1-Phenylpyridazino[4,5-*d*]pyridazine

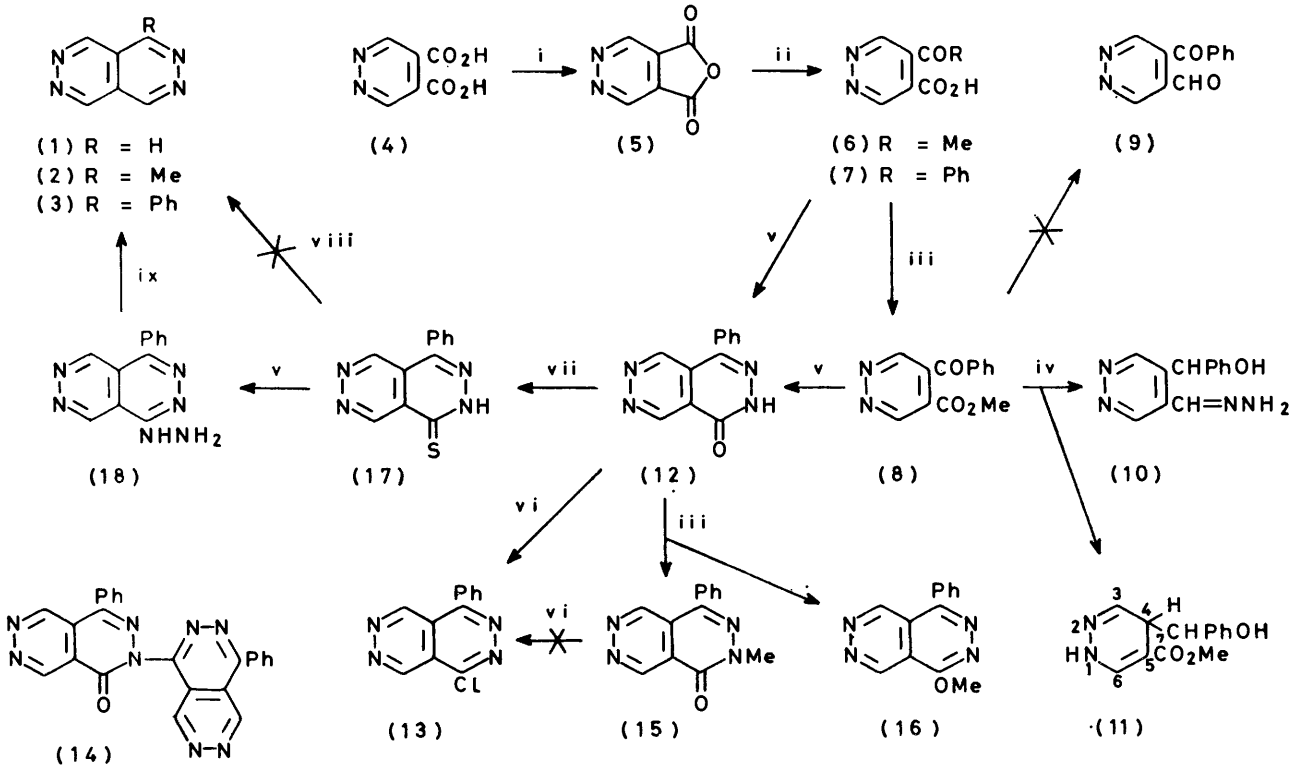
By **Stefano Chimichi** and **Rodolfo Nesi,*** Centro di studio del C.N.R. sulla chimica e la struttura dei composti eterociclici e loro applicazioni, presso l'Istituto di Chimica Organica dell'Università, Firenze, Italy

Treatment of pyridazine-4,5-dicarboxylic anhydride (5) with benzene and aluminium chloride gave 4-benzoylpyridazine-5-carboxylic acid (7) which was converted into its methyl ester (8) by methylation with diazomethane. When the latter was allowed to react with sodium bis-(2-methoxyethoxy)aluminium hydride and hydrazine, the phenyl derivative (3) was not obtained but a hydrazone (10) and a methyl ester (11), whose structures were deducted from spectroscopic data, were isolated. 1-Hydroxy-4-phenylpyridazino[4,5-*d*]pyridazine (12), prepared both from (7) and (8), afforded a chloro-derivative (13) and a thione (17) by reaction with $POCl_3$ and P_2S_5, respectively. Compound (17) reacted smoothly with hydrazine to yield a hydrazino-derivative (18) which was easily transformed into 1-phenylpyridazino[4,5-*d*]pyridazine (3) by treatment with yellow mercuric oxide.

ALTHOUGH in the decade after the synthesis of the parent compound (1) [1] over sixty derivatives have been reported,[2-4] no monoalkyl- or monoaryl-pyridazino-[4,5-*d*]pyridazines have been synthesised. We now describe the preparation of 1-phenylpyridazino[4,5-*d*]-pyridazine (3) from pyridazine-4,5-dicarboxylic anhydride (5), which we recently obtained in high yield by dehydration of the corresponding acid (4) with dicyclohexylcarbodi-imide in anhydrous tetrahydrofuran at room temperature.[5]

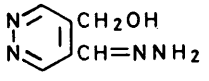
Several attempts to convert compound (5) into the keto-acid (6), a key intermediate for the synthesis of the methyl derivative (2), by treatment with malonic acid [6] or organocadmium compounds [7] were until now unsuccessful. On the contrary, the anhydride (5) reacted smoothly with anhydrous benzene and aluminium chloride to give 4-benzoylpyridazine-5-carboxylic acid (7) which was transformed into the ester (8) by methylation with diazomethane. Attempts to reduce selectively the keto-ester (8) into the formyl derivative (9) failed. When the former was allowed to react with sodium bis-(2-methoxyethoxy)aluminium hydride at −70 °C and the reaction mixture treated with hydrazine, the phenyl derivative (3) was not obtained; instead we isolated the hydrazone (10) and the dihydropyridazine (11), whose structures followed from spectral evidence.

The i.r. spectrum of (10) in carbon tetrachloride displays three bands at 3 620, 3 545, and 3 450 cm^{-1} for the OH and NH_2 groups, whereas the u.v. spectrum, with a maximum at 321 nm, was comparable with that of compound (19).[4e] The ^1H n.m.r. spectrum shows four single-proton doublets at δ 9.29, 9.18, 6.29, and 6.08 and



SCHEME i, Dicyclohexylcarbodi-imide; ii, benzene–$AlCl_3$; iii, CH_2N_2; iv, sodium bis-(2-methoxyethoxy)aluminium hydride–N_2H_4 at −70 °C; v, N_2H_4; vi, $POCl_3$; vii, P_2S_5; viii, Raney nickel; ix, HgO

three singlets at δ 7.92 (1 H), 7.83 (2 H), and 7.33 (5 H). These resonances, whose assignment (Table) was carried out on the basis of chemical shifts and deuterium exchange, were in full agreement with the proposed structure.



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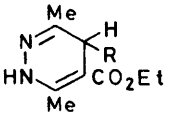
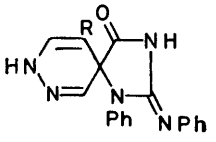


(20) R = CH_2OH
(21) R = CO_2Et



(22) R = CO_2Et

N.m.r. spectra (90 MHz; δ values; J in Hz; internal tetramethylsilane as reference)

Compound	Solvent	δ	Assignment
(3)	$CDCl_3$	7.62—7.96 (m)	Ph
		9.81 (d) } $J_{4.8}$ 0.7	4-H
		9.87 (d)	5-H
		9.91 (dd) $J_{5.8}$ 1.7	8-H
(7)	$(CD_3)_2SO$	7.43—7.87 (m)	Ph and NH
		9.54 (d) } $J_{3.6}$ 1	3-, 6-H
		9.68 (d)	
(8)	$CDCl_3$	3.76 (s)	Me
		7.4—7.8 (m)	Ph
		9.31 (d) } $J_{3.6}$ 1.2	3-, 6-H
		9.72 (d)	
(10)	$(CD_3)_2SO$	6.08 (d) [a] } J 4.5	C*H*–OH
		6.29 (d) [b]	OH
		7.33 (s)	Ph
		7.83br (s) [b]	NH_2
		7.92 (s)	C*H*=NNH_2
		9.18 (d) } $J_{3.6}$ 1.1	3-, 6-H
		9.29 (d)	
(11)	$(CD_3)_2SO$	3.58 (s)	Me
		3.76 (dd) } $J_{3.4}$ 4	4-H
		4.52 (dd) [c] $J_{4.7}$ 5.3	7-H
		5.35 (d) [b] $J_{7.OH}$ 4	OH
		6.68 (d) $J_{1.6}$ 4.2	3-H
		7.12 (d)	6-H
		7.21 (m)	Ph
		9.65br (d) [b]	NH
(12)	$(CD_3)_2SO$	7.55—7.8 (m)	Ph
		9.52 (d) } $J_{5.8}$ 1.3	5-, 8-H
		9.91 (d)	
		13.3br (s) [b]	NH
(13)	$CDCl_3$	7.5—7.9 (m)	Ph
		9.83 (d) } $J_{5.8}$ 1	5-, 8-H
		10.0 (d)	
(15)	$CDCl_3$	3.96 (s)	NMe
		7.6 (s)	Ph
		9.6 (d) } $J_{5.8}$ 1.3	5-, 8-H
		10.1 (d)	
(16)	$CDCl_3$	4.41 (s)	OMe
		7.6 (s)	Ph
		9.78 (d) } $J_{5.8}$ 1.3	5-, 8-H
		9.96 (d)	
(17)	$(CD_3)_2SO$	7.5—7.86 (m)	Ph and NH
		9.51 (d) } $J_{5.8}$ 1.3	5-, 8-H
		10.14 (d)	

[a] Signal collapses to a singlet on deuteriation. [b] Signal disappears on deuteriation. [c] Signal collapses to a doublet on deuteriation.

The i.r. spectrum in carbon tetrachloride of compound (11), for which several tautomeric structures could be taken into consideration, exhibits two bands at 3 620 and 3 455 cm^{-1} for the OH and NH groups, and a strong band at 1 685 cm^{-1} attributable to a conjugated ester CO group. Apart from a hypsochromic effect for the absorption at lower wavelength due to the phenyl group, the u.v. spectrum, characterised by a maximum at 323 nm, closely resembles those of the 1,4-dihydropyridazines (20) [4e] and (21).[8]

Besides a singlet (3 H) and a structured signal (5 H) at δ 3.58 and 7.21 for the methyl and phenyl protons, the n.m.r. spectrum in $(CD_3)_2SO$ (Table) shows two doublets of doublets (1 H) at δ 3.76 and 4.52, three single-proton doublets at δ 5.35, 6.68, and 7.12 and a broad doublet (1 H) at δ 9.65 which were assigned to the H-4, H-7, OH, H-3, H-6, and NH protons respectively on the basis of chemical shifts, deuterium exchange, and double resonance experiments.

Whereas the resonance at δ 3.76 was comparable with that of the H-4 proton of compound (20),[4e] those at δ 6.68 and 7.12 were in good agreement with the chemical shifts of the dihydropyridazine ring protons of the heterospirane (22) [9] in the same solvent. Irradiation at δ 9.65 reduces the H-6 doublet to a singlet whereas irradiation at δ 5.35 causes the H-7 multiplet to turn into a doublet; the same results were also obtained when the resonance at δ 9.65 and 5.35 were removed by deuteriation. Finally the H-3 and H-4 signals change into a singlet and a doublet, respectively, by mutual irradiation.

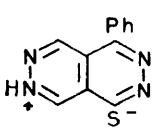
The keto-ester (8) cyclised with hydrazine in methanol to give 1-hydroxy-4-phenylpyridazino[4,5-*d*]pyridazine (12) which was also obtained by heating the acid (7) with the same reagent in water–butane-1,4-diol. The hydroxy-derivative (12) reacted smoothly with boiling phosphorus oxychloride but only a small amount of 1-chloro-4-phenylpyridazino[4,5-*d*]pyridazine (13) was isolated from the reaction mixture; the low yield of this intermediate was probably due to the formation of compound (14) by a side-reaction previously reported in the chlorination of pyridazine-,[10] phthalazine-,[11] and pyridazino-pyridazine derivatives.[4a,12] Since, on the basis of the chlorination of 6-methyl-1,6-naphthyridin-5(6*H*)-one.[13] the conversion of the *N*-methyl derivative (15) into (13) could represent an attractive alternative procedure, compound (12) was treated with diazomethane to give 2-methyl-4-phenylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one (15) as the main product with a small amount of the isomer (16).

Unfortunately, when compound (15) was heated with phosphorus oxychloride in a sealed tube at 160 °C for 3 h most of the starting material was recovered unchanged, whereas increasing the reaction time (to 16 h) caused much decomposition and afforded only tars. Treatment of compound (12) with phosphorus pentasulphide in boiling anhydrous pyridine gave 4-phenylpyridazino[4,5-*d*]pyridazin-1(2*H*)-thione (17) in quantitative yield.

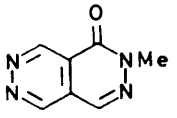
The i.r. spectrum of (12) exhibits a broad structured

band at 3 000—2 700 cm^{-1} for the NH group of the oxo-structure. The spectrum of (17) shows a different pattern between 3 000 and 1 800 cm^{-1} with two maxima at 2 700 and 1 850 cm^{-1}; such absorption, attributable to an NH^+ group, strongly suggested a zwitterionic structure in the solid state, probably of the type (17a).

Compound (17) did not afford the phenyl derivative (3) by reaction with Raney nickel at different temperatures, but it was converted into 1-hydrazino-4-phenylpyridazino[4,5-*d*]pyridazine (18) by refluxing with hydrazine hydrate in ethanol. The latter was then transformed in



(17a)



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good yield into 1-phenylpyridazino[4,5-*d*]pyridazine (3) by reaction with yellow mercuric oxide at room temperature. Compound (3) is a yellow solid, m.p. 192 °C, much more soluble than the parent compound (1) in most organic solvents. Its n.m.r. spectrum in $CDCl_3$ shows an AMX pattern (J_{AM} and $J_{AX} \neq 0$, J_{MX} 0 Hz) for the heteroaromatic ring protons; a doublet of doublets and two doublets are present at δ 9.91, 9.87, and 9.81 which were assigned to the H-8, H-5, and H-4 protons, respectively, on the basis of the greater deshielding effect of the phenyl group on H-8 and by comparison of the coupling constants (Table) with those of 2-methylpyridazino-[4,5-*d*]pyridazin-1(2*H*)-one (23).[4c]

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were measured for dispersions in potassium bromide with a Perkin-Elmer 457 spectrometer and u.v. spectra for solutions in methanol with a Cary 14 recording spectrophotometer. ^1H N.m.r. spectra were recorded with a Perkin-Elmer R 32 instrument; chemical shifts are reported in p.p.m. downfield from internal tetramethylsilane. Analytical t.l.c. and column chromatography were performed on silica gel plates (Merck F_{254}) and silica gel 60 (Merck; 230—400 mesh), respectively. Sodium bis-(2-methoxyethoxy)aluminium hydride (Red-Al) refers to a 63% solution in toluene (Ega Chemie) and light petroleum to the fraction of b.p. 30—50°. Extracts were dried over sodium sulphate and solvents were removed under reduced pressure.

4-Benzoylpyridazine-5-carboxylic Acid (7).—Aluminium chloride (3.71 g) was added portionwise at room temperature to pyridazine-4,5-dicarboxylic anhydride (5) (1.9 g) in anhydrous benzene (250 ml), and the mixture was stirred at 60—70 °C for 18 h. Ice-cold aqueous sodium carbonate (1M; 100 ml) was added and the solvent was removed to give a residue which was treated again with aqueous sodium carbonate (1M; 100 ml), boiled for 5 minutes, and filtered hot; acidification of the filtrate with concentrated hydrochloric acid (pH 1—2) precipitated the *acid* (7) (1.6 g), m.p. 218°, after two crystallisations from water. Concentration of the mother-liquors afforded a second crop (0.32 g, overall yield 66.5%) of the same product (Found: C, 63.0; H, 3.6; N, 12.3. $C_{12}H_8N_2O_3$ requires C, 63.2; H, 3.5; N, 12.3%); $\nu_{max.}$ 2 440br, 1 850br, 1 710, and 1 680 cm^{-1}; $\lambda_{max.}$ 251 nm (log ε 4.08).

Methyl 4-Benzoylpyridazine-5-carboxylate (8).—A suspension of compound (7) (1.35 g) in ether (100 ml) was treated with a slight excess of ethereal diazomethane and set aside overnight. Removal of the solvent gave the *ester* (8) (1.3 g, 90.7%) as a pale yellow solid, which was purified by column chromatography with ether–light petroleum (3 : 2 v/v) as eluant, m.p. 87—88 °C (Found: C, 64.3; H, 4.2; N, 11.8. $C_{13}H_{10}N_2O_3$ requires C, 64.5; H, 4.2; N, 11.6%); $\nu_{max.}$ 1 735 and 1 675 cm^{-1}; $\lambda_{max.}$ 252 nm (log ε 4.06).

Reaction of Compound (8) *with Sodium Bis-(2-methoxyethoxy)aluminium Hydride and Hydrazine.*—Sodium bis-(2-methoxyethoxy)aluminium hydride (1.45 ml) in anhydrous tetrahydrofuran (10 ml) was added dropwise under nitrogen to a stirred solution of the ester (8) (1.05 g) in the same solvent (30 ml) at −70 °C and stirring was continued at the same temperature for 4 h. The reaction mixture was then hydrolysed very slowly with aqueous acetic acid (1 : 1 v/v; 2 ml) in tetrahydrofuran (5 ml) and the suspension rapidly filtered through a sintered glass funnel into a flask containing hydrazine (95%; 0.45 ml) in methanol (20 ml) at −70 °C. The semi-solid material was washed with tetrahydrofuran (3 × 5 ml) and washings were collected in the same flask. The solution was then stirred at −70 °C under nitrogen for 1 h, allowed to rise to room temperature, and set aside overnight. The reaction mixture was filtered and the filtrate evaporated to dryness to give an oily orange residue which was kept in a vacuum desiccator (potassium hydroxide and sulphuric acid) for two days, treated with water (20 ml), and extracted with chloroform (3 × 50 ml). The chloroform extracts were concentrated (25 ml) and cooled to give *4-(phenylhydroxymethyl)pyridazine-5-carbaldehyde hydrazone* (10) (0.15 g) as a pale yellow solid, m.p. 161—163 °C (from ethyl acetate) (Found: C, 62.9; H, 5.4; N, 24.3. $C_{12}H_{12}N_4O$ requires C, 63.15; H, 5.3; N, 24.55%); $\lambda_{max.}$ 235sh and 321 nm (log ε 3.85 and 4.15).

Evaporation to dryness of the chloroform filtrate afforded a semi-solid residue which was purified by column chromatography with ether as eluant to yield *methyl 1,4-dihydro-4-(phenylhydroxymethyl)pyridazine-5-carboxylate* (11) (0.2 g), m.p. 151—152 °C (from ether) (Found: C, 63.2; H, 5.8; N, 11.2. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.7; N, 11.4%); $\lambda_{max.}$ 220sh and 323 nm (log ε 3.86 and 3.6).

1-Hydroxy-4-phenylpyridazino[4,5-d]*pyridazine* (12).—(*a*) A solution of the ester (8) (0.8 g) and hydrazine (95%; 0.22 ml) in methanol (10 ml) was refluxed for 30 min. After cooling, the reaction mixture was filtered to give *compound* (12) (0.66 g), m.p. 270° (from methanol). Concentration of the filtrate afforded a further 0.04 g of (12) (94.5%) (Found: C, 64.0; H, 3.6; N, 25.0. $C_{12}H_8N_4O$ requires C, 64.3; H, 3.6; N, 25.0%); $\nu_{max.}$ 3 300—2 700br and 1 675 cm^{-1}; $\lambda_{max.}$ 225sh, 245sh, and 298 nm (log ε 4.08, 3.94, and 3.83).

(*b*) Hydrazine hydrate (98%; 0.12 ml) was added to a suspension of the keto-acid (7) (0.5 g) in water (10 ml) and the mixture was stirred at 95 °C until the solid was completely dissolved; butane-1,4-diol (15 ml) was added and the solution was heated at 150—160 °C for 1 h. Removal of water was facilitated by suspending a glass tube connected to a vacuum source about two inches above the surface of the solution. After being kept overnight in the

refrigerator the solid was filtered off, washed with water, and dried to give a product (0.32 g) identical (m.p. and i.r. spectrum) with material prepared by method (*a*). The mother-liquors were diluted with water (5 ml) and set aside to yield a second crop of the same product (0.06 g, overall yield 77.4%).

Methylation of Compound (12) *with Diazomethane*.—A suspension of compound (12) (0.5 g) in ether (40 ml) and methanol (5 ml) was treated with an excess of ethereal diazomethane and left overnight. Removal of the solvent afforded a yellow solid (0.52 g) which largely consisted of 2-*methyl*-4-*phenylpyridazino*[4,5-d]*pyridazin*-1(2H)-*one* (15) with a small amount (*ca.* 10%; t.l.c. and n.m.r. spectrum) of 1-*methoxy*-4-*phenylpyridazino*[4,5-d]*pyridazine* (16) which was removed by fractional sublimation at 85 °C and 0.02 mmHg. Compound (15) was obtained by increasing the temperature of the sublimation bath to 115—120 °C, m.p. 211 °C (after crystallisation from ethyl acetate) (Found: C, 65.3; H, 4.3; N, 23.3. $C_{13}H_{10}N_4O$ requires C, 65.5; H, 4.2; N, 23.5%); $\nu_{max.}$ 1 675 cm^{-1}; $\lambda_{max.}$ 235sh and 304 nm (log ε 4.02 and 3.87).

1-*Chloro*-4-*phenylpyridazino*[4,5-d]*pyridazine* (13).—Compound (12) (0.25 g) was added to freshly distilled phosphorus oxychloride (25 ml) heated at 100 °C, and the mixture was refluxed for 1 h. Removal of the solvent afforded a sticky brown residue which was treated with crushed ice, made weakly basic with a saturated solution of sodium carbonate, and extracted with ether (3 × 50 ml) as quickly as possible. The brown solid left after evaporation of the dried ethereal extracts was sublimed at 130 °C and 0.05 mmHg to yield the *chloro-derivative* (13) (0 08 g, 296.%), m.p. 169—170 °C (from ethyl acetate) (Found: C, 59.6; H, 3.0; N, 23.2; Cl, 14.3. $C_{12}H_7N_4Cl$ requires C, 59.4; H, 2.9; N, 23.1; Cl, 14.6%); $\nu_{max.}$ 1 500, 1 450, 1 380, 1 340, 1 280, 920, 780, and 710 cm^{-1}; $\lambda_{max.}$ 297 nm (log ε 4.02).

4-*Phenylpyridazino*[4,5-d]*pyridazine*-1(2H)-*thione* (17).—Phosphorus pentasulphide (0.35 g) was added to a solution of the hydroxy-derivative (12) (0.23 g) in anhydrous pyridine (15 ml) and the mixture refluxed with stirring for 1 h. The solid residue left after removal of the solvent was treated with water (25 ml), set side overnight, and filtered to give *compound* (17) (0.24 g, quantitative yield). A sample obtained by several crystallisations from ethyl acetate gradually decomposed at temperatures >260 °C (Found: C, 59.9; H, 3.5; N, 23.4; S, 13.2. $C_{12}H_8N_4S$ requires C, 60.0; H, 3.4; N, 23.3; S, 13.3%); $\lambda_{max.}$ 253, 265sh, and 370 nm (log ε 4.15, 4.08, and 4.09).

1-*Hydrazino*-4-*phenylpyridazino*[4,5-d]*pyridazine* (18).—A mixture of the thione (17) (0.3 g) and hydrazine hydrate (98%; 0.7 ml) in ethanol (5 ml) was refluxed until evolution of hydrogen sulphide ceased (*ca.* 2 h). After cooling, *compound* (18) was filtered off as a brown solid (0.29 g, 97.5%), m.p. 294—295 °C (from dimethyl sulphoxide) (Found: C, 60.5; H, 4.4; N, 35.1. $C_{12}H_{10}N_6$ requires C, 60.5; H, 4.2; N, 35.3%); $\nu_{max.}$ 3 380, 3 200, and 1 630 cm^{-1}; $\lambda_{max.}$ 270 and 355 nm (log ε 4.12 and 3.72).

1-*Phenylpyridazino*[4,5-d]*pyridazine* (3).—Yellow mercuric oxide (0.52 g) was added to a suspension of compound (18) (0.25 g) in aqueous ethanol (1 : 1 v/v; 8 ml) and the mixture was stirred at room temperature for 24 h. Removal of the solvent left a brown residue which was sublimed at 145° and 0.03 mmHg to give *compound* (3) (0.18 g, 82.4%), m.p. 192 °C (from benzene) (Found: C, 69.4; H, 4.05; N, 27.2. $C_{12}H_8N_4$ requires C, 69.2; H, 3.9; N, 26.9%); $\nu_{max.}$ 3 075, 3 060, 1 515, 1 450, 1 360, 1 270, 1 180, 920, 770, 760, 700, and 600 cm^{-1}; $\lambda_{max.}$ 284 nm (log ε 3.96).

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