Addition Reactions of Heterocyclic Compounds. Part 74.[1] Products from Dimethyl Acetylenedicarboxylate with Thiourea, Thioamide, and Guanidine Derivatives

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Benzimidazole-2-thione with dimethyl acetylenedicarboxylate (DMAD) in acetonitrile gave a fused thiazolidinone derivative, but in methanol a fused thiazinone was obtained. Structures were assigned to adducts from other thioureas by comparison with the ^{13}C n.m.r. spectra for these compounds. A method has been developed for distinguishing between the possible structural types of adducts for guanidine and amidine derivatives with DMAD using ^1H and ^{13}C n.m.r. spectroscopy. Products from various thioamides and DMAD were identified from their n.m.r. and other spectra.
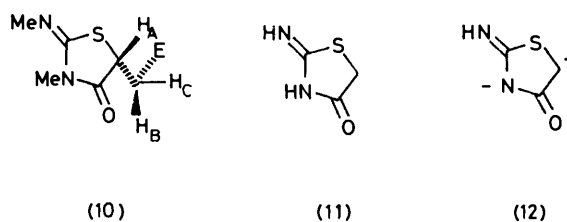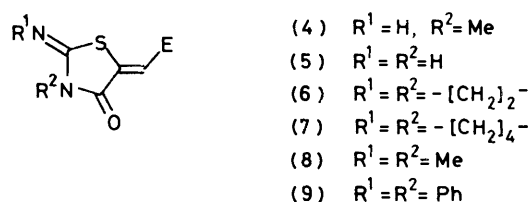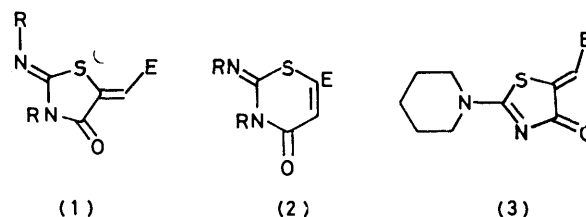
THIOUREAS possessing at least two N–H bonds react with dimethyl acetylenedicarboxylate (DMAD) to give '1 : 1 molar-MeOH ' adducts.[2-6] The sulphur adds *trans* to the triple bond and a nitrogen atom condenses with an ester group. This can lead to structural types (1) and (2), and compounds of both types have been claimed. The thiazolidinone type (1) has been proved by X-ray crystallography for (3) [7] and (4),[8] by ' unambiguous ' syntheses of (5) [9] and (6),[10] and by some degradative work.[11]

All the evidence put forward so far in support of structural type (2) is either equivocal or incorrectly interpreted. Firstly, the assignment of structures from fragmentation patterns deduced from high-resolution mass spectra [5] is unreliable when isomerism to an alternative structure might occur on electron impact or on the probe. Secondly, one cannot exclude structure (10) for the reduction product of the *NN'*-dimethylthiourea adduct on the ground [5] of too large a coupling constant (J 9.8 Hz) between H_A and H_B, since such parameters cannot be reliably predicted.[12] Finally, the partial exchange of H_A in (10) on treatment with a mixture of deuterium oxide, sodium carbonate, and dioxan [5] is not inconsistent with the lack of any exchange of the methylene protons of (11), since the latter process would have to occur via the dianion (12).

Recently McKillop *et al.*[13] reported that benzimidazole-2-thione (13) reacted with DMAD in either methanol or acetic acid to give mixtures of two ' 1 : 1 molar-MeOH ' adducts. One adduct was identified as (15) [type (1)] by X-ray crystallography but the other adduct, which was not isolated, was only tentatively assigned structure (16) from its ^1H n.m.r. spectrum. However, we have found that the thione (13) and DMAD reacted in wet or dry acetonitrile to give only (15), and in dry methanol to give only (16). The adduct (15) was converted into (16) by refluxing in dry methanol. This rearrangement was probably catalysed by basic impurities, since it did not take place if the methanol contained a few drops of acetic acid. A possible mechanism (Scheme 1) involves ring-opening by attack of methoxide on the strained cyclic amide, followed by ring-closure on the other ester group. Similarly (15) was converted into the acid (17) by sodium hydroxide in aqueous tetrahydrofuran, and

into the ethyl ester (18) by ethanol containing a trace of sodium hydroxide. The thione (13) and DMAD reacted in a mixture of acetonitrile and water to give a precipitate of the 1 : 1 molar adduct (14), which could be cyclised into (15) in dry acetonitrile or into (16) in dry methanol.

The structure proposed for (16) is supported by the

(1)   (2)   (3)

(4) $R^1 = H$, $R^2 = Me$
(5) $R^1 = R^2 = H$
(6) $R^1 = R^2 = -[CH_2]_2-$
(7) $R^1 = R^2 = -[CH_2]_4-$
(8) $R^1 = R^2 = Me$
(9) $R^1 = R^2 = Ph$

(10)   (11)   (12)

$E = CO_2Me$

presence of a deshielded aromatic proton (τ 1.43—1.60) in the ^1H n.m.r. spectrum, as observed for (19), and by the strong similarities in the ^{13}C n.m.r. spectra of (16) (Figure 1) and (19) (Table 1).

Alternative structures considered for (16) are (20), (21), and (22). The first two, as *S*-acyl thioureas, would be

expected to ring-open more readily than (15) in methanol and are difficult to reconcile with the clear formation of (14), while structure (22), should the analogy with the ¹H n.m.r. spectrum of (23) (Table 2) pertain, would not possess the low-field aromatic proton observed.

SCHEME 1
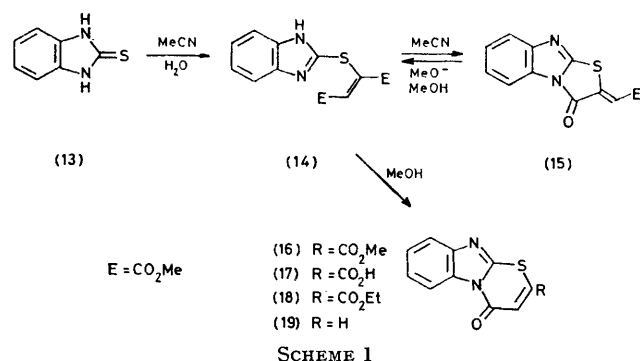
Measurements on a Dreiding model of the adduct (14) showed that the angle of attack (α) (Figure 2) from the lone pair of electrons on the 3-nitrogen atom was nearer to the preferred value [14] for nucleophilic attack on an ester group when the product was (15) ($\alpha = 90°$) rather than (16) ($\alpha = 121°$). One can generally conclude that (15) appears to be the product of kinetic control, and (16) of thermodynamic control, of the reaction mode.

The ¹³C n.m.r. spectra of (15) and (16) show several marked differences (Figure 1). The non-benzenoid C-H resonance in (15) is at higher field (δ 112.9) than in (16)
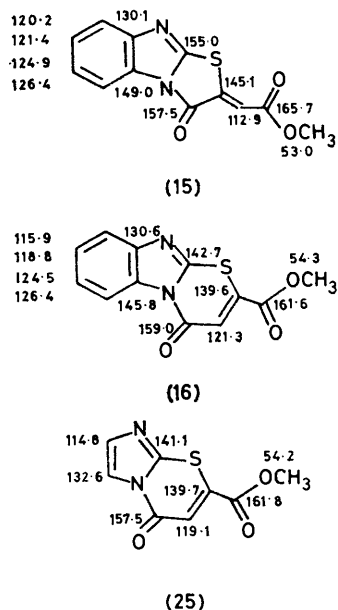

FIGURE 1   ¹³C N.m.r. data for (15), (16), and (25)

(δ 121.3, assigned from an undecoupled spectrum) and the ester carbonyl carbon is at lower field. Furthermore the carbons attached to sulphur are at lower field in (15), the relatively large deshielding of 9a-C in (15) being attributable to the effects of strain. These data offer

Compound	Carbon resonances	CO₂CH₃ resonances	
(3)	2-C, 175.9; 4-C, 178.8; 5-C, 147.2; 6-C, 116.5; 2',6'-C, 50.1, 50.4; 3',5'-C, 25.6, 26.3; 4'-C, 23.4	52.5	167.8
(6)	2-C, 158.3; 4-C, 159.4; 5-C, 148.2; 6-C, 116.3; CH₂, 61.8; CH₂, 41.8	52.7	166.3
(7)	2-C, 144.5; 3-C, 165.6; 5-C, 149.3; 6-C, 114.2; 4 × CH₂, 49.1, 27.8, 25.1, 44.1	52.4	166.6
(8)	2-C, 141.3; 4-C, 164.9; 5-C, 150.8; 6-C, 115.3; CH₃, 29.2; CH₂, 39.0	52.5	166.5
(9)	2-C, 141.2; 4-C, 164.2; 5-C, 151.2; 6-C, 116.3; phenyl-C in normal range	52.4	166.2
(19)	2-C, 137.8; 3-C, 116.9; 4-C, 160.1; 5a-C, 148.4; 6,7,8,9-C, 116.1, 118.6, 124.6, 126.4; 9a-C, 130.8; 10a-C, 148.4		
(23)	1-C, 135.2 (s); 2-C, 115.5 (d); 3-C, 162.9 (s); 4a-C, 167.4 (s);[b] 5a-C, 127.4 (s); 6-C, 126.4 (d); 7-C, 128.2 (d);[b] 8-C, 128.3 (d);[b] 9-C, 116.3 (d); 9a-C, 139.9 (s)	55.3	166.8[b]
(29)	2-C, 97.0 (s); 2-CH₃, 30.3 (q); 2-OCH₃, 50.7 (q); 4-C, 166.2 (s); 5-C, 147.2 (s); =CHCO₂Me, 113.3 (d)	52.7	167.2
(30)	2-C, 137.6 (s), =CH₂, (90.0 (t); 4-C, 164.8 (s); 5-C, 145.0 (s); =CHCO₂Me, 109.9 (d)	52.1	166.4
(35)	2-C, 148.1 (s); =CHCO₂Me, 113.9 (d); 3-C, 165.7 (s); 5-C, 52.3 (t); 6-C, 42.8 (t); 7a-C, 114.6 (s); 7a-OCH₃, 52.1 (q);[b] N-CH₃, 32.9 (q)	52.3[b]	167.1
(36)	2-C, 117.1 (s); OCH₃, 51.3 (q);[b] 4-C, 163.7 (s); 5-C, 147.1 (s); =CHCO₂Me, 112.9 (d); N-CH₃, 28.0 (q); N-CH₂, 42.1 (t) and 42.4 (t); CH₂CH₃, 13.5 (q) and 13.9 (q)	51.9[b]	167.5
(39)[a]	2-C, 99.8 (s); Ph-C=O, 188.5 (s); 2-OCH₃, 50.2 (q); 4-C, 164.7 (s); 5-C, 145.8 (s); =CHCO₂Me, 114.0 (d); C₆H₅, 129.1 (d),[c] 129.9 (d),[c] 134.5 (d), and 132.0 (s)	52.3	166.4
(49)	2-C, 76.3 (s); 2-CH₂, 39.9 (t); 4-C, 191.1 (s); 4a-C, 120.9 (s); 5-C, 138.8 (d);[b] 6-C, 120.1 (d); 7-C, 132.9 (d);[b] 8-C, 114.8 (d); 8a-C, 139.4 (s); N-CH₃, 39.1 (q)	52.5 53.7	169.2 169.9
(60)	2-C, 145.1 (s), 4-C, 163.2 (s); 5-C, 139.6 (s);[b] =CHCO₂Me, 96.2 (d); C₆H₅, 121.3 (d),[c] 122.3 (d), 122.6 (d),[c] 127.6 (d), 127.7 (d), 128.1 (d),[c] 128.3 (d),[c] 128.6 (d), 129.0 (d), 132.9 (s), 137.2 (s),[b] 137.5 (s)[b]	51.7	164.7
(63)	2-C, 110.0 (d); 3-C, 124.6 (d); 5-C, 136.4 (s); 6-C, 114.4 (d); 7-C, 160.9 (s);[b] 8a-C, 166.8 (s)[b]	53.6	166.0[b]

[a] Spectrum recorded in hexadeuteriodimethyl sulphoxide. [b] Assignments could be interchanged. [c] Doubly degenerate.

a method of distinguishing type (1) and type (2) adducts. Thus the adduct from the thione (24) and DMAD in methanol is assigned the type (2) structure (25) (Figure 1) rather than (26), while the spectrum of the bicyclic adduct (6) strongly resembles that of (15). The spectra

(20) R¹=E, R²=H   (22)
(21) R¹=H, R²=E

(23)

E = CO₂Me
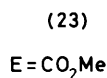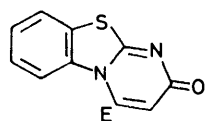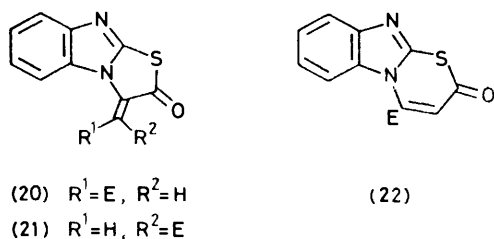
of the adducts (4) and (7)—(9) show strong similarities in the resonances of common carbon atoms, and are assigned as type (1) adducts from the ester carbonyl and olefinic C–H resonances. However, compared with (6) and (15) the lactam carbon resonance is *ca.* 6 p.p.m. downfield and the resonance of the central carbon of the thiourea moiety is *ca.* 12 p.p.m. upfield, the latter reflecting the absence of a fused five-membered ring and lack of strain. The spectrum of adduct (3) is quite different. The resonances of the 2- and 4-C atoms (δ 175.9 and 178.8) strongly support the representation of
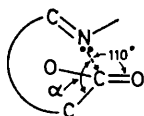

Figure 2   Definition of angle α in (14)

the structure as the resonance hybrid (27), a conclusion endorsed by the N–C bond lengths [7] (1.31—1.34 Å) of the resonating system.

Recently Swiss workers [15] have used measurements of ¹³C–¹H coupling constants to distinguish type (1) and type (2) adducts. Using their criteria, an undecoupled ¹³C n.m.r. spectrum of (16) supported the structural assignment by showing no detectable coupling between 3-H and the lactam carbon; a coupling of *ca.* 6.4 Hz is expected of a type (1) adduct.

Ethanethioamide with DMAD in methanol is reported [5b] to give the ' 1 : 1 ' adduct (28). However, the ¹³C n.m.r. spectrum shows the presence of a quaternary carbon (δ 97.0) and strong similarities to the spectrum of (4), so the structure must be (29). When the reaction was performed in acetonitrile, compound (30), previously

thought to be (31),[2] was obtained, which was converted into (29) by refluxing in methanol, possibly by tautomerism to (31) and nucleophilic addition. Compound (30) shows a pair of coupled olefinic protons (*J* 2.4 Hz) in its ¹H n.m.r. spectrum and a triplet resonance (δ 90.0) in the partially decoupled ¹³C n.m.r. spectrum, which eliminate structure (31). The conversion of (30) into (29) in methanol was not inhibited by acetic acid. The tri-substituted thioureas (32) and (34) both gave analogous ' 1 : 1 ' adducts, (36) and (35), with DMAD in methanol. Such products may be formed by addition of methanol to an intermediate (*e.g.* 33) (Scheme 2).

These adducts are of interest since they both possess an *sp*³ carbon attached to two nitrogen, one oxygen, and one sulphur atom and this leads to very low field ¹³C resonances [(36) δ 117.1 and (35) 114.6]. Hydrolysis of (36) by methanolic hydrogen chloride gave the known thiazolin-2,4-dione (37).

2-Oxo-2-phenylethanethioamide (38) reacted analogously with DMAD in methanol to give (39), but in acetonitrile gave the ' 2 : 1 molar-MeOH ' adduct (40).

(24)   (25)

(26)   E = CO₂Me   (27)
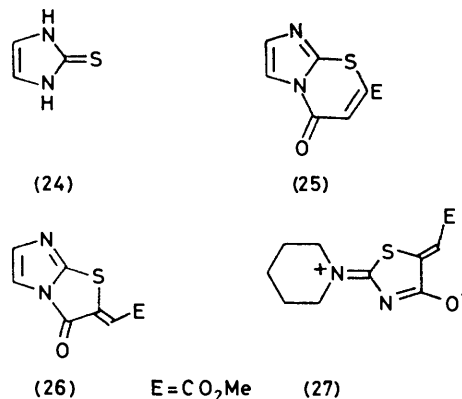
The chemical-ionisation mass spectrum did not show a molecular ion, but did show peaks assignable to the fragment ions (41) and (43), consistent with cleavage at (a). The structure is further supported by the ¹H n.m.r. spectrum. The product is probably formed by addition of the thioamide *via* sulphur to (41) or (44) although the unlikely addition *via* nitrogen to give the alternative structure (42) cannot be rigorously excluded.

(28)   (29)   (30)   (31)

E = CO₂Me
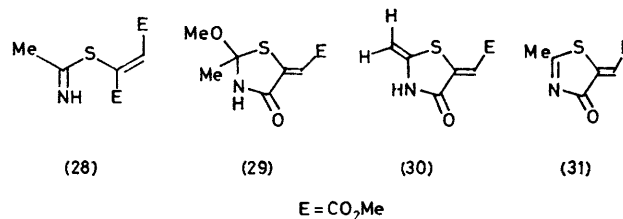
In contrast benzenecarbothioamide gave only the ' 1 : 1-molar-MeOH ' adduct (45)[15] in both methanol and acetonitrile. 2-Aminobenzenecarbothioamide (47), which possesses three adjacent nucleophilic centres, reacted with DMAD as a thioamide to give the deep red

TABLE 2

[1]H N.m.r. data (measured at 60 MHz in deuteriochloroform, shifts in τ, J in Hz)

Compound	Proton resonances	CO_2CH_3 resonances
(14) [a]	4 × Ar-H, 2.52—2.98; vinyl-H, 3.29; N-H, 2.61 (br)	6.31, 6.65
(15)	Vinyl-H, 2.85 (s); 5-H, 2.04—2.18 (m); 6-, 7-, 8-H, 2.22—2.83 (m)	6.14
(16)	3-H, 2.58 (s); 6-H, 1.43—1.60 (m); 7-, 8-, 9-H, 2.17—2.74 (m)	6.00
(17) [a]	3-H, 2.70 (s); 6-H, 1.46—1.65 (m); 7-, 8-, 9-H, 2.02—2.72 (m)	
(18)	3-H, 2.58 (s); 6-H, 1.43—1.72 (m); 7-, 8-, 9-H, 2.17—2.89 (m); $CO_2CH_2CH_3$, 5.57 (t) and 8.56 (q)	
(19) [a]	2-H, 1.74 (d); 3-H, 3.22 (d); 6-H, 1.50—1.75 (m); 7-, 8-, 9-H, 2.20—2.70 (m); ($J_{2,3}$ 10.2)	
(23)	3-H, 3.40 (s); 4 × Ar-H, 2.26—2.82 (m)	5.96
(25)	3-H, 2.59 (s); 6-H, 2.08 (d); 7-H, 2.60 (d) ($J_{6,7}$ 1.7)	6.05
(26)	Vinyl-H, 2.86 (s); 5-H, 2.63 (d); 6-H, 2.89 (d) ($J_{5,6}$ 1.6)	6.24
(29)	2-CH$_3$, 8.05 (s); 2-OCH$_3$, 6.79; vinyl-H, 3.26 (s)	6.22
(30) [a]	=CH$_2$, 5.19 (d) and 5.41 (d) (J 2.4); =CHCO$_2$Me 3.61 (s)	6.36
(35) [a]	Vinyl-H, 3.44 (s); 5-H$_2$ and 6-H$_2$, 6.12—7.06 (m); 7-CH$_3$, 7.56 (s); 7a-OCH$_3$, 6.75 (s)	6.27
(36)	2-OCH$_3$, 6.81 (s); 3-CH$_3$, 7.16 (s); vinyl-H, 3.16 (s); NCH$_2$CH$_3$, 7.36 (t) and 8.93 (q) (J 7.2)	6.24
(37)	NCH$_3$, 6.91 (s)	6.12
(39)	2-OCH$_3$, 6.50 (s); 2 × Ar-H, 1.85—2.07 (m); 3 × Ar-H, 2.38—2.80 (m); N-H, 2.22 (b); [b] vinyl-H, 3.18 (s)	6.27
(40)	2 × Ar-H, 1.60—1.78 (m); 8 × Ar-H, 2.32—2.72 (m); N-H, 2.07 (s); [b] vinyl-H, 3.71 (s)	6.29
(45)	2 × Ar-H, 1.70—1.87 (m); 3 × Ar-H, 2.12—2.50 (m); vinyl-H, 3.00 (s).	6.18
(46)	2 × Ar-H, 2.33—2.76 (m); 2 × Ar-H, 3.03—3.45 (m); NH$_2$, 1.89 (b); [b] vinyl-H, 3.17 (s)	6.24
(49)	NH, 6.20 (br); [b] 2-CH$_2$, 6.71 (d) and 7.02 (d), (J 14.0); =NCH$_3$, 6.47 (s); 5-H, 1.66 (d); 6-H, 3.22 (t); 7-H, 2.75 (t); 8-H, 3.43 (d) ($J_{5,6}$ 8.1, $J_{7,8}$ 8.0)	6.30 6.34
(54)	NH, 1.51 (br); [b] vinyl-H, 3.67 (s); 3-H, 3.24 (d); 4 × Ar-H, 2.36—3.02 (m) ($J_{1,3}$ 2.4)	6.19, 6.64
(56)	3-H, 3.03 (s); 6-H, 1.83—2.03 (m); 3 × Ar-H, 2.49—2.87 (m); 10-H, 3.63 (s)	6.15
(57)	4-H and 6-H, 1.56 (d); 5-H, 3.03 (t); CHCO$_2$Me, 4.38 (s) ($J_{4,5} = J_{5,6}$ = 4.7)	6.32
(58)	3-H and 4-H, 2.80—3.02 (m); 5-H, 2.50 (t); 6-H, 1.66 (d); CHCO$_2$Me, 4.36 (s) ($J_{5,6}$ 6.7)	6.35
(59)	4-H and 6-H, 1.50 (d); 5-H, 3.01 (t) ($J_{4,5}$ 5); vinyl-H, 3.07	6.24, 6.35
(60)	10 × Ar-H, 2.82 (s); 5 × Ar-H, 3.25—3.75 (m); vinyl-H, 4.09 (s)	6.89

TABLE 2 (continued)

Compound	Proton resonances	CH_2CH_3 resonances
(61) [a,c]	Ar-H, 2.56—2.68; 3 × Ar-H, 2.86—3.00 (m); vinyl-H, 4.56 (s); 2 × NH, −1.57 (b) and −0.71 (b)	6.30
(62) [a]	Vinyl-H, 4.69 (s)	6.28
(63) [a]	2-H, 2.65 (d); 3-H, 1.73 (d); 6-H, 3.28 (s) ($J_{2,3}$ 5.0)	6.10
(64)	10 × Ar-H, 2.86 (s); 5 × Ar-H, 3.18—3.50 (m) and 3.79—3.94 (m); 5-H, 4.35 (s); 6-H, 1.90 (d) ($J_{5,6}$ 7.9)	
e	1-, 8-H, 1.44 (d); 4-, 5-H, 1.78 (d); 4 × Ar-H, 2.06—2.54 (m); vinyl-H, 3.46 (s) ($J_{1,2} = J_{7,8}$ = 8.4. $J_{3,4} = J_{5,6}$ = 7.8)	6.18, 7.28
f	1-H, 8-H, 1.45 (d); 4,5-H, 1.76 (d); 4 × Ar-H, 2.08—2.53 (m); 2 × vinyl-H, 3.12 (d),[d] 4.02 (d),[d] (J 9.6)	6.17
g	2-H, 2.78; vinyl-H, 3.90; 4-H, 5-H, 6-H, 2.66—2.94 (m); 7-H, 2.22—2.38 (m)	

[a] Spectrum recorded in hexadeuteriodimethyl sulphoxide. [b] Disappears on addition of D$_2$O. [c] 100 MHz. [d] Assignments could be interchanged. [e] Dimethyl (acridin-9-ylthio)fumarate. [f] Methyl (E)-3-(acridin-9-yl)acrylate. [g] Dimethyl (E)-3-(indol-3-ylthio)fumarate.

adduct (46). The presence of a primary amino-group in the product was inferred from a broad two-proton resonance (τ 1.89) in the [1]H n.m.r. spectrum and by bands at 3 360 and 3 260 cm^{-1} in the i.r. spectrum. The

(32)   (33)

(34)   (35)   (36)

$E = CO_2Me$
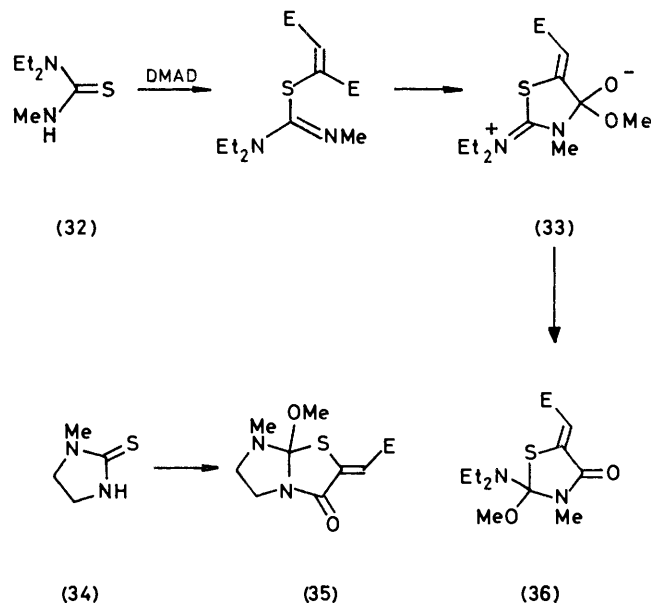
SCHEME 2

u.v. spectrum showed a band at 480 nm (ε 8 510) which disappeared on acidification and which can be associated with charged resonance forms no longer possible after protonation of the amino-group. The 1 : 1-molar adduct (49) obtained from the secondary thioamide (48), was identified from the large coupling constant (J 14 Hz) for

the side-chain methylene protons and the quaternary carbon resonance (δ 76.3) in its n.m.r. spectra. Adducts (50),[16] (51),[17] and (52),[18] obtained from similar compounds containing two nucleophilic centres three atoms apart, have analogous structures.


(37)   (38)   (39) R = MeO

(40) R = PhCOC—S

(41) R = positive charge

(42) R = Ph—C—C—NH

(43)   (44)   E = CO₂Me

E = CO_2Me
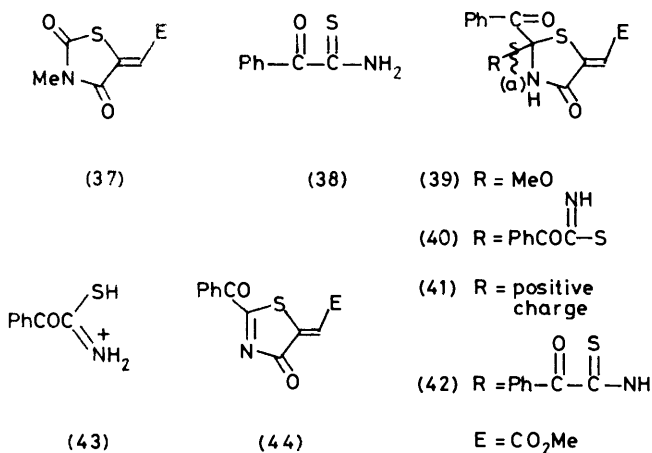
Indoline-2-thione (53) with DMAD in cold methanol gave the fumarate (54), which was cyclised into (56) by refluxing methanol or acetic acid but not by dioxan or acetonitrile; (56) possessed a low-field aromatic proton. Cyclisation may therefore occur *via* the tautomer (55) or the anion of (54) (Scheme 3). Indole-3-thiol and acridine-9(10H)-thione with DMAD in methanol gave adducts similar to (54), all of which possessed one high-field ester methyl group. The corresponding adduct from methyl propiolate and acridine-9(10H)-thione showed a normal ester methyl resonance in spite of the fact that the Z-arrangement about the vinyl group, shown by the coupling constant[19] for the vinyl protons (9.6 Hz), would put the ester group above the aromatic


(45) R = H
(46) R = NH₂

(47) R = H
(48) R = Me
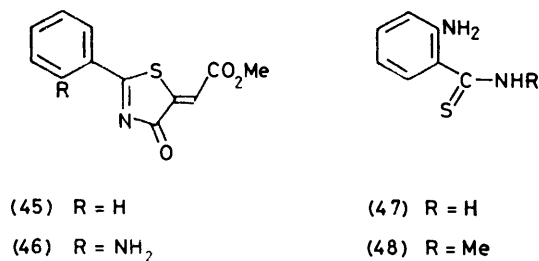
system. The higher field (^{1}H n.m.r.) ester groups of (54) and its analogues must therefore be closer to the sulphur atoms, and are presumably shielded by the ring systems nearby.

Pyrimidine-2(1H)-thione and pyridine-2(1H)-thione with DMAD in methanol gave the 2 : 1 molar adducts (57) and (58), but the pyrimidine in acetonitrile yielded only the fumarate (59).[20]

The ' 1 : 1 molar-MeOH ' adducts of guanidine derivatives with DMAD have been assigned both pyrimidone structures [21-23] and imidazolidinone structures.[24,25] Recent crystallographic studies have shown that 1,2,3-

(49)   (50)

(51)   (52)

E = CO_2Me

(53)   (54)

AcOH or MeOH

(56)   E = CO₂Me   (55)

SCHEME 3
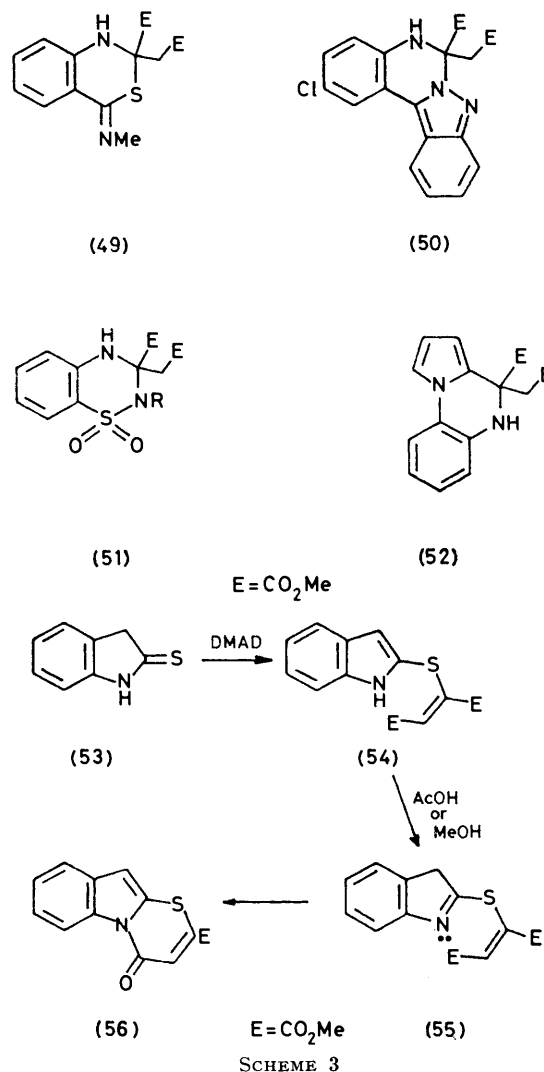
triphenylguanidine forms a five-membered ring structure (60)[26] while 2-aminobenzothiazole forms a six-membered ring structure (23).[27] The ^{13}C n.m.r. signals of the β-enaminic carbons of these two adducts are quite different [(60), δ 96.2; (23), δ 115.5] and offer a method for distinguishing these adduct types. Furthermore the n.m.r. signals of the β-enaminic hydrogens are quite distinct [(60), τ 4.09; (23), τ 3.40], though the adduct (61) (τ 4.50) may be a better model for the smaller ring system, since in (60) the ester group is not planar with the enaminic system and the adjacent phenyl group may affect the resonance position of the β-hydrogen. The

(57) X = N
(58) X = CH

(59)

E = CO₂Me
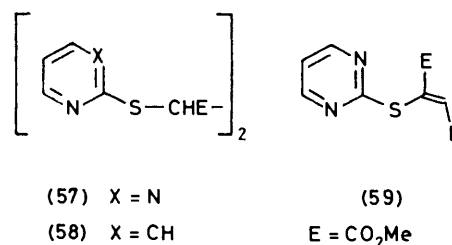
adduct from guanidine itself and DMAD showed a β-enaminic proton resonance at τ 4.69, in accordance with the five-ring structure (62), though other tautomeric formulations could be written.

The adduct from 2-aminothiazole showed β-carbon and proton resonances at δ 114.4 and τ 3.28, respectively, confirming the proposed [28] six-ring structure (63).

(60)　　　　　　**(61)**　　　　　　**(62)**

(63)　　　　　　**(64)**

E = CO₂Me
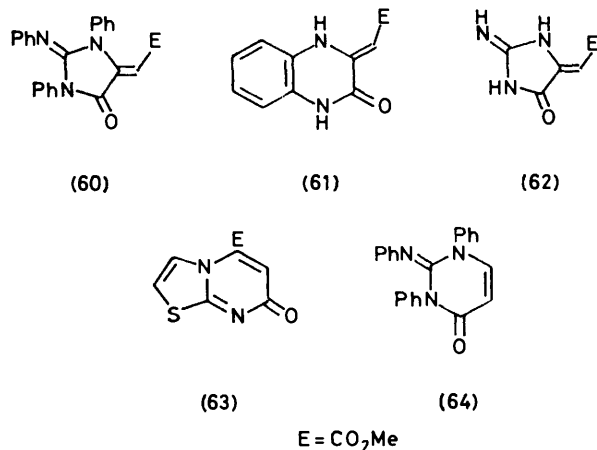
1,2,3-Triphenylguanidine reacted with methyl propiolate as expected to give the six-membered ring compound (64).

EXPERIMENTAL

The instruments and chromatographic procedures have been described previously.[29] I.r. spectra were measured in Nujol, u.v. spectra in dry methanol (M) or dry methanol acidified with 1 drop of 72% perchloric acid (A). Methanol was dried with magnesium and distilled. Acetonitrile was dried with calcium hydride. The following compounds were prepared by literature methods: benzimidazo-[2,1-b][1,3]thiazin-4-one [30] (19) (33.4%) (from ethanol-chloroform), m.p. 167—169 °C (lit.,[30] 168—169 °C, 56.7%); 1-methylimidazolidine-2-thione [31] (34) (60.3%), m.p. 130—132 °C (lit.,[32] 131.5—132 °C); 2-oxo-2-phenylethanethio-amide [33] (38) (69.6%), m.p. 92—94 °C (lit.,[33] 97 °C, 88%); 2-aminobenzenecarbothioamide [34] (47) (65%), m.p. 122—123 °C (lit.,[34] 121—121.5 °C), N-methyl-2-aminobenzene-carbothioamide [35,36] (48) (37%), m.p. 101—102 °C (lit.,[36] 101—102°); indoline-2-thione [37] (31.3%), m.p. 141—144 °C (lit.,[37] 145—148 °C, 44%). NN-Diethyl-N'-methylthiourea was obtained from methyl isothiocyanate and diethylamine as a white sticky oil (94%) (pure by ¹H n.m.r.). The following adducts were prepared by refluxing equimolar quantities of substrate and DMAD in ca. 10 volumes of methanol: (4) (49.8%), m.p. 168—169 °C (lit.,[11] 166—167 °C, 50%); (6) (64.6%), m.p. 195—197 °C (lit.,[10] 196—197 °C, 75.3%); (23) (61.7%), m.p. 184—185 °C (lit.,[27] 183—185 °C, 92%); (7) (59.6%) m.p. 102—104 °C (lit.,[27] 103—103.5 °C, 87%); (8) (69.5%) m.p. 157—158 °C (lit.,[11] 156—157 °C, 76%); (9) (62.3%), m.p. 128—130 °C (lit.,[11] 129—131 °C, 68%); (61) m.p. 227 °C (lit.,[38] 227 °C); (63) (55.4%), m.p. 268—273 °C (lit.,[28] 268—272 °C, 52%).

The Reaction of Benzimidazole-2-thione (13) *with DMAD.*—(a) DMAD (4.75 g) was added to a stirred suspension of benzimidazole-2-thione (5.00 g) in methanol (100 ml), refluxed for 3 h, and then cooled to −14 °C. Filtration

gave *methyl 4-oxo-4H-benzimidazo[2,1-b][1,3]thiazine-2-carboxylate* (16) (4.83 g, 55.7%) as yellow microneedles (from methanol), m.p. 172.5—173 °C (Found: C, 55.4; H, 3.1; N, 10.8. C₁₂H₈N₂O₃S requires C, 55.4; H, 3.1; N, 10.8%); ν_max. 3 062m, 1 745s, 1 703s, and 1 590m cm⁻¹.

(b) The use of acetonitrile (150 ml) instead of methanol gave (E)-2-(*methoxycarbonylmethylene*)*benzimidazo*[2,1-b]-[1,3]*thiazolid-3-one* (15) (4.23 g, 48.8%) as yellow-orange plates (from acetone), m.p. 191—193 °C (lit.,[13] 192—193 °C; lit.,[39] 190—192 °C) (Found: C, 55.5; H, 3.2; N, 10.5. Calc. for C₁₂H₈N₂O₃S C, 55.4; H, 3.1; N, 10.8%); ν_max. 3 060m, 1 735s, 1 700s, 1 621m, and 1 610s cm⁻¹.

(c) A mixture of acetonitrile (140 ml) and water (14 ml) as solvent gave (15) (3.92 g, 45.2%).

(d) DMAD (4.75 g) was added to a stirred mixture of 1,3-dihydrobenzimidazole-2-thione (5.00 g), acetonitrile (100 ml), and water (50 ml). The mixture was stirred at room temperature for 20 min, during which time the thione dissolved and a pale yellow precipitate formed. Filtration gave crude dimethyl (benzimidazol-2-ylthio)fumarate (14) as a yellow powder, m.p. 135—142 °C; ν_max. 1 730s, 1 709s, 1 609s, and 1 599s cm⁻¹.

Reactions of (15).—(a) The adduct (15) (0.48 g) was refluxed in methanol (100 ml) for 30 min. Evaporation of the solution gave (16) (0.46 g, 95.8%).

(b) Repetition of (a) but with the addition of acetic acid (5 ml) gave a quantitative recovery of (15).

(c) The adduct (15) (0.30 g) was refluxed in ethanol (30 ml) containing sodium hydroxide (3 mg) for 30 minutes. Evaporation gave *ethyl 4-oxo-4H-benzimidazo[2,1-b][1,3]-thiazine-2-carboxylate* (18) as yellow microneedles (from ethanol), m.p. 135—137 °C (Found: C, 56.7; H, 3.8; N, 10.0. C₁₃H₁₀N₂O₃S requires C, 56.9; H, 3.7; N, 10.2%); ν_max. 3 061s, 1 743s, 1 702s, and 1 590m cm⁻¹.

(d) Refluxing (15) in t-butyl alcohol (30 g) or ethanol (30 ml) for 30 min gave only starting material.

(e) The adduct (15) (0.26 g) was refluxed for 2 h with a solution of sodium hydroxide (44 mg) in tetrahydrofuran (10 ml) and water (10 ml). Cooling and acidifying with 1M hydrochloric acid (1.2 ml) precipitated 4-oxo-4H-*benzimidazo[2,1-b][1,3]thiazine-2-carboxylic acid* (17) (0.21 g, 85.4%) as pale yellow prisms (from dioxan), m.p. 224—226 °C (Found: C, 53.6; H, 3.0; N, 10.0. C₁₁H₆N₂-O₃S·0.5C₄H₈O₂ requires C, 53.8; H, 3.5; N, 9.7%); ν_max. 1 695s, 1 608s, and 1 595s cm⁻¹.

Cyclisation of (14).—(a) Crude (14) (0.50 g) was refluxed in acetonitrile (20 ml) for 30 min. Evaporation of the solvent yielded (15) (0.44 g, 98.9%).

(b) Crude (14) (0.50 g) was refluxed in methanol (20 ml) for 30 min. Evaporation of the solvent yielded (16) (0.42 g, 94.4%).

Reaction of 4-Imidazoline-2-thione (24) *with DMAD.*—(a) The thione (3.00 g) and DMAD (4.26 g) were refluxed in methanol (50 ml) for 2 h [the addition of acetic acid (15 ml) made no difference]. Filtration of the cooled solution gave *methyl 4-oxo-4H-imidazo[2,1-b][1,3]thiazine-2-carboxy-late* (25) (3.43 g, 54.4%) as yellow plates (from methanol), m.p. 183—185 °C (Found: C, 45.8; H, 3.1. C₈H₆N₂O₃S requires C, 45.7; H, 2.9; N, 13.3%); ν_max. 1 720infl., 1 711s, 1 680s, 1 580s, and 1 510s cm⁻¹.

(b) The thione (24) (1.66 g) and DMAD (2.45 g) were refluxed in acetonitrile (50 ml) for 3 h. Filtration of the cooled solution gave a yellow-orange solid (1.63 g, 46.8%) consisting of a 2:1 mixture of (25) and *methyl 3-oxo-imidazo[2,1-b][1,3]thiazolidin-2-ylideneacetate* (26) by ¹H

n.m.r. spectroscopy. The compounds could not be separated by column chromatography on alumina.

Reaction of Ethanethioamide with DMAD.—(a) Ethanethioamide (3.00 g) and DMAD (5.67 g) were stirred together in methanol (80 ml) at room temperature for 8 h. Next day filtration gave methyl (Z)-2-methoxy-2-methyl-4-oxo-1,3-thiazolidin-5-ylideneacetate (29) (2.81 g, 38.0%) as colourless needles (from methanol) m.p. 157—159 °C [lit.,[5b] m.p. 149 °C (decomp.) for another structure] (Found: C, 44.5; H, 5.3; N, 6.3. $C_8H_{11}NO_4S$ requires C, 44.2; H, 5.1; N, 6.5%); $\nu_{max.}$ 3 160br, 1 699s, 1 628s, and 1 610s cm⁻¹; $\lambda_{max.}$ (M) 249 (ε 3 700) and 306 nm (10 100).

(b) Ethanethioamide (3.00 g) and DMAD (5.67 g) were stirred together in acetonitrile (100 ml) for 2 h. Filtration gave methyl (Z)-2-methylene-4-oxo-1,3-thiazolidin-5-ylideneacetate (30) (3.51 g, 46.2%) as yellow-orange microneedles (from acetone), m.p. 158—161 °C (Found: C, 45.6; H, 3.7; N, 7.5. $C_7H_7NO_3S$ requires C, 45.4; H, 3.8; N, 7.6%); $\nu_{max.}$ 3 155br, 1 698s, 1 679s, 1 612s, and 1 592s cm⁻¹.

(c) Repeating reaction (b) in acetic acid gave (30) (1.82 g, 24.0%).

Conversion of (30) *into* (29).—The adduct (30) (0.40 g) was refluxed in methanol (20 ml) or methanol (15 ml) and acetic acid (5 ml), for 2 h. Evaporation of the solvent gave (29) (0.47 g, 100%).

Reaction of (32) *with DMAD.*—The thiourea (32) (3.50 g) and DMAD (3.41 g) were refluxed in methanol (100 ml) for 2 h. The solvent was evaporated and the residue chromatographed on an alumina column. Chloroform eluted methyl (Z)-2-diethylamino-2-methoxy-4-oxothiazolidin-5-ylideneacetate (36) (3.20 g, 46.3%) as a yellow oil which gradually solidified at −14 °C to give a white powder (from hexane), m.p. 75—76 °C (Found: C, 49.9; H, 7.0; N, 9.6. $C_{12}H_{20}N_2O_4S$ requires C, 50.0; H, 7.0; N, 9.7%); $\nu_{max.}$ 1 703infl, 1 690s, and 1 612s cm⁻¹; $\lambda_{max.}$ (M) 253.5 (ε 8 000) and 310 nm (8 300); $\lambda_{max.}$ (A) 256 (ε 7 400) and 304 nm (7 600).

Hydrolyses of (36).—The adduct (34) (0.30) was refluxed in tetrahydrofuran (10 ml) containing 0.2M aqueous hydrochloric acid (20 ml) for 2 h. Chloroform (50 ml) now extracted methyl Z-3-methyl-2,4-dioxothiazolidin-5-ylideneacetate (37) (0.17 g, 72.2%) as colourless needles (from ethanol) m.p. 111—112 °C (lit.,[11] 112—113 °C); $\nu_{max.}$ 1 750s, 1 690br, and 1 622s.

Reaction of (34) *with DMAD.*—The thione (34) (1.00 g), DMAD (1.22 g) and methanol (15 ml) were stirred overnight. After evaporating most of the mixture it was cooled to −14 °C. Filtration gave methyl (Z)-perhydro-7a-methoxy-7-methyl-3-oxoimidazo[2,1-b][1,3]thiazol-2-ylideneacetate (35) (0.84 g, 37.8%) as colourless rods, m.p. 92—96 °C (Found: C, 46.2; H, 5.3; N, 10.7. $C_{10}H_{14}N_2O_4S$ requires C, 46.2; H, 5.5; N, 10.8%); $\nu_{max.}$ 3 060m, 1 694s, 1 688s, 1 654m, 1 635w, and 1 610s cm⁻¹.

Reaction of 2-Oxo-2-phenylethanethioamide (38) *with DMAD.*—(a) The thioamide (2.20 g) and DMAD (1.90 g) were refluxed in methanol (50 ml) for 3 h and left overnight at −14 °C. Filtration gave methyl (Z)-2-benzoyl-2-methoxy-4-oxo-1,3-thiazolidin-5-ylideneacetate (39) (2.42 g, 59.8%) as yellow prisms (from methanol), m.p. 217—221 °C (Found: C, 54.8; H, 4.4; N, 4.6%. $C_{14}H_{13}NO_5S$ requires C, 54.7; H, 4.3; N, 4.6%); $\nu_{max.}$ 3 180m, 3 080infl, 1 693s, 1 610m, 1 600m, and 1 581m cm⁻¹; $\lambda_{max.}$ (M) 256 (ε 13 800) and 302 nm (10 800); $\lambda_{max.}$ (A) 254.5 (ε 14 300) and 301 nm (12 000).

(b) The thioamide (2.50 g) and DMAD (2.15 g) in acetonitrile were stirred at room temperature for 1 h and left

overnight. Filtration gave methyl Z-2-benzoyl-2-(1-imino-2-oxo-2-phenylethylthio)-4-oxo-1,3-thiazolidin-5-ylidene-acetate (40) as cream prisms (from acetonitrile), m.p. 152—157 °C (Found: C, 57.5; H, 3.9; N, 6.3%. $C_{21}H_{16}N_2O_5S_2$ requires C, 57.3; H, 3.7; N, 6.4%); $\nu_{max.}$ 3 150m, 1 690s, 1 666s, 1 621m, 1 597m, 1 590m, and 1 575m cm⁻¹.

Reaction of 2-Aminobenzenecarbothioamide (47) *with DMAD.*—DMAD (1.86 g) was added to a stirred solution of the thioamide (2.00 g) in methanol (40 ml). The mixture turned deep red immediately and after 30 min the precipitate of methyl 2-(2-aminophenyl)-4-oxo-1,3-thiazolidin-5-ylideneacetate (46) was collected as deep red microneedles (from chloroform), m.p. 217—221.5 °C (Found: C, 54.8; H, 4.0; N, 10.6. $C_{12}H_{10}N_2O_3S$ requires C, 55.0; H, 3.8; N, 10.7%); $\nu_{max.}$ 3 360m, 3 260m, 1 691s, 1 645m, 1 622m, 1 603m, and 1 584w cm⁻¹; $\lambda_{max.}$ (M) 246.5infl. (ε 9 200), 264infl. (4 800), 319 (13 500), and 375 nm (13 400); $\lambda_{max.}$ (A) 228infl. (ε 7 800) and 311 nm (9 400).

Reaction of N-Methyl-2-aminobenzenecarbothioamide (48) *and DMAD.*—The thioamide (48) (1.50 g) and DMAD (1.28 g) were refluxed in methanol (40 ml) for 6 h. Evaporation and trituration of the residue with ether gave methyl 2-methoxycarbonyl-4-methyliminobenzo[d]-3,1-thiazin-2-ylacetate (49) (1.21 g, 43.5%) as yellow prisms (from methanol), m.p. 123—125 °C (Found: C, 54.6; H, 5.4; N, 8.9. $C_{14}H_{16}N_2O_4S$ requires C, 54.5; H, 5.2; N, 9.1%); $\nu_{max.}$ 3 370s, 1 745s, 1 724s, 1 613s, 1 588m, and 1 513s cm⁻¹; $\lambda_{max.}$ (M) 236 (ε 22 900), 276.5 (6 300), and 319 nm (8 500).

Reaction of Indoline-2-thione with DMAD.—The thione (1.50 g) and DMAD (1.50 g) in methanol (40 ml) were stirred overnight. On refluxing the resulting solution for 5 h an orange-red precipitate formed. Filtration gave methyl 4-oxo-4H-indolo[2,1-b][1,3]thiazine-2-carboxylate (56) (0.43 g, 16.5%) as scarlet needles (from toluene), m.p. 212—215 °C (Found: C, 60.2; H, 3.6; N, 5.3%. $C_{13}H_9NO_3S$ requires C, 60.2; H, 3.5; N, 5.4%); $\nu_{max.}$ 1 730infl., 1 723s, 1 690s, 1 613m, 1 602s, 1 580s, and 1 542s cm⁻¹. On cooling the filtrate to −14 °C dimethyl (indol-2-ylthio)fumarate (54) (1.03 g, 35.2%) precipitated as yellow microneedles (from methanol), m.p. 88—90 °C (Found: C, 57.7; H, 4.6; N, 4.9. $C_{14}H_{13}NO_4S$ requires C, 57.7; H, 4.5; N, 4.8%); $\nu_{max.}$ 3 380s, 3 120w, 3 070w, 1 740s, 1 726s, 1 705s, 1 690s, 1 610m, and 1 597m cm⁻¹.

Refluxing (54) (100 mg) in acetonitrile or dioxan for 8 h caused no change, but in methanol (5 ml) or acetic acid (5 ml) for 30 min cyclisation into (56) took place in 87% and 76% yield, respectively.

Dimethyl (Indol-3-ylthio)fumarate.—1H-Indole-3-thiol (1.50 g, obtained as described [40]), methanol (30 ml), and dimethyl acetylenedicarboxylate (1.50 g) were refluxed overnight under nitrogen. Evaporation of the solvent and trituration with ether gave the thiofumarate as yellow microneedles (1.61 g) (from methanol-ether), m.p. 96 °C (Found: C, 57.5; H, 4.5; N, 5.0. $C_{14}H_{13}NSO_4$ requires C, 57.7; H, 4.5; N, 4.8%); $\nu_{max.}$ 3 420s, 1 730s, 1 678m, 1 615w, and 1 580s cm⁻¹.

Reaction of Pyrimidine-2(1H)-thione with DMAD.—(a) The thione (1.50 g) and DMAD (1.90 g) were refluxed in methanol (50 ml) for 12 h and cooled to −14 °C. Filtration gave dimethyl meso-2,3-di(pyrimidin-2-ylthio)butane-1,4-dioate (57) (1.09 g, 42.8%) as white needles (from dichloromethane), m.p. 160—162 °C (Found: C, 45.6; H, 4.2; N, 15.0. $C_{14}H_{14}N_4O_4S_2$ requires C, 45.9; H, 3.9; N, 15.3%), $\nu_{max.}$ 1 982w, 1 935w, 1 736s, 1 700m, 1 580s, and 1 556s

cm^{-1}; $\lambda_{max.}$ (M) 247.5 (ε 17 520) and 285 (8 020) cm^{-1}. (A) 248 (ε 17 050) and 289 nm (10 000).

(b) (*With D. J. M. Lucas*). The thione (1.0 g) was stirred overnight at room temperature with DMAD (1.3 g) in calcium hydride-dried acetonitrile (50 ml), when all suspended solid had dissolved. The solvent was removed *in vacuo* at room temperature and the residual oil, in the minimum amount of ether, was cooled to -19 °C, when dimethyl (*pyrimidin-2-ylthio*)*fumarate* (59) crystallised as colourless needles (0.79 g) [from light petroleum (b.p. 40—60 °C)], m.p. 85—87 °C (Found: C, 47.2; H, 4.3. $C_{10}H_{10}$-N_2O_4S requires C, 47.3; H, 4.0%).

Reaction of Pyridine-2(1H)-thione with DMAD.—DMAD (2.52 g) was slowly added to a solution of the thione (2.00 g) in methanol (50 ml) at room temperature. The reaction mixture warmed up rapidly and on standing overnight a precipitate was produced. Filtration gave *dimethyl meso-2,3-di-(2-pyridylthio)butane-1,4-dioate* (58) (0.98 g, 29.8%), m.p. 174—176 °C; $\nu_{max.}$ 1 735s, 1 578m, and 1 536m cm^{-1}.

Reaction of Acridine-9(10H)-thione with DMAD.—DMAD (0.94 g) was added to a stirred suspension of the thione (1.40 g) in methanol (70 ml). The deep red colour due to the thione was rapidly discharged and after 5 min a cream precipitate had formed. Next day filtration gave *dimethyl* (*acridin-9-ylthio*)*fumarate* (1.42 g, 60.6%) as yellow plates (from methanol), m.p. 195—198 °C (Found: C, 64.5; H, 4.4; N, 3.9%. $C_{19}H_{15}NO_4S$ requires C, 64.6; H, 4.3; N, 4.0%); $\nu_{max.}$ 1 732m, 1 708m, 1 628m, 1 599m, and 1 588s cm^{-1}.

Reaction of Acridine-9(10H)-thione with Methyl Propiolate.—Methyl propiolate (0.36 g) was added to a stirred suspension of the thione (0.90 g) in warm methanol (50 ml). Next day the precipitate of *methyl* (*acridin-9-ylthio*)-*acrylate* (0.68 g, 54.0%) was collected as yellow plates (from methanol), m.p. 189—193.5° (Found: C, 69.2; H, 4.5; N, 4.8%. $C_{17}H_{13}NO_2S$ requires C, 69.1; H, 4.4; N, 4.7%); $\nu_{max.}$ 3 080w, 1 700s, 1 660w, 1 625m, 1 570m, 1 550m, and 1 522m cm^{-1}.

Reaction of 1,2,3-Triphenylguanidine and DMAD.—The guanidine (6.00 g) and DMAD (3.00 g) were stirred together at room temperature for 1 h and left to stand overnight. Filtration gave *methyl* (Z)-1,3-*diphenyl-2-phenylimino-4-oxoimidazolidin-5-ylideneacetate* (60) (5.93 g, 71.5%) as pale yellow cubes (from ethyl acetate), m.p. 217—219 °C (lit.,[23] m.p. 225 °C, 75%) (Found: C, 72.4; H, 4.8; N, 10.7. $C_{24}H_{19}N_3O_3$ requires C, 72.5; H, 4.8; N, 10.6%); $\nu_{max.}$ 1 750s, 1 714s, 1 699s, 1 654s, 1 593s, and 1 497s cm^{-1}.

Reaction of Guanidine and DMAD.—Guanidine hydrochloride (4.00 g) was dissolved in a solution of sodium hydride (2.00 g) in methanol (100 ml). DMAD (5.95 g) was added and the mixture stirred overnight. Filtration gave methyl Z-2-imino-4-oxoimidazolidin-5-ylideneacetate (62) (1.62 g, 22.9%) as a pale yellow powder (from methanol), m.p. >300 °C (lit.,[25] 345 °C).

Reaction of 1,2,3-Triphenylguanidine with Methyl Propiolate.—The guanidine (5.00 g) and methyl propiolate (1.46 g, 1.56 ml) were refluxed together in methanol (70 ml) for 8 h. The solvent was evaporated and the residue chromatographed on alumina. A band, eluted with chloroform, gave a sticky oil on evaporation. This material was re-chromatographed, monitoring successive fractions by ^{1}H n.m.r. spectroscopy. Combination of appropriate fractions, evaporation, and trituration with ether gave 2,3-*dihydro-1,3-diphenyl-2-phenyliminopyrimidin-4(1H)-one* (64) (1.53 g, 25.9%), as white microcrystals (from chloro-

form–ether), m.p. 138—140 °C (Found: C, 77.9; H, 5.0; N, 12.4. $C_{22}H_{17}N_3O$ requires C, 77.8; H, 5.1; N, 12.4%); $\nu_{max.}$ 3 082m, 1 697s, 1 649s, 1 591s, and 1 498m cm^{-1}.

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