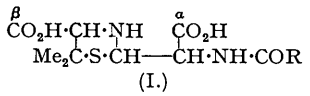
500. *Syntheses in the Penicillin Field. Part III. The Preparation of Model Thiazolines and Thiazoles.*

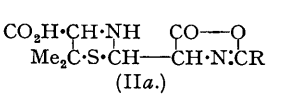
By A. H. Cook and J. A. Elvidge.

A projected route to penicillins from thiazolines is outlined. Useful intermediates of the thiazoline series from acylamidomalonic and acylamidocyanoacetic esters were sought unsuccessfully, although corresponding members of the thiazole series were obtained and studied.

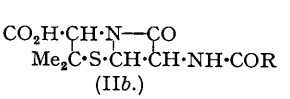
It was early recognised that cyclodehydration of penicilloic acids (I) provided a possible route to synthetic penicillins irrespective of the uncertainty then prevailing concerning the correct structure of the natural antibiotics; clearly each of the favoured representations, (II*a*) and (II*b*), is potentially so derivable. Treatment of penicilloic derivatives with various dehydrating agents was found indeed to afford weak, often transitory, antibacterial activities, but it soon became clear that the difficulties inherent in this direct approach were so formidable as to preclude its eventual usefulness. Consequently, it was decided to investigate the preparation and cyclisation of thiazoline analogues of the penicilloates, namely the dehydropenicilloates (III). The possibility was foreseen that the α-carboxyl group of these compounds might prove sufficiently stable for azlactonisation to be effected in the normal manner. Alternatively it appeared that cyclisation of the α-esters to thiazolinyl-alkoxyoxazoles (IV) might be feasible, and that thiazolinyl-oxazolones (V) might be thence obtained by replacing appropriate substituents R′ by H. In either event the product was to have been reduced to the thiazolidinyl-oxazolone (II*a*) which might well have isomerised to the β-lactam structure (II*b*) by internal self-acylation.



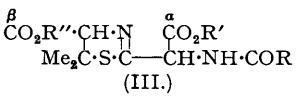
(I.)



(II*a*.)



(II*b*.)



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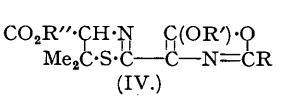

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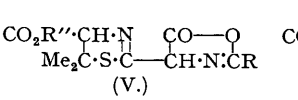

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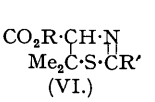


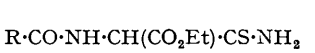
(VI.)

In this paper the results are recorded of initial experiments directed towards these objectives (further work along these lines is described in " The Chemistry of Penicillin," Princeton Univ. Press, 1949, Chap. XXII, and in later Parts of this Series). First, it was necessary to study methods for preparing Δ^2-thiazolines derived from penicillamine, and secondly it had to be demonstrated that reduction of such thiazolines to the corresponding thiazolidines could be effected under mild conditions.

Cyclodehydration of *N*-acylpenicillamines constituted the first example of the preparation of thiazolines from penicillamine (Merck, *M.* 35; *op. cit.*, p. 470). Another method, discovered at almost the same time, consisted in heating penicillamine ethyl ester hydrochloride with thioacetamide whereby hydrogen sulphide was evolved, ammonium chloride separated, and ethyl 2 : 5 : 5-trimethylthiazoline-4-carboxylate (VI; R = Et, R′ = Me) was isolated as an oil characterised as its hydrochloride (Bentley, Catch, Cook, Heilbron, and Shaw, *CPS.* 267; *op. cit.*, p. 938). The same compound was obtained under similar conditions, though less conveniently, by use of acetonitrile in place of thioacetamide. These procedures did not seem generally applicable, however, the analogous reaction with thiobenzamide, for example, not being achieved. Moreover attempts to condense penicillamine methyl ester hydrochloride with *phenylacetamidocarbethoxythioacetamide* (VII; R = CH_2Ph) resulted only in formation of an unidentified substance which was also obtained by the action of heat on the thioamide alone. This thioamide and the n-*hexoamido*-analogue (VII; R = n-C_5H_{11}) were prepared from the corresponding phenylacet- and *n*-hexo-amidocarbethoxyacetonitrile which in turn were obtained (*idem, op. cit.*, pp. 725, 727) by reducing ethyl oximinocyanoacetate to the hitherto unknown ethyl aminocyanoacetate, followed by acylation with the appropriate acid chlorides.

It was then found that the condensations with penicillamine derivatives to yield thiazolines could be extended to ethyl malonate (Cook, Elvidge, Heilbron, and Levy, *CPS.* 443; *op. cit.*, p. 885). Thus when the latter ester was heated with penicillamine methyl ester a mixture of methyl 5 : 5-dimethyl-2-carbethoxymethylthiazoline-4-carboxylate (VI; R = Me, R′ = $CH_2{\cdot}CO_2Et$) and the acylpenicillamine (VIII; R = OEt) resulted, the latter being characterised as the N-*malonamyl* derivative (VIII; R = NH_2). An attempted condensation of penicillamine methyl ester with hexoamidomalonic ester, however, did not yield a thiazoline (dehydropenicilloate) useful for penicillin synthesis.

Before real progress in synthesising penicillins *via* thiazolines could be made a method of reducing the thiazoline ring system to the corresponding thiazolidine system had to be found. The first example of such a reduction was afforded by the conversion of the above ethyl 2 : 5 : 5-trimethylthiazoline-4-carboxylate (VI; R = Et, R′ = Me) to the corresponding thiazolidine by means of an excess of aluminium amalgam in moist ether. The product was characterised as a thiazolidine by means of its crystalline hydrochloride and by scission with mercuric chloride to yield acetaldehyde, isolated as its 2 : 4-dinitrophenylhydrazone (Bentley, Catch, Cook, Heilbron, and Shaw, *loc. cit.*) Several examples of this type of reduction were later encountered (cf. Parts VII and VIII of this Series, to be published) and of particular interest was the reduction of the " dehydropenilloate " (VI; R = Me, R′ = $CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2Ph$) (Barltrop, Abraham, Baker, Chain, and Robinson, *CPS.* 463; *op. cit.*, p. 938). The fact that thiazolines could be reduced with neutral aluminium amalgam made the approach to penicillins *via* thiazolines attractive, since penicillins are stable to this reagent and were indeed purified by its action in earlier work on the natural penicillins obtained from *P. notatum* (see Abraham and Chain, *Brit. J. Exp. Path.*, 1942, **23**, 103).



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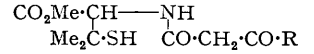

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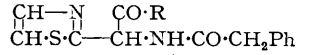

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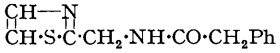

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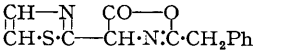

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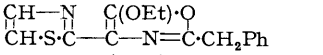


(XII.)

The failure of (VII; R = CH_2Ph) to condense with penicillamine methyl ester to yield a thiazoline prompted closer investigation of its nature and, in particular, of its reaction with α-halogeno-carbonyl compounds. In the manner characteristic of thioamides, (VII; R = CH_2Ph) condensed with diethyl bromoacetal to yield a thiazole (IX; R = OEt), isolated as the free *base* and the *hydrobromide hydrate*.

Since (IX; R = OEt) was readily obtainable and in view of the known stability of the thiazole ring system and the absence of reactive groups in (IX) other than those appertaining

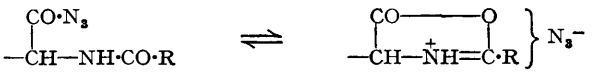
to the α-acylamido-acid portion of the molecule, it was decided to utilise it for studying certain possible methods of synthesising oxazolones, in particular (XI). The methods studied comprised (*a*) dehydration of the acid (IX; R = OH) (*b*) thermal elimination of hydrazoic acid from the azide (IX; R = N_3), and (*c*) cyclisation of the acylamido-esters (IX; R = OEt or O·CHPh$_2$) with phosphorus pentachloride.

(IX; R = OEt) was hydrolysed readily by aqueous sodium hydroxide to give the *acid* (IX; R = OH) which, when pure, appeared to be stable at ordinary temperatures. The crude acid, however, lost carbon dioxide slowly in the solid state or very rapidly in chloroform solution, to afford the *compound* (X), also obtained on heating the acid to its melting point. It was not surpising, therefore, that treatment of (IX; R = OH) with acetic anhydride also gave (X), and other attempts to azlactonise the acid by using acetic anhydride in pyridine or by the action of acetic anhydride, with and without pyridine, on the sodium salt (IX; R = ONa) were likewise unsucessful. The instability of the acid (IX; R = OH) resembled that of the penicilloic acids (I) (containing a thiazolidine instead of a thiazole ring), and it seemed unlikely that related acids of the thiazoline series would prove sufficiently stable for normal azlactonisation to be achieved. This was later confirmed since 5 : 5-dimethyl-2-*p*-nitrobenzamidocarboxymethylthiazoline-4-carboxylic acid (VI; R = H, R′ = CH(CO$_2$H)·NH·CO·C$_6$H$_4$·NO$_2$) could not be isolated after hydrolysis of methyl 5 : 5-dimethyl-2-*p*-nitrobenzamidocarbethoxymethylthiazoline-4-carboxylate, the only isolable product being the dehydropenilloate analogue (VI; R = H, R′ = CH$_2$·NH·CO·C$_6$H$_4$·NO$_2$) (Cook, Elvidge, and Heilbron, *CPS.* 680; *op. cit.*, p. 886).

The acid (IX; R = OH) was therefore treated with diazomethane to yield a crude *ester* (IX; R = OMe) from which the crystalline *hydrazide* (IX; R = NH·NH$_2$) was prepared. The latter compound was also obtained from (IX; R = OEt) and hydrazine hydrate. With nitrous acid the hydrazide yielded the *azide* (IX; R = N_3). In benzene at 60° it evolved gas steadily and a product was isolated which was unexpectedly found to be the *amide* (IX; R = NH_2), identified with an authentic specimen prepared from (IX; R = OEt) and ammonia. Further attempts to prepare the oxazolone (XI) by eliminating the elements of hydrazoic acid from (IX; R = N_3) similarly failed. Only the amide (IX; R = NH_2) was isolated after treating the azide with acetic anhydride in dimethylaniline, acetic anhydride alone, dry pyridine, or dimethylaniline at 70°, or by shaking it in benzene with excess of silver oxide. The unusual transformation of the azide (IX; R = N_3) into the amide (IX; R = NH_2), thus observed under a variety of conditions, may be explained by assuming that the azide was hydrated. Water of hydration may be loosely associated, ·CH·CON$_3$,H$_2$O, or it may be bound in more intimate fashion as in the equivalent structures, ·CH·CO·NH·NH·NO and ·CH·CO·NH·N:N·OH. In each case formation of the amide could occur through loss of nitrous oxide (N_2O). A similar transformation was observed by Thompson and Wolfrom (*J. Amer. Chem. Soc.*, 1946, **68**, 1509), while a less close analogy is offered by the reaction undergone by certain disubstituted hydrazines with nitrous acid in producing amines by the loss of nitrous oxide from an unstable intermediate :

$$RR'N\cdot NH_2 \longrightarrow RR'N\cdot NH\cdot NO \longrightarrow RR'NH + N_2O$$

Whatever the actual mechanism of the above change or the precise structure of the compound (IX; R = N_3), its essentially acid-azide nature was clearly demonstrated by the reaction with benzylamine. Benzylammonium azide was formed together with the *benzylamide* (IX; R = NH·CH$_2$Ph), also obtained from (IX; R = OEt) and benzylamine. Thus the azide (IX; R = N_3) behaved in this reaction like an acid halide, acting as an acylating agent. The reaction with benzylamine could also be explained, however, by assuming the azide to be in reality an oxazolone hydrazoide, but the result of the experiments with pyridine, dimethylaniline, and silver oxide did not reveal any oxazolone character as indicated by the scheme :



There existed little hope, therefore, of converting related α-acylamido-acid azides, which could no doubt have been prepared in the thiazoline series, into the oxazolones. Nevertheless, the method succeeded admirably in a simple case, for hippuric acid azide afforded a 90% yield of 2-phenyloxazolone when warmed in chloroform solution.

In an attempt to prepare oxazolones by the third method, (*c*), the thiazole ester (IX; R = OEt) was heated with phosphorus pentachloride, whereupon cyclodehydration occurred,

to yield the crystalline 5-*ethoxy*-4-2′-*thiazolyl*-2-*benzyloxazole* (XII). The ester (IX; R = OEt) was not changed by heating it with the possible alternative cyclising reagents, acetic anhydride and fused sodium acetate. Since (XII) represented a stable end-product from which the thiazolyl-oxazolone could not be obtained, the *benzhydryl* ester (IX; R = O·CHPh$_2$) was prepared from (IX; R = OH) and diazodiphenylmethane and treated with phosphorus pentachloride; it was hoped that the 5-benzhydryloxy-oxazole would have resulted and this compound might well have undergone hydrogenolysis to the required oxazolone. Unfortunately however, a stable phosphorus chloride *complex* resulted on attempted cyclisation.

Further experiments with these thiazoles were discontinued but the experience gained was applied to the solution of problems encountered in the thiazoline series (cf. Parts V, VII, and VIII of this Series, to be published).

Experimental.

Acylamidocarbethoxythioacetamides.—Ethanol (600 c.c.), in which sodium (1 g.) had been dissolved, was cooled to −10° and saturated with dry hydrogen sulphide. Ethyl phenylacetamidocyanoacetate (57·7 g.) (*op. cit.*) was then added and the mixture heated overnight in a sealed vessel at 50—60°. The solution was evaporated to small bulk *in vacuo*, the residue was dissolved in chloroform, and the solution washed with water. Evaporation gave a white product (44 g.), m. p. 112—115°. From chloroform–light petroleum, *phenylacetamidocarbethoxythioacetamide* crystallised as clusters of flattened needles, m. p. 114—115° (Found: C, 56·1; H, 5·7; N, 9·7. $C_{13}H_{16}O_3N_2S$ requires C, 55·7; H, 5·7; N, 10·0%). The compound was readily soluble in dilute aqueous sodium hydroxide. n-*Hexoamidocarbethoxythioacetamide*, prepared similarly from ethyl *n*-hexoamidocyanoacetate (1·2 g.) and a saturated solution of hydrogen sulphide in ethanol (25 c.c.) containing dissolved sodium (25 g.), crystallised from ether–light petroleum in prisms (0·7 g.), m. p. 83° (Found: C, 50·8; H, 7·6; N, 10·5. $C_{11}H_{20}O_3N_2S$ requires C, 50·8; H, 7·7; N, 10·8%).

Preparation of Thiazolines.—DL-Penicillamine ethyl ester hydrochloride, when heated with thioacetamide, gave ethyl 2 : 5 : 5-trimethylthiazoline-4-carboxylate and thence the hydrochloride. The latter product could not be reduced catalytically with Adams's catalyst or with palladium on polyvinyl alcohol, but the base was successfully reduced with aluminium amalgam to the corresponding thiazolidine in 60% yield (*op. cit.*, p. 938).

Penicillamine methyl ester, prepared by treating the hydrochloride (2 g.) with aqueous sodium hydrogen carbonate and extracting the mixture with chloroform, was heated with phenylacetamidocarbethoxythioacetamide (2·7 g.) at 170° for 30 minutes, whereupon ammonia and hydrogen sulphide were evolved. The reaction product was dissolved in chloroform, and the solution was extracted with 3·5% hydrochloric acid (6 × 20 c.c.), washed with water (3 × 20 c.c.), and chromatographed on magnesium oxide (column, 20 × 1 cm.). A pale red zone moved down the column, followed by a darker and broader band. The eluate from the latter, when evaporated and treated with ether, deposited a little red crystalline material, m. p. 190—192°. By rendering the hydrochloric acid extract alkaline with ammonia and back-extracting the turbid solution with chloroform, a further quantity of the *substance*, m. p. 192°, resulted (total yield, 0·3 g.); it formed pale pink prisms from chloroform (charcoal) on addition of ether and light petroleum (Found: C, 62·2; H, 6·0; N, 16·3%). The same substance arose in small yield by heating phenylacetamidocarbethoxythioacetamide alone at 170—200° for 30 minutes.

The base from penicillamine methyl ester hydrochloride (2 g.) was heated at 170° with ethyl hexoamidomalonate (3·7 g.) (Bentley, Catch, Cook, Elvidge, Heilbron, and Shaw, *CPS.* **63**; *op. cit.*, p. 776). Effervescence occurred for some 8 minutes. The mixture was cooled and stirred with ether, and unchanged hexoamidomalonate (2·2 g.) collected. The ethereal filtrate was extracted with dilute hydrochloric acid, the extract was made alkaline with sodium hydrogen carbonate, and the resultant emulsion extracted with ether. From the ethereal layer the *styphnate* of penicillamine methyl ester disulphide was obtained; it crystallised from ethyl acetate–ether only after addition of a few drops of methanol; the solvated prisms had m. p. 71° (Found: C, 37·95, 38·1; H, 5·0, 5·3; N, 11·5. $C_{18}H_{27}O_{12}N_5S_2,CH_3{\cdot}OH$ requires C, 37·9; H, 5·2; N, 11·65%).

Penicillamine methyl ester (from 4 g. of hydrochloride), mixed with ethyl malonate (5 c.c.), was added dropwise to ethyl malonate (10 c.c.) kept at 175°. After a further 10 minutes, the mixture was distilled (twice) under reduced pressure to yield an apparently homogeneous oil (2·5 g.), b. p. 156°/0·018 mm., which, however, was found to consist of a mixture of (VI; R = Me, R′ = $CH_2{\cdot}CO_2Et$) and (VIII; R = OEt) (Found: C, 48·9; H, 6·7; N, 5·4. $C_{11}H_{19}O_5NS$ requires C, 47·7; H, 6·9; N, 5·1. $C_{11}H_{17}O_4NS$ requires C, 51·0; H, 6·6; N, 5·4%). When kept at room temperature, the oil partly solidified. Recrystallisation of the solid from ethanol–water gave plates, m. p. 109—111°, of methyl 5 : 5-dimethyl-2-carbethoxymethylthiazoline-4-carboxylate (VI) (*op. cit.*, p. 885). Treatment of the remaining oily material with concentrated aqueous ammonia overnight afforded the N-*malonamyl* derivative (VIII; R = NH_2) of penicillamine methyl ester, which separated from ethanol or acetone–light petroleum as prisms, m. p. 107—108° (Found: C, 43·75; H, 6·6; N, 11·1. $C_9H_{16}O_4N_2S$ requires C, 43·6; H, 6·5; N, 11·3%).

Preparation of Thiazole Derivatives.—Phenylacetamidocarbethoxythioacetamide (5·6 g.), diethyl bromoacetal (4·2 g.) (Hartung and Adkins, *J. Amer. Chem. Soc.*, 1927, **49**, 2520), and alcohol (3 c.c.) were heated under gentle reflux for 1 hour, and the resulting dark syrup set aside to crystallise. The 2-*phenylacetamidocarbethoxymethylthiazole hydrobromide* (3·5 g.) was washed with chloroform and recrystallised from chloroform–ether to form hydrated leaflets, m. p. 110—111° (frothing; with softening from 105°) (Found: C, 45·1; H, 4·8; N, 6·9. $C_{15}H_{17}O_3N_2BrS,H_2O$ requires C, 44·7; H, 4·7; N, 6·9%). Shaking a chloroform solution of this hydrobromide with aqueous sodium hydrogen carbonate afforded 2-*phenylacetamidocarbethoxymethylthiazole*, which crystallised from ethanol–water as

feathery needles, m. p. 93° (Found : C, 59·0; H, 5·4; N, 9·2. $C_{15}H_{16}O_3N_2S$ requires C, 59·2; H, 5·6; N, 9·2%). Light absorption (ethanol) : Max., 2420 A.; $E^{1\%}_{1\,cm.}$ = 220.

A portion (987 mg.) of the preceding ester was shaken with 0·509N-sodium hydroxide (6·37 c.c.) for 15 minutes, and the filtered solution (diluted with water to 20 c.c.) was treated at 0° with 0·436N-hydrochloric acid (7·43 c.c.), whereupon a white solid (0·8 g.), m. p. 68—70° (vigorous frothing), separated. *2-Phenylacetamidocarboxymethylthiazole*, purified by slow reprecipitation at 0° from sodium hydroxide solution (charcoal), formed small needles, m. p. 79° (vigorous frothing) (dried over phosphoric oxide at room temperature and pressure) (Found : C, 56·7; H, 4·6; N, 9·95. $C_{13}H_{12}O_3N_2S$ requires C, 56·5; H, 4·3; N, 10·15%). The resolidified melt had m. p. 98° alone or in admixture with the decarboxy-compound obtained by dissolving the thiazole-acid in cold chloroform, adding light petroleum, and cooling the mixture to 0°; *2-phenylacetamidomethylthiazole* formed plates, m. p. 98° (Found : C, 62·3; H, 5·5; N, 11·7. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·1%). Whereas the dried purified thiazole acid, m. p. 79° (decomp.), appeared to be stable at room temperature (completely soluble in aqueous alkali after 120 hours), the crude acid slowly lost carbon dioxide : thus after 48 hours, a 400-mg. sample contained 215 mg. of material insoluble in alkali.

The remaining portion of 2-phenylacetamidocarboxymethylthiazole was treated with an excess of ethereal diazomethane, and the crude methyl ester heated with hydrazine hydrate (10 c.c.) in ethanol (5 c.c.) for 5 minutes on the steam-bath. Evaporation of the solution *in vacuo* left the *hydrazide* of 2-phenylacetamidocarboxymethylthiazole (0·6 g.), which crystallised from *iso*propanol as needles, m. p. 177° (Found : N, 19·7. $C_{13}H_{14}O_2N_4S$ requires N, 19·3%). A solution of the preceding hydrazide (325 mg.) in glacial acetic acid (5 c.c.) and 0·436N-hydrochloric acid (2·58 c.c.) was cooled to 0°, stirred, and treated dropwise during 15 minutes with sodium nitrite (90 mg.) in water (4 c.c.). After a further 15 minutes, ice-water (100 c.c.) was slowly added and the buff-coloured precipitate of the *azide* was collected, washed with water, and dried *in vacuo* over phosphoric oxide; yield, 210 mg.; m. p. 80—81° (decomp.). The azide (70 mg.) was treated with benzylamine (5 drops), whereupon heat was evolved and a solid separated. The latter, freed from red gum with 1 : 1 ethanol–ether, consisted of characteristic hexagonal plates of benzylammonium azide, identified with authentic material, m. p. 163° (decomp.), obtained from hydrazoic acid and benzylamine in ether. The red filtrate was warmed on the steam-bath for 20 minutes, and a second product precipitated from ethyl acetate by addition of ether. This material was identified with the *benzylamide* of 2-phenylacetamidocarboxymethylthiazole and formed groups of fine needles, m. p. 140°, from ethanol–light petroleum (or ill-formed laths from ethanol–water), obtained by boiling 2-phenylacetamidocarbethoxymethylthiazole (20 mg.) under reflux with benzylamine (2 drops) in ethanol (0·5 c.c.) for 30 minutes (Found : C, 65·3; H, 5·4. $C_{20}H_{19}O_2N_3S$ requires C, 65·75; H, 5·2%).

Azlactonisation Experiments.—(*a*) When freshly prepared phenylacetamidocarboxymethylthiazole was treated with cold acetic anhydride, it dissolved during 5—10 minutes with evolution of carbon dioxide. By evaporation *in vacuo*, an alkali-insoluble solid was obtained, recognised as 2-phenylacetamidomethylthiazole by mixed m. p. determination. A solution of 2-phenylacetamidocarboxymethylthiazole in dilute aqueous sodium hydroxide (1 equiv.) was lyophilised. The fluffy *sodium* salt (100 mg.) (freely water-soluble) was set aside for 16 hours with a cold mixture of acetic anhydride (2 c.c.) and dry pyridine (4 c.c.). Evaporation *in vacuo* then afforded a yellow gum, together with a small quantity of pale yellow needles, m. p. 89—90°, insoluble in aqueous sodium hydrogen carbonate. The m. p. was depressed to 73° when the *substance* was mixed with 2-phenylacetamidomethylthiazole. Attempts at purification gave only gums.

(*b*) The previously described thiazole azide (80 mg.) was heated in benzene at 60°. Gas was evolved and most of the solid passed into solution. On addition of light petroleum to the filtrate, a flocculent solid separated (Found : C, 56·8; H, 4·7; N, 15·5. $C_{13}H_{13}O_2N_3S$ requires C, 56·7; H, 4·7; N, 15·3%), which did not depress the m. p. of the authentic *amide* of 2-phenylacetamidocarboxymethylthiazole (long needles, m. p. 196°, from ethanol–water) prepared by heating 2-phenylacetamidocarbethoxymethylthiazole (20 mg.) in ethanol (1 c.c.) with concentrated aqueous ammonia (3 c.c.) for 10 minutes. The amide was also obtained from the acid azide in other ways, as already described.

Hippuric acid hydrazide (300 mg.) was dissolved in 2N-hydrochloric acid (3 c.c.), diluted with water (10 c.c.), and cooled to 0°. Sodium nitrite (150 mg.) in water (5 c.c.) was added dropwise, with stirring, and the white precipitate extracted into chloroform. The dried solution (Na_2SO_4) was treated with diazomethane, but there appeared to be no reaction. After 15 minutes, the solution was heated and evaporated to dryness *in vacuo*. The residual pale oil crystallised rapidly and the solid, washed with light petroleum (b. p. 60—80°), had m. p. 88—89° (yield : 230 mg., 92%). Recrystallised rapidly from ethanol, 2-phenyloxazolone had m. p. 91°; it was apparently formed on warming the hippuric azide.

(*c*) 2-Phenylacetamidocarbethoxymethylthiazole (1 g.) in chloroform (15 c.c.) (which had been shaken with phosphoric oxide) was treated with phosphorus pentachloride (2 g.), and the solution kept warm on the steam-bath for 1 hour. The liquid was shaken with excess of ice-cold aqueous sodium hydrogen carbonate, washed with water, dried (Na_2SO_4), and evaporated, to yield a brown gum which became a powdery solid (0·5 g.), m. p. 130—133°, on trituration with ether. Crystallisation from ethyl acetate (charcoal) by the addition of light petroleum afforded lustrous prismatic needles, m. p. 138°, of *5-ethoxy-4-2′-thiazolyl-2-benzyloxazole* (Found : C, 62·8; H, 4·9; N, 9·8. $C_{15}H_{14}O_2N_2S$ requires C, 62·9; H, 4·9; N, 9·8%). Light absorption (in ethanol) : Max., 2780 A.; $E^{1\%}_{1\,cm.}$ = 770. The material was soluble in concentrated hydrochloric acid. Freshly prepared 2-phenylacetamidocarboxymethylthiazole (1·5 g.) was treated overnight with an excess of ethereal diazodiphenylmethane (Staudinger, Anthes, and Pfenniger, *Ber.*, 1916, **49**, 1932). The acid did not dissolve but was slowly replaced by a deposit of the required ester (0·7 g.), m. p. 123° (from the filtrate 2-phenylacetamidomethylthiazole was precipitated by light petroleum; some decarboxylation of the starting material had therefore occurred). *2-[Phenylacetamido(carbobenzhydryloxy)methyl]thiazole* (IX; R = $CHPh_2$) crystallised from chloroform–light petroleum as ragged-ended laths, m. p. 123° (Found : C, 70·55; H, 5·2; N, 6·5. $C_{26}H_{22}O_3N_2S$ requires C, 70·6; H, 5·0; N, 6·3%). The preceding ester (0·6 g.), phosphorus pentachloride (1·5 g.),

and dry chloroform (15 c.c.) were warmed together on the steam-bath for 1 hour. When the mixture was worked up as in the previous cyclisation experiment, a bluish-green crystalline residue resulted, m. p. 140—145°. This phosphorus chloride *complex* was firmly adsorbed on charcoal but on repeated crystallisation from chloroform–light petroleum pale yellow plates, m. p. 150° (to a red liquid), were eventually obtained (Found : C, 56·4; H, 3·3%).

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