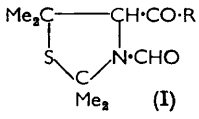
447. *Thiazolidines in the Synthesis of Penicillamine Peptides.*

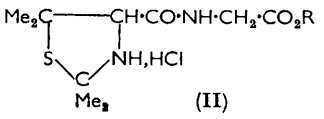
By F. E. King, J. W. Clark-Lewis, G. R. Smith, and Roy Wade.

DL-3-Formyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid, when coupled by the Süs method with aniline and with glycine methyl and ethyl esters, gave products isolated as the thiazolidine hydrochlorides. The D-acid was converted by mixed anhydride coupling and subsequent deformylation into D-4-*N*-methoxycarbonylmethylcarbamoyl-2 : 2 : 5 : 5-tetramethylthiazolidine hydrochloride, an intermediate applicable to the synthesis of a D-penicillamine analogue of glutathione.

Thiazolidinecarboxylic acids are useful for the synthesis of peptides from α-amino-β-mercapto-acids, as illustrated recently for glutathione.[1] These thiazolidines [2] may be prepared by interaction of amino-mercapto-acids and either aldehydes or ketones, but only the *iso*propylidene derivatives of cysteine [1,3,4] and penicillamine [3] have so far been applied to peptide synthesis. Unsuccessful attempts to couple [5] the thiazoline derived from *N*-acetyl-DL-penicillamine led us to investigate thiazolidine derivatives of penicillamine as intermediates in peptide synthesis instead of the thiazolines, thereby eliminating also the reduction stage entailed with thiazolines.



(I)



(II)

The known DL-formylthiazolidine [6] (I; R = OH) was condensed with aniline by the phosphorus trichloride coupling procedure [7] and the resulting anilide (I; R = NHPh) readily converted by methanolic hydrogen chloride into DL-2 : 2 : 5 : 5-tetramethyl-4-phenylcarbamoylthiazolidine hydrochloride. Similar condensation of the acid (I; R = OH) with glycine ethyl and methyl esters, followed by alcoholysis of the intermediate formyl compounds, gave the thiazolidine dipeptide hydrochlorides (II; R = Et and Me). The methyl ester hydrochloride (II; R = Me) prepared in this way [8] has also been obtained by interaction of DL-penicillaminylglycine methyl ester hydrochloride and acetone.[9]

The phosphorus trichloride coupling procedure caused racemisation [1] of the formylthiazolidinecarboxylic acid derived from L-cysteine, and was therefore avoided in preparing D-penicillamine derivatives. Preparation of D-3-formyl-4-*N*-methoxycarbonylmethylcarbamoyl-2 : 2 : 5 : 5-tetramethylthiazolidine (I; R = NH·CH_2·CO_2Me) was achieved instead by mixed anhydride coupling of the D-acid (I; R = OH) with glycine methyl ester as already described for the L-cysteine analogue.[1] The product was found to be dimorphic (m. p.s 88—89° and 120—121°) and was obtained initially in the less stable, lower-melting form. Removal of the formyl group with methanolic hydrogen chloride then gave the D-dipeptide ester hydrochloride (II; R = Me) in which the thiol grouping is still masked and the amine function is exposed for further coupling to a tripeptide derivative, *e.g.*, by reaction with phthaloylglutamic anhydride as for the cysteine analogue.[1]

The compounds illustrate further the value of thiazolidine intermediates [1,4] in the synthesis of α-amino-β-mercapto-acid derivatives. The formyl group is readily removed

[1] King, Clark-Lewis, and Wade, *J.*, 1957, 880.
[2] Cook and Heilbron in "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 921.
[3] Sheehan and Armstrong, 122nd Meeting Amer. Chem. Soc., 1952, Abs. No. 23, p. 15M.
[4] Sheehan and Yang, *J. Amer. Chem. Soc.*, 1958, **80**, 1158.
[5] Swindin, Thesis, Nottingham, 1953.
[6] "The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 960.
[7] Süs and Hoffman, *Annalen*, 1951, **572**, 96.
[8] Smith, Thesis, Nottingham, 1953.
[9] Heilbron and Cook, B.P. 681,900/1952; *Chem. Abs.*, 1954, **48**, 735.

with alcoholic hydrogen chloride which leaves the thiazolidine ring intact, and the latter may then be opened with mercuric chloride; subsequent treatment with hydrogen sulphide then liberates the thiol function. Some of the compounds described here formed the subject of a preliminary announcement by Sheehan and Armstrong.[3]

Experimental

DL-3-*Formyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic Acid*.—*N*-Acetyl-DL-penicillamine (10 g.) in 1·07N-hydrochloric acid (160 c.c.) was boiled under nitrogen for 16 hr. before evaporation under reduced pressure (nitrogen), and the residue was dried azeotropically. The penicillamine hydrochloride crystallised when triturated with anhydrous ether, and when boiled with acetone (100 c.c.) it gave 2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid hydrochloride (9·45 g.; 80%), m. p. 199° (decomp.). The hydrochloride (7·5 g.) was stirred with 98% formic acid (35 c.c.) and sodium formate (2·5 g.) at 20° during addition in 1 hr. of acetic anhydride (15 g.). Next day water (15 c.c.) was added and the solution was evaporated to dryness under reduced pressure; recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave DL-3-formyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid (6·8 g.; 94%) in colourless plates, m. p. 141° (lit.,[6] m. p. 141—142°).

DL-3-*Formyl*-2 : 2 : 5 : 5-*tetramethyl*-4-*phenylcarbamoylthiazolidine*.—Phosphorus trichloride (0·9 c.c.) was added to the above formyl compound (1·9 g.) and aniline (1·5 c.c.) in dry benzene (50 c.c.), and the mixture was boiled under reflux for 5 hr. before being evaporated to dryness under reduced pressure. The residue insoluble in aqueous sodium carbonate consisted of DL-3-*formyl*-2 : 2 : 5 : 5-*tetramethyl*-4-*phenylcarbamoylthiazolidine* which crystallised from aqueous ethanol (charcoal) in prisms, m. p. 178—179° raised to 182° by recrystallisation (Found: C, 62·0; H, 6·6; N, 9·3. $C_{15}H_{20}O_2N_2S$ requires C, 61·6; H, 6·9; N, 9·6%).

DL-2 : 2 : 5 : 5-*Tetramethyl*-4-*phenylcarbamoylthiazolidine Hydrochloride*.—The foregoing anilide (0·21 g.) was boiled for 5 min. with anhydrous methanol (25 c.c.) containing dry hydrogen chloride (2%), and the solution then stored at room temperature. Next day the solution was evaporated under reduced pressure and the residue, when triturated with dry ether, gave DL-2 : 2 : 5 : 5-*tetramethyl*-4-*phenylcarbamoylthiazolidine hydrochloride* (0·12 g.; 56%), m. p. 206—208° (decomp.), which crystallised from methanol–ether in prisms, m. p. 212° (decomp.) (Found: C, 56·1; H, 6·9; N, 9·5. $C_{14}H_{20}ON_2S$,HCl requires C, 55·9; H, 7·0; N, 9·3%).

DL-4-N-*Ethoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine Hydrochloride*.—A mixture of DL-3-formyl-2 : 2 : 5 : 5-tetramethylthiazolidine-4-carboxylic acid (1·9 g.), freshly distilled glycine ethyl ester (1·7 g.), dry benzene (50 c.c.), and phosphorus trichloride (0·9 g.) was heated in a steam-bath for 5 hr. Evaporation of the solution left a residue which was dissolved in ether, and the solution was washed with aqueous sodium carbonate and dried ($MgSO_4$) before evaporation under reduced pressure. The residue was boiled with 1·5% ethanolic hydrogen chloride (25 c.c.) for 5 min., then kept for 14 hr. before evaporation under reduced pressure. Recrystallisation of the residue from dry methanol–ether gave DL-4-N-*ethoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine hydrochloride* in needles, m. p. 200° (decomp.) (Found: C, 46·6; H, 7·3; N, 8·9. $C_{12}H_{22}O_3N_2S$,HCl requires C, 46·4; H, 7·5; N, 9·0%).

DL-4-N-*Methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine Hydrochloride*.—The formyl compound (1·9 g.) and freshly distilled glycine methyl ester (1·7 g.) were treated with phosphorus trichloride in benzene as described above for the ethyl ester, and the neutral formyl ester was precipitated from benzene with light petroleum (b. p. 60—80°). Removal of the formyl group with dry methanolic hydrogen chloride gave DL-4-*N*-methoxycarbonylmethylcarbamoyl-2 : 2 : 5 : 5-tetramethylthiazolidine hydrochloride (0·97 g.; 38%), which crystallised from dry methanol–ether in prisms, m. p. 219—220° (decomp.) (lit.,[9] m. p. 225—227°) (Found: C, 44·7; H, 7·0; N, 9·1. Calc. for $C_{11}H_{20}O_3N_2S$,HCl: C, 44·5; H, 7·1; N, 9·4%).

D-3-*Formyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*-4-*carboxylic Acid*.—Crude potassium benzylpenicillin was hydrolysed in batches of 1 g. or 2 g. with 0·1N-sulphuric acid (or hydrochloric acid), and the D-penicillamine, isolated as the mercury derivative, was converted by acetone into the thiazolidine hydrochloride, m. p. 198° (decomp.). The hydrochloride was converted by formylation as described above for the racemic compound into D-3-formyl-2 : 2 : 5 : 5-thiazolidine-4-carboxylic acid (5·18 g.; 13% from the crude potassium benzylpenicillin, 67 g.),

m. p. 180—181°, $[\alpha]_D^{20}$ +53·7° (1% in EtOH) (lit.,[10] m. p. 179—180°, $[\alpha]_D$ +54°) (Found: C, 49·5; H, 6·9; N, 6·4. Calc. for $C_9H_{15}O_3NS$: C, 49·7; H, 7·0; N, 6·4%).

D-3-*Formyl*-4-N-*methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine*.—The formylthiazolidinecarboxylic acid (5·2 g.) in dry chloroform (60 c.c.) was treated at 0° with triethylamine (3·32 c.c.) and *iso*butyl chloroformate (3·14 c.c.), and after 10 min. a suspension of finely powdered glycine methyl ester hydrochloride (3·3 g.; 1·1 mol.) and triethylamine (3·65 c.c.; 1·1 mol.) in dry chloroform (30 c.c.) was added. Next day the solution was washed with water, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$) before removal of the chloroform under reduced pressure. The residue of D-3-*formyl*-4-N-*methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine* crystallised from ethyl acetate–light petroleum in prisms (2·74 g.; 40%), m. p. 88—89°, $[\alpha]_D^{21}$ +52·9° (0·5% in $CHCl_3$) (Found: C, 50·1; H, 7·1; N, 9·6. $C_{12}H_{20}O_4N_2S$ requires C, 50·0; H, 7·0; N, 9·7%). The dipeptide derivative was dimorphic, the more stable form having m. p. 120—121° (alone or when mixed with the material of m. p. 88—89°) and $[\alpha]_D^{23}$ +52·4° (0·5% in $CHCl_3$) (Found: C, 50·7; H, 7·1; N, 10·2%). Recrystallisation of the compound of m. p. 88—89° from ethyl acetate–hexane and seeding with the higher-melting form gave the dipeptide derivative in elongated prisms, m. p. 120—121°.

D-4-N-*Methoxycarbonylmethylcarbamoyl*-2 : 2 : 5 : 5-*tetramethylthiazolidine Hydrochloride*.—The above formyl dipeptide ester (2 g.) was boiled for 5 min. with dry (Mg) methanol (60 c.c.) containing hydrogen chloride (1·5%), and the solution was cooled and evaporated under reduced pressure below 30° (bath). The residue crystallised when stored overnight in a vacuum over sulphuric acid and sodium hydroxide. Recrystallisation from methanol–ether (sodium-dried) gave the *thiazolidine hydrochloride* (1·56 g.; 76%) in prisms, m. p. 189—191° (decomp.), $[\alpha]_D^{26}$ +49·5° (0·5% in MeOH), which effloresced in a vacuum over sulphuric acid (Found, on dried material: C, 44·0; H, 7·3; N, 9·0. $C_{11}H_{20}O_3N_2S$,HCl requires C, 44·5; H, 7·1; N, 9·4%).

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UNIVERSITY OF NOTTINGHAM, ENGLAND.
UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, February 2nd*, 1959.]

[10] " The Chemistry of Penicillin," Princeton Univ. Press, Princeton, 1949, p. 468.