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ISOTHIAZOLE CHEMISTRY—VIII

BASE-CATALYSED DIMERIZATION OF N-ALKYL-3-ISOTHIAZOLONES A SYNTHESIS OF 2,4-BISMETHYLENE-1,3-DITHIETANES

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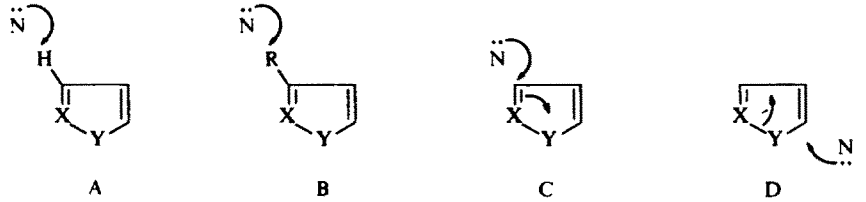
Abstract—N-Alkyl-3-isothiazolones bearing a free 5-position are readily dimerized by base to 2,4-bismethylene-1,3-dithietanes. The dimerization mechanism involves attack by the 5-anion on the S—N bond of a second molecule. The action of base on the corresponding N-acyl-3-isothiazolones affords only polymeric material, in a reaction which is evidently concerted with 5-anion formation. The potential role of thioketene intermediates is discussed.

INTRODUCTION

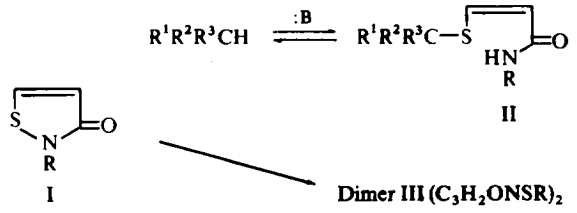
5-MEMBERED adjacent-atom heterocycles undergo a variety of ring cleavage reactions when subjected to the action of bases and nucleophiles. These may result in stable molecules[1,2] or in highly reactive intermediates which undergo subsequent transformations;[3,4] detailed investigations of the mechanisms have been established in some cases, such as the isoxazolium salts[3] and the 1,2-dithiolium salts.[5] In broad outline there would appear to be four basic mechanisms operative; (A) Proton abstraction adjacent to heteroatom[3,6] (which will be favoured especially where anion stabilization is possible) (B) Nucleophilic displacement of the heterocycle from a substituent group[7] ((A) is the special case where the substituent is H). (C) Nucleophilic addition to a C=X or C=Y bond[5,8] (D) Direct nucleophilic attack on the X—Y bond.[9]

Examples of each type are known, and it is to be expected that competition between the modes of reaction will be encountered, perhaps with relatively trivial alteration in conditions. The S—N bond cleavage of N-alkyl-3-isothiazolones by carbanions apparently represents such a case, the mechanisms A and D taking precedence in accord with the nature of the carbanion employed. We have previously reported[10] the mechanism of S—N bond cleavage in 3-hydroxyisothiazole by cyanide ion—a simple carbon nucleophile and have subsequently[11] extended this work to the action of a range of carbanions on N-ethyl-3-isothiazolone (I, R = Et). The products (II) were stable to the basic reaction conditions providing that one of R_1, R_2, R_3 = H, but otherwise reverted to starting materials. When this happened, a competing side reaction led to the formation of a highly insoluble dimer III. We were readily able



to show that III resulted purely from the action of base on I, the same product being formed in ethanolic ethoxide alone, or, more slowly, in dimethylformamide/sodium hydride. A series of dimers could be prepared from I (R = Me, Et, $CH_2\phi$) and its 4-bromo- and 4-deuterioderivatives (R = Et).

Similar formation of dimers have been reported from the action of bases on 5-phenyl-N-methylisoxazolium salts[12] and 4-phenyl-1,2,3-thiadiazole[13] (after N_2 loss). In both cases it seemed likely that the dimers arose by coupling of the reactive intermediates generated.



Structures of the dimers from N-alkyl-3-isothiazolones

The dimer from N-ethyl-3-isothiazolone was obtained as a highly insoluble, pale cream, microcrystalline powder, which could only be purified by repeated washing with a range of solvents. The IR spectrum showed bands at 3270 (NH), 1645 (C=O) and 1625 (C=C) cm^{-1}, characteristic of the α,β-unsaturated secondary amide function

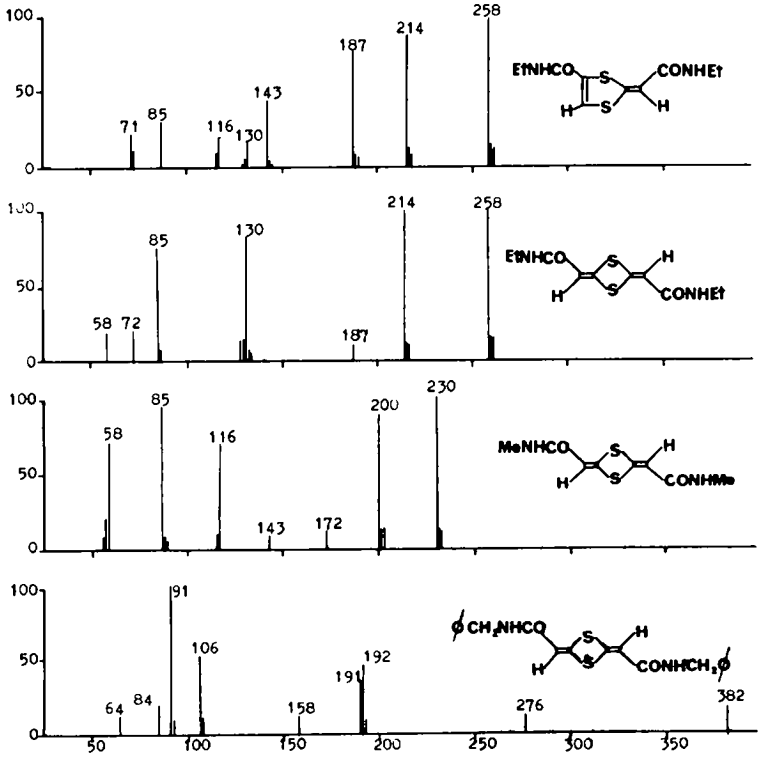
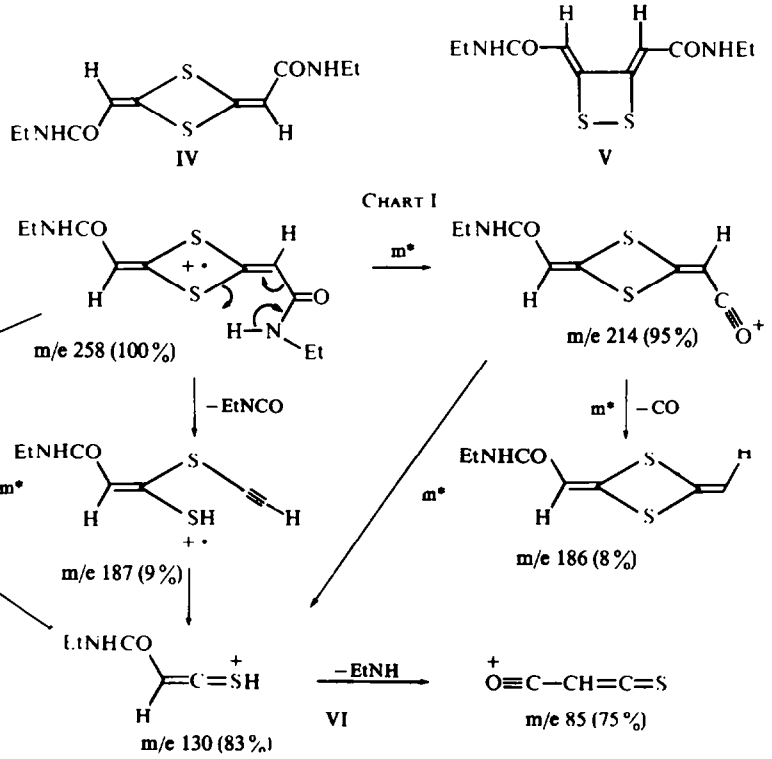


FIG. 1 Mass spectra of 2,4-bismethylene-1,3-dithietanes (70 eV. Direct insertion probe).

present in the alkylmercaptoacrylamides II (R = Et), but was otherwise unrevealing. The presence of this structural feature was confirmed by the NMR spectrum (accumulated by computer, due to low solubility) which showed signals for two magnetically equivalent CO—NH—Et groups. The only other signal observed was a two-proton singlet at τ 3·80, a value corresponding to that observed in the *cis*-3-alkylmercaptoacrylamides II for the α-proton. The total proton count and the absence of vinylic splitting confirmed that there was no β −H on the acrylamide systems, while the complete equivalence of the chemical shifts for each type of proton required that a high degree of symmetry be present. The only two structures consistent with these data were those of the desaurin IV and the isomeric 3,4-bismethylene-1,2-dithietane V.* A decision between these two structures in favour of IV was reached by examination of the mass spectrum, and is supported by consideration of the mechanism of formation.

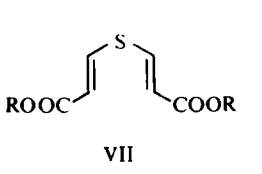
The mass spectra of the dimers are shown in Fig. 1, and the fragmentation pattern for IV is shown in Chart I. The absence of ions showing loss of S or S_2 was taken as evidence against the 1,2-dithietane structure V. The mass spectra of several desaurins have recently been discussed by Yates, Lynch and Weiler.[14] Allowing for the fragmentation characteristics of the N-ethylcarboxamido- group, the results presented here are in excellent agreement with those reported. The ion structures presented in Chart I are purely rationalisations, and rearranged structures may well apply.



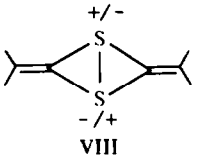
* The stereochemistry implicit in IV and V is not, of course, mandatory. The groups attached to each exocyclic double bond can be interchanged, provided that either a plane or a twofold axis of symmetry is present.

The major fragmentation pathway observed is de-dimerization with H-transfer to give the ion *m/e* 130 (VI), although a certain amount of direct de-dimerization (*m/e* 129—not due to M^{++}) is observed. A comparison with the spectrum of the 4-deuterio-isomer shows that this H-transfer does not arise from the exocyclic methylene group, as was proposed in analogous cases;[14] It is presumed to arise in IV from the sterically more accessible NH of the amide function, as shown in Chart I.

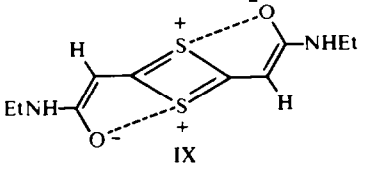
The 2,4-bismethylene-1,3-dithietane system has been known since 1877,[15] although the correct structure was not proposed until 1890,[16] and subsequently established beyond doubt by chemical degradation[17] and by X-ray analysis.[18] The literature reveals no systematic study of the chemistry of the system, although UV data have been recorded for a number of compounds. The dimer III (R = Et) shows a substantial bathychromic shift and increase in intensity (λ_{max} 293 sh, 306 (36600), 325 (30950) mμ compared to the *cis*-3-mercaptoacrylamides II (λ_{max} 275 (14000) mμ) and the β,β'-thiodiacrylic ester VII.[19] This effect is consistent with the proposal[20] of dipolar contributions, involving transannular S—S overlap (VIII) as well as the normal delocalization effects (IX). Conjugation through the 3p orbitals of sulphur is favoured by the planarity[18] of the system, and X-ray analysis[18] shows that S_1—S_3 and C_2—C_4 distances are indeed substantially less than the sums of the van der Waals radii. Similar arguments involving delocalization through sulphur have been suggested by Kirby[21] to explain the increased conjugation observed in the series X—XI—XII.



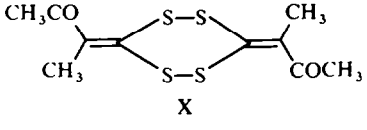
VII



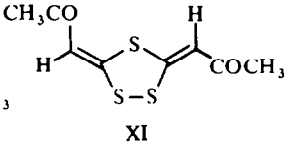
VIII



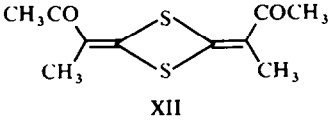
IX



X

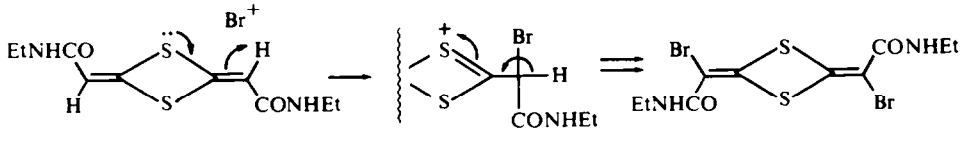


XI



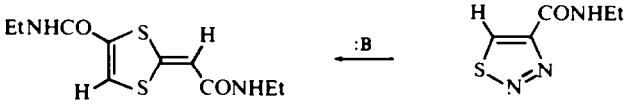
XII

Chemical degradation of the dimer from I was unrewarding, the system showing the inertness to acid and base which had been remarked upon by earlier workers. Reduction by zinc and alkali[17] was ineffective in this case; bromination led only to electrophilic substitution, presumably *via* an addition-elimination mechanism as illustrated. The product was independently prepared by base-catalysed dimerization of 4-bromo-N-3-isothiazolone.



Although the structural assignment IV appeared quite sound, the main evidence on which it rested was the NMR spectrum (showing a 2H-singlet) and the mass spec-

trum (showing mainly fragmentation due to —CONHEt, and dedimerization). Previous experiences with the mass spectra of isomeric molecules[22] led us to prepare the dimer XIII, isomeric with IV, by the method of Raap.[13] The mass spectrum (Fig. 1) was quite distinct from that of IV, and, moreover, the NMR spectrum (Experimental) showed two magnetically nonequivalent protons, as would be expected.

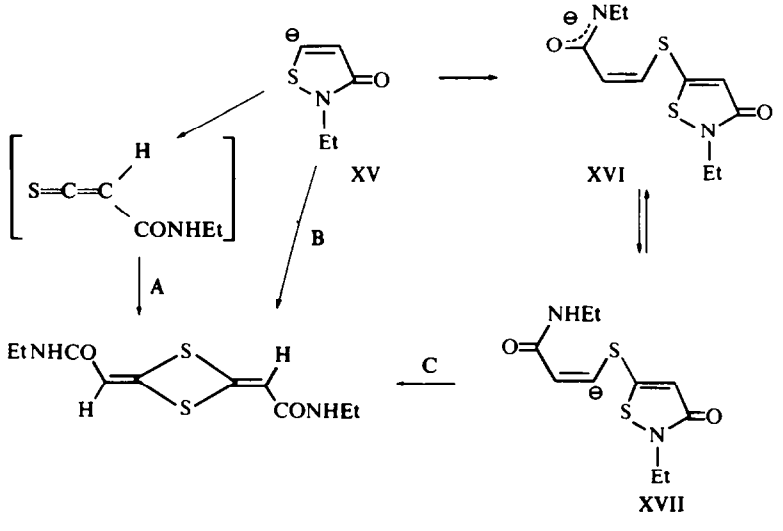


IIIX

Mechanism of dimerization

The formation of 2,4-bismethylene-1,3-dithietanes (IV) provides grounds for some interesting speculation as to the mechanism. Since the reaction does not occur in 5-substituted derivatives (Me, ϕ) of I, and takes place in aprotic media as well as in solvents capable of nucleophilic addition (cf. mechanisms C and D), it is evident that the reaction is initiated through the 5-anion (mechanism A). The acidity of H adjacent to heteroatoms in such systems is well documented,[23,24] and we were able to observe base catalysed exchange in 5-deuterio-N-ethyl-3-isothiazolone as an equilibrium process preceding dimer formation. Further, dimerisation of 4-deuterio-N-ethyl-3-isothiazolone gave a product in which the NMR signal at τ3·80 was absent, establishing that the protons responsible for this signal were originally H_4 in the starting material, as required by IV.

CHART II



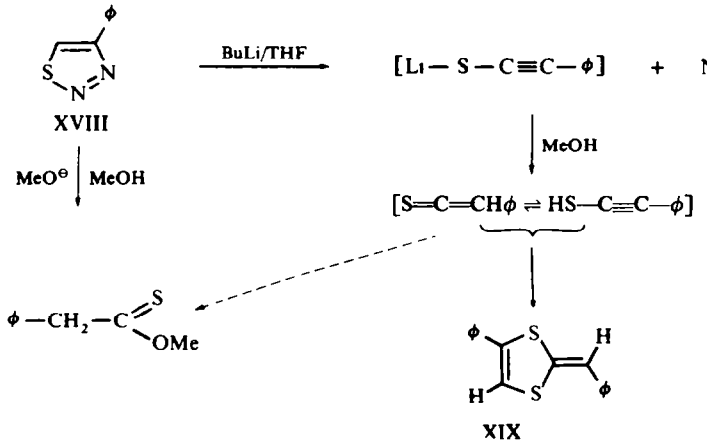
There are three plausible mechanisms which can be proposed, all involving the 5-anion XV, outlined in Chart II.

Route B (direct dimerization of the 5-anion) and Route C (attack of the 5-anion of N-ethyl-3-isothiazolone) should be distinguishable by the rate dependence on base

concentration. This proved to be linear, as required by Route C, over several half-lives. There was no observed buildup of intermediates. It might be expected that some protonation of XVI could occur. However, we have already shown[1] that attack on the S—N bond by a tertiary carbanion (XV in this case) is rapidly reversible, the equilibrium lying well over to the reactant (XV) side. Thus XVI would be expected to react further, or revert to starting materials, during the course of the reaction.

Route A (intramolecular formation of the thioketene XIV, followed by dimerization) could also be consistent with the rate data obtained. Dickore and Wegler[25] have reported dimerization of thioketenes to 2,4-bismethylene-1,3-dithietanes, although the stereochemistry of the reaction was not elucidated.* Thioketenes are known only as unstable, highly reactive compounds, although they have been proposed as reaction intermediates in a number of cases. Arens *et al.* have recorded the formation of dithioesters[29] R—CH_2—CSSR from alkynethiolates, and 5-alkyl-1,2,3,4-thiatriazoles[30] from 1-acetylthioalkynes and azide ion. The reaction mode of the (presumed) thioketenes in these transformations is parallel to that of the ketenes themselves, and this tends to be confirmed by later work.[31–33] On this basis we would expect the thioketene XIV to react preferentially with the solvent in the alcohol/alkoxide systems used to generate IV.

CHART III



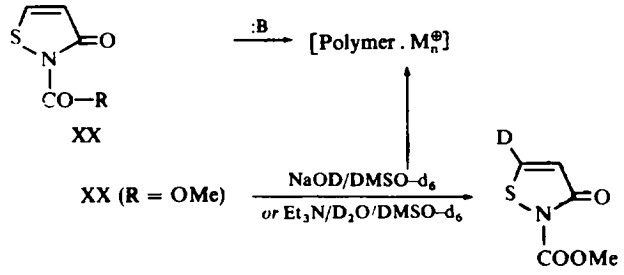
Raap[13,33] has recently shown that 2,α-diphenyl-1,4-dithiafulvene[34] (XIX) results from the action of base on 4-phenyl-1,2,3-thiadiazole (XVIII) as shown in Chart III. This report led us to examine the action of base on N-ethyl-3-isothiazolone specifically for evidence of a thioketene intermediate. A careful search revealed no trace of thioneesters, and in the presence of amines we were also unable to find any trace of thioamides. The dimer produced in these reactions was not the same as that (XIII *vide. supra*) formed from the corresponding thiadiazole. Thus although a thioketene intermediate offers a logical explanation for the reactions outlined in Chart IV, we feel confident in rejecting it for the formation of dimers from N-alkyl-3-isothiazolones.

* The stereochemistry of IV is based on the requirements of Route A, but experimentally unsupported. The NMR data tends to indicate only one isomer present, but we do not consider this compelling evidence in the absence of standard comparison compounds. There is, moreover, no reason to assume that dimerization of XIV would necessarily produce a mixture of stereoisomers.

In this case we propose attack by the 5-anion XV upon a neutral molecule, a normal nucleophilic cleavage of the S—N bond for which we have ample precedent.[9–11]

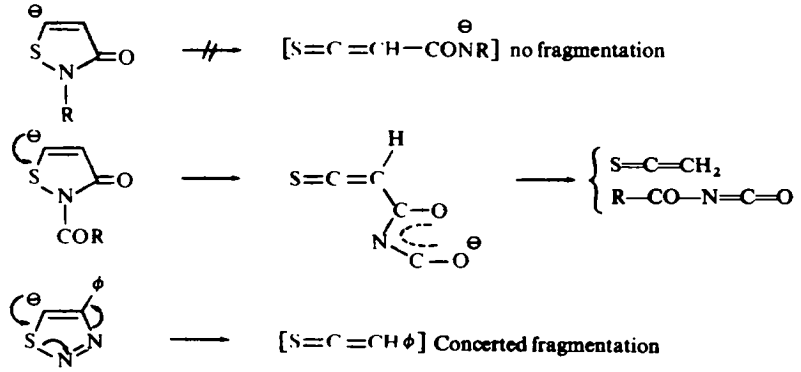
Polymerization of N-*acyl*-3-*isothiazolones*

The ease of the dithietane synthesis led us to extend the base-catalysed dimerization to the N-acyl-3-isothiazolones, since this would open a route to known dithietanes by further transformations. The reaction was of necessity carried out in aprotic media, to avoid solvolysis of the reactants. In contrast to the smooth reactions recorded above, the N-acyl-3-isothiazolones XX (R = H, Me, Et, —OMe, $CO(CH_2)_2$ COOEt) uniformly precipitated red-brown, polymeric solids as the metal salts. Recovery of



the polymer from the salts indicated no overall pattern of reaction. Where there was no potential carbanion site in R (R = H, OEt), analytical data was close to that of the starting material (i.e. direct polymerization). In other cases there was direct evidence for further condensations involving —CO and —COOR groups in the acyl chain.

As before, the reaction was completely suppressed by substituents in the 5-position (5-Me-XX, R = OMe), implicating the 5-anion of XX. The usual D-exchange experiments were carried out, using N-carbomethoxy-3-isothiazolone (XX, R = OMe) and both $Et_3N/DMSO/D_2O$ and NaOD/DMSO-d_6. (The former medium was ineffective in D-exchange or dimerization on N-ethyl-3-isothiazolone; the latter effected both). With both reagents polymerization occurred relatively fast, as evidenced by loss of the signals for *both* H_4 and H_5, with concomitant colour development. There was no evidence for H_5-exchange, however, and we conclude that polymerization is concerted with 5-anion generation in this case. The results of exchange are compatible with the comparison between isothiazoles and isothiazolium salts[23,35] and confirm the greater tendency towards ring cleavage or fragmentation which would be expected from the electron-withdrawing effect of the acyl-group.



In the absence of any firm structure for the products, speculation as to the mechanism is hardly warranted; a thioketene-type ring cleavage is quite attractive, and could also lead to fragmentation, as indicated. Huisgen, Sauer and Sturm[36] have recorded spontaneous ring fragmentation of 5-substituted tetrazoles on acylation; in this case the situation is no doubt assisted by the excellent leaving group incorporated as part of the ring (cf. 1,2,3-thiadiazoles).

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Unicam SP200 spectrophotometer, and refer to Nujol mulls unless otherwise indicated. UV spectra were measured on a Unicam SP800 in 90% EtOH; extinction coefficients are given in parentheses where measured. NMR Spectra were measured at 60 MHz on a Perkin–Elmer R.10 spectrometer, and are quoted as τ-values throughout, with coupling constants in Hz. Mass spectra were recorded on an AEI MS 902 spectrometer. Microanalyses were carried out by the Australian Microanalytical Service at the University of Melbourne.

2,4-Bis(N-ethylcarboxamido)methylene-1,3-dithietane

N-Ethyl-3-isothiazolone (0·65 gm, 0·005 mole) was stirred under N_2 at room temp with a soln of NaOEt in EtOH, (from 0·11 gm Na in 50 ml dry EtOH). Precipitation of the product commenced within min, and was complete in 30 min. Filtration and washing with hot EtOH, benzene and DMSO afforded the dithietane in 85% yield as a colourless microcrystalline powder m.p. 268–270° dec. Physical and analytical data have been reported previously.[11]

The same product was obtained by similar treatment of N-ethyl-3-isothiazolone with sodium hydride in dimethylformamide,[11] potassium triphenylmethide in dimethoxyethane,[11] 5N NaOH or sodamide in liquid ammonia at −78°.

2,4-Bis(α-deuterio-α-N-ethylcarboxamido)methylene-1,3-dithietane

4-Deuterio-N-ethyl-3-isothiazolone was prepared as described previously[9] and subjected to the same reaction as described above. The resultant 1,3-dithietane was identical in all respects, except that the molecular ion occurred at *m/e* 260 (as required for a dideuterio derivative), and the NMR spectrum showed complete absence of the signal at 3·80.

2,4-Bis(N-methylcarboxamido)methylene-1,3-dithietane

N-Methyl-3-isothiazolone[9] (0·57 gm, 0·005 mole) was stirred under N_2 for 16 hr in t-BuOH (50 ml) containing, t-BuOK (0·56 gm, 0·005 mole). The product was filtered and washed with hot EtOH and benzene, affording 0·50 gm (88%) pale cream powder m.p. 250°. (Found: C, 41·4; H, 4·6; N, 11·9; S, 27·7. $C_8H_{10}O_2N_2S_2$ requires: C, 41·7; H, 4·4; N, 12·2; S, 27·8%); IR: ν_{max} 3200, 1640 cm^{-1}; UV: λ_{max} 293 sh, 305 (35500), 322 (30420) mμ.

2,4-Bis(N-benzylcarboxamido)methylene-1,3-dithietane

N-Benzyle-3-isothiazolone (0·57 gm, 0·003 mole; prepared by benzylation of 3-hydroxyisothiazole in acetonitrile over K_2CO_3) was stirred in 5N NaOH for 2 hr at 20° under N_2 and the insoluble solid (0·50 gm, 88%) recrystallized from DMSO to give pale yellow prisms m.p. 270° dec. (Found: C, 62·2; H, 5·1; N, 7·3; S, 16·6. $C_{20}H_{18}O_2N_2S_2$ requires: C, 62·8; H, 4·8; N, 7·3; S, 16·7%); IR: ν_{max} 3280, 1640 cm^{-1}; UV: λ_{max} 295 sh, 309, 325 mμ; NMR (d6-DMSO): 1·4 (br.t., 2H), 2·71 (m, 10H), 3·7 (s, 2H), 5·65 (br.d., 4H).

2,4-Bis(α-bromo-α-N-ethylcarboxamido)methylene-1,3-dithietane

(a) The dithietane (1·03 gm, 0·004 mole) was refluxed 1 hr in $CHCl_3$ (50 ml) containing Br_2 (1·44 gm, 0·009 mole), and the product was recrystallized from DMSO by addition of water to give 1·4 gm (87%) colourless microcrystalline powder m.p. 250–254° dec. (Found: C, 28·9; H, 2·9; N, 6·6; S, 15·5; Br, 38·4. $C_{10}H_{12}O_2N_2S_2Br_2$ requires: C, 28·8; H, 2·9; N, 6·7; S, 15·4; Br, 38·4%); IR: ν_{max} 3380, 1670 cm^{-1}; UV: λ_{max} 310 sh, 325 (38400), 340 (38750) mμ; NMR (d_6-DMSO): 1·7 (broad t, 2H), 6·8 (m, 4H), 8·96 (t, 6H); *mass spectrum.* molecular ion at *m/e* 414, 416, 418 in the ratio 1:2:1.

(b) N-Ethyl-3-isothiazolone (0·516 gm, 0·004 mole) in AcOH (17 M, 10 ml) was treated dropwise with

Br_2 (0·80 gm, 0·005 mole) stirred for 1 hr, poured into water and continuously extracted with ether. Evaporation and sublimation at 50°/0·1 mm afforded *4-bromo-N-ethyl-3-isothiazolone* (0·76 gm, 90%) as a hygroscopic cream solid m.p. 39–42°; IR: ν_{max} 1610 br cm^{-1}; UV: λ_{max} 283 (7550) mμ; NMR ($CDCl_3$); 1·67 (s, H), 6·09 (q, 2H), 8·65 (t, 3H); *mass spectrum*, molecular ion at *m/e* 207, 209 in the ratio 1:1, as required for C_5H_6ONSBr. This product (0·63 gm, 0·003 mole) was stirred in ethanolic NaOEt as described above for N-ethyl-3-isothiazolone, and gave the same dibromocompound (0·58 gm, 93%) as described under (a).

Kinetics of dimerization of N-*ethyl-3-isothiazolone*

Stock solns of N-ethyl-3-isothiazolone (10^{-3}M) in 90% EtOH containing NaOH (M, M/2 and M/4—prepared by accurate serial dilution) were maintained at 23°. Aliquots were withdrawn at intervals, diluted 10-fold to quench the reaction, and the UV spectra were recorded over the range 220–350 mμ.

Dimer formation was followed by plotting $A_{322\,m\mu}$ *vs* t, and instantaneous rate measurements were obtained by drawing tangents to the curves at points of equal residual substrate concentration. The results are expressed below, relative to the corresponding rate for the M/4 NaOH soln. There was a well defined isobestic point at 282 mμ.

$[OH^-]$	(1)	(2)	(3)	(4)	Mean
M	4·00	3·78	4·14	4·35	4·07
M/2	2·05	1·88	1·99	2·20	2·03

N-*Ethyl-1,2,3-thiadiazole-4-carboxamide*

1,2,3-Thiadiazole-4-carbonyl chloride[37] (0·077 mole) was treated with $EtNH_2$ (0·2 mole) in dry benzene (100 ml) at 5° for 2 hr and poured into water. Recovery of the product and crystallization from EtOH gave *N-ethyl-1,2,3-thiadiazole-4-carboxamide* (90%), m.p. 135–136°. (Found: C, 37·9; H, 4·0; N, 26·7; S, 20·5. $C_5H_7N_3OS$ requires: C, 38·2; H, 4·5; N, 26·7; S, 20·4%); IR: ν_{max} 3360, 1640 cm^{-1}; NMR ($CDCl_3$): 0·69 (s, H), ca. 2·25 (br, s, H), 6·37 (m, 2H), 8·66 (t, 3H).

2,ω-*Bis*(N-*ethylcarboxamido*)-1,4-*dithiafulvene*

The above 1,2,3-thiadiazole (0·015 mole) in THF (20 ml) was added slowly (N_2, 20°, stirring) to a suspension of NaH (0·015 mole) in the same solvent (20 ml). After 15–20 min stirring, water was carefully added, the precipitated solid collected and recrystallized from EtOH. *2,ω-Bis*(N-*ethylcarboxamido*)-1,4-*dithiafulvene* (65%) was obtained as a buff solid m.p. 238–240°. (Found: C, 46·0; H, 5·5; S, 23·8; mol. weight (mass spectrum) 258. $C_{10}H_{14}N_2O_2S_2$ requires: C, 46·5; H, 5·5; S, 24·7%); IR: ν_{max} 3400, 1610 cm^{-1}; NMR (d_6-DMSO): 2·6 (br, s H) 2·3 (br, s, H), 2·43 (d, J = 1·2), 2·51 (s), 3·83 (d, J = 1·2), 3·85 (s), ca. 6·8 (m, 4H), 8·91 (t, 3H), 8·96 (t, 3H). Signals at (2·43 + 2·51) and at (3·83 + 3·85) each integrated as one proton. This is ascribed to the presence of *cis* and *trans* isomers,[38] with H_5 and H_{ω} coupled through sulphur[39] only in one isomer.

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