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THE SYNTHESIS OF ANNULATED PYRIDAZINES BY CYCLOADDITION OF AZODICARBOXYLATES TO VINYL HETEROCYCLES

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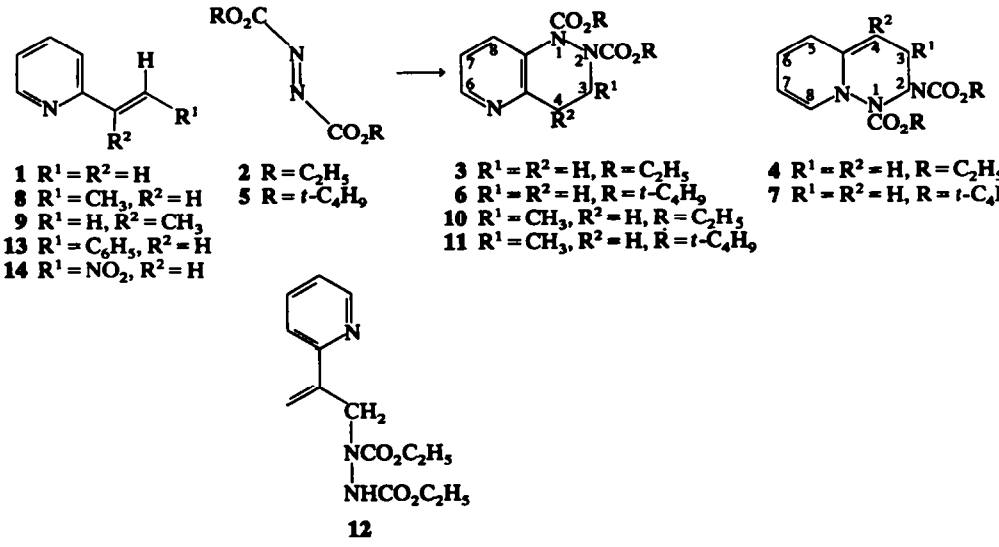
Abstract—Reaction between 2-vinyl pyridine and azodicarboxylates **2** or **5** gives *N,N'*-disubstituted tetrahydropyrido[3,2-c]pyridazines **3** and **6**, and dihydro-3*H*-pyrido[1,2-c]triazines **4** and **7**; 2-(prop-1-en-1-yl)-pyridine **8** gives hydropyridopyridazines **10** and **11** but 2-(prop-1-en-2-yl)pyridine **9** gives mainly the 'ene' addition product **12**. From 4-vinyl-pyridine and esters **2** or **5** diesters of tetrahydropyrido[3,4-c]pyridazine-1,2-dicarboxylic acid, **25** and **26** are obtained, and from 2-methyl-5-vinylpyridine both possible cyclisation products, the tetrahydro-pyrido[2,3-c]pyridazines **33** and **36**, and -pyrido[4,3-c]pyridazines **34** and **37**. The di-*t*-butyl esters **6**, **11**, **26**, and **37** are quantitatively decarbalkoxylated in TFA, giving tetrahydropyridopyridazines **16**, **18**, **27**, and **41**; of these, the first three were oxidized to give pyrido[2,3-c]-pyridazine **15**, its 3-methyl derivative **19**, and pyrido[3,4-c]pyridazine **28** respectively. A dihydropyrido[4,3-c]-pyridazine **42** was obtained from compound **41**. Thieno[2,3-c]-pyridazine **48** has been similarly prepared from 2-vinylthiophen, but 2-(prop-1-en-2-yl)thiophen gave an ene addition compound **51** and a dihydrothienopyridazine **50**. Reactions with other vinylpyridines, and with vinylfurans, were unsuccessful.

On rearrangement of the phenyl-hydrazone from 4,5,6,7-tetrahydro-4-oxo-isoxazolo[2,3-a]pyridinium bromide a compound was obtained which was thought to be a pyrido[3,2-c]pyridazine.[1] Inspection of the literature revealed, at that time, only one reported synthesis of a methylpyrido[3,2-c]pyridazine **20**, by diazotisation of 3-amino-2-(prop-1-en-2-yl)pyridine.[2] After the completion of our synthesis, which is described below, but before the publication of our preliminary communication,[3] papers by Kost, Terent'ev, and their co-workers reported a synthesis of pyrido[3,2-c]pyridazines by a cycloaddition route similar to our own;[4-7] the two routes are alike in the initial step, but differ in aromatisation procedures. We have applied our synthesis also to produce pyrido[3,4-c]pyridazine **18**, reduced pyrido[2,3-c]- **35** and pyrido[4,3-c]-pyridazines **42**, and thieno[3,2-c]pyridazine **48**.

We chose to approach the pyridopyridazines from readily available vinylpyridines and azodicarboxylates. There are examples in the literature of the use of vinylpyridines in the Diels-Alder reaction; self-condensation to give 5-(2-pyridyl)quinoline,[8,9] addition of acetylenedicarboxylates to give many products,[10,11] and of *N*-phenylmaleimide to give 1:2 adducts.[12] On the other hand azodicarboxylates react with styrene to give adducts of a type in which two azodicarboxylate molecules are involved; the monoadducts could not be obtained.[13-16] A trial experiment, using benzene as solvent, and a 1:1 ratio of 2-vinylpyridine **1** and diethyl azodicarboxylate **2** showed the azodicarboxylate to have disappeared after 26 hours boiling, although 2-vinylpyridine was still present. A gas chromatogram of the crude reaction mixture showed, apart from vinylpyridine, three major peaks. Chromatographic separation provided two of the major products, and analysis showed them to be isomers, $C_{13}H_{17}N_3O_4$, and hence 1:1-adducts. From the ^{1}H NMR spectra the isomer obtained in greater yield (13%) was the tetrahydropyrido[3,2-c]pyridazine **3**, and that in smaller yield the dihydro-3*H*-pyrido[1,2-c]triazine **4**. In both cases the downfield signals indicated an α-substituted pyridine system to be present. In the compound **3** a multiplet δ2.7–3.7 (4H) was due to the non-equivalent protons on C3 and C4: in the latter compound a doublet of doublets due to H4 could not be seen, but was clearly visible on the di-*t*-butyl ester **7** (see below).

Further experiments aimed at increasing the yield of adduct **3** involved changes in the proportion of reagents and change of solvent. No advantage was gained by using more azodicarboxylate; higher boiling hydrocarbon solvents gave more products and a lower yield of adduct **3**. In chloroform the reaction was faster and the yield was better, but the best results were with acetonitrile, the reaction being complete in 6.5 hours, with a yield of 18% of adduct **3**.

Difficulty in the later stages of the synthesis led us to react di-*t*-butyl azodicarboxylate **5** with 2-vinylpyridine **1**; here the best solvent was benzene, giving a maximum yield of 23% of adduct **6** with a small amount of adduct **7**. The propenylpyridines **8** and **9** were treated with diethyl azodicarboxylate, and the propenylpyridine **8** also with the di-*t*-butyl ester **5**. The cycloaddition in benzene using 2-(prop-1-en-1-yl)pyridine **8** was slower than that of 2-vinylpyridine (ethyl ester 36 h compared with 26 h; *t*-butyl ester 15 days against 8 days) and the yields of adduct **10** and **11** were poorer (7.6% and 10%). Both effects could be due to steric hindrance. In both cases the ^{1}H NMR spectra supported



1 $R^1 = R^2 = H$
8 $R^1 = CH_3$, $R^2 = H$
9 $R^1 = H$, $R^2 = CH_3$
13 $R^1 = C_6H_5$, $R^2 = H$
14 $R^1 = NO_2$, $R^2 = H$

2 $R = C_2H_5$
5 $R = t\text{-}C_4H_9$

3 $R^1 = R^2 = H$, $R = C_2H_5$
6 $R^1 = R^2 = H$, $R = t\text{-}C_4H_9$
10 $R^1 = CH_3$, $R^2 = H$, $R = C_2H_5$
11 $R^1 = CH_3$, $R^2 = H$, $R = t\text{-}C_4H_9$

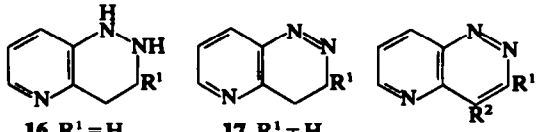
4 $R^1 = R^2 = H$, $R = C_2H_5$
7 $R^1 = R^2 = H$, $R = t\text{-}C_4H_9$

12

the proposed structure; notable was a signal at δ1.4(3H, d) and one at δ4.9(1H, m), the latter collapsing to a pair of doublets on double irradiation at δ1.4. On the other hand, reaction between the isopropenylpyridine **9** and the diethyl ester **2** gave one major product in 90% yield (on unrecovered isopropenylpyridine). Analysis showed the product to be $C_{14}H_{19}N_3O_4$, that is a 1:1 adduct, but the ^{1}H NMR spectrum showed signals at δ1.2 (6H, $2CH_3CH_2$), 4.1 (4H, two overlapping q, CH_3CH_2), 4.6 (2H, s, CH_2), 5.4 and 5.9 (each 1H, brs), 7.0–7.4 (m, 3H), 8.0 (1H, br, NH), and 8.5 (1H, d of d, α-pyridine). This spectrum rules out the cycloadduct, but fits well with the 'ene' reaction product **12**. Attempts to obtain adducts from stilbazole **13** or β-nitrovinylpyridine **14** failed.

With the cycloaddition accomplished, we attempted hydrolysis of the diethyl ester **3**. Many products were formed even under a nitrogen atmosphere, but the only isolated material was a small sample of the parent pyrido[3,2-c]pyridazine **15**. Cold trifluoroacetic acid converted the di-*t*-butyl ester **6** quantitatively into the tetrahydro-pyridazine **16**. Our most successful oxidation procedure is in two stages; mercuric oxide gives an unstable intermediate whose spectral characteristics indicate that it is largely the dihydro derivative **17**, and this is converted by oxygen into pyridopyridazine **15**. The ^{1}H NMR spectrum showed signals at δ7.8 (H7, d of d, $J_{7,8}$5 and $J_{6,7}$4 Hz), 8.15 (H4, d of d, $J_{3,4}$4 and $J_{4,8}$1 Hz), 8.85 (H8, br d, $J_{7,8}$5 Hz), 9.2 (H6, d of d, $J_{6,7}$4 Hz, $J_{6,8}$ = 2 Hz), and 9.55 p.p.m. (H3, d, $J_{3,4}$ = 6 Hz). The yield from **16** to **15** is approximately 44%. In a similar manner, the adduct **11** gave the tetrahydropyridopyridazine **18**, and 3-methylpyrido-pyridazine **19**. The major change in the ^{1}H NMR spectrum of compound **19** compared with that of **15** was in the simplification of the signal for H4, showing only cross-ring coupling.

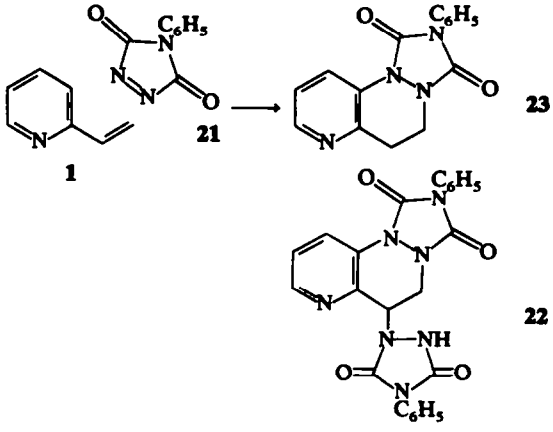
We have briefly examined the reaction between the triazolinedione **21** and 2-vinylpyridine, a reaction which in the hands of Kost, Terent'ev, *et al.*[6] has given good yields of 2:1 adducts of type **22**.



16 $R^1 = H$
18 $R^1 = CH_3$

17 $R^1 = H$

15 $R^1 = R^2 = H$
19 $R^1 = CH_3$, $R^2 = H$
20 $R^1 = H$, $R^2 = CH_3$



1 **21** **23**

22

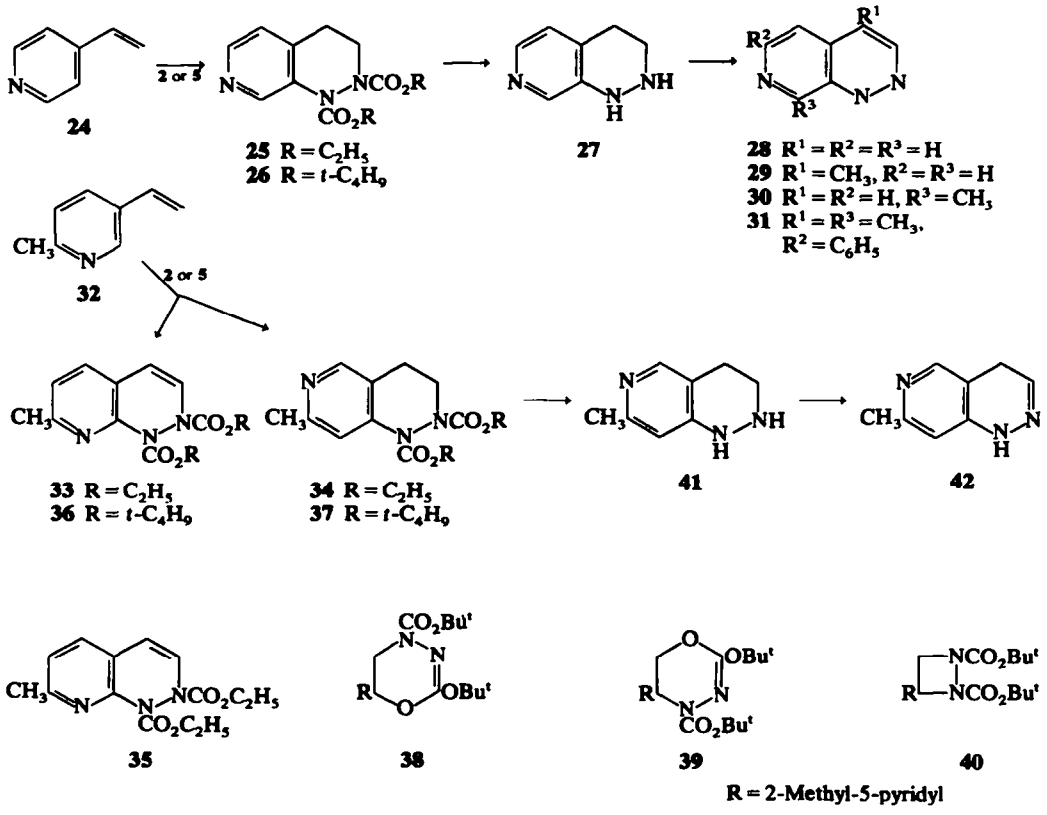
However, although we isolated a very small amount of the 1:1 cycloadduct **23** we have not found pure adducts such as **22**.

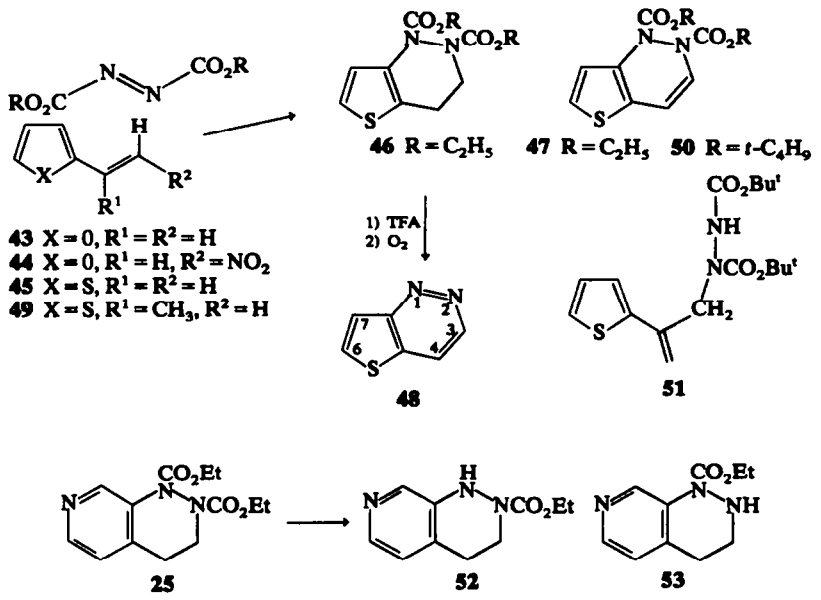
The pyrido[3,4-c]pyridazines are as little studied as the isomers, and the reported synthesis[27] of compounds **29** to **31** similarly involves diazotisation of an *ortho*-aminovinylpyridine. Reaction between 4-vinylpyridine **24** and the azodicarboxylates **2** or **5** gave the tetrahydropyrido[3,4-c]pyridazines **25** and **26**, in 13 and 16% yield respectively. The ^{1}H NMR spectrum of the di-*t*-butyl ester **26** showed two singlets (each 9H) at δ1.4 and 1.5, and signals at δ2.4–3.5 (H3 and H4,4'), 4.1–4.8 (H3'), 7.0 (H5, d, $J_{5,6}$5 Hz), 8.15 (H6, d, J 5 Hz), and 8.9 p.p.m. (H8, brs). Treatment of the ester **26** with TFA gave, in

almost quantitative yield, tetrahydropyrido[3,4-c]pyridazine **27**, oxidized to the parent pyrido[3,4-c]pyridazine **28**. The ^{1}H NMR spectrum of compound **28** showed signals at δ7.6 (H5, d, $J_{5,6}$6 Hz), 7.8 (H4, d, $J_{3,4}$5.8 Hz), 8.7 (H6, d, J6 Hz), 9.35 (H3, d, J5.8 Hz), and 9.85 p.p.m. (H8, s).

From a 3-vinylpyridine, such as the readily available compound **32**, it should be possible to reach either, or both, of the remaining pyrido[2,3-c]- or pyrido[4,3-c]pyridazines. After reaction between compound **32** and ester **2** we isolated three compounds, two being isomers, $C_{14}H_{19}N_3O_4$, and the other having the formula $C_{14}H_{17}N_3O_4$. The two isomers were 1:1 adducts, and inspection of their ^{1}H NMR spectra showed that the major isomer (5.3% yield) was tetrahydropyrido[4,3-c]pyridazine **34**, while the minor isomer (3.7%) was the tetrahydropyrido[2,3-c]pyridazine **33**. Both isomers showed absorptions due to the ester groups, to the methyl group, and to the methylene groups at positions 3 and 4; in the aromatic region compound **34** showed signals at δ7.6 (H8) and 8.1 p.p.m. (H5), while compound **33** showed a pair of doublets δ6.9 and 7.35 p.p.m., (J 7 Hz) due to H6 and H5 respectively. The third product was the dihydropyrido[2,3-c]pyridazine **35**; in this case, in addition to ester and methyl signals the ^{1}H NMR spectrum showed absorptions at δ5.95 (H4, d, $J_{3,4}$6.5 Hz), 6.95 (H6, d, $J_{5,6}$8 Hz), 7.1 (H3, d, J 6.5 Hz), and 7.3 p.p.m. (H5, d, J 8 Hz). Reaction between the 3-vinylpyridine **32** and di-*t*-butyl azodicarboxylate **5** similarly gave three products, two being isomers of formula, $C_{18}H_{27}N_3O_4$. The isomers were readily identified as the tetrahydropyrido[2,3-c]pyridazine **36** (3.5%) and the tetrahydropyrido[4,3-c]pyridazine **37** (5.5%). The third component, an oil, showed in the ^{1}H NMR spectrum a 2,5-disubstituted pyridine system, two nonequivalent signals (9H each), and a -CH-CH_2-grouping, δ3.25 (1H, d of d, J 14 and 9 Hz), 4.2 (1H, d of d, J 14 and 3 Hz), and 5.2 p.p.m. (1H, d of d, J 9 and 3 Hz). These structural elements could be found either in the diazetidine **40** or in the isomeric oxadiazines **38** or **39**; both systems have been reported[17,18] as formed in analogous cycloadditions of azodicarboxylates with alkenes. Of the three possibilities we prefer the oxadiazines, and of these the more likely seems **38** in view of the normal mode of addition of azodicarboxylates to vinylpyridines. Briefly, the chemical shifts are in reasonable agreement with those reported for oxadiazines; the geminal coupling constant in the diazetidines is 9–9.5 Hz, in the oxadiazines 13.5 Hz.

Because of the small quantities of adduct obtained, attempts were made to aromatize only the tetrahydropyrido[4,3-c]pyridazine **37**. The *t*-butyloxycarbonyl groups were quantitatively removed in TFA. The intermediate **41**, characterized by its spectra, was dehydrogenated to the dihydropyrido[4,3-c]pyridazine **42**, which we could not further oxidize. The ^{1}H NMR spectrum of compound **42** showed signals at δ2.4 (3H, s), 3.3 (2H, d, J 3 Hz, H4), 6.4 (1H, s, H8), 6.8 (1H, t, J 3 Hz, H3), 8.0 (1H, s, H5), and 8.4 p.p.m. (1H, br, exch D_2O, NH).





Our efforts to extend the route to obtain furopyridazines and thienopyridazines have been less successful. From 2-vinylfuran **43** and either of the esters, **2** or **5**, mixtures were obtained from which no simple adducts could be isolated. A similar result was obtained from 2-(2-nitrovinyl)furan **44**. From 2-vinylthiophen **45** and the diethyl ester **2** or di-*t*-butyl ester **5**, mixtures of products were obtained which could not be separated by chromatography, but showed, in the mass spectrogram, molecular ions corresponding to the tetrahydro-**46** and dihydro-thieno[3,2-c]pyridazine **47**. A sample of the mixture from the di-*t*-butyl ester **5** was treated with TFA and then oxidized, giving, after chromatography, a small yield of thieno[3,2-c]pyridazine **48**, with m.p. and NMR spectrum very similar to those reported.[19] Reaction between 2-(prop-1-en-2-yl)thiophen **49** and the di-*t*-butyl ester **5** was rapid (14 h in boiling benzene compared with 8 days for 2-vinylpyridine). Two products were isolated, the dihydrothieno[3,2-c]pyridazine **50** (10%) and the 'ene' addition product **51** (23.5%). In the ^{1}H NMR spectrum the cyclo adduct **50** showed signals at δ1.5 (18H, s), 2.0 (3H, s), 6.6 (H3, brs), and 7.1 p.p.m. (2H, s, H6 and H7). The 'ene' product **51** showed signals at δ1.45 and 1.5 (each 9H, s), 4.4 (2H, s), 5.05 (1H, s), 5.45 (1H, s), 6.65 (1H, brs, exch D_2O), 6.8–7.5 p.p.m. (3H, m, thienyl H).

The ethyl carbamates, such as compound **3**, were in all cases prepared much more rapidly than the *t*-butylcarbamates, and a good method for removing the ethoxycarbonyl groups would provide a considerable improvement in the synthesis. We have tried trimethylsilyl iodide, said[20] to give clean, rapid cleavage of esters, on the diethyl ester **25**. After 24 h at 50° there was no further change in the NMR spectrum of the mixture, and work-up gave the monoethyl ester **52**, as shown by the mass spectrum and the ^{1}H NMR signals at δ1.2 (3H, q), 2.8 (2H, t), 3.25 (2H, t), 4.25 (3H, q CH_2CH_3, overlying NH), 6.95 (H5, d, J 6 Hz), and 8.1 p.p.m. (H6, d, J 6 Hz). The upfield shift in the pyridine proton absorptions lead us to prefer formula **52** to the isomeric **53**. After a further 40 h at 50° with fresh TMSI the second ethoxycarbonyl group was removed, but the product was impure, and only a low yield of pyrido[43-c]pyridazine **28** was obtained. On a larger scale the cleavage was even less successful.

We have done little work which could lead to positive statements as to the mechanism of the cycloaddition. Such cycloadditions have been said to be concerted; in our case the combination of an electron-deficient dienophile, and (in the case of the vinyl pyridines) an electron-deficient diene may account for the low yields and long reaction times. We have been unsuccessful in attempts to isolate pure compounds from the higher molecular weight products so we cannot say which competing pathways are used. It is interesting to note that 'ene' reactions, when available, compete very favourably against the cycloaddition. Our observation that acceleration by polar solvents is only moderate suggests that the cycloaddition is concerted rather than stepwise in some dipolar mode.

EXPERIMENTAL

M.ps. were determined on a Kofler heated stage and are uncorrected. Chromatography was on Woelm alumina (activity shown thus–IV), or on 40 × 20 cm preparative plates of Merck silica gel P_F254. Ultraviolet spectra were recorded for solutions in 95% EtOH and infrared spectra for solutions in $CHCl_3$.

Starting materials. 2- and 4-vinylpyridine, and 2-methyl-5-vinylpyridine were purchased; 2-(prop-1-en-1-yl)pyridine **8** was prepared by dehydration[21] of 1-(2-pyridyl)-propan-1-ol;[22] 2-(prop-1-en-2-yl)-pyridine **9** by dehydration (sulphuric acid)[23] of 2-(2-pyridyl)propan-2-ol;[24] 1-phenyl-2-(2-pyridyl)ethene **13** from benzaldehyde and α-picoline;[25] 2-(β-nitrovinyl)pyridine **14** from pyridine-2-aldehyde and nitromethane;[26,27] 2-vinylfuran **43** from 2-furylacrylic acid;[28] 2-(β-nitrovinyl)furan **44** from furfural and nitromethane;[29] 2-vinylthiophen **45** as

described in "Organic Syntheses";[30] and 2-(prop-1-en-2-yl)thiophen **49** by dehydration (oxalic acid) of 2-(2-thieno)propan-2-ol.[31] Diethyl azodicarboxylate was purchased; di-*t*-butyl azodicarboxylate was prepared as described in "*Organic Syntheses*".[32]

General procedure for reactions between azodicarboxylates and vinyl heterocycles.

Solutions of the azodicarboxylate (0.05 mole) and the vinyl heterocycle (0.05 mole) in acetonitrile (for ester **2**) or benzene (for ester **5**) (100 ml), were boiled under nitrogen. The reaction was followed by GLC (OV 101, 30%; 120°) for ester **2**, or TLC (toluene, ethyl acetate 1:3) for ester **5**, and stopped when no ester remained. Reaction times are summarised below;

Heterocycle	**1**	**9**	**8**	**24**	**32**	**49**	**45**	**43**
Reaction Time **2** (h)	6.5	5	36*	14	5.5	1	0.5	1
Reaction Time **5** (h)	192		360	264	144	14	7	3

* In benzene

Evaporation of the solvent was followed by chromatography on alumina (300–400 g, IV), which gave unreacted vinyl heterocycle (~10%), and then products which were further separated by PLC. The individual products are listed.

2-*Vinylpyridine and ester* **2**. The oil eluted with benzene: petrol (1:1) (1.87 g) was separated by PLC (toluene, ethyl acetate; 1:3). The band of highest R_F crystallized from cyclohexane, m.p. 93–94° (0.27 g, 2.3%) was *diethyl* 1,2-*dihydro*-3H-*pyrido*[1,2-c]1,2,3-*triazine*-1,2-dicarboxylate, **4**. (Found: C, 56.35; H, 6.3; N, 15.3. $C_{13}N_{17}N_3O_4$ requires C, 55.9; H, 6.15; N, 15.05%); λ_{max} 258, 260 and 267 nm (log ε 3.49, 3.5 and 3.44); ν_{max} 1700, 1661, and 1300 cm^{-1}; $\delta(CDCl_3)$ 1.1-1.6 (6H, m), 3.6 (1H, d of d, J 13 and 8 Hz, H3), 4.0–4.6 (5H, m, CH_3CH_2 and H3'), 5.35 (1H, d of d, J 8 and 3 Hz, H4), 7.1–7.9 (3H, m, H5, 6, 7), and 8.5 p.p.m. (1H, br d of d, J 4 and 2 Hz, H8). A fluorescent compound of lower R_F was distilled, b.p. 140°/5 × 10^{-4} mm Hg, and shown to be diethyl 1,2,3,4-*tetrahydropyrido*-[3,2-c]*pyridazine*-1,2-*dicarboxylate*, **3**, (1.55 g, 13.2%). (Found: C, 56.35; H, 6.3; N, 15.3. $C_{13}H_{17}N_3O_4$ requires C, 55.9; H, 6.15; N, 15.05%); λ_{max} 233 and 269 nm (log ε 3.9 and 3.58); ν_{max} 1710, 1320 cm^{-1}; δ ($CDCl_3$) 1.0–1.5 (6H, m, CH_3CH_2), 2.5–5.0 (8H, m, CH_3CH_2O and CH_2CH_2), 7.1 (1H, d of d, J 8 and 4 Hz, H7), 8.05 (1H, d of d, J 8 and 2 Hz, H8), and 8.25 p.p.m. (1H, d of d, J 4 and 2 Hz, H6).

2-*Vinylpyridine and ester* **5**. Similar work-up gave unreacted vinylpyridine (1.07 g), and two isomers. The isomer with higher R_F was an oil, b.p. 185°/10^{-4} mm Hg, *di-t-butyl* 1,2-*dihydro*-3H-*pyrido*[1,2-c]*triazine*-1,2-*dicarboxylate*, **7**, (0.35 g, 2.7%). (Found: C, 61.2; H, 7.8; N, 12.5. $C_{17}H_{25}N_3O_4$ requires C, 60.9; H, 7.45; N, 12.55%); λ_{max} 253, 261, and 262 nm (log ε 3.27, 3.28, 3.17); ν_{max} 1710, 1660, 1305, 1295, 1170 and 1140 cm^{-1}; δ ($CDCl_3$) 1.45 (9H, s), 1.50 (9H, s), 3.5 (1H, d of d, J 14 and 8 Hz, H3), 4.35 (1H, d of d, J 14 and 4 Hz, H3'), 5.3 (1H, d of d, J 8 and 4 Hz, H4), 7.0–7.9 (3H, m; H5, 6, 7) and 8.5 p.p.m. (1H, d of d, J 5 and 1 Hz, H8). The band of lower R_F b.p. 195–200°/10^{-4} mm Hg, was *di-t-butyl* 1,2,3,4-*tetrahydropyrido*[3,2-c]*pyridazine*-1,2-*dicarboxylate*, **6**, (3.3 g, 19.7%). (Found: C, 60.8; H, 7.6; N, 12.65. $C_{17}H_{25}N_3O_4$ requires C, 60.9; H. 7.45; N, 12.55%); λ_{max} 234 and 281 nm (log ε 3.89, 3.6); ν_{max} 1710, 1330, 1156 cm^{-1}; $\delta(CDCl_3)$ 1.4 (9H, s), 1.5 (9H, s), 2.8–3.8 (3H, m, $CHCH_2$), 4.45 (1H, m), 7.05 (1H, d of d J 8 and 6 Hz, H7) 8.0 (1H, d of d, J 8 and 1 Hz, H8), and 8.2 p.p.m. (1H, d of d, J 6 and 1 Hz, H6).

2-1-*Propen*-1-*yl*)*pyridine* **8** *with ester* **2**. From propenylpyridine **8** (3.7 g) and ester **2** (5.4 g), worked up as described, were obtained compound **8** (0.7 g, 19%), and *diethyl* 1,2,3,4-*tetrahydro*-3-*methylpyrido*-[3,2-c]-*pyridazine*-1,2-*dicarboxylate* **10**, b.p. 195–200°/10^{-4} mm Hg (0.56 g, 7.6%). (Found: C, 57.05; H, 6.6; N, 14.45. $C_{14}H_{19}N_3O_4$ requires C, 57.35; H, 6.5; N, 14.35%); λ_{max} 233 and 280 nm (log ε 4.04 and 3.67); ν_{max} 1710 and 1325 cm^{-1}; $\delta(CDCl_3)$ 1.1–1.5 (9H, m), 2.2 (1H, d of d, J 17 and 1 Hz, H4), 3.35 (1H, d of d, J 17 and 7 Hz, H4'), 3.9–4.5 (4H, m, CH_3CH_2O), 4.85 (1H, m, H3), 7.1 (1H, d of d, J 8 and 5 Hz, H7), 8.1 (1H, d of d, J 8 and 1 Hz, H8), and 8.25 p.p.m. (1H, d of d, J 5 and 1 Hz, H6). M^+ 293.

Propenylpyridine **8** *and ester* **5**. Work-up gave propenylpyridine **8** (0.73 g, 12%), and *di-t-butyl* 1,2,3,4-*tetrahydro*-3-*methylpyrido*[3,2-c]-*pyridazine*-1,2-*dicarboxylate* **11**, b.p. 125°/10^{-4} mm Hg (1.94 g, 15%). (Found: C, 61.9; H, 7.75; N, 12.05. $C_{18}H_{27}N_3O_4$ requires C, 61.85; H, 7.8; N, 12.25%.); λ_{max} 235 and 283 nm (log ε 3.99 and 3.66); ν_{max} 1700, 1340, and 1160 cm^{-1}; $\delta(CDCl_3)$ 1.45 (12H, m), 1.5 (9H, s), 2.65 (1H, d of d, J 18 and 1 Hz, H4), 3.3 (1H, d of d, J 18 and 7 Hz, H4'), 4.8 (1H, m, H3), 7.05 (1H, d of d, J 8 and 5 Hz, H7), 8.05 (1H, d of d, J 8 and 1 Hz, H8), and 8.2 p.p.m. (1H, d of d, J 5 and 1 Hz, H6).

2-(*Prop*-1-*en*-2-*yl*)*pyridine* **9** *and ester* **2**. After recovered pyridine **9** (0.5 g, 15%), the major product was *diethyl* N-(2-(2-*pyridyl*)-*prop*-1-*en*-3-yl)*hydrazo*-N,N'-*dicarboxylate*,[12] m.p. 75–76° (cyclohexane), (5.9 g, 90%). (Found: C, 57.65; H, 6.8; N, 14.05. $C_{14}H_{19}N_3O_4$ requires C, 57.35; H, 6.5; N, 14.35%); λ_{max} 232 and 277 nm (log ε 3.88, 3.6); ν_{max} 3400, 1720, 1110 cm^{-1}; δ ($CDCl_3$) 1.2 (6H, tr), 4.1 (4H, q), 4.6 (2H, s), 5.4 (1H, s), 5.9 (1H, s), 7.0 (1H, m), 7.3–7.4 (2H, m), 7.95 (1H, brs, exch. D_2O), and 8.50 p.p.m. (1H, d of d, J 5 and 1 Hz). M^+ 293.

4-*Vinylpyridine* **24** *and ester* **2**. After removal of unreacted 4-vinylpyridine (2g; 35%), the only identified product was *diethyl* 1,2,3,4-*tetrahydropyrido*[3,4-c]-*pyridazine*-1,2-*dicarboxylate* **25**, b.p. 175–190/10^{-4} mm Hg (1.1 g, 13% on unrecovered vinylpyridine). (Found: C, 55.8; H, 6.3; N, 15.05. $C_{13}H_{17}N_3O_4$ requires C, 55.9; H, 6.15; N, 15.05%); λ_{max} 233 and 277 nm (log ε 4.19 and 3.74); ν_{max} 1720, 1325, 1305 cm^{-1}; δ ($CDCl_3$) 1.1–1.5 (6H, m) 2.5–3.7 (3H, m, $CHCH_2$), 3.8–4.8 (5H, m, H3 + CH_3CH_2O), 7.15 (1H, d, J 5 Hz, H5), 8.3 (1H, d, J 5 Hz, H6), and 9.0 p.p.m. (1H, s, H8). M^+ 279.

4-*Vinylpyridine* **24** *and ester* **5**. Unreacted pyridine **24** (1.7 g, 32%), was followed by *di-t-butyl* 1,2,3,4-*tetrahydropyrido*[3,4-c]*pyridazine*-1,2-*dicarboxylate*, **26**, b.p. 185–195°/10^{-4} mm Hg, (1.8 g, 16%, on unrecovered pyridine). (Found: C, 60.9; H, 7.7; N, 12.5. $C_{17}H_{25}N_3O_4$ requires C, 60.9; H, 7.45; N, 12.55%); λ_{max} 235 and 277 nm (log ε 3.9, 3.52); ν_{max} 1715, 1210, 1150 cm^{-1}; δ ($CDCl_3$) 1.4 (9H, s), 1.5 (9H, s), 2.4–3.5 (3H, m, CH_2CH), 4.1–4.8 (1H, m), 7.0 (1H, d, J 5 Hz, H5), 8.15 (1H, d, J 5 Hz, H6), and 8.9 p.p.m. (1H, brs, H8).

2-*Methyl*-5-*vinylpyridine* **32** *and ester* **2**. From pyridine **32** (2.8 g) and azoester **2** (4.0 g), were isolated unchanged pyridine (1.27 g, 45%), and three products. In order of decreasing R_F these were 1) *Diethyl* 1,2-*dihydro*-7-*methylpyrido*[2,3-c]*pyridazine* **35**, b.p. 170–200°/3 × 10^{-4} mm Hg (70 mg., 1.9%). M^+ 291; δ ($CDCl_3$) 1.0–1.6 (6H, m, CH_3CH_2O), 2.55 (3H, s), 3.9–4.5 (4H, m, CH_3CH_2O), 5.95 (1H, d, J 6–7 Hz, H4), 6.95 (1H, d, J 3 Hz, H6), 7.1 (1H, d, J 6–7 Hz, H3), and 7.3 p.p.m. (1H, d, J 8 Hz, H5). 2) *Diethyl* 1,2,3,4-*tetrahydro*-7-*methylpyrido*[2,3-c]*pyridazine*-1,2-*dicarboxylate* **33**, b.p. 210–220°/10^{-4} mm Hg (0.14 g, 3.7%). (Found: C, 57.6; H, 6.7; N, 14.25. $C_{14}H_{19}N_3O_4$ requires C, 57.35; H, 6.5; N, 14.35%); λ_{max} 228 and 282 nm (log ε 3.97, 3.79); ν_{max} 1715 cm^{-1}; δ ($CDCl_3$) 1.0–1.5 (6H, m), 2.5 (3H, s), 2.6–4.5 (8H, m, CH_3CH_2O and CH_2CH_2), 6.9 (1H, d, J

7–8 Hz, H6), and 7.35 p.p.m. (1H, d, J 7–8 Hz, H5); M^+ 293. 3) *Diethyl* 1,2,3,4-*tetrahydro*-7-*methylpyrido*[4,3-c]*pyridazine*-1,2-*dicarboxylate* **34**, m.p. 103.5–105 (from cyclohexane), (0.204 g, 5.3%). (Found: C, 57.65; H, 6.5; N, 14.45. $C_{14}H_{19}N_3O_4$ requires C, 57.35; H, 6.5; N, 14.35%); λ_{max} 239, 268, and 277 nm (log ε 4.06, 3.48, 3.38); ν_{max} 1720 cm^{-1}; δ ($CDCl_3$) 1.1–1.5 (6H, m), 2.5 (3H, s) 2.6–3.8 (3H, m, CH_2CH), 3.8–4.8 (5H, m, CH_3CH_2O+H3), 7.6 (1H, s, H8), and 8.1 p.p.m. (1H, s, H5); M^+ 293.

2-*Methyl*-5-*vinylpyridine* **32** *and ester* **5**. After separation of unchanged vinylpyridine (1.4 g, 23%), three compounds were obtained; in order of descending R_F these are 1) *Di*-t-*butyl* 1,2,3,4-*tetrahydro*-7-*methylpyrido*[2,3-c]*pyridazine*-1,2-*dicarboxylate* **36**, b.p. 170–175°/10^{-4} mm Hg (0.46 g, 3.5%). (Found: C, 62.25; H 7.95; N, 12.4. $C_{18}H_{27}N_3O_4$ requires C, 61.9; H, 7.75; N, 12.0%); λ_{max} 229 and 282 nm (log ε 3.93, 3.73); ν_{max} 1710, 1150 cm^{-1}; δ ($CDCl_3$) 1.4 (9H, s), 1.5 (9H, s), 2.5 (3H, s), 2.6–3.8 (3H, m, CH_2CH), 4.1–4.7 (1H, m, H3), 6.85 (1H, d, J 8 Hz, H6), and 7.3 p.p.m. (1H, d, J 8 Hz, H5). 2) t-*Butyl* 2-t-*butoxy*-5,6-*dihydro*-6-(2-*methylpyrid*-5-*yl*)*oxa*-3,4-*diazine*-4-*carboxylate*, **38**. b.p. 190–200°/10^{-4} mm Hg, (0.22 g, 1.7%). *m/e*$^+$ 293 (M–56), 237, 193, 167, 149, 146, 132, 131, 123, 122, 121, 120 (100%), 119, 105, 93, 57, 56 a.m.u.; λ_{max} 261, 267, and 274 nm (log ε 3.82, 3.95, 3.79); ν_{max} 1720, 1660, 1610, 1160, 1140 cm^{-1}; δ ($CDCl_3$) 1.5 (9H, s), 1.55 (9H, s), 2.55 (3H, s), 3.25 (1H, d of d, J 14 and 9 Hz, H5), 4.2 (1H, d of d, J 14 and 3 Hz, H5'), 5.2 (1H, d of d, J 9 and 3 Hz, H6), 7.1 (1H, d, J 7–8 Hz), 7.5 (1H, d of d, J 7–8 and 2 Hz), and 8.4 p.p.m. (1H, brs); ^{13}C NMR shifts: δ 24.2 (CH_3), 28.0, 28.1 (CH_3C), 44.9 (C5), 74.3 (C6), 80.7, 82.8 (O–*C*), 123.2, 129.0, 134.2, 147.2, 152.4, and 159.3 p.p.m. 3) *Di*-t-*butyl* 1,2,3,4-*tetrahydro*-7-*methylpyrido*–[4,3-c]*pyridazine*-1,2-*dicarboxylate*, **37**, b.p. 150–160/10^{-4} mm Hg, (0.73 g, 5.5%). (Found: C, 61.7; H, 7.9; N, 12.2. $C_{18}H_{27}N_3O_4$ requires C, 61.9; H, 7.75; N, 12.05%); λ_{max} 243, 268, and 277 nm (log ε 4.00, 3.53, 3.40); ν_{max} 1710, 1140 cm^{-1}; δ ($CDCl_3$) 1.4 (9H, s), 1.5 (9H, s), 2.5 (3H, s), 2.6–3.5 (3H, m, $CHCH_2$), 4.2–4.7 (1H, m, H3), 7.7 (1H, s, H8), and 8.2 p.p.m. (1H, s, H5).

2-(*Prop*-1-*en*-2-*yl*)*thiophen* **49** *and ester* **5**. The propenylthiophen **49**, (0.62 g) and ester **5** (1.15 g) were dissolved in benzene (10 ml). Reaction was complete after 10 h at the b.p.; evaporation of solvent gave an oil, separated by PLC (10 plates; toluene, ethyl acetate 9:1) into three bands. 1) *Di*-t-*butyl* 1,2-*dihydro*-4-*methylthieno*[3,2-c]-*pyridazine*-1,2-*dicarboxylate* **50**, b.p. 150–170/10^{-4} mm Hg, (0.17 g, 10%). (Found: C, 58.05; H, 6.75; N, 7.95. $C_{17}H_{24}N_2O_4S$ requires C, 57.95; H, 6.3; N, 7.95%); λ_{max} 229, 269, and 307 nm (log ε 3.98, 3.80, 3.73); ν_{max} 1725 cm^{-1}; δ ($CDCl_3$) 1.5 (18H, s), 2.0 (3H, s), 6.6 (1H, brs, H3), and 7.1 p.p.m. (2H, s, H6 and H7). 2) *Di*-t-*butyl* N-(2-(2-*thieno*)*prop*-1-*en*-3-*yl*)*hydrazo* N,N'-*dicarboxylate* **51**, b.p. 170–185/10^{-4} mm Hg, (0.416 g, 23.5%). (Found: C, 57.95; H, 7.45; N, 8.2. $C_{17}H_{26}N_2O_4S$ requires C, 57.6; H, 7.35; N, 7.9%); λ_{max} 266 and 297 nm; ν_{max} 3400, 1720 cm^{-1}; δ ($CDCl_3$) 1.45 (9H, s), 1.50 (9H, s), 4.40 (2H, s, CH_2), 5.05 (1H, s), 5.45 (1H, s), 6.65 (1H, brs, exch. D_2O, NH), and 6.8–7.5 p.p.m. (3H, m, thiophen H). 3) Inseparable mixture (0.46 g).

General procedure for removal of t-butyloxycarbonyl groups, and for oxidation of the hydrazo compounds.

a) The di-*t*-butyl cycloadduct (0.5 g) was dissolved in TFA (5 ml). After 30 min at room temperature, the TFA was removed under vacuum, the residue basified with saturated Na_2CO_3 solution, and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$), filtered, and evaporated to give virtually pure tetrahydropyridopyridazines in almost quantitative yield. The ^1H NMR data for these compounds, which gave inconsistent analyses, are collected in the Table.

b) Red mercuric oxide (0.2–0.3 g) was added to a solution of the tetrahydropyridopyridazine in chloroform (5 ml) at room temperature. The mixture was stirred until a colour change (yellow to green) occurred, (approx 15–30 min), then filtered. The filtrate was diluted with more chloroform, and oxygen was bubbled through the solution (~60 h, reaction checked by TLC). The mixture was filtered, solvent removed, the resultant oil extracted with hot cyclohexane, again filtered, and finally the pyridopyridazine crystallized from cyclohexane.

Pyrido[3,2-c]*pyridazine* **15**. Obtained in overall yield of 42% from compound **6**, m.p. 89–91° (lit.[5,7] m.p. 89°). (Found: C, 64.4; H, 3.95; N, 31.65. Calc. for $C_7H_5N_3$; C, 64.1; H, 3.8; N, 32.05%); λ_{max} 263, 306, and 318 nm (log ε 3.59, 3.62, 3.65); ^1H NMR recorded in discussion.

3-*Methylpyrido*[3,2-c]*pyridazine* **19**. Obtained in overall yield of 38.7% from compound **11**, m.p. 99–101° (yellow needles). (Found: C, 66.2; H, 4.75; N, 29.1. $C_8H_7N_3$ requires C, 66.3; H, 4.85; N, 28.95%); λ_{max} 265, 276, 314, and 327 nm (log ε 3.67, 3.60, 3.75, 3.80); δ ($CDCl_3$) 2.85 (3H, s), 7.55 (1H, d of d, J 4 and 8 Hz, H7), 7.75 (1H, d, J < 1 Hz, H4), 8.65 (1H, q of d, J 8, 2, and < 1 Hz, H8), and 9.0 p.p.m. (1H, d of d, J 4 and 2 Hz, H6); M/e$^+$ 145 (100%), 117 (M–N_2), 116, 92, 91, 90, 64, 63, 52, 51 and 50 a.m.u.

Pyrido[3,4-c]*pyridazine* **28**. Obtained in 52% yield from compound **26**, m.p. 138° (yellow needles). (Found: C, 63.8; H, 3.7; N, 32.35. $C_7H_5N_3$ requires C, 64.1; H, 3.8; N, 32.05%); λ_{max} 284 (log ε 3.58); ^1H NMR spectrum given in discussion.

1,4-*Dihydro*-7-*methylpyrido*[4,3-c]*pyridazine* **42**. From compound **37**, after oxidation, was obtained the *dihydro compound* **42**, m.p. 151–153°. (M^+ 147.0789; $C_8H_9N_3$ requires 147.0796); λ_{max} 225 and 300 nm (log ε 3.99, 3.74); ν_{max} 3410, 1660 cm^{-1}; ^1H NMR δ ($CDCl_3$) 2.4 (3H, s), 3.3 (2H, d, J 3 Hz, CH_2), 6.4 (1H, s, H8), 6.8 (1H, t, J 3 Hz, H3), 8.0 (1H, s, H5), and 8.4 p.p.m. (1H, brs, exch. D_2O, NH); ^{13}C NMR δ ($CDCl_3$) 23.7 (CH_3) 29.7 (C4), 105.3 (C3), 107.8 (C4a), 137.8 (C8), 146.0 (C8a), 147.4 (C5), and 158.8 p.p.m. (C7). M/e$^+$ 147(M^+), 146(100%), 119, 92, 91, 65, 52 and 51 a.m.u.

Thieno[3,2-c]*pyridazine* **48**. From the reaction between vinylthiophen **45** (0.55 g) and ester **5** (1.15 g), after chromatography, an oil was obtained (1.04 g), shown by mass spectrometry to be a mixture of tetra- and dihydrothioenopyridazine diesters. The oil was treated with TFA and oxidized, and from the products, by PLC, was isolated the thienopyridazine **48**, m.p. 98.5–99° (lit.[19] m.p. 97.5–98.5°), (70 mg). (Found: C, 53.2; H, 2.9; N, 20.7. Calc. for $C_6H_4N_2S$; C, 52.95; H, 2.95; N, 20.6%); λ_{max} 234, 277, and 304 nm (log ε 4.97, 3.75, 3.40); ν_{max} 1720, 1399, 1205 cm^{-1}; δ ($CDCl_3$) 7.25 (2H, S, H6 and

Table 1. ^1H NMR absorptions of tetrahydropyridopyridazines ($CDCl_3$)

Compound	H1 and H2	H3	H4	H5	H6	H7	H8	Other	J values (Hz)
16	5.05	3.15 m	2.90 m	—	7.9 d of d	⟨6.85 m⟩		—	$J_{6,7}4$; $J_{6,8}3$
18	6.2	⟨1.9–3.8⟩		—	8.0 t	7:1 d	7.1 d	1.15 (3H, d)	$J_{6,7}3$, $J_{6,8}3$
27	5.65	3.1 t	2.75 t	6.9d	7.85d	—	7.95s	—	$J_{5,6}5$
41	5.9	3.1 t	2.65 t	7.85 s	—	—	6.25 s	2.3 (3H, s)	

H7), 7.95 (1H, d, J 6 Hz, H4), and 9.0 p.p.m. (1H, d, J 6 Hz, H3); M/e$^+$ 136 (M$^+$), 108 (M–N_2), 85, 83, 82, 69, 63, 58, 57 (100%), and 45 a.m.u.

Reaction between 2-vinylpyridine **1** *and phenyltriazolinedione* **21**. Freshly prepared *t*-butyl hypochlorite (1.4 g) was added to a solution of *N*-phenylurazole (2.4 g) in dry acetone (90 ml) at −40°, giving the deep red colour of compound **21**. Freshly distilled 2-vinylpyridine **1** (1.05 g) was added, and the solution allowed to warm to room temperature, then boiled (1 h). The solvent was removed to give a yellow oil, which was chromatographed on alumina (120 g, 14 cm column). No appreciable product was eluted until $CHCl_3$/benzene(1:3) was used; the resulting solid (0.26 g) was chromatographed on two plates (eluent methanol/ethyl acetate 1:19). Thus was obtained the *cycloadduct* **23**, m.p. 152–153° (from CCl_4), (0.19 g, 6.8%). (M$^+$ 280.0961; $C_{15}H_{12}N_4O_2$ requires 280.0960); λ_{max} 223, 260, and 292 nm (log ε 4.06, 4.11, 3.66); ν_{max} 1765, 1710, 1420 cm^{-1}; δ ($CDCl_3$) 3.3 (2H, t,), 4.1 (2H, t), 7.1–7.6 (6H, m, C_6H_5 + H7), 8.5 (1H, d of d, J 4.5 and 1 Hz, H6), and 8.65 p.p.m. (1H, d of d, J 8.5 and 1 Hz, H8); *m/e*$^+$ 280 (100%), 149, 133 (exact mass 133.0642, $C_7H_7N_3$ requires 133.0640), 105, 104, 78, 44, and 40 a.m.u.

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