501. *Syntheses in the Penicillin Field. Part IV. Some 2-Substituted Thiazolines and their Reactivity.*

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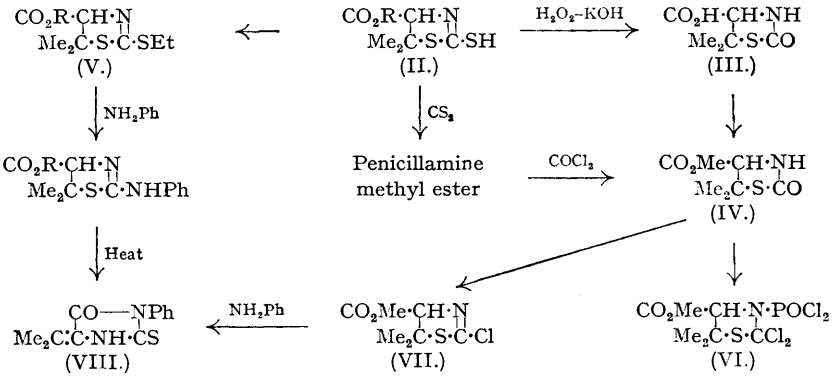
The 2-*mercaptothiazoline* (II; R = Me) was converted into *methyl* 5 : 5-*dimethylthiazolid*-2-*one*-4-*carboxylate* (IV) which was also obtained otherwise. Neither (II) nor (IV) condensed satisfactorily with representative compounds containing " reactive " methylene groups. Alkali-metal derivatives of the latter compounds failed also to react as expected with the 2-*chlorothiazoline* (VII) obtained from (IV), (VII) being converted into an iso*thiocyanate* regarded as (X). With aniline both (VII) and the 2-*ethylthio*-derivative (V) afforded 3-*phenyl*-5-iso*propylidene*-2-*thiohydantoin* (VIII).

Dehydropenicilloate derivatives (I) were required as intermediates in a projected synthesis of penicillins (see Parts III and V of this Series). In continued attempts to prepare such thiazolines the possibility was examined of condensing appropriate 2-substituted (*e.g.*, 2-mercapto- or 2-chloro-)thiazolines with suitable compounds having a reactive methylene group (*e.g.*, ethyl acylamidoacetates). The attempts were uniformly unsuccessful and the present account is concerned chiefly with the preparation and chemistry of the simple thiazolines such as (II) and (VII) which were involved.

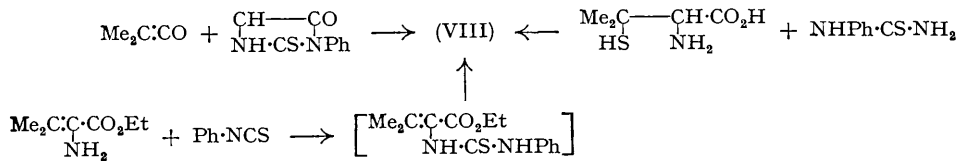
$CO_2Me{\cdot}CH{\cdot}N$ CO_2Et
$Me_2C{\cdot}S{\cdot}C—CH{\cdot}NH{\cdot}CO{\cdot}R$
(I.)



After unsatisfactory efforts to induce penicillamine to react smoothly with thiocarbonyl chloride penicillamine ethyl ester and carbon disulphide had been shown to afford the 2-mercapto-thiazoline (II; R = Et) (Bentley, Catch, Cook, Heilbron, and Shaw, *CPS.* 267; " The Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 466). In a similar manner there was obtained the corresponding *methyl* ester (II; R = Me) which could be hydrolysed to the corresponding *carboxylic acid* (II; R = H) and on oxidation with alkaline hydrogen peroxide gave 5 : 5-*dimethylthiazolid*-2-*one*-4-*carboxylic acid* (III). The structure of this product was indicated by its esterification to (IV) which was also obtained from penicillamine methyl ester and phosgene.

Attempts to condense (II; R = H or Me) or the analogous products (III) and (IV) with compounds containing " reactive " methylene groups (*e.g.*, 2-phenyl-5-oxazolone, 3-phenyl-5-*iso*oxazolone, or 1-phenyl-3-methyl-5-pyrazolone) were abortive. Again, ethylation of (II; R = Me) afforded the corresponding *S*-ethyl derivative (V; R = Me), the structure of which was evidenced by its basic property as contrasted with the pseudo-acidic nature of the parent

ester; the *S*-ethyl compound proved however no more useful than the foregoing thiazolines in attempted condensations with reactive methylene groups, and a still more reactive thiazoline was therefore sought. The corresponding *ethyl* ester (V; R = Et), prepared similarly, reacted with aniline to give the corresponding 2-*anilinothiazoline* which on being heated afforded the *thiohydantoin* derivative (VIII). The structure of the last compound was established by its synthesis from acetone and 1-phenyl-2-thiohydantoin; it was also obtained by interaction of ethyl α-amino-ββ-dimethylacrylate and phenyl *iso*thiocyanate (cf. the preparation of the corresponding hydantoin using phenyl *iso*cyanate; Bouveault and Wahl, *Bull. Soc. chim.*, 1901, [iii], **25**, 913), or of penicillamine and of *N*-phenylthiourea [with phenyl *iso*thiocyanate penicillamine ethyl ester yielded *N*-phenylthioureidopenicillamine ethyl ester, which on fusion lost hydrogen sulphide and formed (VIII) (*op. cit.*, p. 948)] :

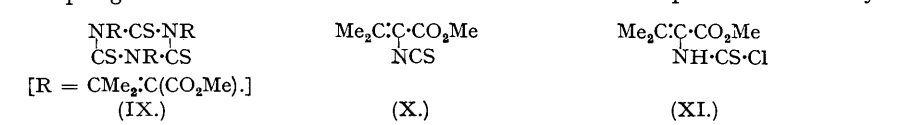


It was interesting that phenyl *iso*thiocyanate had what appeared to be a catalytic action in converting the above-mentioned anilinothiazoline into (VIII).

Heating (IV) with phosphorus pentachloride gave a comparatively stable *compound* for which the representation (VI) seems satisfactory. Several attempts to eliminate the elements of phosphorus oxychloride from the complex by treatment with sodium hydrogen carbonate, heating to 90° in a high vacuum, or chromatography on alumina resulted only in the phosphorylated compound being recovered unchanged. Efforts were then made to prepare the desired chlorothiazoline by treating the thiazolidone (IV) with phosphorus trichloride or thionyl chloride; these reagents were however without effect. Phosphorus oxychloride at 140° afforded a halogen-free oil, whilst stannic chloride gave a tin complex; neither product was further examined. Success was achieved however by use of phosphorus oxychloride and dimethylaniline (cf. Baddiley and Topham, *J.*, 1944, 678). *Methyl 2-chloro-5 : 5-dimethyl-*Δ^2*-thiazoline-4-carboxylate* (VII) was stable at 0°, but at room temperature slowly lost hydrogen chloride, and it reverted to the parent thiazolidone (IV) on exposure to atmospheric moisture. The structure (VII) was confirmed in that heating the compound with aniline afforded the thiohydantoin derivative (VIII) which was not obtainable from (IV).

The chlorothiazoline (VII) was treated under a variety of conditions with the sodium, potassium, lithium, or magnesium derivatives of ethyl malonate, acetoacetate, hexo- or phenylacet-amidomalonate, or hexoamidoacetate, but the desired condensation products were not detected. In some of these experiments, however, products of another kind were obtained.

For example, heating the chlorothiazoline under reflux with ethyl sodioacetoacetate in a hydrocarbon diluent gave a high-melting solid which on the basis of composition and molecular weight is regarded as the iso*thiocyanurate* (IX). This compound was obtained in small yield when attempting to condense the chlorothiazoline with other compounds such as hydantoin.



(IX.) (X.) (XI.)

The action of two equivalents of ethyl potassiohexoamidomalonate on the chlorothiazoline led to the formation of a halogen-free oil which was probably the monomeric iso*thiocyanate* (X). The compound possessed the typical mustard-oil odour and reacted with aniline to form the thiohydantoin derivative (VIII). Clearly the chlorothiazoline resembled a vinyl chloride in its reluctance to condense with alkali-metal derivatives. Reactions, when they did occur, indicated ready ring-scission; indeed, the changes observed may be represented as proceeding through the thiocarbamyl chloride (XI), which satisfactorily accounts for the ready evolution of hydrogen chloride, and the formation of (IX) and (X).

Experimental.

2-Mercapto-5 : 5-dimethylthiazoline-2-carboxylic Acid.—Penicillamine methyl ester hydrochloride (20 g.) was treated with aqueous sodium hydrogen carbonate, the free base extracted by chloroform (3 × 100 c.c.), and the solvent removed *in vacuo*. The residue was heated under gentle reflux with

carbon disulphide (140 c.c.) and ethanol (300 c.c.) for 2 hours. The solution was evaporated *in vacuo* to *ca.* 50 c.c., hot water (50 c.c.) added, and the filtrate cooled. *Methyl 2-mercapto-5 : 5-dimethylthiazoline-4-carboxylate* (15 g.) crystallised, and was recrystallised from ethanol–water, whence it formed colourless needles, m. p. 106—107° (Found : C, 41·05; H, 5·6; N, 6·3. $C_7H_{11}O_2NS_2$ requires C, 41·0; H, 5·4; N, 6·8%). The preceding compound (0·5 g.) was heated under reflux for 1 hour with 2N-hydrochloric acid (20 c.c.), and the solution evaporated to dryness; the residue, consisting of *2-mercapto-5 : 5-dimethylthiazoline-4-carboxylic acid*, crystallised from chloroform–light petroleum in needles, m. p. 145° (yield, 0·4 g.) (Found : C, 37·45; H, 4·7; N, 7·5. $C_6H_9O_2NS_2$ requires C, 37·65; H, 4·75; N, 7·2%).

5 : 5-Dimethylthiazolid-2-one-2-carboxylic Acid.—The above acid (2·66 g.) in N-potassium hydroxide (63 c.c.) was treated with 3% aqueous hydrogen peroxide (73 c.c.), whereupon the temperature quickly rose to 50° and began to drop after 20 minutes. The solution was evaporated to dryness *in vacuo*, and the residue extracted with ethyl acetate (3 × 5 c.c.). The extract was added to warm light petroleum, and, on cooling, colourless needles of *5 : 5-dimethylthiazolid-2-one-4-carboxylic acid* (1·6 g.) were obtained and recrystallised in similar manner; the acid had m. p. 180° (Found : C, 41·1; H, 5·1; N, 7·7. $C_6H_9O_3NS$ requires C, 41·1; H, 5·15; N, 8·0%). The same compound was obtained by similar oxidation–hydrolysis of the methyl and ethyl esters of the 2-mercaptothiazoline-acid. Prepared from the acid (0·2 g.) by means of ethereal diazomethane, *methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate* crystallised from chloroform–light petroleum in needles, m. p. 82—83° (Found : C, 44·5; H, 5·9; N, 7·25. $C_7H_{11}O_3NS$ requires C, 44·4; H, 5·9; N, 7·4%). To a stirred mixture of penicillamine methyl ester hydrochloride (17 g.), water (150 c.c.), sodium hydrogen carbonate (21·5 g.), and chloroform (100 c.c.), a 20% solution of carbonyl chloride in toluene (50 c.c.) was added slowly. The chloroform layer was washed with water and evaporated. From chloroform–light petroleum, methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate (12·7 g.) formed needles, m. p. 82°, identical with the compound obtained previously.

Ethyl 5 : 5-Dimethylthiazoline-4-carboxylates.—Ethyl 2-mercapto-5 : 5-dimethylthiazoline-4-carboxylate (10 g.) in ice-cold water (39 c.c.) containing sodium hydroxide (1·82 g.) was shaken mechanically overnight with ethyl sulphate (7 g.). The oil was taken up in ether and distilled *in vacuo*. *Ethyl 2-ethylthio-5 : 5-dimethylthiazoline-4-carboxylate* (yield, 6 g.) is a heavy oil, b. p. 122—123°/5 mm. (Found : C, 48·7; H, 7·2; N, 5·35. $C_{10}H_{17}O_2NS_2$ requires C, 48·6; H, 6·9; N, 5·55%). It (0·73 g.) was heated with aniline (0·28 g.) at 90—95° for 2 hours, ethanethiol being evolved. On cooling, the product slowly crystallised and was recrystallised from ethanol–water, to afford *ethyl 2-anilino-5 : 5-dimethylthiazoline-4-carboxylate* (0·8 g.) as needles, m. p. 125—126° (Found : C, 60·5; H, 6·6; N, 10·5. $C_{14}H_{18}O_2N_2S$ requires C, 60·4; H, 6·5; N, 10·1%). This anilino-compound (0·28 g.) was heated to 120—130° for 30 minutes; it melted and resolidified. Crystallisation from ethanol gave long needles of *3-phenyl-5-isopropylidene-2-thiohydantoin* (0·2 g.), m. p. 254—257° (decomp.) [Found : C, 62·3; H, 5·35; N, 11·9%; *M* (cryoscopic in camphor), 250. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·0%; *M*, 232].

Other Syntheses of 3-Phenyl-5-isopropylidene-2-thiohydantoin.—(*a*) 1-Phenyl-2-thiohydantoin (Marckwald, Neumark, and Stelzner, *Ber.*, 1891, **24**, 3278) (2 g.) in dry pyridine (2·3 c.c.) was treated with acetone (1 c.c.), followed by piperidine (1·7 c.c.). The mixture was heated under reflux for 5 minutes and poured into water (50 c.c.). The filtrate was acidified to give the *iso*propylidene compound (2·1 g.), m. p. 254—257° (decomp.), identical (mixed m. p.) with the material described above.

(*b*) Ethyl α-amino-ββ-dimethylacrylate (0·18 g.) in ethanol (0·5 c.c.) was treated with phenyl *iso*thiocyanate (0·17 g.) in ethanol (0·5 c.c.). After seeding, long needles of the *iso*propylidene compound crystallised, m. p. 254—257° (decomp.) (0·27 g.).

(*c*) Penicillamine hydrochloride (0·93 g.) and *N*-phenylthiourea (Hugershoff, *Ber.*, 1899, **32**, 3659) (0·76 g.) were heated together at 110° for 1 hour. The melt resolidified. The product crystallised from ethanol in long needles of the *iso*propylidenethiohydantoin (1 g.), m. p. 254—257° decomp.).

(*d*) Ethyl 2-anilino-5 : 5-dimethylthiazoline-4-carboxylate (0·05 g.) in ethanol (3 c.c.) was treated with phenyl *iso*thiocyanate (0·045 g.). After 1 hour the *iso*propylidenethiohydantoin (0·04 g.), m. p. 254—257° (decomp.), had separated.

Methyl 2-Chloro-5 : 5-dimethylthiazoline-4-carboxylate.—A mixture of methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate (0·3 g.) and phosphorus pentachloride (0·4 g.) was heated at 100° for 55 minutes, and the product extracted with ether. The phosphorus chloride *derivative* (VI) (0·2 g.) crystallised from acetone–water at 0° as lustrous plates, m. p. 104° (Found : C, 23·3; H, 3·2; N, 4·3. $C_7H_{10}O_3NCl_4SP$ requires C, 23·3; H, 2·8; N, 3·9%). The thiazolidone (0·6 g.) and phosphorus oxychloride (5 c.c.) were heated together in a sealed tube at 140° for 3 hours, and the resultant mixture was distilled to afford a colourless pleasant-smelling *oil* (Cl and P absent), b. p. 175°/0·003 mm. [Found : C, 49·1; H, 5·75. $C_7H_{10}O_2NS$ (?) requires C, 48·8; H, 5·8%]. A solution of the thiazolidone (18 g.) in dimethylaniline (36 c.c.) and phosphorus oxychloride (72 c.c.) was heated under reflux for 3 hours. The excess of oxychloride was removed *in vacuo* as completely as possible, the dark viscous residue, diluted with some chloroform, was poured slowly on crushed ice, and the mixture stirred for 5 minutes. The product was extracted with ether (2 × 100 c.c.) which was then washed with ice-cold water (4 × 15 c.c.), dried (Na_2SO_4), and distilled, eventually under reduced pressure, to yield *methyl 2-chloro-5 : 5-dimethyl-Δ²-thiazoline-4-carboxylate* as an almost colourless oil, b. p. 90/4 mm. (Found : C, 40·5; H, 4·9. $C_7H_{10}O_2NClS$ requires C, 40·5; H, 4·8%). This oil appeared to be stable indefinitely at 0° in a sealed tube; at room temperature hydrogen chloride was slowly evolved. On exposure to atmospheric moisture, the oil gradually set to a crystalline mass, m. p. 84—85° alone or on admixture with methyl 5 : 5-dimethylthiazolid-2-one-4-carboxylate. Heating the 2-chlorothiazoline (50 mg.) with aniline (40 mg.) at 115—120° for 1·5 hours afforded, after crystallisation from ethanol, long silky needles, m. p. 252—256°, recognised as 3-phenyl-5-*iso*propylidene-2-thiohydantoin (see above).

Condensations attempted with the 2-Chlorothiazoline.—Ethyl acetoacetate (0·64 g.) was added to powdered sodium (0·11 g.) in dry benzene (5 c.c.), and the mixture was heated under reflux to complete the reaction. After cooling, methyl 2-chloro-5 : 5-dimethylthiazoline-4-carboxylate (1·0 g.) was added, and the mixture heated under reflux once more for 20 hours. Sodium chloride was removed and the filtrate evaporated to give a yellow residue which was washed with cold methanol. Recrystallisation from ethanol provided very pale yellow prisms, m. p. 206—208°, of the iso*thiocyanurate* [2 : 4 : 6-*tri*-

thio-1 : 3 : 5-*tri*-(1-*carbomethoxy*isobut-1-*enyl*)*hexahydro*-1 : 3 : 5-*triazine*] (IX) [Found : C, 49·4; H, 5·4; N, 8·0%; *M* (cryoscopic in camphor), 450. $C_{21}H_{27}O_6N_3S_3$ requires C, 49·1; H, 5·3; N, 8·2%; *M*, 513].

A mixture of anhydrous sodium acetate (0·1 g.), hydantoin (0·1 g.), and the 2-chlorothiazoline (0·2 g.) was heated in glacial acetic acid (4 c.c.) at 100° for 24 hours and then evaporated *in vacuo*. By extraction of the residue with ether, pale yellow prisms were obtained and identified as the above *iso*thiocyanurate by mixed m. p.

Ethyl *n*-hexoamidoacetate (1 g.) (*op. cit.*) in ether was treated with ethereal triphenylmethylsodium (1 equiv.), followed by the 2-chlorothiazoline (1 g.). After 24 hours sodium chloride was removed and the filtrate distilled, eventually in a high vacuum at 100°. Some triphenylmethane sublimed and a crystalline residue was left in the retort. Recrystallisation of the residue from ethanol gave pale yellow prisms which did not depress the m. p. of the above *iso*thiocyanurate, and there remained a little ethanol-insoluble material, m. p. *ca.* 220°, which was probably *p*-benzhydryltetraphenylmethane (see below).

A solution of ethyl *n*-hexoamidomalonate (1·35 g.) in ether was treated with ethereal triphenylmethylsodium (1 equiv.), followed by the 2-chlorothiazoline (1 g.). After 24 hours the ether was washed with water and evaporated, and the residue fractionally crystallised from aqueous ethanol and ether–light petroleum, to yield triphenylmethane, m. p. 74—75°. An attempt to isolate a reaction product by distilling the mother-liquors in a high vacuum led to the isolation of hardly-volatile *p*-benzhydryltetraphenylmethane which formed very pale yellow plates, m. p. 223—224°, from benzene–methanol (Found : C, 93·3; H, 6·3. Calc. for $C_{38}H_{30}$: C, 93·8; H, 6·2%). Tschitschibabin (*Ber.*, 1908, **41**, 2427) records m. p. 227° for this self-condensation product of triphenylmethyl.

A mixture of ethyl *n*-hexoamidoacetate (1 g.), the 2-chlorothiazoline (2 g.), and benzene (10 c.c.) was added to powdered potassium (0·195 g.) under light petroleum (b. p. 60—80°). After 7 days at room temperature the mixture was filtered and concentrated *in vacuo* to crystallisation. From benzene–light petroleum a halogen-free *product* (unidentified) separated as pale yellow prisms, m. p. 180—181° [Found : C, 48·3; H, 5·8%; *M* (cryoscopic in camphor), 168. $C_7H_{10}O_2NS$ requires C, 48·8; H, 5·8%; *M*, 172]. The same substance (0·1 g.), m. p. 183° (a mixture showed no depression), was isolated after the 2-chlorothiazoline (1 g.) had been boiled under reflux for 14 hours with an ethereal suspension of the derivative formed from ethyl *n*-hexoamidomalonate (1·35 g., 1 equiv.) and powdered potassium (0·19 g.).

A potassium derivative, formed by treating ethyl *n*-hexoamidomalonate (2·7 g.) with powdered potassium (0·38 g.) under ether (15 c.c.), was heated under reflux with the 2-chlorothiazoline (1 g., 0·5 equiv.) in benzene (15 c.c.) for 16 hours. The mixture was washed with water (5 × 25 c.c.), filtered, dried (Na_2SO_4), concentrated *in vacuo*, and treated with light petroleum, whereupon unchanged hexoamidomalonate crystallised. Distillation of the filtrate yielded a halogen-free, mobile, pale yellow oil, b. p. 100°/2 mm., which smelled of mustard oil and reacted overnight with ethereal aniline to form long needles, m. p. 252°, of 3-phenyl-5-*iso*propylidene-2-thiohydantoin (see above).

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