Ring Nitrogen Functionalization of 2-Aminothiazol-4-acetic Acid Derivatives. I. Synthesis and Properties of Novel 2-Aminothiazole *N*-Oxides

Ettore Perrone*, Marco Alpegiani, Franco Giudici, Angelo Bedeschi, Renato Pellizzato and Giuliano Nannini

Ricerca e Sviluppo Chimico, Farmitalia Carlo Erba,
Via Imbonati 24, 20159 Milano, Italy

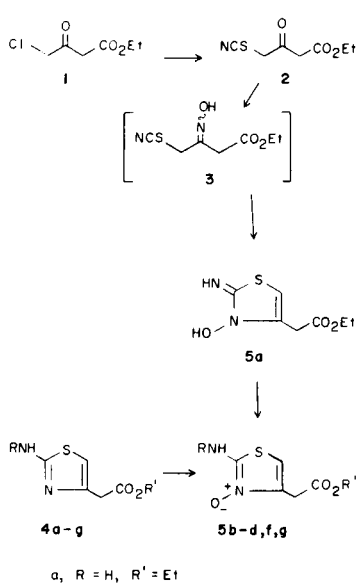
Received June 13, 1983

Cyclization of thiocyanomethylketone oximes with hydroxylamine hydrochloride and oxidation of 2-aminothiazole derivatives with peracids are shown to afford the same products, which can be formulated either as 2-imino-3-hydroxy-2,3-dihydrothiazolines or 2-aminothiazole *N*-oxides. Compounds of this type bearing at position 4 an acetic or α-oxyiminoacetic residue are useful synthons for highly active β-lactam antibiotics; the problems connected with their preparation in a suitably protected form are examined. Scope and limitations of this previously unreported oxidation of the thiazole nucleus are discussed. All the products show limited stability in alkaline media: the 4-acetic derivatives, in addition, undergo a transposition to afford 4-methylidenethiazolidines. Possible types of isomerism and tautomerism are discussed in the light of the acquired spectral data. The uv and ir spectra of the compounds synthesized lend support to their formulation as 2-aminothiazole *N*-oxides.

J. Heterocyclic Chem., **21**, 1097 (1984).

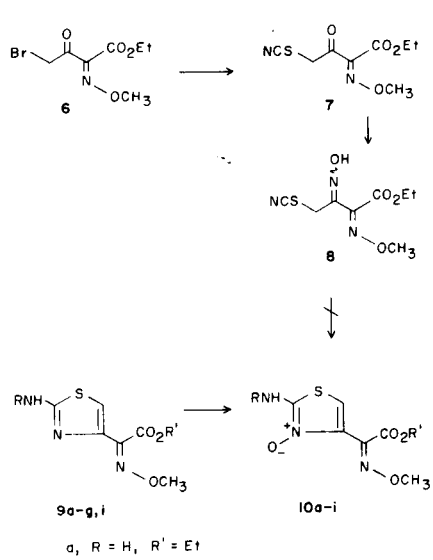
Among the manifold applications of thiazole derivatives, a particularly significant one has been the recent coupling of 2-amino-4-[*(Z)*-1-carboxy-1-methoxyimino]-methylthiazole with 7-aminocephalosporanates, which has resulted in the development of some of the most promising antibiotics of the last generation [1a-g]. Several papers and a plethora of patents have appeared on the subject since, contemplating different types of substitution on the thiazole nucleus. We, among others, took part in this effort and, beside more classical studies [2], devoted our attention to the introduction of heteroatomic functionalities (OH, OAlk, NH_2) on the thiazole ring nitrogen. Rewardingly, some of the cephalosporins synthesized along this line were proven to possess potent and unusual antimicrobial activity [3]. The objects of the present work are the synthetic and structural aspects connected with the 3-hydroxythiazolines used as synthons in the preparation of part of the novel antibiotics. The 3-alkoxy and 3-amino derivatives will be described in a forthcoming paper.

Chart 1



a, R = H, R' = Et
b, R = CH_3CO, R' = Et
c, R = HCO, R' = Et
d, R = Ph_3C, R' = Et
e, R = $ClCH_2CO$, R' = Et
f, R = $ClCH_2CO$, R' = H
g, R = $ClCH_2CO$, R' = $CHPh_2$

Chart 2



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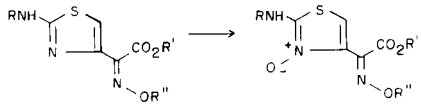
d, R = HCO, R' = Et
e, R = $ClCH_2CO$, R' = H
f, R = HCO, R' = H
g, R = $ClCH_2CO$, R' = $CHPh_2$
h, R = R' = H
i, R = HCO, R' = $CHPh_2$

Synthetic Aspects.

Despite countless studies on the chemistry of 2-aminothiazoles, little attention has been paid to 2-imino-3-hydroxy-2,3-dihydrothiazolines [4a]; until now, cyclization of α-thiocyanomethylketone oximes [5,6] is the sole reported access to this class of compounds. Examining this approach, we soon realized that 4-carboxymethyl substituted compounds could conveniently be obtained (Chart 1), but not the more interesting 4-(1-carboxy-1-methoxyimino)-methyl analogs (Chart 2) [7]. Thus, **5a** hydrochloride was prepared in high yield from ethyl 4-chloroacetoacetate by sequential reaction with potassium thiocyanide and hydroxylamine, but repeated attempts to achieve a similar ring closure on the 2-methoxyiminoacetoacetate **8** were not fruitful. *N*-Oxidation of 2-aminothiazoles, although unreported in the literature [8], was then considered. Once some requirements (to be discussed here) were fulfilled, the use of peracids (in particular *m*-chloroperbenzoic and permaleic acid) was found to be expedient, enabling us to obtain a series of 4-acetic derivatives bearing on the acetate methylene, as requested by our structure-activity studies, a methoxyimino group (Chart 2), a suitably protected hydroxyimino [9], a few homologated alkoxyimino and a bulky carboxy-substituted alkoxyimino group [10] (Chart 3).

Chart 3



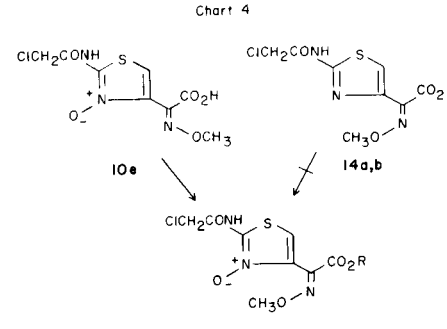
11a,c,d,f,g,l-u **12a,b,d,e,g-i,m,q,u,v**

a, R = $ClCH_2CO$, R' = R'' = Et
b, R = $ClCH_2CO$, R' = H, R'' = Et
c, R = H, R' = Et, R'' = C_3H_7
d, R = $ClCH_2CO$, R' = Et, R'' = C_3H_7
e, R = $ClCH_2CO$, R' = H, R'' = C_3H_7
f, R = R'' = H, R' = Et
g, R = $ClCH_2CO$, R' = Et, R'' = H
h, R = $ClCH_2CO$, R' = R'' = H
i, R = $ClCH_2CO$, R' = H, R'' = CPh_3
l, R = $ClCH_2CO$, R' = Et, R'' = CPh_3
m, R = $ClCH_2CO$, R' = CH_2COCH_3, R'' = CPh_3
n, R = Ph_3C, R' = Et, R'' = $CMe_2CO_2CHPh_2$
o, R = Ph_3C, R' = Et, R'' = $CMe_2CO_2Bu^t$
p, R = H, R' = Et, R'' = $CMe_2CO_2CHPh_2$
q, R = $ClCH_2CO$, R' = Et, R'' = $CMe_2CO_2CHPh_2$
r, R = Ph_3C, R' = H, R'' = $CMe_2CO_2Bu^t$
s, R = Ph_3C, R' = CH_2COCH_3, R'' = $CMe_2CO_2Bu^t$
t, R = H, R' = CH_2COCH_3, R'' = $CMe_2CO_2Bu^t$
u, R = $ClCH_2CO$, R' = CH_2COCH_3, R'' = $CMe_2CO_2Bu^t$
v, R = $ClCH_2CO$, R' = H, R'' = $CMe_2CO_2Bu^t$

The synthesis of the compounds requested for our studies made us acquainted with scope and limitations of the new oxidative approach. *N*-Oxidation proceeded at a reasonable rate only when the 2-amino group was acylated. Under the conditions required to oxidize the acylamino substrates, the free-amino thiazoles were almost unaffected; more severe conditions led to untractable mixtures where the hoped-for products could not even be detected. The free-amino compounds had to be obtained by oxidation of the acylamino derivatives followed by removal of the protecting group (*e.g.*, **9a→9c→10c→10a**). 2-Tritylamino thiazoles were completely inert to *m*-chloroperbenzoic and permaleic acid, while pertrifluoroacetic acid caused detritylation instead of *N*-oxidation (*e.g.*, **9b→9a**); oxidated 2-tritylamino compounds could be obtained by performing tritylation as the last step (*e.g.*, **5a→5d**; **10a→10b**). Protection was required for the carboxy group as well; free carboxymethylthiazoles (*e.g.*, **4f, 9f, 11v**) afforded unworkable mixtures on attempted *N*-oxidation, even if in this instance the hoped-for products could be detected among other ill-defined components.

N-Oxidation was particularly slow on the *E*-alkoxymes (*e.g.*, **14b**, Chart 4), probably because of steric crowding, to the point that prevailaing side-reactions prevented isolation of **15b**.

Chart 4



10e **14a,b** **15a,b**

a, R = H
b, R = $CHPh_2$

All compounds, free or *N*-acylated, showed limited stability under alkaline conditions. Thus, cleavage of the ethyl esters (*e.g.*, **5b, 5d, 10b, 10c**) was ordinarily not possible. However, as it was found later, this reaction could be accomplished in a number of instances (*i.e.*, for **10c, 12a, 12d**) under strictly defined conditions, when rapid separation of the formed sodium carboxylates prevented their further degradation in the alkaline medium. 2-Acylamino-3-oxides can be titrated as weak acids in aqueous solutions; *e.g.*, **10e** is a diprotic acid with pK_A's of 3.4 and 6.2. This is reflected in the experimental finding that esters like **10c** can be partially extracted from an organic solvent even with aqueous sodium hydrogen carbonate. This behaviour complicates the separation of the products from *m*-chlorobenzoic acid, but can be exploited for purification from unreacted starting material providing that acidification soon follows (see experimental part, entry **10d**). The oxidated compounds are acylated at the exocyclic nitrogen, although this is probably not the primary acylation site (*vide infra*). 2-Aminothiazole derivatives and their ox-

ides behave differently when exposed to excess formacetic anhydride (equimolecular amounts of acetic anhydride and formic acid heated for a few hours at 50-60°), the first giving formamido and the second exclusively acetamido products (*e.g.*, **4a** gives **4c**, while **5a** gives **5b**).

The limits of the oxidative step summarized above, coupled with the sensitiveness of the products in alkali, posed some problems in the synthesis of the acids to be used as acylating agents for the preparation of the cephalosporanic antibiotics. A suitably protected 2-amino-4-carboxymethylthiazole *N*-oxide (**5f**, Chart 1) had to be obtained by hydrolysis of a diphenylmethyl ester with trifluoroacetic acid (synthetic sequence: **4e**→**4f**→**4g**→**5g**→**5f**). In the methoxyimino series (Chart 2) the fully deprotected amino acid **10h** and the required protected synthon **10e** were first obtained through their diphenylmethyl esters (synthetic sequence: **9c**→**9e**→**9g**→**10g**→**10e**). In the deblocking of the chloroacetamido group with thiourea, the thiazole nucleus acts as a base and thiouronium salts cannot be isolated; *e.g.* **10c** gave directly a mixture of **10a** and 2-iminothiazolidin-4-one, in part as free bases and in part as hydrochlorides. As the formyl protecting group can be removed without the problem of accompanying by-products, a similar sequence was followed to obtain **10f**.

In further experiments, large scale preparation of **10e** could be accomplished by cleaving its ethyl ester **10c** under controlled conditions. This last method could be used for the preparation of the ethoxyimino and propoxyimino synthons (Chart 3, entries **12b, 12e**). The trityloxyiminoacetic acid **12i** was selected as a protected equivalent of the hydroxyimino synthon **12h** [11]. Since hydrolysis of diphenylmethyl esters cannot be performed in the presence of the labile trityloxy moiety, we resorted to the use of acetonyl esters, which are instantaneously cleaved, in a titration-like fashion [12a,b], by dilute alkali (synthetic sequence: **11g**→**11l**→**11i**→**11m**→**12m**→**12i**). A suitably protected 2-carboxy-2-propoxyiminoacetic acid precursor was envisaged in **12u**, a compound bearing two ester functionalities cleavable under extremely mild and selective conditions. An added problem in this instance was offered by a sluggish alkylation step (reaction of the free oxime with the bromoisobutyrate) which prevented the use of the chloroacetyl protecting group in the early stages of the synthesis. The readily prepared tritylamino derivatives **11n, 11o** had to be converted into the free acids (a step which proved successful only for **11o** since selective hydrolysis of the hindered ethoxycarbonyl moiety was not possible on **11n**), the obtained acid **11r** protected with chloroacetone, and the tritylamino group replaced by chloroacetamido before the prescribed oxidation and final ester cleavage could be safely accomplished (synthetic sequence: **11o**→**11r**→**11s**→**11t**→**11u**→**12u**→**12v**). Finally, an *E* oxime representative (**15a**, Chart 4), required for comparison and for structure-activity studies, was prepared by acid-catalyzed isomerisation of the *Z* isomer **10e**.

Structural Aspects.

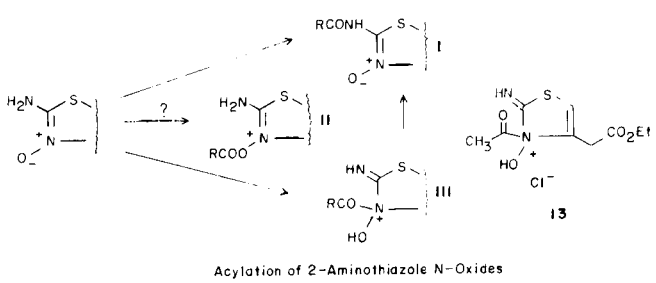
Oxidation Site.

Since stable oxidation products of thiazoles have never been described and 2-acetamidobenzothiazole has once been reported to give an *S*-oxide upon reaction with peracids [13], a conclusive evidence that we were dealing with *N*-oxidation was desired. This evidence is offered by the identity (mp, tlc, ir, nmr) of different samples of **5b**, obtained either by oxidation of **4b**, or by cyclisation of the thiocyanide **2** followed by acetylation.

Acylation Site.

The *N*-oxidated compounds here described have three possible sites of acylation, and three different regioisomers (I, II, III, Scheme I) can be formulated. The exocyclic acylamino structure I of most of our products descends from their origin (*i.e.*, oxidation of 2-acylaminothiazoles); the amino group can be unmasked and then acylated again, thus demonstrating that acylation occurs at the exocyclic nitrogen. However, when entry **5a** was treated with acetyl chloride, different conditions resulted either in the separation of **5a** hydrochloride (the mother liquors containing the structure I product, **5b**) or of a new, reactive product (ν CO = 1825 cm^{-1}) depending on the type of solvent and dilution. This new compound, which was assigned structure **13**, is a powerful acetylating agent [14], and in fact is converted into **5b** by the mere presence of a base, *e.g.*, triethylamine. These results can find a rationale by considering that formation of *N*-acylammonium salts is a reversible process [15], and therefore salts of type III can probably be isolated only if the equilibrium is shifted by their poor solubility in the reaction media: otherwise half a molar equivalent of the starting material can act as a base allowing the formation of half a molar equivalent of the type I product.

Scheme I



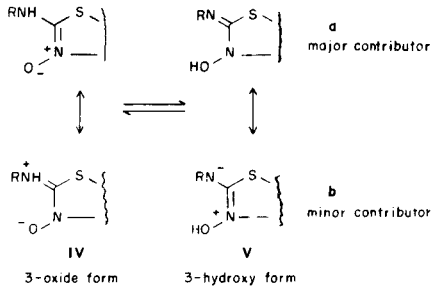
Acylation of 2-Aminothiazole N-Oxides

Oxime Geometry.

Since *syn*-CO oxime geometry had been recognized as a vital factor in previous structure-activity studies [10], our concern was to maintain this configuration, already ascer-

tained in starting materials **9a** and **11f** [1c,d] through the various steps of the synthesis. The preparation of an authentic sample of the anti *(E)* methoxyimino acid **15a** by isomerisation of **10e** (Chart 4) showed that this goal had been achieved, while the failure in isolating **15b** from oxidation of the *anti*-CO methoxyimino precursor **14b** suggests that the products bearing the sterically more demanding oxymes (**12b, 12e, 12m, 12n**) should safely be assigned the *Z* configuration for the mere fact that they had been prepared by *N*-oxidation. Comparison between the nmr spectra of **10e** and **15a** revealed that when the thiazole nucleus is oxidated the H-5 proton resonance is almost unaffected by the oxime geometry, in striking contrast with their precursors, where a significant (0.5 ppm) downfield shift characterizes the anti isomers.

Scheme II

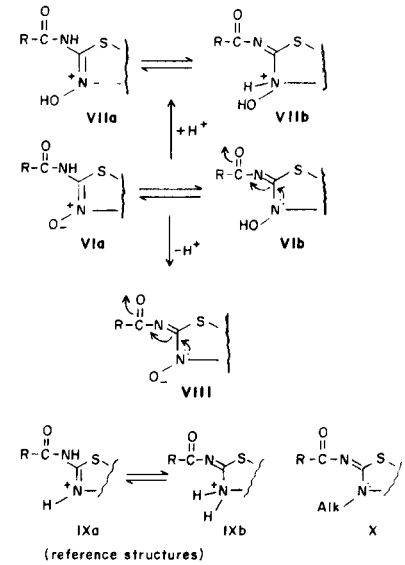


Tautomerism and Mesomerism in 2-Aminothiazole N-Oxides

Aminothiazole/Iminothiazoline Tautomerism.

The general predominance of the 2-aminothiazole over the 2-imino-2,3-dihydrothiazoline tautomer has been well established; to our knowledge on a single occasion a non-fixed 2-iminothiazoline protomer has been isolated [16], and even this is object of debate [17]. The occurrence of the former structure in entries of type **4, 9, 11** should be passed without comment, were not for the fact that the iminothiazoline alternative has been recently suggested for similar compounds [18a,b]. The *N*-acylated products here described (*e.g.*, **4b, 4c, 4e, 9c, 9d, 11a, 11d, 11l**) exhibit a very strong ir absorption around 1550 cm^{-1} (amide II band), which is anticipated in a secondary amide but not in an acylimine; this is consistent with the literature data for structurally related compounds [19]. Further support to the aminothiazole form is lent by uv spectroscopy, where the experimental data available in the literature [4b,20 21], corroborated by theoretical calculations [4b], indicate that when the extranuclear amino (imino) group is acylated a sharp difference exists between the observed spectra of the thiazole and the 2,3-dihydrothiazoline form, the latter showing a strong absorption over 300 nm. The *N*-acylated entries described in this paper (type **4, 9, 11**) do not exhibit this band and should be assigned the aminothiazole structure.

Scheme III



Tautomerism of 2-Acylaminothiazole N-Oxides in Acidic, Neutral and Alkaline Media

2-Aminothiazole 3-Oxide/2-Imino-3-hydroxythiazoline Tautomerism.

Little is known about the protomerism of 2-aminothiazole 3-oxides; the only comment is from Entenmann [15], who seems to prefer the *N*-oxide form for the free-amino bases and the 3-hydroxy form for their hydrochlorides and *N*-acyl derivatives. Recalling the consideration proposed by Jaffè [22] for 4-aminopyridine 1-oxide, we can account for a possible preference of the *N*-oxide form in the free amino bases (Scheme II); tautomer IV is stabilized over V by the N-H (larger than O-H) bond energy, and by the greater contribution of its canonical form **b** to resonance (at least when R is H).

Routine spectroscopic methods, however, in most instances do not provide an unequivocal answer. Mass spectrometry has been proposed [23] for the study of *N*-oxide/-*N*-hydroxy tautomerism, the two forms being expected to originate M-16 and M-17 signals, respectively, but a more recent study revealed that an equilibrium between tautomers can occur in the inlet system [24]; thus, the fact that compounds such as **5b** and **10b** show strong peaks of the first type has little significance. In the ir spectrum the aromatic *N*-oxide absorption, if any exists, is weak, while inspection of NH and OH stretchings in systems were strong intra- and inter-molecular hydrogen bonding occurs might be misleading. More conclusive, in our opinion, is the analysis of the CO region for the 2-acylamino derivatives, where a 1680-1700 cm^{-1} absorption, coupled with a band at 1540-1570 cm^{-1}, which is often the strongest in the spectrum, adds support for the presence of a secondary amide, and thence for the *N*-oxide form VIa (Scheme III).

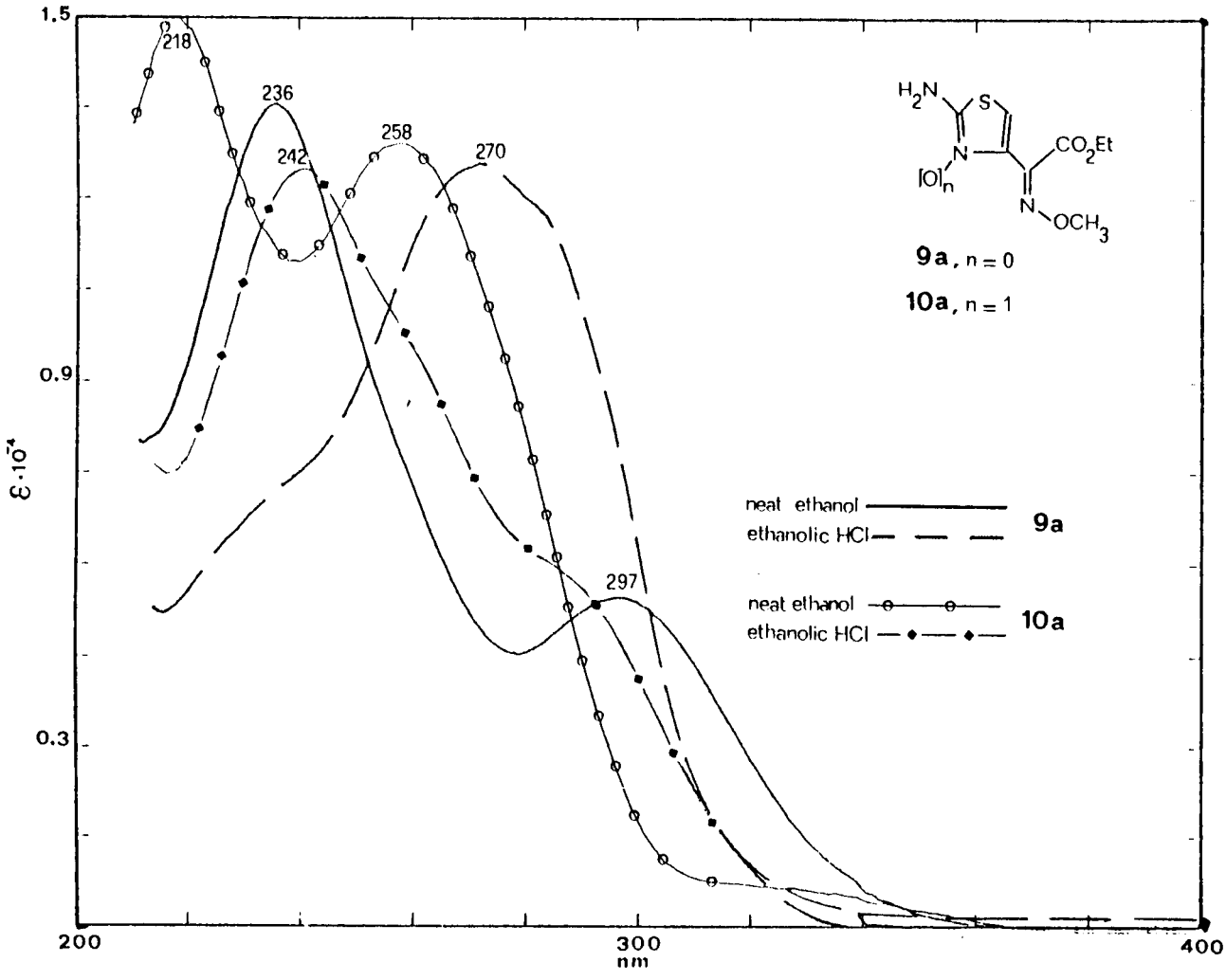


Figure 1. Uv spectrum of 2-amino-4-[(*Z*)-1-carbethoxy-1-methoxyimino]methylthiazole **9a** and its *N*-oxide **10a**.

Figures 1 and 2 report the uv spectra of two representative *N*-oxidated products, the free-amino entry **10a** and its chloroacetylated counterpart **10c**.

To gain further clues, the spectra of the latter [25] in acid, alkaline and neutral media were compared with the corresponding ones of its precursor, **9c** (Figure 3). Impressive similarities are apparent in 0.01*M* ethanolic hydrogen chloride, where two alternative structures, the acylamino VIIa and acylimino VIIb (Scheme III), are possible for **10c**; these structures have their close equivalents in forms IXa and IXb of the protonated parent thiazole **9c**. Since IXa is the commonly accepted form for the latter, the observed spectral analogies should suggest that the 2-acylamino structure VIIa is the preferred one for the oxidated compounds in acidic media. On the other hand in 0.01*M* ethanolic potassium hydroxide, where the oxidated products (pK_A *ca* 6.2) exist as the acylamino anions VIII, **10c** shows a particularly long wavelength maximum (316 nm). It should be appreciated that structure VIII has a p-π-π conjugation of the type found in 'fixed' (*i.e.*, 3-alkyl) acyliminothiazolines X, which in fact are reported [4b,20] to possess uv maxima at over 300 nmr [26]. In the absence of the base, this long-wavelength maximum is not present, **10c** showing a broad absorption with λ max at 263 nm; thus in neutral media the predominance of the 2-acylamino *N*-oxide form can be inferred, even if the asymmetry of the band might suggest a mixture of structures being present [27]. As a conclusion, we believe that spectral ir and uv evidence for the *N*-acylated compounds is consistent with the *N*-oxide structure and, granted that it be so, the same must hold for the free-amino entries as well [28].

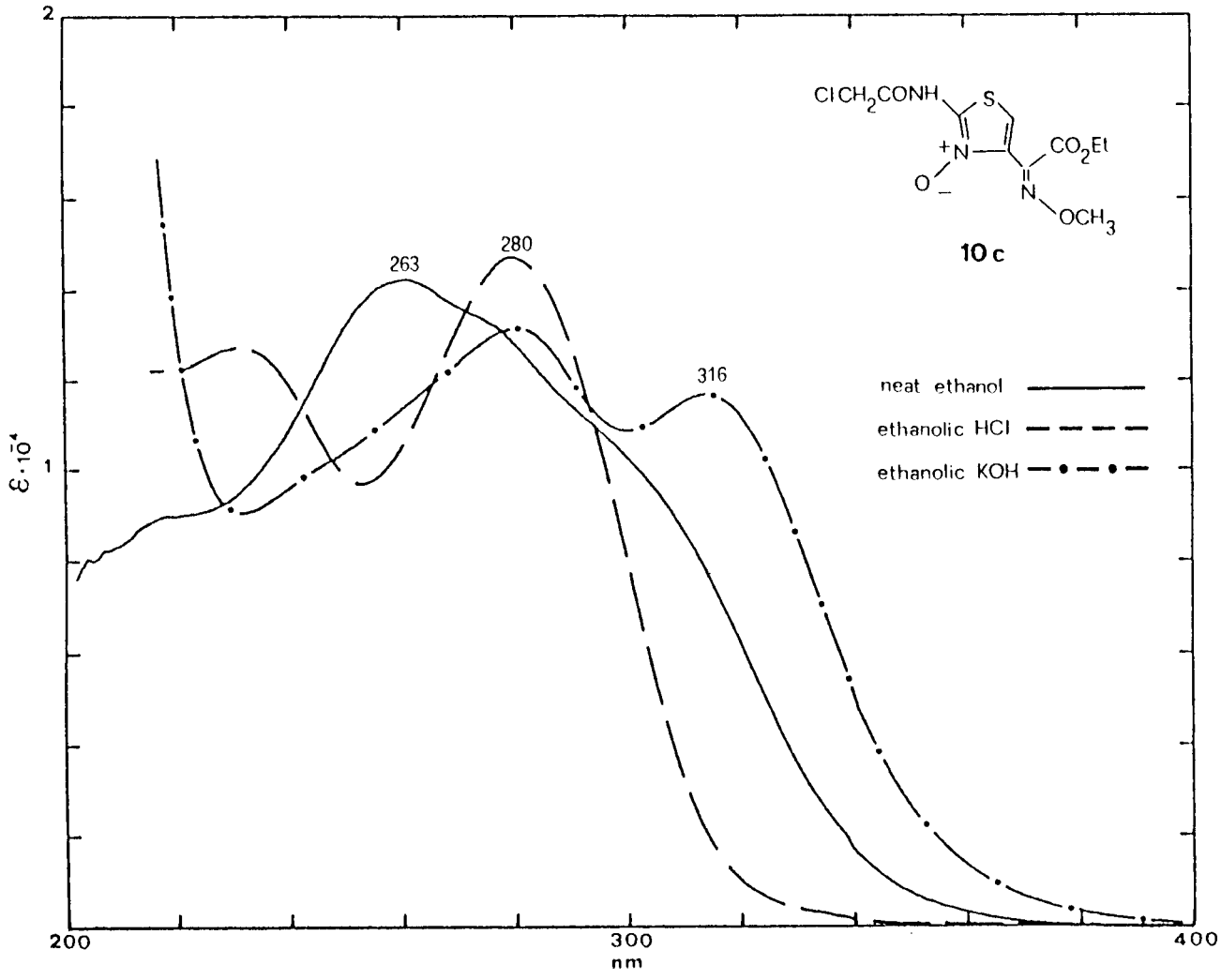
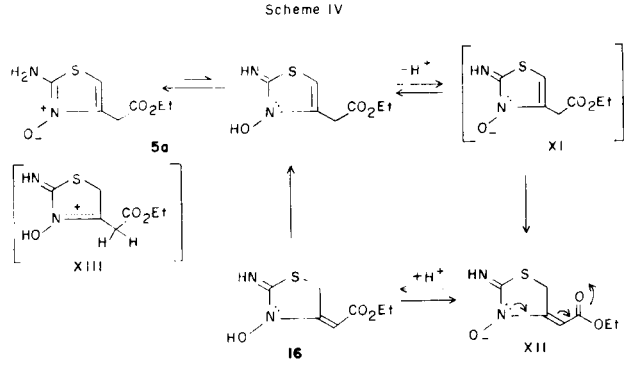


Figure 2. Uv spectrum of 4-[(*Z*)-1-carbethoxy-1-methoxyimino]methyl-2-chloroacetamidothiazole *N*-oxide **10c** in neutral, acidic and alkaline media.

2-Amino-4-methylthiazole/2-Imino-4-methylidenethiazolidine Tautomerism.

During the course of our uv studies, we observed that alkaline treatment of compound **5a** hydrochloride, after generation of the free base has been achieved, results in the development of an unusually strong, long wavelength maximum (341 nm, ϵ 25000) which cannot be explained by the mere formation of the corresponding 2-imino-3-hydroxylate anion. The absence of a similar phenomenon in the methoxyimino analog **10a** (Figure 4) was an important clue for considering the possibility that a transposition has occurred, resulting in an exocyclic double bond conjugated with the carbethoxy moiety (Scheme IV, species **16**). Similar transposition in 3-substituted 2,3-dihydrothiazol-

Scheme IV



2-Amino-4-carbethoxymethylthiazole N-Oxide/2-Imino-3-hydroxy-4-carbethoxymethylidenethiazoline Tautomerism

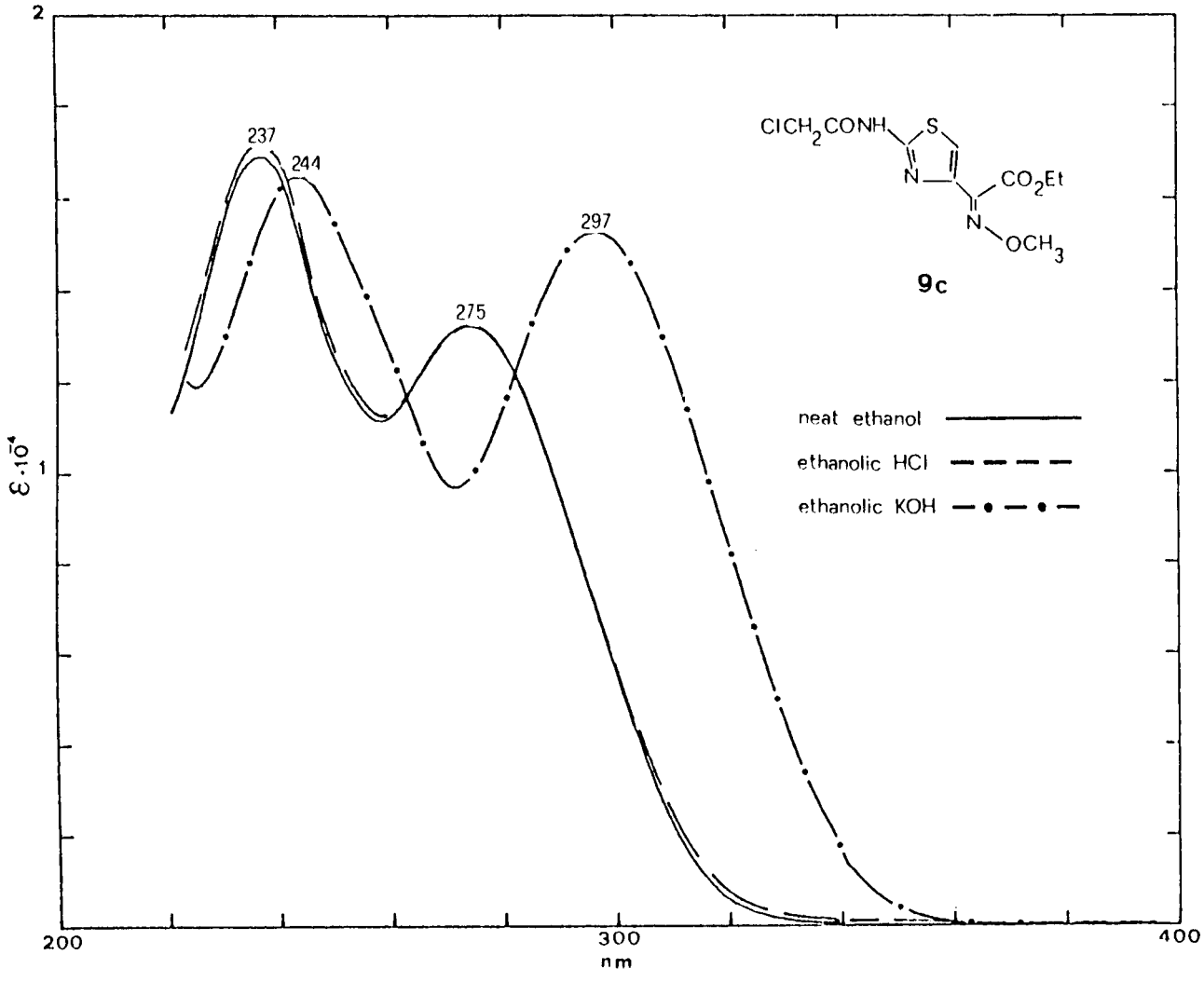


Figure 3. Uv spectrum of 4-[(*Z*)-1-carbethoxy-1-methoxyimino]methyl-2-chloroacetamidothiazole **9c** in neutral, acidic and alkaline media.

ine-4-acetates have recently been reported [29-31], but in our instance the 2-aminothiazole *N*-oxide/2-imino-3-hydroxy-2,3-dihydrothiazoline tautomerism is implicated as well, thus providing for the first time a link between a thiazole and a thiazolidine through a sequence of protomerism.

Conversion from **5a** to **16** must occur through the unstable species XI, which cannot benefit from either the aromatic conjugation proper of the former or the p-π-π conjugation (shown by the arrows) of the latter; the anion XII (λ max 341 nm, ϵ = 25000) is therefore produced in an irreversible process. Kinetic protonation at this point results in the exclusive formation of **16**, which was characterized as its hydrochloride; uv (λ max 286 nm, ϵ = 17000), ir (2600, 1695 and 1625 cm^{-1}) and nmr spectroscopy (δ ppm in deuteriotrifluoroacetic acid: 4.82, d, 2H, endocyclic methylene, coupled with 6.17, t, 1H, J = 2 Hz, exocyclic vinyl proton) leave little doubt about its structure, apart from what concerns the alkene geometry, tentatively assumed to be *E* [32]. Compound **16** can be reverted to its anion XII (sodium ethoxide) and thence recovered upon acidification, but in non-alkaline media the aromatic *N*-oxide form **5a** should be a more stable alternative. In fact, when isolation of a pure sample of the free base **16** was attempted, the starting material **5a** was obtained instead. This conversion is slower, but can easily be followed by nmr spectroscopy, when **16** hydrochloride is dissolved in trifluoroacetic acid [33]; it should involve protonation of the double

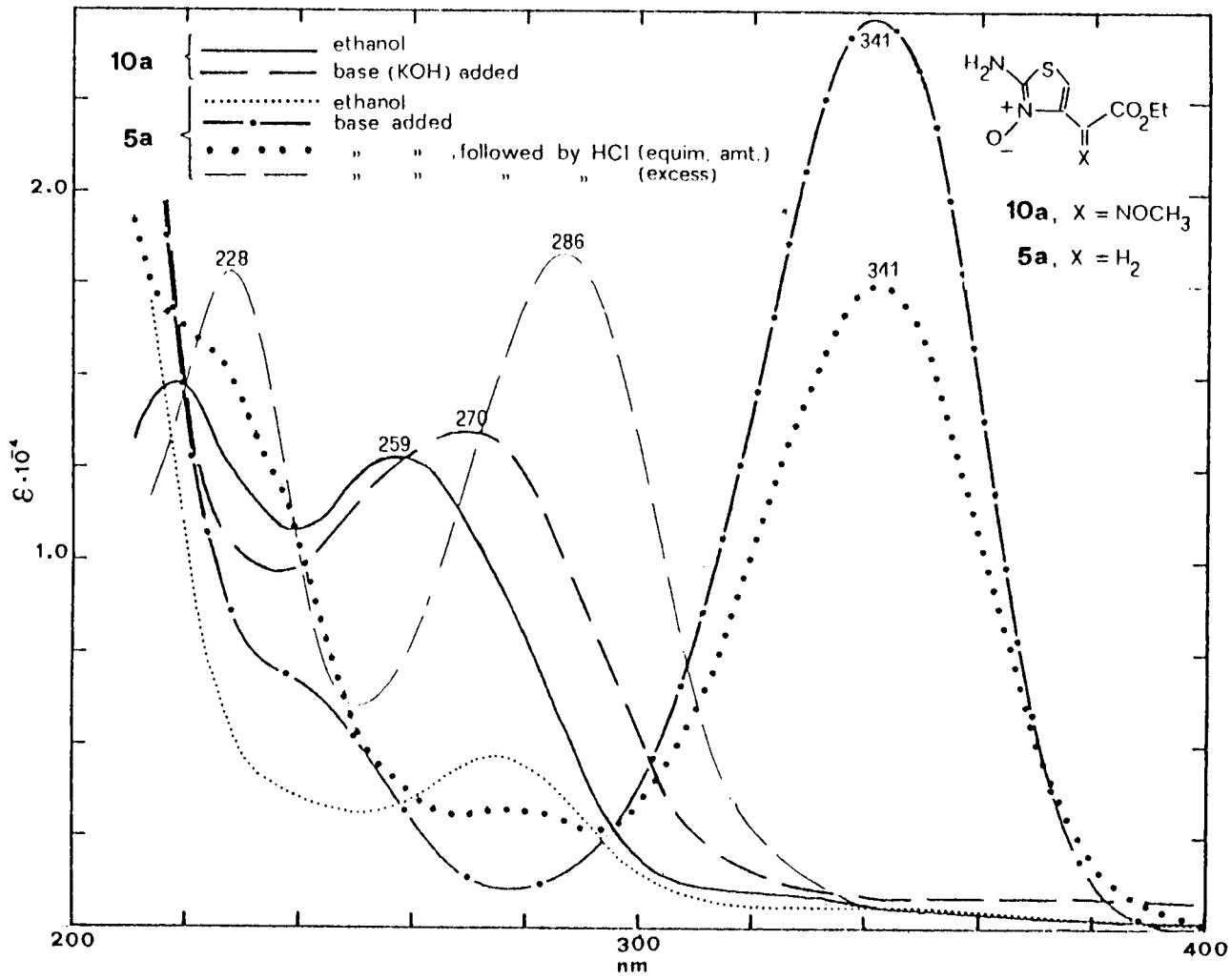


Figure 4. Effect of alkali on the uv spectra of 2-amino-4-[(*Z*)-1-carbethoxy-1-methoxyimino]methylthiazole *N*-oxide **10a** and of 2-amino-4-carbethoxymethylthiazole *N*-oxide **5a**.

bond to give the resonance-stabilised carbonium ion XIII. In fact, use of deuteriotrifluoroacetic acid resulted in the incorporation of one deuterium atom in the acetate methylene, the endocyclic vinyl position still integrating for one full proton; this nicely shows that **16** and **5a** are not in equilibrium and species XIII, if implicated, must give **5a** in a fast, irreversible step. We believe that the facile transposition of the 2-imino-3-hydroxythiazolidine **16** into **5a** can be considered a further clue suggesting that the protomeric equilibrium of the latter (and other related compounds) lies well on the part of the 'aromatic' 2-amino *N*-oxide form.

EXPERIMENTAL

Melting points were taken on a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 297 spectrometer; nmr spectra on a Hitachi-Perkin Elmer R24 B instrument using tetramethylsilane as internal standard. Ultraviolet spectra were taken on a Carlo Erba Strumentazione Spectracomp 601. Mass spectra were recorded on a CH-7 Varian MAT spectrometer. The percent yields are based on analytically pure samples unless otherwise stated and are not optimized.

4-Carbethoxymethyl-2-formamidothiazole (**4c**).

2-Amino-4-carbethoxymethylthiazole (5 g) was added in portions with external cooling to formacetic anhydride (from 3.84 ml of acetic anhydride and 1.7 ml of formic acid). Evaporation *in vacuo* after 1 hour left the product as a crystalline mass which was collected after trituration with ethyl ether, 5.23 g (91%), mp 119-120°; ir (potassium bromide): 3450, 3180, 3100, 3050, 2700, 1735, 1700, 1580, 1290, 1185, 1025 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.25 (t, 3H, CH_3), 3.75 (s, 2H, CH_2CO), 4.15 (q, 2H, OCH_2), 7.05 (s, 1H, H-5), 8.50 (s, 1H, HCO), 10.35 (bs, 1H, exch deuterium oxide, CONH) ppm.

Anal. Calcd. for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08; S, 14.96. Found: C, 44.71; H, 4.76; N, 13.14; S, 15.06.

4-Carbethoxymethyl-2-tritylaminothiazole (**4d**).

2-Amino-4-carbethoxymethylthiazole (18.6 g, 0.1 mole) in dichloromethane (150 ml) was treated (ice bath) with triethylamine (18.5 ml, 0.13 mole) and triphenylchloromethane (33.4 g, 0.12 mole). After 20 hours stirring at room temperature the reaction mixture was sequentially wash-

ed with water, 2% hydrochloric acid and brine. Removal of the solvent from the organic layer left the product, which was crystallized from ethyl ether-light petroleum, 40.6 g (95%), mp 114-115°; nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3), 3.5 (s, 2H, CH_2CO), 4.15 (q, 2H, OCH_2), 6.10 (s, 1H, H-5), 6.65 (bs, 1H, NH), 7.25 (s, 15H, Ph) ppm.

Anal. Calcd. for $C_{26}H_{24}N_2O_2S$: C, 72.86; H, 5.64; N, 6.54; S, 7.48. Found: C, 72.81; H, 5.60; N, 6.42; S, 7.26.

4-Carboxymethyl-2-chloroacetamidothiazole (**4f**).

Ethyl ester **4e** [34] (2.62 g) in 20 ml of ethanol was stirred for 3 hours with 2*N* aqueous sodium hydroxide (20 ml). The mixture was diluted with water (80 ml) and washed with ethyl acetate. Addition of 23% hydrochloric acid to the aqueous layer afforded part of the product as a white powder; a second crop was collected by extraction with ethyl acetate. Crystallization from water gave pure **4f**, 1.6 g (68%), mp 201-202°; ir (potassium bromide): 3430, 3200, 3040, 2500, 1700, 1680, 1580, 1430, 1405, 1340, 1230, 1130 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 3.65 (s, 2H, CH_2CO), 4.35 (s, 2H, $ClCH_2$), 6.97 (s, 1H, H-5), 12 (broad band, exch deuterium oxide, NH) ppm.

Anal. Calcd. for $C_7H_7ClN_2O_3S$: C, 35.82; H, 3.02; N, 11.94; S, 13.66; Cl, 15.10. Found: C, 35.83; H, 2.91; N, 11.86; S, 13.51; Cl, 15.01.

2-Chloroacetamido-4-diphenylmethoxycarbonylmethylthiazole (**4g**).

Compound **4f** (12 g) suspended in acetonitrile (280 ml) was stirred with diphenyldiazomethane (10 g) for 4 hours at room temperature. The solvent was evaporated and the residue taken up in ethyl acetate. After decomposing the excess reagent with a few drops of 23% hydrochloric acid, the solution was sequentially washed with water and aqueous sodium hydrogen carbonate. The dried organic layer afforded upon evaporation a residue which, when taken up in ethyl ether, soon crystallized. Filtration gave **4g** as a white powder, 15 g (73%), mp 112-123° (from isopropyl ether); ir (potassium bromide): 3430, 3180, 3060, 1730, 1650, 1580, 1550, 1360, 1200, 1165, 1140 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 3.9 (s, 2H, CH_2CO), 4.4 (s, 2H, $ClCH_2$), 6.8 (s, 1H, $CHPh_2$), 7.05 (s, 1H, H-5), 7.30 (s, 10H, Ph) ppm.

Anal. Calcd. for $C_{20}H_{17}ClN_2O_3S$: C, 59.92; H, 4.28; N, 6.99. Found: C, 59.83; H, 4.25; N, 6.77.

4-Carbethoxymethyl-3-hydroxy-2-imino-2,3-dihydrothiazoline (**5a**) Hydrochloride.

A solution of ethyl 4-chloroacetoacetate (4 ml, 30 mmoles) in 30 ml of acetonitrile was stirred for 12 hours with potassium thiocyanate (2.91 g, 30 mmoles). Potassium chloride was filtered off, the solvent was removed *in vacuo* and the crude thiocyanide **2** thus resulting was taken up in 10 ml of dry dimethylacetamide and treated with hydroxylamine hydrochloride (2.08 g, 30 mmoles). Complete solubilisation of the latter was followed after several hours by precipitation of **5a** hydrochloride, which was obtained pure by filtration and repeated washings with acetonitrile, 6.5 g (91%), mp 182° dec; ir (nujol): 3280, 3130, 3080, 2530 br, 1730, 1625, 1225 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.28 (t, 3H, CH_3), 3.90 (s, 2H, CH_2CO), 4.15 (q, 2H, OCH_2), 6.85 (s, 1H, H-5), 9.5 (s, 2H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_7H_{11}ClN_2O_3S$: C, 35.22; H, 4.65; N, 11.74; S, 13.43; Cl, 14.85. Found: C, 34.92; H, 4.61; N, 11.73; S, 13.17; Cl, 14.97.

2-Acetamido-4-carbethoxymethylthiazole *N*-Oxide (**5b**).

a) From **5a**.

Formacetic anhydride (obtained by heating at 60° for 2 hours a mixture of acetic anhydride, 9.44 ml, and 99% formic acid, 4.15 ml) was added to a suspension of **5a** hydrochloride (7.17 g, 30 mmoles) in dry chloroform. The mixture was cooled to −10° and then treated under stirring with a solution of triethylamine (4.6 ml, 33 mmoles) in the same solvent. The reaction was complete within ten minutes. Repeated evaporation (benzene) *in vacuo* left a residue which was triturated with water to give the crude product as a solid. Crystallization from dioxane afforded 4.8 g (65%) of analytically pure **5b**, mp 194-195° dec; ir (potassium bromide): 3420, 3110, 1720, 1680, 1540, 1290, 1250, 1210, 1170 cm^{-1}; nmr (hexadeuteriomethylsulphoxide): δ 1.28 (t, 3H, CH_3), 2.20 (s, 3H, CH_3CO), 3.80 (s, 2H, CH_2CO), 4.15 (q, 2H, OCH_2), 7.27 (s, 1H, H-5) ppm. The mass spectrum showed the parent ion at m/e 244; loss of ketene at m/e 202 and then loss of oxygen at 202; loss of OC_2H_5 at m/e 199, followed by CH_3CO at 157 and then by HCN at 130 m/e (base peak).

Anal. Calcd. for $C_9H_{12}N_2O_4S$: C, 44.25; H, 4.95; N, 11.47; S, 13.12. Found: C, 43.92; H, 4.87; N, 11.44; S, 12.88.

Compound **5b** was obtained in sensibly reduced yield when acetic anhydride was used instead of formacetic anhydride in the above reaction. Acetylation with acetyl chloride (1 molar equivalent) in the presence of two or more molar equivalents of triethylamine gave impure **5b** in poor yield. One molar equivalent of base in a diluted chloroform solution resulted in the partial precipitation, after about 45 minutes, of the hydrochloride of the starting material, the mother liquors containing impure **5b**. One molar equivalent of base and one molar equivalent of acetyl chloride in a concentrated dichloromethane solution resulted in the rapid formation (1-5 minutes) of the acylammonium salt **13** (*vide infra*).

b) From **4b**.

2-Acetamido-4-carbethoxymethylthiazole (0.23 g, 1 mmole) in chloroform was kept overnight in the presence of 80% *m*-chloroperbenzoic acid (0.322 g, 1.5 mmoles). The solvent was evaporated and the residue taken up in the minimum amount of hot benzene required for complete dissolution. Cooling of the mixture allowed the separation of a significant amount of *m*-chlorobenzoic acid. The mother liquors were evaporated and the residue could then be crystallized from dioxane to give **5b** (0.15 g, 51%).

4-Carbethoxymethyl-2-formamidothiazole *N*-Oxide (**5c**).

Compound **4c** (0.214 g, 1 mmole) was dissolved in chloroform (10 ml) and allowed to react with 85% *m*-chloroperbenzoic acid (0.322 g) for 48 hours. The solvent was evaporated and the residue crystallized twice from hot acetonitrile to obtain 0.125 g (55%) of the title product as white needles, mp 178-179° dec; ir (potassium bromide): 3105, 1720, 1690, 1540, 1280, 1230, 1095 cm^{-1}; nmr (deuteriochloroform): δ 1.28 (t, 3H, CH_3), 3.9 (s, 2H, CH_2CO), 4.2 (q, 2H, OCH_2), 7.0 (s, 1H, H-5), 8.6 (s, 1H, HCO) ppm.

Anal. Calcd. for $C_8H_{10}N_2O_4S$: C, 41.17; H, 4.38; N, 12.17. Found: C, 41.05; H, 4.41; N, 12.07.

4-Carbethoxymethyl-2-tritylaminothiazole *N*-Oxide (**5d**).

Triethylamine (2.81 ml, 20 mmoles) was added to a suspension of **5a** hydrochloride (2.39 g, 10 mmoles) in chloroform, thus obtaining a clear solution. Triphenylchloromethane (2.79 g, 10 mmoles) was then added portionwise with external cooling. After 1 hour at −5° and 1 hour at room temperature, the reaction mixture was sequentially washed with water, 2% hydrochloric acid and brine. Evaporation left the crude product which was purified by silica gel chromatography eluting in sequence with dichloromethane, dichloromethane-ethyl acetate 1:1 and then with a gradient in ethanol (0→20%). The fractions containing pure **5d** were collected and evaporated; 0.81 g (18%), mp 145-147° dec; ir (potassium bromide): 3430, 3280, 3120, 3050, 3020, 3000-2400 br, 1730, 1525, 1190, 1025 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3), 3.77 (s, 2H, CH_2CO), 4.15 (q, 2H, OCH_2), 6.20 (s, 1H, H-5), 7.2 (15H, m, Ph) ppm.

Anal. Calcd. for $C_{26}H_{24}N_2O_3S$: C, 70.24; H, 5.44; N, 6.30; S, 7.21. Found: C, 69.94; H, 5.43; N, 6.32; S, 7.22.

4-Carboxymethyl-2-chloroacetamidothiazole *N*-Oxide (**5f**).

The diphenylmethyl ester **5b** (2 g, 4.8 mmoles) was stirred for 1 hour at 0° in neat trifluoroacetic acid (20 ml). Evaporation and trituration with ethyl ether gave the title product, 0.9 g (75%), mp 185-187° dec; ir (nujol): 3160, 3100, 1700, 1600, 1555, 1300, 1150, 1100 cm^{-1}; nmr (deuteriodimethylsulphoxide): δ 3.75 (s, 2H, CH_2CO), 4.47 (s, 2H, $ClCH_2$), 7.1 (s, 1H, H-5), 8.2 (bs, 2H, NH and OH) ppm.

Anal. Calcd. for $C_7H_7ClN_2O_4S$: C, 33.55; H, 2.82; N, 11.18. Found: C, 33.26; H, 2.75; N, 10.88.

2-Chloroacetamido-4-diphenylmethoxycarbonylmethylthiazole *N*-Oxide (**5g**).

From **4g** according to the experimental procedure described for the preparation of **5c**, white powder, 64%, mp 169-170° (from chloroform-ethyl ether); ir (potassium bromide): 3420, 3080, 1725, 1700, 1550, 1360, 1290, 1200, 1160, 1105 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 4.0 (s, 2H, CH_2CO), 4.47 (s, 2H, $ClCH_2$), 6.85 (s, 1H, $CHPh_2$), 7.22 (s, 1H, H-5), 7.3 (s, 10H, Ph), 7.65 (bs, 1H, NH) ppm.

Anal. Calcd. for $C_{20}H_{17}ClN_2O_4S$: C, 57.62; H, 4.11; N, 6.72; S, 7.69; Cl, 8.50. Found: C, 57.30; H, 4.16; N, 6.60; S, 7.52; Cl, 8.62.

Ethyl 2-Methoxyimino-3-oxo-4-thiocyanobutanoate (**7**).

Ethyl 2-methoxyimino-3-oxo-4-bromobutanoate [1c] (2.52 g, 10 mmoles) in acetonitrile (20 ml) was stirred overnight in the presence of finely ground potassium thiocyanide (0.97 g, 10 mmoles). The separated potassium bromide was filtered off and the solvent removed to afford the crude title product. An analytical sample was obtained as a syrup after purification by silica gel chromatography (ethyl ether/light petroleum); ir (film): 2990, 2940, 2160, 1740, 1700, 1600, 1370, 1330, 1260, 1205, 1040 cm^{-1}; nmr (deuteriochloroform): δ 1.35 (s, 3H, CH_3), 4.18 (s, 3H, OCH_3), 4.35 (s, 2H, CH_2SCN), 4.36 (q, 2H, OCH_2) ppm.

Anal. Calcd. for $C_6H_{10}N_2O_4S$: C, 41.73; H 4.38; N, 12.17. Found: C, 41.52; H, 4.42; N, 11.87.

Reaction of this material with hydroxylamine hydrochloride, as described for the preparation of **5a**, gave a new product, presumably the oxyme **8**; ir (film): 3340, 2990, 2940, 2160, 1745, 1405, 1370, 1260, 1160, 1035 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (s, 3H, CH_3), 3.90 (s, 5H, OCH_3 and CH_2S), 4.25 (q, 2H, OCH_2) ppm. However, attempted cyclisation of the new product into the prescribed thiazole **10a** under a variety of conditions was unrewarding.

4-[*(Z)*-1-Carbethoxy-1-methoxyimino]methyl-2-formamidothiazole (**9d**).

From **9a** according to the experimental procedure described for the preparation of **4c**, white crystals were obtained, 96%, mp 120-121°; ir (potassium bromide): 3400, 3160, 3060, 3020, 2700, 1735, 1698, 1555, 1285, 1179, 1070, 1040 cm^{-1}; nmr (deuteriochloroform): δ 1.36 (t, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.38 (q, 2H, OCH_2), 7.10 (s, 1H, H-5), 8.70 (s, 1H, HCO) ppm.

Anal. Calcd. for $C_9H_{11}N_3O_4S$: C, 42.02; H, 4.31; N, 16.33; S, 12.46. Found: C, 42.02; H, 4.37; N, 16.23; S, 12.42.

2-Chloroacetamido-4-[*(Z)*-1-methoxyimino-1-diphenylmethoxycarbonyl]-methylthiazole (**9g**).

From **9e** as described for the preparation of **4g** an amorphous solid was obtained, 98%, mp 119-120° (from cyclohexane); ir (potassium bromide): 3450, 3380, 3200, 3060, 3030, 1740, 1690, 1550, 1265, 1190, 1165, 1035 cm^{-1}; nmr (deuteriochloroform): δ 3.97 (s, 3H, OCH_3), 4.20 (s, 2H, $ClCH_2$), 6.90 (s, 1H, $CHPh_2$), 7.09 (s, 1H, H-5), 7.3 (s, 10H, Ph) ppm.

Anal. Calcd. for $C_{21}H_{18}ClN_3O_4S$: C, 56.82; H, 4.09; N, 9.47; S, 7.22; Cl, 7.99. Found: C, 57.15; H, 4.15; N, 9.34; S, 7.29; Cl, 7.66.

2-Formamido-4-[*(Z)*-1-methoxyimino-1-diphenylmethoxycarbonyl]methylthiazole (**9i**).

The ethyl ester **9d** (5.14 g, 20 mmoles) was added to a solution of sodium hydroxide (1.6 g) in water a(90 ml). After 90 minutes at 20°, 10% hydrochloric acid was added to bring the *p*H to 7.0 and some unreacted starting material was recovered by washing with ethyl acetate. The aqueous solution was then made acid (*p*H 1) to extract the acid **9f** (2.9 g), which without purification was treated with diphenyldiazomethane (2.5 g) in acetonitrile (25 ml). The benzhydryl ester **9i** spontaneously crystallized from the reaction mixture, 4.5 g (56%), mp 159-160°; nmr (deuteriochloroform): δ 3.97 (s, 3H, OCH_3), 6.83 (s, 1H, $CHPh_2$), 7.10 (s, 1H, H-5), 7.30 (s, 10H, Ph), 8.70 (s, 1H, HCO), 12.0 (bs, 1H, CONH) ppm.

Anal. Calcd. for $C_{20}H_{17}N_3O_4S$: C, 60.74; H, 4.33; N, 10.63. Found: C, 60.83; H, 4.35; N, 10.59.

2-Amino-4-[*(Z)*-1-carbethoxy-1-methoxyimino]methylthiazole *N*-Oxide (**10a**).

The chloroacetamido derivative **10c** (1 g, 3.11 mmoles) dissolved in dimethylacetamide (5 ml) was stirred with thiourea (0.237 g, 3.11 mmoles) until tlc showed complete conversion to the title product and 2-iminothiazolin-4-one (2 hours). Part of the latter was filtered off after evaporation under high vacuum and trituration with chloroform. Isolation of **10a** from the mother liquors could be accomplished, with considerable losses, by sequential washing with a small amount of brine, removal of the solvent and crystallization from acetone-ethyl ether, 0.35 g, (46%), mp 122-125° dec; ir (potassium bromide): 3460, 3410, 3340, 3270, 1720, 1615, 1290, 1200, 1175, 1040 cm^{-1}; nmr (deuteriochloroform): δ 1.28 (t, 3H, CH_3), 3.95 (s, 3H, OCH_3), 4.28 (q, 2H, OCH_2), 6.77 (s, 1H, H-5), 6.9 (bs, 2H, exch deuterium oxide) ppm. This compound was correctly analyzed after conversion to its hydrochloride (ethanolic hydrogen chloride), mp 167-168° (from ethanol-ethyl ether); ir (potassium bromide): 3340, 3260, 1715, 1625, 1550, 1300, 1200, 1170, 1030 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.28 (t, 3H, CH_3), 4.00 (s, 3H, OCH_3), 7.30 (s, 1H, H-5), 9.90 (bs, 3H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_6H_{12}ClN_3O_4S$: C, 34.11; H, 4.30; N, 4.92; S, 11.38; Cl, 12.58. Found: C, 33.97; H, 4.30; N, 14.79; S, 11.67; Cl, 12.33.

4-[*(Z)*-1-Carbethoxy-1-methoxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**10c**).

4-[*(Z)*-1-Carbethoxy-1-methoxyimino]methyl-2-chloroacetamidothiazole [1d] (294 g, 0.96 mole) was added to a solution of permaleic acid in chloroform (from maleic anhydride, 132 g, in 2 ℓ of chloroform, stirred for 2 hours at 0° in the presence of 36% hydrogen peroxide, 254 ml) and the mixture was stirred for 18 hours at room temperature. After washing with sodium hydrogen carbonate (130 g in 800 ml of water) and water, the organic layer was dried over sodium sulfate and evaporated. The residue was triturated with hot (70-80°) ethanol (1.5 ℓ), cooled, filtered and washed with ethyl ether to obtain 173 g (55%) of title product, mp 149-150°; ir (potassium bromide): 3400, 3060, 1730, 1690, 1550, 1375, 1280, 1120, 1060, 905 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.26 (t, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.32 (q, 2H, OCH_2), 4.56 (s, 2H, $ClCH_2$), 7.77 (s, 1H, H-5) ppm. The mass spectrum showed the parent ion at 321 m/e, loss of oxygen at 305 and then of CO_2Et at 232, loss of CH_2Cl at 272, the aminothiazole and chloroacetyl fragments at, respectively, 229 and 77 m/e (base peak).

Anal. Calcd. for $C_{10}H_{12}ClN_3O_5S$: C, 37.33; H, 3.76; N, 13.06; S, 9.96; Cl, 11.02. Found: C, 37.11; H, 3.90; N, 12.88; S, 9.84; Cl, 10.93.

4-[*(Z)*-1-Carbethoxy-1-methoxyimino]methyl-2-formamidothiazole *N*-Oxide (**10d**).

Compound **9d** (5.14 g, 20 mmoles) in chloroform (15 ml) was stirred overnight with 85% *m*-chloroperbenzoic acid (5 g). The precipitated *m*-chlorobenzoic acid was filtered off, and the solution was extracted with aqueous sodium carbonate. The organic layer was discarded, the aqueous layer was made acid and extracted with ethyl acetate. Evaporation of the solvent left a residue which was dissolved in the minimum amount of hot benzene. A second portion of *m*-chlorobenzoic acid was filtered off upon cooling. The benzene mother liquors were evaporated to give the crude product. Trituration of the latter with ethyl ether gave a clear solution from which pure **10d** soon separated as white crystals, 1.95 g (36%), mp 155-156° dec; ir (potassium bromide): 3450, 3240, 3100, 1735, 1680, 1540, 1280, 1040 cm^{-1}; nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_3), 4.05 (s, 3H, OCH_3), 4.35 (q, 2H, OCH_2), 7.35 (s, 1H, 5-H), 8.65 (s, 1H, HCO), 12.7 (bs, 1H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_9H_{11}N_3O_5S$: C, 39.56; H, 4.06; N, 15.38; S, 11.73. Found: C, 39.66; H, 4.17; N, 15.36; S, 12.02.

4-[*(Z)*-1-Carboxy-1-methoxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**10e**).

a) From **10g**.

The benzhydryl ester **10g** (25 g, 54.3 mmoles) was stirred at 25° for 90 minutes in 99% formic acid (250 ml) containing anisole (25 ml) [35]. Evaporation under vacuum left a syrup which was treated dropwise under stirring with ethyl ether (250 ml) to precipitate the title product as a

white powder. A virtually pure compound was obtained after washing the collected powder with several portions of ethyl ether (120 ml), 15 g (94%); an analytical sample was further crystallized from methanol, mp 157° dec; ir (potassium bromide): 3320, 1710, 1560, 1360, 1060; nmr (hexadeuteriodimethylsulphoxide): δ 4.03 (s, 3H, OCH_3), 4.53 (s, 2H, $ClCH_2$), 7.66 (s, 1H, H-5), 8.60 (bs, 2H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_8H_8ClN_3O_5S$: C, 32.71; H, 2.74; N, 14.31; S, 10.91; Cl, 12.07. Found: C, 32.89; H, 2.83; N, 14.02; S, 10.77; Cl, 11.96.

b) From **10c**.

The ethyl ester **10c** (220 g, 0.68 mole) suspended in 99% ethanol (1450 ml) was treated with 35% sodium hydroxide (124 ml) while keeping the temperature between 15 and 20°. Complete dissolution of the starting material was soon followed by separation of the sodium salt of the title product. The latter was collected by filtration after 7 hours, washed with ethanol, and converted into the free acid by acidification with cold diluted hydrochloric acid. The filtered product was washed with ice-cold water, triturated with ethanol (600 ml) and filtered again, thus obtaining **10e** as a white powder, 160 g (80%), mp 150-153° dec.

4-[*(Z)*-1-Carboxy-1-methoxyimino]methyl-2-formamidothiazole *N*-Oxide (**10f**).

The benzhydryl ester **10i** (1.7 g, 4.1 moles) was dissolved in trifluoroacetic acid (10 ml) containing anisole (1 ml). After 2 hours stirring at room temperature the mixture was concentrated *in vacuo* and the residue triturated, in sequence, with ethyl ether and chloroform to afford 0.95 g (94%) of the title product **10f**, mp 160° violent dec; nmr (hexadeuteriodimethylsulphoxide): δ 3.92 (s, 3H, OCH_3), 7.63 (s, 1H, H-5), 7.9-8.6 (broad band, 2H, exch deuterium oxide), 8.45 (s, 1H, HCO) ppm.

Anal. Calcd. for $C_7H_7N_3O_5S$: C, 34.29; H, 2.87; N, 17.14; S, 13.07. Found: C, 34.03; H, 2.93; N, 17.05; S, 12.98.

2-Chloroacetamido-4-[*(Z)*-1-methoxyimino-1-diphenylmethoxycarbonyl]-methylthiazole *N*-Oxide (**10g**).

From **9g** as described for the preparation of **10c**, white crystals were obtained, 53%, mp 167-168° (from methanol); nmr (hexadeuteriodimethylsulphoxide): δ 4.02 (s, 3H, OCH_3), 4.53 (s, 2H, $ClCH_2$), 6.98 (s, 1H, $CHPh_2$), 7.39 (s, 10H, Ph), 7.72 (s, 1H, H-5) ppm.

Anal. Calcd. for $C_{21}H_{18}ClN_3O_5S$: C, 54.84; H, 3.94; N, 9.13; S, 6.97; Cl, 7.70. Found: C, 55.06; H, 4.01; N, 9.16; S, 6.68; Cl, 7.72.

The starting material **9g** present in the ethanolic liquors could be recycled to afford an additional crop of **10g**, thus increasing the yield to approximately 65%.

2-Amino-4-[*(Z)*-1-carboxy-1-methoxyimino]methylthiazole *N*-Oxide (**10h**).

Compound **10e** (587 mg, 2 mmoles) in dimethylacetamide (2 ml) was stirred with thiourea (152 mg, 2 mmoles) for two hours at room temperature. Ethyl ether was added to separate a sticky syrup. The surnatant liquor was decanted off. This procedure was repeated twice replacing ethyl ether with ethyl acetate; a yellowish powder was eventually obtained, consisting of a mixture of 2-iminothiazolin-4-one and the hydrochloride of the title product. Rapid crystallization of this material from boiling water (partial decomposition occurring) afforded pure **10h**, 170 mg (39%), mp 210°; nmr (hexadeuteriodimethylsulphoxide, deuteriotrifluoroacetic acid): δ 4.01 (s, 3H, OCH_3), 7.25 (s, 1H, H-5), 9.5 (bs, 2H, exch deuterium oxide), 13.3 (s, 1H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_6H_7N_3O_4S$: C, 33.17; H, 3.25; N, 19.34; S, 14.70. Found: C, 32.99; H, 3.18; N, 19.14; S, 14.63.

2-Formamido-4[*(Z)*-1-methoxyimino-1-diphenylmethoxycarbonyl]methylthiazole *N*-Oxide (**10i**).

From **9i** as described for the preparation of **5c**, a white powder was obtained, 61%, mp 172-173° dec (from ethanol/ethyl ether); nmr (deuteriochloroform): δ 4.01 (s, 3H, OCH_3), 7.01-7.4 (m, 12H, $CHPh_2$ and H-5), 8.02 (s, 1H, HCO), 11.8 (bs, 1H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_{20}H_{17}N_3O_5S$: C, 58.38; H, 4.17; N, 10.121. Found: C, 58.40: H, 4.21; N, 10.17.

2-Amino-4-[*(Z)*-1-carbethoxy-1-propoxyimino]methylthiazole (**11c**).

1-Bromopropane (21.86 ml) in acetone (200 ml) was added to a stirred mixture of ethyl 2-hydroxyiminoacetoacetate (34.8 ml) and potassium carbonate (45.3 g) in the same solvent (150 ml), while keeping the temperature at 20°. After 5 hours the solid was filtered, washed with acetone and discarded. The acetone liquors were collected and evaporated to give an oil which was partitioned between water and dichloromethane. Crude ethyl 2-propoxyiminoacetoacetate, 33.7 g, was obtained upon evaporation of the organic layer. A solution of this material in dichloromethane (140 ml) containing a catalytic amount of *p*-toluenesulphonic acid (27 mg) was treated with a solution of bromine (7.67 ml) in the same solvent (40 ml). After 3.5 hours stirring at room temperature the mixture was repeatedly washed with water and the solvent evaporated to afford crude ethyl 4-bromo-2-hydroxyiminoacetoacetate, 39.5 g. This in turn was allowed to react with thiourea (10.52 g) in 50% aqueous ethanol (190 ml) for 2 hours at room temperature, after which time potassium hydrogen carbonate was added in portions to a *p*H of about 7.5. The precipitate was filtered after 30 minutes stirring to give 22.87 g (58%) of title product **11c**, mp 136-137°; ir (potassium bromide): 3450, 3260, 3180, 3120, 1720, 1615, 1540, 1265, 1185, 1020 cm^{-1}; nmr (deuteriochloroform): δ 0.90 (t, 3H, $CH_2CH_2CH_3$), 1.30 (t, 3H, CH_2CH_3), 1.30-1.85 (m, 2H, $CH_2CH_2CH_3$), 4.10 (t, 2H, $OCH_2CH_2CH_3$), 4.28 (q, 2H, OCH_2CH_3), 5.8 (broad band, 2H, exch deuterium oxide), 6.60 (s, 1H, H-5) ppm.

Anal. Calcd. for $C_{10}H_{15}N_3O_3S$: C, 46.68; H, 5.87; N, 16.33; S, 12.46. Found: C, 46.53; H, 5.64; N, 16.12; S, 12.31.

4-[*(Z)*-1-Carbethoxy-1-propoxyimino]methyl-2-chloroacetamidothiazole (**11d**).

Compound **11c** (23 g, 89 mmoles) stirred in dimethylacetamide (50 ml) was treated at 0° with chloroacetyl chloride (8.16 ml, 107 mmoles). After 30 minutes at 0° and 30 minutes at room temperature, the mixture was poured into ice-water with good stirring. The solid was collected, triturated with water and filtered again. Oven-drying at 60° furnished the title product, 28.2 g (94%), mp 88-90°; ir (potassium bromide) 3260, 3180, 3120, 3040, 2970, 1740, 1690, 1550, 1370, 1330, 1255, 1180, 1135, 1070, 1050, 990 cm^{-1}; nmr (deuteriochloroform): δ 0.90 (t, 3H, CH_3), 1.31 (t, 3H, CH_3), 1.30-1.85 (m, 2H, $CH_2CH_2CH_3$), 4.12 (t, 2H, $OCH_2CH_2CH_3$), 4.21 (s, 2H, CH_2Cl), 4.33 (q, 2H, OCH_2CH_3), 7.10 (s, 1H, H-5) ppm.

Anal. Calcd. for $C_{12}H_{16}ClN_3O_4S$: C, 43.18; H, 4.83; N, 12.59. Found: C, 42.97; H, 4.81; N, 12.43.

4-[*(Z)*-1-Carbethoxy-1-hydroxyimino]methyl-2-chloroacetamidothiazole (**11g**).

From 2-amino-4-[*(Z)*-1-carbethoxy-1-hydroxyimino]methyl-2-chloroacetamidothiazole [1c], according to the procedure described for **11d**, a white solid (88%) was obtained retaining half a molar equivalent of dimethylacetamide (nmr, analysis), mp 145-147°; ir (potassium bromide): 3600-3150, 3250, 3210, 3100, 3060, 2980, 2930, 2900, 1730, 1665, 1560, 1290, 1180, 1000, 970 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.30 (t, 3H, CH_3), 4.30 (q, 2H, OCH_2), 4.39 (s, 2H, $ClCH_2$), 7.50 (s, 1H, H-5), 11.8 (s, 1H, NOH), 12.6 (bs, 1H, CONH) ppm.

Anal. Calcd. for $C_9H_{10}ClN_3O_4S \cdot \frac{1}{2}C_4H_9NO$: C, 39.42; H, 4.33; N, 14.62; Cl, 10.58. Found: C, 39.55; H, 4.31; N, 14.48; Cl, 10.62.

4-[*(Z)*-1-Carboxy-1-trityloxyimino]methyl-2-chloroacetamidothiazole (**11i**).

Compound **11l** (4 g, 7.5 mmoles) in ethanol (25 ml) was stirred for 3 hours at 25° with 35% aqueous sodium hydroxide. Work-up as for **4f** gave the product, 36 g (94%), mp 163-165° dec; (from ethyl ether-light petroleum); ir (potassium bromide): 3430, 3110, 2980, 2930, 3000-2300, 1720, 1690, 1540, 1280, 1230, 1020 cm^{-1}; nmr (hexadeuterioacetone): δ 4.32 (s, 2H, $ClCH_2$), 6.0 (bs, 2H, exch deuterium oxide), 7.25 (m, 15H, Ph), 7.40 (s, 1H, H-5) ppm.

Anal. Calcd. for $C_{26}H_{20}ClN_3O_4S$: C, 61.72; H, 3.98; N, 8.30. Found: C, 61.54; H, 4.01; N, 8.13.

4-[*(Z)*-1-Carbethoxy-1-trityloxyimino]methyl-2-chloroacetamidothiazole (**11l**).

Compound **11g** (2.92 g, 10 mmoles) in dry dimethylformamide (10 ml) was stirred for 24 hours in the presence of triethylamine (1.39 ml, 11

mmoles) and triphenylchloromethane (3.08 g, 11 mmoles). The reaction mixture was poured into cold water (100 ml) under stirring, to form a precipitate which was collected, washed with water and dried, thus obtaining the title product as a 1:1 solvate with dimethylformamide, 4.5 g (74%), mp 122-123°; ir (potassium bromide): 3440, 3170, 3080, 3090, 3030, 2890, 2930, 2850, 2750, 1730, 1690, 1600, 1580, 1550, 1490, 1285, 1180, 980 cm^{-1}; nmr (deuteriochloroform): δ 1.38 (t, 3H, CH_3), 3.97 (s, 2H, $ClCH_2$), 4.35 (q, 2H, OCH_2), 7.05 (s, 1H, H-5), 7.20 (s, 15H, Ph) ppm.

Anal. Calcd. for $C_{31}H_{31}ClN_4O_5S \cdot C_3H_7NO$: C, 61.32; H, 5.15; N, 9.23; S, 5.28; Cl, 5.84. Found: C, 61.09; H, 5.09; N, 9.01; S, 5.36; Cl, 6.11.

4-[*(Z)*-1-Acetonyloxycarbonyl-1-trityloxyimino]methyl-2-chloroacetamidothiazole (**11m**).

A solution of the acid **11i** (8 g, 15.8 mmoles) in dry dimethylformamide was stirred overnight in the presence of chloroacetone (2.39 ml, 30 mmoles) and triethylamine (2.32 ml, 16 mmoles). The precipitated salts were filtered off and the solvent was removed *in vacuo* to give an amorphous solid which crystallized from cyclohexane, 7.3 g (82%), mp 100-102°; ir (potassium bromide): 3450, 3090, 3060, 3030, 2930, 2860, 1750, 1735, 1695, 1630, 1550, 1280, 1170, 970 cm^{-1}; nmr (deuteriochloroform): δ 2.2 (s, 3H, CH_3), 3.62 (s, 2H, $ClCH_2$), 4.45 (s, 2H, OCH_2), 7.33 (s, 15H, Ph), 7.56 (s, 1H, H-5) ppm.

Anal. Calcd. for $C_{29}H_{24}ClN_3O_5S$: C, 61.97; H, 4.30; N, 7.48; Cl, 6.31. Found: C, 62.03; H, 4.34; N, 7.35; Cl, 6.26.

4-[*(Z)*-1-Carbethoxy-1-(2-diphenylmethoxycarbonyl-2-propoxyimino)]-methyl-2-tritylaminothiazole (**11n**).

4-[*(Z)*-1-Carbethoxy-1-hydroxyimino]methyl-2-tritylaminothiazole [1d] (20 g, 43.7 mmoles) in dimethylsulphoxide (90 ml) was stirred for 6 hours at room temperature with potassium carbonate (9.1 g, 65.6 mmoles) and diphenylmethyl 2-bromo-2-methylpropionate (16 g, 48.1 mmoles). The mixture was poured into ice-water (400 ml), stirred for 10 minutes and the formed precipitate was filtered, washed with water, dried at 50° *in vacuo* to afford 30 g of the title product (97%), mp 70-73°; ir (potassium bromide): 3390, 3080, 3060, 3025, 2980, 2935, 1740, 1590, 1570, 1490, 1530, 1280, 1175, 1155, 970 cm^{-1}; nmr (deuteriochloroform): δ 1.24 (t, 3H, CH_3), 1.52 (s, 6H, CMe_2), 4.28 (q, 2H, OCH_2), 6.40 (s, 1H, H-5), 6.75 (s, 1H, $CHPh_2$), 7.3 (m, 25H, Ph) ppm.

Anal. Calcd. for $C_{48}H_{39}N_3O_5S$: C, 72.75; H, 5.54; N, 5.92. Found: C, 72.47; H, 5.49; N, 5.75.

4-[*(Z)*-1-(2-*t*-Butoxycarbonyl-2-propoxyimino)-1-carbethoxy]methyl-2-tritylaminothiazole (**11o**).

4-[*(Z)*-1-Carbethoxy-1-hydroxyimino]methyl-2-tritylaminothiazole (100 g, 0.219 mole), *t*-butyl-2-bromo-2-methylpropionate (58.6 g, 0.26 mole), and potassium carbonate (75 g, 0.54 mole) in dimethylsulphoxide (500 ml) were stirred overnight at room temperature. The reaction mixture was poured into ice-water (1.2 ℓ) ans stirred for 1 hour. The precipitate was collected by filtration, repeatedly washed with water and dried under vacuum at 50°, thus obtaining the title product, 122.4 g (82%). Repeated crystallizations from cyclohexane gave samples containing a steady 2:5 molar amount of DMSO (accurate nmr integration), mp 122-124°; ir (potassium bromide): 3420, 3080, 3060, 3025, 2980, 2935, 1740, 1730, 1590, 1530, 1305, 1280, 1170-1140, 1060-1020, 970 cm^{-1}; nmr (deuteriochloroform): 2d 1.35 (t, 3H, CH_3), 1.44 (s, 9H, *t*-Bu), 1.50 (s, 6H, CMe_2), 4.40 (q, 2H, OCH_2), 6.68 (s, 1H, H-5), 6.80 (bs, 1H, NH), 7.33 (s, 15H, Ph) ppm.

Anal. Calcd. for $C_{34}H_{37}N_3O_5S \cdot \frac{1}{2}C_2H_6OS$: C, 66.29; H, 6.30; N, 6.66; S, 7.12. Found: C, 66.19; H, 6.38; N, 6.62; S, 7.28.

4-[*(Z)*-1-Carbethoxy-1-(2-diphenylmethoxycarbonyl-2-propoxyimino)]methyl-2-chloroacetamidothiazole (**11q**).

A solution of compound **11n** (30 g, 42 mmoles) in 99% formic acid (190 ml) was diluted with distilled water (60 ml) under stirring, to obtain a finely divided suspension which was stirred for 7 hours at room temperature. The reaction mixture was then poured into ice-water (500 ml) and the solid collected. This solid was dissolved in ethyl acetate, washed with aqueous sodium carbonate and precipitated again by dropwise addition of light petroleum, to obtain a white powder (30 g after oven-drying) consisting of 2-amino-4-[*(Z)*-1-carbethoxy-1-(2-diphenylmethoxycarbonyl-2-propoxyimino)]methyl-2-chloroacetamidothiazole **11p**, in admixture with triphenylmethanol; nmr (deuteriochloroform, hexadeuteriodimethylsulphoxide): δ 1.30 (t, 3H, CH_3), 1.55 (s, 6H, CMe_2), 4.40 (q, 2H, OCH_2), 6.62 (s, 1H, H-5), 6.80 (s, 1H, $CHPh_2$), 6.82 (bs, 2H, NH_2), 7.30 (m, Ph) ppm. Without purification, this material was dissolved in dimethylacetamide (60 ml) and treated with chloroacetyl chloride (4.72 g, 42 mmoles) for 30 minutes at 0° and 1 hour at room temperature. Water was then added to separate a gum, which was decanted and dissolved in ethyl acetate. The solution was washed with aqueous sodium hydrogen carbonate, dried and evaporated. Fractionation of the crude product by column chromatography (silica gel, ethyl acetate-cyclohexane) afforded pure **11q**, 13.5 g (59% overall), mp 158-160°; ir (potassium bromide): 3470, 3080, 3060, 3020, 2980, 2920, 2850, 1740, 1595, 1550, 1485, 1285, 1170, 1155, 1005 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_3), 1.59 (s, 6H, CMe_2), 4.22 (s, 2H, $ClCH_2$), 4.37 (q, 2H, OCH_2), 6.86 (s, 1H, H-5), 7.04 (s, 1H, $CHPh_2$), 7.05-7.45 (m, 10H, Ph) ppm.

Anal. Calcd. for $C_{26}H_{26}ClN_3O_6S$: C, 57.35; H, 4.82; N, 7.72. Found: C, 57.39; H, 4.87; N, 7.69.

4-[*(Z)*-1-(2-*t*-Butoxycarbonyl-2-propoxyimino)-1-carboxy]methyl-2-tritylaminothiazole (**11r**).

Compound **11o** (56 g, 93 mmoles) in methanol (500 ml) was refluxed with aqueous 2*N* sodium hydroxide (90 ml) for 2 hours. The reaction mixture was concentrated *in vacuo* and then partitioned between ethyl acetate and aqueous 0.5*N* hydrochloric acid. The organic layer was evaporated to leave a syrup, which was crystallized from carbon tetrachloride-light petroleum to afford the title compound (28 g, 52%), mp 168-169° dec; ir (potassium bromide): 3420, 3290, 3120, 3050, 3000-2300, 2980, 2930, 2850, 1720, 1530, 1180, 970 cm^{-1}; nmr (hexadeuteriomethylsulphoxide): δ 1.38 (s, 15H, CMe_2 and *t*-Bu), 6.83 (s, 1H, H-5), 7.35 (m, 15H, Ph), 8.84 (bs, 1H, NH) ppm.

Anal. Calcd. for $C_{32}H_{33}N_3O_5S$: C, 67.23; H, 5.82; N, 7.35; S, 5.61. Found: C, 67.55; H, 6.01; N, 7.15; S, 5.48.

4-[*(Z)*-1-Acetonyloxycarbonyl-1-(2-*t*-butoxycarbonyl-2-propoxyimino)]-methyl-2-tritylaminothiazole (**11s**).

A solution of the acid **11r** (10 g, 17.5 mmoles) in dimethylformamide (50 ml) was stirred for 20 hours with bromoacetone (17.6 ml, 21 mmoles) and triethylamine (2.45 ml, 17.5 ml). The reaction mixture was poured into ice water and the separate solid was partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. Removal of the solvent and silica gel chromatography (ethyl acetate-cyclohexane mixtures) gave the title product as an amorphous solid, 7 g (64%), mp 132-135°; ir (potassium bromide): 3400, 3090, 3050, 3020, 2980, 2930, 2850, 1750, 1730, 1530, 1270, 1160, 1140, 970 cm^{-1}; nmr (deuteriochloroform): δ 1.41 (s, 9H, *t*-Bu), 1.50 (s, 6H, CMe_2), 2.21 (s, 3H, $COCH_3$), 4.72 (s, 2H, OCH_2CO), 6.7 (bs, 1H, NH), 6.83 (s, 1H, H-5), 7.25 (s, 15H, Ph) ppm.

Anal. Calcd. for $C_{35}H_{37}N_3O_6S$: C, 66.96; H, 5.94; N, 6.69. Found: C, 66.81; H, 6.01; N, 6.53.

4-[*(Z)*-1-Acetonyloxycarbonyl-1-(2-*t*-butoxycarbonyl-2-propoxyimino)]-methyl-2-chloroacetamidothiazole (**11u**).

The tritylamino derivative **11s** (7 g, 11.1 mmoles) was added into ice-cold, stirred formic acid (100 ml), and the obtained solution was then diluted by dropwise addition of water (30 ml). The mixture was stirred for 4 hours at room temperature, concentrated *in vacuo* and the residue diluted with water (100 ml); partition between ethyl acetate and diluted aqueous hydrogen carbonate, followed by removal of the solvent from the organic layer, afforded a crude sample of 4-[*(Z)*-1-acetonyloxycarbonyl-1-(2-*t*-butoxycarbonyl-2-propoxyimino]methyl-2-aminotiazole **11t** (6.2 g). Without purification, this material was dissolved in dry dimethylacetamide (25 ml) and allowed to react with chloroacetyl chloride (0.95 ml, 12.2 mmoles) for 1 hour at 0° and 30 minutes at room temperature. The reaction mixture was poured into ice-water and the separated gum chromatographed on silica gel (ethyl ether-cyclohexane as eluants) to afford the title compound, 3.2 g (62% from **11s**), as a white powder; nmr (deuterio-

chloroform): δ 1.40 (s, 9H, *t*-Bu), 1.50 (s, 6H, CMe_2), 2.25 (s, 3H, $COCH_3$), 4.25 (s, 2H, $ClCH_2$), 4.80 (s, 2H, OCH_2), 7.55 (s, 1H, H-5), 10.8 (bs, 1H, NH) ppm.

Anal. Calcd. for $C_{15}H_{24}ClN_3O_7S$: C, 46.80; H, 5.24; N, 9.10. Found: C, 46.51; H, 5.32; N, 8.98.

4-[(*Z*)-1-Carbethoxy-1-ethoxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**12a**).

By following the experimental procedure described for the preparation of **10c**, 4-[(*Z*)-1-carbethoxy-1-ethoxyimino]methyl-2-chloroacetamidothiazole [1d] was converted into the title compound (56%), mp 108-110° (from isopropyl ether); ir (potassium bromide): 3430, 2985, 2920, 1735, 1695, 1545, 1300, 1270, 1200, 1120, 1050, 1030, 930 cm^{-1}; nmr (deuteriochloroform): δ 1.33 (t, 6H, CH_3), 4.36 (s, 2H, $ClCH_2$), 4.38 and 4.39 (each q, 2H, OCH_2), 7.31 (s, JH, H-5), 10.40 (bs, 1H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_{11}H_{14}ClN_3O_5S$: C, 39.35; H, 4.20; N, 12.51. Found: C, 39.51; H, 4.27; N, 12.38.

4-[(*Z*)-1-Carboxy-1-ethoxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**12b**).

Aqueous sodium hydroxide (35%) (21 ml) was added to a suspension of ethyl ester **12a** (34.3 g, 102 mmoles) in ethanol (400 ml). After stirring for 7 hours at room temperature, work-up as described for the preparation of **10e** from **10c** afforded the title product, 22.2 g (70.6%), mp 147-148° dec; ir (potassium bromide): 3410, 3100, 3050, 1710, 1550, 1290, 1200, 1120, 1030 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.25 (t, 3H, CH_3), 4.20 (q, 2H, OCH_2), 4.42 (s, 2H, $ClCH_2$), 7.43 (s, 1H, H-5), 8.0 (bs, 2H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_9H_{10}ClN_3O_5S$: C, 35.13; H, 3.27; N, 13.66. Found: C, 35.27; H, 3.36; N, 13.49.

4-[(*Z*)-1-Carboxy-1-propoxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**12e**).

The ethyl ester **11d** (16.5 g, 49.4 mmoles) was oxidized with permaleic acid, according to the experimental procedure described for **10c**, to afford the *N*-oxide **12d**; nmr (deuteriochloroform): δ 0.95 (t, 3H, CH_3), 1.35 (t, 3H, CH_3), 1.70 (m, 2H, $OCH_2CH_2CH_3$), 4.15 (t, 2H, $OCH_2CH_2CH_3$), 4.33 (q, 2H, OCH_2CH_3), 4.40 (s, 2H, $ClCH_2$), 7.30 (s, 1H, H-5) ppm. This material was dissolved in ethanol (90 ml) and stirred for 7 hours at 25° with 35% aqueous sodium hydroxide (5 ml), whereupon the sodium salt of the title product was collected by filtration and converted into the free acid with hydrochloric acid, 8.74 g (55%), mp 151-152° (from water); ir (potassium bromide): 3400, 3100, 2960, 2940, 3000-2300 br, 1710, 1550, 1290, 1015 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 0.9 (t, 3H, CH_3), 1.63 (m, 2H, $OCH_2CH_2CH_3$), 4.03 (t, 2H, $OCH_2CH_2CH_3$), 4.37 (s, 2H, $ClCH_2$), 7.40 (s, 1H, H-5), 9.5 (bs, 2H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_{10}H_{12}N_3O_5S$: C, 37.33; H, 3.76; N, 13.06; S, 9.97; Cl, 11.02. Found: C, 37.30; H, 3.72; N, 12.97; S, 9.77; Cl, 11.25.

4-[(*Z*)-1-Carboxy-1-hydroxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**12h**).

Compound **11g** (8 g, 27 mmoles) was subjected to oxidation with permaleic acid according to the general procedure described for **10c**. The reaction mixture was extracted with aqueous sodium hydrogen carbonate, and the organic layer discarded. Acidification to *p*H 6 and back-extraction with ethyl acetate of the aqueous extracts, followed by removal of the solvent, left 4-[(*Z*)-1-carbethoxy-1-hydroxyimino]methyl-2-chloroacetamidothiazole *N*-oxide **12g** as a foam, 5.5 g (65%); nmr (hexadeuteriodimethylsulphoxide): δ 1.30 (t, 3H, CH_3), 4.30 (q, 2H, OCH_2), 4.49 (s, 2H, $ClCH_2$), 5.0 (bs, 2H, exch deuterium oxide), 7.40 (s, 1H, H-5) ppm. This material, without further purification, was dissolved in 99% ethanol (40 ml) and stirred for 2 hours at 25° with 35% aqueous sodium hydroxide (4.1 ml). The resulting precipitate was filtered, washed with ethanol and ethyl ether and dried, to give the sodium salt of the title product, 3 g (60%). Acidification afforded the free acid, mp 142-144° dec; ir (potassium bromide): 3650-3300, 3050, 3000-2200, 1700, 1550, 1300, 1185, 970, 950 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 4.31 (s, 2H, $ClCH_2$), 5.4 (bs, 3H, exch deuterium oxide), 7.10 (s, 1H, H-5) ppm.

4-[(*Z*)-1-Carboxy-1-trityloxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**12i**).

A solution of acetonyl ester **12m** (4.75 g, 8.2 mmoles) in tetrahydrofuran (200 ml) and water (60 ml) was treated dropwise at 0° under nitrogen with aqueous 0.1*N* sodium hydroxide (164 ml). Hydrochloric acid (1*N*) was added, the mixture concentrated *in vacuo* and then extracted with ethyl acetate. Evaporation of the solvent and trituration with ethyl ether left the title product as a white powder, 1.7 g (40%), mp 148-150° dec; ir (potassium bromide): 3440, 3100, 3050, 3030, 2920, 2850, 1700, 1545, 1280, 970 cm^{-1}.

Anal. Calcd. for $C_{26}H_{20}ClN_3O_5S$: C, 59.82; H, 3.86; N, 8.05. Found: C, 59.63; H, 3.95; N, 7.89.

4-[(*Z*)-1-Acetonyloxycarbonyl-1-trityloxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**12m**).

From **11m** as described for the preparation of **10c** a white powder was obtained (83%); ir (potassium bromide): 3440, 3050, 2920, 1750 sh, 1735, 1695, 1549, 1275, 1165, 960 cm^{-1}; nmr (deuteriochloroform): δ 2.18 (s, 3H, CH_3), 4.0 (s, 2H, $ClCH_2$), 4.93 (s, 2H, OCH_2), 6.98 (s, 1H, H-5), 7.35 (br s, 15H, Ph) ppm.

Anal. Calcd. for $C_{29}H_{24}ClN_3O_6S$: C, 60.25; H, 4.18; N, 7.27. Found: C, 60.31; H, 4.16; N, 7.12.

4-[(*Z*)-1-Carbethoxy-1-(2-diphenylmethoxycarbonyl-2-propoxyimino)]-methyl-2-chloroacetamidothiazole *N*-Oxide (**12q**).

From **11q** as described for the preparation of **10c**, **12q** was obtained in 76% yield, mp 168-172° dec; nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_3), 1.60 (s, 6H, CMe_2), 4.30 (s + q, 4H, CH_2Cl and OCH_2), 6.46 and 6.95 (each s, 1H, H-5 and $OCHPh_2$), 7.36 (m, 10H, Ph), 9.9 (broad band, 1H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_{26}H_{26}ClN_3O_7S$: C, 55.76; H, 4.68; N, 7.50. Found: C, 55.52; H, 4.72; N, 7.37.

4-[(*Z*)-1-(2-*t*-Butoxycarbonyl-2-propoxyimino)-1-carboxy]methyl-2-chloroacetamidothiazole *N*-Oxide (**12v**).

The acetonyl ester **11u** (4.2 g, 91 mmoles) was oxidized with permaleic acid according to the general methodology. After 2 days at 0°, the reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (17 g) and concentrated *in vacuo* to afford a foam, which upon trituration with ethyl ether-light petroleum gave 3.55 g of crude *N*-oxide **12u** as a yellowish powder. To this material, dissolved in tetrahydrofuran (200 ml) and water (65 ml), 0.1*N* aqueous sodium hydroxide (145 ml) was added within 20 minutes at 0° under stirring in a nitrogen atmosphere. After further 15 minutes, aqueous 1*N* hydrochloric acid (14.8 ml) was added, most of the organic solvent removed *in vacuo*, and the resulting aqueous solution extracted with ethyl acetate. Evaporation of the organic layer left a foam which dissolved in ethyl ether (50 ml); after few minutes, separation of the title product as a white crystalline powder occurred, 1.4 g (37% from **11u**), mp 144-145° dec; ir (potassium bromide): 3300-2300, 1740, 1725, 1690, 1570, 1300, 1150 cm^{-1}; nmr (hexadeuteriodimethylsulphoxide): δ 1.42 (s, 9H, *t*-Bu), 1.46 (s, 6H, CMe_2), 4.51 (s, 2H, $ClCH_2$), 7.48 (s, 1H, H-5), 7.2-8.3 (broad band, 2H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_{15}H_{20}ClN_3O_7S$: C, 42.71; H, 4.78; N, 9.96; Cl, 8.40; S, 7.60. Found: C, 42.46; H, 4.77; N, 9.78; Cl, 8.51; S, 7.62.

3-Acetyl-4-carbethoxymethyl-3-hydroxy-2-imino-2,3-dihydrothiazolinium Chloride (**13**).

A suspension of **5a** hydrochloride (0.5 g, 2.1 mmoles) in dichloromethane (2 ml) was treated with triethylamine (0.3 ml, 2.1 mmoles) and acetyl chloride (0.15 ml, 2.1 mmoles) under cooling, to obtain a clear solution which soon separated a white precipitate. After 20 minutes the solid was collected, rapidly washed with fresh dichloromethane and kept in a vacuum desiccator over phosphorus pentoxide; 0.37 g (63%), mp 135-136°; ir (nujol): 3150, 1825, 1750, 1625, 1570, 1190, 1140, 1040 cm^{-1}; nmr (deuteriotrifluoroacetic acid): δ 1.34 (s, 3H, CH_3), 2.51 (s, 3H, $COCH_3$), 3.72 (s, 2H, CH_2CO), 4.29 (q, 2H, OCH_2), 6.85 (s, 1H, H-5), 11.2 (s, 2H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_9H_{13}ClN_2O_4S$: C, 38.50; H, 4.66; N, 9.98. Found:

C, 38.45; H, 4.70; N, 9.91.

This compound was rapidly hydrolysed by the water contained in a commercial sample of hexadeuteriodimethylsulphoxide, affording the starting material and acetic acid (50% in the time of preparing an nmr sample and scanning); a trace of the acetamido derivative **5b** could be detected.

2-Chloroacetamido-4-[*(E)*-1-methoxyimino-1-diphenylmethoxycarbonyl]-methylthiazole (**14b**).

From **14a** as described for the preparation of **4g**, **14b** was obtained in 90% yield, mp 142-145° (from isopropyl ether); ir (potassium bromide): 3200, 3060, 3030, 1745, 1660, 1560, 1160, 1060, 1030 cm^{-1}; nmr (deuteriochloroform): δ 4.10 (s, 3H, OCH_3), 4.20 (s, 2H, $ClCH_2$), 7.05 (s, 1H, C*H*Ph_2), 7.30 (s, 10H, Ph), 7.85 (s, 1H, H-5), 9.5 (br s, 1H, exch deuterium oxide) ppm.

Anal. Calcd. for $C_{21}H_{18}ClN_3O_4S$: C, 56.82; H, 4.09; N, 9.47. Found: C, 56.97; H, 4.11; N, 9.40.

4-[*(E)*-1-Carboxy-1-methoxyimino]methyl-2-chloroacetamidothiazole *N*-Oxide (**15a**).

The *(Z)*-methoxyiminoacetic acid **10e** (2 g, 6.8 mmoles) was dissolved in tetrahydrofuran (250 ml) saturated with dry hydrogen chloride, the clear solution was let stand three hours and then evaporated *in vacuo* to afford the crude hydrochloride of the title product as a white foam. Water was added to obtain a solution which soon separated **15a** as a white powder, 1.3 g (65%), mp 169-171° dec; nmr (hexadeuteriodimethylsulphoxide): δ 4.07 (s, 2H, OCH_3), 4.51 (s, 2H, $ClCH_2$), 7.61 (s, 1H, H-5) ppm; the starting material **10e**, added into the same nmr tube, gave signals at 4.03, 4.53, 7.66 ppm.

Anal. Calcd. for $C_6H_6ClN_3O_5S$: C, 32.71; H, 2.74; N, 14.31. Found: C, 32.65; H, 2.86; N, 14.12.

4-Carbethoxymethylidene-3-hydroxy-2-iminothiazolidine (**16**) Hydrochloride.

A solution of **5a** hydrochloride (120 mg, 0.5 mmole) in ethanol (10 ml) was treated with ethanolic 0.01*N* sodium ethoxide (150 ml, 1.5 mmoles). After 30 minutes, ethanolic 0.2*N* hydrogen chloride (75 ml, 1.5 mmoles) was added and the solution evaporated *in vacuo* to leave a solid which was extracted with methanol-acetone. Crystals of **16** hydrochloride separated upon partial evaporation of the solvent, mp 119-120°; uv (ethanol): λ max 286 (ε = 17000); ir (potassium bromide): 3200, 2940, 2600, 1695, 1625, 1570, 1250, 1050 cm^{-1}; nmr (deuteriotrifluoroacetic acid): δ 1.41 (t, 3H, CH_3), 4.37 (q, 2H, OCH_2), 4.82 (d, 2H, J = 2 Hz, SCH_2C=CH), 6.17 (t, 1H, J = 2 Hz, SCH_2C=C*H*) ppm.

Anal. Calcd. for $C_7H_{11}ClN_2O_3S$: C, 35.22; H, 4.65; N, 11.74. Found: C, 35.15; H, 4.71; N, 11.69.

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[26] 2-Acylamino-3-methoxy-2,3-dihydrothiazolines, closer models to the 2-imino-3-hydroxy tautomer than the 3-alkyl derivatives, will be presented in a forthcoming paper; they do show the characteristic long-wavelength absorption (about 305 nm) anticipated by this analogy.

[27] No evidence for the presence of tautomeric mixtures in any of the compounds described in this paper could be drawn from nmr spectroscopy.

[28] By comparing the mesomeric stabilization of tautomers IV and

V (Scheme 2) in the two instances R = H and R = acyl it may be appreciated that canonical structure **b** gives more contribution to the *N*-oxide protomer IV in the first instance, and to the *N*-hydroxy protomer V in the second.

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