498. *Syntheses in the Penicillin Field. Part I. The Reactions between Oxalyl Chloride and Certain Thiazolidines.**

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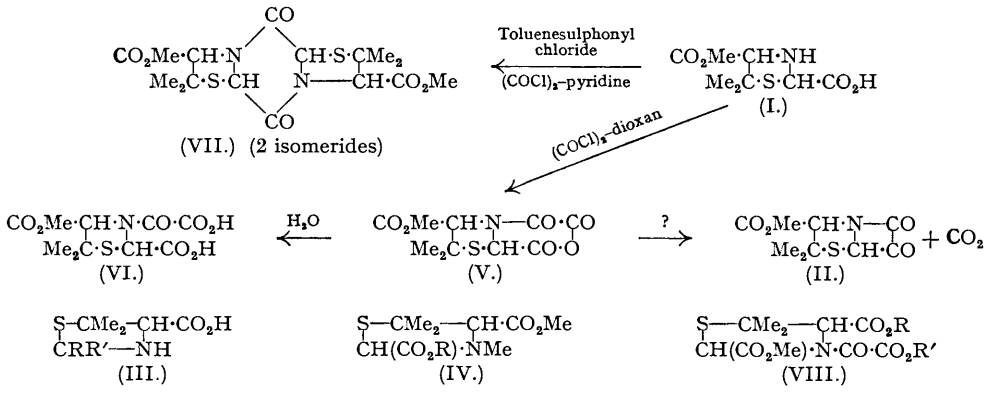
Various thiazolidines bearing a free NH-group and a carboxyl group in the 2- or the 4-position were treated with oxalyl chloride in pyridine or in dioxan. Under the latter conditions *anhydrides* of *carboxy-3-oxalothiazolidines* formed the main products; with appropriate reagents these afforded 3-*oxalo*- or 3-*alkoxalyl-thiazolidines*, representatives of which were independently synthesised. In pyridine the major reaction was one of dehydration to complex *diketopiperazines* which in several instances were isomeric with *diketopiperazines* obtained with other acid chlorides. Similar thiazolidines lacking a free 2- or 4-carboxyl group afforded only 3-*oxalothiazolidines* and *oxalylbis-3-thiazolidines*.

It was observed that interaction of 4-*carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylic acid* (I) and oxalyl chloride under mild conditions led to evolution of carbon dioxide, and in view of supporting observations this reaction was examined more closely in the hope that it might be associated with the formation of the keto-β-lactam (II) which would be a desirable intermediate for the ultimate synthesis of penicillins. The apparent simplicity of this reaction soon proved, however, to be deceptive and the present paper records the results of a more systematic examination of the interaction of oxalyl chloride with various thiazolidines as a preliminary to investigating more labile products.

Endeavours were first made to obtain (I) by esterification of the more easily accessible 2-carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (III; R = H, R′ = CO_2Me)



(VII.) (2 isomerides) (I.) (VI.) (V.) (II.)

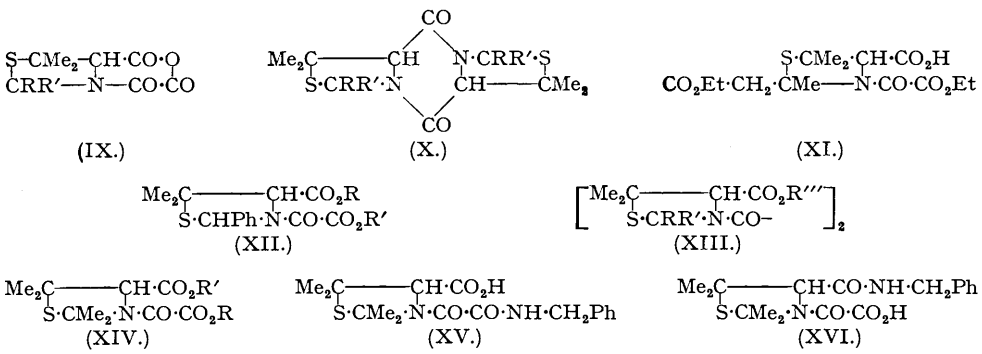
(III.) (IV.) (VIII.)

* A very small part of the work described in this Series was carried out during the war-time Anglo-American co-operative research project on penicillin. None of the present work, however, is described in " The Chemistry of Penicillin," Princeton Univ. Press, 1949.

(see below), followed by half-hydrolysis. Treatment of (III; R = H, R′ = CO_2Me) with diazomethane, however, gave mainly dimethyl 3 : 5 : 5-trimethylthiazolidine-2 : 4-dicarboxylate (IV; R = Me) (*hydrochloride*) which was hydrolysed to 4-*carbomethoxy*-3 : 5 : 5-*trimethylthiazolidine*-2-*carboxylic acid* (IV; R = H) (*benzylamine* salt); this formulation is justified by the half-hydrolysis of the analogous compound lacking the *N*-Me group which afforded the 2-carboxy-derivative. (I) was eventually prepared (*a*) by interaction of penicillamine methyl ester and potassium glyoxylate, and more practicably (*b*) by a similar interaction with methyl dimethoxyacetate to give *dimethyl* 5 : 5-*dimethylthiazolidine*-2 : 4-*dicarboxylate* (*hydrochloride*), followed by half-hydrolysis to (I) [identified with the product of (*a*)] which was conveniently isolated as its *benzylamine* salt.

(I) reacted with oxalyl chloride in dioxan to give the *oxalo-carboxylic anhydride* (V) which with water afforded the *oxalo-carboxylic acid* (VI). In pyridine with oxalyl chloride, (I) afforded a product of unelucidated structure which was at one time (erroneously) thought to be (II), but the main product was a dimeric anhydride, *i.e.*, a *diketopiperazine* (VII). It had been very early observed in these laboratories that toluene-*p*-sulphonyl chloride, among other acid halides, readily converted thiazolidine-4-carboxylic acids into complex diketopiperazines so that the formation of (VII) at first occasioned no surprise. However, although a diketopiperazine was formed when (I) was treated with toluene-*p*-sulphonyl chloride, it was isomeric, presumably stereoisomeric, with the earlier material. Stereoisomeric forms of (VII) are theoretically possible, and the isolation of other pairs of isomerides of this kind suggests that the identity of the acid chloride may be important generally in deciding the steric configuration of the anhydride.

2-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid* (III; R = H, R′ = CO_2Me), obtained from penicillamine and methyl dimethoxyacetate, reacted with ethoxalyl chloride in chloroform–pyridine to give 2-*carbomethoxy*-3-*ethoxalyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid* (VIII; R = H, R′ = Et), whereas with oxalyl chloride in dioxan the *oxalo-carboxylic anhydride* (IX; R = H, R′ = CO_2Me) was obtained. The latter reacted with ethanol to give exclusively the *ethoxalyl-carboxylic acid* (VIII; R = H, R′ = Et) [converted into the mixed *ester* (VIII; R = Me, R′ = Et) by diazomethane], and with water to give the 3-*oxalo-carboxylic acid* (VIII; R = R′ = H) isolated as its *dibenzylamine* salt. Interaction of (III; R = H, R′ = CO_2Me) with oxalyl chloride in pyridine alone was vigorous and a small quantity of a



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

(XII.) (XIII.)

(XIV.) (XV.) (XVI.)

product of empirical formula $C_9H_{11}O_4NS$ was obtained; however this showed none of the properties to be expected of a relatively labile keto-β-lactam, and its nature remains unelucidated. In pyridine, (III; R = H, R′ = CO_2Me) and toluene-*p*- or benzene-sulphonyl chloride gave a *diketopiperazine* (X; R = H, R′ = CO_2Me), possibly a mixture of stereoisomerides.

These results prompted an investigation of some further thiazolidines, some of which offered fewer possibilities of complication.

2 : 5 : 5-Trimethyl-2-carbethoxymethylthiazolidine-4-carboxylic acid (III; R = Me, R′ = CH_2CO_2Et) and oxalyl chloride reacted vigorously, the thiazolidine undergoing dehydration, as in the case of other examples, to yield a *diketopiperazine* (X; R = Me, R′ = $CH_2{\cdot}CO_2Et$). Part of the original thiazolidine, however, evidently formed the oxalo-carboxylic anhydride (IX; R = Me, R′ = $CH_2{\cdot}CO_2Et$) since when it was treated with chloroform containing ethanol the crystalline *carboxylic acid* (XI) was obtained. It was noteworthy that in this case the same diketopiperazine (X; R = Me, R′ = $CH_2{\cdot}CO_2Et$) was obtained by using toluene-*p*-sulphonyl chloride.

2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (III; R = H, R′ = Ph) and oxalyl chloride in dioxan gave the *anhydride* (IX; R = H, R′ = Ph), affording with ethanol the

ethoxalyl-acid (XII; R = H, R′ = Et), the structure of which was confirmed as in an earlier case by direct preparation. The compound (XII; R = H, R′ = Et) obtained from the the anhydride and ethanol was accompanied by an *isomeride* which is almost certainly represented by (XII; R = Et, R′ = H), the alternative product of ring-scission. Treatment of the parent thiazolidine with oxalyl chloride in pyridine, on the other hand, gave one form of the *diketopiperazine* (X; R = H, R′ = Ph) together with the *oxalyl-dicarboxylic acid* (XIII; R = H, R′ = Ph, R″ = H). The latter was esterified to give one form of the *diester* (XIII; R = H, R′ = Ph, R″ = Me), two other forms resulting from the condensation of *methyl 2-phenyl-5 : 5-dimethylthiazolidine-4-carboxylate* with oxalyl chloride in dioxan. It was of interest to find that the foregoing diketopiperazine (X; R = H, R′ = Ph) isomerised in a boiling mixture of hydrochloric and acetic acids and that the resulting *isomeride* was identical with the diketopiperazine formed from the parent thiazolidine (III; R = H, R′ = Ph) and toluene-*p*-sulphonyl chloride.

2 : 2 : 5 : 5-Tetramethylthiazolidine-4-carboxylic acid (III; R = R′ = Me) with oxalyl chloride in dioxan afforded the *anhydride* (IX; R = R′ = Me) and thence the 3-*ethoxalyl-*, the 3-*methoxalyl-*, and the 3-*oxalo-thiazolidine* (XIV) (R = Et, Me, and H, respectively; R′ = H), the last two compounds giving rise to the same *dimethyl* ester (XIV; R = R′ = Me). With ethoxalyl chloride in chloroform–pyridine, 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid gave (XIV; R = Et, R′ = H) directly, from which the 3-N-*benzyloxamyl* derivative (XV) was prepared. The compound (XV) was also obtained by treating the anhydride (IX; R = R′ = Me) with benzylamine, though when the reaction was performed in dioxan a second *benzylamide* was formed to which structure (XVI) is assigned, stereoisomerism being impossible. By contrast with the reaction in dioxan, 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid reacted in pyridine with oxalyl chloride to yield a *diketopiperazine* (X; R = R′ = Me), isomeric with one obtained by use of toluene-*p*-sulphonyl chloride (Cook, Elvidge, Hall, Heilbron, and Shaw, *CPS*, 270; " The Chemistry of Penicillin," Princeton Univ. Press, 1949, pp. 967—968). The ester, methyl 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylate, with oxalyl chloride in dioxan gave, as might have been expected, the *oxalylbis-3-thiazolidine* (XIII; R = R′ = R″ = Me) together with the 3-*oxalo-carboxylate* (XIV; R = H, R′ = Me) which was converted into the *diester* (XIV; R = R′ = Me) by diazomethane.

Experimental.

Preparation of Thiazolidines.

2-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylic Acid.*—A mixture of penicillamine hydrochloride (5 g.), methyl dimethoxyacetate (3·75 g.), and acetic acid (20 c.c.) was heated on the steam-bath for 30 minutes and then evaporated *in vacuo*, and the residue treated with aqueous potassium acetate and extracted with chloroform (4 × 25 c.c.). Evaporation of the extract gave a gum which crystallised on being rubbed with ether. 2-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid* (5 g.) separated from ethyl acetate–light petroleum in laths, m. p. 140—142° (Found: C, 43·7; H, 6·2; N, 6·3. $C_8H_{13}O_4NS$ requires C, 43·8; H, 6·0; N, 6·4%).

The above thiazolidine (0·5 g.) was treated with an excess of ethereal diazomethane, and the product distilled in a high vacuum to yield an oil (0·45 g.) which was treated with ethereal hydrogen chloride. *Dimethyl* 3 : 5 : 5-*trimethylthiazolidine*-2 : 4-*dicarboxylate hydrochloride* crystallised from ethyl acetate–light petroleum in thin needles, m. p. 129—130° (Found: C, 41·7; H, 6·4. $C_{10}H_{18}O_4NClS$ requires C, 42·3; H, 6·4%). The base (0·95 g.) in methanol (10 c.c.) was hydrolysed with 0·1N-sodium hydroxide (40·7 c.c.), added in portions during 2—3 hours. The solution was washed with chloroform, just acidified with hydrochloric acid, and extracted with chloroform. Removal of the chloroform gave a gum which, in ether, with benzylamine afforded *benzylamine* 4-*carbomethoxy*-3 : 5 : 5-*trimethylthiazolidine*-4-*carboxylate* as laths, m. p. 164—165°, from methanol (Found: C, 56·6; H, 7·0; N, 7·9. $C_{16}H_{24}O_4N_2S$ requires C, 56·5; H, 7·1; N, 8·2%). This salt (0·5 g.) in water (10 c.c.) was treated with 0·5N-hydrochloric acid (3 c.c.), and the solution extracted with chloroform (4 × 10 c.c.). Evaporation of the extract gave 4-*carbomethoxy*-3 : 5 : 5-*trimethylthiazolidine*-4-*carboxylic acid* (0·3 g.) which crystallised from ethyl acetate–light petroleum in laths, m. p. 145° (Found: C, 46·3; H, 6·5; N, 6·1. $C_9H_{15}O_4NS$ requires C, 46·3; H, 6·5; N, 6·0%).

4-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-2-*carboxylic Acid.*—(*a*) Penicillamine methyl ester hydrochloride (4 g.), potassium glyoxylate (3 g.), and acetic acid (40 c.c.) were heated together on the steam-bath for 40 minutes, and the solution was then evaporated *in vacuo*. Treatment of the residue in ethyl acetate with benzylamine gave benzylamine 4-carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylate (1·5 g.) which crystallised from ethyl acetate in needles, m. p. 143°, identical with the salt described below.

(*b*) Penicillamine methyl ester hydrochloride (150 g.), acetic acid (500 c.c.), and methyl dimethoxyacetate (100 g.) were heated together on the steam-bath for 3 hours, and then acetic acid was removed *in vacuo*. The residue was treated with excess of aqueous potassium hydrogen carbonate and extracted with chloroform (5 × 200 c.c.). Removal of the chloroform gave a pale brown oil (100 g.) which distilled at 110° in a high vacuum to yield *dimethyl* 5 : 5-*dimethylthiazolidine*-2 : 4-*dicarboxylate* as a viscous oil which solidified when set aside and crystallised from light petroleum in stout prisms, m. p. 70° (Found: C, 46·4; H, 6·8; N, 5·8. $C_9H_{15}O_4NS$ requires C, 46·3; H, 6·5; N, 6·0%). Mixing of ethereal solutions of hydrogen chloride and the thiazolidine gave the *hydrochloride* which separated from ethyl acetate–light

petroleum in needles, m. p. 138° (decomp.) (Found: C, 40·5; H, 6·0. $C_9H_{16}O_4NClS$ requires C, 40·1; N, 6·0%).

(i) The crude oily 2 : 4-dicarboxylate (1·14 g.) in methanol (15 c.c.) was hydrolysed with 0·1N-sodium hydroxide (48·4 c.c.), added in portions during 3 hours. The solution was acidified and extracted with chloroform, and the extract evaporated *in vacuo*. Treatment of the residue in ethyl acetate with benzylamine afforded *benzylamine 4-carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylate* (1 g.) which crystallised in needles, m. p. 143—144° (Found: C, 55·2; H, 6·8; N, 8·3. $C_{15}H_{22}O_4N_2$ requires C, 55·2; H, 6·8; N, 8·5%). (The D-form of this salt has been described by Merck, *M.* 66; *op. cit.*, p. 964). Addition of hydrochloric acid to the benzylamine salt (0·12 g.) in water, followed by extraction with chloroform and evaporation of the extract gave a gum which solidified when rubbed with ether. From ethyl acetate–light petroleum, *4-carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid* separated in fine needles, m. p. 115° (Found: C, 43·9; H, 6·1; N, 6·5; S, 14·6. $C_8H_{13}O_4NS$ requires C, 43·8; H, 6·0; N, 6·4; S, 14·6%).

(ii) The pure crystalline 2 : 4-dicarboxylate (26·5 g.) in methanol (100 c.c.) was hydrolysed with 0·5N-sodium hydroxide (215 c.c.), added in 10 portions during 3 hours. The solution was evaporated to low bulk *in vacuo* and then extracted with chloroform. The aqueous phase was acidified with 1·84N-hydrochloric acid (61 c.c.) and extracted with chloroform (6 × 60 c.c.). Evaporation of the chloroform layer gave a syrup, which after being seeded, set to a white solid (17 g.), m. p. 115°, identical with the 2-carboxylic acid described above.

Methyl 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylate.—Penicillamine methyl ester hydrochloride (1·2 g.) and benzaldehyde (0·7 g.) were warmed together on the steam-bath. The initial syrup rapidly set to a white solid, m. p. 174° (decomp.), which was washed with ether. *Methyl 2-phenyl-5 : 5-dimethylthiazolidine-4-carboxylate hydrochloride* (1·4 g.) crystallised from chloroform–ether in prisms, m. p. 175° (decomp.) (Found: N, 4·9. $C_{13}H_{18}O_2NClS$ requires N, 4·9%). This ester did not dissolve in aqueous sodium hydrogen carbonate, unlike the corresponding thiazolidinecarboxylic acid hydrochloride of m. p. 172—173° (decomp.) (*op. cit.*, p. 962), and a mixture of the two had m. p. *ca.* 155° (decomp.). Copp, Duffin, Smith, and Wilkinson (*op. cit.*, p. 963; *CPS.* 688) give m. p. 154° for the methylthiazolidinecarboxylate hydrochloride.

Reactions with Acid Chlorides.

Reactions of 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic Acid.—The thiazolidine (5 g.) in dry dioxan (40 c.c.) was treated with oxalyl chloride (5 g.) with cooling. After being kept overnight the solution was evaporated *in vacuo*, and the gum dissolved in ether. A white solid (3 g.) was gradually deposited. *4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic-3-glyoxylic anhydride* (V) separated from ethyl acetate–light petroleum in needles, m. p. 128—130° (decomp.) (Found: C, 43·8; H, 4·2; N, 5·3. $C_{10}H_{11}O_6NS$ requires C, 43·9; H, 4·1; N, 5·1%). The anhydride (0·1 g.) was dissolved in warm water, and the solution evaporated *in vacuo* over phosphoric oxide to yield a solid residue. *4-Carbomethoxy-3-oxalo-5 : 5-dimethylthiazolidine-2-carboxylic acid* (0·1 g.) crystallised from ethyl acetate–light petroleum in needles, m. p. 124—125° (decomp.) (Found: C, 40·9; H, 4·8; N, 4·9. $C_{10}H_{13}O_7NS$ requires C, 41·2; H, 4·5; N, 4·8%). 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid (3 g.) in dry pyridine (15 c.c.) was treated with oxalyl chloride (2·5 g.) with cooling. A vigorous reaction occurred with formation of a dark brown solution and precipitate, and carbon dioxide was evolved. After being kept overnight at room temperature the solution was heated on the steam-bath for 10 minutes and then evaporated *in vacuo*. The dark brown residue was dissolved in chloroform (150 c.c.), and the solution washed with 2% aqueous sodium hydrogen carbonate (25 c.c.), 0·5N-hydrochloric acid (2 × 25 c.c.), and water (2 × 25 c.c.). The dried chloroform solution was evaporated to small bulk (10 c.c.), and the solution passed through a column of alumina. A brown band passed rapidly down the column, much dark material being adsorbed at the top. Evaporation of the eluate afforded a brown gum which became powdery when rubbed with ether. The *compound* (0·3 g.) crystallised from chloroform–light petroleum in plates, m. p. 225—230° (decomp.) (Found: C, 49·7, 48·15; H, 5·4, 5·3; N, 6·35; S, 14·4. $C_9H_{11}O_4NS$ requires C, 47·2; H, 4·8; N, 6·15; S, 14·0. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5; N, 7·0; S, 15·9%). 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid (3·0 g.) in pyridine (15 c.c.) was treated with oxalyl chloride (2·5 g.) with cooling. After working up as described above, *dimethyl 3 : 6-diketo-5′ : 5′ : 5″ : 5″-tetramethyldithiazolidino(3′ : 2′-1 : 2)(3″ : 2″-4 : 5)piperazine-4′ : 4″-dicarboxylate* (VII) crystallised from chloroform–light petroleum in laths, m. p. 170° (Found: C, 47·8; H, 5·5; N, 7·1; S, 15·8. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5; N, 7·0; S, 15·9%). 4-Carbomethoxy-5 : 5-dimethylthiazolidine-2-carboxylic acid (0·3 g.) in pyridine (5 c.c.) was treated with toluene-*p*-sulphonyl chloride (0·4 g.), and the solution heated on the steam-bath for 30 minutes. The solution was evaporated to dryness *in vacuo*, and the residue dissolved in chloroform and washed with N-hydrochloric acid and 5% aqueous sodium hydrogen carbonate. Evaporation of the dried chloroform solution *in vacuo* gave a syrup which crystallised when rubbed with ethanol. The isomeric *diketopiperazine* (0·1 g.) separated from ethanol in needles, m. p. 195—197° (Found: C, 48·3; H, 5·5. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5%). The same compound was obtained by use of benzenesulphonyl chloride.

Reactions with 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic Acid.—This compound (1·0 g.) in chloroform (5 c.c.) containing pyridine (1·5 c.c.) was kept for 2 hours with ethoxalyl chloride (0·7 g.). The solution was evaporated, excess of aqueous sodium hydrogen carbonate added, and the solution extracted with ether. The aqueous phase was acidified and again extracted with ether, the extract giving a gum which solidified to white needles. *2-Carbomethoxy-3-ethoxalyl-5 : 5-dimethylthiazolidine-4-carboxylic acid hydrate* separated from ethyl acetate–light petroleum and then had m. p. 95° (yield, 0·5 g.) (Found: C, 43·3; H, 6·0; N, 4·3. $C_{12}H_{17}O_7NS,H_2O$ requires C, 42·8; H, 5·7; N, 4·15%). This acid (0·1 g.) was treated with excess of ethereal diazomethane, and the solution evaporated to give *dimethyl 3-ethoxalyl-5 : 5-dimethylthiazolidine-2 : 4-dicarboxylate* (0·1 g.) which separated from light petroleum in hexagonal prisms, m. p. 93—94° (Found: C, 46·7; H, 5·8; N, 4·1. $C_{13}H_{19}O_7NS$ requires C, 46·8; H, 5·7; N, 4·2%). 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (1·0 g.) in dry dioxan (2 c.c.) was treated with oxalyl chloride (0·8 c.c.) with cooling. A white solid (0·7 g.) was gradually deposited.

2-*Carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylic*-3-*glyoxylic anhydride* (IX; R = CO_2Me, R′ = H) separated from ethyl acetate–light petroleum in needles, m. p. 173—175° (decomp.) (Found : C, 43·7; H, 4·25; N, 5·3. $C_{10}H_{11}O_6NS$ requires C, 43·9; H, 4·1; N, 5·1%). The anhydride (0·1 g.) was dissolved in dry ethanol (1 c.c.), and the solution evaporated *in vacuo*. The resultant gum crystallised completely (yield, 0·12 g.). After recrystallisation from ethyl acetate–light petroleum it had m. p. 94—95°, undepressed by the 3-ethoxalyl-4-carboxylic acid described above. The anhydride (0·1 g.) was dissolved in warm water (0·3 c.c.), and the clear solution evaporated *in vacuo* over phosphoric oxide. A portion of the residual gum was dissolved in dry ether (the anhydride was insoluble in this solvent), and the solution treated with benzylamine (0·1 g.), whereupon the *bisbenzylamine* 2-*carbomethoxy*-5 : 5-*dimethylthiazolidine*-4-*carboxylate*-3-*glyoxylate* (0·1 g.) was obtained in white laths, m. p. 204—205° (decomp.), from methanol–ether (Found : C, 57·3; H, 6·5; N, 7·9. $C_{24}H_{31}O_7N_3S$ requires C, 57·0; H, 6·2; N, 8·3%). The remainder of the gum crystallised from dry ether–pentane to give prisms, m. p. 157° (decomp.), of 2-*carbomethoxy*-3-*oxalo*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid* (Found : C, 41·7; H, 4·8. $C_{10}H_{13}O_7NS$ requires C, 41·2; H, 4·5%). 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (2·0 g.) was dissolved in pure dry pyridine (15 c.c.) cooled to 0°, and added slowly with stirring to the ice-cold complex from oxalyl chloride (1·4 g.) and dry pyridine (15 c.c.). The mixture became coloured, and the addition complex dissolved with effervescence. After being kept overnight at 0° (some solid separated), the mixture was warmed for 30 minutes on the steam-bath and evaporated to dryness *in vacuo*. The brown residue was dissolved in chloroform and extracted with N-hydrochloric acid (2 × 15 c.c.) and saturated sodium hydrogen carbonate solution (2 × 15 c.c.); after being washed with water, the chloroform layer was dried, evaporated to 20 c.c., and passed through alumina, a brownish-coloured eluate being collected in two portions. These were separately evaporated, and treated with dry ether to yield, respectively, 95 mg. of pale buff-coloured solid (m. p. 175—180°) and 120 mg. (m. p. 170—180°). These solids, insoluble in aqueous ammonium hydrogen carbonate, were combined and dissolved in chloroform, and the solution was treated with light petroleum. After an initial flocculent precipitate had been rejected, and on cooling and scratching, the liquor deposited needles, m. p. 195—197°. Following several recrystallisations, the *product* had m. p. 202—203° (Found, on different preparations : C, 47·0, 47·6; H, 4·4, 4·4; N, 6·15; S, 14·2. $C_9H_{11}O_4NS$ requires C, 47·2; H, 4·8; N, 6·15; S, 14·0%). Light absorption (chloroform) : Max., 2640 A.; $E^{1\%}_{1\,cm.} = 460$. 2-Carbomethoxy-5 : 5-dimethylthiazolidine-4-carboxylic acid (2·0 g.) in pyridine (10 c.c.) was warmed with toluene-*p*-sulphonyl chloride (2·0 g.) for 20 minutes and kept overnight at room temperature. After evaporation to dryness *in vacuo*, the residue was dissolved in chloroform and washed with 2N-hydrochloric acid, sodium hydrogen carbonate, and water, and the chloroform extract re-evaporated. The crystalline residue, m. p. 175—180°, was washed with ether and recrystallised, first from ethanol and then from chloroform–light petroleum, to yield *dimethyl* 3 : 6-*diketo*-5′ : 5′ : 5″ : 5″-*tetramethyldithiazolidino*(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)*piperazine*-2′ : 2″-*dicarboxylate* (X; R = H, R′ = CO_2Me) as white laths, m. p. 186—187° (to an opaque liquid which cleared at 204—205°) (Found : C, 46·9; H, 4·8; N, 6·95. $C_{16}H_{22}O_6N_2S_2$ requires C, 47·8; H, 5·5; N, 7·0%). The preparation was repeated using benzenesulphonyl chloride (1·6 g.). The diketopiperazine crystallised from chloroform–light petroleum in short prisms, m. p. 186—187° (clearing at 190°) not depressed on admixture with the previous specimen (Found : C, 47·9; H, 5·5; N, 6·5%).

Reactions of 2 : 5 : 5-*Trimethyl*-2-*carbethoxymethylthiazolidine*-4-*carboxylic Acid*.—The thiazolidine (0·3 g.) (Clayton, Elks, Hems, and Robinson, *CPS.* 201; *op. cit.*, p. 965), dissolved in dried pyridine (15 c.c.), was cooled in ice and added slowly to an ice-cold mixture of oxalyl chloride (3·3 c.c.) and dry pyridine (7 c.c.). A vigorous reaction took place as addition proceeded, with much charring. A solid black mass formed which, on being broken up, appeared to redissolve with effervescence. After being kept overnight at room temperature the mixture was evaporated to dryness and treated with chloroform containing ethanol. The solution was extracted with dilute hydrochloric acid and then with aqueous sodium hydrogen carbonate, and washed with water. Acidification of the sodium hydrogen carbonate extract, after treatment with charcoal, gave an oil which crystallised after a few days. On dissolution in ether and dilution with pentane, 3-*ethoxalyl*-2 : 5 : 5-*trimethyl*-2-*carbethoxymethylthiazolidine*-4-*carboxylic acid* formed colourless laths which after further crystallisation had m. p. 137—138° (Found : C, 50·0; H, 6·5; N, 4·1; S, 9·4. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9; S, 8·9%). After chromatography of the neutral fraction from the chloroform–ethanol, a white solid (600 mg.), m. p. 175°, was obtained. The compound crystallised from ethyl acetate in massive prisms or cubes, m. p. 199—200°, and showed no depression in m. p. when mixed with the 3 : 6-*diketo*-2′ : 5′ : 5′ : 2″ : 5″ : 5″-*hexamethyl*-2′ : 2″-*di*-(*carbomethoxymethyl*)*dithiazolidino*(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)*piperazine* prepared in good yield from the thiazolidine and toluene-*p*-sulphonyl chloride in the usual way (Found : C, 54·6; H, 6·8; N, 5·75; S, 13·6. $C_{22}H_{34}O_6N_2S_2$ requires C, 54·3; H, 7·0; N, 5·75; S, 13·2%).

Reactions with 2-*Phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylic Acid*.—The thiazolidine (Clayton, Elks, Hems, and Robinson, *CPS.* 201; *op. cit.*, p. 962) was dissolved in dry dioxan (25 c.c.), and oxalyl chloride (1·8 g.) added with cooling. After 1 hour, the solution was evaporated *in vacuo*, and the gum treated with ether, whereupon rapid crystallisation occurred. 2-*Phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylic*-3-*glyoxylic anhydride* separated from ethyl acetate–light petroleum in hexagonal plates, m. p. 145° (decomp.) (yield, 1·7 g.) (Found : C, 57·7; H, 4·5; N, 5·1. $C_{14}H_{13}O_4NS$ requires C, 57·7; H, 4·5; N, 4·8%). The anhydride (0·5 g.) was heated with ethanol for 1—2 minutes. The clear solution was evaporated *in vacuo*, and the gum crystallised from ether–light petroleum. Two kinds of crystals were deposited, which were separated mechanically. 4-*Carbethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*-3-*glyoxylic acid* formed rosettes, m. p. 157—158° (decomp.) (yield, 0·2 g.) (Found : C, 56·0; H, 5·7; N, 4·5. $C_{16}H_{19}O_5NS$ requires C, 56·9; H, 5·7; N, 4·1%), and 3-*ethoxalyl*-2-*phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylic acid*, needles, m. p. 140° (decomp.) (yield, 0·3 g.) (Found : C, 56·4; H, 6·0. $C_{16}H_{19}O_5NS$ requires C, 56·9; H, 5·7%). 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (1·0 g.) was dissolved in chloroform (5 c.c.) containing pyridine (1·5 c.c.) and treated with ethoxalyl chloride (1·0 g.) with cooling. After 2 hours, the solution was evaporated to small bulk *in vacuo*, excess of aqueous sodium hydrogen carbonate was added, and the solution extracted with ether. The aqueous phase was acidified with hydrochloric acid and again extracted with ether. Evaporation of the ether yielded the 3-ethoxalyl

derivative as a white crystalline powder (0·9 g.) which crystallised from ether–light petroleum in needles, m. p. 140° (decomp.), undepressed on admixture with the needles described above. 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (7·5 g.) in dry pyridine (40 c.c.) was treated with oxalyl chloride (3·7 c.c.) in pyridine (10 c.c.). The reaction mixture was worked up in the normal way, and after chromatography, a white solid (250 mg.), m. p. 220—225°, was obtained. On recrystallisation from chloroform–light petroleum, 3 : 6-*diketo*-2′ : 2″-*diphenyl*-5′ : 5′ : 5″ : 5″-*tetramethyldithiazolidino*(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)*piperazine* (X; R = H, R′ = Ph) was obtained in clusters of laths, m. p. 240—241° (Found : C, 65·2; H, 5·9; N, 5·95; S, 14·25. $C_{24}H_{26}O_2N_2S_2$ requires C, 65·8; H, 5·9; N, 6·4; S, 14·6%). This compound (70 mg.) was heated under reflux with glacial acetic acid (3 c.c.) and concentrated hydrochloric acid (2 c.c.) overnight; on cooling, a crystalline solid (50 mg.), m. p. 255—258°, separated. This, an isomeric *diketopiperazine*, crystallised from chloroform–light petroleum in long needles, m. p. 263—264° (Found : C, 65·3; H, 6·0; N, 5·8%), depressed to 240—250° on admixture with the previous diketopiperazine. 2-Phenyl-5 : 5-dimethylthiazolidine-4-carboxylic acid (1·3 g.) in pyridine (10 c.c.) was treated with toluene-*p*-sulphonyl chloride (1·0 g.). The solution was warmed for 10 minutes; a pink colour developed and white crystals slowly separated (300 mg., m. p. 268—271°). Recrystallisation from chloroform–light petroleum gave a diketopiperazine as fine needles, m. p. 270—271° (Found : C, 65·5; H, 6·3; N, 6·5. Calc. for $C_{24}H_{26}O_2N_2S_2$: C, 65·8; H, 5·9; N, 6·4%), which showed no depression in m. p. when mixed with the previously described compound of m. p. 263—264°. Acidification of the sodium hydrogen carbonate extract from preparation of the diketopiperazine of m. p. 240—241° gave a solid acid which was partly purified by dissolution in sodium hydrogen carbonate (charcoal), re-acidification, and dissolution in ether, some brown insoluble material being removed. The clear yellow solution was treated with a slight excess of ethereal diazomethane and evaporated to small bulk, and the solid, m. p. 192—196°, was collected. *Oxalylbis*-3-(4-*carbomethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*) crystallised from dioxan–water in cubes, m. p. 205—206° (Found : C, 60·0; H, 5·8; N, 4·7. $C_{28}H_{32}O_6N_2S_2$ requires C, 60·4; H, 5·8; N, 5·0%).

Reactions of Methyl 2-*Phenyl*-5 : 5-*dimethylthiazolidine*-4-*carboxylate.* The thiazolidine hydrochloride (2·9 g.) in chloroform was shaken with aqueous potassium acetate, and the oily base, obtained by evaporating the dried chloroform solution, was treated with oxalyl chloride (1·3 g.) in dry dioxan (20 c.c.). After 30 minutes, the solution was evaporated *in vacuo*, and the residue stirred with ether and light petroleum. Recrystallisation from chloroform–light petroleum afforded prisms (0·7 g.), m. p. 208°, of an isomeric *oxalylbis*-3-(4-*carbomethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*) (Found : C, 60·0; H, 5·6; N, 5·0%; *M*, cryoscopic in camphor, 544). Mixed with the preceding isomer, the m. p. was depressed to 185—204°. The mother-liquors were washed with aqueous sodium hydrogen carbonate and the gummy neutral material chromatographed in ether on alumina to yield a third *oxalylbis*-3-(4-*carbomethoxy*-2-*phenyl*-5 : 5-*dimethylthiazolidine*) (0·5 g.), crystallising from acetone–light petroleum in needles, m. p. 167—168° (Found : C, 60·4; H, 5·9; N, 4·7%; *M*, cryoscopic in camphor, 567).

Reactions of 2 : 2 : 5 : 5-*Tetramethylthiazolidine*-4-*carboxylic Acid.*—The thiazolidine hydrochloride (10 g.) (McOmie, Abraham, Baker, Chain, and Robinson, *CPS.* 32; these authors give a better description than that previously recorded, *op. cit.*, pp. 463—464) was stirred with oxalyl chloride (12 g.) and dry dioxan (150 c.c.) for 48 hours. Unchanged material (mixed m. p.) was collected (3·6 g.) and the filtrate evaporated *in vacuo* to yield a crystalline solid (3·6 g.) which was washed free from oil with dry ether. From dry dioxan—ether, 2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic*-3-*glyoxylic anhydride* formed prisms, m. p. 160° (decomp.) (Found : C, 49·6; H, 5·5. $C_{10}H_{13}O_4NS$ requires C, 49·4; H, 5·35%). The anhydride (0·5 g.) was warmed with ethanol (5 c.c.) and the solution evaporated *in vacuo*. The gum was dissolved in ether, and light petroleum was added, whereupon crystals separated. 3-*Ethoxalyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* (0·4 g.) separated from ether–light petroleum in lath clusters, m. p. 119—120° (decomp.) (Found : C, 49·8; H, 6·6; N, 4·8; S, 11·35. $C_{12}H_{19}O_5NS$ requires C, 49·8; H, 6·6; N, 4·8; S, 11·1%). 2 : 2 : 5 : 5-Tetramethylthiazolidine-4-carboxylic acid (1 g.) in chloroform (5 c.c.) containing pyridine (1·5 c.c.) was treated with ethoxalyl chloride (1 g.) with cooling. After 3 hours the solution was evaporated *in vacuo*, and the gum treated with aqueous sodium hydrogen carbonate and extracted with ether. The aqueous phase was acidified and extracted with ether. Evaporation of the latter extract gave the 3-ethoxalyl derivative as a white solid (0·8 g.) which after recrystallisation from ether–light petroleum had m. p. 120—121°, undepressed in admixture with the previously described ethoxalyl compound. By heating the authentic 3-ethoxalyl derivative with an excess of benzylamine in dioxan for 30 minutes on the steam-bath, cooling the mixture, and adding dilute aqueous hydrochloric acid, the 3-oxalylbenzylamide was obtained, crystallising from aqueous ethanol in square plates, m. p. 104—105°, identical with the benzylamide next prepared. Reaction of the anhydride with benzylamine in the absence of solvent gave, after treatment with dilute aqueous hydrochloric acid, 3-N-*benzyloxamyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* (XV) which crystallised from aqueous ethanol in hydrated square plates, m. p. 105—106° (Found : C, 55·3; H, 6·6; N, 7·5. $C_{17}H_{22}O_4NS,H_2O$ requires C, 55·4; H, 6·5; N, 7·6%). When the anhydride was first dissolved in dioxan and then treated with benzylamine, 3-*oxalo*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxybenzylamide* was obtained on acidification; it crystallised from dioxan–water in long laths, m. p. 134—135° (Found : C, 58·0; H, 6·8; N, 7·2. $C_{17}H_{22}O_4NS$ requires C, 58·3; H, 6·3; N, 8·0%). With methanol, the anhydride reacted to form 3-*methoxalyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* which separated from ether–pentane in prisms, m. p. 136—137° (Found : C, 47·6; H, 6·3; N, 5·0. $C_{11}H_{17}O_5NS$ requires C, 48·0; H, 6·2; N, 5·1%). Esterification with diazomethane gave the dimethyl ester, m. p. 83°, described below. The anhydride dissolved slowly in cold water to afford 3-*oxalo*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic acid* which crystallised from a little ether, on addition of pentane, in prisms, m. p. 139° (decomp.) (Found : C, 45·7; H, 5·9; N, 5·1. $C_{10}H_{15}O_5NS$ requires C, 46·0; H, 5·75; N, 5·4%). By treating this di-acid with diazomethane in ether, *methyl* 3-*methoxalyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylate* was obtained, which crystallised from methanol–water in long needles, m. p. 83° (Found : C, 49·35; H, 6·6; N, 4·6. $C_{12}H_{19}O_5NS$ requires C, 49·8; H, 6·6; N, 4·8%). 2 : 2 : 5 : 5-Tetramethylthiazolidine-4-carboxylic acid hydrochloride (11·0 g.) was dissolved in dry pyridine (75 c.c.), the solution cooled to 0° and added slowly, with stirring, to a mixture of oxalyl

chloride (6·5 c.c.) and ice-cold pyridine (25 c.c.). A vigorous reaction took place, a hard black mass forming, which redissolved with effervescence. The mixture was set aside overnight at 0° and then evaporated to dryness *in vacuo*, and the black residue dissolved in chloroform (100 c.c.). The solution was extracted with 2N-hydrochloric acid (2 × 50 c.c.) and saturated aqueous sodium hydrogen carbonate (2 × 50 c.c.). The chloroform layer was dried and evaporated, and the residue, redissolved in dry chloroform (35 c.c.), was passed through a column of alumina. Evaporation of the brownish eluate gave a partly crystalline residue which was washed with ethanol–ether (1 : 1) to yield a white solid (800 mg.), m. p. 245—255°. On recrystallisation from hot ethanol, 3 : 6-*diketo*-2′ : 2′ : 5′ : 5′ : 2″ : 2″ : 5″ : 5″-*octamethyldithiazolidino*(3′ : 4′-1 : 2)(3″ : 4″-4 : 5)*piperazine* formed square plates, m. p. 262—263° (Found : C, 56·05; H, 7·7; N, 7·65. $C_{16}H_{26}O_2N_2S_2$ requires C, 56·1; H, 7·6; N, 7·6%).

Reactions of Methyl 2 : 2 : 5 : 5-*Tetramethylthiazolidine*-4-*carboxylate*.—The compound (6 g.) (Copp, Duffin, Smith, and Wilkinson, *CPS*. 19; *op. cit.*, p. 960) was treated with oxalyl chloride (8 g.) in dry dioxan (60 c.c.). After 2·5 hours the solution was evaporated *in vacuo*, and the dark residue triturated with ether. From acetone (charcoal) on addition of water, *oxalylbis*-3-(4-*carbomethoxy*-2 : 2 : 5 : 5-*tetramethylthiazolidine*) (0·8 g.) separated in fine laths, m. p. 173—174° (Found : C, 52·2; H, 7·2; N, 5·9%; *M*, cryoscopic in camphor, 388. $C_{20}H_{32}O_6N_2S_2$ requires C, 52·2; H, 7·0; N, 6·1%; *M*, 460). By extracting the filtrates with aqueous sodium hydrogen carbonate, acidifying the extract, back-extracting with ether, and evaporating the ethereal solution *in vacuo*, *methyl* 3-*oxalo*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylate* (1·5 g.) was obtained and crystallised from ether–pentane (charcoal) in prisms, m. p. 112° (decomp.) (Found : C, 48·0; H, 6·45; N, 5·1. $C_{11}H_{17}O_5NS$ requires C, 48·0; H, 6·2; N, 5·1%). Treatment of this acid with ethereal diazomethane gave methyl 3-methoxalyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylate, m. p. 83°, identical with the preparation already described.

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