499. *Syntheses in the Penicillin Field. Part II. The Anhydrides of 4-Carbomethoxy-3-oxalo-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic Acid.*

By R. Bentley, A. H. Cook, and J. A. Elvidge.

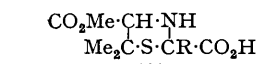
Penicillamine methyl ester was condensed with α-keto*iso*butyric acid to afford two stereoisomeric *4-carbomethoxy-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acids* (I; R = Pr^{i}). With oxalyl chloride in dioxan, these gave two *thiazolidine-2-carboxylic-3-glyoxylic anhydrides*, each of which formed its own series of *products* on ring scission, *e.g.*, with water and ethanol. The action of heat on certain products was examined and also the possibility of effecting ring-contraction of the anhydrides by thermal elimination of carbon dioxide.

Thiazolidine-2-carboxylic acids react smoothly in dioxan with oxalyl chloride to yield, as major products, thiazolidine-2-carboxylic-3-glyoxylic anhydrides, *e.g.*, (I; R = H) ⟶ (II; R = H) (preceding paper). Thiazolidine keto-β-lactams (III; R = H), required as intermediates for a synthesis of penicillins, did not appear to be forthcoming directly from these reactions, and the possibility was therefore examined of eliminating the elements of carbon dioxide from the available anhydrides in order to effect ring-contraction to the desired lactams.

Of α-keto-acids, required for condensation with penicillamine to form thiazolidine-2-carboxylic acids, α-keto*iso*butyric acid was the most easily accessible, being readily obtained from 2-phenyl-4-*iso*propylideneoxazolone, an intermediate in the manufacture of penicillamine. Consequently, the feasibility of the proposed ring-contraction was examined largely with the aid of the 3-glyoxylic anhydrides (see below) prepared from the two forms (*A*, *B*), doubtless stereoisomerides, of *4-carbomethoxy-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (I; R = Pr^{i}) which arose from the condensation of α-keto*iso*butyric acid and penicillamine methyl ester.

The higher-melting form (*A*) reacted with oxalyl chloride in dioxan to give the *anhydride* (II; R = Pr^{i}) (*form* A) which led, as in previous analogous cases of ring scission (preceding paper), to the *oxalo-acid* (IV; R = R′ = H) (*form* A) and the *ethoxalyl* compound (IV; R = Et, R′ = H) (*form* A). The lower-melting form (I; R = Pr^{i}) similarly afforded an *anhydride* (II; R = Pr^{i}) (*form* B) and thence with water and ethanol the *products* (IV; R = R′ = H) and (IV; R = Et, R′ = H) (*forms* B). The ethoxalyl derivatives (IV; R = Et, R′ = H)

(forms *A* and *B*) were also prepared from the parent thiazolidines (I; R = Pr^i) (forms *A* and *B*) and ethoxalyl chloride. Since, however, form *A* of (IV; R = Et, R′ = H) melted with decomposition, a derivative more suitable for purposes of comparison was required. The ethoxalyl compounds *A* from the two sources (I; R = Pr^i) and (II; R = Pr^i) were therefore treated with diazomethane, whereupon each afforded the same *ester* (IV; R = Et, R′ = Me) (*form* A). • Similar esterification of (IV; R = R′ = H) (form *A*) gave the *derivative* (IV; R = R′ = Me) which was also obtained by treating the anhydride (II; R = Pr^i) (form *A*)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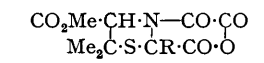
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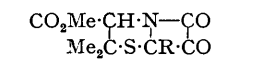
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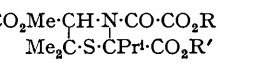
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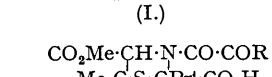
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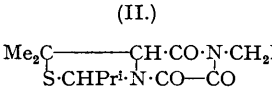
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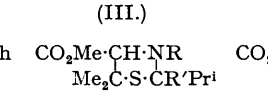
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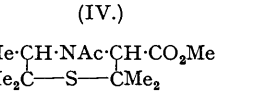
(VIII.)

with methanol to yield an *acid*, presumably (IV; R = Me, R′ = H) and then esterifying this with diazomethane. Form *A* of the anhydride (II; R = Pr^i) with 2 : 4-dinitrophenylhydrazine in dry dioxan afforded a *hydrazide-acid* and with benzylamine a *benzylamide-acid*, very probably [V; R = NH·NH·C$_6$H$_3$(NO$_2$)$_2$ and NH·CH$_2$Ph, respectively]. In addition, a neutral *substance* was isolated from the latter reaction, the same material being obtained also from form *B* of the anhydride (II; R = Pr^i) and benzylamine in the absence of a solvent; on the basis of properties and analyses, structure (VI) is proposed. The formation of a neutral benzylamine derivative, rather than acidic products, from the anhydrides may be attributed to a secondary change occasioned by the vigour of reaction when using undiluted reactants, *viz.*, (V; R = NH·CH$_2$Ph) ⟶ (VI) + MeOH + CO$_2$. Production of only one compound from both forms of the anhydrides suggests that decarboxylation at the 2-position of the thiazolidine ring can result in spatial readjustment. Support for this view was provided by the behaviour of the stereoisomeric thiazolidines (I; R = Pr^i) (forms *A* and *B*) when they were boiled under reflux in ψ-cumene: both isomers were decarboxylated, giving rise to the same product, isolated as a crystalline *hydrochloride* of m. p. 180°. Incidentally, this compound was at first thought to differ from the expected hydrochloride of (VII; R = H, R′ = H) since interaction of penicillamine methyl ester with *iso*butyraldehyde afforded a *hydrochloride* of m. p. 167°. However, a mixture of the two hydrochlorides had unchanged melting point, and the former salt underwent scission with mercuric chloride to yield penicillamine methyl ester and *iso*-butyraldehyde (identified as the 2 : 4-dinitrophenylhydrazone). Furthermore, after the oily base from the lower-melting salt had been heated under reflux in ψ-cumene, the higher-melting hydrochloride was obtained. Hence it is concluded that the latter represents a pure stereoisomer and that, if configurational changes are possible, as in the above cases, the more stable stereoisomer is obtained at elevated temperatures. The pure *stereoisomer* (VII; R = Ac, R′ = CO$_2$Me), prepared from (I; R = Pr^i) (form *A*) by acetylation to the *derivative* (VII; R = Ac, R′ = CO$_2$H) and subsequent methylation, was unchanged by boiling ψ-cumene. That ring expansion might occur to yield the symmetrical thiomorpholine (VIII) was considered a possibility but was not realised. Heating form *A* of the oxalo-acid (IV; R = R′ = H) in xylene caused loss of carbon monoxide and dioxide, and (I; R = Pr^i) (form *A*) was the sole product. There is therefore an appreciable difference in thermal stability between the carboxyl group of the 3-oxalo-substituent and that in the 2-position of the thiazolidine ring, since the latter was eliminated only at the boiling point of ψ-cumene. Compound (IV; R = R′ = H) (form *A*) also lost carbon monoxide and dioxide, when treated with mercuric chloride at ordinary temperature, the thiazolidine ring simultaneously undergoing hydrolytic scission to yield α-keto*iso*butyric acid and penicillamine methyl ester.

In preliminary attempts to effect elimination of carbon dioxide from the anhydride (II; R = Pr^i) (form *A*) by boiling it in xylene or pyridine, and by heating it with powdered glass at 100—160° in the absence of a solvent, the thiazolidine (I; R = Pr^i) (form *A*) was obtained, presumably because traces of water had been present, giving rise to the oxalo-acid (IV; R = R′ = H) as an intermediate. Also obtained by heating (II; R = Pr^i) (form *A*) with powdered glass were a distillable oil, possibly (VII; R = CHO, R′ = H)—the authentic *compound* prepared from the hydrochloride of (VII; R = H, R′ = H) was an oil—and gummy products. The carbon dioxide evolved amounted to 0·38—0·54 mol. From the gummy material, crystalline unchanged anhydride (II; R = Pr^i) (form *A*) was isolated directly, or the acid (IV; R = Et, R′ = H) (form *A*) after treating the original mixture with ethanol, whilst

reaction with methanolic or aqueous mercuric chloride, followed by addition of 2 : 4-dinitrophenylhydrazine, afforded the 2 : 4-*dinitrophenylhydrazones* of α-keto*iso*butyric acid and its methyl ester.

Re-investigation of the thermal behaviour of the anhydrides (II; R = Pr^i) emphasised their reactivity towards water, and particular care was necessary to prevent access of moisture and consequent formation of the ring-scission products (IV; R = R′ = H) which decompose thermally with gas evolution. Thus under strictly anhydrous conditions, no decomposition occurred when the anhydrides (II; R = Pr^i) (forms *A* and *B*) were boiled under reflux in xylene or ψ-cumene. Nor did the recrystallised anhydrides decompose at their melting points, a notable difference from the crude solids (as initially isolated from the oxalyl chloride reaction). However, when the anhydride *A* was heated with dried thoria, both carbon dioxide and carbon monoxide were evolved, but curiously enough the oxalo-acid (IV; R = R′ = H) (form *A*) was isolated (as its *bisbenzylamine* salt) from the reaction mixture. With copper-bronze as catalyst, only carbon dioxide was evolved (as desired), but unfortunately the product appeared to be polymeric; when dry xylene was employed as a diluent, no gas evolution took place. When (II; R = Pr^i) (form *A*) was heated at 140° with dried powdered glass and the light petroleum-soluble portion of the product fractionally distilled in a high vacuum, the crystalline acid (VII; R = CHO, R′ = CO_2H) was isolated and identified with an authentic specimen prepared from (I; R = Pr^i) (form *A*). An oil, also obtained from the distillation, gave a 2 : 4-dinitrophenylhydrazone which became resinous and could not be purified.

In view of the thermal behaviour of the 3-oxalo-acid (IV; R = R′ = H) (form A) which loses both carbon monoxide and dioxide, it is uncertain how the *N*-formyl compounds (VII; R = CHO, R′ = H and CO_2H) arose. It is conceivable, however, that they were formed from the required keto-β-lactam (III; R = Pr^i) by hydrolytic scission during isolation, followed by decarboxylation in the case of (VII; R = CHO, R′ = H). It is also possible that (III; R = Pr^i) was present in the oil which was isolated and gave rise to the unstable 2 : 4-dinitrophenylhydrazone. In view of the repeated failures to obtain more tangible evidence for the formation of a keto-β-lactam, it became clear that the desired ring contraction was not being effected to any degree potentially useful and the investigation was therefore discontinued.

Experimental.

*4-Carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic Acids.—Penicillamine methyl ester hydrochloride (10 g.) and α-keto*iso*butyric acid (7·0 g.) (Ramage and Simonsen, *J.*, 1935, 534) were warmed in a little methanol for 10 minutes on the steam-bath. The viscous gum was washed with dry ether; the ethereal washings very slowly deposited crystals of *4-carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic acid hydrochloride which crystallised from ethyl acetate in compact clumps of prisms, m. p. 129—130° (decomp.) (Found: N, 4·6. $C_{11}H_{20}O_4NClS$ requires N, 4·7%). To the gum, water (100 c.c.) was added slowly with stirring. After several hours, the resulting solid (7·5 g.), m. p. 155—160° (decomp.), was collected and recrystallised from aqueous ethanol to yield *4-carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic acid (*form* A) as plates (parallelograms), m. p. 180—181° (decomp.) (Found: C, 50·3; H, 7·5; N, 5·6. $C_{11}H_{19}O_4NS$ requires C, 50·6; H, 7·3; N, 5·4%). An excess of potassium acetate was added to the filtrate, and the solution extracted with chloroform. Evaporation of the latter *in vacuo* gave a crystalline residue (1·9 g.), m. p. 125—130°, which was washed with pentane–ether. The isomeric *thiazolidine-acid* (*form* B) crystallised from benzene in fine needles, m. p. 123—125° (decomp.) (Found: C, 50·9; H, 7·3; N, 5·25%). Penicillamine methyl ester hydrochloride (2·0 g.), α-keto*iso*butyric acid (1·2 g.), and potassium acetate (1·0 g.) were dissolved in water (25 c.c.); the clear solution quickly became cloudy, depositing an oil which crystallised when cooled and scratched. The solid (1·7 g.), m. p. 125—127°, was recrystallised from benzene to form fine needles, m. p. 125—127° (decomp.), undepressed when mixed with form *B* above.

Anhydrides.—The thiazolidine (form *A*) (1·5 g.) was dissolved in dry dioxan (10 c.c.), and oxalyl chloride (1·2 c.c.) was added dropwise with cooling. The clear solution was kept overnight at room temperature and evaporated to dryness *in vacuo*, and the crystalline residue recrystallised several times from dry xylene and dry chloroform–pentane, to yield prismatic needles, m. p. 137—138°, of *4-carbomethoxy-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic-3-glyoxylic anhydride (*form* A) (Found: C, 49·4; H, 5·5; N, 4·4; S, 10·4. $C_{13}H_{17}O_6NS$ requires C, 49·5; H, 5·4; N, 4·4; S, 10·2%).

Form *B* of the thiazolidine-acid (1 g.) in dry dioxan (10 c.c.) was treated similarly with oxalyl chloride (1 c.c.), to yield *form* B of the *anhydride*, which was sublimed in a high vacuum and crystallised from dry xylene and dry ether–pentane to afford slender rods, m. p. 139° (Found: C, 49·6; H, 5·5. $C_{13}H_{17}O_6NS$ requires C, 49·5; H, 5·4%). A mixture of the anhydrides *A* and *B* had m. p. *ca.* 120°.

Reaction Products of the Anhydrides.—(*a*) The anhydride *A* (200 mg.) was treated with ethanol (5 c.c.) and after 16 hours the solution was distilled with water. *Form* A of *4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-iso*propylthiazolidine-2-carboxylic acid crystallised from ethanol–water in prisms, m. p. 178° (decomp.) (Found: C, 50·4; H, 6·5; N, 3·9. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9%). Treatment of this compound with ethereal diazomethane gave, on evaporation *in vacuo*, *form* A of *dimethyl 3-ethoxalyl-5 : 5-dimethyl-2-iso*propylthiazolidine-2 : 4-dicarboxylate which crystallised from methanol–water in compact prisms, m. p. 141° (Found: C, 51·3; H, 6·8. $C_{16}H_{25}O_7NS$ requires C, 51·2; H, 6·7%). Form *A* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (0·3 g.),

dissolved in dry chloroform (10 c.c.) containing pyridine (0·2 c.c.), was treated with ethoxalyl chloride (0·16 c.c.). After 4·5 hours at room temperature the solution was extracted with aqueous sodium hydrogen carbonate. The aqueous extract was washed with ether, acidified, and re-extracted with ether, evaporation of which yielded form *A* of 4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid, m. p. 175—178°, converted by ethereal diazomethane into the 2 : 4-dicarbomethoxy-compound, m. p. 138—139°, which did not depress the m. p. of the material described above. Interaction of the anhydride *A* (0·4 g.) with dry methanol (2 c.c.) afforded *4-carbomethoxy-3-methoxalyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid*, m. p. 195° (decomp.), unaltered by recrystallisation from methanol–water (Found: C, 48·4; H, 6·0; N, 4·2. $C_{14}H_{21}O_7NS$ requires C, 48·4; H, 6·0; N, 4·0%). Esterification with diazomethane in ether gave a product no longer soluble in aqueous sodium hydrogen carbonate: *dimethyl 3-methoxalyl-5 : 5-dimethyl-2-isopropylthiazolidine-2 : 4-dicarboxylate* separated from methanol–water in prisms, m. p. 116—117° (Found: C, 50·0; H, 6·5; N, 4·3. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9%). The anhydride *A* (100 mg.) was set aside with water (several drops) for 16 hours, and the resulting material recrystallised from ethyl acetate–light petroleum (or ether–pentane) to form elongated prisms, m. p. 149° (decomp.), of *form* A of *4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (Found: C, 46·5; H, 6·0; N, 4·3. $C_{13}H_{19}O_7NS$ requires C, 46·8; H, 5·7; N, 4·2%). Treatment of this di-acid with ethereal diazomethane provided the 2 : 4-dicarbomethoxy-3-methoxalyl compound, identical with that already described. The anhydride *A* was kept at room temperature for 16 hours with 2 : 4-dinitrophenylhydrazine in dry dioxan. Water and chloroform were then added, the mixture was shaken, and the chloroform layer separated and extracted with aqueous sodium hydrogen carbonate. Acidification of the reddish extract, followed by re-extraction with chloroform and evaporation of that solvent, afforded a gum which crystallised under ether–light petroleum. From ethanol–water, pale yellow hexagonal plates, m. p. 195° (decomp.), of the dinitrophenylhydrazide, probably *2-carboxy-4-carbomethoxy-5 : 5-dimethyl-2-isopropylthiazolidine-3-glyoxalo-2′ : 4′-dinitrophenylhydrazide*, crystallised (Found: C, 44·1; H, 4·6; N, 13·3. $C_{19}H_{23}O_{10}N_5S$ requires C, 44·4; H, 4·5; N, 13·6%). Anhydride *A* (100 mg.) was treated with benzylamine, a vigorous reaction taking place. Chloroform (15 c.c.) was added and the solution was washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The alkaline extract was filtered, chilled in ice, and acidified. A white solid separated, soluble in ammonium hydrogen carbonate with effervescence. Several crystallisations from ethanol gave the benzylamide (most likely *2-carboxy-4-carbomethoxy-5 : 5-dimethyl-2-isopropylthiazolidine-3-glyoxalobenzylamide*) as feathery needles, m. p. 163—164° (decomp.) (Found: C, 56·0; H, 6·5. $C_{20}H_{26}O_6N_2S$ requires C, 56·9; H, 6·2%). By treating the anhydride *A* with benzylamine and, when evolution of heat had ceased, dissolving the gum in ethanol and adding dilute hydrochloric acid almost to turbidity, a different *benzylamine* derivative, possibly (VI), separated; it was insoluble in dilute acid and alkali and crystallised from ethanol–water in prismatic needles, m. p. 189° (decomp.) (Found: C, 62·7; H, 6·4; N, 7·8. $C_{18}H_{22}O_3N_2S$ requires C, 62·4; H, 6·4; N, 8·1%).

(*b*) In ethanol, anhydride *B* dissolved to form *4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (*form* B) which separated from ethanol–water in clusters of plates, m. p. 126° (Found: C, 50·3; H, 6·3; N, 4·3. $C_{15}H_{23}O_7NS$ requires C, 49·9; H, 6·4; N, 3·9%). The identical thiazolidine (mixed m. p. undepressed) was produced by acylating form *B* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (0·3 g.) with ethoxalyl chloride (0·16 c.c.) in dry chloroform (10 c.c.) containing pyridine (0·2 c.c.). With water, anhydride *B* afforded *4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (*form* B) which crystallised from ether–pentane in prisms, m. p. 135—136° (decomp.) (Found: C, 47·1; H, 6·0; N, 4·6. $C_{13}H_{19}O_7NS$ requires C, 46·8; H, 5·7; N, 4·2%). Benzylamine reacted vigorously with anhydride *B* to form a neutral derivative which separated from ethanol–water in prisms, m. p. 186° (decomp.) (Found: C, 62·8; H, 6·3; N, 7·7%), apparently identical with the material (see above) from anhydride *A*.

Thermal Behaviour of Certain Thiazolidines and the Oxalo-anhydrides.—4-Carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*) (1 g.) was heated under reflux in pure dry ψ-cumene (20 c.c.) for 50 minutes. 0·64 Mol.-equiv. of a gas was evolved, completely absorbed by concentrated potassium hydroxide solution. The ψ-cumene was distilled off *in vacuo*, and the residue treated with ethereal hydrogen chloride. From chloroform–ether a pure stereoisomer of *methyl 5 : 5-dimethyl-2-isopropylthiazolidine-4-carboxylate hydrochloride* (0·7 g.) crystallised as clusters of prisms, m. p. 180° (decomp.) (Found: N, 5·6. $C_{10}H_{20}O_2NClS$ requires N, 5·5%). The same compound, m. p. 180° (decomp.) (mixed m. p. 180°) was similarly obtained from form *B* of the thiazolidine-2-carboxylic acid. Treatment of the decarboxylation product (0·5 g.) with hot 10% mercuric chloride in methanol (10 c.c.), followed by addition of aqueous 5% mercuric chloride (10 c.c.) and water (80 c.c.), yielded a white precipitate (1 g.), m. p. *ca.* 110°, the filtrate from which with 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid afforded pale orange laths of the derivative of *iso*butyraldehyde, m. p. 182° (not depressed in admixture with an authentic specimen). The white precipitate was dissolved in moist ethyl acetate and decomposed with hydrogen sulphide. Mercuric sulphide was filtered off and the ethyl acetate evaporated *in vacuo*, to leave a residue of needle-shaped crystals, m. p. 170°, recognised as the hydrochloride of penicillamine methyl ester by mixed m. p. determination and ferric chloride colour (purple in dilute aqueous sodium hydrogen carbonate).

Penicillamine methyl ester hydrochloride (1 g.) was stirred with *iso*butyraldehyde (1 c.c.), whereupon the mixture became warm and syrupy and then set to a solid (1·3 g.), m. p. 162—164°, which was washed with ether and recrystallised several times from chloroform–ether. *Methyl 5 : 5-dimethyl-2-isopropylthiazolidine-4-carboxylate hydrochloride* formed prisms, m. p. 167° (decomp.) (C, 47·0; H, 7·7; N, 5·4. $C_{10}H_{20}O_2NClS$ requires C, 47·2; H, 7·9; N, 5·5%). This hydrochloride (1 g.) was made alkaline with aqueous sodium hydrogen carbonate, the oil extracted with chloroform, and the oil obtained on evaporating the chloroform solution was heated under reflux in ψ-cumene (10 c.c.) for 1 hour. After removal of the solvent *in vacuo* and addition of ethereal hydrogen chloride, the high-melting form of the thiazolidine hydrochloride was obtained (mixed m. p. undepressed). Form *A* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (2 g.) in pyridine (25 c.c.) was treated with

acetyl chloride (1 c.c.). After 1·5 hours, excess of pyridine was removed *in vacuo*, and the residue dissolved in chloroform (50 c.c.). The solution was washed with dilute hydrochloric acid and water and evaporated, and the residue treated with ether. *4-Carbomethoxy-3-acetyl-5 : 5-dimethyl-2-isopropylthiazolidine-2-carboxylic acid* (1·3 g.) formed prisms, m. p. 152°, from ethyl acetate–light petroleum (Found : C, 51·9; H, 6·8. $C_{13}H_{21}O_6NS$ requires C, 51·5; H, 6·9%), and reacted with diazomethane to give *dimethyl 3-acetyl-5 : 5-dimethylisopropylthiazolidine-2 : 4-dicarboxylate* (1 g.) which crystallised from methanol–water as prisms, m. p. 100° (Found : C, 52·4; H, 7·1; N, 4·4. $C_{14}H_{23}O_5NS$ requires C, 53·0; H, 7·3; N, 4·4%). The diester (0·7 g.) was recovered unchanged (m. p. and mixed m. p. 99—100°) after being heated under reflux in ψ-cumene (10 c.c.) for 1 hour. Portions of 4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*) (2 × 0·1 g.) were heated at 150°, and heated under reflux in dry xylene, till gas evolution ceased, after which (by evaporation in the case of the xylene experiment, and crystallisation from ethanol–water) form *A* of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid was obtained as plates, m. p. 180—181°, undepressed when mixed with an authentic specimen. 4-Carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*) (0·7 g.) in methanol was added to a hot 10% solution of mercuric chloride in 1 : 1 aqueous methanol (20 c.c.), whereupon gas was slowly evolved. After several days the mixture was diluted with water (80 c.c.), and the white precipitate collected. The filtrate afforded the 2 : 4-dinitrophenylhydrazone of α-keto*iso*butyric acid as pale yellow laths (0·2 g.), m. p. 189—190° (undepressed on admixture with authentic material, m. p. 195°), which crystallised from ethanol–water or benzene (Found : C, 44·9; H, 4·6; N, 19·0. Calc. for $C_{11}H_{12}O_6N_4$: C, 44·6; H, 4·1; N, 18·9%). Rimington (*Onderstepoort J. Vet. Sci.*, 1935, **5**, 445) gives m. p. 189—191°. From the mercuric chloride precipitate, penicillamine methyl ester hydrochloride, m. p. 170°, was recovered as previously described.

The anhydride (form *A*) (200 mg.) in pyridine (5 c.c.) was heated on the steam-bath for 2 hours. Excess of pyridine was evaporated *in vacuo*, and the residue dissolved in chloroform. After extraction with aqueous hydrochloric acid and then sodium hydrogen carbonate, the chloroform was removed *in vacuo* to yield a trace of neutral material which, when washed with ether, afforded an unidentified yellow solid, m. p. 65—70° (decomp.). Acidification of the hydrogen carbonate extract precipitated a gum; this slowly solidified and from ethanol–water crystallised as thin laths, m. p. 180—181° (decomp.) (Found : C, 50·3; H, 7·5; N, 5·6. Calc. for $C_{11}H_{19}O_4NS$: C, 50·6; H, 7·3; N, 5·4%), which did not depress the m. p. of 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (form *A*). The same thiazolidine was similarly obtained after heating the anhydride (form *A*) (200 mg.) under reflux in xylene (10 c.c.) containing quinoline (0·5 c.c.) for 1·5 hours, and also after heating a mixture of the anhydride *A* (350 mg.) and powdered glass (from two 5 × ⅝″ test tubes) at 150—160° for 2 hours. The anhydride *A* (150 mg.) was mixed with a moderately large excess of thoria and heated at 110° in a high vacuum. Slightly impure anhydride *A* sublimed as prisms, m. p. 118—120° (decomp.) (Found : C, 49·6; H, 5·8. Calc. for $C_{13}H_{17}O_6NS$: C, 49·5; H, 5·4%). The sublimate and thoria were recombined and heated at 130—140° under atmospheric pressure for 1 hour. On evacuation of the vessel, a crystalline sublimate formed which was acidic and readily soluble in ether. The anhydride (form *A*) (1 g.), mixed with powdered glass (previously maintained at 190° *in vacuo*), was heated at 150—160° for 1·5 hours, moisture being excluded by a calcium chloride tube. The product was extracted from the powdered glass with chloroform, and the solution passed through a column of alumina to yield, on evaporation of the eluate, a neutral brown oil, possibly impure *methyl 3-formyl-5 : 5-dimethyl-2-isopropylthiazolidine-4-carboxylate* (Found : C, 53·95; H, 7·7; N, 5·3. $C_{11}H_{29}O_3NS$ requires C, 53·9; H, 7·8; N, 5·7%). An attempt to prepare authentic material by slowly treating a mixture of methyl 5 : 5-dimethyl-2-*iso*propylthiazolidine-4-carboxylate hydrochloride (1 g.), sodium formate (350 mg.), and anhydrous formic acid (10 c.c.) with acetic anhydride (5 c.c.) led to the isolation of a neutral oil which could not be induced to crystallise. In other experiments, the anhydride *A* was heated at 150—160° with dried powdered glass in a current of purified dried nitrogen, and the evolved carbon dioxide (0·38 and 0·54 mol. on different occasions) determined. By the procedure previously described an oil was isolated (Found : C, 53·0; H, 7·5; N, 5·8%). This was heated with mercuric chloride (2 g.) in methanol (20 c.c.) for 30 minutes, water was added, and the filtrate treated with the dinitrophenylhydrazine reagent. A pale yellow derivative separated which crystallised from ethanol as laths, m. p. 179° alone or on admixture with the 2 : 4-*dinitrophenylhydrazone* (yellow laths, m. p. 178°, from methanol) of methyl α-keto*iso*butyrate (Found : C, 46·9; H, 4·7; N, 17·8. $C_{12}H_{14}O_6N_4$ requires C, 46·45; H, 4·5; N, 18·1%) which was prepared (*a*) from α-keto*iso*butyric acid methylated with diazomethane and (*b*) by a similar esterification of the acid 2 : 4-dinitrophenylhydrazone. The oily product from a further experiment with powdered glass was not chromatographed; the oil crystallised partly almost at once, and the solid of m. p. 128—130° (decomp.) was shown to consist substantially of unchanged anhydride *A* by interaction with ethanol to give 4-carbomethoxy-3-ethoxalyl-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid, m. p. 178—179° (Found : C, 49·9; H, 6·3; N, 3·7. Calc. for $C_{15}H_{23}O_7NS$: C, 49·9; H, 6·4; N, 3·9%), by interaction with benzylamine to give material (Found : C, 63·0; H, 6·5. Calc. for $C_{18}H_{22}O_3N_2S$: C, 62·4; H, 6·4%) of m. p. 186—188° alone or on admixture with the neutral benzylamine derivative previously described, and by formation, on exposure to atmospheric moisture, of an acid which was shown to be 4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid by reaction with diazomethane to give the 2 : 4-dicarbomethoxy-3-methoxalyl derivative, m. p. 115—117°. Treatment of the remaining recovered anhydride with hot methanolic mercuric chloride led, by a method already outlined, to isolation of α-keto*iso*butyric acid 2 : 4-dinitrophenylhydrazone identified by its m. p. and mixed m. p.

The oxalo-anhydride *A*, freshly prepared from 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (2·08 g.) and oxalyl chloride (2 c.c.) in dry dioxan (20 c.c.), was redissolved in dioxan (10 c.c.), and the solution added to rigorously dried thorium oxide (11 g.). After mixing, the solvent was removed at 60° *in vacuo*, and the residual mixture heated at 145—150° for 2 hours; 1·05 mols. of gas (155 c.c. at N.T.P.) were evolved which consisted of carbon dioxide (52%) and monoxide (48%). The thoria was extracted with chloroform and the extract evaporated, whereupon

crystals separated. Recrystallisation from xylene afforded prismatic needles, m. p. 135—136°, identified as form *A* of the anhydride by mixed m. p. determination and also by interaction with ethanol to give the 3-ethoxalylthiazolidine, m. p. 174—176° (decomp.). Extraction of the non-crystalline material, obtained from the chloroform, with aqueous sodium hydrogen carbonate left a (neutral) oil from which no solid derivative resulted. Acidification of the alkaline solution and extraction with ether also afforded an oil which, however, yielded a salt with ethereal benzylamine. From methanol–ether, the *bisbenzylamine* salt of 4-carbomethoxy-3-oxalo-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid formed small needles, m. p. 171—172° (Found : C, 59·1; H, 6·8; N, 7·7. $C_{27}H_{37}O_7N_3S$ requires C, 59·2; H, 6·8; N, 7·7%). When regenerated from this salt the di-acid crystallised and with diazomethane in ether gave the known dimethyl 3-methoxalyl-5 : 5-dimethyl-2-*iso*propylthiazolidine-2 : 4-dicarboxylate (form A).

Form *A* of the anhydride, prepared in the usual fashion from 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (4 g.) and oxalyl chloride (2·5 c.c.) in dioxan (30 c.c.) but in a flask containing dried powdered glass, was heated at 130—140° for 3 hours. Extraction of the mixture with chloroform afforded a brown oil (3·7 g.) which had a camphor-like odour. The oil was repeatedly extracted with boiling light petroleum, and the extract distilled in a high vacuum to give an almost colourless neutral oil, b. p. $80^\circ/10^{-4}$ mm. (Found : C, 52·6; H, 7·3; N, 7·05; S, 11·5%). The oil afforded a flocculent yellow derivative with the 2 : 4-dinitrophenylhydrazine reagent. This failed to crystallise from benzene–light petroleum or ethanol–water, and chromatography in benzene on alumina gave only a resin. The gummy residue from the foregoing distillation on being heated to 120° in a high vacuum yielded a solid sublimate. This crystallised from ether–pentane in flattened prisms (Found : C, 49·5; H, 6·7%), m. p. 178—179° alone or on admixture with 4-*carbomethoxy*-3-*formyl*-5 : 5-*dimethyl*-2-iso*propylthiazolidine*-2-*carboxylic acid* (m. p. 183—184°, from chloroform–pentane) (Found : C, 49·5; H, 6·4. $C_{12}H_{19}O_5NS$ requires C, 49·8; H, 6·6%) which was prepared by treating 4-carbomethoxy-5 : 5-dimethyl-2-*iso*propylthiazolidine-2-carboxylic acid (1 g.) in cold anhydrous formic acid (10 c.c.) with acetic anhydride (5 c.c.), added dropwise.

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