Pyridazine Chemistry. Part 28.[1,2] Synthesis of Pyrazolo- and Isoxazolo-pyridazines starting from 5-Aminopyridazin-4-yl Aryl Ketones

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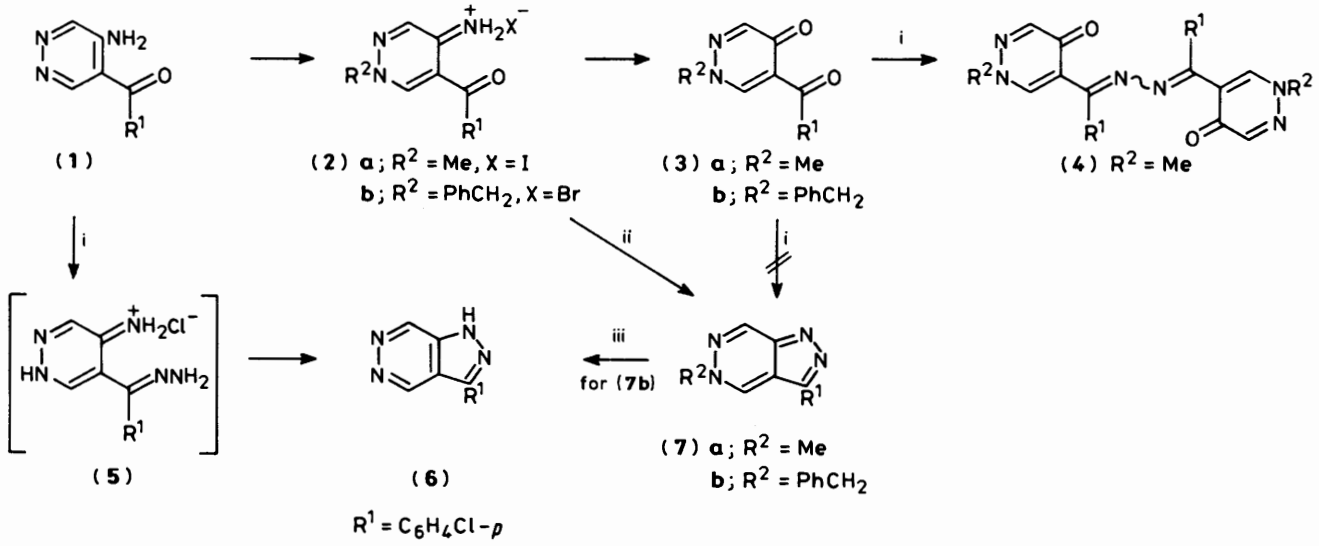
Procedures for the preparation of 3-arylpyrazolo[3,4-*d*]pyridazines [*e.g.* (**6**)] as well as 1- or 5-substituted derivatives thereof [(**8a**), (**8b**), (**7a**), and (**7b**)] and 3-arylisoxazolo [4,5-*d*]pyridazines [*e.g.* (**11**)] are reported.

The synthesis of isoxazolo[4,5-*d*]pyridazines and pyrazolo[3,4-*d*]pyridazines, which are of biological interest,[3,4] is usually achieved by ring closure reactions of bifunctional derivatives of the corresponding five-membered heteroaromatics.[5] However, recently several studies concerned with the preparation of 3-arylpyrazolo[3,4-*d*]pyridazines *via* annelation of appropriately substituted pyridazines have been published.[6] This prompted us to report a further approach to the title ring systems starting with 5-aminopyridazin-4-yl aryl ketones. Preparation of these novel heteroaromatic analogues of 2-aminobenzophenone as well as their alkylation and acylation behaviour has also been described recently.[7,1] In order to minimize overlap of aromatic proton signals in the n.m.r. spectra of the target compounds, 5-aminopyridazin-4-yl *p*-chlorophenyl ketone[7] (**1**) was used as the starting material.



Scheme 1. *Reagents:* i, NH_2NH_2·HCl; ii, NH_2NH_2·H_2O; iii, $AlCl_3$–toluene

Attempts to convert 5-(*p*-chlorobenzoyl-1-methylpyridazin-4(1*H*)-one (**3a**), easily obtained from the amino ketone (**1**) *via* the iminium iodide (**2a**),[1] into the 5-methylpyrazolo[3,4-*d*]pyridazine (**7a**) by reaction with hydrazine hydrochloride failed. Instead of a cyclized product a compound was formed, for which the structure of the azine (**4**) is proposed on the basis of spectroscopic and analytical evidence. Whereas the reactivity of the pyridazinone carbonyl group in (**3a**) is obviously too low to permit pyrazole ring formation, this problem can be overcome by employing the more reactive iminium compound (**2a**) as the starting material. Thus, (**2a**) on treatment with hydrazine hydrate in ethanolic solution at room temperature gave (**7a**) (94%). In order to gain access to the *N*-unsubstituted 3-arylpyrazolo[3,4-*d*]pyridazine (**6**), the corresponding 5-benzyl derivative (**7b**) was prepared from compound (**2b**) in an analogous manner. Removal of the benzyl moiety from compound (**7b**) was found to take place smoothly on reaction with aluminium chloride in toluene at 60 °C,† according to a method reported in the literature.[8]

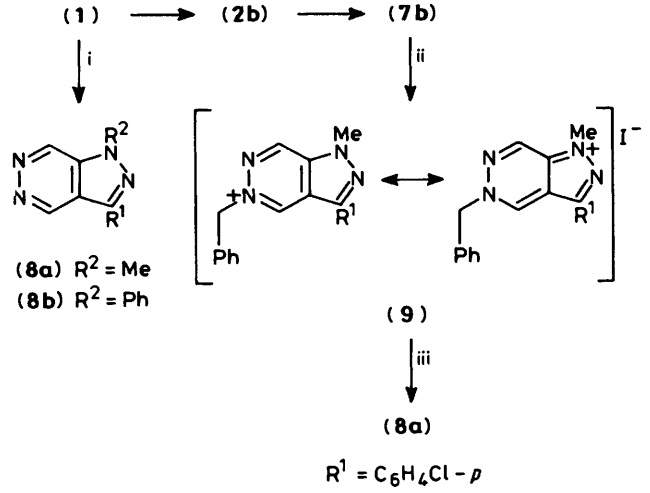
It was thought that the protonation of compound (**1**) would influence the reactivity of the C-5 atom towards nucleophiles in a similar manner to 2-alkylation. Thus, a simple one-step synthesis (72% yield) of (**6**) was achieved by reaction of compound (**1**) with an excess of hydrazine hydrochloride in refluxing ethanol. Since the u.v. spectrum of compound (**6**) closely resembles that of compound (**8a**) (see below), (**6**) is formulated in the tautomeric form shown in Scheme 1. The products obtained on treatment of compound (**1**) with methylhydrazine hydrochloride or phenylhydrazine hydrochloride, respectively, again proved to be pyrazolo[3,4-*d*]pyridazines;‡ however, spectroscopic data did not primarily distinguish between the two isomeric structures (1- or 2-

† Attempts to remove the benzyl group by hydrogenolysis (Pd–C) or protolytically (HBr–$MeCO_2H$) were unsuccessful.

‡ The moderate yields of compounds (**8a**) and (**8b**) (30, 50%) result from comparably low conversion rates as shown by isolation of substantial amounts of unchanged starting material even after a reaction time of 10 days.

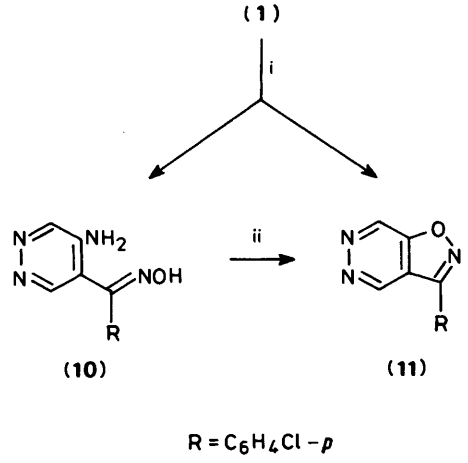
substituted) to be taken into consideration. Eventually, nuclear Overhauser effect (n.O.e.) experiments clearly showed the new compounds to be (**8a**)* and (**8b**), respectively. This, together with the results of the reaction of compound (**1**) with hydroxylamine hydrochloride discussed below, allows the assumption that the first step in the reaction of compound (**1**) with hydrazine hydrochlorides is nucleophilic attack at the oxo group rather than substitution of the amino group.

Since alkylation of the 5-benzyl compound (**7b**) should take place preferentially at N-1 for steric and electronic reasons, treatment of compound (**7b**) with an appropriate alkyl halide, followed by debenzylation of the quaternary intermediate was expected to provide an efficient route to 1-alkyl substituted 3-arylpyrazolo[3,4-*d*]pyridazines.† This proved to be the case and was demonstrated by the reaction sequence (**7b**) ⟶ (**9**) ⟶ (**8a**) (Scheme 2).



Scheme 2. *Reagents:* i, NH_2NHR^2·HCl; ii, MeI; iii, $AlCl_3$–toluene

The amino ketone (**1**) and hydroxylamine hydrochloride in refluxing ethanol gave colourless needles (m.p. 226—228 °C) in 22% yield, the elemental composition of which ($C_{11}H_6ClN_3O$) gave a clear indication that the compound was an isoxazolopyridazine. Spectroscopy, however, did not permit unequivocal differentiation between structure (**11**) and an isoxazolo[3,4-*d*]pyridazine isomer for the product. In contrast to the reaction of (**1**) with hydrazine or its derivatives, work-up of the mother liquor gave a reaction intermediate (50% yield), which was identified as 5-aminopyridazin-4-yl *p*-chlorophenyl ketone oxime (**10**)·H_2O. Besides the three singlets at 8.25, 8.70, and 7.50 p.p.m. (pyridazine and phenyl protons) the ^1H n.m.r. spectrum of a sample purified by repeated crystallisation‡ exhibited signals at 11.95 and 6.15 p.p.m. (intensity ratio 1:2) which were removed by the addition of D_2O attributable to the NOH and the NH_2 protons, respectively. This, together with a



Scheme 3. *Reagents:* i, NH_2OH·HCl; ii, 150 °C

$\nu_{C=N}$ absorption in the i.r. spectrum and m.s. molecular weight determination§ excludes any other possible structure. In turn, the oxime (**10**) could be cyclized simply by heating (150 °C) to yield compound (**11**) m.p. 226—228 °C, which unequivocally shows the latter to be 3-(*p*-chlorophenyl)isoxazolo[4,5-*d*]-pyridazine. In summary, compound (**11**) can be prepared from compound (**1**) in 58% overall yield.

Application of this type of reaction to *vic*-aminoformylpyridazines as well as transformations of (**1**) into pyrido- and pyrimido-pyridazines are at present under investigation.

Experimental

M.p.s were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. I.r. spectra were recorded for KBr pellets on a JASCO IRA-1 spectrophotometer, u.v. spectra were recorded for solutions in methanol on a Beckman 25 spectrophotometer. ^1H N.m.r. spectra were measured on either a Varian EM 390 (90 MHz) instrument or a Bruker WM 250 (250 MHz) spectrometer (Me_4Si as the internal reference). Mass spectra were obtained on a Varian MAT CH-7 instrument (e.i.: 70 eV; f.a.b.: butanetriol—xenon). T.l.c. was performed using Merck aluminium sheets pre-coated with Kieselgel 60 F_{254}, column chromatography was carried out on Merck Kieselgel 60 (70—230 mesh).

p-*Chlorophenyl* 2,5-*Dihydro*-2-*methyl*-5-*oxopyridazin*-4-*yl Ketone Azine* (**4**).—A solution of 5-(*p*-chlorobenzoyl)-1-methylpyridazin-4(1*H*)-one[1] (**3a**) (124 mg, 0.5 mmol) and hydrazine monohydrochloride (68 mg, 1 mmol) in ethanol (20 ml) was refluxed for 6 h and left at room temperature for 14 h. After removal of the solvent, the residue was treated with water and extracted with dichloromethane. Evaporation of the extract and washing of the residue with boiling methanol afforded a *yellow solid* (102 mg, 83%), m.p. 265—270 °C (Found: C, 58.15; H, 3.85; N, 16.5. $C_{24}H_{18}Cl_2N_6O_2$ requires C, 58.43; H, 3.68; N, 17.03%); $\nu_{max.}$ 3 040, 2 950, 1 605, 1 585, 1 490, 1 080, and 835 cm^{-1}; δ_H [90 MHz; $(CD_3)_2SO$] 3.85 (6 H, s, Me), 7.40—7.70 (8 H, AA'BB', *J* 9 Hz, C_6H_4Cl), 7.90, and 8.65 (each 2 H, s, pyridazine-H); *m/z* 492, 494, 496 (M^+, 3, 2, 0.6%) and 381, 383, 385 [(M^+ − 111), 100, 51, 12].

* The δ values in the ^1H n.m.r. spectrum of (**8a**) in $CDCl_3$ solution correspond well with the data recently reported for 1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine.[6b]

† T.l.c. experiments showed that compound (**6**) on treatment with methyl iodide affords the 5-methylated compound (**7a**) as the main product rather than (**8a**).

‡ The crude product obviously consists of a mixture of *E* and *Z* isomers, as shown by ^1H n.m.r. spectroscopy. Since only the major component (*ca.* 60%) could be isolated uncontaminated by the other isomer, no definitive conclusion with respect to the configuration at present can be drawn. However, comparison of the u.v. spectrum with data reported for (*E*)- and (*Z*)-2-aminobenzophenone oximes[9,10] suggests the isolated compound to be the *Z*-isomer.

§ Whereas the electron-impact (e.i.) mass spectrum of compound (**10**) only showed peaks of fragment ions, the fast atom bombardment (f.a.b.) mass spectrum exhibited significant peaks at *m/z* 249 and 251 (M^+ + 1).

3-(*p-Chlorophenyl*)-5-*methyl*-5H-*pyrazolo*[3,4-*d*]*pyridazine* (**7a**).—A solution of 5-(*p*-chlorobenzoyl)-1,4-dihydro-1-methylpyridazin-4-ylideneammonium iodide[1] (**2a**) (375 mg, 1 mmol) and hydrazine hydrate (250 mg, 5 mmol) in ethanol (20 ml) was left at room temperature for 2 h. The residue obtained on evaporation was recrystallized from propan-2-ol to afford *yellow needles* (230 mg, 94%), m.p. 260—263 °C (decomp.) (Found: C, 58.65; H, 3.8; N, 22.7. $C_{12}H_9ClN_4$ requires C, 58.91; H, 3.71; N, 22.90%); $\nu_{max.}$ 3 060, 2 960, 2 920, 1 590, 1 410, 1 360, and 1 080 cm^{-1}; δ_H [90 MHz; $(CD_3)_2SO$] 4.40 (3 H, s, Me), 7.55—8.25 (4 H, AA'BB', *J* 9 Hz, C_6H_4Cl), and 9.50 and 10.20 (each 1 H, d, *J* 1.5 Hz, 7-H, 4-H); *m/z* 244, 246 (M^+, 61, 21%), and 80 (100).

5-*Benzyl*-3-(p-*chlorophenyl*)-5H-*pyrazolo*[3,4-d]*pyridazine* (**7b**)·H_2O.—Preparation as described for (**7a**), employing 1-benzyl-5-(*p*-chlorobenzoyl) 1,4-dihydropyridazin-4-ylideneammonium bromide[1] (**2b**) (404 mg, 1 mmol) as the starting material. Recrystallisation from ethanol afforded *yellow needles* (322 mg, 95%), m.p. 255—260 °C (decomp.) (Found: C, 63.7; H, 4.6; N, 16.4. $C_{18}H_{13}ClN_4 \cdot H_2O$ requires C, 63.81; H, 4.46; N, 16.54%); $\nu_{max.}$ 3 050, 2 970, 1 590, 1 420, 1 385, 1 200, and 1 090 cm^{-1}; δ_H [90 MHz; $(CD_3)_2SO$] 5.80 (2 H, s, CH_2), 7.30—7.50 (5 H, m, Ph), 7.50—8.25 (4 H, AA'BB', *J* 9 Hz, C_6H_4Cl), and 9.45 and 10.45 (each 1 H, d, *J* 1.5 Hz, 7-H, 4-H).

3-(p-*Chlorophenyl*)-1H-*pyrazolo*[3,4-d]*pyridazine* (**6**).—(*a*) To a stirred suspension of anhydrous aluminium chloride (266 mg, 2 mmol) in dry toluene (30 ml) was added compound (**7b**) (160 mg, 0.5 mmol), and the mixture was heated to 60 °C for 1.5 h. It was then cooled, diluted with water (2 ml) and the precipitate removed and washed with water; on recrystallisation from aqueous ethanol it gave *colourless needles* (70 mg, 60%), m.p. 310—320 °C (decomp.) (Found: C, 57.1; H, 3.25; N, 24.1. $C_{11}H_7ClN_4$ requires C, 57.28; H, 3.06; N, 24.29%); $\nu_{max.}$ 3 050, 3 000, 2 750, 1 600, 1 480, 1 420, 1 240, 1 100, and 1 000 cm^{-1}; $\lambda_{max.}$ 240, 274, and 290sh nm (log ε 4.23, 3.93, and 3.87); δ_H [90 MHz; $(CD_3)_2SO$] 7.55—8.20 (4 H, AA'BB', *J* 9 Hz, C_6H_4Cl), 9.70, 10.00 (each 1 H, d, *J* 1.5 Hz, 7-H, 4-H), and 14.50 (1 H, br, NH); *m/z* 230, 232 (M^+, 100, 31%).

(*b*) A solution of 5-aminopyridazin-4-yl *p*-chlorophenyl ketone[7] (**1**) (233 mg, 1 mmol) and hydrazine monohydrochloride (274 mg, 4 mmol) in ethanol (30 ml) was refluxed for 30 h after which it was diluted with water (20 ml) and cooled. The precipitate was recrystallized to yield the pure product (166 mg, 72%).

5-*Benzyl*-3-(p-*chlorophenyl*)-1-*methyl*-1H-*pyrazolo*[3,4- d]-*pyridazin*-5-*ium Iodide* (**9**).—A mixture containing compound (**7b**)·H_2O (338 mg, 1 mmol), potassium carbonate (138 mg, 1 mmol), and methyl iodide (568 mg, 4 mmol) in acetone (50 ml) was left at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was washed with water and recrystallized from methanol to afford *colourless needles* (393 mg, 85%), m.p. 240—247 °C (Found: C, 48.95; H, 3.45; N, 12.05. $C_{19}H_{16}ClIN_4$ requires C, 49.32; H, 3.49; N, 12.11%); $\nu_{max.}$ 3 070, 3 040, 2 980, 1 600, 1 530, 1 430, 1 390, and 1 085 cm^{-1}; δ_H [90 MHz; $(CD_3)_2SO$] 4.45 (3 H, s, Me), 6.10 (2 H, s, CH_2), 7.35—7.65 (5 H, m, Ph), 7.70—8.30 (4 H, AA'BB', *J* 9 Hz, C_6H_4Cl), and 10.10 and 11.05 (each 1 H, d, *J* 1.5 Hz, 7-H, 4-H).

3-(p-*Chlorophenyl*)-1-*methyl*-1H-*pyrazolo*[3,4-d]*pyridazine* (**8a**).—(*a*) To a stirred suspension of anhydrous aluminium chloride (266 mg, 2 mmol) in dry toluene (30 ml) was added compound (**9**) (231 mg, 0.5 mmol), and the mixture was heated to 60 °C for 2 h. After concentration under reduced pressure, aqueous sodium hydroxide (1M; 10 ml) was added, and the suspension was extracted with dichloromethane. Evaporation of the extract and recrystallisation from benzene–light petroleum (b.p. 50—70 °C) gave colourless crystals (116 mg, 95%), m.p. 200—203 °C (Found: C, 59.2; H, 3.85; N, 22.5. $C_{12}H_9ClN_4$ requires C, 58.91; H, 3.71; N, 22.90%); $\nu_{max.}$ 3 060, 2 960, 1 490, 1 420, 1 235, 1 115, 1 090, and 830 cm^{-1}; $\lambda_{max.}$ 241, 276, and 305sh nm (log ε 4.30, 4.01, and 3.92); δ_H [250 MHz; $(CD_3)_2SO$] 4.26 (3 H, s, Me), 7.58 (2 H, d, *J* 9 Hz, 3'-H and 5'-H of C_6H_4Cl), 8.10 (2 H, d, *J* 9 Hz, 2'-H and 6'-H of C_6H_4Cl), 9.83 (1 H, d, *J* 1.5 Hz, 7-H; shows n.O.e. on irradiation at 4.26 p.p.m.), and 9.91 (1 H, d, *J* 1.5 Hz, 4-H).

(*b*) A solution of the amino ketone (**1**)[7] (233 mg, 1 mmol), methylhydrazine (184 mg, 4 mmol), and 2M-hydrochloric acid (2 ml) in ethanol (30 ml) was refluxed for 5 days. After the addition of further methylhydrazine (184 mg, 4 mmol) and 2M-hydrochloric acid (2 ml), refluxing was continued for a further 5 days. The mixture was evaporated, treated with water, and extracted with dichloromethane. Evaporation of the extract gave a brown solid which was subjected to column chromatography. Elution with dichloromethane–methanol (96:4) afforded compound (**8a**) (78 mg, 32%) and subsequently unchanged starting material (94 mg, 40%).

3-(p-*Chlorophenyl*)-1-*phenyl*-1H-*pyrazolo*[3,4-d]*pyridazine* (**8b**).—A solution of the amino ketone (**1**)[7] (233 mg, 1 mmol) and phenylhydrazine hydrochloride (578 mg, 4 mmol) in ethanol (30 ml) was refluxed for 8 days. Water (20 ml) was added, and the precipitated solid was recrystallized from methanol to give colourless *needles* (160 mg, 52%), m.p. 205—208 °C (Found: C, 66.65; H, 3.8; N, 18.05. $C_{17}H_{11}ClN_4$ requires C, 66.56; H, 3.61; N, 18.26%); $\nu_{max.}$ 3 060, 1 600, 1 540, 1 500, 1 420, 1 225, 1 150, and 1 090 cm^{-1}; δ_H [250 MHz; $(CD_3)_2SO$] 7.50—7.75 (5 H, m, 3'-H and 5'-H of C_6H_4Cl and 3''-H, 4''-H, and 5''-H of Ph), 7.96 (2 H, d, *J* 8 Hz, 2''-H and 6''-H of Ph; shows n.O.e. on irradiation at 9.94 p.p.m.), 8.23 (2 H, d, *J* 9 Hz, 2'-H and 6'-H of C_6H_4Cl; shows n.O.e. on irradiation at 10.06 p.p.m.), 9.94 (1 H, d, *J* 1.5 Hz, 7-H), and 10.06 (1 H, d, *J* 1.5 Hz, 4-H).

Reaction of the Amino Ketone (**1**) *with Hydroxylamine Hydrochloride*.—A solution of the amino ketone (**1**)[7] (233 mg, 1 mmol) and hydroxylamine hydrochloride (417 mg, 6 mmol) in ethanol (20 ml) was refluxed for 20 h after which water (20 ml) was added and the mixture was cooled. The precipitated solid was recrystallized from ethanol to give 3-(p-*chlorophenyl*)-*isoxazolo*[4,5-*d*]*pyridazine* (**11**) (51 mg, 22%) as colourless needles, m.p. 226—228 °C (Found: C, 56.9; H, 2.85; N, 17.95. $C_{11}H_6ClN_3O$ requires C, 57.03; H, 2.61; N, 18.14%); $\nu_{max.}$ 3 110, 1 595, 1 475, 1 410, 1 320, 1 080, 960, and 865 cm^{-1}; δ_H[90 MHz; $(CD_3)_2SO$] 7.70—8.30 (4 H, AA'BB', *J* 9 Hz, C_6H_4Cl) and 10.15—10.25 (2 H, AB, *J* 1.5 Hz, 4-H, 7-H); *m/z* 231, 233 (M^+, 17, 6%) and 177, 179 [(M^+ − 54), 100, 28].

The mother liquor was concentrated under reduced pressure to a volume of *ca.* 20 ml, neutralized by addition of dilute sodium hydroxide, and extracted with chloroform–propan-2-ol (9:1). Evaporation of the extract gave crude (*E*)- *and* (*Z*)-5-*aminopyridazin*-4-*yl* p-*chlorophenyl ketone oxime* (**10**) as a pale yellow solid (130 mg, 50%). A sample was purified by repeated recrystallisation from methanol to afford colourless *crystals*, m.p. 227—230 °C (Found: C, 50.05; H, 4.05; N, 20.95. $C_{11}H_9ClN_4O \cdot H_2O$ requires C, 49.54; H, 4.16; N, 21.01%); $\nu_{max.}$ 3 310, 2 780, 1 620, 1 565, 1 400, and 1 000 cm^{-1}; $\lambda_{max.}$ 254 nm (log ε 4.49); δ_H[90 MHz; $(CD_3)_2SO$] 6.15 (2 H, br s, removed by D_2O, NH_2), 7.50 (4 H, s, C_6H_4Cl), 8.25, 8.70 (each 1 H, s, pyridazine-H), and 11.95 (1 H, s, removed by D_2O, NOH); *m/z* (f.a.b.) 249, 251 [(M^+ + 1), 100, 35%].

Thermal Conversion of the Oxime (**10**) *into the Isoxazole* (**11**).—The crude oxime (**10**) (130 mg, 0.5 mmol) was heated *in*

vacuo (10^{-2} mbar) to 150 °C for 2 h. The pure product (**11**) was obtained directly by sublimation (83 mg, 72%).

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