268. *Studies in the Azole Series. Part VIII. The Interaction of α-Amino-nitriles and Carbethoxy*isothiocyanate.

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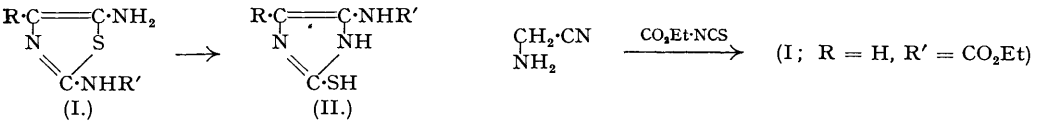
Several α-amino-nitriles have been brought into reaction with carbethoxy*iso*thiocyanate (ethyl *iso*thiocyanatoformate) to give, according to substitution and experimental conditions, derivatives of *N*-carbethoxythioureido-compounds or of 5-amino-2-carbethoxyaminothiazoles (*e.g.*, I; R = H, R′ = CO_2Et). Some of these, besides undergoing the expected reactions, may be isomerised to 4(or 5)-carbethoxyamino-2-mercaptoglyoxalines (*e.g.*, II; R = H, R′ = CO_2Et) which can be desulphurised to 4(or 5)-carbethoxyaminoglyoxalines, so confirming the assigned structures. Ethyl α-aminocyanoacetate, bearing the strongly electronegative carbethoxy-group, does not exhibit all these reactions, the derived thiazole easily reverting to the thioureido-compound without giving a cyclic isomeride.

It was shown (Part VI, Cook, Downer, and Heilbron, this vol., p. 1262) that certain 5-amino-2-benzamidothiazoles (I; R′ = Bz) isomerised under the influence of weak alkali into 5-benzamido-2-mercaptoglyoxalines (II; R′ = Bz). The compounds (I) were prepared by the



(I.) (II.)

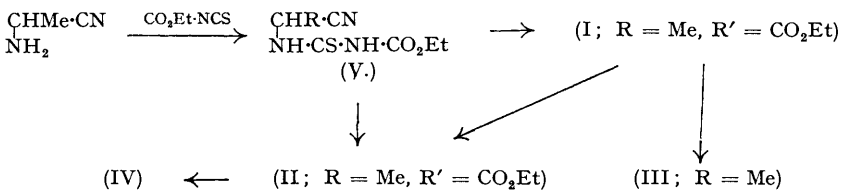
action of benzoyl *iso*thiocyanate on α-amino-nitriles. The present paper describes the reactions taking place between α-amino-nitriles and carbethoxy*iso*thiocyanate (ethyl *iso*thiocyanatoformate).

Equimolecular quantities of aminoacetonitrile and carbethoxy*iso*thiocyanate interacted to give a primary amine. The latter could be diazotised, formed a *monoacetyl* derivative, and condensed with benzaldehyde to give a *benzylidene* derivative. Having regard to reactions discussed in earlier parts of this series, the new amine is therefore formulated as 5-*amino*-2-*carbethoxyaminothiazole* (I; R = H, R′ = CO_2Et). As with the analogous compounds described in Part VI (*loc. cit.*), treatment of this with another molecular quantity of carbethoxy*iso*thiocyanate led to the formation of (probably) 2-carbethoxyamino-5-carbethoxythioureidothiazole (III; R = H). Boiling (I; R = H, R′ = CO_2Et) with aqueous sodium carbonate led to its

(III.) (IV.)

isomerisation, desulphurisation of the product affording 4(or 5)-carbethoxyaminoglyoxaline (IV; R = H), completely identified with the product with this formulation described by Balaban (*J.*, 1930, 268); this structural proof supports the interpretation of similar transformations noted below and confirms the arguments given in Part VI (*loc. cit.*). The isomerised product from (III) must therefore also be cyclic and is clearly 4(or 5)-*carbethoxyamino*-2-*mercaptoglyoxaline* (II; R = H, R′ = CO_2Et). The latter formed a *monoacetyl* derivative, probably on the sulphur atom.

Pure α-aminopropionitrile and carbethoxy*iso*thiocyanate when brought together in equimolecular quantities gave an unstable colourless compound, obviously α-*carbethoxythioureidopropionitrile* (V; R = Me) which isomerised on standing to a base having properties similar to those of (I; R = H, R′ = CO_2Et) and which accordingly must be 5-*amino*-2-*carbethoxyamino*-4-*methylthiazole* (I; R = Me, R′ = CO_2Et); curiously enough, this compound



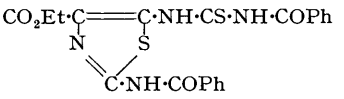
was also obtained directly from crude α-aminopropionitrile and carbethoxy*iso*thiocyanate and, like other compounds of its type, it reacted further with carbethoxy*iso*thiocyanate to give

2-*carbethoxyamino*-5-*carbethoxythioureido*-4-*methylthiazole* (III; R = Me). When either (V) or (I; R = Me, R′ = CO_2Et) was boiled with aqueous sodium carbonate another isomeride was formed which, having regard to its thiolic properties and mode of formation, is formulated as 5-*carbethoxyamino*-2-*mercapto*-4-*methylglyoxaline* (II; R = Me, R′ = CO_2Et); elimination of the thiol group from the latter by means of Raney nickel gave 5-*carbethoxyamino*-4-*methylglyoxaline* (IV; R = Me).

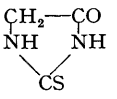
In entirely similar fashion carbethoxy*iso*thiocyanate and α-aminobenzyl cyanide afforded α-*carbethoxythioureidobenzyl cyanide* and 5-*amino*-2-*carbethoxyamino*-4-*phenylthiazole*; these were converted as expected into the *benzylidene* derivative of 5-amino-2-carbethoxyamino-4-phenylthiazole, 5-*acetamido*-2-*carbethoxyimino*-3-*acetyl*-4-*phenylthiazoline*, and 2-*carbethoxyamino*-5-*carbethoxythioureido*-4-*phenylthiazole*, by isomerisation into 5-*carbethoxyamino*-2-*mercapto*-4-*phenylglyoxaline*, and thence by desulphurisation into 5-*carbethoxyamino*-4-*phenylglyoxaline*.

The results of this communication and of Part VI (*loc. cit.*) suggested that such reactions might provide a facile route to intermediates useful in purine syntheses. Experiments were accordingly carried out employing ethyl aminocyanoacetate. This amino-nitrile and benzoyl *iso*thiocyanate afforded successively *ethyl* 5-*amino*-2-*benzamidothiazole*-4-*carboxylate* (I; R = CO_2Et, R′ = Bz) and *ethyl* 2-*benzamido*-5-*benzoylthioureidothiazole*-4-*carboxylate* (VI)

(VI.)



(VII.)



(cf. Part VI, *loc. cit.*). The former, however, on boiling with aqueous potassium carbonate underwent hydrolysis to 5-*amino*-2-*benzamidothiazole*-4-*carboxylic acid* without rearrangement, for when the product was refluxed with ethanolic hydrogen chloride the *hydrochloride* of the original ester-base was formed. Similarly on acetylation the re-esterified product yielded *ethyl* 5-*acetamido*-2-*benzimido*-3-*acetylthiazoline*-4-*carboxylate* identical with that prepared from the original compound. Efforts to isomerise (I; R = CO_2Et, R′ = Bz) by more drastic treatment with alkali resulted only in extensive changes and formation of 2-thiohydantoin (VII).

On the other hand, carbethoxy*iso*thiocyanate reacted with ethyl aminocyanoacetate to give a product which had at most only very weak basic properties and failed to undergo any obvious reaction with nitrous acid. It was, however, converted into the *hydrochloride* or *hydrobromide* of an isomeric base by fairly prolonged treatment with the appropriate acid. These salts were diazotised by nitrous acid, and there can be little doubt that the primary product is *carbethoxythioureidocarbethoxyacetonitrile* (V; R = CO_2Et) which isomerises in presence of acids to give salts of *ethyl* 5-*amino*-2-*carbethoxyaminothiazole*-4-*carboxylate* (I; R = R′ = CO_2Et); this change was consonant with the alteration observed in light absorption. The salts reverted to the thiourea derivative when attempts were made to obtain the free base. The isomerisation ensued also with further reaction when (V; R = CO_2Et) was brought into contact with more carbethoxy*iso*thiocyanate in pyridine, *ethyl* 2-*carbethoxyamino*-5-*carbethoxythioureidothiazole*-4-*carboxylate* (III; R = CO_2Et) being formed. Treatment of (V; R = CO_2Et) with acetic anhydride effected a rather similar change with formation of *ethyl* 2-*carbethoxyamino*-5-*acetamidothiazole*-4-*carboxylate*. The action of sodium hydroxide or alkoxide on (V; R = CO_2Et) afforded a sodium salt which was apparently only a salt of the *iso*-form of the thiourea; when methylated, the sodium salt gave an S-*methyl* derivative, the acyclic structure of which was reflected in its absorption spectrum when compared with the spectra of (V; R = CO_2Et) and (III; R = CO_2Et). Finally, treatment of (V; R = CO_2Et) with ammonia failing to yield the required glyoxaline, this part of the project was abandoned.

Efforts were made to effect reactions of the above kind but without introducing the benzoyl or carbethoxy-blocking groups. Interaction of thiocyanic acid and aminoacetonitrile under various conditions, however, gave only the salt, *aminoacetonitrile* (*cyanomethylammonium*) *thiocyanate*, for its benzoylation yielded hippuronitrile. Similarly, only α-*aminobenzyl cyanide thiocyanate* or *ethyl aminocyanoacetate thiocyanate* could be obtained from the appropriate bases, no subsequent rearrangement even to thioureas being observed.

It is clear that the possibility of effecting the complete series of changes described above with any one nitrile depends markedly on the nature of the compound employed, and perhaps more on the electronegative character of the group attached to the amino-nitrile carbon atom. For instance, using carbethoxy*iso*thiocyanate, the thioureido-compounds derived from amino-aceto- or -propio-nitrile isomerise almost spontaneously into thiazole derivatives; that from α-aminobenzyl cyanide cyclises with less readiness, and, using ethyl aminocyanoacetate,

the cyclic structure of the product is maintained only with difficulty or when further substitution renders reversion to the thioureido-form impossible. It is as yet impossible to distinguish the effect of differing substitution in the *iso*thiocyanate molecule, and experiments to elucidate this are in progress.

Experimental.

5-Amino-2-carbethoxyaminothiazole.—Ethyl chloroformate (100 c.c.) was added with stirring to a boiling solution of potassium thiocyanate (100 g.) in acetone (1 l.); after cooling, potassium chloride was filtered off and washed with acetone (200 c.c.). Fractionation of the solution, eventually in a vacuum, gave carbethoxy*iso*thiocyanate (55 g., 41%), b. p. 56°/18 mm. (cf. Dixon and Taylor, *J.*, 1908, **93**, 697).

Carbethoxy*iso*thiocyanate (19·6 g.) was added dropwise to aminoacetonitrile (8·4 g.) in ether (150 c.c.) with stirring at 0°. The colourless crystals (20 g.) which separated were filtered off and crystallised from ethanol in colourless needles of *5-amino-2-carbethoxyaminothiazole* (I; R = H, R′ = CO_2Et), m. p. 124° (Found : C, 38·5; H, 5·0; N, 22·2. $C_6H_9O_2N_3S$ requires C, 38·5; H, 4·8; N, 22·4%). Light absorption (ethanol) : $\lambda_{max.}$ = 2600 A., ϵ = 15,500. It diazotised and coupled with β-naphthol, giving a red precipitate. On addition of an ethereal solution of hydrochloric acid to the thiazole in alcohol, the hydrochloride, m. p. 180° (decomp.), was formed immediately. It combined with a further molecule of carbeth*iso*thiocyanate on boiling in pyridine to give a greenish-yellow solid, presumably the carbethoxythioureido-derivative (III; R = H).

The preceding thiazole (1 g.) was warmed gently on the steam-bath with acetic anhydride (2 c.c.) and sulphuric acid (1 drop) for 3 mins. The crystals (1 g.) which formed recrystallised from methanol in colourless needles of *5-acetamido-2-carbethoxyaminothiazole*, m. p. 243° (Found : C, 42·4; H, 4·7. $C_8H_{11}O_3N_3S$ requires C, 41·9; H, 4·8%). Light absorption (ethanol) : $\lambda_{max.}$ = 2870 A., ϵ = 12,000.

5-Amino-2-carbethoxyaminothiazole was refluxed with 1 equiv. of benzaldehyde in alcohol. The *benzylidene* derivative, which base quickly separated, crystallised from chloroform in buff needles, m. p. 260° (decomp.) (Found : C, 56·7; H, 4·7; N, 14·8. $C_{13}H_{13}O_2N_3S$ requires C, 56·7; H, 4·7; N, 15·3%). Light absorption (chloroform) : $\lambda_{max.}$ = 3560 A., ϵ = 22,000.

4(or 5)-*Carbethoxyamino-2-mercaptoglyoxaline.*—5-Amino-2-carbethoxyaminothiazole (16 g.) was heated on the steam-bath for 10 mins. with 5% aqueous sodium carbonate (80 c.c.). The cold solution was neutralised with hydrochloric acid, kept at 0°, and the crude product crystallised from ethyl acetate to give colourless irregular prisms of 4(or 5)-*carbethoxyamino-2-mercaptoglyoxaline* (II; R = H, R′ = CO_2Et), m. p. 173° (Found : N, 22·0. $C_6H_9O_2N_3S$ requires N, 22·4%). Light absorption (ethanol) : $\lambda_{max.}$ = 2690 A., ϵ = 13,850. The glyoxaline gives a deep blue solution in sodium hydroxide.

The foregoing compound (1 g.) in ethanol (25 c.c.) was refluxed with Raney nickel (*ca.* 2 g.) for 40 mins. The filtrate from the nickel was evaporated to dryness in a vacuum, and the product (0·45 g.) crystallised from water to give colourless scintillating prisms of 4(or 5)-carbethoxyaminoglyoxaline (IV; R = H), m. p. 181° (Found : C, 46·6; H, 5·9; N, 27·2. Calc. for $C_6H_9O_2N_3$: C, 46·4; H, 5·85; N, 27·1%). The compound coupled with sodium diazobenzene-*p*-sulphonate to give a carmine dye.

4(or 5)-Carbethoxyamino-2-mercaptoglyoxaline was warmed with acetic anhydride containing sulphuric acid. On cooling, yellow needles separated which were recrystallised from chloroform–light petroleum in clusters of pale yellow needles of 4(or 5)-*carbethoxyamino-2-acetylthioglyoxaline*, m. p. 169° (Found : C, 41·7; H, 4·8. $C_8H_{11}O_3N_3S$ requires C, 41·9; H, 4·8%). Light absorption (chloroform) : $\lambda_{max.}$ = 2560, 3150, 3260 A., ϵ = 10,100, 7,800, 7,800, respectively. The acetyl derivative was readily hydrolysed by water.

5-Amino-2-carbethoxyamino-4-methylthiazole.—Acetaldehyde cyanohydrin (40 g.) was kept overnight with methanol (20 c.c.) and liquid ammonia (11·7 c.c.), and the excess of ammonia removed in a vacuum. Part of this crude α-aminopropionitrile (10 g.) in ether (50 c.c.) was treated with carbethoxy*iso*thiocyanate (8 c.c.) in ether (25 c.c.) at *ca.* 10°. The clear yellow solution was kept for 6 days, and the yellow solid (3·7 g.) filtered off (a further crop was obtained from the filtrate). Crystallisation from ethanol gave yellow needles of *5-amino-2-carbethoxyamino-4-methylthiazole* (I; R = Me, R′ = CO_2Et), m. p. 145° (Found : C, 41·5; H, 5·5; N, 21·0. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9%). Light absorption (chloroform) : $\lambda_{max.}$ = 2650 A., ϵ = 7450. The crude α-aminopropionitrile (30 g.) (above) was fractionally distilled in a vacuum, and the colourless fraction (11 g.) collected, b. p. 60—75°/20 mm. Carbethoxy*iso*thiocyanate (10 c.c.) in ether (25 c.c.) was added to the purified α-aminopropionitrile (11 g.) in ether (25 c.c.) with stirring at 0° to − 5°. The clear liquid was left overnight, and the long colourless needles (4 g.), m. p. 108°, filtered off, a further crop (3·3 g.) being obtained on evaporating the ether in a vacuum and washing with ether–light petroleum. Crystallisation from ethanol gave colourless needles of *α-carbethoxythioureidopropionitrile* (V; R = Me), m. p. 108° (Found : C, 42·4; H, 5·6; N, 20·5. $C_7H_{11}O_2N_3S$ requires C, 41·8; H, 5·5; N, 20·9%). Light absorption (chloroform) : $\lambda_{max.}$ = 2640 A., ϵ = 15,600. It slowly cyclised to the yellow thiazole on standing. Refluxing with ethanol for 1 hr. or heating at 118° for 10 mins. gave a quantitative yield of 5-amino-2-carbethoxyamino-4-methylthiazole, m. p. and mixed m. p. 145°. Carbethoxy*iso*thiocyanate (3 c.c.) was added cautiously to the crude α-aminopropionitrile (1·5 c.c.). The yellow solid from the vigorous reaction was rubbed with ether (20 c.c.) and crystallised from pyridine, giving cream-coloured needles of *2-carbethoxyamino-5-carbethoxythioureido-4-methylthiazole* (III; R = Me), m. p. 233° (Found : N, 16·7. $C_{11}H_{16}O_4N_4S_2$ requires N, 16·8%). Light absorption (dioxan) : $\lambda_{max.}$ = 2600, 3240 A., ϵ = 21,600, 7650, respectively. The thioureido-derivative was also obtained by boiling 5-amino-2-carbethoxyamino-4-methylthiazole (0·1 g.) with carbethoxy*iso*thiocyanate (3 drops) in pyridine (2 c.c.), diluting with ethanol and filtering; it had m. p. and mixed m. p. 230°.

5-Carbethoxyamino-2-mercapto-4-methylglyoxaline.—α-Carbethoxythioureidopropionitrile (0·7 g.) was refluxed for 10 mins. with 10% aqueous sodium carbonate (10 c.c.), and the clear colourless solution cooled to 0°. The long colourless needles (0·7 g.), m. p. 243°, were collected and crystallised from ethanol to give fine, colourless, hairy needles of *5-carbethoxyamino-2-mercapto-4-methylglyoxaline* (II; R = Me, R′ = CO_2Et), m. p. 244° (decomp.) (Found : C, 42·4; H, 5·6; N, 21·0. $C_7H_{11}O_2N_3S$ requires C, 41·8;

H, 5·5; N, 20·9%). Light absorption (ethanol) : $\lambda_{max.}$ = 2230, 2670 A., ϵ = 6250, 14,300, respectively. The same compound was obtained from the corresponding thiazole.

The preceding glyoxaline (2 g.) in ethanol (40 c.c.) was refluxed with Raney nickel (*ca.* 4 g.) for 1 hr. The filtrate from the nickel was evaporated to dryness in a vacuum, and the white solid (1·1 g.), m. p. 165—166°, crystallised from methanol–ether to give colourless prismatic needles of *5-carbethoxyamino-4-methylglyoxaline* (IV; R = Me), m. p. 167° (decomp.) (Found : C, 49·2; H, 6·8; N, 25·2. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·6; N, 24·9%).

5-Amino-2-carbethoxyamino-4-phenylthiazole.—Carbethoxy*iso*thiocyanate (15 g.) was slowly added to a solution of α-aminobenzyl cyanide (15 g.) in ether (100 c.c.) at 0°. The crude product, which crystallised on keeping, recrystallised from ethanol in almost colourless needles of *α-carbethoxythioureidobenzyl cyanide* (13 g.), m. p. 131° (Found : C, 54·3; H, 4·8; N, 16·0. $C_{12}H_{13}O_2N_3S$ requires C, 54·7; H, 5·0; N, 15·9%). Light absorption (ethanol) : $\lambda_{max.}$ = 2650 A., ϵ = 15,250.

Dilution of the ethanol filtrate from the recrystallised thiourea (above) gave a yellow solid (5 g.), m. p. 166°, which crystallised from ethyl acetate–light petroleum in cream-coloured needles of *5-amino-2-carbethoxyamino-4-phenylthiazole*, m. p. 167° (Found : N, 16·3. $C_{12}H_{13}O_2N_3S$ requires N, 15·9%). The thiourea was stable at room temperature but on being boiled in ethanol for 1½ hours and concentration of the mother-liquor, it gave the above thiazole, mixed m. p. 167°.

Ethereal solutions of carbethoxy*iso*thiocyanate and the preceding thiourea were mixed, and set aside. The crude product which separated crystallised from glacial acetic acid in short buff needles of *2-carbethoxyamino-5-carbethoxythioureido-4-phenylthiazole*, m. p. 194° (Found : C, 48·1; H, 4·9. $C_{16}H_{18}O_4N_4S_2$ requires C, 48·7; H, 4·6%). Light absorption : $\lambda_{max.}$ = 2650, 3380 A., ϵ = 16,550, 5125, respectively.

α-Carbethoxythioureidobenzyl cyanide was warmed with acetic anhydride and sulphuric acid, and the crude product crystallised from aqueous ethanol, large colourless needles of *5-acetamido-2-carbethoxyimino-3-acetyl-4-phenylthiazoline*, m. p. 169°, being obtained (Found : C, 55·0; H, 4·9; N, 12·6. $C_{16}H_{17}ON_3S$ requires C, 55·3; H, 4·9; N, 12·1%). Light absorption (ethanol) : $\lambda_{max.}$ = 2300, 2700 A., ϵ = 48,580, 26,025, respectively.

When α-carbethoxythioureidobenzyl cyanide was treated with the calculated quantity of benzaldehyde in boiling ethanol the *benzylidene* derivative of 5-amino-2-carbethoxyamino-4-phenylthiazole was formed, and crystallised in bright yellow lustrous plates, m. p. 166° (Found : N, 12·2. $C_{19}H_{17}O_2N_3S$ requires N, 12·0%), from ethanol. Light absorption (ethanol) : $\lambda_{max.}$ = 2600, 3850 A., ϵ = 28,450, 19,650, respectively. The compound was also obtained similarly from the corresponding thiazole.

5-Carbethoxyamino-2-mercapto-4-phenylglyoxaline.—α-Carbethoxythioureidobenzyl cyanide (5 g.) was heated to boiling with 10% aqueous sodium carbonate (80 c.c.). The product from the neutralised liquor crystallised from aqueous methanol in small yellow needles of *5-carbethoxyamino-2-mercapto-4-phenylglyoxaline*, m. p. 228° (decomp.) (Found : C, 54·6; H, 5·2. $C_{12}H_{13}O_2N_3S$ requires C, 54·7; H, 4·9%). Light absorption (ethanol) : $\lambda_{max.}$ = 2690, 2960 A., ϵ = 15,775, 15,775.

5-Carbethoxyamino-2-mercapto-4-phenylglyoxaline (1 g.) in ethanol (40 c.c.) was refluxed with Raney nickel (*ca.* 2 g.) for 40 mins. The filtrate from the nickel was evaporated to dryness in a vacuum, and the product (0·5 g.) crystallised from ethyl acetate to give minute colourless needles of *5-carbethoxyamino-4-phenylglyoxaline*, m. p. 172° (Found : N, 18·8. $C_{12}H_{13}O_2N_3$ requires N, 18·6%). Light absorption (ethyl acetate) : $\lambda_{max.}$ = 2640 A., ϵ = 16,150.

Ethyl 5-Amino-2-benzamidothiazole-4-carboxylate.—Benzoyl *iso*thiocyanate (27·5 c.c.) in ether (25 c.c.) was added to ethyl aminocyanoacetate (26 g.) in ether (200 c.c.) with stirring at 0°. The clear solution was kept overnight, and the colourless rosettes (52 g.) were filtered off and washed with ether. *Ethyl 5-amino-2-benzamidothiazole-4-carboxylate* (I; R = CO_2Et, R′ = Bz) recrystallised from *ca.* 10 vols. of methanol as lemon-coloured prisms, m. p. 190° (Found : C, 53·4; H, 4·3; N, 14·6. $C_{13}H_{13}O_3N_3S$ requires C, 53·6; H, 4·5; N, 14·4%). Light absorption (chloroform) : $\lambda_{max.}$ = 3030 A., ϵ = 13,700.

The preceding thiazole (3 g.) in pyridine (7 c.c.) containing benzoyl *iso*thiocyanate (1·5 c.c.) was brought to boiling. On cooling and diluting with methanol (20 c.c.), *ethyl 2-benzamido-5-benzoylthioureidothiazole-4-carboxylate* (VI) (3·4 g.), m. p. 232° (decomp.), separated. It crystallised from pyridine in pale lemon needles, m. p. 232° (decomp.) (Found : C, 55·5; H, 4·3; N, 12·0. $C_{21}H_{18}O_4N_4S_2$ requires C, 55·5; H, 4·0; N, 12·3%). Light absorption (chloroform) : $\lambda_{max.}$ = 2370, 2880, 3630 A., ϵ = 27,250, 30,200, 14,050, respectively.

5-Amino-2-benzamido-4-carbethoxythiazole (3 g.) was refluxed with acetic anhydride (15 c.c.) for 15 mins., and the cold solution stirred into ice-water (200 c.c.) for 15 mins. The crude product (4·2 g.), m. p. 230°, was crystallised from ethanol, giving *ethyl 5-acetamido-2-benzimido-3-acetylthiazoline-4-carboxylate* as colourless needles, m. p. 236° (Found : N, 11·4. $C_{17}H_{17}O_5N_3S$ requires N, 11·2%). Light absorption (chloroform) : $\lambda_{max.}$ = 3000 A., ϵ = 23,250.

Ethyl 5-amino-2-benzamidothiazole-4-carboxylate (5 g.) was refluxed in 2% aqueous potassium carbonate (200 c.c.) for 45 mins., cooled, and filtered from unchanged thiazole (3·7 g.). The filtrate on acidification gave a pale yellow solid (1·2 g.), m. p. 184°, which was purified by repeated precipitation from its solution in ammonia with hydrochloric acid to give *5-amino-2-benzamidothiazole-4-carboxylic acid*, m. p. 206° (Found : C, 50·0; H, 3·5. $C_{11}H_9O_3N_3S$ requires C, 50·2; H, 3·4%). This acid (3·4 g.) was refluxed with 5·5% ethanolic hydrogen chloride (60 c.c.) for 1 hr. with influx of hydrogen chloride. The cream-coloured solid (2·9 g.) crystallised from ethanol to give *ethyl 5-amino-2-benzamidothiazole-4-carboxylate hydrochloride*, m. p. 227° (decomp.), as colourless needles (Found : C, 48·0; H, 4·5; N, 13·2. $C_{13}H_{14}O_3N_3ClS$ requires C, 47·6; H, 4·3; N, 12·8%). The hydrochloride on being refluxed with acetic anhydride gave colourless needles of the diacetyl derivative, m. p. and mixed m. p. 235—236°. Ethyl 5-amino-2-benzamidothiazole-4-carboxylate (5 g.) was refluxed with 10% aqueous sodium hydroxide (100 c.c.) for 45 mins., filtered hot from a little insoluble matter, and just neutralised with acetic acid. The brown crystalline solid (2·2 g.) crystallised from water in orange needles of 2-thiohydantoin (1 g.), m. p. and mixed m. p. 225°. Acidification of the neutralised filtrate gave benzoic acid (0·4 g.), m. p. and mixed m. p. 121°.

Carbethoxy*iso*thiocyanate (26 c.c.) in ether (50 c.c.) was added to ethyl aminocyanoacetate (26 g.) in ether (200 c.c.) with stirring at 0°. The clear solution was kept overnight and the crystals (4·2 g.) which formed were filtered off and washed with ether. *Carbethoxythioureidocarbethoxyacetonitrile* (V; R = CO_2Et) recrystallised from *ca.* 20 vols. of ethanol in colourless irregular plates (37 g.) which decomposed with effervescence at 190° (Found: C, 41·8; H, 5·2; N, 16·0. $C_9H_{13}O_4N_3S$ requires C, 41·7; H, 5·1; N, 16·2%). Light absorption (chloroform): $\lambda_{inflex.}$ = 2720 A., ϵ = 8550. Refluxing of the thioureido-compound (4 g.) with dry 5·5% ethanolic hydrogen chloride (80 c.c.) gave a clear colourless solution. On cooling, *ethyl 5-amino-2-carbethoxyaminothiazole-4-carboxylate hydrochloride* (3·8 g.) separated in colourless needles, m. p. 177° (decomp.) (Found: N, 13·9. $C_9H_{14}O_4N_3SCl$ requires N, 14·2%). Neutralisation of the hydrochloride with dilute sodium carbonate solution gave the original thiourea. The hydrochloride gave a deep brownish-red coloration on diazotisation and coupling with β-naphthol. When the thiourea (3 g.) was heated under reflux with hydrobromic acid until it had all dissolved (*ca.* 5 mins.), it gave colourless needles of *ethyl 5-amino-2-carbethoxyaminothiazole-4-carboxylate hydrobromide* (2·8 g.), m. p. 185°, after crystallising from ethanol (Found: C, 32·2; H, 3·8; N, 12·9. $C_9H_{14}O_4N_3BrS$ requires C, 31·8; H, 4·1; N, 12·4%). Longer refluxing with hydrobromic acid removed part of the nitrogen as ammonium bromide.

The preceding thiourea (2 g.) in pyridine (10 c.c.) containing carbethoxy*iso*thiocyanate (1 c.c.) was brought to boiling. On cooling, *ethyl 2-carbethoxyamino-5-carbethoxythioureidothiazole-4-carboxylate* (III; R = CO_2Et) (2·3 g.), m. p. 209°, separated. It crystallised from pyridine in pale lemon, hairy needles, m. p. 209° (decomp.) (Found: C, 40·0; H, 4·8; N, 14·15. $C_{13}H_{18}O_6N_4S_2$ requires C, 40·0; H, 4·65; N, 14·35%). Light absorption (chloroform): $\lambda_{max.}$ = 2640, 3470 A., ϵ = 19,100, 14,050 respectively.

Carbethoxythioureidocarbethoxyacetonitrile (5 g.) was stirred with 2N-sodium hydroxide solution (65 c.c.) at room temperature. The clear solution first formed quickly deposited pale lemon crystals of the sodium compound. Light absorption (0·5N-NaOH): $\lambda_{max.}$ = 2870 A., ϵ = 17,750. The sodium compound was also obtained in the form of feathery needles by refluxing the thiourea (1 g.) with 1 equiv. of sodium ethoxide in alcohol (10 c.c.) for 80 mins. It reacted strongly alkaline in water and on acidification reverted to the thiourea. The thiourea (1·4 g.) was shaken with methyl sulphate (0·5 c.c.) in 4% sodium hydroxide solution (8 c.c.) for 20 mins. The yellow solid (1·1 g.) crystallised from aqueous methanol to give pale lemon needles of *N-carbethoxy-S-methylisothioureidocarbethoxyacetonitrile*, m. p. 131° (Found: C, 43·3; H, 5·7; N, 15·0. $C_{10}H_{15}O_4N_3S$ requires C, 43·9; H, 5·5; N, 15·4%). Light absorption (chloroform): $\lambda_{max.}$ = 2780 A., ϵ = 12·850.

Carbethoxythioureidocarbethoxyacetonitrile (3 g.) was refluxed with acetic anhydride (10 c.c.) for 30 mins., the solution cooled to *ca.* 0°, and the colourless needles (1·4 g.) filtered off and washed with ether, a further yield (1·2 g.) being obtained by stirring the filtrate with light petroleum–ether. Recrystallisation from acetic anhydride gave *ethyl 2-carbethoxyamino-5-acetamidothiazole-4-carboxylate*, m. p. 122° (Found: C, 43·8; H, 5·1; N, 13·6. $C_{11}H_{15}O_5N_3S$ requires C, 43·8; H, 5·0; N, 13·9%). Light absorption (chloroform): $\lambda_{max.}$ = 2630, 3090 A., ϵ = 15,050, 15,050. Boiling the above monoacetyl derivative (0·5 g.) with water (65 c.c.) gave colourless crystals (0·3 g.) which recrystallised from aqueous ethanol in colourless needles of a *compound*, m. p. 175° (Found: C, 44·3; H, 5·2; N, 15·2. $C_{10}H_{14}O_4N_3S$ requires C, 44·1; H, 5·2; N, 15·4%). Light absorption (chloroform): $\lambda_{max.}$ = 2640, 3080 A., ϵ = 9800, 9800.

Carbethoxythioureidocarbethoxyacetonitrile (2 g.) was heated under reflux with dry 5% methanolic potassium hydroxide; it formed a clear solution which after 30 mins. had deposited the crystalline potassium salt (1·7 g.). This was dissolved in water (50 c.c.), the solution acidified with acetic acid, and the white solid (1·6 g.) crystallised from ethanol to give colourless needles of *carbethoxythioureidocarbomethoxyacetonitrile*, m. p. 164° (Found: C, 39·6; H, 4·6; N, 16·7. $C_8H_{11}O_4N_3S$ requires C, 39·2; H, 4·5; N, 17·1%). Light absorption (chloroform): $\lambda_{max.}$ = 2690, 2820 A., ϵ = 10,780, 10,780. It dissolved momentarily in 2N-sodium hydroxide, the solution quickly depositing crystals of the sodium salt.

Carbethoxythioureidocarbethoxyacetonitrile (5 g.) was heated at 120° with ethanol (25 c.c.) and liquid ammonia (4 c.c.) in a sealed tube for 24 hours. Evaporation of the ethanol and extraction with water left unchanged thiourea (*ca.* 4 g.). The extract oxidised in air, colouring the solution red, and gave a pale yellow precipitate with mercuric chloride suggesting the presence of a thiol group.

Pyridine thiocyanate (1 g.) was rubbed with aminoacetonitrile (0·3 g.) and the resultant paste rubbed with ethyl acetate, giving colourless plates (0·5 g.) which recrystallised from ethyl acetate in prismatic needles of *aminoacetonitrile (cyanomethylammonium) thiocyanate*, m. p. 123° (Found: C, 31·6; H, 4·9; N, 36·7. $C_3H_5N_3S$ requires C, 31·3; H, 4·4; N, 36·5%). This was also obtained by direct addition of ethereal thiocyanic acid to aminoacetonitrile. It was deliquescent, rapidly darkened in air (this instability no doubt accounted for its poor analysis), and hydrolysed in water, giving positive reactions for the thiocyanate ion. Addition of excess of sodium hydroxide solution and benzoyl chloride to this aqueous solution caused separation of hippuric acid nitrile, m. p. 144°.

α-Aminobenzyl cyanide (13·2 g.) in ether (50 c.c.) was added to a slight excess of an ethereal solution of thiocyanic acid. The resulting yellow oil solidified to a colourless crystalline mass which recrystallised from ethyl acetate as colourless rhombs of *α-aminobenzyl cyanide thiocyanate*, m. p. 141·5° (Found: C, 56·2; H, 4·8; N, 22·4. $C_9H_9N_3S$ requires C, 56·5; H, 4·7; N, 22·0%). Refluxing the salt with acetone for 15 mins. and crystallising the gum obtained after evaporation of the solvent from aqueous 2-methoxyethanol gave colourless rods, m. p. 198° (Found: C, 58·8; H, 5·8; N, 15·5%). It contained sulphur but no formulation could be assigned to it. It gave no reactions for an amino-group.

Thiocyanic acid (7·4 g.) in ether (120 c.c.) was added to ethyl aminocyanoacetate (16 g.) in dry ether (115 c.c.) with stirring at 0°. The resulting yellow oil solidified to a colourless crystalline mass (15·5 g., m. p. 108—110°) on standing. It recrystallised from *ca.* 5 vols. of ethyl acetate to give colourless needles of the *thiocyanate* of *ethyl aminocyanoacetate*, m. p. 113—114° (Found: C, 38·6; H, 4·9. $C_6H_9O_2N_3S$ requires C, 38·5; H, 4·8%). This (0·5 g.) was refluxed with pyridine (0·7 c.c.) for 4 mins. and the cold

product crystallised from ethyl acetate (30 c.c.), giving colourless needles of pyridine thiocyanate, m. p. and mixed m. p. with authentic pyridine thiocyanate 101°.

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