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SYNTHESIS OF THIAZOLE AMINO-ACIDS DERIVED FROM NATURAL PEPTIDES

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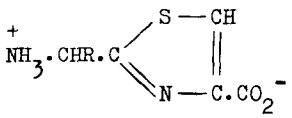
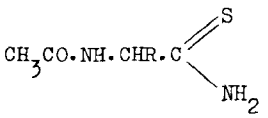
IN connexion with our studies on the antibiotic, Thiostrepton,[1] we have prepared a number of 2-(α-aminoalkyl)-thiazole-4-carboxylic acids (I, R=H, Me, Et and $CHMe_2$). Since thiazole structures have been advanced for degradation products of other peptide antibiotics,[2,3] a brief account of our results is given here.



I



II

The thiazole amino-acids (I) were obtained by reaction of the

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[1] J. Vandeputte and J. D. Dutcher, Antibiotics Annual 560 (1955-56).

[2] P. Brookes, A. T. Fuller and J. Walker, J. Chem. Soc. 689 (1957).

[3] J. M. Waisvisz, M. G. van der Hoeven and B. te Nijenhuis, J. Amer. Chem. Soc. 79, 4524 (1957).

appropriate acetylaminoalkylthioamides (II) with ethyl brompyruvate,[4] and subsequent hydrolysis. Purification was most readily achieved by adsorption on columns of activated charcoal and elution with aqueous phenol, a technique also useful for the isolation of thiazole amino-acids from peptide hydrolysates.

The synthetic compounds show a common ultra-violet absorption maximum at 234-5 mμ (log ε 3.72-3.76 in H_2O), while bands at 772-775 cm^{-1} in the infra-red spectra of the amino acids, and at 720-730 cm^{-1} of their hydrochlorides also appear to be characteristic. Other physical constants are collected in Table 1 (satisfactory analyses were obtained in all cases).

TABLE 1

I,R=	M.p. (dec.)	Hydrochloride m.p. (dec.)	R_F(A)	R_F(B)
H	277-280°	267-268.5°	0.22	0.58
Me	265-267°	233.5-234.5°	0.35	0.62
Et	256-258°		0.44	0.74
$CHMe_2$	252.5-253.5°	258-259°	0.52	0.80

Notes: Melting points are uncorrected. Paper chromatography solvent systems: A, n-BuOH(10), EtOH(10), H_2O(5), $Et.CO_2H$(2), (Ileu, R_F=0.58); B, n-BuOH(10), Me_2CO(10), H_2O(5), dicyclohexylamine (2), (Ileu, R_F=0.64). Ninhydrin colours were yellow turning purple in A.

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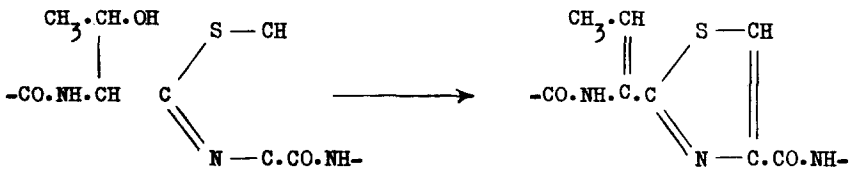
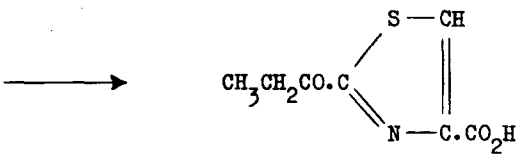
[4] cf. R. H. Wiley, D. C. England and L. C. Behr, Organic Reactions 6, 367 (1951).

Two of these amino acids (I, R=H and Et) are identical with hydrolysis products of Thiostrepton (apart from the question of optical acitivity in the latter case). The published infra-red data show clearly that a third ((I, R=$CHMe_2$) is the racemate of a product from the antibiotic, Micrococcin.[2] The formation of this last thiazole amino-acid has been explained[2] in terms of biogenetic modification of adjacent valine and cysteine residues to a thiazole system in the antibiotic. Our products from Thiostrepton may be similarly derived from glycine and α-aminobutyric acid respectively, but, in view of the low isolated yields (2-3%), the possibility that hydrolysis takes a more complex course than simple opening of peptide bonds must be considered. For example, thiazoles and thiazolines derived from adjacent threonine and cysteine residues might be expected to decompose in a number of ways under hydrolytic conditions, because of the activating effect of the heterocyclic ring. In particular, reverse-aldol and β-elimination reactions would be facilitated. It is noteworthy that formation of a further product



III



IV

from Micrococcin, 2-propionyl-thiazole-4-carboxylic acid (IV), is immediately explicable on the basis of elimination of the β-hydroxyl group of the "threonylthiazole" (III), prior to hydrolysis of the peptide bonds.

We hope to obtain further information on these points through synthesis of the appropriate model compounds.