Ring–Chain Isomerism of Some 4,5-Disubstituted Pyridazines involving Heterospiro-compounds

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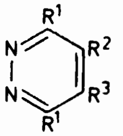
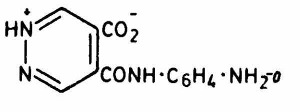
I.r., u.v., and ^1H n.m.r. spectral evidence demonstrated that 5-(*o*-aminophenylcarbamoyl)pyridazine-4-carboxylic acid (4), for which the zwitterionic structure (4a) appeared the most likely in the solid state, existed in dimethyl sulphoxide solution nearly exclusively as 3′,4′-dihydro-3′-oxospiro[pyridazine-5(2*H*), 2′(1′*H*)-quinoxaline]-4-carboxylic acid (18). The equilibrium (4a) $\rightleftharpoons$ (18) was strongly influenced by the nature of the solvent. A study of the behaviour of compounds (5)—(10) enabled us to establish that the spirocyclisation critically depends on both the nature of the substituents on the pyridazine ring and on the nucleophilicity of the group bonded to the phenyl ring.

THIS work arose from a previous study on the reactions of some pyridazine-4,5-dicarboxylic acid derivatives with *o*-phenylenediamine (OPD).

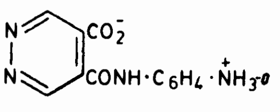
(1) $R^1 = H, R^2 = R^3 = CO_2Et$
(2) $R^1 = H, R^2 = R^3 = CO_2H$
(3) $R^1 = R^2 = H, R^3 = CO_2Et$
(4) $R^1 = H, R^2 = CO_2H, R^3 = CONH\cdot C_6H_4\cdot NH_2\text{-}o$
(5) $R^1 = Me, R^2 = CO_2H, R^3 = CONH\cdot C_6H_4\cdot NH_2\text{-}o$
(6) $R^1 = H, R^2 = CO_2Me, R^3 = CONH\cdot C_6H_4\cdot NH_2\text{-}o$



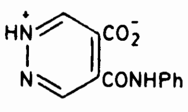
(7) $R^1 = R^2 = H, R^3 = CONH\cdot C_6H_4\cdot NH_2\text{-}o$
(8) $R^1 = Me, R^2 = H, R^3 = CONH\cdot C_6H_4\cdot NH_2\text{-}o$
(9) $R^1 = H, R^2 = CO_2H, R^3 = CONH\cdot C_6H_4\cdot OH\text{-}o$
(10) $R^1 = H, R^2 = CO_2Me, R^3 = CONH\cdot C_6H_4\cdot OH\text{-}o$
(11) $R^1 = H, R^2 = CO_2Me, R^3 = CONH\cdot C_6H_4\cdot OMe\text{-}o$



(4a)



(4b)



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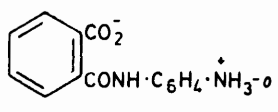

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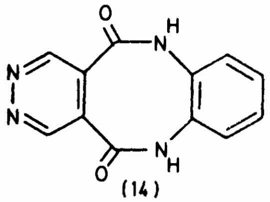

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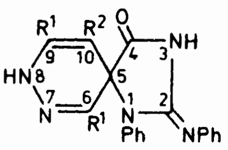
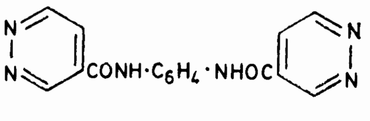


(15) $R^1 = H, R^2 = CO_2Et$
(16) $R^1 = Me, R^2 = CO_2Et$



(17)

6,11-Dihydropyridazino[4,5-*c*][1,6]benzodiazocine-5,12-dione (14), obtained by condensation of diethyl pyridazine-4,5-dicarboxylate (1) with OPD and sodium hydride, was converted into the acid (2) by treatment with boiling aqueous sodium hydroxide; however, when the hydrolysis was carried out under milder conditions, a product $C_{12}H_{10}N_4O_3$ was isolated which was formulated as 5-(*o*-aminophenylcarbamoyl)pyridazine-4-carboxylic acid (4).[1]

RESULTS AND DISCUSSION

The i.r. spectrum of (4) (Table 1), characterized by very broad absorptions with maxima at 3 000, 2 420, and 1 870 cm^{-1} (NH$^+$ or NH$_3^+$), and two bands at 1 525 and 1 315 cm^{-1}(CO$_2^-$), strongly suggested a zwitterionic structure in the solid state. Although even a comparison with the spectra of compounds (12) and (13) [2] did not allow an unambiguous choice between forms (4a and b), the former appeared to account better for the behaviour of the amido-acid in solution (see below). Whereas the i.r. spectrum in dimethyl sulphoxide of the model compound (12), obtained from pyridazine-4,5-dicarboxylic anhydride and aniline, was strictly comparable with that measured in the solid state (Table 1), remarkable differences were observed when compound (4a) was dissolved in the same solvent. Under these conditions no absorption was detectable for NH$_2$ and NH$^+$ (or NH$_3^+$) groups; besides maxima at 3 250 and 3 190 cm^{-1} (NH) and a broad band in the range 3 100—2 400 cm^{-1}

(dimeric carboxylic OH), the spectrum now exhibits two nearly superimposed bands at *ca.* 1 680 cm^{-1} attributable to the stretching vibrations of amide and strongly conjugated acid CO groups. In the light of this behaviour it appeared reasonable to assume that the compound under investigation drastically changes on going from the solid state to the dimethyl sulphoxide solution; this hypothesis was corroborated by u.v. analysis. The spectrum of (4) in $(CH_3)_2SO$ (Figure 1a), with a strong maximum at 313 nm, shows a quite different pattern with respect to that of the amido-acid (12) in the same solvent (curve b); on the other hand, apart from some differences in intensity, it resembles that of the heterospiro-compound (15) (curve c), recently obtained by condensation of the ester (1) with 1,3-diphenylguanidine and sodium hydride.[3] These results clearly ruled out a pyridazine structure and suggested the presence in the molecule of a dihydropyridazine moiety with NH–C=C–CO_2H conjugation. The spectral data reported above could be rationalised on the basis of the conversion of compound (4a) into the isomeric heterospiro-compound (18) through intramolecular nucleophilic attack of the aromatic NH_2 group at position 5 of the pyridazine ring. This ring closure, favoured by the presence of a strong electron-withdrawing NH$^+$ group at position 2, agreed well with our previous results on the spirocyclisation reactions of some pyridazine derivatives with 1,3-binucleophiles.[3]

TABLE 1

Characteristic i.r. absorption frequencies

Compound	Mode	
(4a)	KBr	3 380, 3 320, 3 180br, 3 000br, 2 820br, 2 700—2 100vbr, 2 100—1 700vbr, 1 665, 1 525, 1 315
(4a) $\longrightarrow$ (18)	$(CH_3)_2SO$	3 250, 3 190, 3 100—2 400vbr, 1 680, 1 675
(5a)	KBr	3 450, 3 345, 3 230, 2 700—2 300vbr, 2 250—1 850vbr, 1 675, 1 600, 1 405
(5a) $\rightleftarrows$ (19)	$(CH_3)_2SO$	3 220br, 3 150—2 400vbr, 2 000—1 750vbr,[a] 1 680
(6)	KBr	3 380, 3 210br, 3 100—2 750br, 1 740, 1 675
(6) $\longrightarrow$ (21)	$(CH_3)_2SO$	3 250, 3 190, 3 080, 2 980, 1 680
(7)	KBr	3 310, 3 160br, 3 100—2 700vbr, 1 660
	$(CH_3)_2SO$	3 350, 3 220, 3 100—2 750vbr, 1 670
(9)	KBr	3 400, 3 140br, 2 700—2 150vbr, 2 050—1 700vbr, 1 655, 1 545, 1 320
	$(CH_3)_2SO$	3 400—2 700vbr, 2 700—2 100vbr, 2 050—1 750vbr, 1 720, 1 670, 1 540
(10)	KBr	3 420, 3 300—2 600vbr, 1 740, 1 720, 1 670, 1 640
(11)	KBr	3 250br, 1 735, 1 670, 1 640
(12)	KBr	3 300, 2 820, 2 700—2 100vbr, 2 100—1 700vbr, 1 670, 1 650, 1 555, 1 320
	$(CH_3)_2SO$	3 300—2 700vbr, 2 650—2 150vbr, 2 100—1 700vbr, 1 675, 1 550
(13)	KBr	3 390, 3 250br, 3 000—2 700vbr, 2 700—2 150vbr, 2 100—1 750vbr, 1 655, 1 635, 1 530, 1 310
(17)	KBr	3 280br, 1 670, 1 650

[a] This band, attributable to the NH$^+$ group of the zwitterionic structure (5a), could only be detected with a concentrated solution.

The equilibrium (4a) $\rightleftarrows$ (18) was much influenced by the nature of the solvent; the heterospiro-structure still predominates in methanol solution, as could be deduced from the u.v. maximum at 308 nm (Figure 1d), whereas the absence of a sharp absorption above 300 nm for the curve e indicated the prevalence of the form (4a) or (4) in water. Finally the equilibrium appeared almost completely shifted to the left in aqueous hydrochloric acid (curve f); under these conditions spirocyclisation was prevented by the presence of an NH_3^+ group whereas protonation of the nitrogen atom at position 1′ promoted the ring opening of form (18).

A careful study of the ^1H n.m.r. spectra fully confirmed the foregoing conclusions. Whilst the spectrum of compound (12) in $(CD_3)_2SO$ (Table 2) was characterized by two doublets at δ 9.57 and 9.61, only two very weak signals were hardly detectable in the same region for the pyridazine ring protons of the acid (4a) in the same solvent. On the contrary the resonances of the dihydropyridazine protons at positions 6 and 3, and the 2-NH group in structure (18) were easily recognized as a singlet at δ 6.74 and two mutually coupled doublets at δ 7.49 and 10.58, respectively, these chemical shifts being strictly comparable with those of the corresponding protons of the spiro-compound (15).[3]

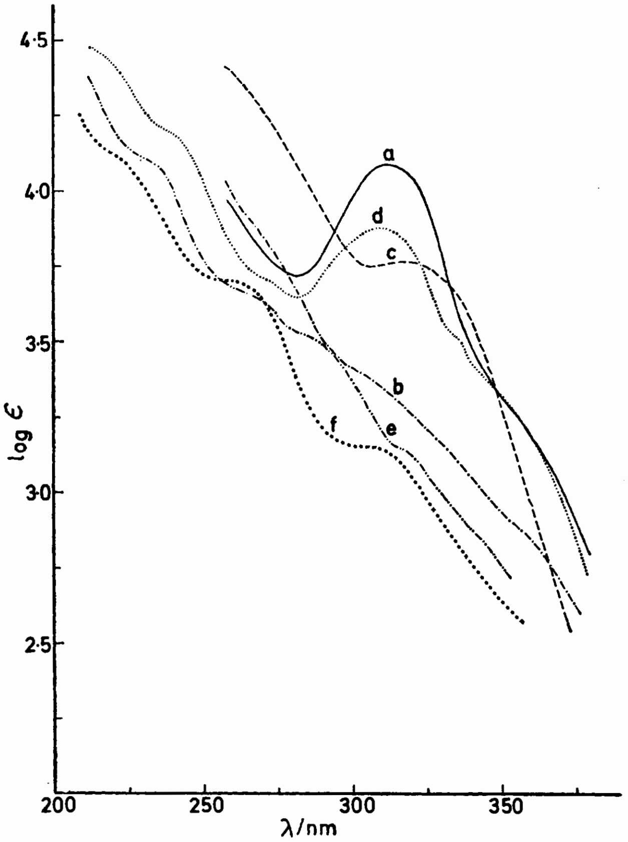


FIGURE 1 U.v. spectra of compounds (4) (a, dimethyl sulphoxide; d, methanol; e, water; and f, 0.1N aqueous hydrogen chloride), (12) and (15) (b and c, dimethyl sulphoxide)

Although the low solubility of compound (4a) hindered spectra being taken in CD_3OD and D_2O solutions, the results obtained by adding deuterium chloride to the $(CD_3)_2SO$ solution were in agreement with the u.v. data reported above. A catalytic amount of acid caused enhancement of two signals between δ 9.6 and 9.8 together with a reduction in the resonances due to structure (18), which completely disappeared on addition of 8—9 drops of DCl to the sample (Table 2).

After this type of isomerism, hitherto unknown in the chemistry of pyridazine derivatives, was firmly established, we resolved to study the behaviour of compounds (5)—(10) in order to ascertain the influence of both the nature of the substituents on the pyridazine system and of the nucleophilicity of the XH group bonded to the aromatic ring. For 3,6-dimethyl-5-(*o*-aminophenylcarbamoyl)pyridazine-4-carboxylic acid (5),[1] the i.r. data (Table 1) suggested a dipolar structure, probably of the type (5a), in the solid state; since, on the other hand, the i.r. and u.v. spectra in $(CH_3)_2SO$ (Table 1 and Figure 2a) closely resembled those of the form (18), we concluded that the spiro-structure (19) still predominates in this solvent. However the equilibrium (5a) $\rightleftharpoons$ (19) is now more sensitive to the solvent with a remarkable shift towards the open form on going from dimethyl sulphoxide to methanol (Figure 2b).

The n.m.r. spectrum (Table 2) was characterised by two singlets at δ 1.8 and 2.17, and a slightly broad signal of lower intensity at δ 2.71 which, on the basis of the chemical shifts of the methyl groups of compounds (16) [3] and (8),[1] were assigned to the 3- and 6-Me groups of the structures (19) (75—80%) and (5a) (20—25%), respectively.

The two signals at highest field vanished upon addition of a drop of DCl to the sample which gives rise, under

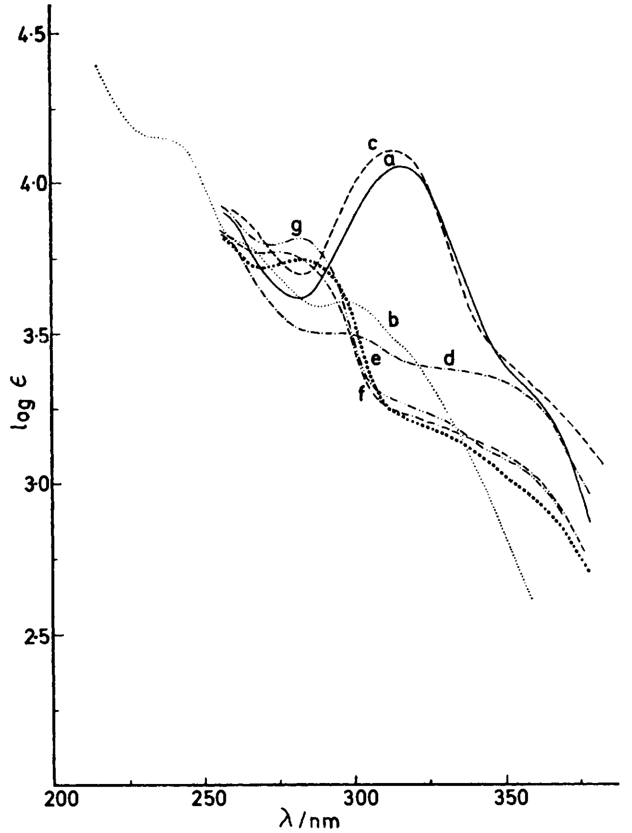
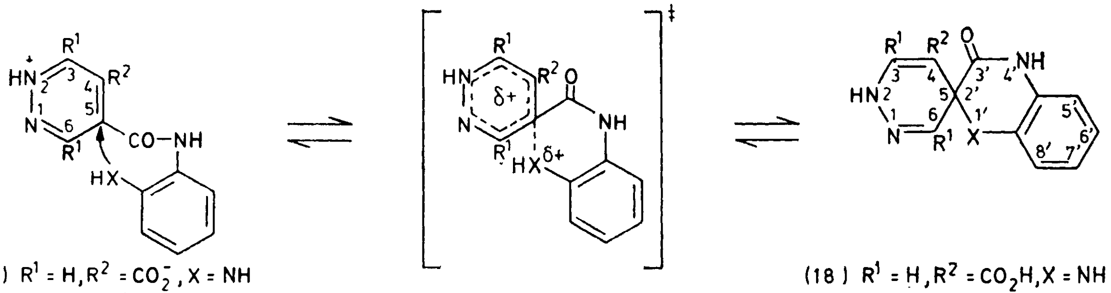
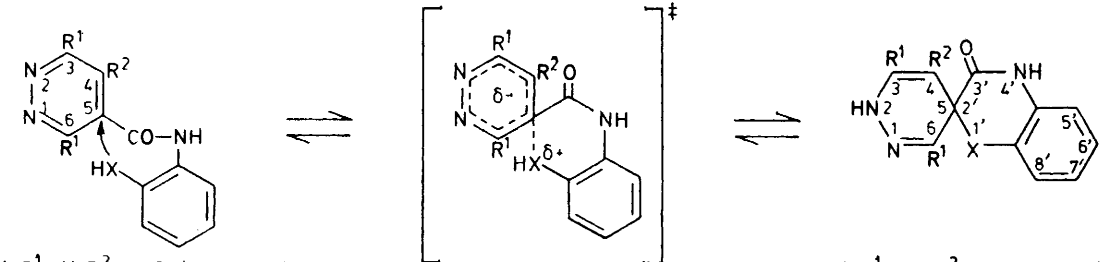


FIGURE 2 U.v. spectra of compounds (5) (a, dimethyl sulphoxide and b, methanol), (6), (7), and (9)—(11) (c—g, dimethyl sulphoxide)



(4a) $R^1 = H, R^2 = CO_2^-, X = NH$
(5a) $R^1 = Me, R^2 = CO_2^-, X = NH$
(9a) $R^1 = H, R^2 = CO_2^-, X = O$

(18) $R^1 = H, R^2 = CO_2H, X = NH$
(19) $R^1 = Me, R^2 = CO_2H, X = NH$
(20) $R^1 = H, R^2 = CO_2H, X = O$



(6) $R^1 = H, R^2 = CO_2Me, X = NH$
(7) $R^1 = R^2 = H, X = NH$
(10) $R^1 = H, R^2 = CO_2Me, X = O$

(21) $R^1 = H, R^2 = CO_2Me, X = NH$
(22) $R^1 = R^2 = H, X = NH$
(23) $R^1 = H, R^2 = CO_2Me, X = O$

these conditions, to a pattern containing only the resonances of the pyridazine form.

In accord with previous results on the condensation of esters (1) and (3) with 1,3-diphenylguanidine and sodium hydride,[3] the spirocyclisation reaction appeared not to be confined to pyridazine derivatives of the type (4a) and (5a) but was critically influenced by the presence of a strong electron-withdrawing group at position 4.

TABLE 2

^{1}H N.m.r. spectra (90 MHz; δ values, internal tetramethylsilane as reference)

Compound	Solvent	Chemical shift, coupling constant (J/Hz)		Assignment
(4a) $\longrightarrow$ (18)	$(CD_3)_2SO$	6.3—6.9(m)		ArH_4 and 1'-H
		6.74(s)		6-H
		7.49 (d) [a]	4	3-H
		10.27br(s) [b]		4'-H
		10.58br(d) [b]	4	2-H
(4a) $\longleftarrow$ (18)	$(CD_3)_2SO$ + DCl [c]	7.4—7.8(m)		ArH_4
		9.73(d) 9.91(d)	1	3-, 6-H
(5a) $\rightleftarrows$ (19)	$(CD_3)_2SO$ + D_2O [d]	1.8(s)		3-, 6-Me (19)
		2.17(s)		
		2.71br(s)		3-, 6-Me (5a)
		6.4—7.4(m)		ArH_4 (5a) and (19)
(5a) $\longleftarrow$ (19)	$(CD_3)_2SO$ + DCl [e]	2.82(s) 2.88(s)		3-, 6-Me
		7.4—7.8(m)		ArH_4
(6) $\longrightarrow$ (21)	$(CD_3)_2SO$	3.48(s)		CO_2Me
		6.4—6.85(m)		ArH_4 and 1′-H
		6.78(s)		6-H
		7.54(d) [a]	4.2	3-H
		10.35br(s) [b]		4'-H
		10.71br(d) [b]	4.2	2-H
(7)	$(CD_3)_2SO$	5.06br(s) [b]		NH_2
		6.5—7.3(m)		ArH_4
		8.16(dd)	$J_{3.5}$ 2.2	4-H
		9.48(dd)	$J_{5.6}$ 5.2	6-H
		9.71(dd)	$J_{3.6}$ 1.2	3-H
		10.06br(s) [b]		NH
(9a)	$(CD_3)_2SO$	6.25vbr(s) [b]		N^+H and OH
		6.7—7.15(m)		ArH_3
		7.93(m)		ArH_1
		9.49(d) 9.57(d)	1	3-, 6-H
		10.06br(s) [b]		NH
(10)	$CDCl_3$	3.92(s)		CO_2Me
		6.68—7.12(m)		ArH_3 and OH
		7.45(m)		ArH_1
		9.11br(s) [b]		NH
		9.36(d) 9.44(d)	1	3-, 6-H
(11)	$CDCl_3$	3.82(s)		OMe
		3.91(s)		CO_2Me
		6.8—7.2(m)		ArH_3
		8.35(m)		ArH_1
		8.55br(s) [b]		NH
		9.42(d) 9.52(d)	1	3-, 6-H
(12)	$(CD_3)_2SO$	7.0—7.8(m)		Ph and N^+H
		9.57(d) 9.61(d)	1	3-, 6-H
		10.68br(s) [b]		NH
(17)	$(CD_3)_2SO$	7.25—7.82(m)		ArH_4
		8.11(dd)	$J_{5.6}$ 5.4	5-H
		9.50(dd)	$J_{3.5}$ 2.5	6-H
		9.66(dd)	$J_{3.6}$ 1	3-H
		10.40br(s) [b]		NH

[a] Signal collapses to a singlet on deuteriation. [b] Signal disappears on deuteriation. [c] 8—9 Drops of 37% deuterium chloride in D_2O were added to the sample. [d] The pattern (chemical shifts and relative intensities) of the Me groups resonances did not change by addition of deuterium oxide (1—2 drops) to the sample. [e] A drop of 37% deuterium chloride in D_2O was added to the sample.

The frequency shift of the CO ester stretching vibration from the solid state (1 740 cm^{-1}) to the $(CH_3)_2SO$ solution (1 680 cm^{-1}) and the u.v. and n.m.r. spectra (Figure 2c, Table 2), strictly comparable with those of acid (4a), clearly indicated that the amido-ester (6), prepared from (4) and diazomethane, exists almost exclusively in dimethyl sulphoxide as methyl 3′,4′-dihydro-3′-oxo-spiro[pyridazine-5(2*H*),2′(1′*H*)-quinoxaline]-4-carboxylate (21). In marked contrast no spiro-structure of type (22) was detected when amide (7), obtained together with the pyridazine (17) by condensation of ester (3) with OPD and sodium hydride, was dissolved in the same solvent.

The u.v. spectrum (Figure 2d) shows a quite different pattern with respect to the one of compound (6) and the n.m.r. spectrum (Table 2) was characterized by a signal at δ 5.06 for the NH_2 group and an AMX system at lower field for the pyridazine ring protons.

Replacement of the NH_2 group bonded to the aromatic ring with the less nucleophilic OH drastically influenced the behaviour of compounds (9) and (10), recently synthesised in our laboratory.[4] Spectral evidence led us to conclude that the hydroxy-derivatives exist in solution too as the open forms (9a) and (10), respectively. In particular the i.r. spectrum of the acid (9), with characteristic absorptions for NH^+ and CO_2^-, exhibits only minor differences on going from the solid state to the $(CH_3)_2SO$ solution (Table 1), whereas the u.v. spectra of (9) and (10) were nearly identical with that of the methoxy-derivative (11) (Figure 2e—g); finally, as for compound (7), no resonance was detected in their n.m.r. spectra (Table 2) attributable to the dihydropyridazine protons of the heterospiro-structures (20) and (23).

EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 457 spectrometer for dispersions in potassium bromide and for solutions in dry dimethyl sulphoxide with a 0.1 mm CaF_2 cell, respectively. U.v. spectra were recorded with a Cary 14 recording spectrophotometer and ^{1}H n.m.r. spectra with a Perkin-Elmer R32 instrument; chemical shifts are reported in p.p.m. downfield from internal tetramethylsilane. Analytical t.l.c. was performed on silica gel plates (Merck F_{254}). Sodium hydride refers to an 80% dispersion in oil (Merck-Schuchardt).

5-(*Phenylcarbamoyl*)*pyridazine*-4-*carboxylic Acid* (12).—Dicyclohexylcarbodi-imide (1.25 g) was added to a suspension of finely ground pyridazine-4,5-dicarboxylic acid (2) (1 g) in anhydrous tetrahydrofuran (100 ml) and the mixture was stirred overnight at room temperature. After removal of dicyclohexylurea by filtration, the tetrahydrofuran solution was treated with aniline (0.61 g) and stirred for 1 h; the pale yellow solid which separated was filtered off and dried to yield the *acid* (12) (1.15 g, 88.5%), m.p. 199—201° (decomp.) (from water) (Found: C, 59.5; H, 3.8; N, 17.1. $C_{12}H_9N_3O_3$ requires C, 59.3; H, 3.7; N, 17.3%).

Methyl 5-(o-*Aminophenylcarbamoyl*)*pyridazine*-4-*carboxylate* (6).—A suspension of compound (4) (0.85 g) in ether (50 ml) was treated with an excess of ethereal diazomethane and set aside overnight. The mixture was filtered to give a pale yellow product (0.74 g) containing almost exclusively the *amido-ester* (6) (t.l.c. in chloroform–methanol 20 : 1 v/v); an analytical sample, obtained by dissolution at room temperature in dimethyl sulphoxide and immediate reprecipitation with water, melted at 162—163° (Found: C, 57.1; H, 4.4; N, 20.3. $C_{13}H_{12}N_4O_3$ requires C, 57.35; H, 4.4; N, 20.6%).

Reaction of Ethyl Pyridazine-4-*carboxylate* (3) *with OPD*.—OPD (0.71 g) and sodium hydride (0.2 g) were stirred in anhydrous tetrahydrofuran (20 ml) until evolution of hydrogen subsided; ester (3) (1 g) in the same solvent (10 ml) was added and the mixture was stirred at room temperature for 18 h. After removal of the solvent, the residue was treated with ice-cold water (25 ml) and neutralized with concentrated hydrochloric acid. The solid which separated was filtered off, dried, and washed with ether to give NN'-*bis*(*pyridazine*-4-*carbonyl*)-o-*phenylenediamine* (17) (0.35 g), m.p. 265° (decomp.) (from methanol) (Found: C, 60.15; H, 3.8; N, 26.2. $C_{16}H_{12}N_6O_2$ requires C, 60.0; H, 3.8; N, 26.2%).

The aqueous filtrate was extracted with methylene chloride (3 × 100 ml); evaporation of the dried extracts left a solid residue which was treated with ether and filtered to yield N-(o-*aminophenyl*)*pyridazine*-4-*carboxamide* (7) (0.3 g), m.p. 154—156° (from ethyl acetate) (Found: C, 61.9; H, 4.7; N, 25.9. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.15%).

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