangement to form ethyl thiolcarbamate (VIII; R = Et), and this is true in all solvents tried (cf. Davies and Maclaren, *loc. cit.*). The same isomerization also occurs with α-chloropropionitrile. According to Fleischer's results (*Ber.*, 1876, **9**, 991), cyanomethyl thiolcarbamate would be expected from the interaction of chloroacetonitrile and ammonium thiolcarbamate (VIII; R = NH_4). However, it is now found that the only product isolated from this vigorous reaction is biscyanomethyl sulphide (IX).

It is seen that the conversion of (I) into (IV) apparently involves the addition of water to the thiocyanato-group, and the abstraction of water from the amido-group. The first reaction is not surprising in acid solution (cf. Arapides, *Annalen*, 1888, **249**, 7), whereas the almost complete dehydration of an amide to a nitrile is not usual in aqueous solution. A hydrolytic environment seems essential to the change, which has only been effected in acid and so far has not been wrought by heat alone. However, the driving force of the reaction cannot be the tendency to form a strong base in acid, since (IV; R = H) is readily extracted with ether from 2N-sulphuric acid. A likely intermediate in the rearrangement is the heterocyclic compound



(X) which would be formed by internal condensation of the hydroxy-form (I*a*) of (I; R = H), in the same way as γ-hydroxycrotononitrile gives unstable α-aminofuran (Culvenor, Davies, and Haley, *J.*, 1950, 3123). Fission of (X) as shown by the dotted line would yield (IV*a*). The implications of this type of change will be considered in a later communication.

Experimental.

Preparation of α-Thiocyanato-amides.—Thiocyanatoacetamide was prepared according to Miolati (*loc. cit.*).

α-Chloropropionamide (25 g.) and potassium thiocyanate (25 g.) were refluxed in 80% alcohol (100 ml.) for 4 hours. The precipitated ammonium chloride was filtered off, and the filtrate was evaporated on the water-bath to yield a yellow oil. This oil was continuously extracted with hot benzene, and the extract on cooling deposited the product as long colourless needles. *α-Thiocyanatopropionamide* (I; R = Me), recrystallized from benzene, had m. p. 86—86·5° (Found: N, 21·3; S, 24·4. $C_4H_6ON_2S$ requires N, 21·5; S, 24·6%).

α-Bromophenylacetamide (10 g.) and potassium thiocyanate (5 g.) were refluxed in 90% alcohol (150 ml.) for 1½ hours; the solvent was then evaporated, and the residue recrystallized from water as colourless needles of *α-thiocyanatophenylacetamide* (I; R = Ph), m. p. 143—145° (Found: C, 56·5; H, 4·3. $C_9H_8ON_2S$ requires C, 56·3; H, 4·2%).

Selenocyanatoacetamide was prepared by the method of Frerichs (*Abs.*, 1903, **84**, i, 609).

Cyanomethyl Thiolcarbamate ("iso*Thiohydantoin*").—Miolati's instructions (*loc. cit.*) are misleading, since if the acid concentration is greater than 10N., no yield is obtained. Finely powdered thiocyanatoacetamide (2 g.) was suspended in 2N-sulphuric acid (20 ml.), and the mixture kept at room temperature for 2 days. The resulting clear solution was extracted with ether (3 × 15 ml.), and the dried extract (Na_2SO_4) gave the thiolcarbamate (IV; R = H), which crystallized from chloroform as colourless needles (1·85 g., 93%), m. p. 74—75·5° (Found: C, 31·0; H, 3·4; N, 24·5. Calc. for $C_3H_4ON_2S$: C, 31·2; H, 3·4; N, 24·2%). This compound showed no basic properties, but was readily soluble in water. Precipitates were obtained on mixing its aqueous solution with aqueous solutions of silver nitrate, mercuric chloride, or copper sulphate. When heated with acetic anhydride and a few drops of pyridine, it produced a black tar.

Under exactly the same conditions as the above α-thiocyanatopropionamide was isomerized to form 1-*cyanoethyl thiolcarbamate* (IV; R = Me), which crystallized from benzene–light petroleum as colourless micro-rhombs, m. p. 60—63°, in 90% yield (Found: C, 36·4; H, 4·5. $C_4H_6ON_2S$ requires C, 36·9; H, 4·6%).

Elementary selenium was the only product isolated when selenocyanatoacetamide was treated with 2N-sulphuric acid as above.

α-Thiocyanatophenylacetamide was treated with sulphuric acid of concentrations varying from 2N. to 20N., with sulphuric acid in alcohol, and with dry hydrogen chloride in alcohol, but in no case could any product be isolated corresponding to (IV).

Reactions of Cyanomethyl Thiolcarbamate and Related Compounds.—The thiolcarbamate (0·5 g.) in a mixture of alcohol (5 ml.) and concentrated hydrochloric acid (5 ml.) was refluxed for 2 hours, then concentrated to half its volume and diluted with water. The precipitate, which formed on cooling, crystallized from water as colourless needles, m. p. 125—126°, identical with 2 : 4-diketothiazolidine (III; R = H).

Under exactly the same conditions, α-thiocyanatophenylacetamide yields 2 : 4-diketo-5-phenylthiazolidine (III; R = Ph), m. p. 130—132°.

Reaction with aniline. When equal weights of the thiolcarbamate and aniline were heated together gently in a test-tube, a vigorous reaction occurred, ammonia and a thiol were evolved, and the mixture solidified. The product was filtered off from a small amount of oil, washed with 50% acetic acid, and crystallized from alcohol, forming needles, m. p. 237—238°, undepressed by admixture with *s*-diphenylurea. No other product could be isolated, and the reaction proceeded in exactly the same manner with the higher homologue.

Reaction with mercuric chloride. Hot aqueous solutions of cyanomethyl thiolcarbamate (0·5 g.) and mercuric chloride (1·0 g.) were mixed, and the mixture was boiled and allowed to cool. The precipitate was filtered off, washed with water, and crystallized from water or aqueous alcohol, forming colourless plates of the *mercury* derivative (V; R = H), m.p. 127—128° (Found: C, 14·0; H, 1·5; S, 18·6. $C_4H_4N_2S_2Hg$ requires C, 13·9; H, 1·2; S, 18·6%).

Similarly, 1-cyanoethyl thiolcarbamate is converted into the *mercury* derivative (V; R = Me), which crystallizes from alcohol as colourless needles, m. p. 139° (Found: C, 20·0; H, 2·5; N, 7·3. $C_6H_8N_2S_2Hg$ requires C, 19·2; H, 2·2; N, 7·5%).

Reaction with chloro-2 : 4-dinitrobenzene. To cyanomethyl thiolcarbamate (0·4 g.) and chloro-2 : 4-dinitrobenzene (0·4 g.) in alcohol (5 ml.), sodium hydroxide (0·16 g.) in 80% alcohol (5 ml.) was added. After 1 hour at room temperature, the resulting crystalline precipitate (0·2 g.), had m. p. 139—140°, and dilution of the filtrate with water yielded a further crop (0·25 g., m. p. 137—139°) of 2 : 4-*dinitrophenylthioacetonitrile* (VI; R = H). It crystallized from alcohol as pale yellow needles, m. p. 139·5—140·5° (Found: C, 40·1; H, 2·3; S, 13·3. $C_8H_5O_4N_3S$ requires C, 40·2; H, 2·1; S, 13·4%).

Similarly, the cyanoethyl ester gave α-(2 : 4-*dinitrophenylthio*)*propionitrile* (VI; R = Me) as pale yellow plates (alcohol), m. p. 108·5—109° (Found: C, 42·7; H, 2·9. $C_9H_7O_4N_3S$ requires C, 42·6; H, 2·8%.

Also methyl thiolcarbamate (VIII; R = Me) yielded methyl 2 : 4-dinitrophenyl sulphide, m. p. 127—128°. Bost, Turner, and Norton (*J. Amer. Chem. Soc.*, 1932, **54**, 1985) report m. p. 128°.

Attempted Syntheses of α-Cyanomethyl Thiolcarbamates (IV).—Chloroacetonitrile (3·2 ml.) and ethyl thioncarbamate (VII) (5·25 g.), dissolved in alcohol, were kept at 40° for 6 days. The precipitated ammonium chloride was filtered off, and the filtrate evaporated to yield a yellow liquid which solidified. The crystals were filtered off, washed with methanol, and recrystallized from benzene–light petroleum; they had m. p. 102·5—103·5°, undepressed by admixture with ethyl thiolcarbamate (VIII; R = Et).

α-Chloropropionitrile was synthesised by a new method based on Darzens's reaction (*Compt. rend.*, 1911, **152**, 1601). Acetaldehyde cyanohydrin (35 g.) and pyridine (40 g.) were mixed, evolving heat. The mixture was cooled in an ice-bath, and thionyl chloride (62 g.) was added dropwise during 20 minutes with shaking. After 2 hours at room temperature, the mixture was heated in an oil-bath at 110° until no more sulphur dioxide was evolved, and then poured into brine (250 ml.). The mixture separated into two layers and was extracted with ether (4 × 100 ml.), and the combined extracts were dried ($CaCl_2$) and distilled. After two distillations α-chloropropionitrile was obtained as a colourless liquid, b. p. 120—122° (22·5 g., 50%).

α-Chloropropionitrile and ethyl thioncarbamate (VII) did not react when refluxed in benzene for 8 hours. An equimolar mixture of the reactants was refluxed without solvent for 1½ hours and then distilled under reduced pressure. Apart from unchanged reactants, the only other fraction isolated had b. p. 115—120°/28 mm. This solidified and crystallized from benzene–light petroleum as plates, m. p. 104—105°, identified as ethyl thiolcarbamate (VIII; R = Et).

Chloroacetonitrile (1·5 ml.) and ammonium thiolcarbamate (2 g.) (VIII; R = NH_4) were mixed in alcohol (5 ml.). After some minutes, the suspension boiled spontaneously and, after 3 hours, the mixture was evaporated to dryness and extracted with ether. This extract yielded a colourless oil, which solidified on cooling and crystallized from benzene–light petroleum as colourless plates, m. p. 45—46°, apparently biscyanomethyl sulphide (IX) (Found: C, 43·5; H, 3·6; S, 28·3. Calc. for $C_4H_4N_2S$: C, 42·8; H, 3·6; S, 28·5%). Steinkopf, Herold, and Stöhr (*Ber.*, 1920, **53**, 1012) give 47·5°. The same product was obtained when the reactants were mixed alone; the reaction proceeds spontaneously and must be moderated by external cooling.

Infra-red Spectra.—We thank Dr. J. B. Willis, of C.S.I.R.O., for the following report: "Thiocyanatoacetamide (I; R = H), examined as a suspension in 'Nujol,' gave a band at 2166 cm.$^{-1}$,

due to the C≡N vibration. Bands were also found at 1600 cm.$^{-1}$ (NH bonding) and 1686 cm.$^{-1}$ (C=O stretching). '*iso*Thiohydantoin' gave a band at 2257 cm.$^{-1}$, which is attributed to a C≡N vibration, and bands at 1621 and 1698 cm.$^{-1}$. This is quite compatible with the formula proposed (IV; R = H) but not with the alternative formulæ (II, or its amino- or enol tautomers)."

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