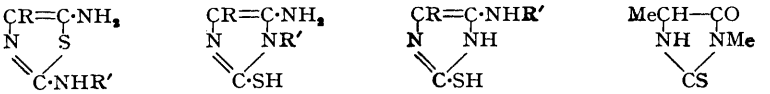
411. *Studies in the Azole Series. Part IX. The Interaction of α-Amino-nitriles and Alkyl* iso*Thiocyanates.*

By A. H. Cook, J. D. Downer, and Sir Ian Heilbron.

Aminoacetonitrile and ethyl α-aminocyanoacetate react with methyl *iso*thiocyanate to give 5-amino-2-methylaminothiazoles (*e.g.*, IV). Unlike the corresponding 5-amino-2-acylamino-thiazoles (Parts VI and VIII) which isomerise in the presence of mild alkali to give 5-acylamino-2-mercaptoglyoxalines, the 5-amino-2-methylaminothiazoles give 5-amino-2-mercapto-1-methylglyoxalines (*e.g.*, VII).

Previous papers in this Series (Parts VI and VIII, this vol., pp. 1262, 1340) showed that acyl-*iso*thiocyanates react with α-amino-nitriles to give substituted 2 : 5-diaminothiazoles (I) which rearrange in presence of mild alkali to give 5-acylamino-2-mercaptoglyoxalines (II) presumably through the intermediate (II*a*). In the case of ethyl α-aminocyanoacetate, however, the



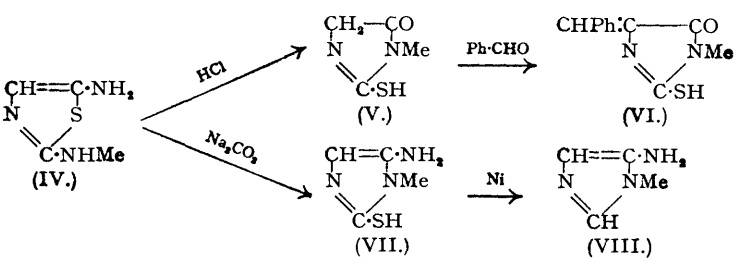
(I.) (II*a*.) (II.) (III.)

(R = H, Me, Ph; R′ = Ph·CO, CO_2Et.)

products obtained by reaction with either benzoyl or carbethoxy-*iso*thiocyanate, containing two strongly electronegative groups (I; R = CO_2Et, R′ = CO_2Et or PhCO), failed to give any cyclic isomeride on treatment with alkali. It was then thought that this stability might be overcome by introducing a more electropositive substituent in place of the acyl group in the 2-position of the thiazole. Accordingly, the present paper describes the reaction between α-amino-nitriles and methyl *iso*thiocyanate and the rearrangement of the products in alkali.

Mouneyrat and later Delépine (*Bull. Soc. chim.*, 1903, **29**, 1198) examined this reaction in the case of α-aminopropionitrile, obtaining a crude viscous reaction product which they failed to purify but which gave 3 : 5-dimethyl-2-thiohydantoin (III) on acid hydrolysis.

It has now been established that equivalent quantities of aminoacetonitrile and methyl *iso*thiocyanate afford a base which can be diazotised. Having regard to reactions discussed in earlier parts of this series it is formulated as 5-*amino*-2-*methylaminothiazole* (IV). Its hydrolysis with concentrated hydrochloric acid gave 3-methyl-2-thiohydantoin (V) which was further identified by the preparation of its 5-*benzylidene* derivative (VI). The formation of (V) is



(IV.) (V.) (VI.) (VII.) (VIII.)

paralleled by the hydrolysis of 5-amino-2-benzamidothiazole (Part VI of this series). On adding (IV) to dilute aqueous sodium carbonate an exothermic reaction took place with the formation of a pseudo-acidic isomeride which also exhibited basic properties; thus it formed a *hydrochloride*, combined with methyl *iso*cyanate, and underwent diazotisation. These reactions seemed incompatible with the glyoxaline structure (II; R = H, R′ = Me) already proved in earlier cases. It was soon evident, however, that the rearrangement had stopped at the intermediate stage (II*a*; R = H, R′ = Me), because refluxing the isomeride with concentrated hydrochloric acid resulted in the isolation of 3-methyl-2-thiohydantoin. The product of rearrangement was therefore formulated as 5-*amino*-2-*mercapto*-1-*methylglyoxaline* (VII), desulphurisation affording 5-*amino*-1-*methylglyoxaline* (VIII) which was unstable but formed a stable *monopicrate* and could be diazotised.

These results encouraged further study employing ethyl α-aminocyanoacetate in place of aminoacetonitrile. This amino-nitrile with methyl *iso*thiocyanate gave 5-*amino*-2-*methylamino*-4-*carbethoxythiazole* (I; R = CO_2Et, R′ = Me), which was characterised by its ability to

diazotise and by the formation of a stable *hydrochloride, benzylidene* derivative, and a diacetyl derivative, *5-acetamido-2-methylimino-4-carbethoxy-3-acetylthiazoline*. The formation of a Schiff's base showed the more basic nature of the parent thiazole compared with the corresponding 5-acylaminothiazoles which failed to react in this way. Refluxing (I; R = CO_2Et, R′ = Me) with aqueous sodium carbonate gave the isomeride, *5-amino-2-mercapto-4-carbethoxy-1-methylglyoxaline* (IIa; R = CO_2Et, R′ = Me), exhibiting both basic and pseudo-acidic properties. Its constitution was confirmed by vigorous hydrolysis which, removing the 4- and 5-substituents, gave 3-methyl-2-thiohydantoin. Further, it diazotised, and the diazonium salt coupled with β-naphthol to give a red dye. The glyoxaline was readily desulphurised by Raney nickel to give *5-amino-4-carbethoxy-1-methylglyoxaline* (cf. VIII), which gave a *hydrochloride* and could be diazotised. Both the glyoxaline (IIa; R = CO_2Et, R′ = Me) and its desulphurisation product failed to react with sodium cyanate under the usual conditions.

Heating the thiazole (I; R = CO_2Et, R′ = Me) with ethanolic ammonia gave *5-amino-2-mercapto-4-carbamido-1-methylglyoxaline* by amide formation and rearrangement of the kind discussed above; it also exhibited basic and pseudo-acidic properties. It was desulphurised by Raney nickel to give *5-amino-4-carbamido-1-methylglyoxaline* which also diazotised. All attempts to cyclise the latter compound to a purine, using ethyl carbonate (cf. Sarasin and Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713) or ethyl chloroformate (Mann and Porter, *J.*, 1945, 751) were unsuccessful, the glyoxaline being recovered. With carbonyl chloride only the *hydrochloride* of the parent base was obtained.

Phenyl *iso*thiocyanate was also allowed to react with ethyl α-aminocyanoacetate, but the product, presumably (I; R = CO_2Et, R′ = Ph) since it readily united with a further molecule of phenyl *iso*thiocyanate, proved much more stable towards alkali than products obtained when using methyl *iso*thiocyanate.

Experimental.

5-Amino-2-methylaminothiazole.—A solution of methyl *iso*thiocyanate (24·5 c.c.) in ether (25 c.c.) was added slowly to aminoacetonitrile (20 g.) in ether (150 c.c.) at 0° with stirring in nitrogen. The crude oil slowly solidified on continued stirring to give a brownish solid (30 g.), m. p. 97°, which when stirred in ethanol, filtered off, and washed with ether gave colourless prisms (21 g.), m. p. 98°. Crystallisation from ethyl acetate (4 vols.) or ethanol (3 vols.) gave almost colourless prisms of *5-amino-2-methylaminothiazole*, m. p. 100° (Found: C, 37·4; H, 5·6; N, 32·7. $C_4H_7N_3S$ requires C, 37·2; H, 5·5; N, 32·5%). Light absorption (chloroform): $\lambda_{\text{inflex.}}$ = 2420 A., ϵ = 12,900.

The preceding thiazole (1 g.) was boiled with concentrated hydrochloric acid (8 c.c.) for 5 mins., water (15 c.c.) added, the solution cooled, and the colourless prismatic needles of 3-methyl-2-thiohydantoin (0·5 g.) filtered off and washed with a little ethanol; m. p. and mixed m. p. with authentic material, 162° (Marckwald, Neumark, and Stelzner, *Ber.*, 1891, **24**, 3285, quote m. p. 162°) (Found: C, 37·3; H, 4·75; S, 24·9. Calc. for $C_4H_6ON_2S$: C, 36·9; H, 4·65; S, 24·6%).

3-Methyl-2-thiohydantoin (0·5 g.), dissolved in acetic acid (4·5 c.c.) containing fused sodium acetate (0·6 g.) and benzaldehyde (0·6 c.c.), was heated in an oil-bath at 140° for 1 hour. On cooling, the yellow needles (0·6 g.), m. p. 205°, were filtered off and washed with ethanol and ether. Crystallisation from ethanol (100 vols.) gave long yellow needles of *5-benzylidene-3-methyl-2-thiohydantoin*, m. p. 204° (Found: C, 60·5; H, 4·4; N, 12·5; S, 14·9. $C_{11}H_{10}ON_2S$ requires C, 60·5; H, 4·6; N, 12·8; S, 14·7%). The 3-methyl-2-thiohydantoin obtained from 5-amino-2-methylaminothiazole above, gave the same benzylidene derivative, m. p. and mixed m. p. 204°.

5-Amino-2-mercapto-1-methylglyoxaline.—5-Amino-2-methylaminothiazole (10 g.) was mixed with 10% aqueous sodium carbonate (25 c.c.); an exothermic reaction immediately commenced and was completed by heating on the steam-bath under nitrogen for 5 minutes, a clear solution being obtained. The thick crystalline precipitate which formed on cooling was stirred with water (20 c.c.) containing a trace of sodium hydrogen sulphite, filtered off, and washed with a little water, ethanol, and finally ether to give colourless prismatic rods (6·5 g.), m. p. 148°, which rapidly darkened on exposure to air. Crystallisation from methanol (10 vols.) gave almost colourless needles, of *5-amino-2-mercapto-1-methylglyoxaline*, m. p. 151° (decomp.) (Found: C, 37·5; H, 5·6; N, 32·3; S, 24·4. $C_4H_7N_3S$ requires C, 37·2; H, 5·5; N, 32·5; S, 24·8%). Light absorption (ethanol): $\lambda_{\text{max.}}$ = 2670 A., ϵ = 13,550.

Boiling the above glyoxaline (0·9 g.) for 2 minutes with concentrated hydrochloric acid (5 c.c.) and crystallisation of the product from ethanol–ether gave colourless silky needles of *5-amino-2-mercapto-1-methylglyoxaline hydrochloride* (0·4 g.), m. p. 222° (decomp.) (Found: N, 25·0; S, 18·9. $C_4H_8N_3ClS$ requires N, 25·4; S, 19·4%). It could be diazotised, and the diazonium salt coupled with β-naphthol to give a red dye.

Refluxing 5-amino-2-mercapto-1-methylglyoxaline (0·5 g.) in concentrated hydrochloric acid (5 c.c.) for 2 hours, cooling, and filtering gave colourless irregular prisms of 3-methyl-2-thiohydantoin (0·2 g.), m. p. and mixed m. p. with an authentic specimen 162°.

5-Amino-2-mercapto-1-methylglyoxaline (1·5 g.), pyridine (8 c.c.), and methyl *iso*cyanate (1·2 c.c.) were refluxed gently for 10 minutes, a crystalline solid (1·0 g.), m. p. 211°, separating. Crystallisation from ethyl acetate–methanol gave colourless micro-crystals of *5-methylureido-2-mercapto-1-methylglyoxaline*, m. p. 212° (Found: C, 39·1; H, 5·5; N, 29·8; S, 17·1. $C_6H_{10}ON_4S$ requires C, 38·7; H, 5·4; N, 30·1; S, 17·2%).

5-Amino-2-mercapto-1-methylglyoxaline (3 g.) was refluxed in ethanol (20 c.c.) with Raney nickel (*ca.* 4 g.) for 40 minutes. Evaporation of the filtrate in a vacuum gave colourless irregular prisms of

5-amino-1-methylglyoxaline (1·3 g.), m. p. 101° (decomp.), which rapidly decomposed in air. It formed a stable *monopicrate*, m. p. 177° (Found : C, 36·8; H, 3·3; N, 26·4. $C_{10}H_{10}O_7N_6$ requires C, 36·8; H, 3·1; N, 25·8%). The base formed a deliquescent hydrochloride with ethanolic hydrochloric acid which could be diazotised, the diazonium salt coupling with β-naphthol to give a red dye.

5-Amino-2-methylamino-4-carbethoxythiazole.—A solution of methyl *iso*thiocyanate (14 c.c.) in ether (15 c.c.) was added to a solution of ethyl α-aminocyanoacetate (26 g.) in ether (100 c.c.), and the clear solution kept overnight. The colourless crystals (30·5 g.), m. p. 162°, which had deposited were filtered off and washed with ether. The filtrate, after several days, gave a further crop of crystals (5 g.), m. p. 162°. Crystallisation from ethanol (10 vols.) gave colourless irregular prismatic rods of *5-amino-2-methylamino-4-carbethoxythiazole*, m. p. 162° (decomp.) (Found : C, 42·0; H, 5·6; N, 20·8; S, 16·0. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9; S, 15·9%). Light absorption (chloroform) : $\lambda_{max.}$ = 2600, 3080, 3050 A.; ϵ = 10,850, 9,050, 9,050, respectively. It was soluble in dilute hydrochloric acid and could be diazotised.

The preceding thiazole (1 g.) on boiling with 3% ethanolic hydrochloric acid (30 c.c.) gave colourless micro-needles of *5-amino-2-methylamino-4-carbethoxythiazole hydrochloride*, m. p. 140° (decomp.) (Found : S, 13·3. $C_7H_{12}O_2N_3SCl$ requires S, 13·5%).

Refluxing 5-amino-2-methylamino-4-carbethoxythiazole (2 g.) with benzaldehyde (1 c.c.) in ethanol (20 c.c.) for 20 minutes and cooling gave a bright yellow solid (0·8 g.), m. p. 180°, which on recrystallisation from ethanol (25 c.c.) gave yellow prismatic needles of the *benzylidene* derivative (0·5 g.), m. p. 182° (Found : C, 57·7; H, 5·1; N, 14·6; S, 11·0. $C_{14}H_{15}O_2N_3S$ requires C, 58·0; H, 5·2; N, 14·5; S, 11·1%). Light absorption (chloroform) : $\lambda_{max.}$ = 2480, 3910 A.; ϵ = 14,450, 18,775, respectively.

5-Amino-2-methylamino-4-carbethoxythiazole (1·5 g.) was refluxed in acetic anhydride (10 c.c.) for 15 minutes, the cold solution stirred with iced water (70 c.c.) for 15 minutes, and the crude product (2 g.), m. p. 197°, filtered off and washed with water. Crystallisation from ethanol (90 c.c.) gave colourless needles of *5-acetamido-2-methylimino-4-carbethoxy-3-acetylthiazoline* (1·7 g.), m. p. 197° (Found : C, 46·1; H, 5·2; N, 14·6; S, 11·3. $C_{11}H_{15}O_4N_3S$ requires C, 46·3; H, 5·3; N, 4·7; S, 11·2%). Light absorption (chloroform) : $\lambda_{max.}$ = 2780, 3070 A.; ϵ = 13,400, 10,850, respectively.

5-Amino-2-mercapto-4-carbethoxy-1-methylglyoxaline.—5-Amino-2-methylamino-4-carbethoxythiazole (12 g.) was refluxed for 45 minutes in 10% aqueous sodium carbonate (150 c.c.), and the crystalline solid (2·3 g.), m. p. 210°, deposited on cooling was filtered off (see below). Crystallisation from ethanol (40 c.c.) (charcoal) gave colourless prisms of *5-amino-2-mercapto-4-carbethoxy-1-methylglyoxaline*, m. p. 211° (decomp.) (Found : C, 42·4; H, 5·5; N, 21·2; S, 15·7. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9; S, 15·9%). Light absorption (ethanol) : $\lambda_{max.}$ = 2280, 2690, 3070 A.; ϵ = 9,050, 10,050, 22,100, respectively. It dissolved in hot aqueous sodium carbonate with a red coloration, was sparingly soluble in dilute hydrochloric acid, and could be diazotised. The filtrate (see above) was neutralised and evaporated to dryness in a vacuum. The residue was extracted with hot methanol (200 c.c.), and the extract concentrated to 40 c.c. and diluted with ether (150 c.c.). Repeated crystallisation from ethyl acetate–ethanol of the cream solid (8 g.), m. p. 271° (decomp.), which was precipitated, gave colourless micro-plates of a *compound*, m. p. 273° (decomp.) (Found : C, 32·0; H, 4·2; N, 30·3; S, 17·5. $C_5H_6O_2N_4S$ requires C, 31·9; H, 4·3; N, 29·8; S, 17·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2560, 2930 A.; ϵ = 11,275, 13,450, respectively. It dissolved in dilute aqueous sodium carbonate, giving a red coloration. On refluxing the preceding compound (1·5 g.) for 20 minutes with 30% hydrochloric acid (12 c.c.), vigorous effervescence occurred, and on cooling cream prisms (0·9 g.) of 3-methyl-2-thiohydantoin, m. p. and mixed m. p. with authentic material 162°, crystallised.

5-Amino-2-mercapto-4-carbethoxy-1-methylglyoxaline (1 g.) was refluxed in ethanol (20 c.c.) with Raney nickel (*ca.* 3 g.) for 45 minutes. The filtrate was evaporated to dryness in a vacuum, and the crude product (0·7 g.) crystallised from ethyl acetate–ethanol, giving colourless rods of *5-amino-4-carbethoxy-1-methylglyoxaline*, m. p. 192° (Found : C, 50·0; H, 6·2; N, 24·8. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·5; N, 24·8%). Light absorption (ethanol) : $\lambda_{max.}$ = 2685 A.; ϵ = 13,775. It dissolved in dilute hydrochloric acid and could be diazotised. Dissolving the base (1·5 g.) in hot ethanol (15 c.c.) containing 6% ethanolic hydrogen chloride (12 c.c.) and diluting with ether (55 c.c.) gave colourless needles (1·5 g.) of *5-amino-4-carbethoxy-1-methylglyoxaline hydrochloride*, m. p. 203° (decomp.) (Found : C, 40·6; H, 5·8; N, 20·4. $C_7H_{12}O_2N_3ClS$ requires C, 40·9; H, 5·9; N, 20·4%).

5-Amino-2-methylamino-4-carbethoxythiazole (4 g.) was heated at 100—110° with ethanol (25 c.c.) and liquid ammonia (5 c.c.) for 24 hours (sealed tube). The crystals (2·2 g.), m. p. 245° (decomp.), crystallised from a large volume of methanol to give colourless irregular prisms of *5-amino-2-mercapto-4-carbamido-1-methylglyoxaline*, m. p. 251° (decomp.) (Found : C, 35·0; H, 5·0; N, 33·0; S, 17·9. $C_5H_8ON_4S$ requires C, 34·9; H, 4·7; N, 32·6; S, 18·6%). Light absorption (ethanol) : $\lambda_{max.}$ = 2680, 3030 A.; ϵ = 9,975, 18,925, respectively. It dissolved in dilute hydrochloric acid and could be diazotised. It gave a red solution in alkali.

The preceding glyoxaline (2·7 g.) was refluxed for 40 minutes in ethanol (220 c.c.) with Raney nickel (*ca.* 6 g.). The crude product (1·9 g.) obtained by evaporation in a vacuum of the filtrate crystallised from ethanol (100 vols.) to give colourless scintillating needles of *5-amino-4-carbamido-1-methylglyoxaline*, m. p. 254° (decomp.) (Found : C, 42·9; H, 6·0; N, 38·6. $C_5H_8ON_4$ requires C, 42·8; H, 5·8; N, 40·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2680 A.; ϵ = 13,300. Heating it with a 20% toluene solution of carbonyl chloride (0·5 g. in 12 c.c.) at 170° (sealed tube) for 16 hours gave 5-amino-4-carbamido-1-methylglyoxaline hydrochloride (0·55 g.), m. p. 257°, which reverted to the base on neutralisation.

Phenyl *iso*thiocyanate (24 c.c.) was added to ethyl α-aminocyanoacetate (26 g.) in ether (100 c.c.) and the mixture allowed to reflux gently. After standing overnight the colourless needles (46 g.), m. p. 200°, were filtered off and crystallised from ethanol to give colourless prisms of *5-amino-2-anilino-4-carbethoxythiazole*, m. p. 200° (Found : C, 54·6; H, 5·1; N, 15·8. $C_{12}H_{13}O_2N_3S$ requires C, 54·7; H, 5·0; N, 16·0%). Light absorption (chloroform) : $\lambda_{max.}$ = 2910 A.; ϵ = 14,750.

The preceding thiazole (2 g.) was dissolved in pyridine (9 c.c.) and boiled for 1 minute with phenyl *iso*thiocyanate (1 c.c.). On cooling and dilution with methanol (40 c.c.) a yellow solid (1·6 g.), m. p. 218°, was obtained which crystallised from dioxan to give yellow needles of *5-phenylthioureido-2-anilino-*

4-*carbethoxythiazole*, m. p. 218° (Found : N, 14·0. $C_{19}H_{18}O_2N_4S_2$ requires N, 14·1%). Light absorption (dioxan) : $\lambda_{max.}$ = 2900, 3700 A.; ϵ = 26,650, 13,350, respectively.

The authors thank Dr. E. A. Braude for the determination of absorption spectra.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
LONDON, S.W.7.

[*Received, February 6th* 1948.]