660. *Chemistry of Micrococcin* P. *Part VI.* Racemisation of 2-(1-Amino-2-methylpropyl)thiazole-4-carboxylic Acid, and Related Studies.*

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Optically active 2-(1-amino-2-methylpropyl)- (I; R = Pr^i) and 2-1′-aminoethyl-thiazole-4-carboxylic acid (I; R = Me) readily undergo racemisation, although the corresponding 2-(1-amino-2-methylpropyl)- (IV; R = Pr^i) and 2-1′-aminoethyl-4-phenylthiazole (IV; R = Me) appear to be optically stable. 2-(1-Amino-2-methylpropyl)thiazole-4-carboxylic acid (I; R = Pr^i) as incorporated into micrococcin *P* is probably of the D-configuration.†

In Part I,[1] it was reported that the amino-acid, 2-(1-amino-2-methylpropyl)thiazole-4-carboxylic acid (I; R = Pr^i), had been isolated in an optically active form as its hydrochloride from the products obtained by the hydrolysis of the antibiotic micrococcin *P* with hot 20% hydrochloric acid. Micrococcin *P* appears to be derived biogenetically from a cysteine-rich peptide,[1,2] and it therefore seemed appropriate to investigate the optical form of the amino-acid (I; R = Pr^i), as the less common D-forms of the natural amino-acids are frequently found incorporated into polypeptide antibiotics.[3] The amino-acid (I; R = Pr^i) can be regarded as being derived from a valyl-cysteinyl residue in the hypothetical precursor [1,2] of micrococcin *P* and the obvious course was to relate the amino-acid (I; R = Pr^i) with natural L-valine.

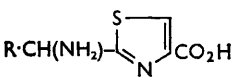
We have previously [4] described the synthesis of DL-2-(1-amino-2-methylpropyl)-thiazole-4-carboxylic acid (I; R = Pr^i) from DL-valine, and the same synthetic methods were therefore applied to L-valine. Benzoylation, esterification with diazomethane, and treatment with methanolic ammonia gave L-α-benzamido-β-methylbutyramide. Dehydration of the latter with phosphoryl chloride in pyridine [5] gave the nitrile, which was converted into the thioamide by the addition of hydrogen sulphide. Benzenesulphonyl chloride and pyridine,[6] which have been commended for use with optically active amides,[7] were used in the DL-series [4] but offered, in this case, no advantage over phosphoryl chloride and pyridine in the preparation of the optically active nitrile. In fact the use of benzenesulphonyl chloride and pyridine resulted in poor conversion at room temperature and considerable racemisation of the resulting nitrile at water-bath temperature. Optical activity was well retained throughout these operations involving reaction at the carbon

* Part V, preceding communication.

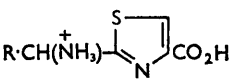
† L- and D- in such cases in this paper refer to the configuration of the α-amino-acid from which the side-chain and $C_{(2)}$ of the ring may be considered to be derived or are in fact derived.

[1] Brookes, Fuller, and Walker, *J.*, 1957, 689.
[2] Brookes, Clark, Fuller, Mijović, and Walker, *J.*, 1960, 916.
[3] Cf. Arnstein, *Ann. Reports*, 1957, **54**, 347; Abraham and Newton, Proc. IVth Internat. Congress Biochem. (Vienna), 1959, **5**, 50.
[4] Brookes, Clark, Majhofer, Mijović, and Walker, *J.*, 1960, 925.
[5] Delaby, Tsatsas, and Lusinchi, *Compt. rend.*, 1956, **242**, 2644.
[6] Stephens, Bianco, and Pilgrim, *J. Amer. Chem. Soc.*, 1955, **77**, 1701.
[7] Peterson and Niemann, *J. Amer. Chem. Soc.*, 1957, **79**, 1389.

atom adjacent to the asymmetric centre; the optical rotation showed a reversal of sign at each stage. Condensation of the L-thioamide with ethyl bromopyruvate gave ethyl L-2-(1-benzamido-2-methylpropyl)thiazole-4-carboxylate with a relatively low, but quite definite, specific rotation. When this product was hydrolysed with acid the resulting L-2-(1-amino-2-methylpropyl)thiazole-4-carboxylic acid (I; R = Pr^i) hydrochloride appeared to have a small dextrorotation, differing significantly numerically from the figure (15·3° at *c* 0·69 in water) recorded [1] for the substance isolated from the hydrolysis products of micrococcin *P*. Sufficient material from the earlier isolation remained for a determination of the optical rotation of the amino-acid hydrochloride from the hydrolysis of micrococcin *P*, and it was comparable in magnitude but of opposite sign to that of the substance obtained by synthesis from L-valine at the concentration (*c* 2·5 in water) studied. Two further isolations of the amino-acid hydrochloride from hydrolyses of micrococcin *P* were then undertaken. In the first of these the product showed a lævorotation in one observation and no perceptible rotation in two others at different concentrations. In the second isolation the product showed lævorotations in three different observations; when two solutions were further examined after an interval, no perceptible rotations were observed. A further preparation of the synthetic product was therefore undertaken and pure recrystallised ethyl L-2-(1-benzamido-2-methylpropyl)thiazole-4-carboxylate was hydrolysed as before, but, in this case, the resulting amino-acid hydrochloride showed no perceptible rotation. We were therefore obliged to conclude that the amino-acid (I; R = Pr^i) undergoes ready racemisation. The fact that it seemed to survive lengthy treatment in strongly acid media without complete racemisation suggests that the cation (II; R = Pr^i) is reasonably stable, and that it is the dipolar ion (III; R = Pr^i) that is stereochemically labile. Lack of material has, however, prevented a more detailed study. Lævorotations * have been observed repeatedly for material isolated from micrococcin *P*, and, as material synthesised from L-valine has shown a dextrorotation, the amino-acid (I; R = Pr^i) incorporated in micrococcin *P* is apparently related configurationally to D-valine.



(I)



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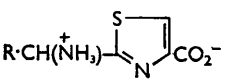


(III)

In the hope of throwing light on this loss of optical activity a similar series of experiments was carried out starting from L-alanine, and, although optical activity was retained throughout the series of intermediates, the final product, 2-1′-aminoethylthiazole-4-carboxylic acid (I; R = Me) hydrochloride, showed no perceptible rotation.

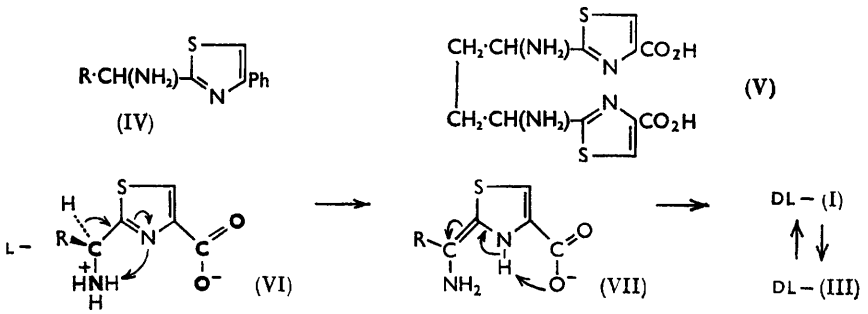
Further experiments were carried out with the object of studying the effects of a 4-substituent other than the carboxyl group on the optical properties of a 2-1′-aminoalkylthiazole. For this purpose D-α-benzamido-β-methylbutyrothioamide and L-α-benzamidopropionothioamide were severally condensed with ω-bromoacetophenone in alcoholic solution in presence of calcium carbonate. Hydrolysis of the products afforded D-2-(1-amino-2-methylpropyl)-4-phenylthiazole (IV; R = Pr^i) and L-2-1′-aminoethyl-4-phenylthiazole (IV; R = Me) hydrochlorides which appeared to be optically stable. However, condensation of L-α-benzamidopropionothioamide and ω-bromoacetophenone in presence of pyridine gave racemic 2-1′-benzamidoethyl-4-phenylthiazole.

These experiments suggest that the apparently ready racemisations of the acids (I; R = Pr^i and Me) are related to the presence of the 4-carboxyl group. Our observations are also in line with the fact that thiostreptoic acid (V), liberated from the antibiotic thiostrepton by acid hydrolysis, also appears to be optically inactive,[8] although the latter

* The sign of rotation recorded previously [1] appears to have been incorrect.

[8] Bodanszky, Sheehan, Fried, Williams, and Birkhimer, *J. Amer. Chem. Soc.*, 1960, **82**, 4747.

could be either a racemate or a *meso*-form. Inspection of a model of 2-(1-amino-2-methylpropyl)thiazole-4-carboxylic acid shows that in the related dipolar ion the preferred conformation should be that (VI; R = Pr^i) in which the atoms shown bold lie in the same



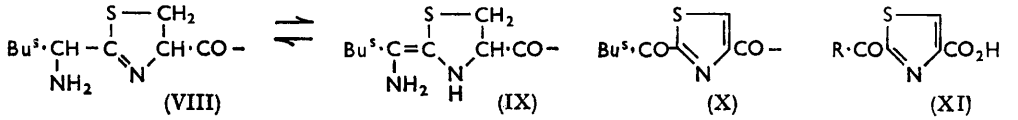
plane as the thiazole ring, and the transfer of a proton from the exocyclic ammonio-group to the ionised carboxyl group might be facilitated by participation of the ring-nitrogen atom as an intermediate " relay station " (VII) in a concerted process involving loss of asymmetry at the asymmetric centre.

Parallel optical behaviour is seen in the thiazoline antibiotic bacitracin A, in which the corresponding asymmetric centre in the terminal 2-(1-amino-2-methylbutyl)thiazolinyl-4-carbonyl residue [9] (VIII) shows similar lability. This portion of the bacitracin A molecule is derived biogenetically from a *N*-terminal L-isoleucyl-L-cysteinyl fragment of a peptide chain and gives rise on acid hydrolysis to L-cysteine and L-isoleucine, accompanied, however, by 0·5 mole of D-alloisoleucine per mole of bacitracin A; [10,11] it has also been proved [11] that it is this terminal L-isoleucyl residue which is concerned in the formation of the alloisoleucine and neither of the other two L-isoleucyl residues in the antibiotic. The stereochemical lability of this asymmetric centre in bacitracin A has been interpreted [11 12] in terms of tautomeric interconversion between the forms (VIII) $\rightleftharpoons$ (IX), and it has more recently been shown [12] that stereochemical equilibration in this instance can take place in the intact antibiotic in 3% acetic acid at room temperature in a few days and in solution at pH 4·52 at 4° in the course of a month. The situation in bacitracin A, however, is further complicated by lack of precise knowledge of the interaction that appears to exist between this area of the molecule and the phenylalanine residue.

Besides showing stereochemical instability the same positions in bacitracin A and in 2-(1-amino-2-methylpropyl)thiazole-4-carboxylic acid (I; R = Pr^i) are involved in remarkably ready oxidative loss of ammonia with generation of carbonyl groups. Thus, bacitracin A is changed by exposure in solution at pH 7 or slightly higher into bacitracin F in which the terminal substituted thiazoline group (VIII) is replaced by the corresponding 2-acylthiazolyl-4-carbonyl group (X) with loss of ammonia and conversion of the thiazoline ring into a thiazole structure; [13] and 2-(1-amino-2-methylpropyl)thiazole-4-carboxylic acid (I; R = Pr^i) is converted with very great ease at room temperature into 2-isobutyryl-thiazole-4-carboxylic acid (XI; R = Pr^i) by treatment with dilute alkaline potassium permanganate solution,[1] a process which similarly converts thiostreptoic acid (V) into the related 2,2′-succinoylbisthiazole-4,4′-dicarboxylic acid.[8] In view of the probable mode of biosynthesis of micrococcin *P* discussed previously [1,2,4] in this series of papers, it is likely

[9] Hausmann, Weisiger, and Craig, *J. Amer. Chem. Soc.*, 1955, **77**, 721.
[10] Craig, Hausmann, and Weisiger, *J. Amer. Chem. Soc.*, 1954, **76**, 2839.
[11] Lockhart, Abraham, and Newton, *Biochem. J.*, 1955, **61**, 534.
[12] Konigsberg and Craig, *J. Amer. Chem. Soc.*, 1959, **81**, 3452.
[13] Hausmann, Weisiger, and Craig, *J. Amer. Chem. Soc.*, 1955, **77**, 730; Weisiger, Hausmann, and Craig, *ibid.*, p. 3123.

that oxidative loss of ammonia at some stage accounts for the appearance of 2-propionylthiazole-4-carboxylic acid (XI; R = Et) among the hydrolytic products from micrococcin *P* rather than 2-1′-aminopropylthiazole-4-carboxylic acid (I; R = Et), although it is not yet possible to say whether 2-propionyl- (XI; R = Et) and 2-(1-amino-2-methylpropyl)-thiazole-4-carboxylic acid (I; R = Pr^{i}) " may be incorporated in micrococcin *P* in the form in which they are isolated after hydrolysis, or the appearance of one as the



(VIII) (IX) (X) (XI)

ketonic and the other as the amino-derivative may be related to the position occupied in the molecule of the antibiotic and to the order of events during hydrolysis." [1] It is of interest that in one laboratory [14] 2-1′-aminopropylthiazole-4-carboxylic acid (I; R = Et) has been obtained on acid hydrolysis of thiostrepton, and a report from another group [8] describes the isolation after similar treatment of thiostrepton of the related keto-acid (XI; R = Et), identical with the fragment isolated from micrococcin *P*,[1] in addition to the amino-acid (I; R = Et). Another theory for the mode of origin of 2-propionylthiazole-4-carboxylic acid (XI; R = Et) in the hydrolysis of micrococcin *P* has been proposed,[14] based on the incorporation of the threonine analogue [I; R = Me·CH(OH)·] into the antibiotic, but is considered unlikely in view of the appearance of α-aminobutyric acid among the products formed by treatment of micrococcin *P* with sodium and liquid ammonia followed by acid hydrolysis.[4]

Micrococcin *P* was the first antibiotic reported [1] to contain thiazole structures showing a definite pattern relating them to cysteine peptide precursors and it is of interest that a similar pattern has emerged from the antibiotics thiostrepton [8,14] and bottromycin.[15]

Experimental

L-Valine and L-alanine were commercial specimens of satisfactory purity (specific rotation and paper chromatography); D-valine, kindly supplied by Dr. D. F. Elliott, had been obtained by resolution of DL-valine.[16]

L-α-*Benzamido*-β-*methylbutyramide*.—(i) L-Valine was benzoylated by the usual Schotten–Baumann method, and the product, after crystallisation from water, had m. p. 113—115°, $[\alpha]_D^{21}$ +22·0° (*c* 4·9 in 95% ethanol); Fox *et al.*[17] record m. p. 131—132° and $[\alpha]_D^{25}$ +21·8° (*c* 4·9 in 95% ethanol). Our lower m. p. may be due to dimorphism, as the m. p. of the D-derivative agreed with that recorded by Fox *et al.* for the L-compound.

(ii) Treatment of the preceding product with ethereal diazomethane afforded *N*-benzoyl-L-valine methyl ester, which crystallised from aqueous methanol as needles, m. p. 113—114°, $[\alpha]_D^{21}$ −8·0° (*c* 5 in methanol); Reihlen and Knöpfle [18] record m. p. 110·5° and $[M]_D$ −18° (*i.e.*, $[\alpha]_D$ −7·7°) (*c* 0·4 in methanol). The D-compound had m. p. 111° and $[\alpha]_D^{24}$ +8·2° (*c* 5 in methanol).

(iii) The preceding ester (4·12 g.) was heated at 110° for 8 hr. in a small stainless-steel bomb with methanol (40 c.c.), which had been saturated with ammonia at 0°. After cooling, the crystalline product (2·23 g., 58%) was collected and washed with ether. The material obtained by evaporation of the combined ether washings and mother-liquors could be re-cycled with methanolic ammonia. Recrystallisation from aqueous methanol gave L-α-*benzamido*-β-*methylbutyramide* as prismatic needles, m. p. 242—244°, $[\alpha]_D^{21}$ +50·3° (*c* 2·5 in dimethylformamide); a sample was sublimed at 215°/15 mm. for analysis (Found: C, 65·4; H, 7·1; N, 12·6. $C_{12}H_{16}N_2O_2$ requires C, 65·4; H, 7·3; N, 12·7%). Fox *et al.*[17] quote m. p. 220—221° for the DL-compound. The D-derivative had m. p. 242°.

[14] Kenner, Sheppard, and Stehr, *Tetrahedron Letters*, 1960, No. 1, 23.
[15] Waisvisz, van der Hoeven, and te Nijenhuis, *J. Amer. Chem. Soc.*, 1957, **79**, 4524.
[16] Birnbaum, Levintow, Kingsley, and Greenstein, *J. Biol. Chem.*, 1952, **194**, 455.
[17] Fox, Pettinga, Halverson, and Wax, *Arch. Biochem.*, 1950, **25**, 21.
[18] Reihlen and Knöpfle, *Annalen*, 1936, **523**, 199.

L-α-*Benzamido*-β-*methylbutyrothioamide*.—(i) Redistilled phosphoryl chloride (0·75 c.c.) was added slowly with ice-cooling to the amide (1·5 g.) in dry pyridine (7·5 c.c.). After ½ hr. at room temperature, the mixture was poured on ice. The aqueous solution was extracted with ether, and the extract was washed with dilute hydrochloric acid and water, dried, and evaporated. The oily nitrile (1·0 g., 72%) rapidly crystallised, and then separated from benzene in prisms, m. p. 118—120°, $[\alpha]_D^{21}$ −52·0° (*c* 1·25 in 95% ethanol). The D-derivative had $[\alpha]_D^{21}$ +52·8° (*c* 1·25 in 95% ethanol).

(ii) The preceding nitrile (600 mg.) was added to liquid hydrogen sulphide (*ca.* 2 c.c.) followed by cold (−80°) ethanol (2 c.c.) containing triethanolamine (50 mg.), and the mixture was heated at 55° for 8 hr. in the manner previously described.[4] The L-*thioamide* crystallised from ethanol as almost colourless needles (620 mg., 89%), m. p. 178—185°; an analytical specimen had m. p. 185—192°, $[\alpha]_D^{24}$ +86·6° (*c* 2·5 in dimethylformamide) (Found: C, 60·9; H, 6·8; N, 11·6. $C_{12}H_{16}N_2OS$ requires C, 61·0; H, 6·8; N, 11·9%). The D-thioamide had m. p. 185°, $[\alpha]_D^{21}$ −85·6° (*c* 2·5 in dimethylformamide).

Ethyl L-2-(1-*Benzamido*-2-*methylpropyl*)*thiazole*-4-*carboxylate*.—The preceding thioamide (400 mg.) was heated under reflux with ethyl bromopyruvate (340 mg.) in ethanol (6 c.c.) for 2 hr. The solvent was removed under reduced pressure, and the residue was taken up in benzene and washed with aqueous sodium carbonate and water. Evaporation of the benzene left a pale yellow oil (540 mg., 96%), which crystallised when rubbed with ethyl acetate. Recrystallisation from aqueous ethanol gave *ethyl* L-2-(1-*benzamido*-2-*methylpropyl*)*thiazole*-4-*carboxylate* as colourless needles, m. p. 119—120°, $[\alpha]_D^{20}$ −3·7° (*c* 2·5 in 95% ethanol) (Found: C, 61·7; H, 6·3; N, 8·2. $C_{17}H_{20}N_2O_3S$ requires C, 61·4; H, 6·1; N, 8·4%).

Partially Racemised, and Racemised, L-2-(1-*Amino*-2-*methylpropyl*)*thiazole*-4-*carboxylic Acid* (I; R = Pr^i) *Hydrochloride*.—(*A*) The previous experiment was repeated, and the crude product was heated under reflux with 20% w/v hydrochloric acid (20 c.c.) for 4 hr. After cooling and ether-extraction to remove benzoic acid, the acid solution was evaporated to dryness. Recrystallisation of the residue from methanol–ethyl acetate (charcoal) gave prismatic needles (300 mg., 75%), m. p. 268—270° (decomp.). Further recrystallisation raised the m. p. to 272° (decomp.), essentially the same as that (269—272°) recorded for the DL-compound [4] (Found: C, 40·7; H, 5·6; N, 11·6. $C_8H_{12}N_2O_2S$,HCl requires C, 40·4; H, 5·5; N, 11·8%). Specific rotations, observed immediately after preparation of the respective solutions, were low but definitely positive, namely, $[\alpha]_D^{21}$ +2·1° (*c* 2·5 in water), $[\alpha]_D^{25}$ +5·2° (*c* 0·5 in water). At this stage there was no reason for expecting anomalous behaviour and later observations on these two solutions were not made. In view of the satisfactory analysis and paper chromatographic examination, contamination with L-(+)-valine is excluded as an explanation of the observed rotations.

(*B*) Recrystallised ethyl L-2-(1-benzamido-2-methylpropyl)thiazole-4-carboxylate (180 mg.) was heated under reflux with 20% hydrochloric acid (10 c.c.) for 4 hr. The benzoic acid was removed by ether-extraction and the aqueous layer was evaporated to dryness, leaving a colourless crystalline residue (135 mg.). This crystallised from methanol–ethyl acetate as colourless prisms (90 mg.), m. p. 259—261° (decomp.), $[\alpha]_D^{22}$ 0° (*c* 2·0 in water).

Variable Specific Rotations observed for 2-(1-*Amino*-2-*methylpropyl*)*thiazole*-4-*carboxylic Acid* (I; R = Pr^i) *Hydrochloride* (a) *Derived from Micrococcin* P, *and* (b) *Synthesised from* L-*Valine*.—Three isolations of the amino-acid hydrochloride have been made from hydrolyses of micrococcin *P* in the manner already described,[1] and the preparations are denoted (i)—(iii). Optical

Specific rotations observed for 2-(1-*amino*-2-*methylpropyl*)*thiazole*-4-*carboxylic acid hydrochloride.*

	Derived from micrococcin *P*				Synthesised from L-valine	
c	(i)	(ii)	(iii)		(i)	(ii)
0·5		−20·8°	−6·2°		+5·2°	
0·69			−12·8°	0° (next day)		
1·25		0				
2·0						0°
2·5	−2·9°	0	−2·1°	0° (in 4 hr.)	+2·1°	

rotations were observed in distilled water at the concentrations shown in the Table. Precautions were taken to ensure thermal equilibrium of solvent and apparatus in the room in which observations were made before the preparation of solutions.

L-α-*Benzamidopropionitrile*.—(i) L-Alanine was benzoylated in the usual way; the product, recrystallised from aqueous methanol, had m. p. 145—147°, $[\alpha]_D^{26}$ +36·6° (*c* 2·5 in 1·5N-potassium hydroxide); Pacsu and Mullen [19] record m. p. 148°, $[\alpha]_D^{20}$ +37·1° (*c* 6·7 neutralised with potassium hydroxide).

(ii) The methyl ester (13·3 g.), prepared with the aid of diazomethane in the usual way, was heated at 100—110° for 7 hr. in an autoclave with methanol (250 c.c.) saturated with ammonia at 0°. The amide separated from aqueous methanol in colourless needles (10·4 g.), m. p. 238—242°, $[\alpha]_D^{20}$ +43·1° (*c* 2·5 in 98% formic acid); Freudenberg and Rhino [20] record m. p. 228—229°, $[\alpha]_{578}^{21}$ +42·2° (*c* 4·9 in formic acid).

(iii) Redistilled phosphoryl chloride (0·92 c.c.) was added slowly with ice-cooling to the preceding amide (1·92 g.) in dry pyridine (7 c.c.) during 15 min. with shaking. After 30 min. at room temperature the mixture was diluted with water (100 c.c.) and extracted with ether. Unchanged amide (0·73 g.) remained undissolved and was collected. Crystallisation from benzene of the residue obtained from the ethereal solution afforded the *nitrile* as colourless prisms (0·27 g.), m. p. 125—127°, $[\alpha]_D^{22}$ −49·3° to −58·1° (*c* 2·5 in 95% ethanol) (Found: C, 68·9; H, 5·7; N, 16·1. $C_{10}H_{10}N_2O$ requires C, 68·8; H, 5·8; N, 16·2%). This preparation had to be repeated a number of times and some variation in specific rotation was observed, indicating slight racemisation and loss of optical purity. The use of toluene-*p*-sulphonyl chloride and pyridine gave better conversion at the temperature of the water-bath but a less optically pure product.

L-α-*Benzamidopropionothioamide*.—The preceding nitrile (1·15 g.) was allowed to react with liquid hydrogen sulphide (*ca.* 5 c.c.) in methanol (16 c.c.) containing triethanolamine (2 drops) at 50—60° for 6 hr. in the usual manner. The L-*thioamide* crystallised from water in prisms (1·25 g.), m. p. 155—156°, $[\alpha]_D^{20}$ +126·5° (*c* 1·25 in dimethylformamide) (Found: C, 57·3; H, 5·7; N, 13·0. $C_{10}H_{12}N_2OS$ requires C, 57·7; H, 5·8; N, 13·4%).

Ethyl L-2-1′-*Benzamidoethylthiazole-4-carboxylate*.—A solution of the preceding thioamide (1·04 g.) and ethyl bromopyruvate (0·99 g.) in ethanol (12 c.c.) was boiled under reflux for 2 hr., and the mixture was worked up in the manner described above for the analogous reaction. *Ethyl* L-2-1′-*benzamidoethylthiazole-4-carboxylate* crystallised from aqueous ethanol in colourless flattened needles (0·9 g.), m. p. 124°, $[\alpha]_D^{21}$ +9·4° (*c* 2·5 in methanol) (Found: C, 58·9; H, 5·1; N, 8·7. $C_{15}H_{16}N_2O_3S$ requires C, 59·2; H, 5·3; N, 9·2%).

The ester (700 mg.) was heated under reflux with 20% hydrochloric acid (15 c.c.) for 4 hr. Benzoic acid was extracted with ether and the aqueous phase was taken to dryness. The residue crystallised from methanol–ethyl acetate; the resulting 2-1′-aminoethylthiazole-4-carboxylic acid hydrochloride (0·4 g.) showed no perceptible optical activity (*c* 2·5 in water).

D-2-(1-*Benzamido-2-methylpropyl*)-4-*phenylthiazole*.—A mixture of D-α-benzamido-β-methylbutyrothioamide (470 mg.) and ω-bromoacetophenone (400 mg.) in methanol (3 c.c.) was heated under reflux in presence of powdered calcium carbonate (200 mg.) for 2½ hr. The solution was diluted somewhat with hot methanol, filtered, and concentrated. The *product* crystallised from aqueous methanol in colourless needles (350 mg.), m. p. 126°, $[\alpha]_D^{22}$ −35·5° (*c* 2·5 in dimethylformamide) (Found: C, 71·3; H, 6·0; N, 8·2. $C_{20}H_{20}N_2OS$ requires C, 71·4; H, 6·0; N, 8·3%).

D-2-(1-*Amino-2-methylpropyl*)-4-*phenylthiazole* (IV; R = Pr^i) *Hydrochloride*.—The preceding substance (350 mg.) was heated on the water-bath for 3½ hr. with 20% hydrochloric acid (10 c.c.). The aqueous phase was extracted with ether and taken to dryness. The residue was taken up in water and basified, and the amine was extracted with ether. The ethereal solution was dried ($MgSO_4$), concentrated, and saturated with hydrogen chloride. Solvent and excess of hydrogen chloride were removed under reduced pressure and the residue was crystallised from methanol–ethyl acetate, giving D-2-(1-*amino-2-methylpropyl*)-4-*phenylthiazole hydrochloride* as colourless plates (190 mg.), m. p. 201—202°, $[\alpha]_D^{22}$ −7·7° (*c* 2·14 in water) unchanged after 72 hr. (Found: C, 57·8; H, 6·2; N, 10·4. $C_{13}H_{16}N_2S,HCl$ requires C, 58·1; H, 6·4; N, 10·4%). A solution in 0·08N-ethanolic potassium hydroxide showed $[\alpha]_D^{24}$ +23·8° (*c* 1·7), unchanged after 24 hr.; when this solution was evaporated to dryness with as little mechanical loss as possible with 8% ethanolic hydrogen chloride, the residue then had $[\alpha]_D^{22}$ −5·9° in water (calc. with reference to initial weight of substance).

L-2-1′-*Benzamidoethyl-4-phenylthiazole*.—(*A*) A mixture of L-α-benzamidopropionothioamide

[19] Pacsu and Mullen, *J. Biol. Chem.*, 1940, **136**, 335.
[20] Freudenberg and Rhino, *Ber.*, 1924, **57**, 1547.

(300 mg.), ω-bromoacetophenone (280 mg.), and pyridine (0·2 c.c.) in methanol was boiled under reflux for 2 hr. When the solution was concentrated to small bulk the product crystallised. Recrystallisation from aqueous methanol afforded needles (0·29 g.) of racemic 2-1′-*benzamidoethyl*-4-*phenylthiazole*, m. p. 162—164°, $[\alpha]_D^{25}$ 0° (*c* 1·25 in chloroform) (Found: C, 70·0; H, 5·3; N, 8·8. $C_{18}H_{16}N_2OS$ requires C, 70·1; H, 5·2; N, 9·1%).

(*B*) The L-thioamide (300 mg.), ω-bromoacetophenone (280 mg.), and powdered calcium carbonate (200 mg.) in methanol were similarly boiled under reflux for 2 hr. Recrystallisation of the product from aqueous methanol gave colourless needles (0·46 g.) of L-2-1′-*benzamidoethyl*-4-*phenylthiazole*, m. p. 136—138°, $[\alpha]_D^{22}$ +38·7° (*c* 2·5 in dimethylformamide) (Found: C, 69·9; H, 5·4; N, 8·7; S, 10·2. $C_{18}H_{16}N_2OS$ requires C, 70·1; H, 5·2; N, 9·1; S, 10·4%).

(*C*) Partially racemised L-thioamide (416 mg., $[\alpha]_D^{23}$ +78·6°) was condensed with ω-bromoacetophenone (398 mg.) as described in (*B*) (above). Crystallisation from aqueous methanol afforded, as successive fractions, (i) racemic material (230 mg.), m. p. 161—163°, $[\alpha]_D^{23}$ 0°, identical with the substance isolated as in (*A*) (above), and (ii) the L-derivative (200 mg.), m. p. 138—140°, $[\alpha]_D^{23}$ +34·3° (*c* 2·3 in dimethylformamide).

L-2-1′-*Aminoethyl*-4-*phenylthiazole* (IV; R = Me) *Hydrochloride*.—L-2-1′-Benzamidoethyl-4-phenylthiazole (300 mg.) was hydrolysed with hot 20% hydrochloric acid (10 c.c.) in the usual way (4½ hr.). The crude product was taken up in water and basified, and the amine was recovered in ether and converted into the hydrochloride in the manner described above. L-2-1′-*Aminoethyl*-4-*phenylthiazole hydrochloride* crystallised from methanol–ethyl acetate in needles (120 mg.), m. p. 225—226°, $[\alpha]_D^{25}$ +11·4° (*c* 2·0 in water) (Found: C, 54·6; H, 5·3; S, 13·6. $C_{11}H_{12}N_2S$,HCl requires C, 54·9; H, 5·4; S, 13·3%). A solution in 0·08N-ethanolic potassium hydroxide showed $[\alpha]_D^{25}$ −10·9° (*c* 1·0), unchanged after 24 hr.; when this solution was taken to dryness with 8% ethanolic hydrogen chloride, with as little mechanical loss as possible, the residue then had $[\alpha]_D^{24}$ +8·6° in water (calc. with reference to initial weight of substance).

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