Preparation and Reactions of 2-Amino- and 2-Acetamido-4-methylthiazole-5-carbohydrazides: Revision of the Literature

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The literature reports that 2-acetamido-4-methylthiazole-5-carbohydrazide is formed by treating ethyl 2-acetamido-4-methylthiazole-5-carboxylate with hydrazine are incorrect; ethyl 2-amino-4-methylthiazole-5-carboxylate is produced in this reaction. Since authentic 2-acetamido-4-methylthiazole-5-carbohydrazide has a m.p. 87° higher than that of the compound described as such in the literature, the status of the substances prepared from the latter must be questioned.

DURING an investigation of rotational isomerism in heterocyclic compounds we wished to study thiazoles having a C=O group at position 2 or 5. The initial aim was to examine 2-amino- and 2-acetamido-4-methylthiazole-2-carbaldehydes, ostensibly known compounds prepared *via* the corresponding carbohydrazides. It transpired that the literature [1-3] relating to this group of compounds contains a number of errors; the present account is therefore concerned with clarifying the earlier reports † about the preparation and reactions of 2-amino- and 2-acetamido-4-methylthiazole-5-carbohydrazides rather than with the properties of the 5-carbaldehydes. To facilitate comparison of the previous results with those obtained here, the two sets of transformations are set out in Schemes 1 and 2, and a possible interpretation of the main features is shown in Scheme 3. The detailed nature of the Schemes obviates the need for lengthy discussion of the work.

Ethyl 2-amino-4-methylthiazole-5-carboxylate (1) reacts sluggishly with hydrazine, and the use of forcing procedures in an attempt to achieve a more complete conversion led to increased disruption of the thiazole ring (possibly by the formation of 1,2,4-triazole derivatives [4]). The best yield of the carbohydrazide (2) obtained here (45%) is lower than that of ref. 1 (57%); the procedure of ref. 2 leaves the amino-ester (1) unchanged. It was confirmed that the product [1] formed by treating the carbohydrazide with nitrous acid is the carbonyl azide (3). However, the yellow crystalline material [1] obtained by warming the azide with acetic acid–acetic anhydride is a complex mixture which does not show the

† Surprisingly, the authors of ref. 2 (1964) do not cite ref. 3 (1962) or ref. 1 (1945).

[1] K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, 1945, **22A**, 343.

[2] A. B. Sen and S. S. Chatterjee, *J. Indian Chem. Soc.*, 1964, **41**, 465.

[3] L. W. Toan and D. Tefas, *Farmacia (Bucuresti)*, 1962, **10**, 19.

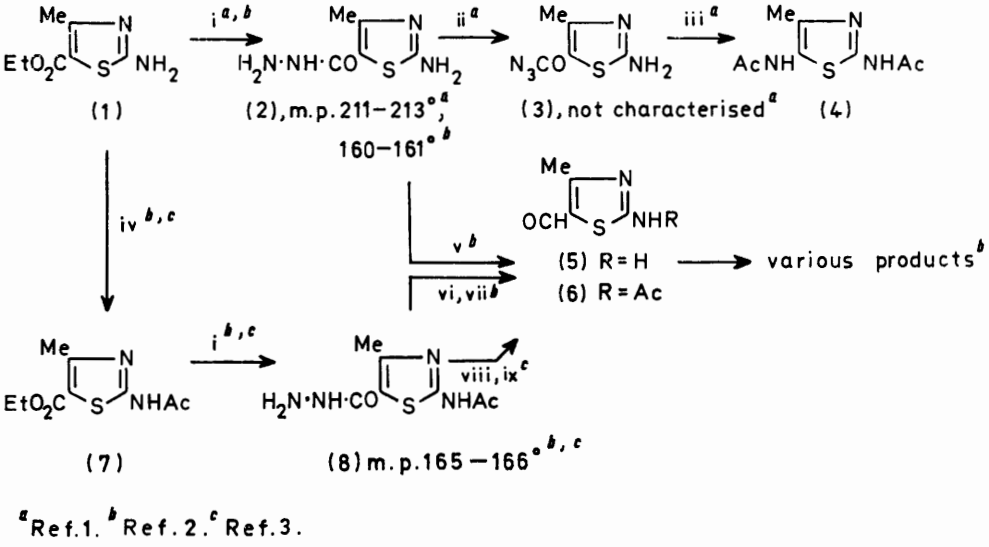
[4] R. G. Dickinson, N. W. Jacobsen, and R. G. Gillis, *Austral. J. Chem.*, 1975, **28**, 859 and earlier papers.

spectrometric features expected for the diacetamido-compound (4).

The most serious discrepancy between the present and previous studies is in the nature of the reaction between the 2-acetamido-5-ester (7) and hydrazine. *A priori* the reported [2,3] formation (Scheme 1) of the 2-acetamido-5-carbohydrazide (8) appears the most probable outcome:

The lower part of Scheme 2 shows the products obtained by treating the amino-carbohydrazide (2) with acetic anhydride alone, or with acetic anhydride and then water or hydrazine. Since it was thought that the terminal hydrazide nitrogen atom should be the most nucleophilic centre of the amino-carbohydrazide, structure (9) was provisionally allocated to the monoacetyl

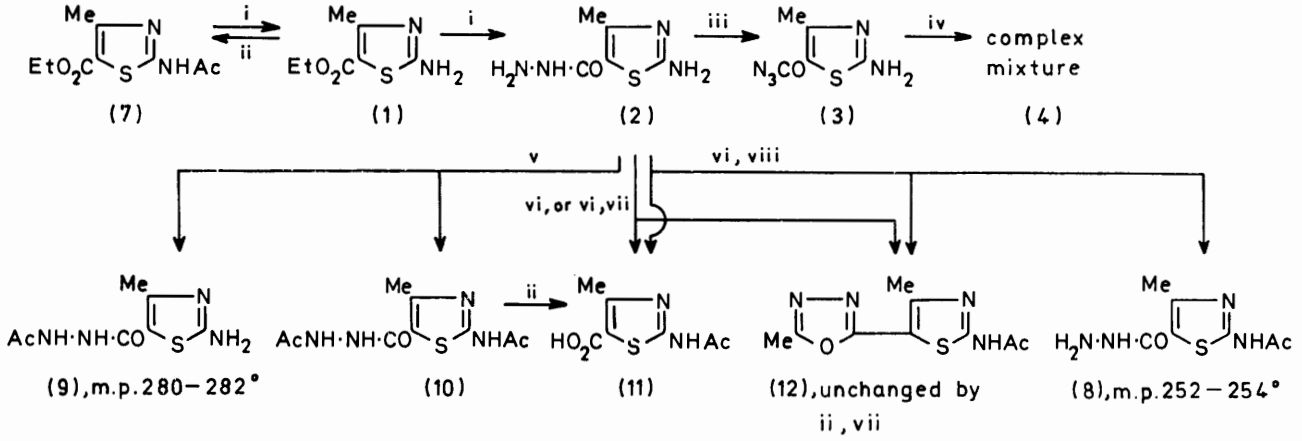
SCHEME 1 Previous work



Ref. 1. Ref. 2. Ref. 3.

Reagents: i, N_2H_4–EtOH, reflux; ii, $NaNO_2$–HCl–H_2O; iii, AcOH–Ac_2O, warm; iv, Ac_2O–H_2SO_4, 100 °C; v, $K_3Fe(CN)_6$–NH_3–H_2O, 20 °C; vi, $PhSO_2Cl$–alkali, 10 °C; vii, K_2CO_3–HO·$[CH_2]_2$·OH, 160 °C; viii, $PhSO_2Cl$–C_5H_5N, 20 °C; ix, Na_2CO_3–HO·$[CH_2]_2$·OH, 160 °C.

SCHEME 2 Present work; compounds (8)—(12) are new



Reagents: i, N_2H_4–EtOH, reflux; ii, Ac_2O–AcOH, reflux; iii, $NaNO_2$–HCl–H_2O; iv, Ac_2O–AcOH, warm; v, Ac_2O, 20 °C; vi, Ac_2O, reflux; vii, H_2O; viii, N_2H_4.

in fact (Scheme 2) the first product is the 2-amino-5-ester (1), and whether this remains as such or is partly converted into the amino-carbohydrazide (2) depends upon the conditions used. The obvious possibility that the literature product (m.p. 165—166°) was the impure 2-amino-5-ester (m.p. 179—179.5°) is precluded by the analytical data.[2,3] However, since the product is depicted as the key intermediate in further synthetic work it was considered essential to know the m.p. of the compound truly represented by structure (8).

derivative formed under mild conditions. Consideration of the way in which the 5-carboxylic acid (11), an unexpected product, is generated suggested the formation of an intermediate which should lead to the 2-acetamido-5-carbohydrazide (8) on treatment with hydrazine. The correctness of structures (8) and (9) for the monoacetyl compounds was confirmed by spectrometric examination (see Experimental section).

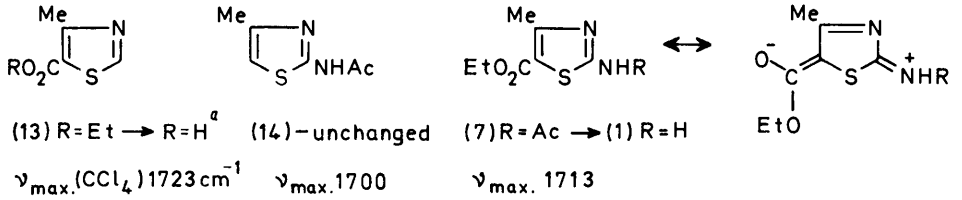
The marked mesomeric effect in the acetamido-ester (7) revealed by the i.r. data (Scheme 3A) explains the

preference of nucleophilic attack by hydroxide ion and hydrazine (Scheme 2) for the acetamido rather than the ester C=O group. With the isomeric ethyl 2-acetamidothiazol-4-ylacetate (15; R = Ac), where the effect does not operate, the reported behaviour [3] (preferential attack at the ester group, Scheme 3B) was verified in the present work, and conversion of the amino-ester (15; R = H) into the corresponding carbohydrazide (16; R = H) was found to occur readily. The sequences in Scheme 3C are merely illustrative since there is no evidence for some of the details; the crucial point is that there must be a fairly stable intermediate (portrayed here as a mixed anhydride) from which the acid (11) and the acetamido-carbohydrazide (8) are formed.

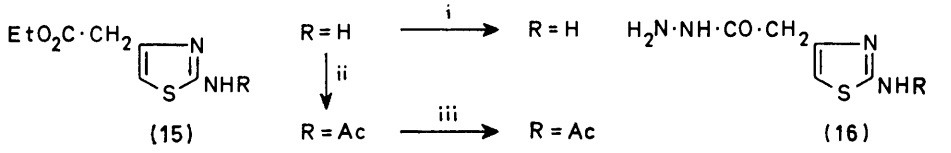
Since the nature of the supposed 2-acetamido-5-carbohydrazide, m.p. 165—166° (Scheme 1) remains obscure there are serious doubts about the status of the materials [2,3] obtained from it.

SCHEME 3 Related experiments and interpretation of results

A. Treatment with KOH–EtOH under standard conditions:

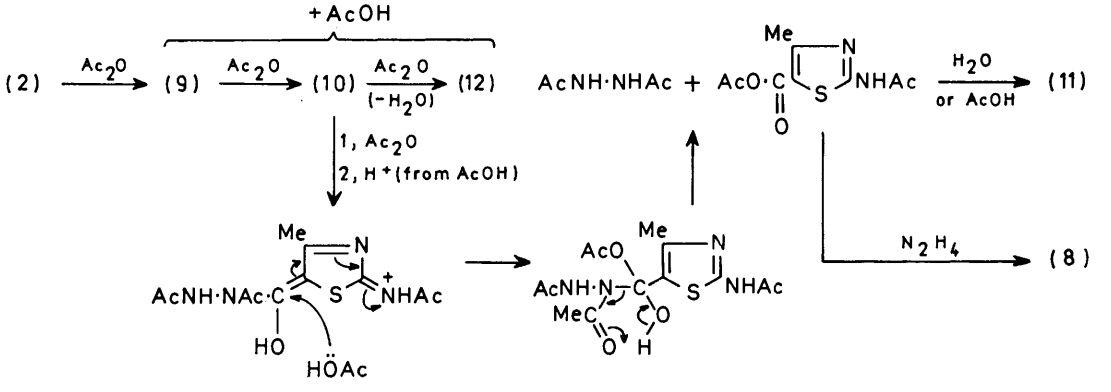


B. Reactions of isomeric 2-aminothiazol-4-ylacetic acid derivatives:



Reagents: i, N_2H_4–EtOH, 20 °C; ii, Ac_2O–AcOH, reflux; iii, N_2H_4–EtOH, reflux.

C. Possible sequences leading to compounds (8)—(12) in Scheme 2:



[a] Ref. 6.

An experiment (conditions of ref. 2) in which a solution of the amino-ester (1) (1 g) and N_2H_4,H_2O (1 ml) in EtOH (6 ml) was boiled under reflux for 3 h resulted in the recovery of unchanged amino-ester (830 mg), identified by n.m.r.

Saturated aq. $NaNO_2$ (0.55 g) was added during 10 min beneath the surface of a stirred solution of the amino-hydrazide (2) (1.42 g) in 2M-HCl (50 ml) at 0 °C. After a further 10 min the solution was neutralized with saturated aq. $NaHCO_3$. The insoluble material was collected, washed, and dried at 20 °C and 20 mmHg to give 2-amino-4-methylthiazole-5-carbonyl azide (3) (0.75 g), τ 1.93 (NH_2) and 7.58 (Me), $\nu_{max.}$ 2 140 cm^{-1}. A suspension of the azide (500 mg) in AcOH (0.6 ml)–Ac_2O (1 ml) was warmed at 50 °C until no

EXPERIMENTAL

General directions are as described in *J. Chem. Soc.* (*C*), 1968, 2674, except that ^{1}H n.m.r., i.r., and u.v. spectra were recorded for solutions in $(CD_3)_2SO$ at 90 MHz, suspensions in Nujol (except where stated), and solutions in MeOH, respectively.

Sequence (1) → (4) *in Scheme* 2.—A solution of ethyl 2-amino-4-methylthiazole-5-carboxylate [3] (1) ($\nu_{max.}$ 1 676 cm^{-1}; 7.44 g) and N_2H_4,H_2O (18 ml) in EtOH (35 ml) was boiled under reflux for 18 h and then kept at 20 °C for 16 h. The insoluble material was collected, washed with EtOH, and dried to give 2-amino-4-methylthiazole-5-carbohydrazide (2) (2.49 g), m.p. 210—211° (lit.,[1] 211—213°; lit.,[2] 160—161°), τ 1.3 (N*H*·NH_2), 2.78 (2-NH_2), 5.75 (NH·N*H*$_2$), and 7.67 (Me), $\nu_{max.}$ 1 643 cm^{-1}, $\lambda_{max.}$ 293 nm (ε 9,600), *m/e* 172 (M^+, 16%) and 141 (100).

more N_2 was evolved, heated to 100 °C for 1 h, and evaporated at 20 mmHg. Addition of H_2O and extraction with EtOAc gave a yellow crystalline solid (480 mg), m.p. >350° (lit.,[1] >260°), shown by t.l.c. and n.m.r. to be a complex mixture.

Interconversion (1) ⇌ (7) *in Scheme* 2.—A solution of the amino-ester (1) (9.3 g) and Ac_2O (10 ml) in AcOH (25 ml) was boiled under reflux for 1 h. Work-up gave ethyl 2-acetamido-4-methylthiazole-5-carboxylate (7) (10 g), m.p. 222.5—223.5° (lit.,[2] 210°; lit.,[3] 219°), $\nu_{max.}$ ($CHCl_3$) 1 702 cm^{-1} (amide and ester C=O).

Solutions of the foregoing acetamido-ester and N_2H_4, H_2O or N_2H_4,H_2O and H_2O in EtOH were boiled under reflux for 3 or 16 h, cooled, and evaporated at 40 °C and 10 mmHg. The materials so obtained were examined qualitatively by t.l.c. and quantitatively (±10%) by n.m.r. Some of the experiments (see Table) duplicate the conditions stated to give material with m.p. 165—166° in yields of 100 [2] and 76%.[3]

TABLE

Reactions of the acetamido-ester (7) with hydrazine *

(7)	N_2H_4,H_2O	H_2O	EtOH	Time (h)	Composition of products (7)	(1)	(2)
1.05	0.23	0.23	11 †	3	0.4	0.6	
1.05	0.23		11	3	0.4	0.6	
4.56	1.0	1.0	50	3	3.3	1.1	
1.50	1.5		6	3		1.2	
2.28	2.7	3.8	6.5	16		0.2	0.6

* Amounts of solids in g, liquids in ml. † C_6H_6 (not EtOH) as solvent.

Compounds (8)—(12) *in Scheme* 2.—(*a*) A mixture of the amino-hydrazide (2) (430 mg) and Ac_2O (5 ml) was stirred at 20 °C for 3 h and then poured into H_2O (50 ml). The insoluble material was collected and crystallized from H_2O to give N-*acetyl*-N′-2-*amino*-4-*methylthiazole*-5-*carbonylhydrazine* (9) (61 mg), m.p. 280—282° (Found: C, 39.1; H, 4.85; N, 26.3; S, 15.2. $C_7H_{10}N_4O_2S$ requires C, 39.25; H, 4.7; N, 26.2; S, 14.9%), τ 0.80 and 0.36 (each NH), 2.63 (2-NH_2), 7.64 (Me), and 8.13 (Ac), $\nu_{max.}$ 1 658 cm^{-1}, $\lambda_{max.}$ 297 nm (ε 12,000), *m/e* 214 (M^+, 9%) and 141 (loss of AcNH·NH, 100).

(*b*) A mixture of the amino-hydrazide (860 mg) and Ac_2O (10 ml) was stirred at 20 °C for 16 h. MeOH (8 ml) was added and stirring continued for 4 h. Evaporation at 10 mmHg gave material shown by n.m.r. to contain the monoacetyl derivative (9) (220 mg) and a diacetyl compound (950 mg). Crystallization from H_2O gave N-*acetyl*-N′-2-*acetamido*-4-*methylthiazole*-5-*carbonylhydrazine* (10) as a trihydrate (1.1 g). Drying over P_2O_5 at 100 °C and 2 mmHg gave the anhydrous compound (900 mg), double m.p. 235—238° and 252—254° (Found: C, 42.1; H, 4.7; N, 21.9; S, 12.7. $C_9H_{12}N_4O_3S$ requires C, 42.2; H, 4.7; N, 21.9; S, 12.5%), τ 7.48 (Me), 7.83 (2-NH*Ac*), and 8.10 (NH·NH*Ac*), $\nu_{max.}$ 1 660 and 1 632 cm^{-1}, $\lambda_{max.}$ 289 nm (ε 18,000), *m/e* 256 (M^+, 5%) and 141 (100).

(*c*) In separate experiments mixtures of the amino-hydrazide (430 mg) and Ac_2O (5 ml) were boiled under reflux for 1, 3, 5, and 16 h, then evaporated at 100 °C and 20 mmHg. The residues were added to H_2O (50 ml), and the insoluble materials were collected and crystallized from AcOH. Each experiment gave 2-*acetamido*-4-*methylthiazole*-5-*carboxylic acid* (11) (*ca.* 380 mg) (Found: C, 42.2; H, 4.3; N, 13.7; S, 16.2. $C_7H_8N_2O_3S$ requires C, 42.0; H, 4.0; N, 14.0; S, 16.0%), τ 7.48 (Me) and 7.84 (2-NH*Ac*), $\nu_{max.}$ 1 700 cm^{-1}, $\lambda_{max.}$ 288 nm (ε 15 200), *m/e* 200 (M^+, 18%) and 158 (loss of CO_2, 100). On heating, the acid decomposes at *ca.* 285 °C and 2-acetamido-4-methylthiazole, m.p. 134—136° (lit.,[5] 131—132°) sublimes.

(*d*) A mixture of the amino-hydrazide (430 mg) and Ac_2O (5 ml) was boiled under reflux for 5 h, cooled, and filtered under N_2. The precipitate consisted of the 5-carboxylic acid (11) (135 mg). Evaporation of the filtrate gave material shown by n.m.r. to contain the oxadiazole (12) described in the next section.

(*e*) A mixture of the amino-hydrazide (860 mg) and Ac_2O (10 ml) was boiled under reflux for 5 h, cooled to 0 °C, and stirred. NaH_4,H_2O (10 ml) was added during 30 min, the cooling bath was removed, and stirring was continued for 1 h. The insoluble material was collected and crystallized from EtOH to give 2-*acetamido*-4-*methyl*-5-(5-*methyl*-1,3,4-*oxadiazol*-2-*yl*)*thiazole* (12) (120 mg), m.p. 303—305° (Found: C, 45.4; H, 4.3; N, 23.3; S, 13.2. $C_9H_{10}N_4O_2S$ requires C, 45.4; H, 4.2; N, 23.5; S, 13.5%), τ 7.41 (Me), 7.44 (Me), and 7.80 (2-NH*Ac*), $\nu_{max.}$ 1 688 cm^{-1}, $\lambda_{max.}$ 302 nm (ε 16,200), *m/e* 238 (M^+, 22%) and 43 (100). The filtrate was diluted with H_2O (2 ml) and kept at 20 °C for 16 h. The material which had been deposited was collected and crystallized from H_2O to give 2-*acetamido*-4-*methylthiazole*-5-*carbohydrazide* (8) (73 mg), m.p. 252—254° (Found: C, 39.5; H, 4.8; N, 25.9; S, 14.6. $C_7H_{10}N_4O_2S$ requires C, 39.25; H, 4.7; N, 26.2; S, 14.9%), τ 7.53 (Me) and 7.86 (2-NH*Ac*). $\nu_{max.}$ 1 650 cm^{-1}, $\lambda_{max.}$ 278 nm (ε 10,800). *m/e* 214 (M^+, 15%). 183 (loss of NH·NH_2. 85), and 141 (loss of NH·NH_2 and of CH_2:C:O by McLafferty rearrangement of the 2-NHAc group. 100).

(*f*) A mixture of the diacetate (10) (256 mg). Ac_2O (2 ml). and AcOH (0.2 ml) was boiled under reflux for 1 h, and cooled. MeOH (5 ml) was added, and the mixture was stirred at 20 °C for 16 h. The insoluble material (35 mg) was identified by t.l.c. and n.m.r. as the 5-carboxylic acid (11). Evaporation of the filtrate gave a residue containing the diacetate (10), the 5-carboxylic acid (11), and the oxadiazole (12).

(*g*) The oxadiazole (12) (58 mg) was boiled under reflux with Ac_2O (2 ml) and AcOH (0.2 ml) for 1 h. Evaporation, addition of the residue to H_2O (10 ml), and collection of the insoluble material gave the oxadiazole (51 mg).

Reactions of Compounds (15; R = H *or* Ac) *in Scheme* 3B.—A solution of ethyl 2-aminothiazol-4-ylacetate [3] (15; R = H) (1.86 g) and Ac_2O) (2 ml) in AcOH (5 ml) was boiled under reflux for 1 h. Work-up gave ethyl 2-acetamidothiazol-4-ylacetate (15; R = Ac) (2.11 g), m.p. 119—120° (lit.,[3] 119.5°), $\nu_{max.}$ ($CHCl_3$) 1 732 and 1 694 cm^{-1}.

A solution of the amino-ester (15; R = H) (18.6 g) and N_2H_4,H_2O (50 m.) in EtOH (70 ml) was stirred at 20 °C for 3 h. Collection of the insoluble material gave 2-(2-*aminothiazol*-4-*yl*)*acetohydrazide* (16; R = H) (16.6 g), m.p. 161—163° (from H_2O) (Found: C, 34.9; H, 4.5; N, 32.3; S, 18.4. $C_5H_8N_4OS$ requires C, 34.9; H, 4.7; N, 32.55; S, 18.6%), τ 1.04 (N*H*·NH_2), 3.22 (2-NH_2), 3.78 (t, *J* 0.9 Hz, 5-H), 5.83 (NH·N*H*$_2$), and 6.80 (d, *J* 0.9 Hz, CH_2), $\nu_{max.}$ 1 650 cm^{-1}. $\lambda_{max.}$ 257 nm (ε 6 100), *m/e* 172 (M^+, 57%) and 113 (100).

A solution of the acetamido-ester (15; R = Ac) (700 mg), N_2H_4,H_2O (0.15 ml), and H_2O (0.15 ml) in EtOH (0.8 ml) was boiled under reflux for 3 h. Filtration gave 2-(2-acetamidothiazol-4-yl)acetohydrazide (16; R = Ac) (382 mg), m.p. 213—214° (from EtOH–H_2O) (lit.,[3] 210—212°). τ 0.9 (N*H*·NH_2), 3.18 (t, *J* 0.8 Hz, 5-H), 5.82 (NH·N*H*$_2$), 6.61 (d, *J* 0.8 Hz. CH_2), 6.74 (2-N*H*Ac), and 7.90 (2-NH*Ac*).

[5] E. Puscaru, D. Tefas, A. Berechet, and C. Chirita, *Farmacia (Bucuresti)*, 1959, **7**, 513.

$\nu_{max.}$ 1 667 and 1 638 cm^{-1}, $\lambda_{max.}$ 269 (ε 9 850), *m/e* 214 (M^+, 100%).

Experiments in Scheme 3A.—A solution of the acetamido-ester (7) (230 mg) and KOH (100 mg) in EtOH (5 ml) was boiled under reflux for 1 h and then evaporated at 20 mmHg. After the addition of water (20 ml), some starting material (58 mg) was removed by filtration. Acidification of the filtrate with 5M-HCl and extraction with EtOAc gave material (98 mg), shown by t.l.c. and n.m.r. to contain starting material (20 mg) and the amino-ester (1) (78 mg).

2-Acetamido-4-methylthiazole [5] (14) was recovered unchanged after this treatment; the reported [6] complete hydrolysis of ethyl 4-methylthiazole-5-carboxylate (13; R = Et) under these conditions was confirmed.

We thank the S.R.C. for a studentship (to C. W.)

[6/1835 *Received*, 30*th September*, 1976]

[6] E. R. H. Jones, F. A. Robinson, and M. N. Strachan, *J. Chem. Soc.*, 1946, 87.