Allenes. Part 48.[1] A New General Method for the Synthesis of Dihydro-4*H*-1,4-thiazines

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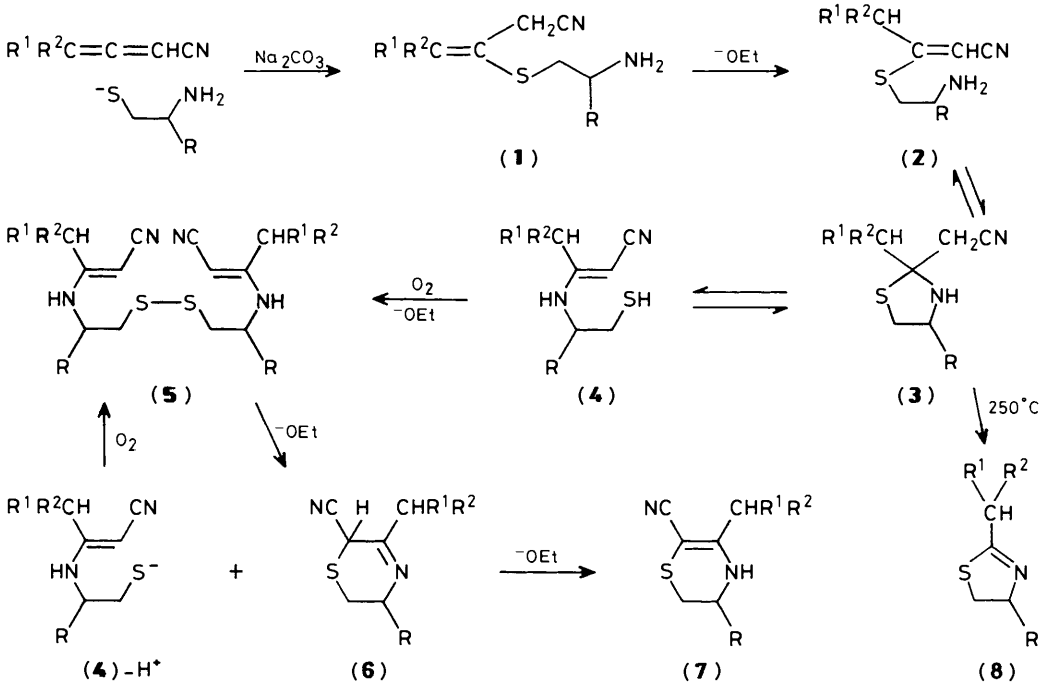
The base-catalysed reaction between allenic nitriles and aminoethanethiol, cystamine, cysteine, cysteine methyl ester, cystine or cystine dimethyl ester in refluxing ethanol, with passage of oxygen through the reaction mixture, gives 80—90% yields of 3-alkyl-5,6-dihydro-4*H*-1,4-thiazine-2-carbonitriles and chiral 5-carboxy and 5-methoxycarbonyl analogues. Detailed investigation and spectroscopic studies have elucidated the seven-step mechanism of this one-pot reaction. Under similar conditions, 2-aminothiophenol failed to give the corresponding 1,4-benzothiazines. Alkaline hydrogen peroxide oxidised the dihydrothiazine to the *S*-oxide quantitatively.

Few simple methods for the synthesis of 2,3-substituted 5,6-dihydro-4*H*-1,4-thiazines from readily available starting materials are found in the chemical literature.[2] We have recently shown that 2-aminoethanethiol adds to allenic nitriles in refluxing ethanol to give first the unconjugated S-adduct (**1**), then the conjugated S-adducts (**2**), followed by the conjugated N-adduct (**4**) and, after flash distillation at 250 °C, the dihydrothiazole (**8**).[3] We now report that the same reagents in refluxing ethanol with 0.5 mol equiv. of strong base (NaOEt gives maximum yields) and in the presence of oxygen gives 3-alkyl-5,6-dihydro-4*H*-1,4-thiazine-2-carbonitrile (**7a**) in up to 90% yield,[4] (Scheme). The best yields are obtained by treating 2-aminoethanethiol hydrochloride and allenic nitrile first with sodium carbonate in 95% ethanol to give the unconjugated S-adduct (**1a**) and then adding sodium ethoxide and passing oxygen. If ethoxide is used from the beginning some decomposition of allenic nitrile by ethoxide is observed.[5a]

The mechanism was investigated using 4-methylhexadienenitrile as follows. (*a*) Monitoring by u.v. spectrophotometry gave maximum absorption at 251 nm, typical for the unconjugated S-adduct (**1a**) after 2 h under reflux with sodium carbonate. (*b*) Addition of sodium ethoxide after 2 h resulted in a gradual shift of $\lambda_{max.}$ from 251 to 260 nm with a small inflexion maximising after 30 min at 275 nm for the conjugated S-adduct (**2a**). Maximum absorption at 260 nm for the conjugated N-adduct (**4a**) was shown after 4 h but some thiazine (**7a**) (15%) had already formed as shown by $\lambda_{max.}$ 303 nm. The absorption at 303 nm and formation of the thiazine (**7a**) had



a; R = H
b; R = CO_2H
c; R = CO_2Me

i; $R^1 = R^2$ = Me
ii; R^1 = Me, R^2 = Et
iii; $R^1 = R^2$ = Et

iv; R^1 = Me, R^2 = Pr
v; R^1 = Me, R^2 = Bu^t

Scheme.

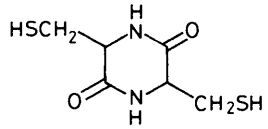
maximised after 19 h. The thiazolidine (**3a**) and the 5,6-dihydro-2*H*-1,4-thiazine (**6a**) show no u.v. maximum and are, therefore, not detected whereas the disulphide bis-adduct (**5a**) shows virtually the same absorption as the N-adduct (**4a**) and, therefore, cannot be distinguished by u.v. spectrophotometry either. (*c*) Intermediates (**1a**), (**4a**), and (**5a**) were isolated or prepared independently and converted under standard conditions into the thiazine (**7a**). Neither compounds (**2a**), (**3a**), nor (**6a**) can be isolated or prepared independently [but (**2a**) has been shown to be present spectroscopically, see above]. The thiazolidine is unstable and is in equilibrium with the S-adduct (**2a**) and the N-adduct (**4a**) with the thermodynamically more stable N-adduct (**4a**) predominating. However, the ready conversion into the dihydrothiazole (**8a**)[3] at 250 °C provides convincing evidence for the thiazolidine intermediate (**3a**). The 2*H*-dihydrothiazine (**6a**), under strongly basic conditions, rearranges fast to the more stable 4*H*-dihydrothiazine (**7a**) and cannot be detected, much less isolated. The disulphide bis-adduct (**5a**) was independently prepared in quantitative yield[6] from the reaction of the readily available cystamine dihydrochloride with 2 equiv. of allenic nitrile. In the presence of ethoxide and oxygen it gives up to 98% of 4*H*-dihydrothiazine (**7a**) after 3.5 h at reflux.* Four steps are thus cut out of the reaction sequence which accounts for the improvement in yield and reduction of reaction time.

Key steps in the thiazine formation are (*a*) the oxidation to the disulphide (**4**)→(**5**) and (*b*) the reductive cyclisation of the disulphide bis-adduct by internal nucleophilic attack (**5**)→(**6**) with –S–S– bond cleavage.[7a,b] The following experiments provided information on essential conditions for the two steps. In the absence of oxygen or oxidising agents a limiting yield of 50% should be obtained as the N-adduct cannot reoxidise to disulphide. Yields between 50 and 60% were obtained in practice as oxygen was not rigidly excluded. A strong base is essential for oxidation of the N-adduct to disulphide. Prolonged heating of aminoethanethiol, allenic nitrile, and sodium carbonate gave no dihydrothiazine. However, the disulphide cystamine with allenic nitrile and sodium carbonate gave a maximum of 40% of dihydrothiazine with 50% of N-adduct (**4**) after 33 h at reflux in ethanol showing clearly that cyclisation of the bis-adduct (**5**) to dihydrothiazine (**6**) takes place under mildly basic conditions but reoxidation of (**4**) to (**5**) does not. Diagnostic spectroscopic constants for thiazines are $\nu_{max.}$ 3 340 (NH) and 2 170 (C=C–CN); $\lambda_{max.}$ 211 (5 800), 250 (5 100), and 303 nm (8 700), the 303 nm maximum arising from a $\sigma \rightarrow \pi^*$ transition of the N–C=C–S chromophore, and complex multiplets for 2- and 3-H, unresolved by a 60 MHz instrument at δ 2.56—3.03 and 3.55—3.76 respectively, due to the magnetic nonequivalence of all four protons.

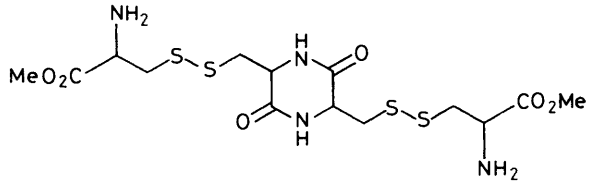
The scope of the dihydrothiazine synthesis was extended by treating allenic nitriles with cysteine and cystine (and their esters) resulting in optically active, chiral 3-carboxy and 3-methoxycarbonyl 5,6-dihydrothiazines. To overcome solubility problems 90% ethanol was used and the reaction monitored by u.v. spectrophotometry. Cysteine hydrochloride with sodium carbonate in 90% ethanol gave the unconjugated adduct (**1b**) after 10 h at reflux. Addition of sodium ethoxide and oxygen gave the N-adduct (**4b**) after reflux for 2 h and the 5,6-dihydrothiazine-3-carboxylic acid (**7b**) after reflux for a further 9.5 h, the latter could only be isolated as an oil. Conversion into the methyl ester with dry methanolic hydrogen chloride gave optically active, crystalline (**7c**) in 48% overall yield. This yield was improved to 71% by using the disulphide cystine despite its lack of solubility (0.009% in water, similar for alcohol). Suspension in 90% alcohol with sodium carbonate and dropwise addition of allenic nitrile gave the bis-adduct (**5b**) after 10 h at reflux but oxygen had to be passed from the beginning to prevent reduction to thiol and formation of the S-adduct (**1b**).† Following the addition of sodium ethoxide and continuing to pass oxygen a quantitative conversion into thiazine-3-carboxylic acid was observed after 6 h at reflux. The free acid was again not obtained crystalline and was converted into the crystalline methyl ester (HCl, MeOH) (**7c**) in 71% yield.‡

The spectroscopic constants for the methyl 2,3-dihydrothiazine-3-carboxylate were similar to those of the 2,3-dihydrothiazines prepared from 2-aminoethanethiol. The longest wavelength maximum in the u.v. is now at 298 nm [ε 6 600) [*cf.* 303 nm for (**7a**)]. The protons on C-2 and C-3 are again nonequivalent and show complex signals.

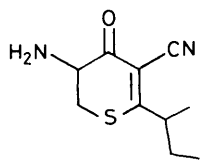
The carboxylate anion of cysteine or cystine is too weak a nucleophile (or electrophile) to enter into any reaction with the allenic nitrile. However, the ester carbonyls in cysteine ethyl ester and cystine dimethyl ester are active electrophiles and the reagent is now trifunctional, which gives rise to by-products such as dioxopiperazines (**9**) and (**10**), thienones (**11**),§ diazines (**12**), and polymers.



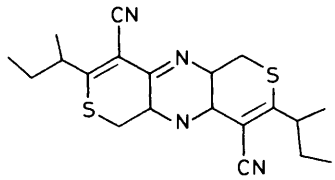
(**9**)



(**10**)



(**11**)



(**12**)

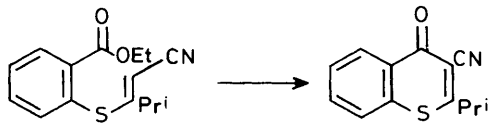
Cysteine ethyl ester and allenic nitrile in the presence of carbonate gave the unconjugated S-adduct which, however, could *not* be converted into dihydrothiazine with sodium ethoxide under a variety of conditions; monitoring by u.v. spectrophotometry that only the thienone (**11**) ($\lambda_{max.}$ 308) was

* Taking into account the cost of starting materials and yields, the cost of dihydrothiazine from cystamine is less than 40% of that prepared from aminoethanethiol.

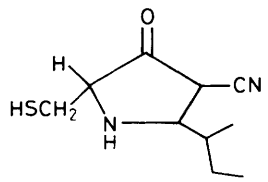
† Reduction of disulphide to thiol does not take place with cystamine or its adducts, but is noticeable with cystine and its adducts.

‡ Other conditions give little or no thiazine, *e.g.* NaOH as base gives mainly 4-methyl-3-oxohexanenitrile and 3-ethoxy-4-methylhex-2-enenitrile, *cf.* ref. 5.

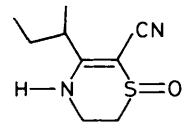
§ I. T. Kay and N. Punja (*J. Chem. Soc. C*, 1970, 2409), similarly obtained a benzothienone (**II**) from ethyl 2-mercaptobenzoate and the allenic nitrile *via* the conjugated S-adduct (**I**).



(**I**) (**II**)



(13)



(14)

formed under reflux in absolute alcohol. This could be isolated as a crude solid but decomposed fast in the presence of water to give the typical enaminic nitrile chromophore at 260—264 nm in the u.v. spectrum with a carbonyl at 1 720 cm^{-1}, possibly the pyrrolone (**13**).

Cystine dimethyl ester, which with sodium carbonate was converted into the bis-N-adduct (**5**; R = CO_2Me) after 16 h at reflux, cannot form the thienone (**11**).* Sodium ethoxide and oxygen gave the methyldihydrothiazine-3-carboxylate in 63% yield together with some dioxopiperazine (**10**). All the experiments using L-cysteine, L-cystine, and L-cystine dimethyl ester, gave highly optically active methyl 2-cyano-5,6-dihydro-3-s-butyl-4*H*-1,4-thiazine-5-carboxylate of rotations $[\alpha]_D$ 118.9°, 107.4°, and 114.8° respectively. The n.m.r. spectrum pointed towards a diastereoisomeric mixture of approximately equal proportions of 3*S*,7*S* and 3*S*,7*R* having been formed in each case. We have no evidence of any significant racemisation at C-3.

3-Alkyl-5,6-dihydro-4*H*-1,4-thiazine-2-carbonitriles are unusually stable and do not react under standard conditions with sodium hydroxide,[7] hydrogen sulphide,[8] or formic acid.[9] Reaction with hydrochloric acid gave either recovery of starting material or poor recovery of a mixture of products which had lost the thiazine spectral features.

m-Chloroperbenzoic acid gave 8% of the corresponding sulphoxide (**14**) and starting material but the reaction was not optimised. Alkaline hydrogen peroxide gave 100% of the crude dihydrothiazine *S*-oxide (**14**) as a hemihydrate (89% after p.l.c. on silica gel). Surprisingly the nitrile side-chain was intact.[5b]

Despite many attempts under varying conditions, the corresponding benzothiazines could not be prepared similarly from 2-aminothiophenol, which gave a conjugated S-adduct[3] as the main product or from 2-aminophenyl disulphide which, even in the presence of oxygen, did not give the bis-N-adduct (model experiments with aniline gave 63% of N-adduct at 120 °C for 23 h); prolonged heating or higher reaction temperatures produced only dimeric allenic nitrile[10] and some S-adduct due to breakdown of the disulphide, and starting material. Distillation of the S-adduct with the bath temperature at 300—350 °C gave the benzothiazole,[3] showing that under extreme conditions the intermediate dihydrobenzothiazole is formed but preferentially eliminates acetonitrile.

Previously benzothiazines were obtained by oxidative ring expansion of dihydrobenzothiazoles†,[a] and the reaction of 2-aminothiophenol with β-diketones,†,[b] both reactions in refluxing Me_2SO.

Experimental

I.r. spectra were determined with Perkin-Elmer 257 and 735 B spectrometers, u.v. spectra for ethanolic solutions with Perkin-Elmer 137, Beckman 25, and Cary 219 spectrometers, n.m.r. with Perkin-Elmer R12B, Jeol 60 and 100 spectrometers in deuteriochloroform unless otherwise stated. Allenic nitriles were prepared as previously reported.[11]

5,6-*Dihydro*-3-*s*-*butyl*-4H-1,4-*thiazine*-2-*carbonitrile* (**7a,ii**).—(*a*) Aminoethanethiol hydrochloride (3.42 g, 0.03 mol) followed by 4-methylhexa-2,3-dienenitrile (3.21 g, 0.03 mol) in ethanol (100 ml, absolute) was added to sodium carbonate (1.59 g, 0.015 mol) dissolved in water (5 ml). Heating under reflux and monitoring by u.v. absorption gave 3-(2-aminoethylthio)-4-methylhex-3-enenitrile quantitatively after 10 h [distilled in a separate experiment 3.5 g, b.p. 124—125 °C/0.8 mmHg (Found: C, 58.7; H, 8.6; N, 15.3; S, 17.4. $C_9H_{16}N_2S$ requires C, 59.0; H, 8.3; N, 15.3; S, 17.4%). $\lambda_{max.}$ 252 nm (ε 3 800); $\nu_{max.}$ 2 245 cm^{-1} (C≡N unconjugated); δ_H 3.43 (2 H, s, CH_2CN)]. Sodium ethoxide (1.02 g, 0.015 mol from 0.23 g of sodium) was added and oxygen passed through for 9 h (monitoring by u.v. until $\lambda_{max.}$ 303 nm had maximised) yielding the *title compound* (5.35 g, 98%), recrystallised (acetone–water, 4.82 g, 88%), m.p. 120 °C (Found: C, 59.2; H, 7.7; N, 15.2; S, 17.4. $C_9H_{14}N_2S$ requires C, 59.3; H, 7.7; N, 15.4; S, 17.6%), $\nu_{max.}$ KBr 3 340br (NH), 2 170 (C=CCN), 1 530, and 1 580 cm^{-1} (NH deform); $\lambda_{max.}$ 250 (5 100) and 303 nm (8 700); δ_H 0.92 (3 H, t, *J* 6 Hz, CH_3CH_2), 1.15 (3 H, d, *J* 6.5 Hz, CH_3CH), 1.48 (2 H, quin., *J* 6 Hz, CH_3CH_2CH), 2.56—3.03 (3 H, m, CH_2S and CH_2CHMe), 3.55—3.76 (2 H, m, $HNCH_2CH_2$), and 4.81 (1 H, br s, exchanges with D_2O); M^+ 182 (100%, $C_9H_{14}N_2S$ requires 182).

(*b*) A mixture of cystamine dihydrochloride (4.5 g, 0.02 mol) and anhydrous sodium carbonate (2.12 g, 0.02 mol) in water (5 ml) with 4-methylhexa-2,3-dienenitrile (4.28 g, 0.04 mol) in ethanol (95%; 300 ml) was heated under reflux for 10 h with oxygen being passed throughout. Evaporation of solvent gave the dinitrile (**5a,ii**) (7.28 g, 99%) [recrystallised in a separate experiment from methanol (6.95 g, 90%) pure 3,12-*di*-*s*-*butyl*-7,8-*dithia*-4,11-*diazatetradeca*-2,12-*diene*-1,14-*dinitrile* (**5a,ii**) had m.p. 111 °C (Found: C, 58.9; H, 8.7; N, 15.3; S, 17.6. $C_{18}H_{30}N_4S_2$ requires C, 59.1; H, 8.8; N, 15.2; S, 17.4%), $\lambda_{max.}$ 260 nm (42 000); $\nu_{max.}$ 3 330 (NH) and 2 190 cm^{-1} (C=CCN); δ_H 3.85 (2 H, s, CHCN), 5.30 (2 H, br t, NH, exchanges D_2O)]. Addition of sodium ethoxide (0.68 g, from sodium 0.23 g) in ethanol (100 ml, absolute), reflux in the presence of oxygen for 5 h and evaporation gave the dihydrothiazine (**7**) (7.30 g, 100%) recrystallised from acetone–water (7.12 g, 97.5%).

(*c*) A mixture of cystamine dihydrochloride (4.5 g, 0.04 mol), 4-methylhexa-2,3-dienenitrile (4.28 g, 0.04 mol), and sodium carbonate (3.18 g, 0.03 mol) after being heated under reflux for 33 h (*i.e.* until no further increase in $\lambda_{max.}$ 303 nm) similarly gave the dihydrothiazine (**7**) (2.9 g, 40%) and the N-adduct (**4a,ii**) (3.65 g, 50%).

(*d*) A mixture of aminoethanethiol hydrochloride (2.37 g, 0.02 mol), 4-methylhexa-2,3-dienenitrile (2.14 g, 0.02 mol), and sodium ethoxide (2.74 g, 0.04 mol) in ethanol (95%; 100 ml), heated under reflux for 4 h, after chromatography (alumina, activ. 3) gave the thiazine (1.4 g, 38%) and 3-(2-mercaptoethylamino)-4-methylhex-2-enenitrile (**4a,ii**) (1.6 g, 43%), m.p. 113 °C (Found: C, 58.5; H, 8.6; N, 15.2. $C_9H_{16}N_2S$ requires C, 58.7; H, 8.7; N, 15.2%), $\lambda_{max.}$ 262 nm (18 100); δ_H 3.82 (1 H, s, C*H*CN). The nitrile (**4a,ii**) (0.92 g, 0.005 mol) when heated with sodium

* Although the amino acid ester could theoretically form a pyrolone by nucleophilic attack of the electron rich C-2 on the carbonyl of the ester these are not formed from amino acid ester with primary amino groups (I. J. Kay and N. Punja, *J. Chem. Soc. C*, 1970, 2409 and unpublished work by Z. T. Fomum and S. R. Landor).

† (*a*) G. Liso, G. Trapani, A. Latrofa, and P. Marchini, *J. Heterocycl. Chem.*, 1981, **18**, 279, converted a number of substituted dihydrobenzothiazines into 4*H*-1,4-benzothiazines by refluxing in Me_2SO in 8—32% yield. They postulated a disulphide intermediate without investigating further. (*b*) S. Miyano, N. Abe, K. Sumoto, and K. Teramoto, *J. Chem. Soc., Perkins Trans. 1*, 1976, 1146, treated diketones with 2-aminothiophenol in Me_2SO (155—170 °C) and obtained dihydro-4*H*-1,4-benzothiazinones in 42—72% yield. They proposed a dihydrobenzothiazole intermediate followed by ring opening and disulphide formation and showed that 2-aminophenyl disulphide in Me_2SO gave the same benzothiazinone in improved yield and even in benzene solution a 40% yield was obtained.

ethoxide (0.34 g, 0.005 mol) in ethanol (30 ml, 95%), and oxygen passed through, gave the thiazine (**7a,ii**) (0.82 g, 90%).

5,6-*Dihydro*-3-*isopropyl*-4H-1,4-*thiazine*-2-*carbonitrile* (**7a,i**).—4-Methylpenta-2,3-dienenitrile (1.86 g, 0.02 mol) and 2-aminoethanethiol hydrochloride (2.27 g, 0.02 mol) when allowed to react as in (*a*) above gave the title compound (3.0 g, 90%), m.p. 142 °C (Found: C, 57.1; H, 7.2; N, 16.6. $C_8H_{12}N_2S$ requires C, 57.1; H, 7.1; N, 16.7%); $\lambda_{max.}$ 250 (3 400) and 303 nm (6 300); $\nu_{max.}$ 3 320 and 2 160 cm^{-1}; δ_H 1.15 (6 H, d, Me_2CH) and 3.105 (1 H, sept., Me_2CH); M^+, 168 (100%).

3-(1-*Ethylpropyl*)-5,6-*dihydro*-4H-1,4-*thiazine*-2-*carbonitrile* (**7a,iii**).—4-Ethylhexa-2,3-dienenitrile (2.42 g, 0.02 mol) and 2-aminoethanethiol hydrochloride (2.27 g, 0.02 mol) similarly gave the title compound (3.64 g, 93%), m.p. 165 °C (Found: C, 61.5; H, 8.2; N, 14.5. $C_{10}H_{16}N_2S$ requires C, 61.2; H, 8.2; N, 14.3%); $\lambda_{max.}$ 251 (4 500) and 303 nm (6 800); $\nu_{max.}$ 3 340 (NH) and 2 170 cm^{-1} (C=CCN); δ_H 0.91 [6 H, t, $(CH_3CH_2)_2$] and 1.49 [2 H, quin., $(CH_3CH_2)_2$]; M^+ 196 (100%).

5,6-*Dihydro*-3-(1-*methylbutyl*)-4H-1,4-*thiazine*-2-*carbonitrile* (**7a,iv**).—4-Methylhepta-2,3-dienenitrile (1.21 g, 0.01 mol) and 2-aminoethanethiol hydrochloride (1.14 g, 0.01 mol) similarly gave the title compound (1.84 g, 89%), m.p. 158 °C (Found: C, 61.1; H, 7.9; N, 14.0. $C_{10}H_{16}N_2S$ requires C, 61.2; H, 8.2; N, 14.3%); $\lambda_{max.}$ 251 (4 400) and 303 nm (7 300); $\nu_{max.}$ 3 320 (NH) and 2 160 cm^{-1} (C=CCN); M^+, 196 (100%).

5,6-*Dihydro*-3-(1,2,2-*trimethylpropyl*)-4H-1,4-*thiazine*-2-*carbonitrile* (**7a,v**).—4,5,5-Trimethylhexa-2,3-dienenitrile (1.35 g, 0.01 mol) and 2-aminoethanethiol hydrochloride (1.14 g, 0.01 mol) similarly gave the title compound (1.90 g, 90%), m.p. 175 °C (Found: C, 62.9; H, 8.7; N, 13.2. $C_{11}H_{18}N_2S$ requires C, 62.9; H, 8.6; N, 13.3%); $\lambda_{max.}$ 251 (3 300) and 304 nm (5 600); $\nu_{max.}$ 3 330 (NH) and 2 170 cm^{-1} (C=CCN); δ_H 0.98 [9 H, s, $(CH_3)_3$], 1.15 (3 H, d, CH_3CH), and 2.85 (1 H, 1, CH_3CH).

Methyl 2-*Cyano*-5,6-*dihydro*-3-*s*-*butyl*-4H-1,4-*thiazine*-5-*carboxylate* (**7c,ii**).—(*a*) Sodium carbonate (2.77 g, 0.262 mol) in water (5 ml) and cysteine hydrochloride (3.075 g, 0.0175 mol) were refluxed with 4-methylhexa-2,3-dienenitrile (1.873 g, 0.0175 mol) in ethanol (150 ml) for 10 h (monitored until $\lambda_{max.}$ 250 nm was maximised). In a separate experiment evaporation of solvent, acidification, and extraction with methanol gave the crystalline *E*/*Z*-2-*amino*-3-(5-*cyano*-3-*methylpent*-3-*en*-4-*ylthio*) *propanoic acid hydrochloride monohydrate* (**1b,ii**), (3.2 g, 80%), m.p. 146—148 °C, $[\alpha]_D^{29}$ +31.8° (*c* 5, MeOH) (Found: C, 42.4; H, 6.4; N, 9.8. $C_{10}H_{19}ClN_2O_3S$ requires C, 42.5; H, 6.8; N, 9.9%); $\lambda_{max.}$ 206 (8 200) and 250 nm (3 600); $\nu_{max.}$ 3 600—2 100br (COOH, NH_2, H_2O, HCl), 2 245 (CH_2CN), and 1 730 cm^{-1} (C=O); δ_H($CDCl_3$·CD_3OD, D_2O), 0.91 and 0.94 (3 H, 2 × t, *E* and *Z* CH_3CH_2), 1.79 and 1.94 (3 H, 2 × s, *E* and *Z* CH_3C), 2.21 and 2.26 (2 H, 2 × q, *E* and *Z* CH_3CH_2C), 3.21 (2 H, d, SCH_2), 3.53 (2 H, s, CH_2CN), and 4.15 (1 H, t, CH_2CHN). Sodium ethoxide (1.19 g, 17.5 mmol) in methanol (15 ml, absolute) under reflux for 2 h with passage of oxygen gave the N-adduct (**4b,ii**), $\lambda_{max.}$ 261 nm and some title thiazine, $\lambda_{max.}$ 300 nm. A further period under reflux for 9.5 h maximised $\lambda_{max.}$ 300 nm. The solvent was evaporated and the residue diluted with water (40 ml) and extracted with chloroform (3 × 20 ml). The aqueous layer was acidified (2M H_2SO_4) and extracted with ether and the extract dried ($MgSO_4$) and evaporated to give the crude acid (**7b,ii**) as an oil, which was converted into the methyl ester (**7c,ii**) with methanol (100 ml, absolute) and hydrogen chloride gas. The resulting mixture was neutralised ($NaHCO_3$), evaporated to quarter bulk, extracted with methylene dichloride (4 × 30 ml) and the extract evaporated and subjected to p.l.c. (SiO_2; $CHCl_3$–MeOH, 10:1) to give *methyl* 2-*cyano*-5,6-*dihydro*-3-*s*-*butyl*-4H-1,4-*thiazine*-5-*carboxylate* (**7c,ii**) (1.81 g, 48%), m.p. 108—109 °C, $[\alpha]_D^{25}$ +118.9° (*c* 1.75, MeOH) (Found: C, 55.1; H, 6.7; N, 11.6; S, 12.8. $C_{11}H_{16}N_2O_2S$ requires C, 55.0; H, 6.7; N, 11.7; S, 13.3%); $\lambda_{max.}$ 251 (5 600) and 298 nm (6 600); $\nu_{max.}$ 3 300 (NH), 2 180 (C=CCN), 1 760, and 1 730 cm^{-1} (CO_2Me); δ_H 0.952 (3 H, t, CH_3CH_2), 1.186 (1.5 H, d, CH_3CH diastereoisomer), 1.205 (1.5 H, d, CH_3CH, diastereoisomer), 1.457 (1 H, quin., CH_2CH), 1.481 (1 H, quin., CH_2CH_3, diastereotopic), 2.658—3.203 (2 H, m, CH_2S), 3.833 (3 H, s, OCH_3), 4.321 (1 H, m, CHNH), and 5.048 (1 H, s, NH); *m*/*z* 240 (M^+) and 180 (100%; M – ·OMe and H–C≡O).

(*b*) L-Cystine (6 g, 0.025 mol) and ethanol (95%, 100 mol) were added to magnetically stirred sodium carbonate (4.03 g, 38 mmol) in water (10 ml), the mixture was warmed to 60 °C; oxygen was then passed through it and 4-methylhexa-2,3-dienenitrile (5.4 g, 0.05 mol) added dropwise. Heating under reflux for 10 h completed formation of the diacid (**5b,ii**) as shown by maximisation of $\lambda_{max.}$ 263 nm. Separate attempts to isolate the pure diacid failed. Refluxing with sodium ethoxide (0.85 g, 12.5 mmol) in ethanol (95%; 10 ml) with passage of oxygen for 6 h gave maximum absorbance at $\lambda_{max.}$ 300 nm. The mixture was evaporated, the residue extracted with water (60 ml), and the extract washed with chloroform (2 × 20 ml), acidified (3M H_2SO_4), and extracted with ether. Evaporation of the extract gave 2-cyano-5,6-dihydro-3-s-butylthiazine-5-carboxylic acid as a semisolid (8.9 g, 79%), which was converted into the methyl ester (MeOH, HCl) (9.17 g, 97% from acid). P.l.c. (silica gel, CH_2Cl_2) gave the title compound (8.5 g, 71% overall), m.p. 109 °C, $[\alpha]_D^{28.5}$ +107.4° (*c* 1.9, MeOH), spectra as in (*a*).

(*c*) Cystine dimethyl ester dihydrochloride (1.37 g, 8 mmol), 4-methylhexa-2,3-dienenitrile (1.71 g, 16 mmol), and anhydrous sodium carbonate (0.848 g, 8 mmol) in ethanol (absolute, 5 ml) were stirred and heated under reflux (bath temp. 120 °C) for 16 h to give maximum absorption at $\lambda_{max.}$ 260 nm. In a separate experiment the pure diester (**5c,ii**) was isolated after treble chromatography (2.3 g, 60%), m.p. 79—81 °C, $[\alpha]_D^{20}$ −215.2° (*c* 0.6, MeOH) (Found: C, 54.6; H, 7.0; N, 11.5; S, 13.4. $C_{22}H_{34}N_4S_2O_4$ requires C, 54.8; H, 7.1; N, 11.6; S, 13.3%); $\lambda_{max.}$ 260 nm (37 100); $\nu_{max.}$ 3 330, 3 130 (NH), 2 190 (C=CCN), and 1 740 cm^{-1} (CO_2Me); δ_H 2.98 (2 H, d, SCH_2CH, *J* 11 Hz), 3.03 (2 H, d, SCH_2CH, *J* 5.5 Hz), 3.81 [8 H, s, $(CHCN)_2$ and $(CO_2CH_3)_2$], 4.15 [2 H, dd, *J* 5.5 and 11 Hz, $(SCH_2CH)_2$, diastereotopic]. Addition of sodium ethoxide (1.09 g, 16 mmol) in ethanol (absolute, 5 ml), passage of oxygen, and refluxing for 4 h maximised $\lambda_{max.}$ 300 nm and work-up as in (*a*) gave the thiazine ester (**7c,ii**) (2.42 g, 63%), m.p. 109—110 °C, $[\alpha]_D^{26}$ 114.8° (*c* 1.5, MeOH), spectra as in (*a*).

5,6-*Dihydro*-2-*cyano*-3-*s*-*butyl*-4H-1,4-*thiazine* S-*Oxide* (**14**).—(*a*) Hydrogen peroxide (30% w/v, 100 vol; 2 ml) was added dropwise with rapid stirring at room temperature to compound (**7a,iii**) (0.18 g, 1 mmol) in ethanol (absolute, 1 ml) and sodium hydroxide (6M; 0.12 ml). The cloudy reaction mixture cleared within 10 min. Extraction with chloroform yielded a colourless oil (0.21 g, 100% for $\frac{1}{2}H_2O$) which on p.l.c. gave the title compound (0.185 g, 89%), as an oil (Found: C, 52.4; H, 7.2; N, 13.1. $C_9H_{14}N_2SO$·$\frac{1}{2}H_2O$ requires C, 52.2; H, 7.3; N, 13.5%); $\lambda_{max.}$ 274 nm (11 400); $\nu_{max.}$ 3 270 and 2 190 cm^{-1} (C=CCN); δ_H 0.92 (3 H, t, CH_3CH_2), 1.24 (3 H, d, CH_3CH), 1.65 (2 H, quin., CH_3CH_2CH), 2.17—3.10 (3 H, m, CH_2SO and $CHCH_3Et$), 3.75 (2 H, m, $NHCH_2$), and 7.69 (1 H, br s, NH).

(*b*) 5,6-Dihydro-5-s-butyl-4*H*-1,4-thiazine-2-carbonitrile (0.64 g, 3.6 mmol) in dichloromethane (10 ml) was added dropwise to *m*-chloroperoxybenzoic acid (0.74 g, 4.3 mol) in dichloromethane (20 ml). After 4 h, extraction with aqueous sodium hydrogen carbonate and evaporation gave starting

thiazine (0.39 g, 61%). Evaporation of the aqueous layer, extraction with chloroform and p.l.c. gave the *S*-oxothiazine (0.064 g, 8%), spectra as in (*a*).

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References

1 Part 47, S. R. Landor, A. Johnson, Z. T. Fomum, and A. E. Nkengfack, *J. Chem. Soc., Perkin Trans. 1*, 1988, 975.
2 *e.g.*, M. Sainsbury, 'Comprehensive Heterocyclic Chemistry,' eds. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 3, p. 1031—1038.
3 S. R. Landor, P. D. Landor, Z. T. Fomum, J. T. Mbafor, and G. W. B. Mpango, *Tetrahedron*, 1984, **40**, 2141.
4 For preliminary publication of some of this work, see Z. T. Fomum, J. T. Mbafor, S. R. Landor, and P. D. Landor, *Heterocycles*, 1982, **19**, 465.
5 P. M. Greaves, P. D. Landor, S. R. Landor, and O. Odyek, *Tetrahedron*, 1974, **30**, 1427; (*a*) isolated 3-ethoxy-4-methylhex-2-enenitrile and 4-methyl-3-oxohexanenitrile; (*b*) alkaline hydrogen peroxide gave allenic amide.
6 *cf.* S. R. Landor, P. D. Landor, Z. T. Fomum, J. T. Mbafor, and A. E. Nkengfack, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1223, obtained quantitative yields of crude bis-adducts from diamines.
7 *e.g.*, A. I. Vogel, 'Textbook of Practical Organic Chemistry,' Longman, London, 4th edn., 1978, p. 479.
8 F. Asinger, H. Offermanns, and D. Neuray, *Ann. Chem.*, 1970, **739**, 32.
9 F. Asinger, A. Sans, H. Offermanns, D. Neuray, and K. H. Lim, *Monatsh. Chem.*, 1971, **102**, 321; F. Asinger, H. Offermans, D. Neuray, and P. Muller, *Monatsh. Chem.*, 1970, **107**, 1295.
10 C. W. N. Cumper, Z. T. Fomum, P. M. Greaves, and S. R. Landor, *J. Chem. Soc., Perkin Trans. 1*, 1973, 885.
11 P. M. Greaves, S. R. Landor, and D. R. J. Laws, *J. Chem. Soc. C*, 1968, 291.

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