Some 5-Unsubstituted Acetylenic and Vinylic 1,2,4-Oxadiazoles

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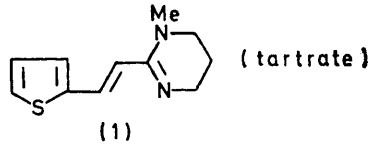
3-*trans*-Styryl-1,2,4-oxadiazoles (2) have been prepared by treating unsaturated amide oximes with trialkyl orthoformates or dimethylformamide dimethyl acetal, and from 1,2,4-oxadiazol-3-ylmethylene(triphenyl)phosphonium chloride (12). Phenylpropiolamide oxime with formyl fluoride gives 3-phenylethynyl-1,2,4-oxadiazole which, on nitration, gives as the main product 3-*p*-nitrophenylethynyl-1,2,4-oxadiazole (4; R = NO_2). This compound has been converted into (4; R = Cl). *p*-Chlorophenylpropiolonitrile gives only 3-amino-5-*p*-chlorophenylisoxazole (15) when treated with hydroxylamine. *trans*-3-(2- and -3-Thienyl)acrylonitrile react more readily with hydroxylamine than do the *cis*-acrylonitriles. Some *cis*-3-styryl-1,2,4-oxadiazoles have been obtained from the corresponding *trans*-compounds by photoisomerization.

It has been reported [1,2] that many 3-substituted 1,2,4-oxadiazoles, particularly 3-*p*-chlorophenyl-1,2,4-oxadiazole, are effective against helminths in small animals. The high anthelminthic activity reported [3] for 'Pyrantel' (1) led us to prepare some 3-styryl-1,2,4-oxadiazoles (2)



(1)

(and similar compounds with heterocyclic groups attached to vinyl side-chains), some related 4,5-dihydro-1,2,4-oxadiazoles (3), and some 3-arylethynyl-1,2,4-oxadiazoles (4).

Of the compounds in the Table, some were made by treating the appropriate amide oximes with triethyl or trimethyl orthoformate in the presence of boron trifluoride,[4] and some by the Wittig reaction (see below) from the phosphorane (5). Several other compounds were made by the reduction of appropriate nitro-compounds, with subsequent Sandmeyer reactions.

We first obtained *p*-methylthiocinnamonitrile (6) by the Meerwein reaction;[5] diazotized *p*-methylthioaniline reacted with acrylonitrile to give the expected chloronitrile, which was dehydrochlorinated by triethylamine, but the overall yield seldom exceeded 4%, and *o*- and *m*-methylthioaniline gave even lower yields. However, *p*-methylsulphinylaniline, prepared [6] by oxidizing *p*-methylthioaniline with hydrogen peroxide in acetone (a procedure reported [7] to be hazardous), or, better, in methylene chloride, gave the nitrile (7) in 25% overall yield from the amine, and we obtained from (7) the corresponding amide oxime (see Scheme 1). This amide oxime did not react readily with formyl fluoride. It was decomposed by triethyl orthoformate, but it gave the oxadiazole (2; R = *p*-MeSO·C_6H_4) when treated with dimethylformamide dimethylacetal (see later). Reduction of the nitrile (7) with titanium(III) chloride gave *p*-methylthiocinnamonitrile (6) from which *p*-methylthiocinnamide oxime was obtained by treatment with hydroxylamine. The amide oxime reacted readily with triethyl or trimethyl orthoformate to give (2; R = *p*-MeS·C_6H_4).

The route to (6) just described was unsuitable for large-scale work. However *p*-thiocyanatoaniline [8] underwent the Meerwein reaction in high yield, and dehydrochlorination of the product gave *p*-thiocyanatocinnamonitrile, which was readily degraded by sodium hydroxide to the corresponding thiol. When the degradation was carried out in the presence of methyl iodide, *p*-methylthiocinnamonitrile (6) was obtained in 88% yield (see Scheme 2).

3-*p*-Methylthiostyryl-1,2,4-oxadiazole was converted into the corresponding sulphoxide (2; R = *p*-MeSO·C_6H_4) by treatment with 1 equivalent of peracetic acid, and into the sulphone (2; R = *p*-$MeSO_2$·C_6H_4) by an excess of the same reagent. The sulphoxide just mentioned, when heated with acetic anhydride, underwent Pummerer rearrangement [9] to give the acetoxymethyl compound (2; R = *p*-AcO·CH_2S·C_6H_4).

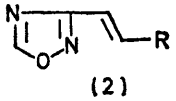
3-*p*-Thiocyanatostyryl-1,2,4-oxadiazole (2; R = *p*-NCS·C_6H_4) was converted in low yield into (2; R = *p*-MeS·C_6H_4) by sodium methoxide, methanethiol in the presence of a base, trimethyl phosphite, or sodium borohydride in methanol. Some of the disulphide (8) was always formed during borohydride reduction; *p*-mercaptocinnamonitrile was also isolated.

In addition to the oxadiazole (2; R = *p*-MeSO·C_6H_4), we obtained (2; R = *p*-O_2N·C_6H_4, *p*-Cl·C_6H_4, and *p*-I·C_6H_4) by treating the appropriate amide oxime with dimethylformamide dimethyl acetal in refluxing benzene. Under these conditions, yields were usually better than those obtained by the use of triethyl (or trimethyl) orthoformate and boron trifluoride. We have no experimental evidence to show whether the hydroxy-group or the amino-group of an *N*-unsubstituted amide oxime is the first to react with the acetal. *N*-Methylbenzamide oxime reacted with the acetal to give benzonitrile and *NNN'*-trimethylurea; here again satisfactory

[1] C. Ainsworth, W. E. Buting, J. Davenport, M. E. Callender, and M. C. McCowen, *J. Medicin. Chem.*, 1967, **10**, 208.
[2] W. E. Buting and C. Ainsworth, U.S.P. 3,356,684/1967.
[3] W. C. Austin, W. Courtney, J. C. Danilewicz, D. H. Morgan, L. H. Lanover, H. L. Howes, J. E. Lynch, J. W. Mcfarland, R. L. Cornwall, and V. J. Theorides, *Nature*, 1966, **212**, 1273.
[4] M. Arbasino and P. Gruenanger, *Chem. Ind.* (Milan), 1963, **45**, 1238.
[5] C. S. Rondestvedt, *Org. Reactions*, 1960, **11**, 189.
[6] S. Ghersetti and M. Pellotti, *Gazzetta*, 1963, **93**, 1000.
[7] C. J. M. Stirling, *Chem. in Britain*, 1969, **5**, 36.
[8] H. P. Kaufmann and W. Oehring, *Ber.*, 1926, **59**, 189.
[9] W. E. Parham and L. D. Edwards, *J. Org. Chem.*, 1968, **33**, 4150.

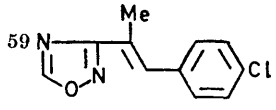
mechanisms can be written for initial reaction with either the hydroxy- or the amino-group.[10]

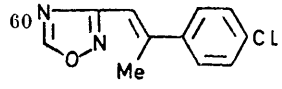
trans-3-Styryl-1,2,4-oxadiazoles (2) and similar compounds

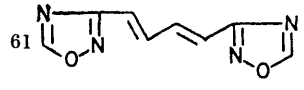


(2)

No.	R	No.	R
1	Ph	30	*m*-NCS·C_6H_4
2	*p*-MeC_6H_4	31 *	*p*-NCS·C_6H_4
3	*p*-CF_3·C_6H_4	32	*p*-$(EtO)_2P(O)SC_6H_4$
4	*o*-NC·C_6H_4	33	*o*-MeSO·C_6H_4
5	*m*-NC·C_6H_4	34	*m*-MeSO·C_6H_4
6	*p*-NC·C_6H_4	35 *	*p*-MeSO·C_6H_4
7	*o*-NH_2·C_6H_4	36	*p*-EtSO·C_6H_4
8	*m*-NH_2·C_6H_4	37	*m*-$MeSO_2$·C_6H_4
9 *	*p*-NH_2·C_6H_4	38	*p*-$MeSO_2$·C_6H_4
10	*p*-NMe_2·C_6H_4	39	*p*-$EtSO_2$·C_6H_4
11	*o*-NO_2·C_6H_4	40	4-Cl-2-Me·C_6H_3
12	*m*-NO_2·C_6H_4	41	*p*-ClC_6H_4·CH=CH
13	*p*-NO_2·C_6H_4	42	10-Chloroanthryl
14	*p*-N_3·C_6H_4	43	1,2,4-Oxadiazol-3-yl
15	*p*-HO·C_6H_4	44	2-Thienyl
16	*p*-MeO·C_6H_4	45	3-Methyl-2-thienyl
17	*p*-FC_6H_4	46	5-Chloro-2-thienyl
18 *	C_6F_5	47	5-Methylthio-2-thienyl
19	*o*-ClC_6H_4	48	5-Methylsulphinyl-2-thienyl
20	*m*-ClC_6H_4	49	5-Methylsulphonyl-2-thienyl
21 *	*p*-ClC_6H_4	50	3-Thienyl
22	*p*-BrC_6H_4	51	2-Pyridyl
23	*p*-IC_6H_4	52	3-Pyridyl
24	*o*-MeS·C_6H_4	53	4-Pyridyl
25	*m*-MeS·C_6H_4	54	1-Oxido-4-pyridinio
26 *	*p*-MeS·C_6H_4	55	2-Furyl
27 *	*p*-EtS·C_6H_4	56	Thiazol-2-yl
28	*p*-$AcOCH_2S$·C_6H_4	57	Thiazol-4-yl
29	*o*-NCS·C_6H_4	58	Isothiazol-5-yl

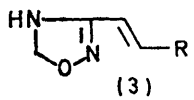
59 

60 

61 

* The preparation and properties of compounds marked with an asterisk are described in the Experimental section of this paper. The preparation and properties of all the other compounds in this Table, and of their synthetic precursors, are described in Supplementary Publication No. SUP 20797 (19 pp, 1 microfiche). [For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.]

The phosphonium salt (12) was obtained in good yield by heating 3-chloromethyl-1,2,4-oxadiazole with triphenylphosphine in acetonitrile, but the phosphorane (5) could not be obtained pure. However, Wittig reactions were successfully carried out by adding one equivalent of sodium ethoxide in ethanol to an ethanolic solution of the chloride (12) and a suitable aldehyde, or by treating a solution of the chloride (12) and an aldehyde in dimethyl sulphoxide with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN). In this way ethylenes were



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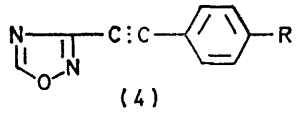

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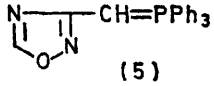
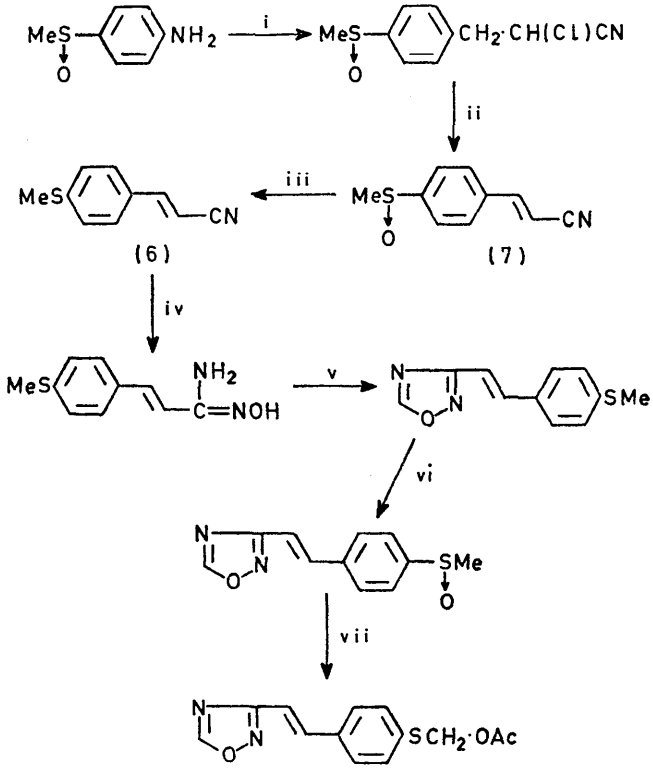


(5)

obtained from a variety of heterocyclic or aromatic aldehydes and from anhydrous chloral. The butadiene (13) was obtained from glyoxal, but little if any of the expected olefin was obtained from heptanal, acetone, or cyclohexanone.



SCHEME 1

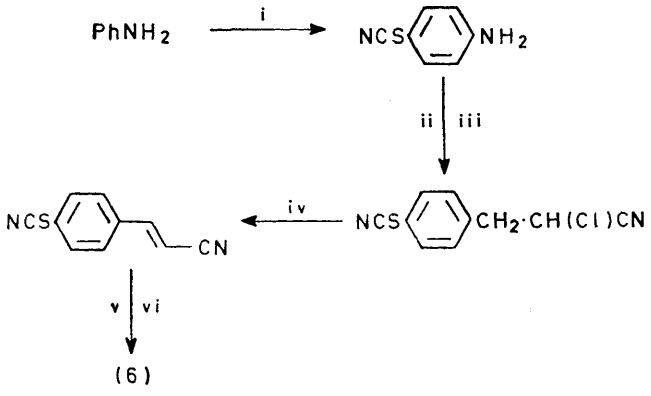
Reagents: i, HNO_2, CH_2=CHCN; ii, NEt_3; iii, $TiCl_3$; iv, NH_2OH; v, $HC(OR)_3$; vi, CH_3CO_3H; vii, Ac_2O; heat.

When *p*-chlorobenzaldehyde was dissolved, together with the salt (12), in ethanol, and the solution was treated with DBN, 1,5-diazabicyclo[5.4.0]undec-5-ene, or sodium bistrimethylsilylamide, it gave (2; R = *p*-Cl·C_6H_4). The reaction proceeded much more slowly in the presence of propylene oxide. Although recrystallization of the unsaturated oxadiazoles (2) usually gave the pure *trans*-isomers, n.m.r. analysis showed that

[10] H. Brederek, W. Kautlehner, and D. Schweizer, *Chem. Ber.*, 1971, **104**, 3475.

the reaction mixture often contained small amounts of the corresponding *cis*-compounds (see below).

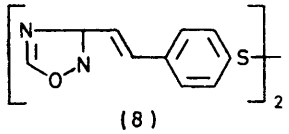
Amide oximes react with lower aliphatic aldehydes [11] and with formaldehyde [12] to give 4,5-dihydro-1,2,4-oxadiazoles. We prepared the oxadiazolines (3; R = *p*-MeC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, and *p*-$MeS{\cdot}C_6H_4$) by heating the appropriate amide oximes in



SCHEME 2

Reagents: i, NaNCS, Br_2; ii, $NaNO_2$,HCl; iii, CH_2=CHCN; iv, NEt_3; v, NaOH; vi, MeI.

aqueous formaldehyde solution. The oxadiazoline (3; R = *p*-ClC_6H_4) was oxidized to the corresponding oxadiazole by nitrous acid or active [13] manganese dioxide.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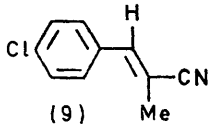
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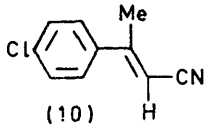
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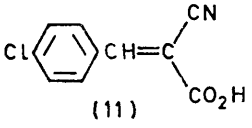
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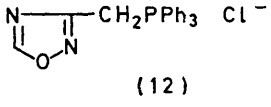
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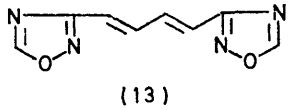
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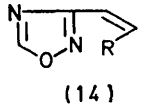
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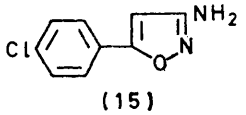

(15)

trans-Unsaturated oxadiazoles (2) usually have $\nu_{max.}$ ($CHBr_3$) *ca.* 970 cm^{-1}. The olefinic protons resonate at τ ($CDCl_3$) *ca.* 2·2 and 2·7 (ABq, *J ca.* 16 Hz). The olefinic protons of the *cis*-isomers (14) (see below) resonate at τ [$CDCl_3$ or $(CD_3)_2SO$] *ca.* 2·7 and 3·2 (*J* 12—13 Hz). The mass spectrum of (2; R = *p*-ClC_6H_4) is reported in the Experimental section; the principal features are loss of hydrogen and of the elements of cyanic acid to give *p*-chlorocinnamonitrile; the nitrile then loses hydrogen to give the 7-chloroquinolinium ion (?). The loss of chlorine is also observed.

The *trans*-compounds (2; R = *p*-ClC_6H_4, *p*-$MeSO{\cdot}C_6H_4$, and *p*-$MeSO_2{\cdot}C_6H_4$) have been converted into the corresponding *cis*-compounds (14) by u.v. irradiation of their ethanolic solutions and separation of the equilibrium mixture of isomers so produced. The *cis*-compounds are more soluble and have lower melting points than the *trans*-isomers, and consequently separation and purification of the *cis*-isomers are tedious and wasteful. We therefore attempted to prepare some *cis*-isomers (14) from the corresponding *cis*-unsaturated nitriles.

Treating a mixture of *cis*- and *trans*-3-(2-thienyl)-acrylonitrile with hydroxylamine under mild conditions gave the *trans*-amide oxime. The less reactive *cis*-nitrile was recovered and heated under reflux with an excess of methanolic hydroxylamine solution, when it gave *cis*-3-(2-thienyl)acrylamide oxime, shown (g.l.c., and n.m.r. and i.r. spectrum) to contain <5% of the *trans*-isomer. Both amide oximes were characterized as their picrates. When the *cis*-amide oxime was treated with triethyl orthoformate and boron trifluoride, only the *trans*-oxadiazole (2; R = 2-thienyl) was isolated. Treatment of the same amide oxime with formyl fluoride at −40° avoided the formation of the *trans*-isomer, but gave an intractable gummy mixture, from which we were unable to isolate the pure *cis*-isomer. We were similarly unable to obtain a *cis*-oxadiazole from a mixture of *cis*- and *trans*-3-(3-thienyl)-acrylonitrile, although we again characterized each amide oxime.

3-Phenylethynyl-1,2,4-oxadiazole (4; R = H) was obtained in 36% yield by heating phenylpropiolamide oxime with ethyl orthoformate and boron trifluoride; the same oxadiazole was obtained in 56% overall yield by treating an ethereal solution of phenylpropiolamide oxime with formyl fluoride and triethylamine and subsequently cyclizing the *O*-formyl amide oxime so produced by boiling it in ethanol.

As expected,[14] the acetylenic oxadiazole (4; R = H) was converted into a mixture of (4; R = NO_2) (68%) and 3-*o*-nitrophenylethynyl-1,2,4-oxadiazole (32%) by treatment with fuming nitric acid at −35°. A similar mixture of isomers was obtained by nitration with fuming nitric acid in acetic anhydride. The isomers were separated chromatographically. The pure isomer (4; R = NO_2) was also obtained in 50·5% yield from (4; R = H) by recrystallization of the mixture of

[11] F. Tiemann, *Ber.*, 1889, **22**, 2412.
[12] J. Saikawa and A. Takai, *J. Pharm. Soc. Japan*, 1965, **85**, 948.
[13] J. A. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.
[14] J. W. Baker, K. E. Cooper, and C. K. Ingold, *J. Chem. Soc.*, 1928, 426.

isomers from ethanol. No *meta*-isomer could be detected by g.l.c. or t.l.c. The nitro-compound (4; R = NO_2) was reduced by titanium(III) chloride to the amine (4; R = NH_2); the amine was converted into (4; R = Cl) by the Sandmeyer reaction.

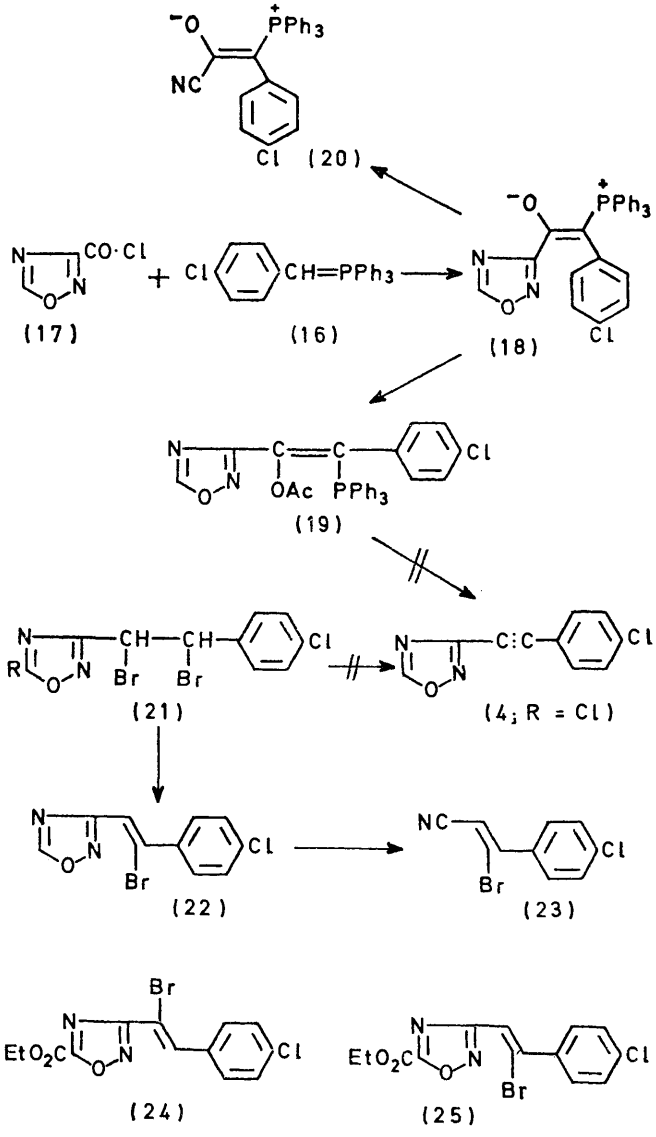
p-Chlorophenylpropiolonitrile was prepared from *p*-chlorobenzyl chloride and cyanomethylenetriphenylphosphorane by a modification of Gough and Trippett's method.[15] When *p*-chlorophenylpropiolonitrile was treated in ethanol at −20° with hydroxylamine it gave no amide oxime but, instead, 3-amino-5-*p*-chlorophenylisoxazole (15). The structure assigned to the isoxazole (15) is supported by its composition and by its n.m.r. spectrum [τ ($CDCl_3$) 2·35 and 2·60 (4H, aromatic), 3·93 (1H, not exchangeable, CH), 5·90br (2H, exchangeable, NH_2)]. For 3-amino-5-phenylisoxazole[16] the corresponding values for the CH and the NH_2 signal are τ ($CDCl_3$) 4·00 and 5·90 respectively, whereas for 5-amino-3-phenylisoxazole[16] they are τ 4·60 and 5·35, respectively. Phenylpropiolamide oxime undergoes thermal cyclization[16] to give 3-amino-5-phenylisoxazole.

In an attempt to find a better synthesis of the acetylene (4; R = Cl) we treated *p*-chlorophenylmethylenetriphenylphosphorane (16) (prepared from *p*-chlorobenzyl bromide and triphenylphosphine) with 3-chlorocarbonyl-1,2,4-oxadiazole[17] (17), and thus obtained the phosphorane (18), which probably[18] exists in the *cis*-ylide form. However we were unable to convert (18) into the acetylene (4; R = Cl); heating[15] the phosphorane (18) alone, in diphenyl ether, or in triethylphosphite degraded the 1,2,4-oxadiazole ring. In the hope of eliminating[19] triphenylphosphine oxide through an enol acetate (19), we heated (18) with acetic anhydride, but again the oxadiazole ring was degraded. When the phosphorane (18) was left in acetic anhydride at room temperature for 4 weeks, the nitrile (20) was isolated. 3-*p*-Chlorostyryl-1,2,4-oxadiazole was not converted into a nitrile under similar conditions.

In an attempt to convert the double bond of 3-*p*-chlorostyryl-1,2,4-oxadiazole into a triple bond we prepared the dibromo-compound (21). The dibromo-compound reacted with an excess of DBN to give an unsaturated bromo-compound, probably (22), but treatment of (22) with more 1,5-diazabicyclo[4.3.0]non-5-ene in refluxing ether, or with 1,5-diazabicyclo[5.4.0]undec-5-ene in cold ether, gave only a bromine-containing nitrile, probably (23). The nitrile (23) was also isolated, together with much starting-material, when the oxadiazole (22) was treated with potassium hydroxide.

The position assigned to the bromine atom in the olefin (22) is supported by n.m.r. data. *trans*-3-*p*-Chlorostyryl-5-ethoxycarbonyl-1,2,4-oxadiazole gave with bromine the expected dibromide, which was converted by DBN into an inseparable mixture of the two isomers (24) and (25). The olefinic protons in this mixture resonate at τ 1·75 and 2·44 ($CDCl_3$), and are present in the ratio 1 : 2 respectively. The latter proton is presumably in the less deshielded position, adjacent to the heterocyclic ring, as in (25). The corresponding proton in the 5-unsubstituted compound (22) has τ 2·40 ($CDCl_3$).

We have frequently encountered unwanted degradation of 5-unsubstituted 1,2,4-oxadiazoles by base; for

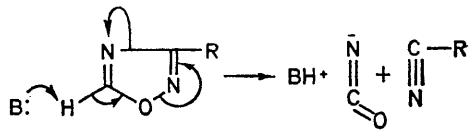


SCHEME 3

example when (2; R = *p*-ClC_6H_4) was heated in pyridine with copper(I) cyanide in an attempt to replace the chlorine atom by a cyano-group, the oxadiazole was slowly converted into *p*-chlorocinnamonitrile. Moreover, when (2; R = *p*-ClC_6H_4) was treated with the sodio-derivative of methanethiol in methanol, no sodium

[15] S. T. D. Gough and S. Trippett, *J. Chem. Soc.*, 1962, 2333.
[16] L. Lopez and J. Barrans, *Compt. rend.*, 1966, 293, 557.
[17] G. I. Gregory, P. W. Seale, W. K. Warburton, and M. J. Wilson, *J.C.S. Perkin I*, 1973, 47.
[18] H. I. Zeliger and J. P. Snyder, *Tetrahedron Letters*, 1970, 3313.
[19] G. Märkl, *Angew. Chem., Internat. Edn.*, 1962, **1**, 160.

chloride was formed, but sodium cyanate was isolated in 94% yield. These reactions can be explained as shown in Scheme 4.



SCHEME 4

EXPERIMENTAL

M.p.s were measured in open capillaries. U.v. spectra were measured for solutions in ethanol. Thin-layer chromatography was carried out on Merck Kieselgel F_{254} plates using benzene containing varying proportions of ethyl acetate. ^{1}H N.m.r. spectra were recorded at 60 MHz.

p-*Methylsulphinylaniline*.—A solution of 40% peracetic acid (Laporte; 13·3 ml) in methylene chloride (25 ml) was added dropwise at 0° during 3 h to a stirred solution of *p*-methylthioaniline (10·0 g) in methylene chloride (40 ml). Ethanol (20 ml) was added and the solvent was removed under reduced pressure. The residue in ethyl acetate was chromatographed on silica MFC (200 g). Elution with ethyl acetate removed the sulphone (1·03 g); further elution with ethanol–ethyl acetate (4 : 1) gave the sulphoxide (10·64 g, 95%), as a low m.p. solid, $\nu_{max.}$ (CS_2) 3460, 3375 (NH_2), and 1050 cm^{-1} (S → O), τ ($CDCl_3$) 7·33 (CH_3), 6·13 (NH_2), and 3·30 and 2·59 (aromatic). The *picrate* had m.p. 175—176° (from ethanol) (Found: C, 40·8; H, 3·2; N, 14·6; S, 8·3. $C_{13}H_{12}N_4O_8S$ requires C, 40·7; H, 3·1; N, 14·6; S, 8·3%).

p-*Thiocyanatoaniline*.—Aniline (465 g) and sodium thiocyanate dihydrate (1·5 kg) were dissolved in glacial acetic acid (3·5 l). The solution was cooled to −10°, then bromine (277 ml, 810 g) was added dropwise at *ca.* −5° during 5 h, with powerful stirring. The mixture was stirred 1 h more, then the solid was filtered off, washed with glacial acetic acid (1·5 l), and dissolved in warm water (10 l). The filtered solution was neutralized to pH 6, giving *p*-thiocyanatoaniline (591 g, 79%), m.p. 55—56° (lit.,[8] 57—58°) (Found: C, 55·6; H, 3·7; N, 18·1; S, 21·5. Calc. for $C_7H_6N_2S$: C, 56·0; H, 4·0; N, 18·7; S, 21·35%). The yield in pilot-plant experiments was 78—80·2%.

2-*Chloro*-3-p-*thiocyanatophenylpropionitrile*.— *p*-Thiocyanatoaniline (589·5 g) was stirred in acetone (1·74 l), and 5N-hydrochloric acid (2·32 l) was added at <20°. Sodium nitrite (302 g) in water (1·2 l) was added at 5—8° during 50 min. Acrylonitrile (400 ml, 322 g) in acetone (2·32 l) was added to the filtered diazonium solution, with stirring, then copper(II) chloride (23 g) was added in small portions, during 20 min, at <33°, with external cooling, until no more nitrogen was evolved. The acetone was removed and the mixture was extracted into methylene chloride (total 2·25 l). The solution was washed with water, dried (Na_2SO_4), filtered, and evaporated. The brown residue (813 g) crystallized when stirred with cyclohexane, giving 2-chloro-3-*p*-thiocyanatophenylpropionitrile (758·5 g, 86·8%), m.p. 49·5—51·5°. Recrystallization of a sample from cyclohexane–light petroleum (b.p. 40—60°) gave the *nitrile*, m.p. 55·5–56·5°, $\lambda_{max.}$ 236 nm (ε 12,200) (Found: C, 53·7; H, 3·4; Cl, 15·8; N, 12·5; S, 14·8. $C_{10}H_7ClN_2S$ requires C, 54·0; H, 3·2; Cl, 15·9; N, 12·6; S, 14·4%). In pilot-plant experiments, the yield was 87—90%.

The following nitriles were prepared similarly: 2-*chloro*-3-p-*trifluoromethylphenylpropionitrile* (50% yield), b.p. 87—91° at 0·08 mmHg, $\lambda_{max.}$ 263 nm (ε 6200) (Found: C, 51·2; H, 3·0; Cl, 15·2; F, 22·7; N, 6·0. $C_{10}H_7ClF_3N$ requires C, 51·4; H, 3·0; Cl, 15·2; F, 24·4; N, 6·0%); 2-*chloro*-3-p-*methylsulphinylphenylpropionitrile* (60% yield), m.p. 88—89° (from benzene), $\lambda_{max.}$ 227 nm (ε 11,200) (Found: C, 52·8; H, 4·5; N, 5·7. $C_{10}H_7ClNOS$ requires C, 52·7; H, 4·4; N, 6·15%); 2-*chloro*-3-p-*methylthiophenylpropionitrile* (4—20% yield), m.p. 58—60°, b.p. 140—165° at 1 mmHg, $\lambda_{max.}$ 260 nm (ε 15,300) (Found: C, 56·5; H, 4·8; N, 6·3. $C_{10}H_{10}ClNS$ requires C, 56·7; H, 4·7; N, 6·6%).

trans-p-*Chlorocinnamonitrile*.— *p*-Chlorocinnamaldehyde (75·0 g) was heated under reflux for 1·5 h in 98% formic acid (350 ml) containing hydroxylamine hydrochloride (72·0 g) and sodium formate (112·5 g). The mixture was allowed to cool, then poured into water (3·5 l). Isolation with the aid of chloroform gave the *nitrile* (64·0 g, 87%), m.p. 76—77° [from benzene–light petroleum (b.p. 40—60°)], $\lambda_{max.}$ 276 nm (ε 22,900) (Found: C, 66·0; H, 3·8; Cl, 21·9; N, 8·3. C_9H_6ClN requires C, 66·1; H, 3·7; Cl, 21·9; N, 8·4%).

3-(2-*Thienyl*)*acrylonitrile*.— Thiophen-2-carbaldehyde (103 g), cyanoacetic acid (71·5 g), ammonium acetate (2·53 g), pyridine (92 ml), and toluene (170 ml) were heated together under reflux for 48 h with azeotropic removal of water. Removal of the solvents and distillation of the dark residue gave the nitrile as a mixture of *trans*- and *cis*-isomers [*ca.* 2 : 1 (g.l.c.)], (68·4 g, 55%), b.p. 104° at 1 mmHg, n_D^{22} 1·6345 (lit.,[20] n_D 1·6373), $\lambda_{max.}$ 308 nm (ε 17,300), $\lambda_{infl.}$ 283 and 272 nm (ε 10,300 and 8800).

3-(3-*Thienyl*)*acrylonitrile*.—This nitrile was prepared, as just described, in 19% yield; it was a mixture of *trans*- and *cis*-isomers [*ca.* 2 : 1 (n.m.r. and g.l.c.)], b.p. 106—110° at 0·4 mmHg, $\nu_{max.}$ ($CHBr_3$) 2220 (C≡N) and 955 cm^{-1} (*trans*-CH=CH), τ ($CDCl_3$) 2·67 and 3·33 (d, *J* 16·5 Hz, *trans*-CH=CH), and 2·89 and 3·72 (d, *J* 12 Hz, *cis*-CH=CH).

trans-p-*Thiocyanatocinnamonitrile*.— 2-Chloro-3-*p*-thiocyanatophenylpropionitrile (746 g) was added to triethylamine (2·5 l) and butanone (600 ml). The suspension was stirred vigorously and heated on a steam-bath. After a few minutes a vigorous reaction occurred and the flask was cooled externally. The suspension was heated under reflux for 25 min, then cooled and filtered. The residue was washed with a mixture of butanone (200 ml) and triethylamine (600 ml), sucked as dry as possible, and washed well with water, giving p-*thiocyanatocinnamonitrile* (430·2 g, 69%), m.p. 157—159°. A sample crystallized from ethanol (charcoal) had m.p. 160—160·5°, $\lambda_{max.}$ 290 nm (ε 27,000) (Found: C, 63·9; H, 3·4; N, 14·8; S, 17·1. $C_{10}H_6N_2S$ requires C, 64·5; H, 3·25; N, 15·0; S, 17·2%). In pilot-plant experiments the yield was 66—77%.

trans-p-*Methylsulphinylcinnamonitrile* (7).—2-Chloro-3-*p*-methylsulphinylphenylpropionitrile (131·5 g) was heated under reflux for 2 h in triethylamine (176 ml) and dry methanol (35 ml). The cooled solution was poured into 2N-hydrochloric acid (865 ml). Isolation with the aid of ethyl acetate gave the *nitrile* (7) (54·5 g, 49%), m.p. 115—117°, $\lambda_{max.}$ 282 nm (ε 22,700) (Found: C, 62·2; H, 5·1; N, 6·9. $C_{10}H_9NOS$ requires C, 62·8; H, 4·7; N, 7·3%).

trans-p-*Methylthiocinnamonitrile* (6).—2-Chloro-3-*p*-methylthiophenylpropionitrile (2·98 g) was heated under reflux for 75 min in triethylamine (6 ml). The cooled mixture was poured into stirred 2N-hydrochloric acid (20 ml) and the crude nitrile (2·075 g, 86%) was filtered off; it had m.p. 58—65°. Recrystallization from aqueous

[20] Chas. Pfizer & Co., B.P. 1,070,116/1967.

methanol gave p-*methylthiocinnamonitrile* (6), m.p. 79°, $\lambda_{max.}$ 330 nm (ε 28,500) (Found: C, 68·45; H, 5·2; N, 7·8. $C_{10}H_9NS$ requires C, 68·55; H, 5·2; N, 8·0%). The same compound, contaminated by *ca.* 20% of *p*-methylthiochlorobenzene, was obtained when *p*-methylsulphinylcinnamonitrile (7) was reduced by acidic titanium(III) chloride solution.

Preparation of trans-p-*Methylthiocinnamonitrile* (6) *from* trans-p-*Thiocyanatocinnamonitrile*.—The thiocyanato-compound (403 g) was stirred in methanol (8 l) at 40°, and sodium hydroxide (96·0 g) in water (400 ml) was added rapidly. The temperature rose to 50°. The resulting suspension was stirred for 5 min, then methyl iodide (130 ml, 296 g) was added. Stirring was continued for 90 min, then triethylamine (200 ml, 145 g) was added. The mixture was stirred for 90 min more, most of the solvent was removed, water (2 l) was added, and the solid was filtered off, washed well with water, and dried under reduced pressure, leaving a yellow-grey powder (372·3 g), m.p. 70—73°. The powder was extracted at 74° with cyclohexane (8 l). The cooled solution deposited the *methylthio-compound* (6) (328·4 g, 88%), m.p. 77·5—78·5°, $\lambda_{max.}$ 238 and 329 nm (ε 11,700 and 27,100) (Found: C, 68·1; H, 4·9; N, 8·2; S, 18·1. $C_{10}H_9NS$ requires C, 68·5; H, 5·2; N, 8·0; S, 18·3%).

p-*Methylthiocinnamamide Oxime*.—The hydroxylamine solution prepared by neutralizing hydroxylamine hydrochloride (483 g) in methanol (final vol., 8·0 l) was heated under reflux with *p*-methylthiocinnamonitrile (622 g) for 4 h. Removal of most of the methanol (7 l) and addition of water (1 l), with final removal of the rest of the methanol and addition of more water (1·5 l), gave the *amide oxime* (589 g, 79·6%), m.p. 138—140°, $\lambda_{max.}$ 230 and 311 nm (ε 12,700 and 27,500) (Found: C, 57·5; H, 5·7; N, 13·5. $C_{10}H_{12}N_2OS$ requires C, 57·7; H, 5·8; N, 13·5%). In pilot-plant experiments the yield was 80—81%.

The following compounds were prepared similarly: p-*methylsulphinylcinnamamide oxime* (60% yield), m.p. 155—160° (decomp.), $\lambda_{max.}$ 299 nm (ε 16,800) (Found: C, 53·7; H, 5·7; N, 11·7. $C_{10}H_{12}N_2O_2$ requires C, 53·6; H, 5·4; N, 12·5%); p-*nitrocinnamamide oxime* (75% yield), m.p. 187—188° (decomp.) (from methanol), $\lambda_{max.}$ 265·5 nm (ε 14,800) (Found: C, 51·7; H, 4·7; N, 20·0. $C_9H_9N_3O_3$ requires C, 52·2; H, 4·4; N, 20·3%); p-*chlorocinnamamide oxime* (52% yield), m.p. 110—111° (from ethanol), $\lambda_{max.}$ 273 nm (ε 17,500) (Found: C, 53·2; H, 5·0; Cl, 17·2; N, 13·85. $C_9H_9ClN_2O,H_2O$ requires C, 52·8; H, 5·4; Cl, 17·3; N, 13·7%).

Reaction of 3-(2-*Thienyl*)*acrylonitrile* (cis–trans-*Mixture*) *with Hydroxylamine*.—3-(2-Thienyl)acrylonitrile (*cis–trans*, *ca.* 1 : 2, see above) (68·14 g) was added to the hydroxylamine solution prepared in methanol (final vol., 1 l) from hydroxylamine hydrochloride (70·6 g). The solution was heated under reflux for 7 h, then evaporated, leaving a gum, which was dissolved in ethyl acetate (1 l). The solution was washed with water, dried (Na_2SO_4), and evaporated, and the residue was extracted with light petroleum (b.p. 60—80°) leaving *trans*-3-(2-thienyl)acrylamide oxime (53·5 g, 74%), m.p. 84°, $\lambda_{max.}$ 308 nm (ε 18,000). The *picrate* had m.p. 153° (decomp.) (from aqueous ethanol), $\lambda_{max.}$ 325 nm (ε 29,400), $\nu_{max.}$ (Nujol) 960 cm^{-1} (*trans*-CH=CH) (Found: C, 39·6; H, 3·0; N, 17·9; S, 7·9. $C_{13}H_{11}N_5O_8S$ requires C, 39·3; H, 2·6; N, 17·6; S. 8·1%). Evaporation of the light petroleum and distillation of the residue gave cis-3-(2-*thienyl*)*acrylonitrile* (7·66 g), b.p. 76° at 0·2 mmHg, $\lambda_{max.}$ 306 and 280 nm (ε 13,100 and 9200) (Found: C, 60·1; H, 3·75; N, 10·1; S, 22·7. $C_7H_5NS,\frac{1}{4}H_2O$ requires C, 60·3; H, 4·0; N, 10·0; S, 22·5%). The nitrile just described (0·50 g) was heated under reflux for 2 days with the methanolic solution (20 ml) of hydroxylamine prepared from hydroxylamine hydrochloride (0·52 g). Removal of methanol and isolation with the aid of ethyl acetate gave *cis*-3-(2-thienyl)-acrylamide oxime as a gum (0·60 g, 97%), $\lambda_{max.}$ 272 nm (ε 8700), τ ($CDCl_3$) 3·3 and 4·2 (d, *J* 12 Hz, CH=CH). The *picrate* had m.p. 129° (from aqueous ethanol), $\lambda_{max.}$ 343 nm (ε 16,900), τ [$(CD_3)_2SO$] *ca.* 3·92 (d, *J* 12 Hz, *cis*-CH=CH) (Found: C, 40·0; H, 2·9; N, 16·6; S, 8·1. $C_{13}H_{11}N_5O_8S,\frac{1}{2}C_2H_5OH$ requires C, 40·0; H, 3·4; N, 16·7; S, 7·7%).

Reaction of 3-(3-*Thienyl*)*acrylonitrile* (cis–trans-*Mixture*) *with Hydroxylamine*.—Treatment of the nitrile with hydroxylamine under reflux for 4 h as in the preceding experiment gave trans-3-(3-*thienyl*)*acrylamide oxime* (38% yield), m.p. 84°, $\lambda_{max.}$ 279, 241, and 234 nm (ε 16,800, 10,700, and 11,300), $\nu_{max.}$ ($CHBr_3$) 952 cm^{-1} (*trans*-CH=CH), τ ($CDCl_3$) 3·66 and 3·11 (d, *J* 16 Hz, *trans*-CH=CH) (Found: C, 49·1; H, 4·7; N, 16·1; S, 18·0. $C_7H_8N_2OS,\frac{1}{8}H_2O$ requires C, 49·4; H, 4·9; N, 16·5; S, 18·8%). *cis*-3-(3-Thienyl)acrylonitrile, isolated as above, had $\lambda_{max.}$ 277 nm (ε 9700), $\lambda_{infl.}$ 231 and 240 nm (ε 5300 and 4000), τ ($CDCl_3$) 2·90 and 4·71 (d, *J* 12 Hz, *cis*-CH=CH).

Treatment of the *cis*-nitrile with hydroxylamine as in the preceding experiment gave *cis*-3-(3-thienyl)acrylamide oxime as an oil in 55% yield, $\lambda_{infl.}$ 275, 265, 254, and 230 nm (ε 4400, 4700, 5000, and 6200). The *picrate* had m.p. 140° (decomp.) (from aqueous ethanol), $\lambda_{max.}$ 355 and 299 nm (ε 13,700 and 10,200) (Found: C, 40·5; H, 3·3; N, 15·5; S, 8·5. $C_{13}H_{11}N_5O_8S,\frac{1}{2}C_2H_5OH$ requires C, 40·0; H, 3·4; N, 16·7; S, 7·7%).

3-*Chloromethyl*-1,2,4-*oxadiazole*.—A solution of chloroacetamide oxime (145·6 g) in trimethyl orthoformate (286 ml) containing boron trifluoride–ether complex (5 ml) was heated for 5 h at 60—70°. 2N-Hydrochloric acid was added to the cooled and stirred solution, and when the mixture was homogeneous, the methanol was removed under reduced pressure at <20°. The residue was extracted with ethyl acetate, and the solution was washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), and evaporated, giving the *oxadiazole* (98·0 g, 62%), b.p. 75—78° at 3 mmHg, no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 30·2; H, 2·5; Cl, 28·7; N, 24·1. $C_3H_3ClNO_2$ requires C, 30·4; H, 2·6; Cl, 29·9; N, 23·7%).

(1,2,4-*Oxadiazol*-3-*ylmethyl*)*triphenylphosphonium Chloride* (12).—The preceding compound (11·85 g) and triphenylphosphine (26·23 g) were heated under reflux in acetonitrile (175 ml) for 2 h. After being left at room temperature for 60 h the mixture was filtered and the filtrate was evaporated. Extraction of the residue with benzene gave a second crop. The total yield of the *salt* (12) was 21·38 g (56%), m.p. 220—221°, $\lambda_{max.}$ 274·5, 267·5, 262, and 227 nm (ε 2850, 3400, 2600, and 26,300) (Found: C, 66·0; H, 4·9; Cl, 9·6; N, 7·2. $C_{21}H_{18}ClN_2PO$ requires C, 66·3; H, 4·8; Cl, 9·3; N, 7·4%).

trans-3-p-*Methylthiostyryl*-1,2,4-*oxadiazole*.— *p*-Methylthiocinnamamide oxime (318 g) and boron trifluoride–ether complex (6 ml) were dissolved in triethyl orthoformate (800 ml) and heated on a steam-bath for 80 min. The solvent was removed under reduced pressure and the residue was treated with charcoal in ethanol. The filtrate after removal of charcoal was reduced in volume to 2·6 l,

then cooled, giving the *oxadiazole* (2; R = *p*-MeS·C_6H_4) (246 g, 75%), m.p. 121·5—122·5°, $\lambda_{max.}$ 236—237 and 322 nm (ε 11,200 and 24,800) (Found: C, 60·5; H, 4·8; N, 12·5. $C_{11}H_{10}N_2OS$ requires C, 60·5; H, 4·6; N, 12·8%).

The following oxadiazoles were prepared similarly: trans-3-p-*chlorostyryl*-1,2,4-*oxadiazole* (2; R = *p*-Cl·C_6H_4) (82% yield), m.p. 134° (from ethanol), $\lambda_{max.}$ 280 nm (ε 30,500) (Found: C, 57·9; H, 3·8; N, 13·3. $C_{10}H_7ClN_2O$ requires C, 58·2; H, 3·4; N, 13·6%); trans-3-p-*nitrostyryl*-1,2,4-*oxadiazole* (2; R = *p*-NO_2·C_6H_4) (60% yield), m.p. 220° (from ethanol), $\lambda_{max.}$ 308 nm (ε 21,000) (Found: C, 55·3; H, 3·5; N, 19·4. $C_{10}H_7N_3O_3$ requires C, 55·3; H, 3·3; N, 19·4%). The same compound was obtained in 71% yield by heating the amide oxime with a slight excess of dimethylformamide dimethyl acetal in benzene for 2 h.

trans-3-p-*Methylsulphinylstyryl*-1,2,4-*oxadiazole*.— *trans*-3-*p*-Methylthiostyryl-1,2,4-oxadiazole (303 g) in methylene chloride (6 l) was stirred at 11—16° and part of a solution of peracetic acid (Laporte, '40%'; 260 ml) in methylene chloride (2·6 l) was added during 5 h, the reaction being monitored by t.l.c. After 2·695 l had been added, the solution contained <2% of the starting material and *ca.* 90·5% of the corresponding sulphoxide. The mixture was shaken with water (8 l), saturated sodium hydrogen carbonate solution (3 l), and finally water (4 l), then dried (Na_2SO_4). The methylene chloride was removed and the residue was recrystallized from toluene (2·42 l), giving the *sulphoxide* (2; R = *p*-MeSO·C_6H_4) (294 g, 90·5%), m.p. 156·5—157°, $\lambda_{max.}$ 287 nm (ε 28,800) (Found: C, 56·3; H, 4·1; N, 12·1; S, 13·9. $C_{11}H_{10}N_2O_2S$ requires C, 56·4; H, 4·3; N, 12·0; S, 13·7%). In a pilot-plant experiment, the yield was 90%.

trans-3-p-*Aminostyryl*-1,2,4-*oxadiazole*.—Acidic titanium(III) chloride solution (15% w/v; 380 ml) was added during 25 min to a stirred solution of *trans*-3-*p*-nitrostyryl-1,2,4-oxadiazole (21·7 g) in acetone (1 l). After a further 30 min, the acetone was removed and solid sodium hydrogen carbonate was added to the stirred solution until the pH was 6—7. The amine (2; R = *p*-NH_2·C_6H_4) was isolated with ethyl acetate and recrystallized from benzene–light petroleum (b.p. 60—80°), giving *needles* (11·6 g, 79%), m.p. 109°, $\lambda_{max.}$ 281 nm (ε 21,000) (Found: C, 64·1; H, 4·8; N, 22·2. $C_{10}H_9N_3O$ requires C, 64·2; H, 4·9; N, 22·5%).

trans-3-p-*Thiocyanatostyryl*-1,2,4-*oxadiazole*.— *trans*-3-*p*-Aminostyryl-1,2,4-oxadiazole (3·74 g) was diazotized in glacial acetic acid (120 ml) and 2N-sulphuric acid (40 ml), and the diazonium solution was added at 0° during 30 min to a stirred solution of potassium thiocyanate (60 g) and copper(I) thiocyanate (6·0 g). The mixture was stirred at 0° for 1 h longer, left overnight, and neutralized (pH 7—8) with sodium hydrogen carbonate. Extraction with chloroform and recrystallization of the product from aqueous ethanol gave the *thiocyanato-compound* (2; R = *p*-NCS·C_6H_4) (2·7 g, 59%), m.p. 135°, $\lambda_{max.}$ 286 nm (ε 32,850) (Found: C, 57·8; H, 3·3; N, 18·1. $C_{11}H_7N_3OS$ requires C, 57·6; H. 3·1; N, 18·3%).

trans-3-p-*Ethylthiostyryl*-1,2,4-*oxadiazole*.—The preceding compound (458 mg) was heated with triethyl phosphite (0·38 ml) for 15 min at 130—135°. The mixture was evaporated to dryness and the residue was chromatographed in ethyl acetate–benzene (1 : 3) on silica, giving the *ethylthiostyryl compound* (2; R = *p*-EtS·C_6H_4) (119 mg, 25%), m.p. 76—79°, raised to 84—85° by sublimation, $\lambda_{max.}$ 321 nm (ε 23,900) (Found: C, 61·8; H, 5·3; N, 12·4. $C_{12}H_{12}N_2OS$ requires C, 62·0; H, 5·2; N, 12·1%). Further elution of the column with acetone gave trans-3-p-(O,O-*diethylphosphatothio*)*styryl*-1,2,4-*oxadiazole* [2; R = *p*-$(EtO)_2P(O)S$·C_6H_4] (517 mg, 74%), m.p. 74—75°, raised to 82° by recrystallization from benzene–light petroleum (b.p. 60—80°), $\lambda_{max.}$ 288 nm (ε 28,300) (Found: C, 49·1; H, 4·9; N, 8·2. $C_{14}H_{17}N_2O_4PS$ requires C, 49·4; H, 5·0; N, 8·2%).

trans-3-(2,3,4,5,6-*Pentafluorostyryl*)-1,2,4-*oxadiazole*.— The chloride (12) (3·8 g) and pentafluorobenzaldehyde (1·96 g) were dissolved in ethanol (250 ml). Ethanolic sodium ethoxide (N; 10 ml) was added to the stirred solution. Stirring was continued for 2 h, then the solvent was removed and water (20 ml) was added. Extraction with ethyl acetate, chromatography on silica in benzene, and recrystallization from light petroleum (b.p. 60—80°) gave the *oxadiazole* (2; R = C_6H_5) (1·38 g, 53%), m.p. 89—91°, $\lambda_{max.}$ 278 nm (ε 28,300) (Found: C, 45·7; H, 1·2; F, 35·5; N, 10·9. $C_{10}H_3F_5N_2O$ requires C, 45·8; H, 1·15; F, 36·2; N, 10·7%).

Reduction of trans-3-p-*Thiocyanatostyryl*-1,2,4-*oxadiazole in Methanol*.—The thiocyanato-compound (458 mg) was heated under reflux in dry methanol (10 ml) under nitrogen, and sodium borohydride (76 mg) was added to the suspension in portions during 4 min. The mixture was heated for 5 min more, then cooled. The solid was filtered off and washed with methanol, then with aqueous sulphur dioxide solution, leaving bis-{*p*-[2-(1,2,4-oxadiazol-3-yl)-vinyl]phenyl} disulphide (8) (306 mg, 75%), m.p. 200°. Recrystallization from aqueous acetone gave the *disulphide* as yellow needles, m.p. 201·5—202·5°, $\lambda_{max.}$ 300—302 and 227 nm (ε 46,500 and 23,200) (Found: C, 58·8; H, 3·6; N, 14·0; S, 15·3%; *m/e* 406. $C_{20}H_{14}N_4O_2S_2$ requires C, 59·1; H, 3·5; N, 13·8; S, 15·8%; *m/e* 406).

When the reaction was carried out at one-tenth of the concentration just described, the disulphide (8) was obtained in 38% yield; concentration of the mother liquors gave *trans*-3-*p*-methylthiostyryl-1,2,4-oxadiazole in 50% yield.

Reaction of N-*Methylbenzamide Oxime with Dimethylformamide Dimethyl Acetal*.—The amide oxime (1·50 g) and the acetal (1·19 g) were heated under reflux in dry benzene (100 ml) for 20 h. The solution was evaporated to dryness, and the residue was recrystallized from light petroleum (b.p. 80—100°) to give *NNN'*-trimethylurea (154 mg, 15%), m.p. 60—63° (Found: C, 46·6; H, 9·5; N, 27·2. Calc. for $C_4H_{10}N_2O$: C, 47·0; H, 9·8; N, 27·4%).

trans-3-p-*Chlorostyryl*-4,5-*dihydro*-1,2,4-*oxadiazole* (3; R = *p*-ClC_6H_4).—*p*-Chlorocinnamamide oxime (4·00 g) was stirred in boiling water (300 ml), and aqueous formaldehyde solution (39% w/v; 12 ml) was added. The mixture was heated under reflux for 30 min and left to cool overnight, when the oxadiazoline (3·68 g, 84%) separated, m.p. 168° (decomp.). Recrystallization of 3·5 g from ethanol (50 ml) gave 3-p-*chlorostyryl*-4,5-*dihydro*-1,2,4-*oxadiazole* (3·18 g, 77%), m.p. 176—178° (decomp.), $\lambda_{max.}$ 274 nm (ε 22,000) (Found: C, 57·55; H, 4·4; Cl, 16·7; N, 13·3. $C_{10}H_9ClN_2O$ requires C, 57·6; H, 4·3; Cl, 17·0; N, 13·4%).

Dehydrogenation of trans-3-p-*Chlorostyryl*-4,5-*dihydro*-1,2,4-*oxadiazole*.—The oxadiazoline (1·04 g) was dissolved in warm ethanol (30 ml), and 6N-sulphuric acid (5 ml) was added. The solution was stirred at <5°, and sodium nitrite (705 mg) in water (6 ml) was added, with stirring, during 11 min. Stirring was continued, and water (5 ml) was added. After 30 min longer, more water (5 ml) was added, the mixture was cooled to −5°, and the solid was filtered off and washed with cold 50% aqueous ethanol and

with water, leaving 3-*p*-chlorostyryl-1,2,4-oxadiazole (480 mg, 46·5%), m.p. 137—138°, identical (i.r. spectrum) with the compound described above.

cis-3-p-*Chlorostyryl*-1,2,4-*oxadiazole* (14; R = *p*-ClC_6H_4).—*trans*-3-*p*-Chlorostyryl-1,2,4-oxadiazole (3·0 g) in dry ethanol (1·5 l) was irradiated at room temperature for 23 h with ultraviolet light of wavelength >300 nm (mercury-vapour lamp). The solution was concentrated to 80 ml and cooled to 0°, when starting-material (830 mg) separated. The solution was further concentrated to *ca.* 20 ml when more starting material (140 mg) separated. Evaporation to dryness gave the crude, solvated *cis*-isomer as a pale yellow solid (2·2 g), m.p. 36°. The solid was dissolved in boiling light petroleum (b.p. 40—60°; 100 ml) and the solution was decanted from a little gum and cooled, giving cis-3-p-*chlorostyryl*-1,2,4-*oxadiazole* (1·45 g, 48%), m.p. 46°, $\lambda_{max.}$ 276 nm (ε 17,300), τ ($CDCl_3$) 1·38 (N=CH), 2·49 and 2·71 (C_6H_4), and 2·92 and 3·50 (d, *J* 12·5 Hz, *cis*-CH=CH) (Found: C, 58·4; H, 3·45; Cl, 17·1; N, 13·6. $C_{10}H_7ClN_2O$ requires C, 58·4; H, 3·45; Cl, 17·2; N, 13·6%).

cis-3-p-*Methylsulphinylstyryl*-1,2,4-*oxadiazole* (14; R = *p*-$MeSO{\cdot}C_6H_4$).—*trans*-3-*p*-Methylsulphinylstyryl-1,2,4-oxadiazole (350 mg) in dry ethanol (350 ml) was irradiated as in the preceding experiment for 6 h. The solution was evaporated to *ca.* 10 ml, when starting material (60 mg) separated and was filtered off. The filtrate was evaporated to dryness, leaving a gum (220 mg), which was purified on a thick silica plate by chromatography in ethyl acetate, giving *cis*-3-*p*-methylsulphinylstyryl-1,2,4-oxadiazole as an oil (130 mg, 49%), $\lambda_{max.}$ 278 nm (ε 15,000), τ [$(CD_3)_2SO$] 7·23 (Me), 2·88 and 3·39 (d, *J* 13 Hz, *cis*-CH=CH), and 1·32 (N=CH). In an experiment on 10 times the scale just described, chromatography on a column of silica MFC (200 g) in chloroform and final elution with chloroform–ethyl acetate (1 : 1) gave the *cis*-sulphoxide in 37% yield and also, in 11·6% yield, *cis*-3-*p*-methylsulphonylstyryl-1,2,4-oxadiazole, m.p. 76—79°, $\lambda_{max.}$ 273 nm (ε 17,000), $\lambda_{infl.}$ 281 nm (ε 15,600), $\nu_{max.}$ (Nujol) 1298 and 1136 cm^{-1} (SO_2Me), τ [$(CD_3)SO$] 6·72 (Me) and 2·70 and 3·21 (d, *J* 12 Hz, *cis*-CH=CH).

3-*Phenylethynyl*-1,2,4-*oxadiazole* (4; R = H).—Phenylpropiolamide oxime (8·21 g) was added to dry ether (150 ml) containing triethylamine (35 ml) and the solution was stirred and cooled to −78°. A solution of formyl fluoride [21] (*ca.* 5 ml) in ether, previously cooled to −78°, was slowly added. Triethylamine hydrofluoride separated at once. The solution was allowed to warm to 0°, then extracted with ice–water. The water was extracted with ether (150 ml) and the combined ether extracts were washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated, leaving the crude formylated amide oxime (9·01 g, 94·4%). Part of the product (8·55 g) was heated under reflux in dry ethanol for 3 h. The solution was evaporated and the residue (7·74 g) was chromatographed on silica MFC (750 g). Elution, finally with benzene–ethyl acetate (3 : 1) gave 3-*phenylethynyl*-1,2,4-*oxadiazole* (4·57 g, 56% from propiolamide oxime), m.p. 65—66°, $\lambda_{max.}$ 275 and 261 nm (ε 17,600 and 21,300), τ ($CDCl_3$) 1·22 (CH) and 2·2—2·8 (aromatic) (Found: C, 70·6; H, 3·8; N, 16·3. $C_{10}H_6N_2O$ requires C, 70·6; H, 3·55; N, 16·5%). The same product was obtained in 36·5% yield by heating phenylpropiolamide oxime with ethyl orthoformate containing boron trifluoride–ether complex as described earlier.

Nitration of 3-*Phenylethynyl*-1,2,4-*oxadiazole*.—Fuming nitric acid (d 1·5; 2·0 ml) was stirred at −35°, and the preceding compound (60 mg) was added during 10 min at <−30°. After 15 min longer at −30°, the solution was poured into ice–water (40 ml), giving an off-white solid (73 mg) (Found: C, 54·45; H, 3·1; N, 18·3. $C_{10}H_5N_3O_3$ requires C, 55·8; H, 2·3; N, 19·6%). Some of the product (70 mg) was chromatographed 9 times on a thick silica plate in benzene–light petroleum (b.p. 60—80°) (4 : 1). The faster-running component (46 mg), m.p. 170—175°, was 3-*p*-nitrophenylethynyl-1,2,4-oxadiazole (see below; i.r. and n.m.r. analysis). The slower-running component (22 mg), m.p. 95—102°, was slightly impure 3-*o*-nitrophenylethynyl-1,2,4-oxadiazole, τ ($CDCl_3$) 1·11 (N=CH), 1·75 (1H, aromatic), and 2·0—2·5 (3H, aromatic).

3-p-*Nitrophenylethynyl*-1,2,4-*oxadiazole* (4; R = NO_2).—Fuming nitric acid (d 1·5; 8 ml) and acetic anhydride (8 ml) were mixed at 10—15° and the mixture was cooled to −35°. 3-Phenylethynyl-1,2,4-oxadiazole (1·15 g) was added to the stirred mixture at <30° during 20 min. The mixture was allowed to warm to room temperature during 30 min. The nitration was carried out 3 times more, and the combined mixture was poured into ice–water (320 ml) giving a cream solid (5·34 g, 92%), similar in composition (g.l.c.) to the crude product obtained in the preceding experiment. Recrystallization from ethanol (115 ml) with seeding and slow cooling gave 3-p-*nitrophenylethynyl*-1,2,4-*oxadiazole* (2·93 g, 51%), m.p. 175—177°, $\lambda_{max.}$ 284 nm (ε 22,400), τ ($CDCl_3$) 1·10 (1H, N=CH), and 1·67 and 2·17 (4H, aromatic) (Found: C, 55·9; H, 2·6; N, 19·5. $C_{10}H_5N_3O_3$ requires C, 55·8; H, 2·3; N, 19·6%).

3-p-*Aminophenylethynyl*-1,2,4-*oxadiazole* (4; R = NH_2).—The preceding compound (2·91 g) in acetone (225 ml) was stirred at 3—7°, and acidic titanium(III) chloride solution (15% w/v; 100 ml) was added during 22 min. The solution was filtered, and the acetone and *ca.* 12 ml of water were removed under reduced pressure. The mixture was cooled for 1 h, then filtered, and the solid was washed with ice-cold 2N-hydrochloric acid (3·2 ml) leaving the crude hydrochloride. The latter was dissolved in 0·5N-hydrochloric acid, and solid sodium hydrogen carbonate was added until the pH was 7. The solid was washed with water, leaving the amine (2·17 g, 87%), m.p. 118—120°. A sample recrystallized from benzene–light petroleum (b.p. 80—100°) had m.p. 122—123°, $\lambda_{max.}$ 315 nm (ε 23,400) (Found: C, 65·6; H, 4·0; N, 22·0. $C_{10}H_7N_3O$ requires C, 64·9; H, 3·8; N, 22·7%).

3-p-*Chlorophenylethynyl*-1,2,4-*oxadiazole* (4; R = Cl).—The preceding compound (2·15 g) was stirred at 0° in N-hydrochloric acid (35 ml), and sodium nitrite (830 mg) in water (5 ml) was added during 17 min. Copper(I) chloride (1·5 g) was dissolved in 10N-hydrochloric acid (6 ml) and the diazonium solution was added. The mixture was stirred for 30 min, then heated to 55°. The product was extracted with chloroform (total 250 ml) and the dark solution was washed with water and with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated, leaving the crude chloro-compound (1·81 g, 76%). This was extracted with benzene giving 3-*p*-chlorophenylethynyl-1,2,4-oxadiazole (1·32 g, 56%), m.p. 116—118°. A *sample* recrystallized from light petroleum (b.p. 80—100°) had m.p. 120·5—121·5°, $\lambda_{max.}$ 286 and 258 nm (ε 20,700 and 2600), τ ($CDCl_3$) 1·08 (N=CH) and 2·32 and 2·56 (aromatic) (Found: C, 58·9; H, 2·7; Cl, 17·2; N, 13·7. $C_{10}H_5ClN_2O$ requires C, 58·7; H, 2·5; Cl, 17·3; N, 13·7%).

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*α-Cyano-*p*-chlorophenacylidene(triphenyl)phosphorane.*—Cyanomethylene(triphenyl)phosphorane (1·85 g) was stirred under dry nitrogen in benzene (50 ml), and *p*-chlorobenzoyl chloride (690 mg) in benzene was added during 30 min. The mixture was left over the week-end under nitrogen, then filtered, and the filtrate was evaporated to dryness. Recrystallization of the residue from ethanol gave the *phosphorane* (336 mg, 19%), m.p. 236—239°, $\lambda_{max.}$ 299 and 276 nm (ε 7900 and 8100) (Found: C, 72·6; H, 4·45; Cl, 8·4; N, 2·5%. $C_{27}H_{19}ClNOP$ requires C, 73·7; H, 4·35; Cl, 8·05; N, 3·2%).

p-*Chlorophenylpropiolonitrile.*—The preceding compound (3·80 g) was heated at 160—200° (bath) and 0·2 mmHg and the distillate was redistilled to give p-*chlorophenylpropiolonitrile* (827 mg, 59%), m.p. 83—84·5°, $\lambda_{max.}$ 282 and 267 nm (ε 21,800 and 26,300) (Found: C, 66·3; H, 2·5; Cl, 21·6; N, 8·5. C_9H_4ClN requires C, 66·9; H, 2·5; Cl, 21·9; N, 8·7%).

Reaction of p-*Chlorophenylpropiolonitrile with Hydroxylamine.*—The preceding compound (323 mg) and hydroxylamine hydrochloride (129 mg) were dissolved in absolute ethanol (20 ml) and the solution was neutralized (to phenolphthalein) at −20° with sodium ethoxide in ethanol. The ethanol was removed at <40° and the residue was recrystallized from aqueous ethanol, giving 3-*amino*-5-p-*chlorophenylisoxazole* (15) (330 mg, 85%), m.p. 141—142°, $\lambda_{max.}$ 265 nm (ε 21,700), τ ($CDCl_3$) 2·35, 2·60 (aromatic), 3·93 (CH), and 5·90 (NH_2) (Found: C, 55·6; H, 4·0; Cl, 18·0; N, 14·0. $C_9H_7ClN_2O$ requires C, 55·6; H, 3·6; Cl, 18·2; N, 14·4%).

p-*Chlorobenzyl(triphenyl)phosphonium Bromide.*—Triphenylphosphine (37·2 g) was heated under reflux in dry benzene (250 ml) for 8 h with *p*-chlorobenzyl bromide (29·8 g). The solid was filtered off and washed with benzene, leaving the bromide (53·1 g, 80%), m.p. 292—295°, $\lambda_{max.}$ 275·5, 268·5, and 225·5 nm (ε 3500, 4400, and 37,100), τ [$(CD_3)_2SO$] 1·9—2·3 (Ph), 2·61 and 2·88 (C_6H_4), and 4·52 (d, *J* 16 Hz, CH_2).

[p-*Chloro-α-*(1,2,4-*oxadiazol-*3-*ylcarbonyl)benzylidene*]*triphenylphosphorane* (18).—The preceding compound (28·25 g) was dissolved in anhydrous ethanol (800 ml) and a solution prepared from sodium (1·38 g) and ethanol (57 ml) was added, with stirring. The solution was evaporated to dryness under reduced pressure, and twice treated with benzene and again evaporated to dryness. The red solid was extracted into benzene (500 ml) and 3-chlorocarbonyl-1,2,4-oxadiazole [29] (4·0 g) in benzene (25 ml) was added. The colour was discharged at once, and crystals (10·97 g) slowly separated. Evaporation of the mother liquors and recrystallization of the residue from benzene gave a second crop (1·32 g). Recrystallization of the first crop from benzene gave the *phosphorane* (18) (3·04 g, 21%), no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 70·0; H, 4·4; Cl, 7·7; N, 5·6; P, 6·1. $C_{28}H_{20}ClN_2O_2P$ requires C, 69·7; H, 4·15; Cl, 7·35; N, 5·8; P, 6·35%).

Reaction of the Phosphorane (18) *with Acetic Anhydride.*—The preceding compound (18) (1·0 g) was dissolved in acetic anhydride (20 ml) and left at room temperature for 20 days. The solution was concentrated at <70° and the solid that separated on cooling was recrystallized from ethanol, giving (*α-cyanocarbonyl-*p-*chlorobenzylidene)triphenylphosphorane* (20), m.p. 240—241°, $\lambda_{max.}$ 316, 274, and 268 nm (ε 8600, 8600, and 8300), $\nu_{max.}$ ($CHBr_3$) 2210 cm^{-1} (C≡N), $\nu_{max.}$ (Nujol) 1660 cm^{-1} (CO·C=PPh_3) (Found: C, 73·8; H, 4·35; Cl, 8·2; N, 3·0. $C_{27}H_{19}ClNOP$ requires C, 73·8; H, 4·35; Cl, 8·05; N, 3·2%).

trans-3-p-*Chlorostyryl-*5-*ethoxycarbonyl-*1,2,4-*oxadiazole.*—*p*-Chlorocinnamamide oxime (anhydrous; 25·74 g) was dissolved in chloroform (300 ml) containing pyridine (10·34 g). Ethyloxalyl chloride (16·5 g) in chloroform (15 ml) was added dropwise, with stirring. Stirring was continued for 1 h then the mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from aqueous ethanol to give the *oxadiazole* (9·76 g, 37%), m.p. 94—95°, $\lambda_{max.}$ 285 and 228 nm (ε 31,500 and 13,000) (Found: C, 56·2; H, 4·2; Cl, 12·7; N, 10·3. $C_{13}H_{11}ClN_2O_3$ requires C, 56·0; H, 4·0; Cl, 12·7; N, 10·05%).

3-[1,2-*Dibromo-*2-(p-*chlorophenyl)ethyl*]-5-*ethoxycarbonyl-*1,2,4-*oxadiazole* (21; R = CO_2Et).—The preceding compound (5·0 g) was treated in chloroform (100 ml) with bromine (1·08 ml). After 1 h the solution was washed with sodium metabisulphite solution, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from aqueous ethanol to give the *dibromide* (21; R = CO_2Et) (7·23 g, 92%), m.p. 105°, no $\lambda_{max.}$ between 220 and 350 nm (Found: C, 35·8; H, 2·7; Br + Cl, 44·55; N, 6·2. $C_{13}H_{11}Br_2ClN_2O_3$ requires C, 35·6; H, 2·5; Br + Cl, 44·55; N, 6·4%).

trans-3-(α- *and* β-*Bromo-*p-*chlorostyryl)-*5-*ethoxycarbonyl-*1,2,4-*oxadiazoles* (24) *and* (25).—The preceding compound (3·63 g) was stirred in dry benzene (20 ml) and 1,5-diazabicyclo[4.3.0]non-5-ene (0·9 ml) was slowly added. The solution was shaken with 2N-hydrochloric acid (50 ml), then with water (50 ml), and dried (Na_2SO_4). The benzene was evaporated and the residue was recrystallized from aqueous ethanol to give a mixture of the bromides (24) and (25) (2·525 g, 85%), m.p. 58—59°, $\lambda_{max.}$ 287—289 nm (ε 16,800) (Found: C, 43·6; H, 2·9; Br + Cl, 32·17; N, 7·7. $C_{13}H_{10}BrClN_2O_3$ requires C, 43·7; H, 2·8; Br + Cl, 32·3; N, 7·8%).

3-[1,2-*Dibromo-*2-(p-*chlorophenyl)ethyl*]-1,2,4-*oxadiazole* (21; R = H).—Treatment of 3-*p*-chlorostyryl-1,2,4-oxadiazole with bromine, as described above, gave the *dibromide* (21; R = H) in 92% yield, m.p. 141—142°, $\lambda_{max.}$ 236 nm (ε 8900) (Found: C, 32·9; H, 2·1; Br + Cl, 53·4; N, 7·6. $C_{10}H_7Br_2ClN_2O$ requires C, 32·8; H, 1·9; Br + Cl, 53·5; N, 7·65%).

trans-3-(β-*Bromo-*p-*chlorostyryl)-*1,2,4-*oxadiazole* (22).—The preceding compound (350 mg) in dry ether (20 ml) was treated dropwise with 1,5-diazabicyclo[4.3.0]non-5-ene (210 mg) in ether (10 ml). The mixture was poured into 2N-sulphuric acid (10 ml) and the ether layer was washed with water and dried (Na_2SO_4), then evaporated. The residue was recrystallized from ethanol to give the *bromide* (22) (150 mg, 55%), m.p. 98—100°, $\lambda_{max.}$ 268 nm (ε 12,800) (Found: C, 42·1; H, 2·2; Br + Cl, 40·1; N, 9·5. $C_{10}H_6BrClN_2O$ requires C, 42·1; H, 2·1; Br + Cl, 40·4; N, 9·8%).

β-*Bromo-*p-*chlorocinnamonitrile* (23).—The preceding compound (285 mg) in acetone (1·425 ml) and water (1·425 ml) was heated under reflux in an atmosphere of nitrogen, and potassium hydroxide (55·8 mg) in water (1·14 ml) was added during 30 min. Water (6 ml) was added and the product was isolated with the aid of ether and chromatographed in benzene–light petroleum (b.p. 60—80°) (1 : 1) to give the nitrile (23) (138 mg, 68%), m.p. 121°, $\nu_{max.}$ ($CHBr_3$) 2208 cm^{-1} (C≡N), τ ($CDCl_3$) 2·47 (CH=) (Found: Br + Cl, 46·8. C_9H_5BrClN requires Br + Cl, 47·6%).

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