Structure and Reactivity of 2-Alkyl- and 2-Alkoxy-thiazolin-5-ones

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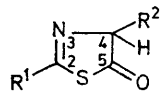
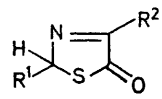
2-Alkylthiazolin-5-ones resemble the 2-aryl compounds in that they are readily enolisable and can easily be acylated on oxygen. In contrast 2-alkoxythiazolin-5-ones do not enolise in polar solvents and can only be acylated with the aid of a strong base such as sodium hydride.

THERE are four possible structures [(I)—(IV)] for the 2,4-disubstituted thiazolin-5-ones (referred to throughout the text simply as thiazolinones). Examination of the



(I)



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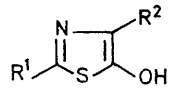

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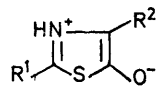


(IV)

i.r. spectra [1] of 4-alkyl-2-phenylthiazolinones has shown that these compounds exist in a keto form [(I) or (II)] in solvents such as chloroform or in the undiluted state, but are enolised to a great extent in polar solvents such as dimethyl sulphoxide (DMSO). The salts of these compounds appear to exist in an enol form [protonated (III)], since they show an OH band in the i.r. spectrum.[1]

The ^{1}H n.m.r. spectra of certain 4-alkyl-2-phenylthiazolinones have been examined.[2] The spectrum of 4-isopropyl-2-phenylthiazolinone indicates that the two methyl groups of the isopropyl group are non-equivalent, since their signals appear as two separate doublets. As the signals do not coalesce on heating this must be due to fundamental asymmetry, not to restricted rotation.[2] The structure of this compound must therefore be (I) (Δ^2-form) rather than (II) (Δ^3-form), since C-4 is asymmetric. The asymmetry is lost on salt formation.

We have studied the n.m.r. spectra and chemical properties of 2-alkyl- and 2-alkoxy-thiazolinones in order to determine the structures of these compounds. 2,4-Dialkylthiazolinones resemble 4-alkyl-2-arylthiazolinones, but the alkoxy-compounds exhibit unexpected properties.

2,4-Dialkylthiazolinones were made by cyclisation of *N*-thioacylamino-acids with phosphorus tribromide [3] or dicyclohexylcarbodi-imide.[4] As in the case of 2-phenylthiazolinones, treatment with acetic anhydride yields the thiazolyl acetate.[3] The thiazolinones are stable, distillable liquids, provided that a 4-substituent is present.

The i.r. spectra of the compounds indicate that they exist in a keto form [$\nu_{max.}$ *ca.* 1730 (C=O) and *ca.* 1635 cm^{-1} (C=N)], and a comparison of the u.v. spectrum (cyclohexane) of 4-isobutyl-2-methylthiazolinone [$\lambda_{max.}$ 245 nm (ε 1·6 × 10^3)] with that of 2,4,4-trimethylthiazolinone [$\lambda_{max.}$ 242 nm (ε 1·67 × 10^3)], which can only exist as structure (I), strongly supports this idea.

The ^{1}H n.m.r. spectrum of 4-isopropyl-2-methylthiazolinone in $CDCl_3$ (Figure 1) confirms this view. The isopropyl methyl groups appear as a pair of doublets (δ 0·82, 0·89, 1·14, and 1·21 p.p.m.) as they do in the spectrum of the 2-phenyl analogue.[2] The isopropyl methine proton signal is a doublet of septets (centred at about δ 2·38 p.p.m.) and the 2-methyl signal is a doublet (δ 2·44 and 2·65 p.p.m.). Addition of D_2O to the $CDCl_3$ solution (Figure 2) causes almost complete disappearance of the 4-H signal, simplifies the isopropyl methine signal, and reduces the 2-methyl signal to a singlet. The 4-proton is thus shown to be readily exchangeable and also to be coupled across five bonds with the 2-methyl protons. Such long-range coupling has already been reported for thiophens.[5] The non-equivalence of the isopropyl methyl groups is attributed to the asymmetry at C-4, but we have not investigated the effect of temperature change.

[1] W. Steglich, G. Höfle, L. Wilschowitz, and G. C. Barrett, *Tetrahedron Letters*, 1970, 169.
[2] E. Glotter and M. D. Bachi, *Israel J. Chem.*, 1970, **8**, 633.
[3] G. C. Barrett and A. R. Chapman, *Chem. Comm.*, 1968, 335.
[4] G. C. Barrett, *J. Chem. Soc.* (*C*), 1971, 1380.
[5] A. B. Hörnfeldt, *Svensk kem. Tidskr.*, 1968, **80**, 343.

The spectrum in [$^2H_6$]DMSO (Figure 3) indicates that the compound is 35% enolised (comparison of 2-methyl signals); a second spectrum, that of the enol form, is superimposed upon the first. A similar experiment

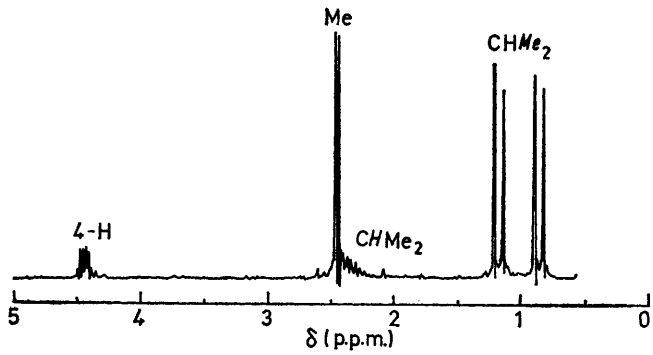


FIGURE 1

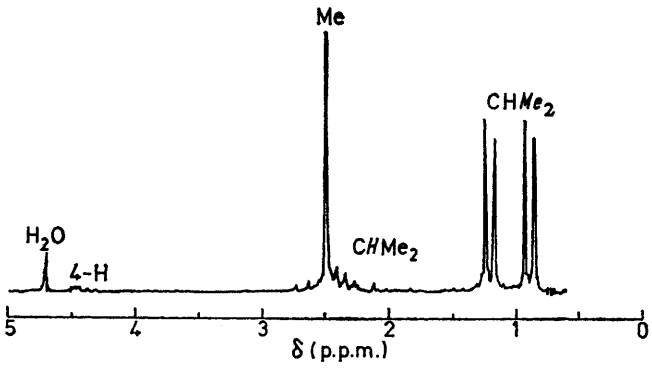


FIGURE 2

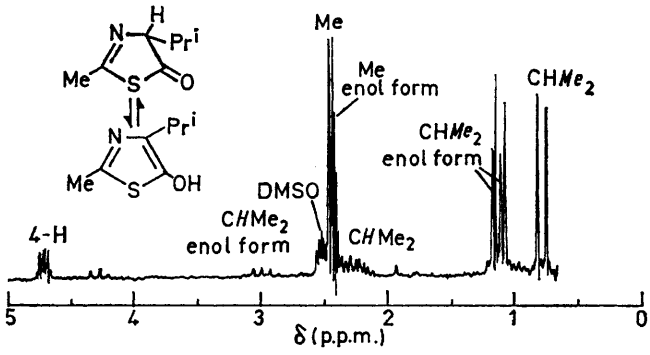
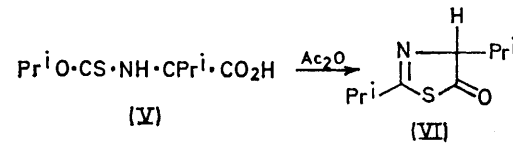


FIGURE 3

with 4-isopropyl-2-phenylthiazolin-5-one showed 80% enolisation.

A consequence of the ease of formation of an anion from 2,4-dialkylthiazolinones is that these compounds are readily acylated under mild conditions. It has already been noticed[3] that treatment of *N*-thioacylamino-acids with acetic anhydride leads directly to the thiazolyl acetate without isolation of an intermediate thiazolinone. Acylation with even a weak acylating agent such as dimethylcarbamoyl chloride in pyridine–benzene proceeds rapidly and exothermically. The product of carbamoylation shows a carbonyl peak at 1745 cm^{-1} in the i.r. spectrum (carbamate), a convenient demonstration that *O*-acylation has taken place. *C*-Acylation would yield an amide having a carbonyl peak in the 1690 cm^{-1} region. The n.m.r. spectrum of the carbamoylated compound shows only one doublet for the isopropyl methyl groups and a singlet for the 2-methyl group.

If the 2-alkyl group is replaced by a 2-alkoxy-group the properties of the thiazolinone are markedly altered. Treatment of *O*-isopropyl *N*-(1-carboxy-2-methylpropyl)-thiocarbamate (V) with acetic anhydride–triethylamine yields the same product as does treatment with dicyclohexylcarbodi-imide (DCC) in tetrahydrofuran, 2-isopropoxy-4-isopropylthiazolinone (VI).



(V) (VI)

The thiazolinone could not be acylated by heating with acetic anhydride–sulphuric acid, with dimethylcarbamoyl chloride in pyridine, or with methyl isocyanate in the presence of triethylamine. The only successful acylation was achieved by generation of the anion with sodium hydride in tetrahydrofuran before treatment with dimethylcarbamoyl chloride. This gave a 20% yield of an *O*-carbamoyl product.

It is thus apparent that the 4-proton in this compound is much less acidic than the 4-proton of 2,4-dialkylthiazolinones. The n.m.r. spectra confirm this. Not only does addition of D_2O not affect the 4-H signal, but the spectrum of a solution in [$^2H_6$]DMSO is identical in form with that of a solution in $CDCl_3$.

A demonstration of the lack of acidity of the 4-proton is the stability of 2-isopropoxythiazolinone unsubstituted in the 4-position. This material may be distilled and kept unchanged for many months. On the other hand, 2-methylthiazolinone is stable only as the hydrochloride or in dilute solution at about 0 °C. 2-Phenylthiazolinone, although isolable, is unstable.[6] Probably the thiazole anion plays a role in the polymerisation and decomposition of these compounds.

The low acidity of the 4-proton of 2-alkoxythiazolinones should confer optical stability upon these compounds, a property not characteristic of 2-arylthiazolinones.[4] Also, since 2-alkoxythiazolinones derived from glycine [*e.g.* (I; $R^1 = Pr^iO$, $R^2 = H$)] are very stable (insofar as polymerisation is concerned) they might be useful in the synthesis of peptides containing glycine, as other thiazolinones are used to introduce other amino-acids.[4]

With regard to optical stability, it is curious that an intermediate 2-benzyloxythiazolinone is invoked to explain the racemisation of the phenylalanine derivative

[6] H. Muxfeldt, J. Behling, G. Grethe, and W. Rogalski, *J. Amer. Chem. Soc.*, 1967, **89**, 4991.

(VII) on treatment with dicyclohexylcarbodi-imide and *p*-nitrophenol.[7] The amino-acid derivative itself is as likely to racemise, as is the thiazolinone, under the influence of various basic products and by-products formed in the course of the reaction. Treatment of the preformed optically active thiazolinone with DCC and nitrophenol would settle the point.

EXPERIMENTAL

U.v. spectra were measured with a Unicam SP 800C spectrophotometer, i.r. spectra with a Perkin-Elmer Infracord 257 and ^{1}H n.m.r. spectra with a Varian HA100 spectrometer for 0·5M-solutions in dimethyl sulphoxide or deuteriochloroform.

$$PhCH_2\cdot O\cdot CS\cdot NH\cdot CH(CH_2Ph)\cdot CO_2H \xrightarrow[p\text{-}NO_2\cdot C_6H_4\cdot OH]{DCC} PhCH_2\cdot O\cdot CS\cdot NH\cdot CH(CH_2Ph)\cdot CO_2\cdot C_6H_4\cdot NO_2\text{-}p$$

Optically active (VII) — Inactive

Merck plates (GF 254) were used throughout for t.l.c. Crosfield M60 silica gel was used for column chromatography.

Thionoesters were made by treatment of imidates with hydrogen sulphide.[8]

O-Isopropyl N-(1-Carboxy-2-methylpropyl)thiocarbamate.—*S*-Methyl *O*-isopropyl xanthate (25·7 g, 0·17 mol) in dioxan (100 ml) was added to a solution of valine (20 g, 0·17 mol) in 3N-sodium hydroxide (100 ml) and the mixture was stirred vigorously for 40 h. Previous experience had shown that this period was necessary for virtually complete reaction. The homogeneous mixture was shaken with ether (2 × 250 ml), from which starting material (7 g) was later recovered, and the aqueous layer was cooled to 5° and acidified with concentrated hydrochloric acid. Solid which precipitated was separated by shaking with ether followed by the usual work-up procedure to give a crystalline solid (30 g, 100% based on unrecovered xanthate). A portion was chromatographed on silica gel in chloroform to give the pure *thiocarbamate*, m.p. 84° (Found: C, 49·5; H, 8·1; N, 6·3; S, 14·5. $C_9H_{17}NO_3S$ requires C, 49·3; H, 7·8; N, 6·4; S, 14·6%).

Similarly were prepared *O-isopropyl N-carboxymethylthiocarbamate*, m.p. 130° (Found: C, 40·7; H, 6·0; N, 7·7. $C_6H_{11}NO_3S$ requires C, 40·7; H, 6·3; N, 7·7%), from isopropyl methyl xanthate and glycine, and *N-thioacetylvaline*, m.p. 109—110° (Found: C, 48·3; H, 7·2; N, 8·2. $C_7H_{13}NO_2S$ requires C, 48·0; H, 7·5; N, 8·0%), from *O*-ethyl thioacetate and valine.

Thiazolin-5-ones.—The foregoing amino-acid derivatives were cyclised with dicyclohexylcarbodi-imide in tetrahydrofuran [4] to give, respectively *2-isopropoxy-4-isopropylthiazolin-5-one*, b.p. 59° at 0·3 mmHg (Found: C, 54·0; H, 7·4; N, 7·4; S, 15·5. $C_9H_{15}NO_2S$ requires C, 53·7; H, 7·5; N, 7·0; S, 15·9%); *2-isopropoxythiazolin-5-one*, b.p. 42—44° at 1 mmHg (Found: C, 45·1; H, 5·8; N, 8·4. $C_6H_9NO_2S$ requires C, 45·2; H, 5·7; N, 8·8%), and *4-isopropyl-2-methylthiazolin-5-one*, b.p. 40° at 1 mmHg (Found: C, 53·3; H, 7·3; N, 8·7. $C_7H_{22}NOS$ requires C, 53·5; H, 7·1; N, 8·9%). All three compounds showed $\nu_{max.}$ (film) 1735—1740 (C=O) and 1635—1640 cm^{-1} (C=N). ^{1}H N.m.r. spectra ($CDCl_3$) are as follows: 2-isopropoxy-4-isopropyl, δ 0·84, 0·91, 1·08, and 1·15 (CH*Me*$_2$), 1·34, 1·37, 1·40, and 1·43 (O·CH*Me*$_2$) (restricted rotation), 2·15, 2·19, 2·22, 2·26, 2·29, 2·32, 2·36, 2·40, 2·425, and 2·465 (doublet of septets, ten lines visible, C*H*Me$_2$), 4·385 and 4·42 (4-H), and septet centred at 6·5 (O·C*H*Me$_2$); 2-isopropoxy, δ 1·33 and 1·39 (O·CH*Me*$_2$), 4·48 (4-H), and 5·1, 5·16, 5·22, 5·28, 5·34, 5·4, and 5·46 (O·C*H*Me$_2$); 4-isopropyl-2-methyl, δ 0·82, 0·89, 1·14, and 1·21 (CH*Me*$_2$), 2·15, 2·20, 2·215, 2·25, 2·28, 2·32, 2 35, 2 39, and 2 52 (doublet of septets partly obscured by 2-Me, C*H*Me$_2$), 2·43 and 2·45 (2Me), and 4·38, 4·40, 4·415, 4·425, 4·44, 4·445sh, 4·46, and 4·485 p.p.m. (4-H doublet of quartets partly overlapping).

4-Isopropyl-2-methylthiazol-5-yl Dimethylcarbamate.—The thiazolinone (1 g, 6·4 mmol) was dissolved in dry pyridine (5 ml) and dimethylcarbamoyl chloride (0 8 g, 7·4 mmol) was added in one portion. After 16 h at room temperature, the mixture was diluted with ether and washed thoroughly with water. The ether layer was dried ($MgSO_4$) and evaporated leaving a brown oil (1·4 g, 96%). A sample was purified on a column of silica gel in benzene–acetone to give the pure *dimethylcarbamate* as a yellow oil (Found: C, 52·2; H, 7·1; N, 12·5. $C_{10}H_{16}N_2O_2S$ requires C, 52·6; H, 7·1; N, 12·3%).

2-Isopropoxy-4-isopropylthiazol-5-yl Dimethylcarbamate.—Sodium hydride (50% dispersion in oil; 0·48 g, 0·01 mol) was added in portions to a cooled (0—5°) and stirred solution of 2-isopropoxy-4-isopropylthiazolin-5-one (2 g, 0·01 mol) in hexamethylphosphoramide. Dimethylcarbamoyl chloride (2·14 g, 0·02 mol) was then added in one portion. Stirring was continued overnight and the mixture was poured into 2% hydrochloric acid and extracted with ether. The crude product obtained by evaporation of the dried ether solution was combined with that from another similar reaction and chromatographed on silica gel in light petroleum–ethyl acetate to give the pure *dimethylcarbamate* (1·3 g, 24%) as a yellow oil (Found: C, 52·4; H, 7·6; N, 10·5. $C_{12}H_{20}N_2O_2S$ requires C, 52·3; H, 7·4; N, 10·3%).

[2/746 *Received*, 29*th March*, 1972]

[7] I. Z. Siemion, D. Konopinska, and A. Szugaj, *Roczniki Chem.*, 1969, **43**, 989.

[8] J. B. Jepson, A. Lawson, and V. D. Lawton, *J. Chem. Soc.*, 1955, 1791.