

**DIRECT AMINATION OF 3(2H)-PYRIDAZINONES:
RE-INVESTIGATION OF THE REACTION OF
3,6-DIMETHOXYPYRIDAZINE WITH HYDRAZINE [†]**

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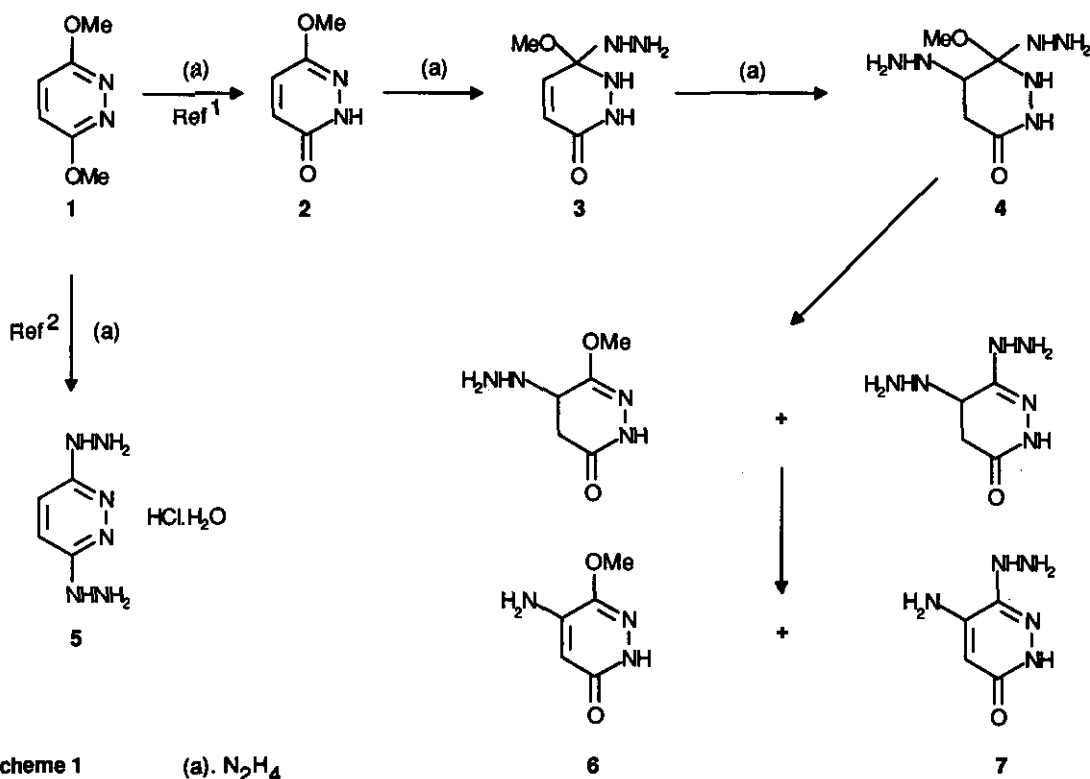
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Abstract - 3,6-Dimethoxypyridazine has been shown to react with hydrazine *via* 4-amination of 6-methoxy and 6-hydrazino-3(2H)-pyridazinones to give 4-amino-6-methoxy- and 4-amino-6-hydrazino-3(2H)-pyridazinones, and not the corresponding 5-amino isomers as previously reported. The published synthesis of the 5-amino isomers, used to confirm the earlier findings, is incorrect as regards 5-amino-6-hydrazino-3(2H)-pyridazinone, which has been prepared by an alternative route. The 4-amination reaction has also been extended to 6-chloro-3(2H)-pyridazinone.

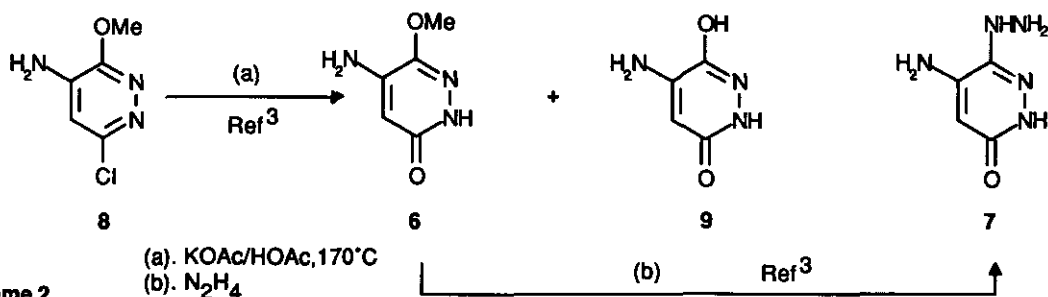
INTRODUCTION

Re-investigation of the reaction of 3,6-dimethoxypyridazine (1) with hydrazine led Elvidge and Pickett¹ to conclude that the product was not 3,6-dihydrazinopyridazine (5) isolated as its "hydrochloride hydrate" as previously reported,² but a mixture of 5-amino-6-methoxy- and 5-amino-6-hydrazino-3(2H)-pyridazinones (6 and 7) formed *via* 6-methoxy-3(2H)-pyridazinone (2, Scheme 1). Subsequently Alazawe and Elvidge³ claimed to confirm this conclusion by rational synthesis of both 6 and 7 (Scheme 2). However, the discovery of the direct amination of 3(2H)-pyridazinones by hydrazine,^{4,5} in which 4-amination is generally observed, led us to

[†]*Dedicated to Professor E.C. Taylor on the occasion of his 70th birthday.*



Scheme 1

(a). N_2H_4 

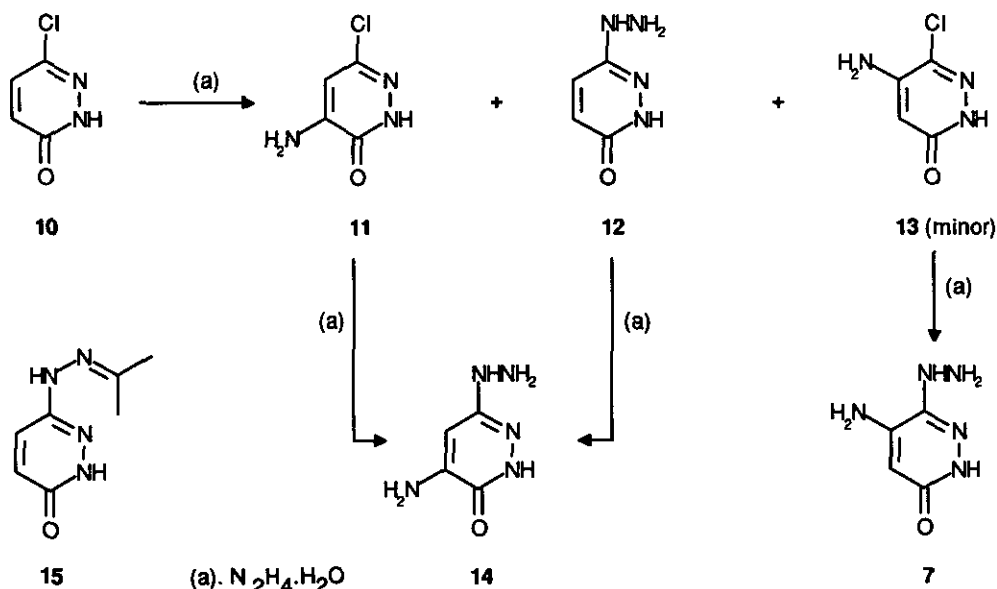
Scheme 2

re-assess the conclusions of Elvidge *et al.* Examination of the published work^{1,3} revealed that, while in general a careful and detailed study had been carried out, there are weaknesses in assigning structures (6) and (7) to the products of Scheme 1. These weaknesses include basing the initial assignments on an unsubstantiated mechanism in which the unlikely intermediate (4) (Scheme 1) was invoked to explain the formation of both products; failing to isolate the methoxy product (6) from reaction of 1, and confirming its structure by comparison of mixtures; using mixed melting points to compare compounds which decompose rather than melt; and failing to consider the alternative 4-amino isomers as potential products.

Our major objectives in re-investigating the reaction of **1** with hydrazine were to identify intermediates, to isolate and compare both products with those from the rational synthesis, and to find additional corroborative evidence for the structural assignments. An additional objective was to extend the hydrazine reaction to potential intermediates and analogues such as 6-chloro-3(2*H*)-pyridazinone (**10**). The latter is readily available and was conveniently used for much of the initial work. The experimental approach adopted was to use short term reactions (0.5 h) with hydrazine hydrate to investigate intermediate formation, and longer reaction times (> 5 h) for the final products.

REACTIONS WITH HYDRAZINE

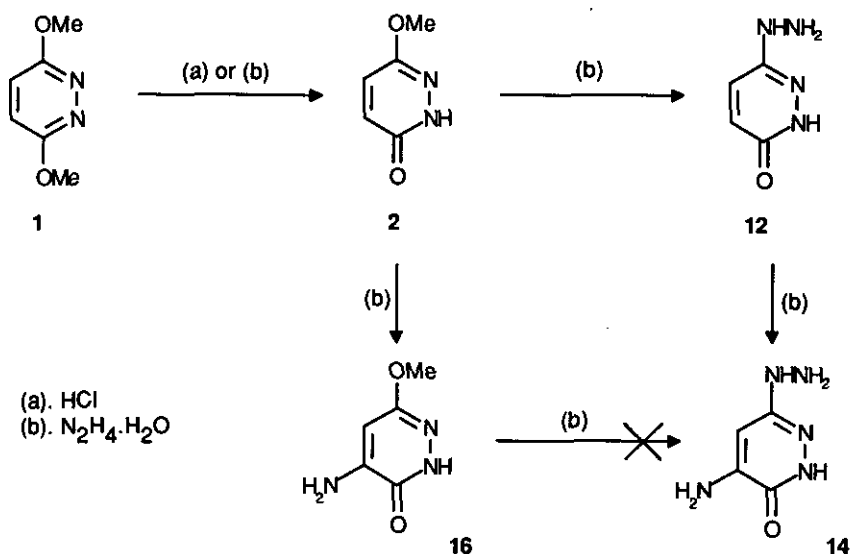
6-Chloro-3(2*H*)-pyridazinone (**10**, Scheme 3)



Short term reaction of **10** with hydrazine hydrate gave about a 70% recovery of material from which were isolated the intermediates 4-amino-6-chloro-3(2*H*)-pyridazinone (**11**, 18%) and 6-hydrazino-3(2*H*)-pyridazinone (**12**, 22%, as its acetone hydrazone, **15**), the final product 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**, 17%), and a little 5-amino-6-chloro-3(2*H*)-pyridazinone (**13**, 4%). The hydrazine(**12**) has been reported to be the product of the reaction of **10** with hydrazine hydrate⁶ and with hydrazine.⁷ A longer reaction time gave a 67% yield of **14**, but this still contained about 5% of the intermediate(**11**), reflecting the poor reactivity towards nucleophiles of the 6-substituent in 4-amino-3(2*H*)-pyridazinones caused by increased electron density on N-1

due to mesomeric donation from the amino group. That the chloro compound(11)and hydrazino compound(12) are intermediates in the formation of 14 was confirmed by their reaction with hydrazine hydrate to give 14 (in 38% and 68% yields, respectively), though reaction of the former was slow and 20% of 11 was recovered after 9 hours. The hydrazine(12)was readily prepared from its acetone hydrazone (15) by brief treatment with hydrazine hydrate and for reaction with hydrazine hydrate(12)was conveniently generated *in situ* from 15. The 5-amino-6-hydrazino-3(2*H*)-pyridazinone (7) may well be a minor product from reaction of 10 with hydrazine hydrate as the minor intermediate(13)was shown to react to give 7.

3,6-Dimethoxypyridazine and 6-methoxy-3(2*H*)-pyridazinone (1 and 2, Scheme 4)



Scheme 4

6-Methoxy-3(2*H*)-pyridazinone (2) was prepared by acid hydrolysis of 3,6-dimethoxypyridazine (1). Short term reaction of 2 with hydrazine hydrate gave a crude product, isolated in about 40% yield, consisting of a 2:1:1 mixture of 4-amino-6-methoxy-3(2*H*)-pyridazinone (16), 4-amino-6-hydrazino-3(2*H*)-pyridazinone (14), and the previously observed intermediate 6-hydrazino-3(2*H*)-pyridazinone (12). 4-Amino-6-methoxy-3(2*H*)-pyridazinone (16) was isolated in 12% yield from this mixture after removal of the more basic hydrazino compounds with dilute acid. Longer term reaction of 2 gave an inseparable mixture of 14 and 16 in about 33% yield. Heating 3,6-dimethoxypyridazine (1) itself with hydrazine hydrate (either in the presence or absence of a little methanol to control sublimation of 1) gave a similar mixture of 14 and 16, not 6 and 7 as reported by Elvidge *et al.*^{1,3} Tlc analysis confirmed the assumption of Elvidge¹ that 6-methoxy-3(2*H*)-pyridazinone (2) is an

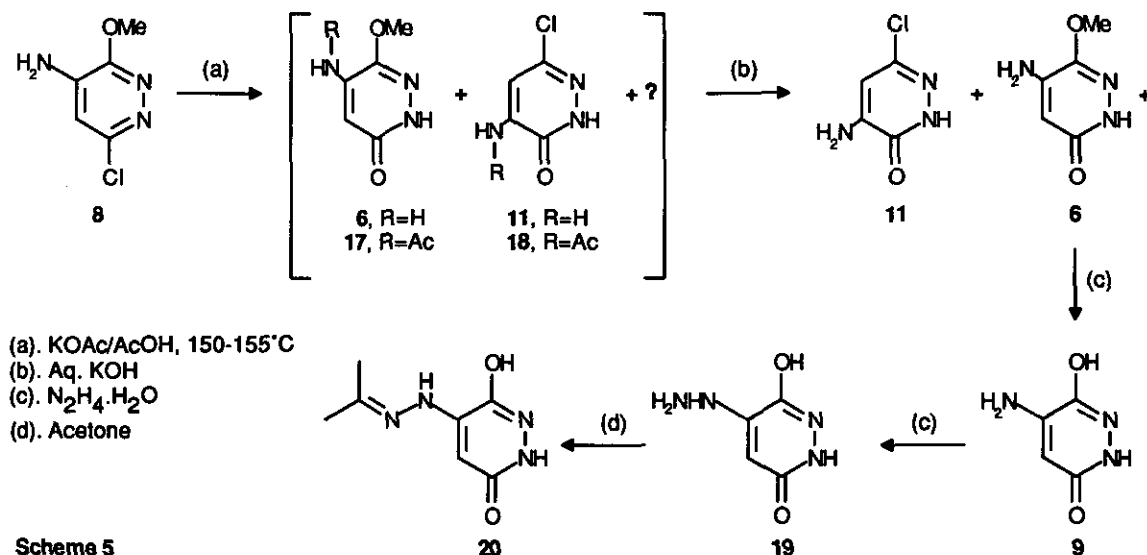
intermediate in the reaction of **1** with hydrazine hydrate, and so 6-hydrazino-3(2*H*)-pyridazinone (**12**) must therefore also be an intermediate. In a reaction closely following one of the literature procedures¹ reaction of **1** with hydrazine hydrate gave a 27% yield (lit.¹ 25%) of a 1:1 mixture of **14** and **16** which could not be separated; tlc analysis of the mother liquors indicated the presence of at least six other components. Even after prolonged reaction of **1** (20 hours), or further reaction of the crude product with fresh hydrazine hydrate, **16** was still present as an impurity in the hydrazino compound (**14**). While **16** may persist because of the poor reactivity of the 6-substituent toward nucleophilic displacement (as seen with the chloro compound (**11**)) tlc analysis following reaction of pure **16** with hydrazine hydrate failed to provide any evidence for the formation of **14**, and it seems unlikely that **16** is an intermediate in the formation of **14**. It may be that **16** slowly undergoes demethylation (to give **9**) and subsequent reaction (as occurs with its isomer (**6**), see below) rather than displacement of the methoxy group.

THE RATIONAL SYNTHESIS OF **6** AND **7**

In Alazawe and Elvidge's rational synthesis of **6** and **7** (Scheme 2) the key step is the selective hydrolysis of the chloro substituent of **8** to give 5-amino-6-methoxy-3(2*H*)-pyridazinone (**6**), using potassium acetate/acetic acid in a Carius tube at 170°C, from which they isolated **6** (30%) and 4-amino-1,2-dihydro-3,6-pyridazinedione (**9**, 60%). Using lightly less vigorous conditions (150°C, sealed vessel) we have found (Scheme 5) that the reaction is complicated by amino group acetylation and, while Alazawe and Elvidge did not describe the use of a hydrolytic work-up, it is advantageous to subject the crude product to alkaline hydrolysis. Thus, the crude product is a mixture of at least five components (including **6**, **11**, **17**, and **18**), hydrolysis of which gave three major components and allowed the isolation of **6** in 33% yield. A second major product, 4-amino-6-chloro-3(2*H*)-pyridazinone (**11**), was isolated as such in 20% yield and also, following incomplete hydrolysis, as its *N*-acetyl derivative (**18**). It may be that, under the conditions of Alazawe and Elvidge, preferential hydrolysis of the chloro compound (**11**) occurred to leave the methoxy and hydroxy pyridazinones (**6** and **9**) as products. The latter compound, if present, was not isolated in the current work.

Having obtained pure 5-amino-6-methoxy-3(2*H*)-pyridazinone (**6**), completion of the rational synthesis called for its reaction with hydrazine to give 5-amino-6-hydrazino-3(2*H*)-pyridazinone (**7**). However, reaction of **6** with hydrazine hydrate failed to yield any of the hydrazino compound (**7**). Instead of displacement, demethylation occurred to give 5-amino-6-hydroxy-3(2*H*)-pyridazinone (**9**) which in turn gave 5-hydrazino-6-hydroxy-3(2*H*)-pyridazinone (**19**). Characterisation of the latter compound is not easy⁴ and so it was derivatised with acetone,

but the hydrazone (20) also lacked a definite melting point. Alazawe and Elvidge³ provide only limited data for the compound claimed to be 7 that is suitable for comparative purposes (the compound decomposes on melting). Comparison of their uv³ and ir¹ data, which was claimed³ to be identical with that of the compound prepared before,¹ reveals a greater similarity with that for the 4-isomer (14) rather than 7. Thus, λ_{max} is given as 273, 232 nm and we find 274, 232, 212 for 14, and 274, 216 for 7, while for the 13 strongest ir peaks given (see Experimental) there is a matching peak ($\nu_{\text{max}} \pm 20 \text{ cm}^{-1}$) found for 14 but only 8 corresponding peaks for 7. The latter also shows a larger number of additional ir peaks not reported by Elvidge *et al.*



Scheme 5

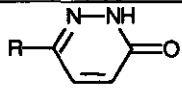
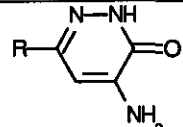
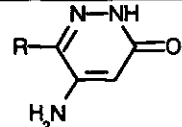
As an alternative approach to the synthesis of 7, 5-amino-6-chloro-3(2H)-pyridazinone (13) was prepared.⁸ This compound is much more reactive than its 4-amino isomer (11), and reaction with hydrazine hydrate readily gave the required reference hydrazino compound (7) in 73% yield.

CONFIRMATION OF STRUCTURAL ASSIGNMENTS

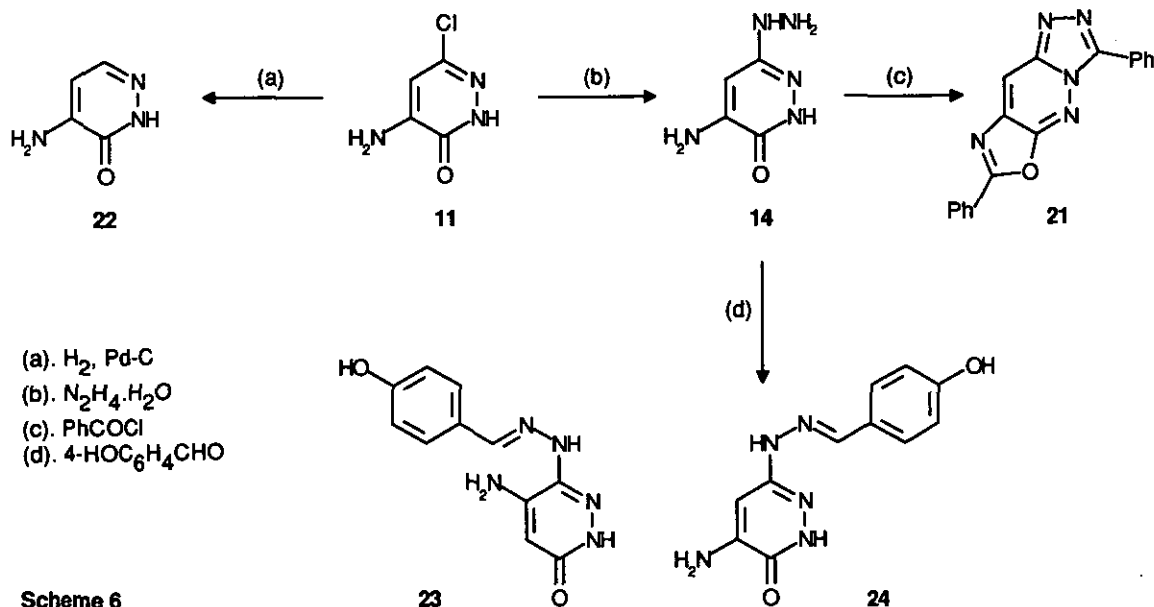
Comparison of the ¹H-nmr spectra of the 6-chloro, 6-hydrazino, and 6-methoxy derivatives of 4- and 5-amino-3(2H)-pyridazinones prepared in this study with those of their 4,5-unsubstituted analogues in all cases revealed the expected upfield shift⁵ of the residual 4- and 5-proton resonances of about 1.2 ppm (Table 1). The 5-amino-6-methoxy-3(2H)-pyridazinone (6) prepared by the rational synthesis is clearly different from the compound

isolated from reaction of hydrazine with 6-methoxy-3(2*H*)-pyridazinone (2), which must be the 4-amino isomer 16.

Table 1: Comparison of the 4-*H* and 5-*H* chemical shifts (δ) of 4- and 5-amino-3(2*H*)-pyridazinones with those of the 4,5-unsubstituted-3(2*H*)-pyridazinones.

of the 4,5-disubstituted 3(2H)-pyridazinones.									
									
R	No.	δ 4-H	δ 5-H	No.	δ 5-H	$\Delta\delta$ 5-H	No.	δ 4-H	$\Delta\delta$ 4-H
Cl	10	6.98	7.53	11	6.18	-1.35	13	5.67	-1.31
OMe	2	6.88	7.17	16	5.84	-1.33	6	5.60	-1.28
NHNH ₂	12	6.70	6.99	14	5.85	-1.14	7	5.50	-1.20

The structure of the 4-amino-6-hydrazino-3(2*H*)-pyridazinone (14) has been confirmed in two ways (Scheme 6).



Firstly, condensation of 14 (either pure or as the crude product from reaction of dimethoxypyridazine) with benzoyl chloride gave the fused compound (21) whose ir spectrum is devoid of NH and C=O bands. Secondly, 14

was also formed by the reaction of hydrazine hydrate with 4-amino-6-chloro-3(2*H*)-pyridazinone (11) and the position of the amino group in 11 was confirmed by hydrogenolysis to give 4-amino-3(2*H*)-pyridazinone (22), which showed the expected⁹ 5,6-proton coupling in its ¹H-nmr spectrum.

Elvidge *et al.* used the 4-hydroxybenzaldehyde hydrazone derivative to characterise what they claimed to be 5-amino-6-hydrazino-3(2*H*)-pyridazinone (7). With both possible products (7 and 14) available we have been able to prepare both 4-hydroxybenzaldehyde hydrazones (23 and 24) and compare their properties with those reported by Elvidge *et al.* (Table 2). The ¹H-nmr data clearly show the difference between the two derivatives, with the diagnostic 5-H resonance of 24 about 0.9 ppm downfield of the 4-H resonance of 23 and matching the value reported by Elvidge and Pickett;¹ their ir data also closely match those for 24. Thus there is no doubt that the hydrazone derivative reported by Elvidge *et al.* is 24, not 23, and therefore the hydrazine itself was 14, and not 7 as claimed.

Table 2: Comparison of selected data for the 4-hydroxyphenylhydrazones of 4- and 5-amino-6-hydrazino-3(2*H*)-pyridazinone (24 and 23) with those published by Elvidge *et al.* for compound 23.

Compound	mp °C	ir: γ_{max} , cm ⁻¹	¹ H-nmr: δ 4- or 5-H
24	281-283	3475, 3349, 3180br, 1607, 1587, 1504, 1264, 1234	6.58
23	277-278	3450, 3305, 3223br, 1640, 1602, 1583, 1510, 1268	5.64
"23" ref ^{1,3}	268-269	3490, 3380, 3200br, 1615, 1590, 1515, 1260, 1240	6.60

CONCLUSIONS

The results clearly show that reactions of hydrazine hydrate with 3(2*H*)-pyridazinones containing displaceable 6-substituents are complicated by amination at the 4-, and to a lesser extent 5-, position in addition to reaction of the 6-substituent. With 6-chloro-3(2*H*)-pyridazinone (10) the same major product, 4-amino-6-hydrazino-3(2*H*)-pyridazinone (14), is obtained irrespective of whether amination or displacement occurs first as both 4-amino-6-chloro-3(2*H*)-pyridazinone (11) and 6-hydrazino-3(2*H*)-pyridazinone (12) both react further with hydrazine to give 14. However, with 6-methoxy-3(2*H*)-pyridazinone (2) there are two major isolable products depending on whether the first step is amination or displacement. Thus, displacement yields 6-hydrazino-3(2*H*)-pyridazinone (12), which is susceptible to amination to give 4-amino-6-hydrazino-3(2*H*)-pyridazinone (14), while preliminary amination gives 4-amino-6-methoxy-3(2*H*)-pyridazinone (16) which is resistant to subsequent displacement of

the methoxy group and does not react to give **14**. Instead, **16** may slowly undergo demethylation and subsequent reaction to give **19**.

The above conclusions can be applied to the reaction of hydrazine hydrate with 3,6-dimethoxypyridazine (**1**) as both 6-methoxy and 6-hydrazino-3(2*H*)-pyridazinones (**2** and **12**) are intermediates, and the two major products are the same 4-amino derivatives (**14** and **16**), not the 5-amino isomers (**6** and **7**) as claimed by Elvidge *et al.*^{1,3} Both compounds have been isolated and compared with the 5-amino isomers so that there is no doubt as to their identity. In addition, the structure of **14** has been confirmed by synthesis and derivatisation.

While Elvidge and Pickett¹ incorrectly identified the products of the reaction of 3,6-dimethoxypyridazine (**1**), it is difficult to understand how their conclusions could have been confirmed by the so called rational synthesis of Alazawe and Elvidge.³ The confirmation that 5-amino-6-methoxy-3(2*H*)-pyridazinone (**6**) was a product was based on comparisons of mixtures, and is clearly unsatisfactory. Of more concern is that, in our hands, reaction of **6** with hydrazine hydrate gave 5-hydrazino-6-hydroxy-3(2*H*)-pyridazinone (**19**) not 5-amino-6-hydrazino-3(2*H*)-pyridazinone (**7**). We believe it is extremely unlikely that Alazawe and Elvidge isolated **7** from the rational synthesis and so their comparisons are invalid. It is possible that Elvidge *et al.* may have obtained different products by using anhydrous hydrazine for some of the reactions with **1** and in the rational synthesis, but we believe that this is extremely unlikely as their 4-hydroxybenzaldehyde derived hydrazone has been firmly identified as **24** and not **23**. Yields from the reactions of hydrazine with **1** and **2** are not good, probably as a consequence of demethylation giving products such as **9** and **19** which are difficult to isolate, and it is possible that the products claimed by Elvidge *et al.* are formed as minor products. However, if **6** is produced from **1** or **2**, then it is present only as a short lived intermediate in the formation of **9** and **19**.

In summary, 3(2*H*)-pyridazinones having 6-chloro, 6-methoxy, and 6-hydrazino substituents all undergo 4-amination as the major reaction with hydrazine, in agreement with the previously observed reactivity of 3(2*H*)-pyridazinones towards hydrazine.^{4,5} Reactions of the chloro and methoxy compounds are complicated by displacement of the 6-substituent, and in the case of methoxy, by demethylation.

EXPERIMENTAL

Evaporations were carried out under reduced pressure. Melting points were determined on an Electrothermal apparatus and are uncorrected. Tlc was carried out using silica gel plates (0.25 mm, Merck SG 60 F254) with elution by dichloromethane:methanol mixtures (10:1 and 4:1) or methanol and detection by uv (254 nm) and

potassium iodoplatinate spray. Hydrazino derivatives were also subjected to tlc, after derivatisation with acetone, using 4:1 dichloromethane:methanol and 2:2:1 acetone:dichloromethane:methanol.

^1H -Nmr spectra were recorded at 360 MHz (Bruker AM360) in DMSO- d_6 ; chemical shifts δ are given in ppm downfield from TMS and coupling constants J are in Hz. Ir spectra were recorded on a Perkin Elmer 883 spectrometer and γ_{max} are given in cm^{-1} . Uv spectra were obtained for solutions in methanol using a Hewlett Packard 8452A. Mass spectra were recorded with a VG 70-70F instrument at 70eV and the parent peaks are reported (m/z).

Microanalytical data, and the bulk of the spectral data, were provided by the Analytical Sciences Department of SmithKline Beecham.

Short term reaction of hydrazine hydrate with 6-chloro-3(2H)-pyridazinone (10)

A stirred mixture of **10**¹⁰ (20.0 g, 0.15 mol) and hydrazine hydrate (200 ml, 4 mol) was heated under reflux for 30 min and then evaporated. Trituration of the residue with warm water (150 ml) acidified to pH 1 with hydrochloric acid gave 3.99 g (18%) of a solid mp 293-294°C. Recrystallisation from 50% aqueous ethanol gave pure 4-amino-6-chloro-3(2H)-pyridazinone (**11**) mp 293-294.5°C, lit.,¹¹ mp 300-301°C. Anal. Calcd for $\text{C}_4\text{H}_4\text{N}_3\text{OCl}$: C, 33.01; H, 2.72; N, 28.87; Cl, 24.36. Found: C, 32.89; H, 2.64; N, 29.28; Cl, 24.27. ^1H -Nmr: 6.18 (s, 1H, 5H); 6.83 (br s, 2H, NH_2); 12.63 (br s, 1H, 2-H). Ms 145/147.

The acidic filtrate from above was allowed to stand to give 1.41 g (5%) of a solid mp 246.5-248°C (decomp.) and evaporation of the filtrate to half volume gave a further 3.3 g (12%). Two recrystallisations from water gave pure 4-amino-6-hydrazino-3(2H)-pyridazinone (**14**) as its hydrochloride mp 248-249°C (decomp.). Anal. Calcd for $\text{C}_4\text{H}_7\text{N}_5\text{O} \cdot \text{HCl}$: C, 27.05; H, 4.54; N, 39.44; Cl, 19.96. Found: C, 26.75; H, 4.63; N, 39.27; Cl, 19.67. A solution of the hydrochloride (3.7 g, 21 mmol) in the minimum of hot water was treated with hydrazine hydrate (1.1 ml, 22 mmol) and cooled to give the free base 2.42 g (83%) mp 252-254°C (decomp.). Recrystallisation from water gave pure 4-amino-6-hydrazino-3(2H)-pyridazinone (**14**) as fine off-white needles mp 254-256°C (decomp.), lit.,¹ gave mp 247-249°C (decomp.) for the isomer (**7**). Anal. Calcd for $\text{C}_4\text{H}_7\text{N}_5\text{O}$: C, 34.04; H, 5.00; N, 49.62. Found: C, 34.02; H, 5.01; N, 49.59. ^1H -Nmr: 3.73 (br s, 2H, NHNH_2); 5.85 (s, 1H, 5-H); 6.05 (br s, 2H, 4- NH_2); 6.73 (s, 1H, NHNH_2); 11.63 (br s, 1H, 2-H). Ir: 3396, 3314, 3207, 1697, 1676, 1606, 1571, 1508, 1320, 1205, 1125, 990, 938, 885, 817, 771; lit.,¹ gave γ_{max} 3400, 3330, 3200, 1700, 1610, 1575, 1550, 1515, 1410, 1320, 1140, 995, 950, 890, 820, 775, for the isomer (**7**). Uv: λ_{max} 274, 232, 212 (ϵ 8500, 13700 and 16200 respectively), lit.,² gave λ_{max} 273, 232 (ϵ 12100, 15400) for the isomer (**7**). Ms: 141.

The acidic filtrate from above was reduced a further 50% in volume to give 3.41 g (ca. 12.5%) of a pale yellow solid consisting largely of 4-amino-6-chloro-3(2*H*)-pyridazinone (**11**). Recrystallisation from the minimum of hot water gave 0.9 g (4%) of the isomeric 5-amino-6-chloro-3(2*H*)-pyridazinone (**13**) mp 292-294°C. Two recrystallisations from acetonitrile gave 0.37 g (2%) of pure **13** as pale pink tinted needles mp 299.5-300.5°C, lit.,⁸ mp 301-302°C. Anal. Calcd for C₄H₄N₃OCl: C, 33.01; H, 2.72; N, 28.87; Cl, 24.36. Found: C, 33.09; H, 2.73; N, 28.89; Cl, 24.03. ¹H-Nmr: 5.67 (s, 1H, 4-*H*); 6.59 (br s, 2H, NH₂); 12.28 (br s, 1H, 2-*H*). Ms: 145/7. The final acidic filtrate from above was treated with an excess of acetone and sodium acetate was added to pH 4. Concentration of the solution gave 4.71 g (18.5%) of a hydrazone mp 265-270°C, and a further 0.9 g (3.5%) was obtained by evaporation of the filtrate and extraction of the residue with a mixture of acetone and 2-propanol. Recrystallisation from 20% aqueous ethanol containing a little acetone gave pure 6-isopropylidenehydrazino-3(2*H*)-pyridazinone (**15**) mp 272-275°C (decomp.). Anal. Calcd for C₇H₁₀N₄O: C, 50.59; H, 6.07; N, 33.72. Found: C, 50.46; H, 6.10; N, 33.94. ¹H-Nmr: 1.85 (s, 3H, CH₃); 1.91 (s, 3H, CH₃); 6.81 (d, *J*=10.0, 1H, 4-*H*); 7.47 (d, *J*=10.0, 1H, 5-*H*); 9.04 (s, 1H, hydrazone-NH); 12.09 (br s, 1H, 2-*H*). Ms: 166.

Long term reaction of hydrazine hydrate with 6-chloro-3(2*H*)-pyridazinone (**10**)

A stirred mixture of **10** (5.0 g, 38 mmol) and hydrazine hydrate (100 ml, 2 mol) was heated under reflux for 7.5 h. The residue after evaporation was triturated with aqueous ethanol to give 3.6 g (67%) of a solid mp 237-240°C. ¹H-Nmr and tlc analysis were consistent with a mixture of 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**) and 4-amino-6-chloro-3(2*H*)-pyridazinone (**11**). Both recrystallisation from water (solid mp 252-255°C) and formation of the hydrochloride salt (solid mp 251-254°C) failed to give **14** free from **11**.

4-Amino-3(2*H*)-pyridazinone (**22**)

A mixture of 4-amino-6-chloro-3(2*H*)-pyridazinone (**11**, 0.7 g, 4.8 mmol), sodium hydroxide (0.28 g, 7 mmol), 10% Pd-C (0.07 g) and water (28 ml) was shaken under hydrogen at atmospheric pressure until the uptake of hydrogen was complete. The filtered mixture was neutralised and concentrated to give 0.4 g (75%) of 4-amino-3(2*H*)-pyridazinone (**22**) mp 227-230°C. Recrystallisation from water gave pure **22** as lustrous plates mp 230-233°C, lit.,¹² mp 228-229°C. ¹H-Nmr: 6.18 (d, *J*=4.7, 1H, 5-*H*); 6.33 (br s, 2H, NH₂); 7.47 (d, *J*=4.7, 1H, 6-*H*); 12.50 (br s, 1H, 2-*H*).

3,7-Diphenyloxazolo[4,5-*e*]triazolo[4,3-*b*]pyridazine (**21**)

A mixture of 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**, 0.25 g, 1.4 mmol) and benzoyl chloride (5 ml, 43 mmol) was heated under reflux for 1 h. The cold mixture was filtered and the solid was washed with ether to give 0.4 g (91%) of 3,7-diphenyloxazolo[4,5-*e*]triazolo[4,3-*b*]pyridazine (**21**), mp 281-283°C.

Recrystallisation from toluene gave pure **21** as a bright yellow solid mp 282-285°C. Anal. Calcd for $C_{18}H_{11}N_5O$: C, 69.00; H, 3.54; N, 22.35. Found: C, 69.46; H, 3.46; N, 22.14. 1H -Nmr: 7.58-7.73 (m, 1H, 7-(or 3-)Ph-4-H); 7.13-7.29 (m, 4H, 3- and 7-Ph-3,5-H); 7.79-7.84 (m, 1H, 3-(or 7-)Ph-4-H); 8.32 (d, $J=7.3$, 2H, 7-(or 3)Ph-2,6-H); 8.42 (d, $J=7.3$, 2H, 3-(or 7-)Ph-2,6-H); 8.83 (s, 1H, 9-H). Ir: 3055, 1655, 1625, 1185, 905, 700. Ms: 313.

Reaction of hydrazine hydrate with 4-amino-6-chloro-3(2H)-pyridazinone (**11**)

A stirred mixture of **11** (0.75 g, 5.2 mmol) and hydrazine hydrate (15 ml, 0.3 mol) was heated under reflux for 9 h and then evaporated. The residue was triturated with aqueous ethanol to give 0.46 g (63%) of a solid. A further 0.11 g (15%) was obtained from the filtrate. The combined solids were digested with 1N hydrochloric acid to leave 0.15 g (20%) of crude **11**. The acidic digest was reduced in volume to give 0.35 g (38%) of 4-amino-6-hydrazino-3(2H)-pyridazinone hydrochloride, mp 249.5-251.5°C (decomp.), identical with that obtained from 6-chloro-3(2H)-pyridazinone (**10**).

Reaction of hydrazine hydrate with 6-hydrazino-3(2H)-pyridazinone (**12**) generated *in situ* from 6-isopropylidenehydrazino-3(2H)pyridazinone (**15**)

A stirred mixture of **15** (0.3 g, 1.8 mmol) was heated under reflux with hydrazine hydrate (6 ml, 0.12 mol) for 5 h. The residue after evaporation was triturated with methanol to give 0.17 g (68%) of 4-amino-6-hydrazino-3(2H)-pyridazinone (**14**), mp 246-247°C (decomp.), identical with that obtained from 6-chloro-3(2H)-pyridazinone (**10**).

6-Hydrazino-3(2H)-pyridazinone (**12**)

6-Isopropylidenehydrazino-3(2H)-pyridazinone (**15**, 1.5 g, 9 mmol) was heated on a steam bath for 5 min with hydrazine hydrate (15 ml, 0.3 mol). The resultant solution was evaporated and the residue was triturated with water to give 0.76 g (67%) of a solid mp 231-235°C (decomp.). Recrystallisation from water gave pure **12** as pale yellow needles mp 237-239°C (decomp.), lit.,^{6,7} mp 235-237°C, 197-199°C. Anal. Calcd for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 44.43. Found: C, 37.72; H, 4.78; N, 44.21. 1H -Nmr: 3.91 (s, 2H, NH_2); 6.70 (d, $J=9.9$, 1H, 4-H); 6.99 (d, $J=9.9$, 1H, 5-H); 7.26 (s, 1H, $NHNH_2$); 11.87 (s, 1H, 2-H). Ms: 126.

5-Amino-6-hydrazino-3(2H)-pyridazinone (**7**)

A mixture of 5-amino-6-chloro-3(2H)-pyridazinone⁸ (**13**, 2.0 g, 14 mmol) and hydrazine hydrate (20 ml, 0.4 mol) was heated under reflux for 4 h and then allowed to cool to give 1.23 g (63%) of 5-amino-6-hydrazino-3(2H)-pyridazinone (**7**), mp 245-247°C (decomp.). Evaporation of the filtrate and trituration of the residue with water gave a further 0.19 g (10%) of **7**. Recrystallisation from water gave pure **7**, mp 250-251°C (decomp.,

followed by resolidification). Anal. Calcd for $C_4H_7N_5O$: C, 34.04; H, 5.00; N, 49.62. Found: C, 34.46; H, 4.91; N, 49.43. 1H -Nmr: 3.86 (s, 2H, $NHNH_2$); 5.50 (s, 1H, 4-*H*); 6.05 (s, 2H, 5- NH_2); 6.77 (s, 1H, $NHNH_2$); 11.14 (s, 1H, 2-*H*). Ir: 3406, 3373, 3300, 3240, 1690, 1631, 1604, 1561, 1510, 1279, 1261, 1204, 1129, 999, 836, 816, 755. Uv: λ_{max} 274, 216 nm (ϵ 8100 and 18600 respectively). Ms: 141.

Hydrolysis of 4-amino-6-chloro-3-methoxypyridazine (8): "rational synthesis" of 5-amino-6-methoxy-3(2*H*)-pyridazinone (6)

A mixture of **8**³ (2.57 g, 16 mmol), anhydrous potassium acetate (3.2 g, 32 mmol), acetic acid (17 ml) and glass balls (3.5 g) was stirred together in a PTFE-lined sealed vessel with an internal temperature of 150-155°C for 4 h. Evaporation of the resultant mixture left a residue, tlc analysis of which indicated the presence of at least 5 components. A suspension of the residue in water (12 ml) was treated with 50% potassium hydroxide (6 ml) and the solution was heated on a steam bath for 40 min (tlc analysis indicated 3 major components), chilled and filtered to give 0.75 g (33%) of 5-amino-6-methoxy-3(2*H*)-pyridazinone (**6**). Recrystallisation from water gave pure **6**, mp 265-267°C, lit.,³ mp 270°C. 1H -Nmr: 3.76 (s, 3H, CH_3), 5.53 (s, 1H, 4-*H*); 6.25 (br s, 2H, NH_2); 11.15 (br s, 1H, 2-*H*).

Neutralisation of the first aqueous filtrate with concentrated hydrochloric acid gave 0.47 g (20%) of 4-amino-6-chloro-3(2*H*)-pyridazinone (**11**), identical with that obtained from 6-chloro-3(2*H*)-pyridazinone (**10**) above. Concentration of the filtrate from **11** gave a further 0.68 g (30%) of crude **6** containing some inorganic material. In a similar experiment, in which the aqueous hydrolysis was incomplete, the first solid to separate from the reaction mixture was 4-acetamido-6-chloro-3(2*H*)-pyridazinone (**18**), obtained in 20% yield. Recrystallisation from ethanol gave pure **18**, mp 262-264°C, lit.,^{12,13} mp 255-256°C, 260-265°C. Anal Calcd for $C_6H_6N_3O_2Cl$: C, 38.42; H, 3.22; N, 22.40. Found: C, 38.72; H, 3.36; N, 22.34. 1H -Nmr: 2.21 (s, 3H, CH_3); 8.00 (s, 1H, 5-*H*); 10.19 (s, 1H, $NHCOCH_3$); 13.35 (br s, 1H, 2-*H*). Ms: 187/189.

Reaction of hydrazine hydrate with 5-amino-6-methoxy-3(2*H*)-pyridazinone (6): "rational synthesis" of 5-amino-6-hydrazino-3(2*H*)-pyridazinone (7)

a). A stirred mixture of **6** (0.25 g, 1.8 mmol) and hydrazine hydrate (5 ml, 0.1 mol) was heated under reflux for 1.5 h. Evaporation of the solution gave a pale yellow solid which was dried *in vacuo* over concentrated sulphuric acid to leave 0.27 g of a cream solid. Tlc analysis was consistent with the presence of some residual **6**, but **7** was not detected. The mass spectrum was consistent with a mixture of **6**, **9**, and **19** (parent peaks at m/z 141, 127, and 142, respectively) in a ratio (1H -Nmr) of about 1:4:2. The crude product (0.22 g) was heated

with 50% aqueous acetone (5 ml) and the mixture was allowed to cool and then filtered to give 72 mg (22%) of **20**, the acetone hydrazone of **19**, identical ($^1\text{H-Nmr}$, ms) to that prepared in (b) below.

The filtrate from **20** was evaporated to remove acetone and left to stand to give 68 mg (30%) of **9**. A further 20 mg (9%) of **9** was obtained from the filtrate on further standing. The combined solids (70 mg) were recrystallised from water to give 30 mg (13%) of 5-amino-6-hydroxy-3(2*H*)-pyridazinone (**9**), mp *ca.* 330°C (decomp.), lit.³ mp 325°C (decomp.). $^1\text{H-Nmr}$: 5.72 (s, 1H, 4-*H*); 6.21 (br s, 2H, *NH*₂); *ca.* 10.2 (vbr s, 1H, *OH*); *ca.* 11.3 (vbr s, 1H, 2-*H*). Ms: 127.

b). The procedure of (a) was repeated but the reaction was allowed to proceed for 16 h to give 0.3 g of a yellow solid. A solution of this solid in 2N sodium hydroxide (1 ml) was treated with charcoal and then acetic acid was added to pH 7. This gave 0.17 g (68%) of 4(5)-hydrazino-6-hydroxy-3(2*H*)-pyridazinone (**19**) which decomposed without melting below 350°C (lit.,^{4,13} mp 225-229°C, >350°C). $^1\text{H-Nmr}$: 4.44 (br s, 2H, *NHNH*₂); 5.97 (br s, 1H, 4-*H*); 9.50 and *ca.* 9.7 (2 x overlapping br s, 2H, *OH* and *NHNH*₂); 12.30 (br s, 1H, 2-*H*). Ms: 142. The hydrazine (**19**, 163 mg, 1.1 mmol) was heated with 50% aqueous acetone (4 ml) and ethanol (2 ml) was added to give a solution which was treated with charcoal and filtered. The volume was reduced to give 103 mg (49%) of the acetone hydrazone (**20**). Recrystallisation from aqueous ethanol gave a buff coloured solid which decomposed without melting below 350°C. Anal. Calcd for $\text{C}_7\text{H}_{10}\text{N}_4\text{O}_2$: C, 46.15; H, 5.53; N, 30.75. Found: C, 46.40; H, 5.48; N, 30.82. $^1\text{H-Nmr}$: 1.94 (s, 3H, *CH*₃); 2.00 (s, 3H, *CH*₃); 6.15 (s, 1H, 4-*H*); 8.48 (s, 1H, *hydrazone-NH*); *ca.* 10.2 (v br, 1H, *OH*); *ca.* 11.9 (v br, 1H, 2-*H*). Ms: 182.

5-Amino-6-(4-hydroxybenzylidenehydrazino)-3(2*H*)-pyridazinone (**23**)

A solution of 4-hydroxybenzaldehyde (0.17 g, 14 mmol) in hot water (5 ml) was treated with charcoal and filtered into a stirred solution of 5-amino-6-hydrazino-3(2*H*)-pyridazinone (**7**, 0.17 g, 12 mmol) in hot water (15 ml) to give 0.22 g (73%) of 5-amino-6-(4-hydroxybenzylidenehydrazino)-3(2*H*)-pyridazinone (**23**), mp 278-280°C. Recrystallisation from methanol gave **23** as a yellow solid, mp 277-278°C (decomp.), lit.,¹ mp see **24** below, which retained some methanol despite exhaustive drying. Anal. Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_5\text{O}_2 \cdot 0.15\text{CH}_3\text{OH}$: C, 53.56; H, 4.68; N, 28.01. Found: C, 53.49; H, 4.63; N, 27.78. $^1\text{H-Nmr}$: 5.64 (s, 1H, 4-*H*); 6.40 (br s, 2H, *NH*₂); 6.79 (d, *J*=8.5, 2H, *Ph-3,5-H*); 7.43 (d, *J*=8.5, *Ph-2,6-H*); 7.92 (s, 1H, *NH*); 9.80 (br s, 2H, *N=CH* and *OH*); 11.29 (br s, 1H, 2-*H*); methanol was detected at δ 3.17 (d) and 4.13 (q). Ir: 3450, 3305, 3223br, 1640, 1602, 1583, 1510, 1268. Ms: 245.

4-Amino-6-(4-hydroxybenzylidenehydrazino)-3(2*H*)-pyridazinone (**24**)

In a similar procedure to that above, 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**, 0.35 g, 2.5 mmol) gave 0.56 g (93%) of a very pale cream coloured solid, mp 275.5-278.5°C (decomp.). Recrystallisation from methanol gave fine pale buff coloured needles of pure **24**, mp 281-283°C (decomp.), lit.,¹ mp for the product wrongly assigned structure(**23**) is given as 268-269°C (decomp.). Anal Calcd for C₁₁H₁₁N₅O₂: C, 53.87; H, 4.52; N, 28.56. Found: C, 53.61; H, 4.51; N, 28.37. ¹H-Nmr: 6.28 (br s, 2H, *NH*₂); 6.54 (s, 1H, 5-*H*); 6.78 (d, *J*=8.6, 2H, *Ph*-3,5-*H*); 7.40 (d, *J*=8.6, 2H, *Ph*-2,6-*H*); 7.79 (s, 1H, *NH*); 9.68 (br s, 1H, *OH*); 10.06 (s, 1H, *N=CH*); 11.76 (br s, 1H, 2-*H*). Ir: 3475, 3349, 3180br, 1607, 1587, 1504, 1264, 1234. Ms: 245.

6-Methoxy-3(2*H*)-pyridazinone (**2**)

A stirred solution of 3,6-dimethoxypyridazine¹⁴ (**1**, 4.0 g, 29 mmol) in concentrated hydrochloric acid (20 ml) was heated under reflux for 30 min and then evaporated. The residue was diluted with water (20 ml) and potassium carbonate was added to pH 7 to give 2.22 g (62%) of **2**, mp 162.5-164.5°C, lit.,¹⁵ mp 162-163°C. A further 0.63 g (16%) of **2** was obtained from the filtrate. The melting point of **2** was unchanged after recrystallisation from ethyl acetate. ¹H-Nmr: 3.74 (s, 3H, *CH*₃); 6.88 (d, *J*=9.9, 1H, 4-*H*); 7.17 (d, *J*=9.9, 1H, 5-*H*); 12.20 (br s, 1H, 2-*H*).

Short term reaction of hydrazine hydrate with 6-methoxy-3(2*H*)-pyridazinone (**2**)

A stirred mixture of **2** (2.75 g, 22 mmol) and hydrazine hydrate (27.5 ml, 0.55 mol) was heated under reflux for 30 min and then evaporated. Trituration of the residue with methanol gave 1.23 g (ca. 40%) of a crude product, the ¹H-Nmr spectrum of which was consistent with a mixture of 4-amino-6-methoxy-3(2*H*)-pyridazinone (**16**), 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**) and 6-hydrazino-3(2*H*)-pyridazinone (**12**) in a ratio of about 2:1:1. A portion of the solid (0.9 g) was warmed with water (20 ml) acidified with hydrochloric acid (to pH 1) and when cool the mixture was filtered to give 0.39 (17%) of **16**, mp 281-286°C. Recrystallisation from water gave 0.27 g (12%) of pure **16**, mp 286-289°C, lit.,¹¹ mp 276-277°C. Anal. Calcd for C₅H₇N₃O₂: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.44; H, 4.89; N, 29.97. ¹H-Nmr: 3.64 (s, 3H, *CH*₃); 5.84 (s, 1H, 5-*H*); 6.35 (br s, 2H, *NH*₂); 11.85 (br s, 1H, 2-*H*). Ms: 141.

Long term reaction of hydrazine hydrate with 6-methoxy-3(2*H*)-pyridazinone (**2**)

A stirred mixture of hydrazine hydrate (3 ml, 60 mmol) and **2** (0.3 g, 2.4 mmol) was heated under reflux for 6 h. Evaporation and trituration of the residue with aqueous methanol gave 0.11 g (ca. 33%) of a mixture of 4-amino-6-hydrazino- and 4-amino-6-methoxy-3(2*H*)-pyridazinones (**14** and **16**), mp 247-249°C.

Reactions of hydrazine hydrate with 3,6-dimethoxypyridazine (**1**)

a). A well stirred mixture of **1**¹⁴ (2.0 g, 14 mmol) and hydrazine hydrate (6 ml, 0.12 mol) was gently heated to the boiling point during 30 min. Tlc analysis indicated the presence of 6-methoxy-3(2*H*)-pyridazinone (**2**). The mixture was then heated under reflux for 6 h, i.e., essentially the method of Elvidge and Pickett.¹ The resultant solution was allowed to cool and the granular precipitate was collected and washed with water and methanol to give 0.42 g (21%) of a solid mp 238-243°C (decomp.). Evaporation of the filtrate and trituration of the residue with aqueous ethanol gave a further 0.13 g (6%). Tlc analysis indicated the presence of 4-amino-6-methoxy-3(2*H*)-pyridazinone (**16**) and 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**) in both samples, while the filtrate contained at least 6 components. The ¹H-Nmr spectrum of the crude product was consistent with a 1:1 mixture of **14** and **16**.

b). A stirred mixture of **1** (0.5 g, 3.6 mmol) and hydrazine hydrate (5 ml, 0.1 mol) was heated with methanol (0.5 ml, added to control sublimation of **1**) under reflux (boiling point about 100°C) for 6 h. When cool the filtrate was filtered to give 0.11 g (22%) of a solid mp 245-250°C (decomp.), and a further 0.08 g (16%) was obtained from the filtrate by evaporation and trituration with aqueous ethanol. Tlc and ¹H-Nmr analysis indicated that the crude product was a mixture of **14** and **16** in a ratio of about 3:2. The crude product (0.14 g) was warmed with dilute hydrochloric acid, and the filtered solution was allowed to stand to give 0.045 g of a crude hydrochloride, mp 232-236°C (decomp.) which was, however, still a mixture of **14** and **16**.

c). In a procedure similar to that of (a) above, **1** (2.0 g, 14 mmol) gave, after 20 h, 0.94 g (47%) of a crude product mp 228-233°C. This was recrystallised firstly from hydrazine hydrate (5 ml) by the addition of methanol (5 ml) to give 0.6 g (30%) of a solid mp 247.5-250°C (decomp.), and then from water to give 0.42 g (21%) of **14**, mp 250.5-252.5°C (decomp.), which still contained 10% of **16**.

d). In a similar procedure to (c) and (d) above, **1** (1.0 g, 7.1 mmol) gave, after 8 h, 0.44 g, (44%) of a 3:1 mixture of **14** and **16**, mp 240-244°C. The crude product (0.40 g) was heated under reflux with hydrazine hydrate (5 ml) for 6 h and the cool solution was then diluted with methanol (5 ml) to give 0.15 g (15%) of a 10:1 mixture of **14** and **16**, mp 246-247°C (decomp.).

Reaction of hydrazine hydrate with 4-amino-6-methoxy-3(2*H*)-pyridazinone (**16**)

Hydrazine hydrate (1 ml, 20 mmol) was heated under reflux with **16** (3 mg, 0.02 mmol) for 7 h, and the solution was evaporated and dried *in vacuo* over concentrated sulphuric acid. Comparison of the residual solid with 4-amino-6-hydrazino-3(2*H*)-pyridazinone (**14**) by tlc analysis failed to provide any evidence for the formation of **14** in this reaction.

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