Nitrile Sulphides. Part 7.[1] Synthesis of [1]Benzopyrano[4,3-*c*]isothiazoles and Isothiazolo[4,3-*c*]quinolines

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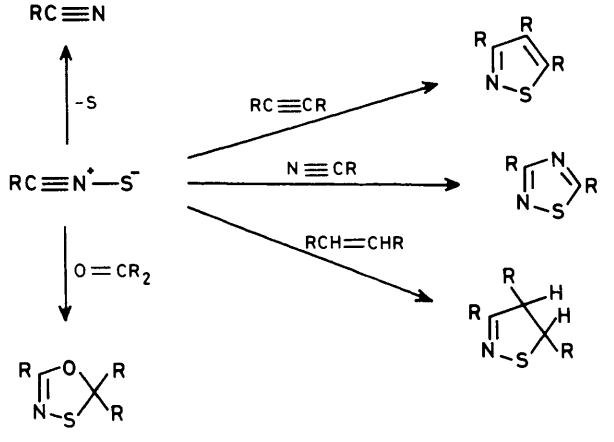
o-Hydroxybenzonitrile sulphide (**1a**), generated by thermal decarboxylation of the corresponding 1,3,4-oxathiazol-2-one, reacts with dimethyl acetylenedicarboxylate to afford methyl 4-oxo-4*H*-[1]benzopyrano[4,3-*c*]isothiazole-3-carboxylate (**6a**), from which the parent ring system (**6c**) can be prepared by hydrolysis and decarboxylation. The same products are formed from the acetoxy analogue (**1b**) *via* hydrolysis of isothiazole (**5b**). *o*-Acetamidobenzonitrile sulphide (**1c**) reacts similarly forming isothiazole (**5c**) and subsequently isothiazolo[4,3-*c*]quinolin-4(5*H*)-one (**7c**) by hydrolysis, ring closure, and decarboxylation. Cycloadditions to ethyl cyanoformate, ethyl propiolate, and diethyl fumarate have also been examined.

The 1,3-dipolar cycloaddition reactions of nitrile sulphides ($RC{\equiv}N^{+}-S^{-}$) are proving of particular value for the synthesis of 5-membered heterocycles incorporating the C=N–S unit. For example, cycloaddition to alkynes, nitriles, alkenes, and carbonyl compounds affords, respectively, isothiazoles,[2] 1,2,4-thiadiazoles,[3] 4,5-dihydroisothiazoles,[4] and 1,3,4-oxathiazoles[5] (Scheme 1). In the absence of a dipolarophile fragmentation



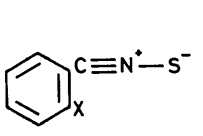
Scheme 1.

leads to sulphur and the corresponding nitrile. Although a variety of nitrile sulphides bearing alkyl, aryl, and occasionally more reactive substituents have been reported, little attention has been paid to *ortho*-substituted aryl derivatives. Howe *et al.*[6] utilised *o*-cyanobenzonitrile sulphide to synthesize *o*-(1,2,4-thiadiazolyl)benzoates as potential herbicides and plant growth regulators, and we have previously reported[7] intramolecular 1,3-dipolar cycloadditions involving *o*-cinnamoyloxy and *o*-phenylpropioloyloxy analogues.

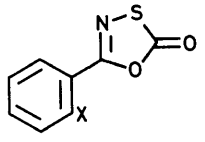
We have now examined the reactions of *o*-hydroxybenzonitrile sulphide (**1a**), its acetyl derivative (**1b**), and *o*-acetamidobenzonitrile sulphide (**1c**), and find that they provide access to some polycyclic heterocycles in addition to the expected 1,3-dipolar cycloadducts.

Results and Discussion

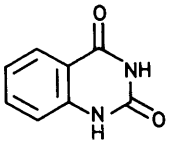
Generation of Nitrile Sulphides.—The route selected for generating the nitrile sulphides involved thermal decarboxylation of the corresponding 1,3,4-oxathiazol-2-ones (**2**).[2] *o*-Hydroxyphenyloxathiazolone (**2a**) was readily prepared (78%) by heating salicylamide with chlorocarbonylsulphenyl chloride in dioxane at *ca.* 100 °C for 1.5 h. The product was separated from traces of *o*-cyanophenol, sulphur, and unchanged amide by chromatography and purified by recrystallisation. It has a good shelf-life and is a valuable source of various *o*-acyloxy derivatives.[8] There was no indication of a competing reaction between ClCOSCl and the phenolic hydroxy group. The acetoxy analogue (**2b**) was initially synthesized from *o*-acetoxybenzamide and ClCOSCl in the usual way, but yields were generally rather low and variable, probably due to prior isomerisation of the starting material to *N*-acetylsalicylamide. Acetylation of *o*-hydroxyoxathiazolone (**2a**) proved to be a much more reliable approach. For instance, the overall yield from salicylamide of oxathiazolone (**2a**) by the former method was 9%, whereas on reversing the order of the steps the yield rose to 72%. Most subsequent *o*-acyloxy derivatives have been prepared by this route. Attempts to synthesize the *o*-amino compound (**2d**) from anthranilamide were unsuccessful,



(**1**)



(**2**)



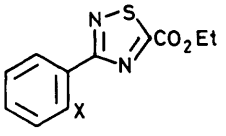
(**3**)

a, X = OH; **b**, X = OAc; **c**, X = NHAc; **d**, X = NH_2

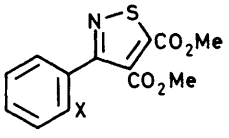
the only isolated product being quinazolinedione (**3**) formed, presumably, by initial reaction of ClCOSCl at the amino group, followed by extrusion of sulphur and cyclisation. On the other hand treatment of *o*-acetamidobenzamide with ClCOSCl yielded the required oxathiazolone (**2c**) (30%).

1,3-*Dipolar Cycloadditions.*—*Ethyl cyanoformate* (*ECF*). It was anticipated that the reactions of oxathiazolones (**2a**)—(**2c**)

would broadly parallel those of simple aryl analogues, thermal decarboxylation affording nitrile sulphides as transient intermediates. This was confirmed by heating in the presence of an excess of ECF,[3,9] which is an ideal dipolarophile for trapping nitrile sulphides. It is highly reactive, it has sufficient stability to allow prolonged reaction times, its relatively low boiling point (*ca.* 115 °C) allows the excess to be removed with the solvent, and the resulting thiadiazole cycloadducts are often easily characterisable crystalline solids. A solution of the phenol–oxathiazolone (**2a**) in xylene was heated under reflux in the presence of ECF (1:2) for 18 h by which time h.p.l.c. analysis indicated that no starting material remained. Removal of the solvent and excess of ECF afforded thiadiazole (**4a**) (85%) as a pale yellow solid. No *o*-cyanophenol could be detected by t.l.c. The product showed ^{13}C n.m.r. peaks at 173.7 and 177.8 p.p.m. characteristic of the heterocyclic ring carbons, C-3 and C-5, of 3-aryl-1,2,4-thiadiazole-5-carboxylates.[10] The acetoxy and acetamido compounds (**2b**)—(**2d**) behaved similarly yielding the thiadiazoles (**4b**) (73%) and (**4c**) (98%). In neither case was nitrile or sulphur detected. The absence of such by-products, which are a common feature of nitrile sulphide reactions,[4a] is a clear indication of the high reactivity of both the dipolarophile and these particular nitrile sulphides.



(**4**)



(**5**)

a, X = OH; **b**, X = OAc; **c**, X = NHAc

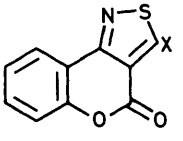
Dimethyl acetylenedicarboxylate (*DMAD*). Having demonstrated that ethyl cyanoformate was capable of intercepting nitrile sulphides (**1a**—**c**) their reactions with DMAD, also a reactive dipolarophile, were examined. Parallel behaviour would be expected to lead to dimethyl 3-arylisothiazole-4,5-dicarboxylates (**5**). This was indeed the case for nitrile sulphides (**1b**) and (**1c**), the isothiazoles (**5b**) (90%) and (**5c**) (67%) being isolated together with *o*-acetoxybenzonitrile (10%) and *o*-acetamidobenzonitrile (33%), respectively. The spectroscopic properties of the adducts were typical of such isothiazoles with, for example, characteristic ^{13}C n.m.r. absorbances for the heterocyclic ring at 163—165, 133—136, and 156 p.p.m. for C–3, C–4, and C–5, respectively. In contrast no such isothiazole (**5a**) was formed from the phenolic nitrile sulphide (**1a**). Thermolysis of a xylene solution of oxathiazolone (**2a**) with DMAD (1:2) yielded *o*-cyanophenol (8%) and a pale yellow solid which was identified as methyl 4-oxo-4*H*-[1]benzopyrano-[4,3-*c*]isothiazole-3-carboxylate (**6a**) (91%) on the basis of its analytical and spectroscopic properties. Elemental analysis and mass spectrometry (M^+, 261) gave a molecular formula $C_{12}H_7NO_4S$. There were ^{13}C n.m.r. peaks (Table) consistent with both the oxobenzopyran and isothiazole rings while the ^1H n.m.r. spectrum shows the presence of only one of the two original methoxycarbonyl groups. Compound (**6a**) presumably results from 1,3-dipolar cycloaddition of nitrile sulphide (**1a**) to DMAD, followed by intramolecular elimination of methanol between the phenolic hydroxy and the methyl ester at the 4-position of the isothiazole cycloadduct (**5a**). That such a process can readily take place was demonstrated by the hydrolysis of the *o*-acetoxy derivative (**5b**). Treatment at room temperature with 5% KOH in aqueous methanol yielded the carboxylic acid (**6b**) (87%) resulting from hydrolysis and intramolecular condensation. Attempts to prepare the phenolic isothiazole (**5a**) by selective hydrolysis of its acetate derivative under milder conditions failed, the only isolated products being the ester (**6a**) and acid (**6b**), together with unchanged starting material. Formation of the ester (**6a**) suggests that selective hydrolysis had taken place, followed by rapid intramolecular expulsion of methanol.

Table. ^{13}C N.m.r. chemical shifts for the benzopyranoisothiazoles (**6a**—**c**) (in $CDCl_3$) and isothiazoloquinoline (**7c**) [in $(CD_3)_2SO$]

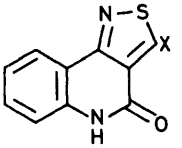
	(**6a**)	(**6c**)	(**6e**)	(**7c**)
C-3	164.0	156.8	164.3	155.2
C-3a	120.8	123.1	120.4	127.9
C-4	154.0	156.2	153.8	157.7
C-5a	152.5	152.5	152.2	138.1
C-6	132.3	131.9	132.1	131.0
C-7	124.8	124.8	124.6	123.8
C-8	124.2	124.2	123.9	122.5
C-9	117.1	117.2	116.8	116.2
C-9a	116.4	116.4	116.1	116.1
C-9b	162.2	161.2	161.9	161.5
CO_2R	159.0		158.4	
Me	53.6			
CH_2Me			63.1	
CH_2Me			13.7	

Availability of the carboxylic acid (**6a**) allows access, for the first time, to the parent 4-oxo-4*H*-[1]benzopyrano[4,3-*c*]-isothiazole ring system (**6c**). Decarboxylation was achieved by heating under reflux a solution of the acid (**6b**) in *o*-dichlorobenzene for 1 h. Removal of the solvent yielded (**6c**) (81%), the ^1H n.m.r. spectrum of which shows an absorption at δ 9.72 characteristic[2] of a proton at the 5-position of an isothiazole. 4*H*-[1]Benzopyrano[4,3-*c*]isothiazoles are a rare group of heterocycles, the only previous examples[7] being 3-aryl derivatives (**6d**) formed by intramolecular cycloadditions involving, for example, *o*-cinnamoyloxybenzonitrile sulphides.

Having established that *o*-acetoxyphenyloxathiazolone (**2b**) could be converted into the [1]benzopyrano[4,3-*c*]isothiazoles, the corresponding reaction for the acetamido compound (**2c**) was examined. By analogy, hydrolysis and ring closure should lead to the isothiazoloquinolines (**7**). In this case more forcing conditions were required; hydrolysis for 1.5 h in boiling 10%



(**6**)



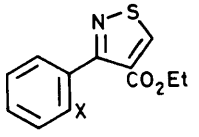
(**7**)

a, X = CO_2Me; **b**, X = CO_2H; **c**, X = H, **d**. X = Ar; **e**, X = CO_2Et

H_2SO_4 followed by thermolysis (20 h) in refluxing xylene afforded isothiazolo[4,3-*c*]quinoline-4(5*H*)-one (**7c**) in 74% yield. The identity of the product follows from its analytical and spectroscopic properties. There are ^{13}C n.m.r. peaks attributable to both isothiazole and quinolinone rings, while the ^1H n.m.r. spectrum shows distinctive signals at δ 11.4 (broad) and δ 9.99 which are assigned, respectively, to NH and the proton at C-3 (5-H of the isothiazole). The expected lactam rather than lactim arrangement is also confirmed by absorptions for the carbonyl group at 1 665 cm^{-1} in the i.r. and at 157.7 p.p.m. in the ^{13}C n.m.r. spectrum. Compound (**7c**) is believed to be the first example of an isothiazole fused [4,3-*c*] to a quinoline.

Ethyl propiolate (*EP*). Apart from DMAD, ethyl propiolate

is the acetylenic dipolarophile most reactive towards nitrile sulphides so far reported.[2,10] In contrast to the reaction with nitrile oxides ($RC{\equiv}N^{+}-O^{-}$) in which isoxazole-5-carboxylates are the major products,[11] a *ca.* 1:1 mixture of 4- and 5-substituted cycloadducts is usually formed with nitrile sulphides. Nitrile sulphide (**1b**) proves to be no exception, thermal decarboxylation of oxathiazolone (**2b**) in the presence of EP (1:4) affording the isothiazoles (**8b**) (47%) and (**9b**) (46%) together with *o*-acetoxybenzonitrile (7%). Similar regioselectivity was observed for EP with nitrile sulphide (**1a**). In this case, however, benzopyranoisothiazole (**6c**) (20%) was formed together with the expected 5-carboxylate (**9a**) (20%) and *o*-cyanophenol (45%). The former compound presumably resulted from initial 1,3-dipolar cycloaddition followed by



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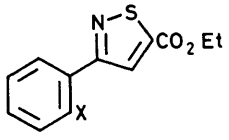
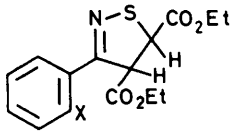


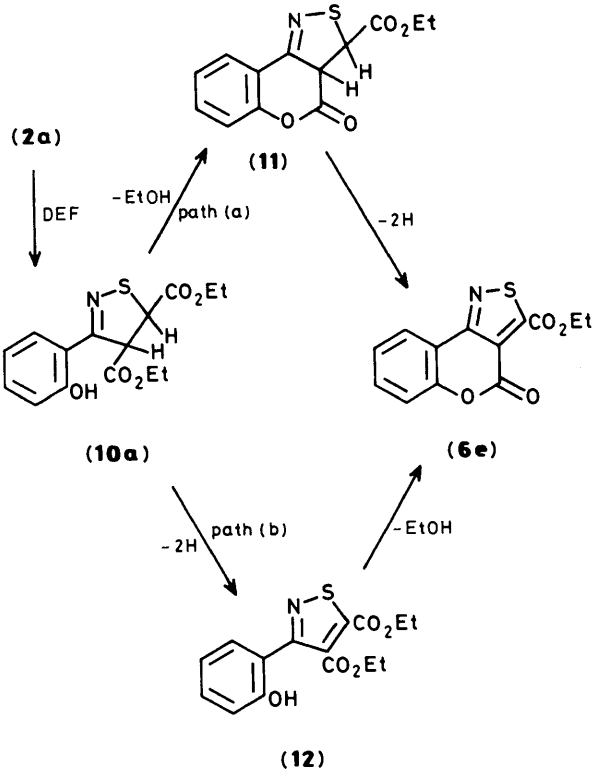
(**9**)



(**10**)

a, X = OH; b, X = OAc; c, X = H

risen to 26%. This sequence of events may be explained by either of the pathways shown in Scheme 2. Both possible intermediates (**11**) and (**12**) would be expected to yield the observed product,



Scheme 2.

intramolecular expulsion of ethanol from the isothiazole (**8a**). These results indicate that the *ortho*-substituents examined here have little or no effect on regioselectivety.

Diethyl fumarate (*DEF*). The last dipolarophile to be examined was DEF. Like electron-deficient alkynes, dialkyl fumarates are sufficiently reactive to undergo cycloaddition to nitrile sulphides, the products in this case being 4,5-dihydroisothiazoles (Δ^2-isothiazolines).[4a] Cycloadditions of nitrile sulphides (**1a**,**b**) to DEF were found not to be as clean reactions as those described above for ECF, DMAD, and EP. However, the expected isothiazolines, (**10a**) (26%) and (**10b**) (56%), were formed although in each case the product was rather unstable and was not fully purified. They were identified by their ^{1}H n.m.r. spectra which each show a distinctive pair of doublets for the 4- and 5-H of the heterocyclic ring at δ 5.2—5.3 and 4.6—4.9. The coupling of 2.7 Hz is consistent with their *trans*-arrangement in the isothiazoline ring. The spectrum of compound (**10a**) also has a sharp singlet at δ 11.15 which is assigned to the phenolic proton. It is noteworthy that this phenolic isothiazoline is much more stable that its isothiazole counterpart (**5a**).

In the reaction of nitrile sulphide (**1a**) with DEF a small quantity (15%) of benzopyranoisothiazole (**6e**) was also isolated. In an attempt to elucidate its mode of formation the reaction was repeated and monitored by ^{1}H n.m.r. spectroscopy. After 18 h at 135—140 °C the presence of adduct (**10a**) was confirmed by the appearance of two doublets at δ 5.19 and 4.65. The yield of benzopyranoisothiazole (**6e**) at that point was determined as 18% by h.p.l.c. analysis, which also confirmed that no starting material remained. The reaction mixture was then heated under reflux for a further 40 h, by which time no isothiazoline could be detected and the yield of compound (**6e**) had

the former by dehydrogenation and the latter by ring closure with displacement of ethanol. Of the two alternatives path (a) is considered to be more likely. Ring closure of compound (**10a**) to (**11**) with elimination of ethanol parallels, albeit at a slower rate, the known behaviour of the DMAD adduct (**5a**) described above, whereas rapid oxidation of 3-aryl-Δ^2-isothiazolines to isothiazoles—the key step in path (b)—is not expected to be favoured under the reaction conditions. Although 3-phenylisothiazoline (**10c**) can be oxidised to the corresponding isothiazole, either at room temperature using sodium hypochlorite[8] or DDQ[4a] or at higher temperatures using sulphur and/or oxygen,[8] under the latter conditions the reaction is slow and low yielding. Failure to detect compound (**11**) by ^{1}H n.m.r. spectroscopy is consistent with the first stage in path (a) being rate-determining; the second step—rapid dehydrogenation of the benzopyranoisothiazoline to benzopyranoisothiazole—is similar to that invoked[7] to explain the formation of an isothiazole rather than an isothiazoline from the intramolecular reaction of *o*-cinnamoyloxybenzonitrile sulphides.

In conclusion, the results described herein demonstrate an efficient synthetic route to [1]benzopyrano[4,3-*c*]isothiazoles *via* *o*-hydroxy- and -acetoxy-benzonitrile sulphides by reaction with DMAD and, to a lesser extent in view of concomitant formation of a monocyclic isothiazole, from ethyl propiolate. Similarly, *o*-acetamidobenzonitrile sulphide provides access, for the first time, to the isothiazolo[4,3-*c*]quinolinone ring system.

Experimental

The instrumentation for recording i.r., ^{1}H and ^{13}C n.m.r. and mass spectra, and the analytical methods used for monitoring

the reactions were as previously described.[12] N.m.r. spectra were recorded in $CDCl_3$ unless otherwise stated.

Preparation of Oxathiazolones (**2a—c**).—5-(o-*Hydroxyphenyl*)-1,3,4-*oxathiazol*-2-*one* (**2a**). This compound was prepared by a modified version of the route described in the literature[13] for 5-aryl derivatives. A solution of salicylamide (1.37 g, 10.0 mmol) and chlorocarbonylsulphenyl chloride (2.0 g, 15 mmol) in dioxane (20 ml) was heated under reflux for 3 h by which time evolution of HCl had ceased and t.l.c. showed no amide remained. Removal of the solvent and excess of ClCOSCl afforded a pale yellow solid. Separation from traces of sulphur and *o*-cyanophenol by flash chromatography and recrystallisation from ethanol yielded the oxathiazolone (**2a**) (78%) as colourless needles, m.p. 83—85 °C (lit.,[14] 80—81 °C); $\nu_{max.}$(Nujol) 3 200 (OH), 1 795 and 1 760 cm^{-1} (C=O); δ_H(80 MHz) 9.70 (1 H, s, OH), and 6.8—7.7 (4 H, m, ArH); δ_C(50 MHz) 170.8 (C-2), 159.1, 158.5, and 109.6 (C-5 and ArC), 134.7, 128.1, 119.9, and 117.8 (ArCH); *m/z* 195 (M^+), 151 ($[M^+ - CO_2]^+$).

5-(o-*Acetoxyphenyl*)-1,3,4-*oxathiazol*-2-*one* (**2b**). This compound was synthesized from salicylamide by two methods: (a) *via* *O*-acetylsalicylamide and (b) from *o*-hydroxyphenyloxathiazolone (**2a**).

Method (a). Salicylamide was converted into *O*-acetylsalicylamide by treatment at *ca.* −20 °C with acetyl chloride (1:1) in diethyl ether in the presence of pyridine. The crude product, after drying, was used for the second stage without further purification. Chlorocarbonylsulphenyl chloride (2.16 g, 16.5 mol) was added dropwise to a solution of *O*-acetylsalicylamide (2.69 g, 15.0 mmol) in dry chloroform and the mixture heated under reflux for 3.5 h. Removal of the solvent and excess of ClCOSCl afforded a yellow oil from which crystallised with time (*ca.* 2 days) a white solid which proved to be *N*-acetylsalicylamide (t.l.c., i.r.). The mother liquor was cooled (*ca.* −20 °C) and triturated with ethanol to yield the oxathiazolone (**2b**) (16%, 9% overall from salicylamide) as white needles, m.p. 71—73 °C (lit.,[14] 70—71 °C); $\nu_{max.}$(Nujol) 1 754 and 1 767 cm^{-1} (C=O); δ_H(200 MHz) 7.1—8.1 (4 H, m, ArH), and 2.34 (3 H, s, Me); δ_C(20 MHz), 172.6 (C-2), 169.2 (*C*OMe), 154.4 (C-5), 148.9 and 118.7 (ArC), 133.4, 129.9, 126.3, and 124.2 (ArCH), and 20.7 (Me); *m/z* 237 (M^+).

Method (b). A solution of the oxathiazolone (**2a**) (3.90 g, 20.0 mmol) and acetyl chloride (1.8 ml, 20 mmol) in diethyl ether (250 ml) with triethylamine (5 ml) was stirred for 1.5 h at room temperature. Evaporation to dryness under reduced pressure and recrystallisation of the residue from hexane afforded the oxathiazolone (**2b**) (86%, 72% overall from salicylamide).

5-(o-*Acetamidophenyl*)-1,3,4-*oxathiazol*-2-*one* (**2c**). A mixture of *o*-acetamidobenzamide (0.89 g, 5.0 mmol), chlorocarbonylsulphenyl chloride (0.72 g, 5.5 mmol), and dioxane was stirred at room temperature for 2 days. Suspended solids were filtered off and the filtrate evaporated under reduced pressure. Flash chromatography of the residue (silica, 40% ethyl acetate in hexane) afforded the *oxathiazolone* (**2c**) (17%, 30% based on consumed amide) as white needles, m.p. 131—133 °C (from cyclohexane–ethyl acetate) (Found: C, 50.6; H, 3.2; N, 11.6. $C_{10}H_8N_2O_3S$ requires C, 50.8; H, 3.4; N, 11.9%); $\nu_{max.}$(Nujol) 3 320 (NH), 1 750 and 1 670 cm^{-1} (C=O); δ_H(80 MHz) 10.41 (1 H, s, NH), 7.0—8.6 (4 H, s, ArH), and 2.17 (3 H, s, Me); δ_C (50 MHz) 170.8 (C-2), 168.5 (CONH), 157.8 (C-5), 138.9 and 111.2 (ArC), 133.7, 129.1, 122.8, and 120.6 (ArCH), and 25.1 (Me); *m/z* 235 (M^+), 192 ($[M - CO_2]^+$). Further elution yielded 2-acetamidobenzonitrile (11%, 20% based on consumed amide) and *o*-acetamidobenzamide (44% recovered).

Attempted preparation of 5-(o-*aminophenyl*)-1,3,4-*oxathiazol*-2-*one* (**2d**). A mixture of anthranilamide (1.36 g, 10.0 mmol), chlorocarbonylsulphenyl chloride (2.0 g, 15 mmol), and dioxane (40 ml) was heated under reflux for 0.5 h by which time no starting material remained (t.l.c.). On cooling, a yellow crystalline precipitate was formed which was identified from its spectroscopic properties as the quinazolinedione (**3**) (0.85 g, 52%), m.p. >350 °C; $\nu_{max.}$(Nujol) 3 250, 3 160, and 3 050 (NH), 1 700 and 1 670 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$, 60 MHz] 10.9 (1 H, s, NH), 10.7 (1 H, s, NH), and 6.8—7.7 (4 H, m, ArH); *m/z* 162 (M^+). There was no evidence for the formation of the oxathiazolone (**2d**).

Reactions with Ethyl Cyanoformate (*ECF*).—*Synthesis of ethyl* 3-*aryl*-1,3,4-*thiadiazole*-5-*carboxylates* (**4**). A solution of 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one (**2a**) (1.95 g, 10.0 mmol) and ECF (2.0 g, 20 mmol) in xylene (25 ml) was heated under reflux for 18 h after which time t.l.c. showed complete consumption of the starting material. There was no trace of *o*-cyanophenol. The solvent and excess of ECF were evaporated under reduced pressure to leave a yellow solid from which was isolated *ethyl* 3-(o-*hydroxyphenyl*)-1,2,4-*thiadiazole*-5-*carboxylate* (**4a**) (2.13 g, 85%) as pale yellow needles, m.p. 93—95 °C (from hexane) (Found: C, 52.7; H, 3.9; N, 11.2. $C_{11}H_{10}N_2O_3S$ requires C, 52.8; H, 4.0; N, 11.2%); $\nu_{max.}$(Nujol) 3 170 (OH), 1 745 cm^{-1} (C=O); δ_H(200 MHz) 10.54 (OH), 6.9—8.3 (4 H, m, ArH), 4.51 (2 H, q, CH_2), and 1.45 (3 H, t, Me); δ_C (50 MHz) 177.8 (C-5), 173.7 (C-3) 157.7, 157.5, and 115.8 (C=O and ArC), 132.9, 129.6, 119.6, and 117.5 (ArCH), 63.3 (CH_2), and 13.9 (Me); *m/z* 250 (M^+).

The corresponding reaction with 5-(*o*-acetoxyphenyl)-1,3,4-oxathiazol-3-one (**2b**) yielded *ethyl* 3-(o-*acetoxyphenyl*)-1,2,4-*thiadiazole*-5-*carboxylate* (**4b**) (73%) as pale yellow needles, m.p. 86—87 °C (from hexane–ethanol) (Found: C, 53.3; H, 4.1; N, 9.4. $C_{13}H_{12}N_2O_4S$ requires C, 53.4; H, 4.1; N, 9.6%); $\nu_{max.}$(Nujol) 1 750 cm^{-1} (C=O); δ_H(80 MHz) 7.0—8.4 (4 H, m, ArH), 4.48 (2 H, q, CH_2), 2.40 (3 H, s, CO*Me*), and 1.41 (3 H, t, CH_2*Me*); δ_C(50 MHz) 178.2 (C-5), 171.2 (C-3), 169.8, and 158.1 (C=O), 149.0 and 124.7 (ArC), 131.7, 131.3, 126.1, 123.8 (ArCH), 62.9 (CH_2), 20.9 (CO*Me*), and 13.8 (CH_2*Me*); *m/z* 292 (M^+).

Reaction of 5-(*o*-acetamidophenyl)-1,3,4-oxathiazol-2-one (**2c**) with ECF (1:15) afforded *ethyl* 3-(o-*acetamidophenyl*)-1,2,4-*thiadiazole*-5-*carboxylate* (**4c**) (98%) as pale yellow needles, m.p. 114—116 °C (from cyclohexane) (Found: C, 53.7; H, 4.6; N, 14.2. $C_{13}H_{13}N_3O_3S$ requires C, 53.6; H, 4.5; N, 14.4%); $\nu_{max.}$(Nujol) 3 190 (NH), 1 745 and 1 693 cm^{-1} (C=O); δ_H(80 MHz) 11.18 (1 H, s, NH), 7.0—8.5 (4 H, m, ArH), 4.43 (2 H, q, CH_2), 2.14 (3 H, s, CO*Me*), and 1.38 (3 H, t, CH_2*Me*); δ_C (50 MHz) 177.7 (C-5), 173.1 (C-3), 168.3 and 157.6 (C=O), 138.0 and 118.1 (ArC), 131.8, 130.5, 122.8, and 120.5 (ArCH), 63.2 (CH_2), 25.0 (CO*Me*), and 13.8 (CH_2*Me*); *m/z* 291 (M^+).

Reactions with Dimethyl Acetylenedicarboxylate (*DMAD*).—*Synthesis of dimethyl* 3-*arylisothiazole*-4,5-*dicarboxylates*. A solution of acetoxyphenyloxathiazolone (**2b**) (3.08 g, 13.0 mmol) and DMAD (3.69 g, 26.0 mmol) in xylene (10 ml) was heated under reflux for 18 h. Removal of the solvent under reduced pressure followed by flash chromatography afforded *o*-acetoxybenzonitrile (0.20 g, 10%) and *dimethyl* 3-(o-*acetoxyphenyl*)*isothiazole*-4,5-*dicarboxylate* (**5b**) (3.93 g, 90%) as white crystals, m.p. 89.5—91 °C (from ethyl acetate–hexane) (Found: C, 53.5; H, 3.9; N, 4.1. $C_{15}H_{13}NO_6S$ requires C, 53.7; H, 3.9; N, 4.2%); δ_H(200 MHz) 7.1—7.6 (4 H, m, ArH), 3.92 (3 H, s, OMe), 3.79 (3 H, s, OMe), and 2.12 (3 H, s, COMe); δ_C(50 MHz) 168.1, 163.1, 162.8, and 158.8 (C=O and C-3), 156.1 (C-5), 147.7 and 126.7 (ArC), 132.8 (C-4), 130.3, 130.2, 125.5, and 122.5 (ArCH), 52.7 and 52.3 (OMe), and 20.2 (CO*Me*); *m/z* 335 (M^+).

The corresponding reaction between acetamidophenyloxathiazolone (**2c**) and DMAD (1:8) afforded *o*-acetamidobenzonitrile (33%) and *dimethyl* 3-(o-*acetamidophenyl*)*isothiazole*-4,5-*dicarboxylate* (**5c**) (24% isolated; 67% by h.p.l.c. analysis) as

white needles, m.p. 144—146 °C (from ethanol) (Found: *m/z* 334.0618. $C_{15}H_{14}N_2O_5S$ requires *M*, 334.06224); $\nu_{max.}$(Nujol) 3 360 (NH), 1 730 cm^{-1} (C=O); δ_H(80 MHz) 9.52 (1 H, s, NH), 7.0—8.4 (4 H, m, ArH), 3.93 (3 H, s, CO_2Me), 3.83 (3 H, s, OMe), 2.08 (3 H, s, COMe); δ_C(50 MHz) 168.2, 164.7, 163.9, and 158.9 (C-3, CONH, and $2CO_2Me$), 155.9 (C-5), 136.4, 136.4, and 134.3 (C-4 and ArC), 130.6, 128.5, 123.5, and 122.7 (ArCH). 53.1 (2 × OMe), and 24.6 (COMe); *m/z* 334 (M^+).

Synthesis of methyl 4-*oxo*-4H-[1]*benzopyrano*[4,3,-c]*isothiazole*-3-*carboxylate* (**6a**). A solution of hydroxyphenyloxathiazolone (**2a**) (1.95 g, 10.0 mmol) and DMAD (2.84 g, 20.0 mmol) in xylene (10 ml) was heated under reflux for 18 h. On cooling a yellow solid precipitated out and was filtered off. Further product was obtained by concentration of the filtrate, trituration of the residue with ethanol, and flash chromatography of the mother liquors. Recrystallisation of these combined fractions from ethanol yielded the *title product* (**6a**) (1.96 g, 75%) as pale yellow needles, m.p. 158—160 °C (Found: C, 55.0; H, 2.7; N, 5.3. $C_{12}H_7NO_4S$ requires C, 55.2; H, 2.7; N, 5.4%); $\nu_{max.}$(Nujol) 1 755 cm^{-1} (C=O); δ_H(200 MHz) 8.18 (1 H, d of d, *J* 8 and *J* 2 Hz, 9-H), 7.2—7.6 (3 H, m, ArH), 4.04 (3 H, s, Me); *m/z* 261 (M^+). ^{13}C N.m.r. chemical shifts are presented in the Table.

Reactions with Ethyl Propiolate (*EP*).—*Synthesis of ethyl* 3-*arylisothiazole*-4-*and*-5-*carboxylates* [(**8**) and (**9**)]. A solution of acetoxyphenyloxathiazolone (**2b**) (1.18 g, 5.0 mmol) and EP (1.96 g, 20.0 mmol) in xylene (20 ml) was heated under reflux for 18 h. Concentration of the reaction mixture and flash chromatography (silica; hexane–ethyl acetate, 5:1) yielded three products. Firstly, *ethyl* 3-(o-*acetoxyphenyl*)*isothiazole*-5-*carboxylate* (**9b**) (0.67 g, 46%) as a yellow oil (Found: *m/z* 291.0569. $C_{24}H_{13}NO_4S$ requires *M*, 291.056 52); $\nu_{max.}$(film) 1 770 and 1 725 cm^{-1} (C=O); δ_H(80 MHz) 8.02 (1 H, s, 4-H), 7.1—7.9 (4 H, m, ArH), 4.40 (2 H, q, CH_2), 2.27 (3 H, s, COMe), 1.39 (3 H, t, CH_2Me); δ_C(50 MHz) 168.9 (C-3), 164.5 (*C*OMe), 159.8 (CO_2Et), 157.3 (C-5), 147.9, and 127.2 (ArC), 130.3, 130.0, 127.1, 126.2, and 123.4 (C-4 and ArCH), 61.9 (CH_2), 20.9 (CO*Me*), and 14.0 (CH_2Me). Secondly, *ethyl* 3-(o-*acetoxyphenyl*)*isothiazole*-4-*carboxylate* (**8b**) (0.68 g, 47%) as a yellow oil (Found: *m/z* 291.0568. $C_{14}H_{13}NO_4S$ requires *M*, 291.056 52); δ_H(80 MHz) 9.30 (1 H, s, 5-H), 7.1—7.7 (4 H, m, ArH), 4.20 (2 H, q, CH_2), 2.04 (3 H, s, COMe), and 1.14 (3 H, t, CH_2Me); δ_C(20 MHz) 168.4 (C-3), 164.2 (*C*OMe), 161.8 (CO_2Et), 154.4 (C-5), 148.0 and 128.3 (ArC), 130.5, 129.9, 125.5, and 122.0 (C-4 and 4 × ArCH), 61.0 (CH_2), 20.5 (CO*Me*), and 13.6 (CH_2Me). Thirdly, *o*-acetoxybenzonitrile (0.04 g, 7%). Attempted distillation (210 °C, 1 mmHg) of both isothiazoles resulted in partial decomposition.

The corresponding reaction between hydroxyphenyloxathiazolone (**2a**) and EP (1:4) afforded three products. Firstly *ethyl* 3-(o-*hydroxyphenyl*)*isothiazole*-5-*carboxylate* (**9a**) (20%) as white crystals, m.p. 97.99 °C (from cyclohexane) (Found: C, 57.6; H, 4.3; N, 5.4. $C_{12}H_{11}NO_3S$ requires C, 57.8; H, 4.4; N, 5.6%): $\nu_{max.}$(Nujol) 3 100 (OH), 1 705 cm^{-1} (C=O); δ_H(80 MHz) 11.24 (1 H, s, OH), 8.11 (1 H, s, 4-H), 6.8—7.7 (4 H, m, ArH), 4.41 (2 H, q, CH_2), and 1.45 (3 H, t, Me); δ_C(50 MHz) 168.7 (C-3), 159.7, 157.6, 156.2, and 117.5 (CO, C-5, and ArC), 131.5, 127.5, 124.2, 119.3, and 117.9 (C-4 and ArCH), 62.2(CH_2), and 13.0 (Me); *m/z* 203 (M^+). Secondly, 4-*oxo*-4H-[1]*benzopyrano*-[4,3-c]*isothiazole* (**6c**) (20%) as pale yellow needles, m.p. 172—174 °C (from ethanol) (Found: C, 59.0; H, 2.5; N, 6.8. $C_{10}H_5NO_2S$ requires C, 59.1; H, 2.5, N, 6.9%); $\nu_{max.}$(Nujol) 3 120 (CH), 1 740 cm^{-1} (C=O); δ_H(80 MHz) 9.72 (1 H, s, 3-H), 8.26 (1 H, d of d, *J* 8 and *J* 2 Hz, 9-H), and 7.2—7.7 (3 H, m, ArH); *m/z* 203 (M^+). ^{13}C N.m.r. chemical shifts are presented in the Table. Thirdly, *o*-cyanophenol (45%).

Reactions with Diethyl Fumarate (*DEF*).—*Synthesis of diethyl* 3-*aryl*-4,5-*dihydroisothiazole*-4,5-*dicarboxylates* (**10**). A solution of acetoxyphenyloxathiazolone (**2b**) (1.18 g, 5.0 mmol) and diethyl fumarate (3.44 g, 20.0 mmol) in dry xylene was flushed with nitrogen and heated under reflux under nitrogen for 18 h. Concentration of the reaction mixture afforded a brown oil which on flash chromatography (silica; 30% ethyl acetate in hexane) yielded sulphur, diethyl fumarate, *o*-acetoxybenzonitrile, and *diethyl* 3-(o-*acetoxyphenyl*)-4,5-*dihydroisothiazole*-4.5-*dicarboxylate* (**10b**) as an unstable yellow oil (1.03 g, 56%) (Found: *m/z* 365.0934. $C_{17}H_{19}NO_6S$ requires *M*, 365.093 30); $\nu_{max.}$(film) 1 770 and 1 730 cm^{-1} (C=O); δ_H(80 MHz) 7.0—7.7 (4 H, m, ArH), 5.32 (1 H, d, *J* 4.5 Hz, 5-H), 4.88 (1 H, d, *J* 4.5 Hz, 4-H), 4.22 (2 H, q, CH_2), 4.02 (2 H, q, CH_2), 2.31 (3 H, s, COMe), 1.27 (3 H, t, CH_2Me), and 0.95 (3 H, t, CH_2Me); δ_C(20 MHz) 170.1, 168.8, and 167.7 (*C*OMe and CO_2Et), and 159.0 (C-3), 148.1 and 126.4 (ArC), 130.4, 130.2, 125.5, and 123.0 (ArCH), 62.1 and 61.8 (CH_2), 60.9 (C-5), 52.4 (C-4), 20.9 (CO*Me*), and 13.8 and 13.3 (CH_2Me). The product was contaminated with traces of *o*-acetoxybenzonitrile; attempted purification resulted in further decomposition.

The corresponding reaction of hydroxyphenyloxathiazolone (**2a**) with DEF (1:4) yielded *o*-cyanophenol and *ethyl* 4-*oxo*-4H-[1]*benzopyrano*[4,3-c]*isothiazole*-3-*carboxylate* (**6e**) (15%) as white needles, m.p. 118—120 °C (from cyclohexane) (Found: C, 56.5; H, 3.3; N, 5.0. $C_{13}H_9NO_4S$ requires C, 56.7; H, 3.3; N, 5.1%); $\nu_{max.}$(Nujol) 1 730 cm^{-1} (C=O); δ_H(80 MHz) 7.1—8.2 (4 H, m, ArH), 4.47 (2 H, q, CH_2), and 1.41 (3 H, t, Me); *m/z* 275 (M^+). ^{13}C N.m.r. chemical shifts are presented in the Table.

The reaction was repeated and monitored by ^1H n.m.r. spectroscopy. After 18 h under reflux the solvent was removed by evaporation at reduced pressure. The ^1H n.m.r. spectrum ($CDCl_3$, 80 MHz) of the residue showed peaks at δ_H 11.15 (1 H, s. OH), 5.19 (1 H, d, *J* 2.7 Hz, 5-H), and 4.65 (1 H, d, *J*, 2.7 Hz, 4-H) attributable to dihydroisothiazole (**10a**) as well as those of DEF, *o*-cyanophenol, and isothiazole (**6e**). The residue was redissolved in xylene and heated under reflux for a further 40 h, by which time the ^1H n.m.r. signals of compound (**10a**) were no longer discernible. H.p.l.c. analysis showed that the yield of isothiazole (**6e**) to be 18% after 18 h and 26% after 58 h.

Hydrolysis of Dimethyl 3-(o-*Acetoxyphenyl*)*isothiazole*-4,5-*dicarboxylate* (**5b**).—A mixture of isothiazole (**5b**) (1.0 g, 3 mmol) and methanolic KOH (5.0 g in 80 ml H_2O, 20 ml MeOH) was stirred at room temperature for 18 h. On acidification to pH 1 a white precipitate (0.64 g, 87%) formed and was identified as 4-*oxo*-4H-[1]*benzopyrano*[4,3-c]*isothiazole*-3-*carboxylic acid* (**6b**), m.p. 171.5—172 °C (decomp.) (Found: *m/z* 246.9940. $C_{11}H_5NO_4S$ requires *M*, 246.993 93); $\nu_{max.}$(Nujol) 2 720 (OH), 1 770 and 1 750 cm^{-1} (C=O). Attempted partial hydrolysis using a saturated solution of $NaHCO_3$ in 50% aqueous methanol yielded only compound (**6b**) and unchanged starting material.

Decarboxylation of 4-*Oxo*-4H-[1]*benzopyrano*[4,3-c]*isothiazole*-3-*carboxylic Acid* (**6b**).—A solution of compound (**6b**) (0.144 g, 0.58 mmol) in *o*-dichlorobenzene (50 ml) was heated under reflux (178 °C) for 1 h. Removal of the solvent under reduced pressure yielded 4-oxo-4*H*-[1]benzopyrano[4,3-*c*]isothiazole (**6c**) as a white solid (0.089 g, 81%). The i.r. and n.m.r. spectra of the product were indistinguishable from those of an authentic sample prepared from ethyl propiolate and the isothiazole (**6b**).

Hydrolysis of Dimethyl 3-(o-*Acetamidophenyl*)*isothiazole*-4,5-*dicarboxylate* (**5c**).—A mixture of compound (**5c**) (0.167 g, 0.50 mmol) and 10% aqueous sulphuric acid was heated under reflux for 1.5 h. The precipitate resulting from addition of NaOH to give pH 6 was dried and suspended in refluxing xylene for 20 h. Cooling and removal of the solvent afforded *isothiazolo*[4,3-c]-*quinolin*-4(5H)-*one* (**7c**) (0.10 g, 74%) as a white solid. M.p. 232—

233 °C (decomp.) (Found: *m/z* 202.0202. $C_{10}H_6N_2OS$ requires *M*, 202.020 08); $\nu_{max.}$(Nujol) 3 115 (NH), 1 665 cm^{-1} (C=O); δ_H [$(CD_3)_2SO$, 80 MHz] 11.5 (1 H, bs, NH), 9.98 (1 H, s, 3-H), and 7.1—8.2 (4 H, m, ArH). ^{13}C N.m.r. chemical shifts are presented in the Table.

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