PREPARATION OF 4-AMINO-3(2H)-PYRIDAZINONES BY DIRECT AMINATION OF 3(2H)-PYRIDAZINONES WITH HYDRAZINE

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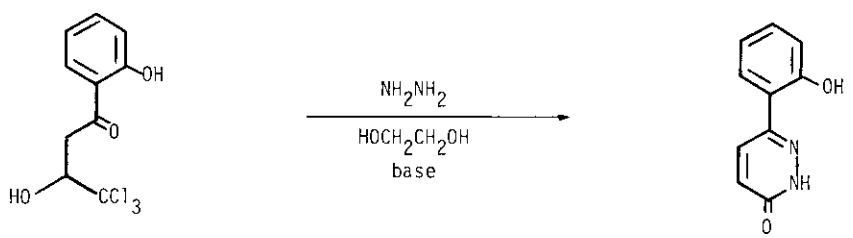
Abstract - Reaction of a variety of 3(2H)-pyridazinones with hydrazine hydrate gives moderate to excellent yields of the corresponding 4-amino-3(2H)-pyridazinones.

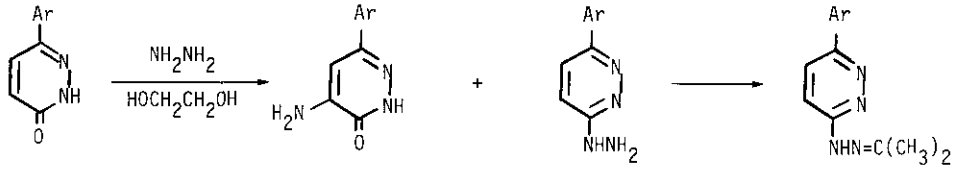
We have been interested for some time in the synthesis of derivatives of amino-phenyl and pyridyl substituted azinones and in their potential as cardiovascular agents, especially compounds structurally related to the positive inotropic agents amrinone, 3-amino-5-(4-pyridyl)-2(1H)-pyridinone, and milrinone, 3-cyano-6-methyl-5-(4-pyridyl)-2(1H)-pyridinone. As part of an earlier programme directed towards the synthesis of the combined β-blocker/vasodilator prizidilol, 3-[2-(3-t-butylamino-2-hydroxypropoxy)phenyl]-6-hydrazinopyridazine, the reported preparation[1] of 6-(2-hydroxyphenyl)-3(2H)-pyridazinone **2b** by reaction of 4-(2-hydroxyphenyl)-4-oxo-1,1,1-trichloro-2-butanol **1** with hydrazine hydrate and an inorganic base in ethylene glycol was repeated. The reaction was successful, but in attempts to optimise the production of **2b** it was found[2] that 4-amino-6-(2-hydroxy-



1 **2b**

phenyl)-3(2H)-pyridazinone **3b** was formed as a major byproduct when the reaction was carried out in the absence of the inorganic base. Treatment of the pyridazinone **2b** with hydrazine hydrate in ethylene glycol also gave **3b** directly, together with a slightly smaller amount of the 3-hydrazinopyridazine **4b**, which was isolated and identified as the acetone hydrazone derivative **5b** (Table I). Similar results were obtained on reaction of 6-phenyl-3(2H)-pyridazinone **2a** and 6-(2-methoxyphenyl)-3(2H)-pyridazinone **2c** with hydrazine hydrate in ethylene glycol, but in the latter case demethylation of the methyl ether also occurred under the reaction conditions.

Table I. Reaction of 6-Aryl-3(2H)-pyridazinones with Hydrazine Hydrate in Ethylene Glycol



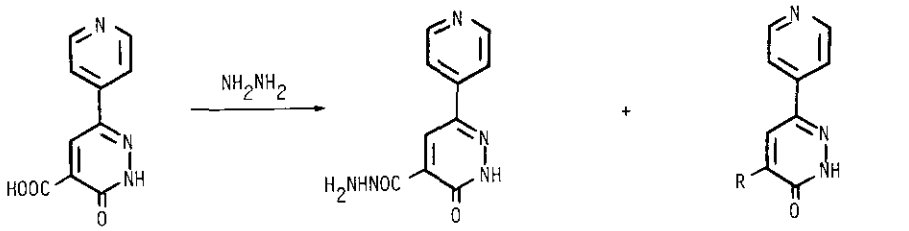
2	3	4	5

	Time, h	Temp, °C	3, % Yield	5, % Yield
2a Ar = C_6H_5	24	180	20	14
b Ar = 2-HOC_6H_4	19	180	37	18
c Ar = 2-$CH_3OC_6H_4$	22	190	15*	15*

*Demethylation occurred: Ar = 2-HOC_6H_4

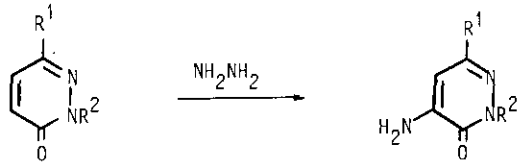
Further study of this somewhat unusual substitution reaction revealed that direct amination of the arylpyridazinones proceeded much more cleanly and efficiently if hot hydrazine hydrate alone was used (see below). Most interestingly, exactly the same type of direct amination of 6-aryl-3(2H)-pyridazinones was discovered simultaneously, also fortuitously, and independently by Singh,[3] who found that reaction of hydrazine hydrate with 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazine-carboxylic acid 6 gave a mixture of the expected hydrazide 7 together with small amounts of 6-(4-pyridinyl)-3(2H)-pyridazinone **8** and the 4-amino derivative **9**. Further limited investigation by Singh[3] of the amination reaction indicated that it might well be a useful general process,[4] and in view of the importance of the

reaction in our studies of 4-amino-3(2H)-pyridazinones, and of its potential application to other π-deficient aromatic and heteroaromatic systems, we now give full details of our investigation.



6 7 8, R = H; 9, R = NH_2

Table II. Direct Amination of 3(2H)-Pyridazinones with Hydrazine Hydrate



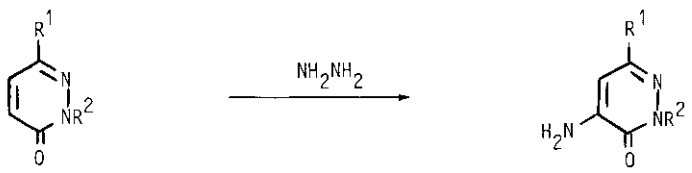
2 3

	R^1	R^2	Time, h	Yield, %
2a	C_6H_5	H	7	66
b	2-HOC_6H_4	H	7	68
d	4-HOC_6H_4	H	7	63
e	4-$H_2NC_6H_4$	H	24	76
f	4-C_5H_4N	H	16	92
g	3-C_5H_4N	H	16	84
h	C_6H_5	CH_3	24	61
i	CH_3	H	8	30
j	H	H	8	24*

* Accompanied by 14% of the 5-amino isomer.

Reaction of a variety of 3(2H)-pyridazinones with boiling hydrazine hydrate resulted in direct amination, and the results are summarised in Table II. With the 6-substituted 3(2H)-pyridazinones (2a, b; d-i) amination occurred exclusively in the 4-position (as far as could be determined); substitution at both the 4- and

Table III. Proton Chemical Shifts of 3(2H)-Pyridazinones and 4-Amino-3(2H)-pyridazinones (DMSO-d_6; 100MHz)

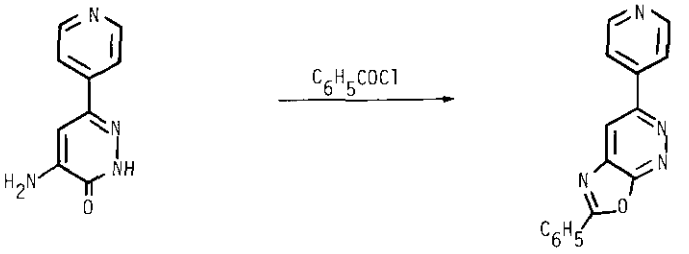


2 3

2	R^1	R^2	δ4-H	δ5-H	δ5-H	Δδ5-H	δNH_2
a	C_6H_5	H	7.02	8.05	6.76	1.29	6.44
b	2-HOC_6H_4	H	6.93	7.94	6.88	1.06	6.63
d	4-HOC_6H_4	H	6.95	7.96	6.69	1.27	6.21
e	4-$H_2NC_6H_4$	H	6.88	7.88	6.62	1.26	6.27
f	4-C_5H_4N	H	7.00	8.05	6.80	1.25	6.45
g	3-C_5H_4N	H	7.00	8.02	6.80	1.22	6.40
h	C_6H_5	CH_3	6.79	7.97	6.76	1.21	6.55
i	CH_3	H	6.77	7.28	6.10	1.18	6.20
j	H	H	6.98	7.52	6.20*	1.32*	6.20*

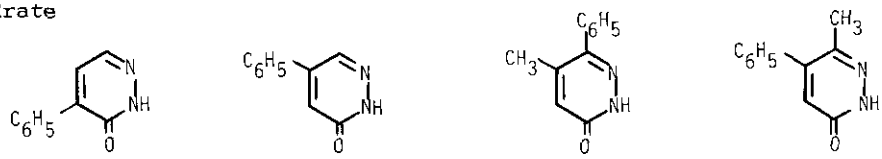
*5-NH_2 isomer: 4-H, δ5.47; Δδ5H = 1.51; 5-NH_2, δ6.40

the 5-position was observed only with 3(2H)-pyridazinone itself (2j). In terms of product characterisation, ^1H nmr spectroscopy was found to be particularly useful for determination of the site of amination, and relevant data for the 3(2H)-pyridazinones and the amino derivatives are given in Table III. It can be seen that the 4-H and 5-H signals in the pyridazinones 2 can be clearly distinguished, with those of the former at higher field, and that the upfield shifts (1.06-1.32 ppm) of the 5-H signals in the aminopyridazinone products 3 are fully consistent with amination having taken place at the 4-position. The data for the 4- and 5-amino-3(2H)-pyridazinones obtained from reaction of the parent azinone 2j are also in full agreement with the general assignments, and further corroborative evidence for 4-amination was obtained in the case of 3f, where reaction with benzoyl chloride gave the oxazolo[5,4-c]pyridazine 10, in analogy with the known reaction of 4-amino-6-chloro-3(2H)-pyridazinone[5].



4f **10**

Table IV. Reaction of Variously Substituted 3(2H)-Pyridazinones with Hydrazine Hydrate



Substrate	**11**	**12**	**13**	**14**
Time, h	26	96	96	72
4-NH_2, %	-[a]	5	11	55
3-$NHNH_2$, %[b]	-[c]	25	22	17
% Recovery	97	57	51	22

[a] 5-Amination would have been expected, but was not observed.

[b] Isolated as the acetone hydrazone derivatives.

[c] A trace of polar material was indicated by tlc analysis.

The simplest mechanism for this direct amination reaction is conjugate addition of hydrazine to the 4-position of the azinone followed by elimination of ammonia and tautomerism of the intermediate thus produced.[6,7] Conjugate addition to the 5-position of the 3(2H)-pyridazinone **2j** can equally well be invoked to explain the formation of the 5-amino isomer in this case (Table II), and the failure to isolate any products of addition to the 5-position in the case of the 6-substituted pyridazinones **2a-i** could be taken to imply steric inhibition of conjugate addition to the 5-position.[8] We are, however, reluctant to invoke this steric argument on two main grounds. First, in almost every reaction except that of **2h**, mixtures of products were produced, and while it was simple to isolate the major products, the 4-amino-3(2H)-pyridazinones, by standard techniques, isolation and characterisation of the minor components of the reaction mixtures proved to be difficult,

and very small amounts of the 5-amino isomers may have been formed but not isolated. Second, experiments designed to probe for a possible steric effect in the hydrazine addition reaction gave ambiguous results (Table IV). Thus, reaction of 4-phenyl-3(2H)-pyridazinone **11** with boiling hydrazine hydrate for 26 h led only to a trace of polar material (tlc), possibly the 3-hydrazino derivative. The 5-phenyl derivative **12** reacted slowly to give, after 96 h, 5% of the 4-amino derivative and 25% of the 3-hydrazinopyridazine. The amount of 4-amino product increased to 11% with 5-methyl-6-phenylpyridazinone **13** but, in contrast to what would be expected if there were a significant steric effect due to substituents in the 5-and 6-positions, the greatest degree of 4-amination, 55%, in this limited series of compounds was observed with the 5-phenyl-6-methyl derivative **14**. At present we have no satisfactory explanation for these relative reactivities.

EXPERIMENTAL

Evaporations were carried out under reduced pressure; organic solutions were dried over magnesium sulphate. Melting points were determined using an Electrothermal or Büchi SMP-20 apparatus and are uncorrected.

Tlc was carried out using silica gel plates (0.25 mm, Merck SG 60 F_{254}) with detection by uv (254, 375 nm) and potassium iodoplatinate spray. Merck silica gel 60 (0.063-0.2 mm) was used for column chromatography. Chloroform and chloroform:methanol mixtures (25:1, 10:1, 4:1) are assigned codes A, B, C and D, respectively.

Ir spectra were recorded on Perkin Elmer 298 or 580-B instruments, using nujol mulls unless otherwise specified.

^{1}H Nmr spectra were recorded at 100 MHz (Jeol 100P) or, where stated, at 60 MHz (Jeol FX 60Q). The solvent was DMSO-d_6 unless otherwise specified. Chemical shifts are given in ppm from TMS or DSS.

Mass spectra were recorded using AE1 MS 902 or VG 70-70F instruments; only the parent peaks are reported.

Microanalysis and DSC-TGA were performed in the Physical Chemistry Department of SK&F Research, which also provided the spectral data.

The pyridazinones used in this study are all known compounds and were prepared according to literature procedures.

GENERAL METHOD FOR REACTIONS IN ETHYLENE GLYCOL. A stirred mixture of the pyridazinone (0.02 mol), hydrazine hydrate (0.12 mol) and ethylene glycol (40 ml) was heated in an oil bath (see Table I). The cooled solution was poured into water (400 ml) and the resultant solid was digested with warm 2N hydrochloric acid to give the crude aminopyridazinone **3**; a second crop was obtained by ethyl acetate extraction of the hydrochloric acid solution. Finally, the latter was treated with an excess of acetone and sodium carbonate was added to pH 6 to give the crude hydrazone **5**.

6-Phenyl-3(2H)-pyridazinone (**2a**, 3 g) gave 4-amino-6-phenyl-3(2H)-pyridazinone (**3a**, 0.7 g, 20%) and 3-isopropylidenehydrazino-6-phenylpyridazine (**5a**, 0.56 g, 14%).

3a: mp 328-331°C (2-methoxyethanol); lit.[9] mp 322-323°C. ^{1}H Nmr: 6.44 (s, 2H, NH_2); 6.76 (s, 1H, pyridazinone 5-H); 7.44 (m, 3H, phenyl 3,4,5-H); 7.75 (m, 2H, phenyl 2,6-H).

5a: mp 162.5-164°C (methanol); lit.[10] mp 163°C.

6-(2-Hydroxyphenyl)-3(2H)-pyridazinone (**2b**, 4 g) gave 4-amino-6-(2-hydroxyphenyl)-3(2H)-pyridazinone (**3b**, 1.58 g, 37%) and 6-(2-hydroxyphenyl)-3-isopropylidene-hydrazinopyridazine (**5b**, 0.98 g, 18%).

3b: lustrous buff platelets, mp 323-329°C (2-methoxyethanol). Anal. calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.43; H, 4.69; N, 20.70. Ir: 1697; 1618; 1580 cm^{-1}. ^{1}H Nmr: 6.63 (br s, 2H, NH_2); 6.88 (s, pyridazinone 5-H) and 6.90 (m, total 3H, phenyl 3,5-H); 7.30 (m, 1H, phenyl 4-H); 7.50 (m, 1H, phenyl 6-H); 11.28 (br s, 1H, OH or NH); 12.76 (br s, 1H, OH or NH). Ms m/z: M^+ 203.

5b: light tan platelets, mp 232-234°C (ethanol). Anal. calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.29; H, 5.90; N, 23.06. Ir: 3270; 1590 cm^{-1}. ^{1}H Nmr: 1.91 (s, 6H, $(CH_3)_2$); 6.52 (br s, 1H, OH or NH); 6.92, 7.30 (2m, 3H, phenyl 3,4,5-H); 7.59 (d, J = 9.5 Hz, 1H, pyridazine 4-H); 7.85 (m, 1H, phenyl 6-H); 8.27 (d, J = 9.5 Hz, 1H, pyridazine 5-H); 9.82 (br s, 1H, OH or NH). Ms m/z: M^+ 242.

6-(2-Methoxyphenyl)-3(2H)-pyridazinone (**2c**, 4 g) gave **3b** (0.61 g, 15%) and **5b** (0.56 g, 12%) respectively.

GENERAL METHOD FOR REACTIONS IN NEAT HYDRAZINE HYDRATE. A stirred mixture of the pyridazinone and hydrazine hydrate (5-20 ml per g, depending on solubility) was heated under reflux (see Tables II and IV) then diluted with an equal volume of water to give the crude aminopyridazinone.

6-Phenyl-3(2H)-pyridazinone (**2a**, 5 g) gave 4.73 g (82%) of a solid which was digested with hot acetonitrile (50 ml) to leave 3.77 g (66%) of a solid, mp 325-330°C. Recrystallisation from DMF gave 4-amino-6-phenyl-3(2H)-pyridazinone **3a**, mp 329-331°C.

6-(2-Hydroxyphenyl)-3(2H)-pyridazinone (**2b**, 10 g) gave 7.23 g (68%) of 4-amino-6-(2-hydroxyphenyl)-3(2H)-pyridazinone **3b**: mp 317-319°C. Dilution of the filtrate with ethanol gave 0.43 g (4%) of a solid which was recrystallised from ethanol to give 0.27 g (2.3%) of 4-hydrazino-6-(2-hydroxyphenyl)-4,5-dihydro-3(2H)-pyridazinone (**15**, see reference 7) as colourless needles, mp 210-211.5°C. Anal. calcd for $C_{10}H_{12}N_4O_2.0.2H_2O$: C, 53.66; H, 5.58; N, 25.03. Found: C, 54.06; H, 5.58; N, 24.74. Ir (saturated $CHBr_3$ solution): 3670; 3590 (H_2O); 1673; 1620; 1600. ^1H Nmr, (50°C): ca. 3.30 (m, 2H, pyridazinone 5,5-H); ca. 4.20 (m, pyridazinone 4-H), obscured by ca. 4.30 (br s, NH_2); 6.90 (m, 2H, phenyl 3,5-H); 7.30 (m, 2H, phenyl 4,6-H); 7.45 (br s, 1H, $NHNH_2$); 9.13 (br s, 1H, pyridazinone NH); 10.94 (s, 1H, OH). The spectrum at 70°C was similar but a signal at δ 4.20 (dd, J = 8 and 10.5 Hz, 1H) was revealed by shift of the NH_2 resonance. Ms m/z: M^+ 220.

6-(4-Hydroxyphenyl)-3(2H)-pyridazinone (**2d**, 2 g) gave 1.35 g (63%) of product, mp ca. 355°C. An analytically pure sample of 4-amino-6-(4-hydroxyphenyl)-3(2H)-pyridazinone **3d** was obtained by recrystallisation from DMF, mp ca. 355-360°C. lit.[3] mp >330°C. Ir: 1654; 1610 cm^{-1}. ^1H Nmr: 6.21 (s, 2H, NH_2); 6.69 (s, pyridazinone 5-H) and 6.82 (m, total 3H, phenyl 3,5-H); 7.55 (m, 2H, phenyl 2,6-H); 9.51 (s, 1H, OH); 12.40 (s, 1H, NH).

6-(4-Aminophenyl)-3(2H)-pyridazinone (**2e**, 9.0 g) gave 7.38 g (76%) of crude 4-amino-6-(4-aminophenyl)-3(2H)-pyridazinone, mp ca. 310-318°C. Recrystallisation from hydrazine hydrate gave an 83% recovery of **3e**, mp 315-322°C (dec.), lit.[3] mp 306-309°C. Ir: 1705; 1670; 1605 cm^{-1}. ^1H Nmr: 5.32 (s, 2H, phenyl NH_2); 6.27 (s,

2H, pyridazinone NH_2); 6.59 (AA', J = 8.5 Hz, phenyl 3,5-H) and 6.62 (s, total 3H, pyridazinone 4-H); 7.42 (BB', J = 8.5 Hz, 2H, phenyl 2,6-H); 12.42 (s, 1H, NH).

6-(4-Pyridyl)-3(2H)-pyridazinone (**2f**, 14 g) gave 12.78 g (84%) of crude 4-amino-6-(4-pyridyl)-3(2H)-pyridazinone **3f**, mp 294-311°C; evaporation of the filtrate and trituration of the residue with water gave a further 1.25 g (8%) of **3f**, mp 265-300°C. Recrystallisation of the first crop from 50% aqueous ethanol gave 8.79 g (58%) of **3f**, mp 309-310.5°C. A second recrystallation gave analytical material, mp 310-311°C, lit.[3] mp 305-307°C. Ir: 1705; 1668; 1627; 1612; 1600 cm^{-1}. ^1H Nmr: 6.45 (br s, 2H, NH_2); 6.80 (s, 1H, pyridazinone 5-H); 7.68 (AA', J = 6 Hz, 2H, pyridine 3,5-H); 8.64 (BB', J = 6 Hz, 2H, pyridine 2,6-H); ca. 12.70 (br s, 1H, pyridazinone NH).

The residue left after evaporation of the recrystallisation filtrates was combined with the second crop and dissolved in a hot mixture of ethanol and acetone, the solution evaporated and the residue digested with hot B. Column chromatography of the soluble material using C gave 0.88 g (4.5%) of a solid, mp 245-247°C, which was recrystallised from aqueous ethanol containing acetone to give 0.75 g (4%) of the acetone hydrazone derivative (**17**) of 4-hydrazino-6-(4-pyridyl)-3(2H)-pyridazinone **16** (see reference 7) as fine needles, mp 246-247 °C. Anal. calcd for $C_{12}H_{13}N_5O$: C, 59.25; H, 5.39; N, 28.79. Found: C, 58.66; H, 5.49; N, 28.55. DSC/TGA indicated a weight loss of ca. 2% at ca. 130°C, and Anal. calcd for $C_{12}H_{13}N_5O.0.1H_2O$: C, 58.81; H, 5.43; N, 28.58. Ir (saturated $CHBr_3$ solution): 3670; 3590 (H_2O); 1655; 1598 cm^{-1}. ^1H Nmr: 2.02 (s, 3H, CH_3); 2.10 (s, 3H, CH_3); 7.18 (s, 1H, pyridazinone 5-H); 7.82 (AA', J = 6 Hz, 2H, pyridine 3,5-H); 8.69 (BB', J = 6 Hz, pyridine 2,6-H) and 8.77 (br s, total 3H, NH=N); 13.10 (br s, 1H, pyridazinone NH). Ms m/z: M^+ 243.

6-(3-Pyridyl)-3(2H)-pyridazinone (**2g**, 2.2 g) gave 1.93 g (84%) of 4-amino-6-(3-pyridyl)-3(2H)-pyridazinone **4g**, very fine colourless needles, mp 288-290°C (50% aqueous ethanol). Ir: 1690; 1620 cm^{-1}. ^1H Nmr: 6.40 (br s, 2H, NH_2); 6.80 (s, 1H, pyridazinone 5-H); ca. 7.40 (dd, J = 8 and 5 Hz, 1H, pyridine 5-H); 8.10 (dt, J = 8, 2 and 2 Hz, 1H, pyridine 4-H); 8.60 (dd, J = 5 and 2 Hz, 1H, pyridine 6-H); 8.95 (d, J = 2 Hz, 1H, pyridine 2-H).

The product was characterised as the hemi-sulphate salt, prepared as follows: A solution of **3g** free base (1.22 g) in hot ethanol (150 ml) was treated dropwise

with an excess of sulphuric acid and the mixture allowed to cool, which gave 1.77 g of a solid, mp 249-252°C. Recrystallisation from 20% aqueous ethanol gave **3g** hemi-sulphate, yellow granular crystals, mp 276-280°C. Anal. calcd for $C_9H_8N_4O.0.5H_2SO_4$: C, 45.57; H, 3.82; N, 23.62; S, 6.76. Found: C, 45.48; H, 3.81; N, 23.48; S, 6.87. Ir: 1675; 1608 cm^{-1}. ^1H Nmr (D_2O): 6.83 (s, 1H, pyridazinone 5-H); 8.13 (m, 1H, pyridine 5-H); ca. 8.85 (m, 2H, pyridine 4,6-H); 9.11 (m, 1H, pyridine 2-H). Ms m/z: M^+, 188.

2-Methyl-6-phenyl-3(2H)-pyridazinone (**2h**, 2.1 g) gave 1.94 g of a two component mixture which was combined with a similar mixture left after evaporation of the filtrate. Column chromatography (A) gave 0.26 g (12%) of recovered **2h**, mp and mmp 111-113°C, 0.25 g of a mixture of **2h** and **3h**, and 1.39 g (61%) of 4-amino-2-methyl-6-phenyl-3(2H)-pyridazinone **3h**, mp 128-130°C. Recrystallisation of the latter from isopropyl acetate gave 0.86 g (38%) of analytically pure **3h**, almost colourless prisms, mp 129-130°C. Anal. calcd for $C_{11}H_{11}N_3O$: C, 65.66, H, 5.51; N, 20.88. Found: C, 65.57; N, 5.47; N, 21.14. Ir (0.5% $CHBr_3$ solution): 1642; 1600 cm^{-1}. ^1H Nmr: 3.71 (s, 3H, CH_3); 6.55 (br s, 2H, NH_2); 6.76 (s, 1H, pyridazinone 5-H); ca. 7.45, 7.75 (2m, total 5H, phenyl protons). Ms m/z: M^+, 201.

6-Methyl-3(2H)-pyridazinone (**2i**, 4.5 g) gave 1.54 g (30%) of 4-amino-6-methyl-3(2H)-pyridazinone **3i**, mp 262-268°C, lit.[11,12] mp 259, 268°C. Ir: 1670; 1605 cm^{-1}. ^1H Nmr (60 MHz): 2.10 (s, 3H, CH_3); 6.10 (s, 1H, pyridazinone 5-H); 6.22 (br s, 2H, NH_2).

3(2H)-Pyridazinone (**2j**, 0.5 g) was allowed to react and then the solution was evaporated and the residue triturated with ethanol, which gave 0.11 g (19%) of 4-amino-3(2H)-pyridazinone **3j** in two crops. Recrystallisation from water gave 0.05 g (9%) of **3j**, mp 232-234°C, lit.[5] mp 228-229°C. Ir: 1680; 1625; 1560 cm^{-1}. ^1H Nmr: 6.20 (d, J = 5 Hz, superimposed on br, total 3H, NH_2 and pyridazinone 5-H); 7.47 (d, J = 5 Hz, 1H; pyridazinone 6-H); 12.37 (br, 1H, NH).

Tlc analysis (D) of the mother liquors from **3j** indicated the presence of at least seven components. The liquor was treated with an excess of acetone, evaporated, and the residue was extracted with B to leave 0.11 g (19%) of a mixture of **3g** and the 5-amino isomer (ratio 1:3 by nmr). Column chromatography (C) gave 0.08 g

(14%) of the more polar 5-amino-3(2H)-pyridazinone, which was recrystallised from water to give 0.025 g (4%) of pure product, mp 293-296°C, lit.[13] mp 286-287°C. ^{1}H Nmr: 5.47 (d, 1H, J = 2.2 Hz, pyridazinone 4-H); 6.40 (br s, 2H, NH_2); 7.38 (d, J = 2.2 Hz, 1H, pyridazinone 6-H); 11.94 (br s, 1H, NH).

4-Phenyl-3(2H)-pyridazinone (**11**, 1.0 g) was heated under reflux with hydrazine hydrate (15 ml) for 26 h. The cooled solution was diluted with water to give 0.8 g (80%) of recovered **11**, mp and mmp 216.5-218°C. Evaporation of the filtrate gave a further 0.17 g (17%) of **11**, tlc analysis (B) of which indicated the presence of only a single polar trace impurity (possibly 3-hydrazino-4-phenylpyridazine).

5-Phenyl-3(2H)-pyridazinone (**12**, 3 g) gave a solution which was evaporated, and the residue was triturated for 5 min with 2N hydrochloric acid on a steam bath. When cool, the mixture was filtered to give a solid (2.06 g) which was dissolved in warm 1N sodium hydroxide solution. Addition of hydrochloric acid to ca. pH 12 gave 0.17 g (5%) of a solid which was recrystallised from 2-methoxyethanol to give pure 4-amino-5-phenyl-3(2H)-pyridazinone, fine colourless needles, mp 299-302°C. Anal. calcd for $C_{10}H_9N_3O$: C, 64.05; H, 5.07; N, 22.20. Found: C, 64.16; H, 4.85; N, 22.45. Ir: 1695; 1640 cm^{-1}. ^{1}H Nmr: 6.05 (br s, 2H, NH_2); ca. 7.50 (m, 5H, phenyl protons); 7.59 (s, 1H, pyridazinone 6-H); ca. 12.60 (br s, 1H, NH). Ms m/z: M^+ 187.

Acidification of the alkaline filtrate gave 1.7 g (57%) of recovered **12**, mp and mmp 192-194°C.

The acidic filtrate from the initial work up was heated for 5 min on a steam bath with an excess of acetone in the presence of sodium acetate (pH 4). Sodium carbonate was then added to pH 6, and removal of acetone by evaporation gave 1.0 g (25%) of 3-isopropylidenehydrazino-5-phenyl-3(2H)-pyridazine, mp 158-162.5°C. Recrystallisation from 1-propanol gave 0.76 g (18%) of analytically pure product, orange granular crystals, mp 162-164°C. Anal. calcd for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24; N, 24.76. Found: C, 69.20; H, 6.42; N, 24.73. Ir: 1605, 1595 cm^{-1}. ^{1}H Nmr ($CDCl_3$): 1.98 (s, 3H, CH_3); 2.09 (s, 3H, CH_3); ca. 7.60 (m superimposed on s, 6H, pyridazine 4-H and phenyl protons); ca. 8.40 (br, 1H, NH); 8.91 (s, 1H, pyridazine 6-H). Ms m/z: M^+ 226.

5-Methyl-6-phenyl-3(2H)-pyridazinone (**13**, 3.74 g) gave a reaction mixture that was worked up in a similar manner to that from **12** above. This gave 1.91 g (51%) of recovered **13**, 0.43 g (11%) of 4-amino-5-methyl-6-phenyl-3(2H)-pyridazinone and 1.06 g (22%) of 3-isopropylidenehydrazino-5-methyl-6-phenylpyridazine.

4-Amino-5-methyl-6-phenyl-3(2H)-pyridazinone: very fine colourless needles, mp 355-360°C (with extensive sublimation >300°C) (2-methoxyethanol). Anal. calcd for $C_{11}H_{11}N_3O$: C, 65.66; H. 5.51; N, 20.88. Found: C, 65.70; H, 5.35; N, 20.69. Ir: 1610 cm^{-1}. ^1H Nmr: 1.88 (s, 3H, CH_3); 5.98 (br, s, 2H, NH_2); ca. 7.40 (m, 5H, phenyl protons); 12.60 (br s, 1H, NH). In addition, singlets at ca. 2.10 and 6.80 probably correspond to ca. 3.7% molar 5-methyl-6-phenyl-3(2H)-pyridazinone. Ms m/z: M^+ 201.

3-Isopropylidenehydrazino-5-methyl-6-phenylpyridazine: pale straw coloured plates, mp 171.5-173.5°C (ethanol). Anal. calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.92; H, 6.80; N, 23.23. Ir: 1600 cm^{-1}. ^1H Nmr ($CDCl_3$): 1.96 (s, 3H, CH_3); 2.07 (s, 3H, CH_3); 2.29 (s, 3H, ring CH_3); ca. 7.40 (m superimposed on s, 6H, pyridazine 4-H and phenyl protons); ca. 8.20 (br, 1H, NH). Ms m/z: M^+ 240.

6-Methyl-5-phenyl-3(2H)-pyridazinone (**14**, 3.0 g) gave a reaction mixture that was worked up as above to give an acidic filtrate and a solid (2.44 g). The latter was triturated with hot ethanol to remove unreacted **14** (ca. 0.66 g, 22%), which left 1.78 g (55%) of crude 4-amino-6-methyl-5-phenyl-3(2H)-pyridazinone. Residual **14** could not be separated from the product by either vacuum sublimation or recrystallisation from 2-methoxyethanol, which still gave the product in a crude state, very fine colourless needles, mp ca. 345°C (extensive sublimation >300°C). Anal. calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.91; H, 5.51; N, 20.31. (Anal. calcd for mixture with 5 mole % of **14**: C, 65.90; H, 5.51; N, 20.61). Ir: 1665; 1600 cm^{-1}. ^1H Nmr: 1.84 (s, 3H, CH_3); 5.35 (br s, 2H, NH_2); 7.20-7.60 (m, 5H, phenyl protons). In addition, singlets at 2.12 and 6.63 probably correspond to 5 mole % of 6-methyl-5-phenyl-3(2H)-pyridazinone. Ms m/z: M^+ 201.

Treatment of the acidic solution with acetone as above gave 0.64 g (17%) of 3-isopropylidenehydrazino-6-methyl-5-phenylpyridazine, mp 188-191°C. Recrystallisation from ethanol gave the pure hydrazone, yellow needles, mp 192-194°C. Anal. calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.32. Found: C, 70.25; H, 6.66; N,

23.40. Ir: 1592 cm^{-1}. ^1H Nmr ($CDCl_3$): 1.96 (s, 3H, CH_3); 2.01 (s, 3H, CH_3); 2.51 (s, 3H, ring CH_3); 7.36 (s, pyridazine 4-H) and 7.42 (m, total 6H, phenyl protons); ca. 8.10 (br, 1H, NH). Ms m/z: M^+ 240.

2-Phenyl-6-(4-pyridyl)oxazolo[5,4-c]pyridazine **10**. A mixture of **3f** (0.25 g) and benzoyl chloride (2.5 ml) was heated under reflux for 30 min. The crude product was collected, washed with ether, suspended in warm water and the suspension was neutralised with potassium carbonate to give 0.3 g (83%) of 2-phenyl-6-(4-pyridyl)oxazolo[5,4-c]pyridazine **10**, mp 268-269.5°C. Recrystallisation from ethanol gave pure **10**, colourless plates, mp 268.5-270°C. Anal. calcd for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.67; N, 20.43. Found: C, 70.11; H, 3.64; N, 20.55. Ir: 1625; 1600; 1581 cm^{-1}. ^1H Nmr (3% DCl/D_2O): 7.40 (m, 3H, phenyl 3,4,5-H); 7.75 (m, 2H, phenyl 2,6-H); 8.37 (AA', J = 6.5 Hz, 2H, pyridine 3,5-H); 8.59 (s, 1H, oxazolopyridazine 4-H); 8.84 (BB', J = 6.5 Hz, 2H, pyridine 2,6-H). Ms m/z: 274.

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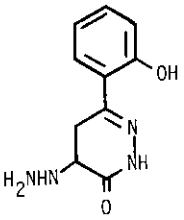
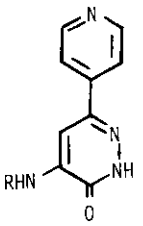
6. Singh (ref. 3) also postulated nucleophilic attack by hydrazine at the 4-position of the pyridazinone, but then suggested what seems to us an unnecessarily elaborate intramolecular reaction for generation of the 4-imino intermediate.
7. Supporting evidence for initial attack by hydrazine at the 4-position of the pyridazinone was obtained by isolation of the hydrazinodihydropyridazinone **15** from the reaction with **2b**. The 4-hydrazinopyridazinone **16** was a minor by-product (characterised as the acetone hydrazone derivative **17**) from the reaction of **2f**. In this latter case, however, the hydrazino product could be



15



16 R = NH_2

17 R = $N{=}C(CH_3)_2$

formed either by oxidation of the dihydro intermediate corresponding to **15** or from the 4-amino compound **3f**.

8. Conjugate addition to pyridazinones has been observed on several occasions. Reaction with Grignard reagents, for example, can occur at the 5-position (H. Jahine, H.A. Zaher, O. Sherif, and M. Seada, Indian J. Chem., Sect. B, 1981, **20B**, 502) but is more common at the 4-position (F.G. Baddar, A. El-Habashi, and A.K. Fateen, J. Chem. Soc., 1965, 3342; A.K. Fateen, S.A.R. Omran, N. Shams, and A.M. Kaddah, Indian J. Chem., Sect. B, 1976, **14B**, 99 (Chem.Abstr., 1976, **85**, 46550n); A.K. Fateen, A.H. Moustafa, A.M. Kaddah, and N.A. Shams, Synthesis, 1980, 457). Similar reactivity patterns have been observed with other nucleophiles (G. Leclerc and C.G. Wermuth, Bull. Soc. Chim. Fr., 1968, 4123; G. Leclerc and C.G. Wermuth, Bull Soc. Chim. Fr., 1969, 2468; E.W. Badger and W.H. Moos, J.Heterocycl.Chem., 1986, **23**, 1515).

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