308. *Studies in the Azole Series. Part XVII. The Preparation and Cyclisation Reactions of Aminocyanoacetamide.*

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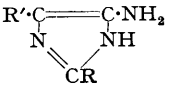
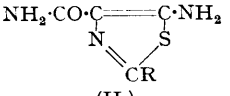
Aminocyanoacetamide has been prepared and cyclised to a variety of 5-aminothiazole-4-carboxyamides and 5-aminoglyoxaline-4-carboxyamides.

Recent parts of this series (Parts XI—XIV, this vol., pp. 1061 *et seq.*) described the use of ethyl aminocyanoacetate in the synthesis of 5-amino-4-carbethoxy-thiazoles and -glyoxalines (I; R′ = CO_2Et) and their further conversion into thiazolopyrimidines and purines, respectively. The latter syntheses comprise variants on a possible more useful approach to purines *via* the unknown 5-amino-4-cyanoglyoxalines (I; R′ = CN). This approach, which is at present under investigation, seeks to complete the pyrimidine ring of the purine system by linking the amino- and the cyano-substituent in (I; R′ = CN) with the facility with which these groups of an α-amino-nitrile may be locked into a glyoxaline ring, as was earlier described. Two routes for the preparation of the requisite compounds (I; R′ = CN) at once claim attention; they are (*a*) the preparation and dehydration of appropriate amides (I; R′ = $CO{\cdot}NH_2$), and (*b*) the preparation and cyclisation of the hitherto undescribed aminomalonitrile. The present communication describes experiments directed towards (*a*), together with some related syntheses.


(I.)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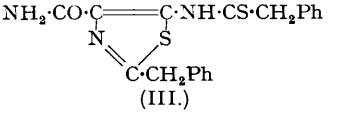
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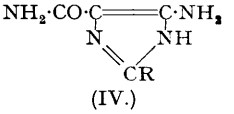
(IV.)

When ethyl aminocyanoacetate was kept with aqueous ammonia at 0°, *aminocyanoacetamide* rapidly separated. Like other α-amino-nitriles studied in this series, the new compound reacted smoothly with carbon disulphide to give a pseudo-acidic compound which must be

5-amino-2-mercaptothiazole-4-carboxyamide (II; R = SH), for on methylation in alkaline solution it was converted into the alkali-insoluble *5-amino-2-methylthiothiazole-4-carboxyamide* (II; R = SMe), which could be diazotised and was characterised as the corresponding 5-*formamido-* and 5-*benzamido*-compound as well as a *diacetyl* compound of unelucidated constitution.

Again, treatment of aminocyanoacetamide with an equimolecular quantity of ethanolic phenyldithioacetic acid gave a new diazotisable base (cf. Cook, Heilbron, and Levy, *J.*, 1947, 1594), *5-amino-2-benzylthiazole-4-carboxyamide* (II; R = CH_2Ph); an excess of the dithio-acid with either aminocyanoacetamide or (II; R = CH_2Ph) gave a compound which could not be diazotised and must be *5-phenylthioacetamido-2-benzylthiazole-4-carboxyamide* (III). A similar reaction between aminocyanoacetamide and sodium dithioformate in cold aqueous solution led to yet another diazotisable base formulated as *5-aminothiazole-4-carboxyamide* (II; R = H).

α-Amino-nitriles have been found to react with *iso*thiocyanates (Cook, Downer, and Heilbron, *J.*, 1948, 1262) to yield in most cases substituted 2 : 4-diaminothiazoles. Aminocyanoacetamide behaved similarly in this respect, reacting with methyl *iso*thiocyanate to give *5-amino-2-methylaminothiazole-4-carboxyamide* (II; R = NHMe). Like others of its class, the last compound was converted into a pseudo-acidic isomeride on treatment with alkali; the isomeride was identical with 5-amino-2-mercapto-1-methylglyoxaline-4-carboxyamide, prepared earlier (*idem, ibid.*) by the interaction of the corresponding ethyl glyoxalinecarboxylate and ammonia. Aminocyanoacetamide reacted similarly with carbethoxy *iso*thiocyanate and also with benzoyl *iso*thiocyanate to give diazotisable bases which are analogously formulated as *5-amino-2-carbethoxyamino-* and *5-amino-2-benzamido-thiazole-4-carboxyamide* respectively.

Finally, it was earlier shown (Cook, Davis, Heilbron, and Thomas, *loc. cit.*) that α-amino-nitriles reacted with thioiminoethers or with formamidine to give 5-aminoglyoxalines. In parallel fashion aminocyanoacetamide and formamidine afforded 5-aminoglyoxaline-4-carboxyamide (IV; R = H), and from thioacetiminobenzyl ether there was obtained *5-amino-2-methylglyoxaline-4-carboxyamide* (IV; R = Me).

The glyoxaline (IV; R = H) and the corresponding 3-methyl compound (Sarasin and Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713) have hitherto been the only known 5-aminoglyoxaline-4-carboxyamides. The former is of particular interest as it appears to be a natural precursor of purines in bacterial synthesis, and accumulates in cultures of *E. coli.* in presence of sublethal quantities of sulphanilamide (Shrive, Ackermann, Gordon, Getzendaner, and Eakin, *J. Amer. Chem. Soc.*, 1947, **69**, 725). The present synthesis makes this compound (as well as its analogues) easily accessible, and its natural occurrence lends significance to the conversion of both it and its analogues into purines to be described in a subsequent communication.

Experimental.

Preparation of Aminocyanoacetamide.—A solution of ethyl aminocyanoacetate (25 g.) in ether (35 c.c.) was cooled to 0° and stirred with ice-cold aqueous ammonia (35 c.c., *d* 0·88). Crystals began to separate after 15 minutes: the solution was stirred occasionally for a further 15 minutes and then filtered. The *aminocyanoacetamide* (11 g.), crystallised from ethyl acetate, separated in glistening white rhombohedral leaflets, m. p. 121° (Found: C, 36·8; H, 5·4; N, 42·5. $C_3H_5ON_3$ requires C, 36·4; H, 5·2; N, 42·4%).

Reaction of Aminocyanoacetamide with Carbon Disulphide.—Aminocyanoacetamide (2·0 g.) was covered with methanol (20 c.c.), and the solution was heated under reflux with excess of carbon disulphide (5 c.c.) for 30 minutes, a yellow solid (2·1 g.) separating from the hot solution as micro-laths. It was purified by dissolving it in 1N-aqueous sodium carbonate and precipitating it with 1N-hydrochloric acid. It was formulated as *5-amino-2-mercaptothiazole-4-carboxyamide* (II; R = SH), m. p. 239° (decomp.) (Found: C, 27·8; H, 2·8; N, 23·8. $C_4H_5ON_3S_2$ requires C, 27·4; H, 2·9; N, 24·0%).

The thiazole (2·0 g.) was methylated by dissolving it in 1N-aqueous sodium hydroxide (5 c.c.), and shaking the solution with an excess (3 c.c.) of methyl sulphate. After 2—3 minutes the solution set to a solid mass and the product, *5-amino-2-methylthiothiazole-4-carboxyamide* (II; R = SMe), m. p. 148°, was collected (2·0 g.), washed with water (20 c.c.) followed by ether (5 c.c.), and recrystallised from ethanol, forming long, thin, slightly tapered rods, m. p. 148° (Found: C, 31·9; H, 3·9; N, 21·9. $C_5H_7ON_3S_2$ requires C, 31·7; H, 3·7; N, 22·2%). (i) This amide (0·5 g.) was heated under reflux for 4 hours with acetic anhydride (100 c.c.). The excess of reagent was removed under reduced pressure, and the residue was extracted with hot ethanol (8 c.c.). On cooling, crystals (0·6 g.) of the *diacetyl* derivative separated, and recrystallised from ethanol in laths, m. p. 192° (Found: C, 39·9; H, 4·0; N, 15·7. $C_9H_{11}O_3N_3S_2$ requires C, 39·6; H, 4·05; N, 15·4%). (ii) 5-Amino-2-methylthiothiazole-4-carboxyamide (1·0 g.) was dissolved in ether (125 c.c.), and the solution treated with an excess of benzoyl chloride (2·0 g.) and shaken for 2 hours with 1N-aqueous sodium hydrogen carbonate (100 c.c.). The *benzoyl* derivative (1·5 g.) was filtered off, dried, and recrystallised from glacial acetic acid, forming laths, m. p. 202° (Found: C, 48·9; H, 3·9; N, 14·3. $C_{12}H_{11}O_2N_3S_2$ requires C, 49·1; H, 3·8; N, 14·3%). (iii) The original amide (0·5 g.) was heated under reflux for 2 hours with formic acid (12 c.c.) and acetic anhydride (12 c.c.), and the solvents removed under reduced pressure. The residue was

dissolved in the minimum quantity of hot acetic acid (5 c.c.), and methanol (15 c.c.) added. The crystals (0·4 g.) of the N-*formyl* derivative recrystallised from glacial acetic acid in laths, m. p. 219·5—220° (Found : N, 19·2. $C_6H_7O_2N_3S_2$ requires N, 19·3%).

Reaction of Aminocyanoacetamide with Phenyldithioacetic Acid.—(i) Aminocyanoacetamide (1·0 g.) was covered with ethanol (35 c.c.), and the solution heated under reflux for 1¼ hours with an excess (3·5 g.) of phenyldithioacetic acid in ether (10 c.c.) and then diluted with crushed ice (120 g.). The milky solution was kept at 0° (1 hour) and then filtered. The product, 5-*phenylthioacetamido*-2-*benzylthiazole*-4-*carboxyamide* (III) (1·9 g.), was washed with ether (20 c.c.), and recrystallised from benzene in thin, white, tapered rods, m. p. 163·5° (Found: C, 62·0; H, 5·1; N, 11·4. $C_{19}H_{17}ON_3S_2$ requires C, 62·1; H, 4·7; N, 11·4%).

(ii) The preceding experiment was repeated with phenyldithioacetic acid (1·7 g.) in ether (10 c.c.) and aminocyanoacetamide (1·0 g.). The product (0·85 g.) was washed with ether, and 5-*amino*-2-*benzylthiazole*-4-*carboxyamide* (II; R = CH_2Ph) was recrystallised from toluene, forming clusters of bifurcated plume-shaped blades, m. p. 144° (Found : C, 56·6; H, 4·5. $C_{11}H_{11}ON_3S$ requires C, 56·8; H, 4·8%).

Reaction of Aminocyanoacetamide with Sodium Dithioformate.—Aminocyanoacetamide (0·5 g.) and sodium dithioformate (0·8 g.) were dissolved in water (4 c.c.). The solution was left at room temperature for 12 hours and then at 0° for 24 hours. The crystals which appeared (0·1 g.) were filtered off and the filtrate was extracted three times with ether (50 c.c.). The extract was concentrated, leaving further yellow crystals. The combined product, 5-*aminothiazole*-4-*carboxyamide* (II; R = H) (0·3 g.), crystallised from toluene in laths, m. p. 140—141° (Found : N, 29·2. $C_4H_5ON_3S$ requires N, 29·3%).

Reaction of Aminocyanoacetamide with Methyl iso*Thiocyanate.*—Aminocyanoacetamide (1·0 g.) was heated under reflux with ethyl acetate (80 c.c.) and methyl *iso*thiocyanate (0·7 g.) for 0·5 hour. The solvent was removed under reduced pressure, and the residue crystallised from methanol. 5-*Amino*-2-*methylaminothiazole*-4-*carboxyamide* (II; R = NHMe) (1·1 g.) separated, m. p. 178° (Found : C, 35·2; H, 4·9; N, 32·8. $C_5H_8ON_4S$ requires C, 34·9; H, 4·7; N, 32·5%).

The preceding compound (1·2 g.) was heated under reflux for 1 hour with 1N-aqueous sodium carbonate (10 c.c.). The solution was then made just acid to litmus with 1N-hydrochloric acid. 5-Amino-2-mercapto-1-methylglyoxaline-4-carboxyamide (0·9 g.) separated, and recrystallised from methanol in laths, m. p. 245°; it gave no depression on mixed m. p. determination with authentic material.

Reaction of Aminocyanoacetamide with Carbethoxy iso*Thiocyanate.*—Aminocyanoacetamide (1·0 g.) was heated under reflux with acetone (40 c.c.) and the *iso*thiocyanate (1·3 g.) for 15 minutes. The solution was cooled and diluted with crushed ice (150 g.). The product (1·6 g.) was crystallised from ethanol, 5-*amino*-2-*carbethoxyaminothiazole*-4-*carboxyamide* (II; R = $NH{\cdot}CO_2Et$) separating in laths which gradually blackened up to 400° without melting (Found : C, 36·5; H, 4·3; N, 23·9. $C_7H_{10}O_3N_4S$ requires C, 36·5; H, 4·4; N, 24·3%).

Reaction of Aminocyanoacetamide with Benzoyl iso*Thiocyanate.*—Aminocyanoacetamide (1·0 g.) and benzoyl *iso*thiocyanate (1·6 g.) were heated under reflux with acetone (30 c.c.) for 15 minutes, a dense yellow precipitate of 5-*amino*-2-*benzamidothiazole*-4-*carboxyamide* (II; R = NH·COPh) being formed. The solution was cooled and the product (1·8 g.) was collected and washed with acetone and with water. It was crystallised from aqueous pyridine in clusters of fine white needles, m. p. 285° (Found : C, 50·5; H, 4·2; N, 21·4. $C_{11}H_{10}O_2N_4S$ requires C, 50·4; H, 3·9; N, 21·4%).

Reaction of Aminocyanoacetamide with Thioacetiminobenzyl Ether Hydrochloride.—Aminocyanoacetamide (0·5 g.) and the thioiminoether hydrochloride (1·0 g.) were dissolved in dry pyridine (5 c.c.). The solution was kept at 80° (10 minutes), then set aside overnight at 0°. The product, 5-*amino*-2-*methylglyoxaline*-4-*carboxyamide hydrochloride*, m. p. 238—240°, was collected, and crystallised from methanol–ether in colourless prisms (Found : C, 33·6; H, 5·6; N, 31·5. $C_5H_9ON_4Cl$ requires C, 34·0; H, 5·1; N, 31·7%).

Reaction of Aminocyanoacetamide with Formamidine Hydrochloride.—Aminocyanoacetamide (5·0 g.) and formamidine hydrochloride (4·0 g.) were heated under reflux in methanol (20 c.c.) for 1 hour. Attempts to isolate the free base led to a brown diazotisable oil, and the solution was treated with a saturated solution of picric acid (10 g.) in methanol. On cooling, a picrate (5·4 g.), m. p. 210—214°, separated, and was recrystallised repeatedly from ethanol to give yellow needles, m. p. 236° (decomp.). The picrate was formulated as that of 4-aminoglyoxaline-5-carboxyamide (IV; R = H), for which Windaus and Langenbeck (*Ber.*, 1923, **56**, 683) report m. p. 240° (decomp.) (Found : C, 33·4; H, 3·4; N, 26·3. Calc. for $C_4H_6ON_4,C_6H_3O_7N_3$: C, 33·8; H, 3·1; N, 27·6%). The low value for nitrogen found for this compound has been commented upon elsewhere (Stetten and Fox, *J. Biol. Chem.*, 1945, **161**, 333).

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