678. *Syntheses in the Penicillin Field. Part VII. The Preparation of Thiazolinyl-amino-oxazole Derivatives.*

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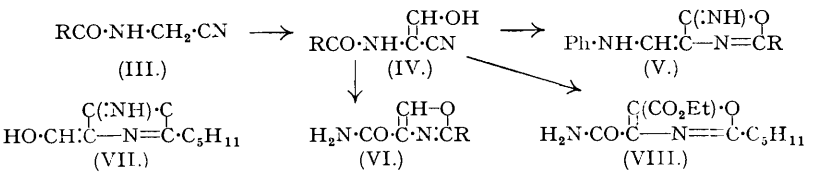
The cyclisation of certain α-acylamido-nitriles yields 5-amino-oxazoles. This reaction was utilised for the preparation of *thiazolinyl-amino-oxazoles*, required for attempts to obtain penicillins by reduction and deamination. Tautomerism in the thiazolinyl-amino-oxazole series is discussed, and the preparation of analogous *thiazolinyl-amino-thiazoles* is described.

During earlier work on penicillin it was observed that ethyl α-phenylacetamidocyanoacetate yielded an isomeride on treatment with phosphorus pentachloride in chloroform. The isomeride was basic, forming a crystalline hydrochloride, and its ultra-violet absorption spectrum showed a maximum at 2600 A.; this isomeride was therefore formulated as the 5-imino-oxazoline (I; R = Et, R′ = CH_2Ph) (Bentley, Cook, Harris, and Heilbron, *CPS*, 386).

(I.) (II.)

A similar observation in the case of ethyl α-benzamidocyanoacetate and further work ("The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 700; *CPS*. 346, 634) indicated that the products of cyclisation of α-acylamido-cyano-esters were generally 5-amino-oxazoles (II), which are tautomerides of the imino-oxazolines (I). Experiments with the benzyl esters of hexoamido- and phenylacetamido-cyanoacetic acids in another connection served to confirm these results.

Benzyl cyanoacetate was treated with sodium nitrite and acetic acid to yield *benzyl oximino-cyanoacetate*, isolated through its *silver* salt. Reduction of this compound with aluminium amalgam in moist ether gave benzyl aminocyanoacetate, obtained as the crystalline *oxalate*; acylation of the amine with phenylacetyl chloride and *n*-hexoyl chloride yielded *benzyl α-phenylacetamidocyanoacetate* and *α-hexoamidocyanoacetate*. Treatment of the last-mentioned compounds with hydrogen chloride in solvents yielded the *amino-oxazole hydrochlorides* (II; R = R′ = CH_2Ph) and (II; R = CH_2Ph, R′ = *n*-C_5H_{11}), which gave the *bases* on treatment with sodium hydrogen carbonate. These compounds showed light-absorption maxima at 2600—2660 A., and yielded transient deep-red colours after diazotisation in acetic–sulphuric acid and coupling with β-naphthol [this latter property resembling that of the 5-aminothiazoles (Cook, Heilbron, and Levy, *J.*, 1947, 1594)].



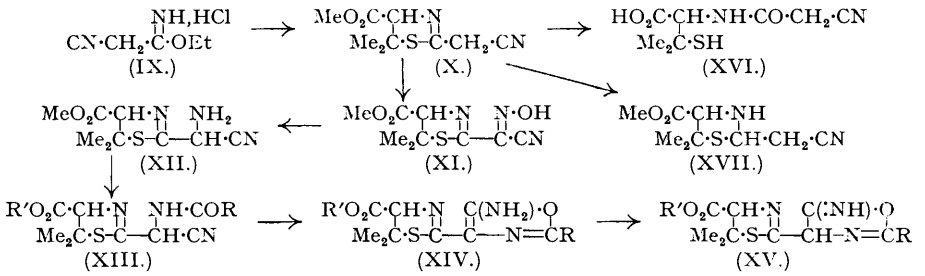
(III.) (IV.) (V.) (VII.) (VI.) (VIII.)

Similar observations were made during attempts to formylate *n*-hexoamidoacetonitrile (III; R = *n*-C_5H_{11}) (Abraham, Baker, Cornforth, Chain, Fawaz, and Robinson, *op. cit.*, p. 700); these experiments, publication of which anticipated our own work of that period, afforded evidence of the transient existence of the required formyl derivative (IV; R = *n*-C_5H_{11}) or a tautomeride thereof, but efforts to isolate this compound led to the oxazole derivatives (V; R = *n*-C_5H_{11}) (by reaction with aniline) and (VI; R = *n*-C_5H_{11}), also obtained in the present work.

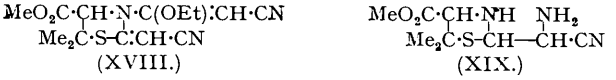
Very similar results were obtained on attempting to introduce an oxalo-residue rather than a formyl grouping. Interaction of (III; R = n-C_5H_{11}) with ethyl oxalate in presence of sodium methoxide in ether afforded a bright-yellow by-product, m. p. 220°, and an oil which gave an intense greenish-purple colour with ferric chloride and yielded a dinitrophenylhydrazone. The oil on distillation formed a crystalline compound isomeric with the expected oxalo-derivative and devoid of enol or carbinol properties. Analogy suggests its formulation as *5-carbethoxy-2-n-amyloxazole-4-carboxyamide* (VIII), which the ultra-violet light absorption supports (see Table). Efforts to formylate *N-carbobenzyloxyaminoacetonitrile* (III; R = O·CH_2Ph) were fruitless.

Earlier attempts to obtain thiazolinyloxazolones resulted in the formation of the stable, isomeric thiazolidylideneoxazolones (Part V; *op. cit.*) from which penicillins could not be obtained by mild reductive treatment. Amino-oxazoles (II) show a formal resemblance to the corresponding thiazolines as indicated by the partial structures below :

and it seemed probable that a thiazolinyl-amino-oxazole would be a stable structure *per se*, the reduction and deamination of which to a penicillin might be achieved. The preparation of compounds possessing a thiazolinyl-amino-oxazole structure was accordingly attempted.



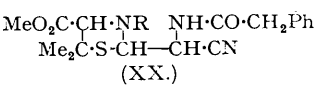
Malononitrile reacted under anhydrous conditions in ether at 0° with one equivalent each of ethanol and hydrogen chloride to yield *cyanoacetimino ethyl ether hydrochloride* (IX). Condensation of this compound with penicillamine methyl ester hydrochloride in aqueous potassium acetate–ether, or better, with penicillamine methyl ester in dry chloroform gave *methyl 5 : 5-dimethyl-2-cyanomethylthiazoline-4-carboxylate* (X). A small amount of a by-product formed in this reaction is tentatively formulated as *methyl 5 : 5-dimethyl-2-cyanomethylene-3-(2-cyano-1-ethoxyvinyl)thiazolidine-4-carboxylate* (XVIII). The structure of the



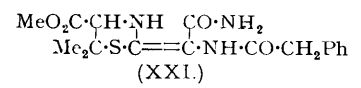
non-crystalline thiazoline (X) was confirmed by hydrolysis and reduction : hydrolysis with cold aqueous–ethanolic sodium hydroxide yielded *N-cyanoacetylpenicillamine* (XVI), isolated through its *benzylamine* salt. The acid (XVI) gave the transient blue colour with ferric chloride characteristic of penicillamine derivatives, and showed no ultra-violet absorption. The ready scission of the thiazoline ring at the S·C bond was thus well exemplified. Reduction of (X) was accomplished with excess of aluminium amalgam, and *methyl 5 : 5-dimethyl-2-cyanomethylthiazolidine-4-carboxylate* (XVII) was isolated. This thiazolidine unlike its precursor (X), formed a stable, crystalline *hydrochloride*.

Nitrosation of the thiazoline (X) was accomplished either by shaking a solution in dioxan–acetic acid with powdered sodium nitrite or by slowly treating a solution in acetic acid with aqueous sodium nitrite. *Methyl 5 : 5-dimethyl-2-oximinocyanomethylthiazoline-4-carboxylate* (XI) was thus obtained in the form of a deep-red oil which was reduced with aluminium amalgam to give methyl 5 : 5-dimethyl-2-aminocyanomethylthiazoline-4-carboxylate (XII), isolated as the crystalline *oxalate*. Reduction of the oximino-group in (XI) therefore occurs preferentially to reduction of the thiazoline ring, which was, however, reduced by means of a large excess of the amalgam ; methyl 5 : 5-dimethyl-2-aminocyanomethylthiazolidine-4-carboxylate (XIX) obtained in this manner being characterised as its crystalline *oxalate* and as the *phenylacetyl* derivative (XX; R = H). The presence of the thiazolidine NH-group in (XX; R = H) was demonstrated

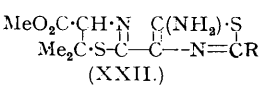
by the formation of a crystalline *hydrochloride* (XX; R = H, HCl) and an N-*carbethoxy*-derivative (XX; R = CO_2Et). Consideration was given to the cyclisation of (XX; R = H)



(XX.)



(XXI.)



(XXII.)

to a thiazolidinyl-amino-oxazole, but attempts to effect this with hydrogen chloride or phosphorus pentachloride were unsuccessful and, in view of the low yields obtained in the reduction of (XII) to (XIX), these experiments were not pursued, the approach to penicillin *via* thiazolines being preferred (see below).

The amino-nitrile (XII) was acylated with *n*-hexoyl, phenylacetyl, and benzoyl chloride to yield the n-*hexoyl*, *phenylacetyl*, and *benzoyl* derivatives (XIII; R = *n*-C_5H_{11}, R′ = Me), (XIII; R = CH_2Ph, R′ = Me), and (XIII; R = Ph, R′ = Me), respectively, as crystalline solids which were the required precursors of the thiazolinyl-amino-oxazoles. These compounds showed a single ultra-violet absorption band with maximum at 2700 A. (see Table).

Absorption Spectra.

Compound.	$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$
Aminocyanomethylthiazolines.		
(XII) oxalate	2380A	260
	3010	930
(XIII; R = C_5H_{11}, R′ = Me)	2690	590
(XIII; R = CH_2Ph, R′ = Me)	3710	570
(XIII; R = Ph, R′ = Me)	2730	650
	2290	550
(XIII; R = C_5H_{11}, R′ = H)	2210	195
	2730	540
(XIII; R = CH_2Ph, R′ = H)	2750	500
	2790 [1]	350
Thiazolinyl-amino-oxazoles and -imino-oxazolines.		
(XIV; R = C_5H_{11}, R′ = Me) hydrochloride	2350	210
	2700	230
	3380	480
(XIV; R = CH_2Ph, R′ = Me) hydrochloride	2420	245
	2680	205
	3360	535
(XIV; R = Ph, R′ = Me) hydrochloride	2820	400
	3540	840
(XIV; R = C_5H_{11}, R′ = H) hydrochloride	2360	240
	2680	200
	3380	650
(XIV; R = CH_2Ph, R′ = H) hydrochloride	2420	245
	2650	220
	3360	575
(XV; R = CH_2Ph, R′ = Me)	2600	365
	2980	365
(XV; R = Ph, R′ = Me)	2290	340
	3240	930
Methylenethiazolidine.		
(XXI)	2870	600
Thiazolinylthiazoles.		
(XXII; R = SH)	3070 [2]	415
	3600	210
(XXII; R = H)	2800 [1]	460
	2900	440
	3050 *	360
(XXII; R = CH_2Ph)	2920	385
	3080 *	350
(XXII; R = CH_2Ph) hydrochloride	2210	360
	2460	390
	2800	290
	3570	320
Aminocyanomethylthiazolidines.		
(XX; R = H)	end absorption	
(XX; R = H·HCl)	end absorption	
Penicillamines.		
(XVI), and benzylamine salt	end absorption [3]	
Oxazoles.		
(II; R=Et, R′ = CH_2Ph)	2500	700
	2600	750
(II; R = CH_2Ph, R′ = CH_2Ph)	2600 [1]	480
(II; R = CH_2Ph, R′ = C_5H_{11})	2620 [1]	400
(II; R = CH_2Ph, R′ = CH_2Ph) hydrochloride	2590	480
	2660	480
(II; R = CH_2Ph, R′ = C_5H_{11}) hydrochloride	2660	450
(VIII)	2450	410
(VI; R = C_5H_{11})	<2200	—

* Inflection. [1] In chloroform. [2] In dioxan. [3] In water.
All measurements were made in ethanol unless stated otherwise.

Attempted cyclisations of the compound (XIII; R = CH_2Ph, R′ = Me) with methanolic hydrogen chloride led only to gummy products, but treatment with phosphorus pentachloride in chloroform or, better, with hydrogen chloride in ethyl acetate, yielded a base, isolated as its *monohydrochloride*. The latter showed ultra-violet absorption compatible with the thiazolinyl-amino-oxazole hydrochloride structure (XIV) (see Table), and treatment with sodium hydrogen carbonate solution liberated the *base* (XV; R = CH_2Ph, R′ = Me), isomeric with the original acyl compound (XIII). The new base showed ultra-violet absorption at shorter wave-lengths

than the hydrochloride (XIV; R = CH_2Ph, R′ = Me) but at longer wave-lengths than the precursor (XIII; R = CH_2Ph, R′ = Me), and was therefore formulated as the thiazolinyl-imino-oxazoline (XV; R = CH_2Ph, R′ = Me), a tautomeride of (XIV). Further evidence for the structure (XV) is given later.

Cyclisation of the benzoyl and hexoyl derivatives (XIII; R = Ph and *n*-C_5H_{11}, R′ = Me) with hydrogen chloride yielded the crystalline *phenyl-* and n-*amyl-oxazole hydrochlorides* (XIV; R = Ph and *n* = C_5H_{11}, R′ = Me). Like the benzyl compound these hydrochlorides yielded the *bases* (XV; R = Ph and C_5H_{11}, R′ = Me) with sodium hydrogen carbonate or diazomethane, although the base corresponding to the *n*-amyl compound was obtained only as an oil. As expected, the hydrochloride (XIV; R = Ph, R′ = Me) showed ultra-violet absorption at longer wave-lengths than (XIV; R = CH_2Ph, R′ = Me). The shift in absorption between the hydrochloride (XIV) and the free base (XV) was the same in the phenyl as in the benzyl series, however, and tautomerism between such forms as (XIV) and (XV) is apparently possible in both series. Unlike the *n*-amyl and benzyl compounds, (XV; R = Ph, R′ = Me) formed a crystalline picrate.

Besides tautomerism between the ring forms (XIV) and (XV) a further possibility of tautomerism in the thiazolinyl-amino-oxazole series, between ring and acyclic forms, was suggested by the observation that (XV; R = *n*-C_5H_{11}, R′ = Me) on distillation afforded a product with ultra-violet absorption maximum at 2700 A., thus resembling the compounds (XIII). Additional information on this type of tautomerism was obtained on attempting to prepare the base (XV; R = CH_2Ph, R′ = Me) from the hydrochloride (XIV; R = CH_2Ph, R′ = Me) with sodium hydroxide. The product was not (XV), but the isomeric (XIII; R = CH_2Ph, R′ = Me), the amino-oxazole ring evidently being opened under alkaline conditions. This was confirmed when the ester hydrochloride (XIV; R = CH_2Ph) in dry pyridine was stored, (XIII; R = CH_2Ph, R′ = Me) being obtained in excellent yield. Similarly, hydrolysis of the hydrochloride (XIV) or the base (XV; R = CH_2Ph, R′ = Me) with the requisite amounts of alkali led to the *acid* (XIII; R = CH_2Ph, R′ = H), obtained also from the acyclic isomer (XIII; R = CH_2Ph, R′ = Me). The acid (XIII; R = CH_2Ph, R′ = H) showed ultra-violet absorption with a maximum at 2700 A., regenerated the ester (XIII; R = CH_2Ph, R′ = Me) with diazomethane, and was cyclised by hydrogen chloride to the *amino-oxazole hydrochloride* (cf. XIV; R = CH_2Ph, R′ = H), which had ultra-violet absorption identical with that of the corresponding ester hydrochloride (XIV; R = CH_2Ph, R′ = Me). The *acid* (XIII; R = *n*-C_5H_{11}, R′ = H) behaved in the same way, yielding the *hydrochloride* of (XIV; R = *n*-C_5H_{11}, R′ = H). The hydrochlorides of (XIV; R = Ph and *n*-C_5H_{11}, R′ = Me or H) afforded the bases (XV; R = Ph and *n*-C_5H_{11}, R′ = Me) on treatment with diazomethane, and were not methylated on the nitrogen atom of the thiazoline ring thus showing no tendency to react in the thiazolidylidene form (cf. "thiazolinyl-oxazolones," Part V). An attempt to obtain the base (XV; R = CH_2Ph, R′ = H) from the appropriate hydrochloride by treatment with potassium acetate or sodium hydrogen carbonate solution, on the other hand, led only to the isolation of (XIII; R = CH_2Ph, R′ = H).

The amino-oxazole ring of the hydrochloride (XIV) or base (XV; R = CH_2Ph, R′ = Me) was hydrolysed by aqueous-ethanolic hydrochloric acid with the formation of an *amide* (XXI), the structure of which is written in the thiazolidylidene form to account for its ultra-violet absorption maximum at 2870 A. and the absence of basic properties, points of close resemblance to the dehydropenicilloates (Part V; cf. also Part VI). The thiazolinyl-amino-oxazole ring system could also be formed under the same conditions, however, since treatment of (XIII; R = CH_2Ph, R′ = Me) with aqueous-ethanolic hydrochloric acid gave a mixture of (XXI) and (XV; R = CH_2Ph, R′ = Me).

The above evidence seems to support the view that the thiazolinyl-amino-oxazoles can undergo the changes (XIV) $\overset{\text{base}}{\underset{\text{acid}}{\rightleftharpoons}}$ (XV) $\rightleftharpoons$ (XIII), although it must be borne in mind that the results do not completely exclude the existence of (XIII) and (XIV) in 2-thiazolidylidene forms (cf. Parts V and VIII). Attempts to link the thiazolinyl-amino-oxazole and thiazolinyl-oxazolone series by treatment of (XIV; R = CH_2Ph) with nitrous acid or nitrosyl chloride were not wholly successful since, although the product showed ultra-violet absorption in agreement with that of the oxazolones (Part V) and an acid obtained by its hydrolysis did not depress the melting point of 2-benzyl-4-(4-carboxy-5 : 5-dimethyl-2-thiazolidylidene)oxazolone, no analytically pure compounds were obtained from these reactions.

Cyclic thio-analogues of the thiazolinyl-amino-oxazoles were also prepared from the amino-nitrile (XII) (cf. Cook, Heilbron, and Levy, Studies in the Azole Series, *J.*, 1947, 1594, 1598;

1948, 201) by the action of carbon disulphide, phenyldithioacetic acid, and sodium dithioformate; these reagents gave the *compounds* (XXII; R = SH, CH_2Ph, and H, respectively), which were converted into the *hydrochlorides*. Thioacylamido-nitriles which are presumably intermediates in the formation of compounds (XXII) from (XII) were not isolated.

Thus a variety of intermediates, required for a synthesis of penicillins involving only reduction and deamination stages, were obtained. In Part VIII efforts to complete the synthesis will be described.

Experimental.

Ethyl 5-Amino-2-benzyloxazole-4-carboxylate.—Ethyl phenylacetamidocyanoacetate (1·0 g.) (*op. cit.*, p. 129) in chloroform (20 c.c.) was warmed on the steam-bath for 5 minutes with phosphorus pentachloride (0·9 g.), and the solution then stirred into excess of ice-cold sodium hydroxide solution. The chloroform was separated and evaporated, and the residue recrystallised from chloroform–light petroleum whereupon *ethyl 5-amino-2-benzyloxazole-4-carboxylate* separated as long, white needles, m. p. 128° (Found: C, 62·9; H, 5·5; N, 11·6. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·7; N, 11·4%). The product depressed the m. p. of the starting material, and formed a crystalline hydrochloride in dry ether.

Benzyl Oximinocyanoacetate.—Benzyl cyanoacetate (40·5 g.) and sodium nitrite (20 g.) in water (100 c.c.) were stirred at 0° during the addition (0·5 hour) of acetic acid (23 c.c.). Stirring was continued for 3 hours and the mixture kept at 0°, overnight. The solid was dissolved in ethanol (250 c.c.), and silver nitrate (41 g.) in water (250 c.c.) was added. The orange precipitate (37 g.) was recrystallised from aqueous dioxan to give the *silver* derivative of benzyl oximinocyanoacetate as orange plates, m. p. 205° (decomp.) (Found: C, 38·7; H, 2·5; N, 9·2. $C_{10}H_7O_3N_2Ag$ requires C, 38·6; H, 2·3; N, 9·0%), which were decomposed in ethanol (250 c.c.) with hydrogen sulphide. Evaporation of the filtrate yielded an oil, which rapidly became solid (25 g.), m. p. 110—113°. Recrystallised from chloroform–light petroleum, *benzyl oximinocyanoacetate* separated as rectangular tablets, m. p. 115° (Found: C, 58·6; H, 3·7; N, 13·6. $C_{10}H_8O_3N_2$ requires, C, 58·8; H, 3·9; N, 13·7%).

Benzyl Aminocyanoacetate and its Acyl Derivatives.—Benzyl oximinocyanoacetate (4 g.) in ether (50 c.c.) was reduced under reflux with aluminium amalgam (0·9 g.) and water (2·0 c.c.) in ethanol (10 c.c.) during 3·75 hours. Ethereal oxalic acid was added to the filtrate, and the white crystalline precipitate (2·3 g.) was recrystallised from acetone–light petroleum; the *oxalate* of benzyl aminocyanoacetate separated as rosettes of needles, m. p. 131° (decomp.) (Found: N, 10·2. $C_{12}H_{12}O_6N_2$ requires N, 10·0%). This oxalate (1·0 g.) in ether (25 c.c.) and sodium hydrogen carbonate (2·0 g.) in water (50 c.c.) were stirred while phenylacetyl chloride (0·8 g.) in ether (5 c.c.) was added during 10 minutes. After 1 hour, the acyl derivative (0·9 g.) was collected; the filtrates yielded a further 0·2 g. Recrystallisation from ethyl acetate gave *benzyl phenylacetamidocyanoacetate* as needles, m. p. 171—172° (Found: C, 70·1; H, 5·3; N, 8·9. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2; N, 9·1%). The oxalate (0·8 g.) was similarly acylated with *n*-hexoyl chloride and *benzyl* n-*hexoamidocyanoacetate* (0·8 g.) was obtained from the ethereal layer on evaporation; recrystallisation from ethanol yielded needles, m. p. 134° (Found: C, 66·6; H, 7·1; N, 9·4. $C_{16}H_{20}O_3N_2$ requires C, 66·6; H, 7·0; N, 9·7%).

Benzyl 5-Amino-2-benzyloxazole-4-carboxylate.—Benzyl phenylacetamidocyanoacetate (0·8 g.) in hot chloroform (30 c.c.) was treated with saturated ethereal hydrogen chloride (20 c.c.). The first crop of crystals, m. p. 129—133° (decomp.), comprised a mixture of product with a little starting material. The filtrate deposited a hydrochloride, m. p. 151—154°, which, recrystallised from ethyl acetate, gave *benzyl 5-amino-2-benzyloxazole-4-carboxylate hydrochloride* in prisms, m. p. 151—153° (Found: C, 63·1; H, 5·1; N, 8·2. $C_{18}H_{17}O_3N_2Cl$ requires C, 62·7; H, 5·0; N, 8·1%). With chloroform and aqueous sodium hydrogen carbonate the hydrochloride yielded *benzyl 5-amino-2-benzyloxazole-4-carboxylate*, m. p. 132 after recrystallisation from chloroform–light petroleum (Found: N, 9·35. $C_{18}H_{16}O_3N_2$ requires N, 9·1%).

Benzyl 5-Amino-2-n-amyloxazole-4-carboxylate.—Benzyl *n*-hexoamidocyanoacetate (0·4 g.) in ethyl acetate (10 c.c.) was treated with saturated ethereal hydrogen chloride (5 c.c.) and ether (10 c.c.), and left over-night. The crystalline product (0·31 g.), m. p. 125° (decomp.), was recrystallised from ethyl acetate, whereupon benzyl 5-amino-2-*n*-amyloxazole-4-carboxylate hydrochloride separate as rosettes of plates, m. p. 125° (decomp.). Treatment with chloroform and aqueous sodium hydrogen carbonate yielded *benzyl 5-amino-2-n-amyloxazole-4-carboxylate*, which recrystallised from chloroform–light petroleum in needles, m. p. 93° (Found: C, 66·2; H, 7·0. $C_{16}H_{20}O_3N_2$ requires C, 66·6; H, 7·0%).

n-*Hexoamido-acetonitrile and -acetamide.*—Aminoacetonitrile sulphate (180 g.) was added to sodium hydroxide (140 g.) in water (750 c.c.) at 0°, followed by ether (500 c.c.), and *n*-hexoyl chloride (150 g.) in ether added to the stirred mixture at 0—5° during 30 minutes. The washed, dried ether solution yielded 120 g. of product and a further 35 g. was obtained by leaving the aqueous phase overnight with ether. *n*-Hexoamidoacetonitrile was a colourless oil, b. p. 120°/5 × 10^{-3} mm., 70°/10^{-5} mm., solidifying at 10° and melting at room temperature (Found: C, 62·0; H, 9·4. Calc. for $C_8H_{14}ON_2$: C, 62·3; H, 9·1%) (cf. Baker *et al.*, *loc. cit.*). Solution in concentrated hydrochloric acid and dilution of the solution with water gave n-*hexoamidoacetamide*, m. p. 174°, crystallised from aqueous acetone (Found: C, 56·0; H, 9·3; N, 16·1. $C_8H_{16}O_2N_2$ requires C, 55·8; H, 9·3; N, 16·3%). The amide was also produced from the nitrile by ammoniacal hydrogen peroxide.

Oxazoles from n-*Hexoamidoacetonitrile.*—Powdered sodium (1·1 g.) was treated with ethyl formate (20 c.c.), and when the sodium had dissolved the above nitrile (7·7 g.) in toluene was added. Next morning the brown sodio-derivative was treated with ice, and the aqueous layer was extracted with chloroform (2 × 30 c.c.), acidified at 0° with acetic acid, and extracted with ether. The washed and dried ether solution yielded a brown oil (*ca.* 2 g.) on evaporation, which gave an intense brown colour with alcoholic ferric chloride, and formed in acetic acid solution a bright red 2 : 4-dinitrophenylhydrazone, m. p. 178—180°. With aniline overnight, it yielded *5-amino-4-formyl-2-n-amyloxazole anil* which

crystallised from ethyl acetate as needles, m. p. 192° (Found: C, 70·0; H, 7·4; N, 15·9. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·5; N, 16·3%). Distillation of the oil at 124°/5 × 10^{-3} mm. gave 2-*n*-amyloxazole-4-carboxyamide which crystallised from acetone–light petroleum as needles, or from methanol–water as laths, m. p. 158° (Found: C, 59·5; H, 7·6; N, 15·1. Calc. for $C_9H_{14}O_2N_2$: C, 59·3; H, 7·7; N, 15·4%). The compound gave a crystalline hydrochloride (clusters of needles, m. p. 129°) but no coloration with ferric chloride.

Sodium methoxide (7·2 g.) was stirred with dry ether (1 l.) while a mixture of ethyl oxalate (20 g.) and *n*-hexoamidoacetonitrile (20·5 g.) in ether was added (2—3 hours). Stirring was continued overnight and the sodio-derivative (27 g.) then treated with water (100 c.c.), ether (100 c.c.), and acetic acid (8·0 c.c.). An unidentified yellow substance separated, which had m. p. 218° (decomp.) after crystallisation from pyridine or precipitation with acid from solution in sodium hydroxide. The ethereal layer was washed with sodium hydrogen carbonate solution and evaporated; the crude oxalyl derivative gave an intense greenish-purple coloration with alcoholic ferric chloride, and formed an orange 2 : 4-dinitrophenylhydrazone. Trituration with concentrated hydrochloric acid, and then with water, gave *n-hexoamido-α-ethoxalylacetamide*, m. p. 194° (decomp.), from acetone (Found: C, 53·6; H, 7·4. $C_{12}H_{20}O_5N_2$ requires C, 53·0; H, 7·35%). Distillation in a high vacuum at 70—80° afforded *5-carbethoxy-2-n-amyloxazole-4-carboxyamide* which crystallised from acetone–water or ether, as needles, m. p. 94—95° (Found: C, 56·8; H, 7·2; N, 10·8. $C_{12}H_{18}O_4N_2$ requires C, 56·7; H, 7·1; N, 11·0%). It gave no coloration with ferric chloride and did not form a 2 : 4-dinitrophenylhydrazone or hydrochloride.

Carbobenzyloxyamidoacetonitrile.—Aminoacetonitrile sulphate (70 g.) in an ice-cold solution of potassium hydroxide (80 g.) in water (500 c.c.) was stirred with ether (300 c.c.) while benzyl chloroformate (80 g.) was added during 30 minutes. Concentration of the washed and dried ethereal layer gave the crude acyl derivative (80 g.) as a mass of needles. *N-Carbobenzyloxyamidoacetonitrile* crystallised from chloroform–light petroleum or ether–light petroleum as needles, m. p. 64° (Found: C, 63·1; H, 5·3; N, 15·0. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3; N, 14·8%).

Cyanoacetimino Ethyl Ether Hydrochloride.—Malononitrile (6·6 g.) (*Org. Synth.*, 1930, **10**, 66; Surrey, *J. Amer. Chem. Soc.*, 1943, **65**, 2471) in dry ether (30·5 g.) and dry ethanol (4·6 g.) was treated with dry hydrogen chloride (1 equiv.) at 0°. After 17 hours at 0°, white leaflets of *cyanoacetimino ethyl ether hydrochloride* (13·5 g., 91%), m. p. 104° (decomp.), had separated from the solution (Found: C, 39·9; H, 6·0. $C_5H_9ON_2Cl$ requires C, 40·4; H, 6·1%).

Methyl 5 : 5-Dimethyl-2-cyanomethylthiazoline-4-carboxylate (X) *and Related Compounds.*—(*a*) Penicillamine methyl ester hydrochloride (80 g.) was converted into the base by treatment with sodium hydrogen carbonate (40 g.) in water (500 c.c.) and extraction with chloroform (2 × 500, 2 × 300 c.c.). The dried chloroform solution was concentrated to 1 l. by evaporation under reduced pressure, and was then treated with cyanoacetimino ethyl ether hydrochloride (59·5 g.). The latter dissolved and ammonium chloride began to separate from the warm solution. After 19 hours, the mixture was extracted with water (2 × 250 c.c.), and the chloroform evaporated to afford an orange oil (67 g.), a portion of which was distilled at 100°/10^{-5} mm. to yield pure *methyl 5 : 5-dimethyl-2-cyanomethylthiazoline-4-carboxylate* (X) as a pale-yellow, viscous oil (Found: N, 13·6. $C_9H_{12}O_2N_2S$ requires N, 13·2%). A second (solid) product was isolated by treating the crude thiazoline with ethyl acetate and light petroleum: from aqueous ethanol *methyl 5 : 5-dimethyl-2-cyanomethylene-3-(2-cyano-1-ethoxyvinyl)thiazolidine-4-carboxylate* (XVIII) separated in rectangular prisms, m. p. 208° (decomp.) (Found: C, 55·1; H, 5·5; N, 13·5. $C_{14}H_{17}O_3N_3S$ requires C, 54·8; H, 5·5; N, 13·7%).

(*b*) Penicillamine methyl ester hydrochloride (13·8 g.), cyanoacetimino ethyl ether hydrochloride (10·2 g.), ether (50 c.c.), and a solution of potassium acetate (14·0 g.) in water (25 c.c.) were shaken for 2 hours. Water (40 c.c.) was added, the ether separated, the aqueous layer extracted with fresh ether, and the combined extracts were washed with water (10 c.c.) and dried (Na_2SO_4). Evaporation of the ether yielded methyl 5 : 5-dimethyl-2-cyanomethylthiazoline-4-carboxylate as an orange oil (13·2 g.).

The thiazoline (2·2 g.) was dissolved in ethanol (20 c.c.) and 0·509N-sodium hydroxide (20·4 c.c.) was added, followed after 3 hours by 0·474N-hydrochloric acid (22·9 c.c.). The solution was stirred with norite and filtered, ethanol was removed under reduced pressure, and the residual solution extracted with ether (4 × 25 c.c.). Evaporation of the dried ethereal solution to about 10 c.c. and addition of ethereal benzylamine gave the *benzylamine* salt of *N*-cyanoacetylpenicillamine as a white crystalline powder (1·8 g.), m. p. 183° (decomp.), from ethanol (Found: C, 55·5; H, 6·8; N, 13·3. $C_{15}H_{21}O_3N_3S$ requires C, 55·7; H, 6·5; N, 13·0%). It was soluble in water but insoluble in chloroform and acetone.

The benzylamine salt (1·5 g.) was dissolved in dilute hydrochloric acid (20 c.c.), and the solution extracted with ether (2 × 20 c.c.). The washed, dried ethereal solution was evaporated and the residue crystallised from ethyl acetate–light petroleum to give *N-cyanoacetylpenicillamine* (XVI), m. p. 139° (Found: C, 45·1; H, 5·5; N, 12·6. $C_8H_{12}O_3N_2S$ requires C, 44·4; H, 5·6; N, 13·0%). The acid gave a brilliant blue colour with ferric chloride solution, which faded when the solution was kept.

Methyl 5 : 5-Dimethyl-2-cyanomethylthiazolidine-4-carboxylate (XVII).—The crude thiazoline (X) (12·3 g.) in ether (500 c.c.) was reduced with aluminium amalgam (20 g.) and water (40 c.c.) under reflux for 17 hours, and the filtered solution was evaporated to an oil which crystallised and was washed with ether–light petroleum (1 : 1); yield, 5·0 g.; m. p. 72—75°. From chloroform–light petroleum *methyl 5 : 5-dimethyl-2-cyanomethylthiazolidine-4-carboxylate* formed hexagonal prisms, m. p. 79° (Found: C, 50·6; H, 6·7; N, 13·0; S, 15·4. $C_9H_{14}O_2N_2S$ requires C, 50·4; H, 6·6; N, 13·1; S, 15·0%). In another preparation the thiazolidine was isolated as its *hydrochloride* which formed needles, m. p. 176° (decomp.), from methanol–ether (Found: C, 43·5; H, 6·1. $C_9H_{15}O_2N_2ClS$ requires C, 43·1; H, 6·0%).

Methyl 5 : 5-Dimethyl-2-aminocyanomethylthiazoline-4-carboxylate (XII).—(i) The crude thiazoline (X) (7·0 g.) [prepared by method (*b*)] in dioxan (50 c.c.) and acetic acid (4·0 g.) was shaken with finely powdered sodium nitrite (4·5 g.) for 18 hours. The mixture was poured into ice–water (250 c.c.) and extracted with chloroform (100, 50, 25 c.c.), which was then washed with water (50 c.c.), dried, and evaporated under reduced pressure below 40° to yield a dark-red oil. The oil was taken up in dry ether (100 c.c.) and added to aluminium amalgam (1·1 g.). To the refluxing solution water (2·2 g.) in ethanol

(20 c.c.) was added during 3·75 hours. The mixture was filtered, and excess of ethereal oxalic acid was added to the filtrate. Recrystallised from ethanol, the *oxalate* of methyl 5 : 5-dimethyl-2-aminocyanomethylthiazoline-4-carboxylate separated as platelets (4·4 g.), m. p. 153° (decomp.) (Found : C, 44·1; H, 5·4; N, 15·2. $C_{20}H_{28}O_8N_6S_2$ requires C, 44·1; H, 5·2; N, 15·4%).

(ii) The crude thiazoline (X) (60 g.) [prepared by method (*a*) above] in acetic acid (160 c.c.) was cooled in ice, and treated with a solution of sodium nitrite (30 g.) in water (150 c.c.), added dropwise with stirring during 1 hour. Stirring was continued for 15 hours under nitrogen, the solution was then poured into water (1000 c.c.), and the oil was extracted with ether (500, 2 × 300 c.c.). The extract was washed with water (2 × 500 c.c.), dried, and refluxed with aluminium amalgam (9·6 g.), while water (20 c.c.) in ethanol (100 c.c.) was added during 2·5 hours. After a further 2·5 hours, the mixture was filtered and the filtrate, washings (ethanol; 100 c.c.), and excess of ethereal oxalic acid were left overnight, giving a white, crystalline precipitate (26·7 g.) of the oxalate of (XII).

Methyl 5 : 5-Dimethyl-2-aminocyanomethylthiazolidine-4-carboxylate (XIX) *and Derivatives.*—The oxalate (2·0 g.) was treated with 0·505N-sodium hydroxide (14·5 c.c.), and shaken with ether (100 c.c.). The ether solution was dried, and reduced at the b. p. with aluminium amalgam (20 g.) and water (4·5 g.) in ethanol (10 c.c.) during 24 hours. Addition of excess of ethereal oxalic acid to the filtrate yielded a white crystalline precipitate (0·6 g.), m. p. 149° (decomp.), which depressed the m. p. of the starting material, and further differed from the latter by being soluble in ethanol. Recrystallised from hot *iso*propanol, the *oxalate* of methyl 5 : 5-dimethyl-2-aminocyanomethylthiazolidine-4-carboxylate (XIX) had m. p. 151° (decomp.) (Found : C, 41·7; H, 5·4; N, 13·7. $C_{11}H_{17}O_6N_3S$ requires C, 41·4; H, 5·4; N, 13·2%).

The oxalate of (XIX) (0·479 g.) was stirred with a mixture of ether (20 c.c.), sodium hydrogen carbonate (1·0 g.), and water (20 c.c.), and phenylacetyl chloride (0·23 g.) in ether (10 c.c.) was added during 20 minutes. After 1·25 hours the ether was evaporated from the washed, dried solution to give an oil which crystallised at 0° from ether–light petroleum (b. p. 60—80°); yield, 0·35 g.; m. p. 102—105°. Recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave *methyl 5 : 5-dimethyl-2-phenylacetamidocyanomethylthiazolidine-4-carboxylate* (XX; R = H) as triangular plates, m. p. 111° depressed on admixture with (XIII; R = CH_2Ph, R′ = Me) (Found : C, 58·9; H, 6·2; N, 12·3. $C_{17}H_{21}O_3N_3S$ requires C, 58·8; H, 6·1; N, 12·1%). When pure, the thiazolidine was sparingly soluble in ether, from which solvent the *hydrochloride* was prepared; the salt crystallised from ethyl acetate as platelets, m. p. 124° (decomp.) (Found : C, 53·4; H, 5·9; N, 10·8. $C_{17}H_{22}O_3N_3ClS$ requires C, 53·2; H, 5·8; N, 10·9%). It was soluble in dioxan, chloroform, ethanol, or *iso*propanol, and insoluble in ether, cold ethyl acetate, or light petroleum.

(XX; R = H) (0·557 g.) in ethyl acetate (10 c.c.) and ether (20 c.c.) was treated with excess of ethyl chloroformate (0·50 g.) and saturated sodium hydrogen carbonate solution (20 c.c.), added dropwise with stirring during 40 minutes. Stirring was continued for 3 hours, and the organic layer was washed, dried, and evaporated. The residual gum in ether (10 c.c.) and ethyl acetate (7 c.c.) was treated with saturated ethereal hydrogen chloride (2·5 c.c.) to precipitate unchanged thiazolidine as hydrochloride (0·14 g.). From the filtrate *methyl 3-carbethoxy-5 : 5-dimethyl-2-phenylacetamidocyanomethylthiazolidine-4-carboxylate* (XX; R = CO_2Et) was obtained. It crystallised from ether–light petroleum as prisms, m. p. 82—83° (Found : C, 57·3; H, 6·1. $C_{20}H_{25}O_5N_3S$ requires C, 57·3; H, 6·0%).

Acyl Derivatives of (XII).—The oxalate of (XII) (10·0 g.) was stirred with ether (250 c.c.), sodium hydrogen carbonate (15 g.), and water (200 c.c.), while *n*-hexoyl chloride (9·0 g.) in ether (20 c.c.) was added during 30 minutes. Stirring was continued for 1·25 hours, and the ethereal phase was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The residual oil was dissolved in ethyl acetate, and light petroleum (b. p. 60—80°) added. After 3 days at 0° the solution had deposited crystals (4·2 + 1·4 g.), m. p. 108—111°. Recrystallised from ethyl acetate and light petroleum, *methyl 5 : 5-dimethyl-2-hexoamidocyanomethylthiazoline-4-carboxylate* (XIII; R = n-C_5H_{11}, R′ = Me) was obtained as rectangular prisms, m. p. 111—113° (Found : C, 55·1; H, 7·0; N, 12·8. $C_{15}H_{23}O_3N_3S$ requires C, 55·4; H, 7·1; N, 12·9%). From ethanol–water laths, m. p. 57—60°, were obtained, presumably a hydrate since further crystallisation from ethyl acetate–light petroleum after drying in a vacuum raised the m. p. to 111—113°.

The oxalate of (XII) (2·0 g.), suspended in a mixture of ether (50 c.c.) and sodium hydrogen carbonate (3·0 g.) in water (50 c.c.), was treated with phenylacetyl chloride (1·5 g.) in ether (10 c.c.) during 50 minutes, and stirring continued for 1·5 hours. The white crystalline product (2·35 g.) had m. p. 105° (decomp.). Recrystallisation from ethanol–water gave *methyl 5 : 5-dimethyl-2-phenylacetamidocyanomethylthiazoline-4-carboxylate* (XIII; R = CH_2Ph, R′ = Me) as sheaves of laths, m. p. 111° (decomp.) (Found : C, 59·2; H, 5·5; N, 12·5. $C_{17}H_{19}O_3N_3S$ requires C, 59·1; H, 5·5; N, 12·2%). It was soluble in ethanol, chloroform, ethyl acetate, and acetone, and insoluble in ether or light petroleum.

The oxalate of (XII) (5·0 g.) was suspended in ether (50 c.c.) and acylated during 1·5 hours with benzoyl chloride (4·0 g.) in the presence of excess of aqueous sodium hydrogen carbonate. The initially sticky product changed to a powder (2·9 g.), m. p. 147—150°. The filtrate was separated, and the dried organic layer was treated with ethereal hydrogen chloride giving a crystalline cyclic product, m. p. 217° (decomp.) (see below). Recrystallisation of the material, m. p. 147—150°, from ethyl acetate–light petroleum (b. p. 60—80°) yielded *methyl 5 : 5-dimethyl-2-benzamidocyanomethylthiazoline-4-carboxylate* (XIII; R = Ph, R′ = Me) as prisms, m. p. 154—155° (decomp.) (Found : C, 58·1; H, 5·0; N, 12·3. $C_{16}H_{17}O_3N_3S$ requires C, 58·0; H, 5·2; N, 12·7%).

Interconversions of 2-Acylamidocyanomethylthiazolines and 4-Thiazolin-2′-yl-amino-oxazoles.—(*a*) (XIII; R = CH_2Ph, R′ = Me) (0·95 g.) was treated for 16 hours with phosphorus pentachloride (0·57 g.) in chloroform (25 c.c.; dried over P_2O_5), and the solution was then stirred with excess of ice-cold sodium hydrogen carbonate for 15 minutes. The washed, dried chloroform solution yielded an oil which was dissolved in ether and treated with hydrogen chloride to give a white precipitate (0·8 g.), m. p. 155° (decomp.). Recrystallised from chloroform and ether, the product had m. p. 160—161° (decomp.), undepressed with that of the material next prepared.

(XIII; R = CH_2Ph, R′ = Me) (19·8 g.) in ethyl acetate (200 c.c.) and ether (150 c.c.) was treated

with saturated ethereal hydrogen chloride (70 c.c.) and the solution left for 20 hours. Recrystallisation of the product (21·3 g.) from ethyl acetate gave the *hydrochloride* (XIV; R = CH_2Ph, R′ = Me) as hexagonal plates, m. p. 165° (decomp.) (Found: C, 53·4; H, 5·2; N, 10·2; Cl, 9·7. $C_{17}H_{20}O_3N_3ClS$ requires C, 53·5; H, 5·2; N, 11·0; Cl, 9·3%). The hydrochloride (8·0 g.) in chloroform (120 c.c.) was shaken with excess of sodium carbonate solution and gave, on evaporation of the chloroform, a solid (6·14 g.), m. p. 121—122°. Recrystallisation from chloroform–light petroleum yielded *5-imino-2-benzyl-4-(4-carbomethoxy-5 : 5-dimethyl-Δ²-thiazolin-2-yl)oxazoline* (XV; R = CH_2Ph, R′ = Me) as rectangular plates, m. p. 125° (Found: C, 59·2; H, 5·4; N, 11·9. $C_{17}H_{19}O_3N_3S$ requires C, 59·1; H, 5·5; N, 12·2%). It was soluble in ether, and yielded the hydrochloride immediately on treatment with hydrogen chloride, but gave no picrate in ether. The hydrochloride of (XIV; R = CH_2Ph, R′ = Me) (156 mg.) in ethanol (2·0 c.c.) was treated with excess of ethereal diazomethane overnight. On evaporation of the solvent, a yellow oil was obtained which crystallised as plates from ether on seeding with (XV; R = $PhCH_2$, R′ = Me); the product had m. p. 112—116° undepressed on admixture with authentic (XV; R = CH_2Ph, R′ = Me).

(*b*) (XIII; R = Ph, R′ = Me) (2·5 g.) in ethyl acetate (30 c.c.) and ether (20 c.c.) was treated with saturated ethereal hydrogen chloride (10 c.c.), and next day the precipitate (2·7 g.) was recrystallised from chloroform–ether giving *5-amino-2-phenyl-4-(4-carbomethoxy-5 : 5-dimethylthiazolin-2-yl)oxazole hydrochloride* (XIV; R = Ph, R′ = Me) as pale yellow prims, m. p. 219° (decomp.) depending on the rate of heating (Found: C, 51·8; N, 5·2; N, 11·0; Cl, 9·6. $C_{16}H_{18}O_3N_3ClS$ requires C, 52·2; H, 4·9; N, 11·4; Cl, 9·6%). Shaking this hydrochloride in chloroform with sodium hydrogen carbonate solution gave *5-imino-2-phenyl-4-(4-carbomethoxy-5 : 5-dimethylthiazolin-2-yl)oxazoline* (XV; R = Ph, R′ = Me) which separated from ethyl acetate–light petroleum (b. p. 60—80°) as long narrow plates, m. p. 160—161° (Found: C, 57·7; H, 5·0; N, 12·5. $C_{16}H_{17}O_3N_3S$ requires C, 58·0; H, 5·2; N, 12·7%). It formed a picrate, m. p. 206—207° (decomp.).

(*c*) (XIII; R = *n*-C_5H_{11}, R = Me) (4·0 g.) in ethyl acetate (25 c.c.) and ether (150 c.c.) was treated with saturated ethereal hydrogen chloride (15 c.c.) for 21 hours, and the *5-amino-2-n-amyl-4-(4-carbomethoxy-5 : 5-dimethylthiazolin-2-yl)oxazole hydrochloride* (XIV; R = *n*-C_5H_{11}, R′ = Me) (4·4 g.) crystallised from chloroform–light petroleum (b. p. 60—80°) to form rosettes of laths, m. p. 133° (decomp.) (Found: C, 49·0; H, 6·3; N, 11·0; Cl, 10·8. $C_{15}H_{24}O_3N_3ClS$ requires C, 49·8; H, 6·7; N, 11·6; Cl, 9·8%). The hydrochloride (3·65 g.) in chloroform was shaken with excess of sodium hydrogen carbonate solution. Evaporation of the dried chloroform solution left a dark green oil, which was taken up in ether and chromatographed on alumina (Spence, type H). The colourless oil (1·6 g.) obtained by evaporation of the eluate showed light-absorption maxima at 2650 A. ($E^{1\%}_{1\,cm.}$ = 380) and 2810 A. ($E^{1\%}_{1\,cm.}$ = 345). With ethereal hydrogen chloride it was reconverted immediately into the hydrochloride, m. p. 127—129°. Distillation of the oil in a high vacuum at 120° yielded a distillate showing light-absorption at 2710 A. ($E^{1\%}_{1\,cm.}$ = 570). A similar oily product was obtained on treatment of the hydrochloride with diazomethane.

(*d*) The hydrochloride of (XIV; R = CH_2Ph, R′ = Me) (0·5 g.) in ethanol (10 c.c.) was treated with 0·528N-sodium hydroxide (2·4 c.c.) during 50 minutes. Next day, removal of ethanol and acidification gave a halogen-free solid, m. p. 100—105° (decomp.), insoluble in sodium hydrogen carbonate solution. Recrystallised from ethanol–water, it separated in prismatic needles (0·31 g.), m. p. 105° (decomp.), of (XIII; R = CH_2Ph, R′ = Me) (Found: N, 11·8. Calc. for $C_{17}H_{19}O_3N_3S$: N, 12·2%). The compound showed light-absorption at 2700—2800 A. ($E^{1\%}_{1\,cm.}$ = 500), and yielded the hydrochloride with ethereal hydrogen chloride.

The hydrochloride of (XIV; R = CH_2Ph, R′ = Me) (0·5 g.) in ethanol (10 c.c.) was kept with 0·528N-sodium hydroxide (4·86 c.c.) for 22 hours. The ethanol was removed by evaporation under reduced pressure, the residue was diluted with a little water, and 0·474N-hydrochloric acid (1 equiv.) was added at 0°. The gummy precipitate rapidly solidified (0·33 g.) and, recrystallised from ethanol–water, *5 : 5-dimethyl-2-phenylacetamidocyanomethylthiazoline-4-carboxylic acid* (XIII; R = CH_2Ph, R′ = H) separated as silky needles, m. p. 129° (decomp.) (Found: N, 12·0. $C_{16}H_{17}O_3N_3S,H_2O$ requires N, 12·0%), soluble in sodium hydrogen carbonate solution.

The hydrochloride of (XIV; R = CH_2Ph, R′ = Me) (200 mg.) was dissolved in pyridine (5 c.c.). After 24 hours, the solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate, and the solution washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water. On evaporation of the dried solution a yellow oil was obtained, which with aqueous ethanol afforded elongated prisms (110 mg.), m. p. 108—109° (decomp.) undepressed on admixture with the authentic ester (XIII; R = CH_2Ph, R′ = Me).

The hydrochloride (XIV; R = CH_2Ph, R′ = Me) (0·5 g.) was dissolved in ethanol (10 c.c.) and 2N-hydrochloric acid (10 c.c.). After 18 hours, the solution was evaporated to dryness under reduced pressure, the residue was dissolved in chloroform, and the solution was extracted with sodium hydrogen carbonate solution. The washed, dry chloroform solution was concentrated to a gum which was crystallised by addition of ethyl acetate. From chloroform–light petroleum (b. p. 60—80°) *methyl 5 : 5-dimethyl-2-(1-phenylacetamido-1-carbamylmethylene)thiazolidine-4-carboxylate* (XXI) separated as prismatic needles, m. p. 186—187° (Found: C, 55·8; H, 5·8; N, 11·9; S, 9·2. $C_{17}H_{21}O_4N_3S$ requires C, 56·2; H, 5·8; N, 11·6; S, 8·8%). The compound yielded no colour with sodium nitroprusside in aqueous-ethanolic sodium hydroxide.

(*e*) The base (XV; R = CH_2Ph, R′ = Me) (0·3 g.) in methanol (10 c.c.) was kept with 0·505N-sodium hydroxide (1·72 c.c.) for 22 hours. Methanol was then removed under reduced pressure, and the residue was diluted with water, extracted with ether, and acidified at 0°. The material obtained by crystallising the precipitate from ethanol had m. p. 119° (decomp.), undepressed on admixture with 5 : 5-dimethyl-2-phenylacetamidocyanomethylthiazoline-4-carboxylic acid obtained as above, and also [yield, 1·64 g.; m. p. 129° (decomp.) (from ethanol)] by hydrolysis of (XIII; R = CH_2Ph, R′ = Me) (2·32 g.) in ethanol (15 c.c.) with 0·505N-sodium hydroxide (13·1 c.c.). Esterification of the acid (XIII; R = CH_2Ph, R′ = H) (100 mg.) in dry acetone (1·5 c.c.) with excess of ethereal diazomethane,

followed by evaporation of the solvent and crystallisation of the residue from ethyl acetate–light petroleum gave the ester (XIII; R = CH_2Ph, R′ = Me) as elongated prisms, m. p. 104—106° (decomp.) undepressed by authentic material.

(*f*) The compound (XIII; R = CH_2Ph, R′ = Me) (200 mg.) in ethanol (7 c.c.) was kept with 2N-hydrochloric acid (5 c.c.) for 17 hours. The solvents were evaporated, the residue was dissolved in chloroform, and the solution was washed, dried, and evaporated to give an oil which crystallised from ethyl acetate. The first crop of cystals (about 35 mg.) had m. p. 181—183°, undepressed by the amide (XXI). On spontaneous evaporation, the filtrates yielded a crystalline residue, m. p. 125°, undepressed on admixture with authentic (XV; R = CH_2Ph, R′ = Me), and exhibiting the correct ultra-violet absorption spectrum for that compound.

The acid (XIII; R = CH_2Ph, R′ = H) (1·64 g.) in ethyl acetate (25 c.c.) and dry ether (50 c.c.) was treated with saturated ethereal hydrogen chloride (7 c.c.); after 17 hours the crystalline product (1·63 g.) was washed with ether, and it then had m. p. 175° (decomp.). Recrystallisation from chloroform–ether gave *5-amino-2-benzyl-4-(4-carboxy-5 : 5-dimethyl-2-thiazolinyl)oxazole hydrochloride* (XIV; R = CH_2Ph, R′ = H) as platelets, m. p. 174° (decomp.) (Found: C, 51·9; H, 4·6; N, 11·5. $C_{16}H_{18}O_3N_3ClS$ requires C, 52·2; H, 4·9; N, 11·4%). It gave with aqueous-ethanolic ferric chloride a stable blue colour, which persisted after the addition of sodium hydrogen carbonate.

(*g*) The ester (XIII; R = *n*-C_5H_{11}, R′ = Me) (0·655 g.) in ethanol (5 c.c.) was treated with 0·505N-sodium hydroxide during 1·5 hours, and the solution kept for 21·5 hours. The solvents were removed at 40°, and the residue was taken up in water (20 c.c.) and chloroform (15 c.c.). The filtered aqueous layer was acidified at 0°, and the separated solid (0·42 g.) was recrystallised from ethanol–water, whereupon 5 : 5-*dimethyl*-2-n-*hexoamidocyanomethylthiazoline*-4-*carboxylic acid* (XIII; R = *n*-C_5H_{11}, R′ = H) separated as needles, m. p. 104—105° (decomp.) (Found: C, 51·3; H, 7·4; N, 12·7. $C_{14}H_{21}O_3N_3S,H_2O$ requires C, 51·1; H, 7·0; N, 12·8%). It gave a permanent blue colour with aqueous ferric chloride. This acid (155 mg.) in ethyl acetate (4 c.c.) and dry ether (20 c.c.) was treated with saturated ethereal hydrogen chloride (3 c.c.), and after 6 hours the crystalline product, m. p. 164° (decomp.), was recrystallised from ethyl acetate, giving *5-amino-2-n-amyl-4-(4-carboxy-5 : 5-dimethyl-2-thiazolinyl)-oxazole hydrochloride* (XIV; R = *n*-C_5H_{11}, R′ = H) as white plates, m. p. 164° (decomp.) (Found: C, 48·6; H, 6·5; N, 11·7; Cl, 10·6. $C_{14}H_{22}O_3N_3ClS$ requires C, 48·3; H, 6·4; N, 12·1; Cl, 10·2%).

(*h*) The hydrochloride (XIV; R = CH_2Ph, R′ = H) (195 mg.) in methanol (5 c.c.) was treated with excess of ethereal diazomethane overnight. Evaporation of solvents and treatment of the residual oil with a little dry ether yielded a solid, m. p. 104—108°. Recrystallised from acetone–water it had m. p. 125°, undepressed on admixture with authentic (XV; R = CH_2Ph, R′ = Me). Its identity was confirmed by its ultra-violet absorption spectrum and conversion into a hydrochloride, m. p. 163° (decomp.) undepressed with authentic material.

The hydrochloride (XIV; R = CH_2Ph, R′ = H) (150 mg.) in chloroform (5 c.c.) was shaken with potassium acetate (1 g.) in water (10 c.c.), and the chloroform layer evaporated to give a residue which crystallised from ethanol–water at 0°. The product (91 mg.) had m. p. 128° (decomp.), undepressed on admixture with authentic (XIII; R = CH_2Ph, R′ = H), and showed ultra-violet light-absorption at 2700—2800 A. The colourless solution in ethanol became yellow on heating and colourless again on cooling.

Thiazolinyl-aminothiazoles.—The oxalate of (XII) (1·0 g.), suspended in ether (40 c.c.), was shaken with 0·83N-sodium hydroxide (44·0 c.c.), and the aqueous layer again extracted with ether (20 c.c.). The combined ethereal solution was dried (Na_2SO_4) and evaporated, and the residue heated under reflux with ether and excess of carbon disulphide for 5·5 hours. Removal of the solvent and trituration of the residue with ether gave a yellow solid, m. p. 169° (decomp.). Recrystallised from hot dioxan by the addition of water, *5-amino-2-mercapto-4-(4-carbomethoxy-5 : 5-dimethyl-2-thiazolinyl)thiazole* (XXII; R = SH) separated as yellow prisms, m. p. 184° (decomp.) (Found: C, 40·6; H, 4·4. $C_{10}H_{13}O_2N_3S_3$ requires C, 39·6; H, 4·3%). The same compound was also obtained by liberating the amino-nitrile with sodium methoxide in methanol, and then treating it with ethereal carbon disulphide in the cold.

The amine oxalate (XII) (1·0 g.) was suspended in ether and treated with a solution of phenyldithioacetic acid in ether (2·4 c.c.; 131 mg./c.c.). The mixture was shaken overnight with 0·505N-sodium hydroxide (11·0 c.c.), and the solution filtered from solid (0·35 g.), m. p. 164°. The ethereal phase from the filtrate was washed, dried, and evaporated, and the residual oil stirred with a little ether. The solid was combined with the above, and *5-amino-2-benzyl-4-(4-carbomethoxy-5 : 5-dimethyl-2-thiazolinyl)thiazole* (XXII; R = CH_2Ph) crystallised from chloroform–light petroleum as white needles, m. p. 165° (Found: C, 56·5; H, 5·4. $C_{17}H_{19}O_2N_3S_2$ requires C, 56·5; H, 5·3%). A solution of this compound (1·0 g.) in ethyl acetate (35 c.c.) was saturated with dry hydrogen chloride, and after 18 hours the crystalline precipitate (1·0 g.) was recrystallised from acetic acid, whereupon the *hydrochloride* of (XXII; R = CH_2Ph) separated as yellow rhombic prisms, m. p. 205° (decomp.) (Found: C, 51·2; H, 5·0; N, 10·4; S, 15·9. $C_{17}H_{20}O_2N_3ClS_2$ requires C, 51·3; H, 5·1; N, 10·6; S, 16·1%). By shaking this with chloroform and sodium hydrogen carbonate solution, the base was regenerated as needles, m. p. 164—165°.

The oxalate (XII) (0·5 g.) was shaken with ether (10 c.c.), sodium dithioformate (0·187 g.), and 0·505N-sodium hydroxide (3·7 c.c.) for 17 hours. The solid was collected, and combined with material obtained from the washed ether solution by evaporation and stirring with fresh ether or benzene. The crude product had m. p. 132°, and after recrystallisation from chloroform–light petroleum, *5-amino-4-(4-carbomethoxy-5 : 5-dimethyl-2-thiazolinyl)thiazole* (XXII; R = H) separated as colourless, glistening prismatic laths, m. p. 143° (Found: C, 44·9; H, 4·8; N, 15·0; S, 23·6. $C_{10}H_{13}O_2N_3S_2$ requires C, 44·3; H, 4·8; N, 15·5; S, 23·6%). It formed a crystalline hydrochloride.

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