SECTION C
Organic Chemistry

Peptides. Part XXI.[1] Dehydrogenation of Some Thiazolines Derived from Cysteine

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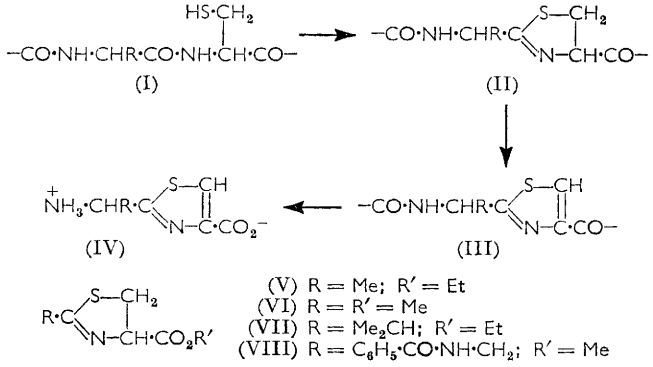
Esters of 2-alkyl-Δ^2-thiazoline-4-carboxylic acids are smoothly dehydrogenated by phenanthraquinone to the corresponding thiazole derivatives. Methyl 2-benzamidomethyl-Δ^2-thiazoline-4-carboxylate is dehydrogenated only slowly by phenenthraquinone but rapidly by manganese dioxide. The possible application of these reactions to the detection of thiazoline rings in peptides is discussed.

THE suggestion that cysteine residues in peptides and proteins may under certain conditions exist in the form of thiazoline derivatives (II) originated in the work of Linderstrøm-Lang and Jacobsen.[2] It was suggested that the liberation of free thiol groups which accompanied the denaturation of certain proteins might be a consequence of the cleavage of thiazoline rings in the intact proteins. Although, as these authors recognised, other factors may also account for the presence of masked thiol groups in native proteins, *e.g.*, cysteine residues may be deeply buried in the tertiary structure and thus inaccessible to chemical reagents before denaturation, subsequent work has shown clearly that the thiol groups of cysteine residues in peptides may under certain conditions react with the peptide chain forming thiazoline derivatives [*i.e.*, (I) ⟶ (II)]. Thus the naturally-occurring tripeptide glutathione (γ-glutamylcysteinylglycine) has been shown to exist in the thiazoline form in strongly acidic solution,[3] and similar transformations have been demonstrated with synthetic cysteine derivatives.[4,5] Only in the case of the antibiotic bacitracin,[6] however, has a naturally-occurring peptide been encountered in which a cysteine residue exists normally as a thiazoline derivative.* Bacitracin was found to undergo the typical acid-catalysed ring opening reaction of a thiazoline derivative (release of a free thiol group with simultaneous loss of ultraviolet absorption at 253 mμ), and strong support for the presence of this structural feature was obtained from experiments on the desulphurisation and oxidation of the antibiotic.[6]



More recently the suggestion has been made that the antibiotic thiostrepton may also contain a thiazoline ring,[8] although this is still unproven. However, the presence of *thiazole* rings (III) in this antibiotic,[8,9] as well as in micrococcin,[10,11] bottromycin,[12] and althiomycin,[13] is well established. Presumably, these thiazoles are derived biogenetically by dehydrogenation of the analogous thiazolines (II). Unlike thiazolines, thiazoles are relatively stable under the normal conditions of peptide hydrolysis, and appear in hydrolysates as the corresponding thiazoleamino-acids (IV). A useful way

* Although not a peptide, firefly luciferin contains a thiazoline ring possibly derived from cysteine.[7]

[1] Part XX, B. J. Millard, *Tetrahedron Letters*, 1965, 3041.
[2] K. Linderstrøm-Lang and C. F. Jacobsen, *Compt. rend. Trav. Lab. Carlsberg*, 1940, **23**, 289; *J. Biol. Chem.*, 1941, **137**, 443.
[3] M. Calvin, in "Glutathione," ed. S. Colowick *et al.*, Academic Press, New York, 1954, p. 3; G. Preaux and R. Lontie, *Biochem. J.*, 1957, **66**, 26P; R. B. M. Martin and J. T. Edsall, *Bull. Soc. Chim. biol.*, 1958, **40**, 1763; D. Garfinkel, *J. Amer. Chem. Soc.*, 1958, **80**, 4833.
[4] (*a*) D. Cavallini, B. Mondovi, and C. de Marco, *Experientia*, 1957, **13**, 436; (*b*) W. Stoffel and L. C. Craig, *J. Amer. Chem. Soc.*, 1961, **83**, 145.
[5] H. A. Smith and G. Gorin, *J. Org. Chem.*, 1961, **26**, 820.
[6] For a review see L. C. Craig, W. Konigsberg, and R. J. Hill, in "Amino Acids and Peptides with Antimetabolic Activity," ed. G. E. W. Wolstenholme and C. M. O'Connor, Churchill, London, 1958, p. 226. E. P. Abraham and G. G. F. Newton, *ibid.*, p. 205.
[7] E. H. White, F. McCapra, G. F. Field, and W. D. McElroy, *J. Amer. Chem. Soc.*, 1961, **83**, 2402; E. H. White, F. McCapra, and G. F. Field, *ibid.*, 1963, **85**, 337.
[8] D. F. W. Cross, G. W. Kenner, R. C. Sheppard, and C. E. Stehr, *J. Chem. Soc.*, 1963, 2143.
[9] M. Bodanszky, J. Fried, J. T. Sheehan, N. J. Williams, J. Alicino, A. I. Cohen, B. T. Keeler, and C. A. Birkhimer, *J. Amer. Chem. Soc.*, 1964, **86**, 2478.
[10] P. Brookes, A. T. Fuller, and J. Walker, *J. Chem. Soc.*, 1957, 689.
[11] P. Brookes, R. J. Clark, B. Majhofer, M. P. V. Mijovic, and J. Walker, *J. Chem. Soc.*, 1960, 925.
[12] J. M. Waisvisz, M. G. van der Hoeven, J. van Peppen, and W. C. M. Zwennis, *J. Amer. Chem. Soc.*, 1957, **79**, 4520; J. M. Waisvisz, M. G. van der Hoeven, J. F. Hölscher, and B. te Nijenhuis, *ibid.*, p. 4522; J. M. Waisvisz, M. G. van der Hoeven, and B. te Nijenhuis, *ibid.*, p. 4524.
[13] D. J. Cram, O. Theander, H. Jager, and M. K. Stanfield, *J. Amer. Chem. Soc.*, 1963, **85**, 1430.

of characterising the rather unstable thiazoline ring system in peptides might therefore be to effect prior dehydrogenation to the stable thiazole analogue, if this could be achieved under mild, selective conditions. The appearance of new thiazoleamino-acids in hydrolysates of the dehydrogenated peptide would then not only *confirm* the original presence of thiazoline systems in the latter, but would also assist in their location in the peptide chain since the substituents [R in (III) and (IV)] are characteristic of the amino-acid immediately preceding the appropriate cysteine residue in the original peptide (I). A number of thiazoleamino-acids (IV) with side chains characteristic of common amino-acids have already been synthesised, and their chromatographic and spectral properties recorded.[8,11] A simple micro method is also available for identification of thiazoleamino-acids of this type,[11] so that the identification of unknown dehydrogenation products should be straightforward.

The dehydrogenation of Δ^2-thiazolines does not seem to have been studied systematically, but Asinger, Thiel, and Schröder [14] mention in a Paper on the dehydrogenation of Δ^3-thiazolines that the Δ^2-isomers are converted by sulphur above 200° into the corresponding thiazoles. For application to peptide derivatives, however, a more attractive possibility was dehydrogenation by quinones, which has been stated to be particularly effective for heterocyclic compounds.[15] In a preliminary survey, the dehydrogenation of the simple thiazolines (V)—(VII) by quinones of varying redox potential (dichlorodicyano-1,4-benzoquinone, tetrachloro-1,2-benzoquinone, chloranil, and phenanthraquinone) was investigated. The thiazolines (V)—(VII) were readily prepared by reaction between the appropriate iminoether hydrochloride and cysteine methyl or ethyl ester hydrochloride in the presence of triethylamine.[4b,5] The progress of dehydrogenation was conveniently followed by measurement of the n.m.r. spectra of aliquots of the reaction solution withdrawn after fixed intervals, and noting the appearance of the 2-methyl resonance of the thiazoles derived from compounds (V) or (VI). Alternatively, after replacement of the solvent by deuteriochloroform, the appearance of both the 2-Me and 4-H signals could be followed. In the case of reactions using phenanthraquinone as the dehydrogenating agent, however, the latter resonance was partly obscured by resonances from the quinone and its reduction product. Disappearance of the signals due to the starting thiazoline could not be used to follow the course of dehydrogenation because of the intervention of side reactions in certain cases and also because, even in reactions where quantitative conversion to thiazole was observed, the rate of appearance of thiazole did not equal the rate of disappearance of thiazoline. Evidently, one or more long-lived intermediates are involved in the dehydrogenation reaction.

It was immediately apparent that the higher-potential quinones were unsuitable for the dehydrogenation of thiazolines. The 2-methylthiazoline ester (V) was destroyed by both chloranil and tetrachloro-1,2-benzoquinone, but no thiazole was produced even after prolonged reaction periods. Dichlorodicyano-1,4-benzoquinone reacted exothermically with compound (VII), but again no thiazole could be detected. On the other hand, phenanthraquinone reacted smoothly, albeit slowly, with compound (V), and the n.m.r. spectrum indicated quantitative conversion to thiazole after 60 hr. in boiling benzene (60% after 40 hr.). The high conversion was confirmed by isolation of ethyl 2-methylthiazole-4-carboxylate from the reaction mixture, and identity was established by comparison with an authentic sample prepared by Hantzsch synthesis. Although the isolated yield was only 40%, the acidic extraction procedure which made use of the weak basicity of thiazoles gave a recovery of only 43% when applied to a sample of pure ethyl 2-methylthiazole-4-carboxylate.

In the course of their studies on the kinetics and mechanism of the dehydrogenation of hydroaromatic systems by quinones, Linstead and his collaborators [16] have observed that reactions involving quinones of low potential such as phenanthraquinone frequently exhibit catalysis by the quinol formed. When phenanthraquinol was added in catalytic amount at the start of the reaction, dehydrogenation was indeed accelerated, and yields of 90—100% were indicated after 20 hr. It seemed likely that this catalysis was due to the presence of a proton source in the reaction mixture, and the effect of added acetic acid and also of change to more polar solvents was therefore investigated. Some representative results for dehydrogenation by phenanthraquinone are collected in Table 1.

TABLE 1

Dehydrogenation of thiazolines by phenanthraquinone

Thiazoline	Solvent/Catalyst	Temp.	Time (hr.)	Thiazole * (%)
(V)	Benzene	80°	40	60
	Benzene	80	60	100
	Benzene/phenanthraquinol	80	20	100
VI)	Benzene/phenanthraquinol	80	20	90
	Chloroform	61	8	50
	Chloroform/phenanthraquinol	61	2	30
	Chloroform/phenanthraquinol	61	8	100
	Chloroform/acetic acid (5%)	61	2	40
	Chloroform/acetic acid (5%)	61	8	100
	Dioxan/phenanthraquinol	101	2	10
	Dioxan/acetic acid (5%)	101	2	100
	Acetic acid	100	0·5	100
(VII)	Acetic acid	100	0·5	100

* From the n.m.r. spectrum.

The most rapid dehydrogenation was achieved with acetic acid as solvent (and catalyst), the reaction being complete in less than 0·5 hr. at 100°. Although simple

[14] F. Asinger, M. Thiel, and L. Schröder, *Annalen*, 1957, **610**, 49; cf. U.S.P. 2,870,158 (*Chem. Abs.* 1959, **53**, 11409*h*.).

[15] L. M. Jackman, in "Advances in Organic Chemistry," vol. II, ed. R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience, New York, 1960, p. 329.

[16] E. A. Braude, L. M. Jackman, and R. P. Linstead, *J. Chem. Soc.*, 1954, 3548.

thiazolines are stable in glacial acetic acid at the reflux temperature, these conditions were considered too severe for sensitive peptide derivatives. Complete dehydrogenation of compound (VI) was also obtained in chloroform solution containing phenanthaquinol (0·05 mole) during 8 hr. at 61°, and these conditions appeared to be the mildest of those examined.

Although these experiments showed that dehydrogenation of simple 2-alkylthiazoline-4-carboxylic esters could easily be achieved, it was considered necessary to test the method on a model compound more closely related to a thiazoline residue within a peptide chain [as in (II)]. This was especially important because, although the methoxycarbonyl or ethoxycarbonyl substituent in the 4-position could be considered a reasonable model for a peptide bond, the electron-donating 2-alkyl substituent was a very poor model for an acylaminoalkyl residue. The latter grouping is generally electron-withdrawing in character, as is shown, for example, in the increased acidity of α-acylamino-acids compared with simple carboxylic acids (*e.g.*, acetylglycine, pK_a 3·6, acetic acid, pK_a 4·8). It was expected that electron-donating substituents attached directly to the thiazoline ring would facilitate dehydrogenation, whereas electron-withdrawing substituents would retard it. These predictions were verified when the dehydrogenation of methyl 2-benzamidomethylthiazoline-4-carboxylate (VIII) by phenanthraquinone was attempted.

The thiazoline (VIII) was readily obtained by reaction between cysteine methyl ester and benzamidomethyl iminoether. It was convenient to follow the course of the dehydrogenation by hydrolysis of the resulting benzamidomethylthiazole ester after removal of phenanthrene derivatives. The 2-aminomethylthiazole-4-carboxylic acid (IV; R = H)] produced was then determined directly by amino-acid analysis with correction for destruction during hydrolysis. Dehydrogenation of the thiazoline (VIII) by phenanthraquinone was attempted in chloroform and dioxan solution, with and without the addition of catalysts (phenanthraquinol and acetic acid), and also in glacial acetic acid solution. Under none of these conditions, however, could the high yields of dehydrogenation product previously obtained with the simple 2-alkylthiazolines (V)—(VII) be achieved, even after extended reaction periods. The best yield of thiazole (22%) was obtained using dioxan–5% acetic acid as solvent for 24 hr. at 110°. Even under these rather vigorous conditions much of the thiazoline remained unchanged, as shown by the appearance of both glycine and cyst(e)ine on the amino-acid ion-exchange chromatograms of the hydrolysed product. The poor yield of thiazole must therefore be attributed to very low reactivity of the thiazoline towards the quinone, rather than to the intervention of side reactions. However, no improvement was effected when the use of higher-potential quinones was reinvestigated. Quinone dehydrogenation was therefore markedly less effective for the benzamidomethylthiazoline (VIII) than for the simple alkylated thiazolines (V)—(VII), and it would presumably be similarly ineffective for thiazoline residues in peptide chains [as in (II)]. An alternative method for achieving mild, specific dehydrogenation of thiazolines was therefore sought.

Manganese dioxide has a high degree of selectivity for allylic positions in oxidation reactions, and this prompted its trial as a possible dehydrogenating reagent for thiazolines. As far as we were aware, no example of its use for the aromatisation of heterocyclic hydroaromatics had appeared in the literature, although since this work was completed the dehydrogenation of a 2,3-dihydroindole by manganese dioxide has been reported.[17] In an exploratory reaction, the benzamidomethylthiazoline (VIII) was stirred in chloroform solution with manganese dioxide, prepared according to the method of Henbest, Jones, and Owen.[18] After 2 days at room temperature, the filtrate was evaporated and yielded directly the corresponding thiazole, which was identified with an authentic sample. However, the yield was only 29%, the remainder of the material being adsorbed on the solid oxidant. Further experiments showed that the dehydrogenation of compound (VIII) could be achieved more efficiently by slowly percolating a dioxan solution of the thiazoline down a column of manganese dioxide. Evaporation of the eluate then yielded the thiazole directly in yields of up to 70%, the remainder of the material again being strongly adsorbed on the column.

The work described above shows that synthetic thiazolines can be dehydrogenated to thiazole derivatives under mild, selective conditions. Although the precise conditions adopted may have to be modified in the light of problems of solubility, adsorption, etc., in individual cases, we believe that the method offers promise for the detection and location of thiazoline residues in peptides. The application of this method to the antibiotic thiostrepton will be the subject of a forthcoming publication.

EXPERIMENTAL

Ethyl 2-Methyl-Δ²-thiazoline-4-carboxylate.—Ethyl acetimidate hydrochloride[19] (10 g.) and L-cysteine ethyl ester hydrochloride (15·1 g.) were suspended in methylene chloride (86 ml.) containing triethylamine (11 ml.) and the reaction mixture stirred for 3 days at room temp. under nitrogen. The precipitated triethylamine hydrochloride and ammonium chloride was collected, washed with ether, and the combined filtrates evaporated. The residue was dissolved in benzene (50 ml.), filtered, and the solvent evaporated. Distillation at 69°/0·15 mm. gave the *thiazoline* (9·5 g., 67·5%) (Found: C, 48·7; H, 6·2; N, 8·1. $C_7H_{11}NO_2S$ requires C, 48·55; H, 6·4; N, 8·1%).

Methyl 2-Methyl-Δ²-thiazoline-4-carboxylate.—Ethyl acetimidate hydrochloride (7·7 g.), L-cysteine methyl ester

[17] A. B. A. Jansen, J. M. Johnson, and J. R. Surtees, *J. Chem. Soc.*, 1964, 5573.

[18] H. B. Henbest, E. R. H. Jones, and T. C. Owen, *J. Chem. Soc.*, 1957, 4909.

[19] A. W. Dox, *Org. Synth.*, Coll. Vol. I, Wiley, New York, 1941, p. 5.

hydrochloride (10·7 g.), and triethylamine (8·4 ml.) similarly yielded the *methyl ester* (8·4 g., 85%), b. p. 69°/0·3 mm., which crystallised immediately with m. p. 22—24° (Found: C, 45·1; H, 5·7; N, 8·6. $C_6H_9NO_2S$ requires C, 45·3; H, 5·7; N, 8·8%).

Ethyl 2-Isopropyl-Δ²-thiazoline-4-carboxylate.—Ethyl isobutyrimidate hydrochloride [20] (7·5 g., 0·05 mole) was treated with L-cysteine ethyl ester hydrochloride (9·25 g.) and triethylamine (6·7 ml.) as described above, to give the *isopropyl thiazoline* (6·7 g., 67%), b. p. 79°/0·15 mm. (Found: C, 53·55; H, 7·4; N, 7·0. $C_9H_{15}NO_2S$ requires C, 53·7; H, 7·5; N, 7·0%).

Methyl 2-Benzamidomethyl-Δ²-thiazoline-4-carboxylate.—Benzamidoacetonitrile [21] (4·0 g., 0·025 mole) was suspended in ether (35 ml.) together with ethanol (1·57 ml., 0·027 mole) and dry hydrogen chloride gas was passed into the suspension for 30 min. at −5°. Methyl benzamidoacetimidate hydrochloride (5·4 g., 90%) crystallised from the reaction mixture and was washed with ether and dried *in vacuo* over phosphorus pentoxide. This iminoether hydrochloride (4·5 g., 0·0186 mole) was treated with L-cysteine methyl ester hydrochloride (3·2 g., 0·0186 mole), and triethylamine (2·53 ml.) in methylene chloride (32 ml.) soln. for 50 hr. at room temp. Crystallisation of the product from benzene gave the *thiazoline* (1·3 g., 25%), m. p. 116° (Found: C, 56·4; H, 5·2; N, 9·8. $C_{13}H_{14}N_2O_3S$ requires C, 56·1; H, 5·1; N, 10·1%).

Dehydrogenation of 2-Alkyl-Δ²-thiazoline-4-carboxylic Esters by Quinones. General Method.— The thiazoline (1 mmole) and quinone (1·4 mmole) were heated in the solvent (3 ml.) as shown in Table 1. In those reactions involving phenanthraquinol as catalyst, the quinol (10 mg.) was added at the start of the reaction. Aliquots (0·5 ml.) were withdrawn from the reaction mixture at various time intevals and the degree of dehydrogenation was determined by measurement of the n.m.r. spectra. Where benzene was used as the reaction solvent the spectra were determined directly on the aliquot from the reaction mixture. In the other cases, the solvent was removed from the aliquot by evaporation and acetic acid, if present, was removed by standing the reaction products overnight, at room temperature, in ether solution (5 ml.) over solid sodium carbonate. The ether was then evaporated and the n.m.r. spectra were determined using deuteriochloroform as solvent.

Nuclear Magnetic Resonance Spectra (60 Mc./sec.) of Thiazolines and Thiazoles.— Ethyl 2-methyl-Δ²-thiazoline-4-carboxylate had τ (benzene soln.), 9·07 (triplet, J = 7 c./sec.) and 6·04 (quartet, J = 7 c./sec.) (ethyl ester); 8·1 (doublet, J = 1·7 c./sec.) (2-Me); and 7·02, 6·56, and 5·15 p.p.m. (ABX pattern, J_{AB} = 11·1 c./sec., J_{AX} = 9·8 c./sec., J_{BX} = 8·0 c./sec.) (5-H_A, 5-H_B, and 4-H); in deuteriochloroform soln., τ, 8·69 (triplet) and 5·75 (quartet) (ethyl ester); 7·75 (doublet) (2-Me); and 6·45 and 4·99 p.p.m. (A_2X pattern) (5-H_2 and 4-H). Ethyl 2-methylthiazole-4-carboxylate had τ (benzene soln.), 8·88 (triplet) and 5·79 (quartet) (ethyl ester); 7·67 (2-Me), and 3·13 p.p.m. (5-H); in deuteriochloroform soln., τ, 8·62 (triplet) and 5·61 (quartet) (ethyl ester); 7·25 (2-Me), and 1·94 p.p.m. (5-H). The other thiazolines and thiazoles examined gave similar spectra apart from resonances due to different 2- and 4-substituents.

Isolation of Ethyl 2-Methylthiazole-4-carboxylate.—Ethyl 2-methyl-Δ²-thiazoline-4-carboxylate (216 mg., 1·25 mmole) and phenanthraquinone (360 mg., 1·75 mmole) were heated under reflux in benzene (3 ml.) for 70 hr., and the solvent was then evaporated. The products were taken up in ether (5 ml.) and the solution was filtered and extracted with N-hydrochloric acid (4 × 5 ml.). The combined acid extracts were washed with ether (2 × 2 ml.), brought to pH 2, and set aside at room temp. for 2 hr. Concentrated hydrochloric acid (2 ml.) was added and the solution extracted with ether (3 × 5 ml.). The aqueous solution was adjusted to pH 8 with N-aqueous sodium hydrogen carbonate and extracted with chloroform (4 × 5 ml.). The chloroform extracts were dried ($MgSO_4$) and evaporated, yielding the white crystalline product (85 mg., 40%), m. p. 54—55°, identified as ethyl 2-methylthiazole-4-carboxylate by comparison with an authentic sample (m. p. 57°).

The above extraction procedure was repeated using a sample of pure ethyl 2-methylthiazole-4-carboxylate (214 mg., 1·25 mmole), of which 43% was recovered.

Isolation of Methyl 2-Methylthiazole-4-carboxylate.—Methyl 2-methyl-Δ²-thiazoline-4-carboxylate (199 mg., 1·25 mmole) and phenanthraquinone (360 mg., 1·75 mmole) were heated under reflux for 40 hr. in benzene (3 ml.) in the presence of phenanthraquinol (20 mg.) and the solvent was then evaporated. The reaction mixture was worked up as in the preceding experiment and yielded the crystalline *thiazole* (74 mg., 45%), m. p. 58° after sublimation at 80°/11 mm. (Found: C, 45·6; H, 4·6; N, 8·7. $C_6H_7NO_2S$ requires C, 45·85; H, 4·5; N, 8·9%).

Dehydrogenation of Methyl 2-Benzamidomethyl-Δ²-thiazoline-4-carboxylate.—(*a*) *By quinones. General Procedure.* The thiazoline (0·2 mmole) and quinone (0·28 mmole) were heated in the solvent (0·5 ml.) for 24 hr. at 110° in a sealed tube, and the solvent was then evaporated. The residue was taken up in acetone (5 ml.) and the solution was set aside overnight at room temp. to allow the reoxidation of quinol to quinone. The acetone was then replaced by chloroform (10 ml.) containing dioxan (1 ml.) and the quinone was removed by extraction with 20% aqueous sodium hydrogen sulphite (6 × 20 ml.). After drying ($MgSO_4$), the solution was evaporated and one-twentieth of the product was hydrolysed for 22 hr. at 110° *in vacuo* in 6N-hydrochloric acid (1 ml.). The acid was then evaporated *in vacuo* and the amount of 2-aminomethylthiazole-4-carboxylic acid in one-tenth of the hydrolysate was determined by ion-exchange chromatography (Beckman 120B Amino-Acid Analyser).* When the above extraction

TABLE 2

Dehydrogenation of methyl 2-benzamidomethyl-Δ²-thiazoline-4-carboxylate by quinones

Quinone	Solvent/Catalyst	Thiazole %
Phenanthraquinone	Chloroform/Phenanthraquinol *	13
Phenanthraquinone	Dioxan/Phenanthraquinol *	3
Phenanthraquinone	Acetic acid	10
Phenanthraquinone	Dioxan/Acetic acid (5%)	22
Phenanthraquinone	Chloroform/Acetic acid (5%)	13
1,4-Benzoquinone	Chloroform	4
Tetrachloro-1,2-benzoquinone	Chloroform	3

* Phenanthraquinol (5 mg.) added to initial reaction mixture.

* Details of the ion-exchange chromatography of thiazole amino-acids will be published separately.

[20] S. M. McElvain and J. W. Nelson, *J. Amer. Chem. Soc.*, 1942, **64**, 1825.

[21] A. Klages and O. Haack, *Ber.*, 1903, **36**, 1646.

procedure was applied to a mixture of authentic methyl 2-benzamidomethylthiazole-4-carboxylate (50 μmole), phenanthraquinone (34 μmole) and phenanthraquinol (34 μmole), amino-acid analysis of the acidic hydrolysate showed a recovery of 67·5%. The yields quoted in Table 2 are corrected for this recovery.

(*b*) *By manganese dioxide.* Methyl 2-benzamidomethyl-Δ^2-thiazoline-4-carboxylate (100 mg., 0·36 mmole) in dioxan (2 ml.) was applied to a column prepared from a slurry of activated manganese dioxide [18] (3 g.) in dioxan, and the column was eluted with dioxan (20 ml.) under gravity. The product (68 mg., 68%) emerged from the column after an elution time of *ca.* 3 hr. and was recrystallised from aqueous methanol; m. p. 136°, alone and in admixture with authentic *methyl 2-benzamidomethylthiazole-4-carboxylate*, m. p. 136°, prepared by methylation (diazomethane) of 2-benzamidomethylthiazole-4-carboxylic acid [8] (Found: C, 56·45; H, 4·5; N, 10·1. $C_{13}H_{12}N_2O_3S$ requires C, 56·5; H, 4·4; N, 10·1%).

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