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Potentially Tautomeric 1,2,3,4-Tetrahydro-1,4-dioxo-5*H*-pyridazino[4,5-*b*]indole

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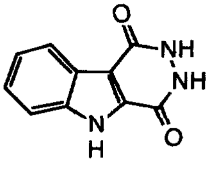
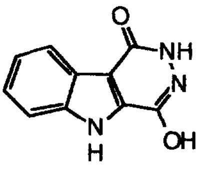
Abstract: The tautomeric 1,4-dioxygenated pyridazinoindole **1** exists in aqueous solution as a mixture of all four tautomeric forms **1a** - **1d**. The predominant tautomeric form is the 4-hydroxy-1-oxo compound **1b**. The relative abundance of the four forms **1a** $\rightleftharpoons$ **1b** $\rightleftharpoons$ **1c** $\rightleftharpoons$ **1d** at equilibrium is $10^{4.93}:10^{8.03}:10^{3.61}:1$.

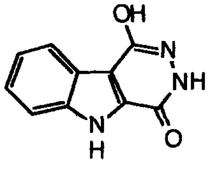
As part of our study of extended heterocyclic systems with potential DNA-intercalating properties[1] and in continuation of our studies of potentially tautomeric fused ring pyridazinones,[2,3] we have examined the tautomeric equilibrium position for 1,2,3,4-tetrahydro-1,4-dioxo-5*H*-pyridazino[4,5-*b*]indole **1**. Unlike the tautomeric pyridazin-3,6-dione system which has three possible tautomeric forms,[4] the 1,4-dioxygenated pyridazinoindole can exist not only in the dioxo form **1a** and the dihydroxy form **1d**, but there is also the possibility of two non-equivalent monohydroxy mono-oxo forms **1b** and **1c**. Potentially tautomeric systems arising from the mobility of the hydrogen atom at the 5-position are discounted, as molecular orbital calculations[5] suggest that the energies for such structures preclude them from contributing significantly to the tautomeric equilibrium. Equally, by comparison with the preferred equilibrium positions for the phthalazin-1-one system[6] and the 1- and 4-oxopyridazin[3,4-*b*]indoles,[3] zwitterionic structures are considered to have little or no importance in the tautomeric system **1**.



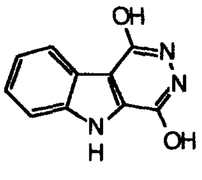
1a



1b



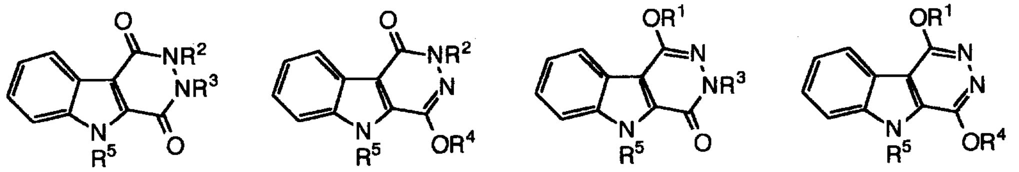
1c



1d

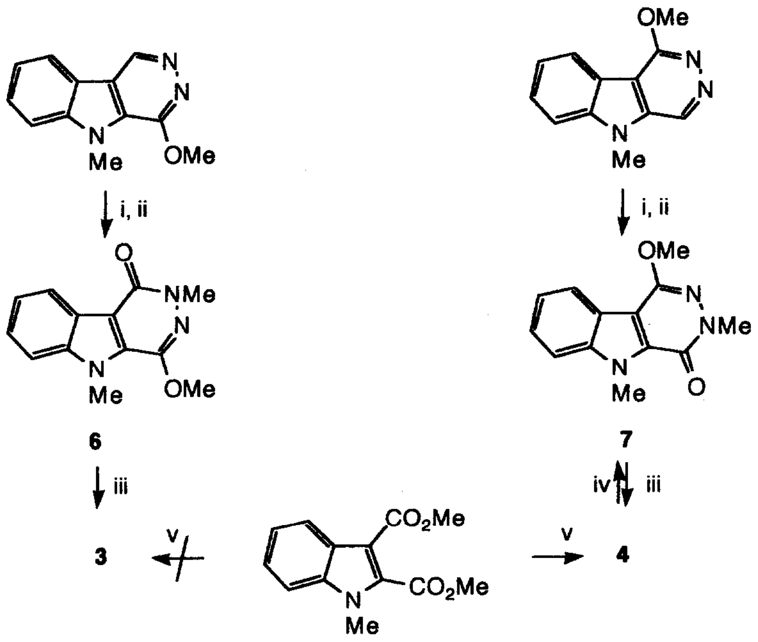
Although the tautomeric system **1** was known[7,8] at the start of this work, the synthesis of the potentially tautomeric systems **2** - **4** and the fixed-form model compounds **5** - **8** had not been described previously.

Dedicated to Professor Alan R. Katritzky, FRS on the occasion of his 65th birthday.



2a R^5 = Me, R^2, R^3 = H	**2b** R^5 = Me, R^2, R^4 = H	**2c** R^5 = Me, R^1, R^3 = H	**2d** R^5 = Me, R^1, R^4 = H
3a R^2, R^5 = Me, R^3 = H	**3b** R^2, R^5 = Me, R^4 = H		
4a R^3, R^5 = Me, R^2 = H		**4c** R^3, R^5 = Me, R^1 = H	
5 R^2, R^3, R^5 = Me	**6** R^2, R^4, R^5 = Me	**7** R^1, R^3, R^5 = Me	**8** R^1, R^4, R^5 = Me

The 5-methyl system **2** was readily prepared by a procedure analogous to that described for the preparation of the parent potentially tautomeric compound **1**, but the partially fixed-form systems **3** and **4** were most readily obtained by solvolysis of the corresponding methoxy derivatives **6** and **7**, which were prepared from the known 4- and 1-methoxy-5-methylpyridazino[3,4-*b*]indoles,[3] respectively, as shown in Scheme 1. It is noteworthy that the reaction of dimethyl 1-methylindole-2,3-dicarboxylate with methylhydrazine is regiospecific and produces 3,5-dimethylpyridazino[3,4-*b*]indole **4** to the complete exclusion of the 2,5-dimethyl isomer **3**. This observation reflects the greater susceptibility of the 2-methoxycarbonyl group to nucleophilic attack, compared with the 3-ester.



Scheme 1. (i) MeI in MeOH (ii) $K_3Fe(CN)_6$, KOH in dioxane (iii) HCl under reflux in MeOH (iv) Me_2SO_4, K_2CO_3 under reflux in acetone (v) $MeNHNH_2$ under reflux in propan-2-ol

The fixed dioxo system **5** was obtained from the reaction of 1,2-dimethylhydrazine with dimethyl 1-methylindole-2,3-dicarboxylate and the fixed dimethoxy system **8** was obtained from the 1,4-dichloro compound upon reaction with sodium methoxide. As was noted in the study of the mono-oxygenated pyridazino[3,4-*b*]indoles,[3] it was found to be impossible to synthesis by an analogous procedure the corresponding methoxy derivatives not possessing a methyl group at the 5-position. Attempts to prepare the non-N-methylated compound *via* the 5-benzyl derivative were also unsuccessful.[1c]

The fixed form structures **5** - **8** were uniquely characterised by their ^{1}H NMR spectral data. With the exception of compound **6** for which the signals for the 4-methoxy group and the 5-NMe group were coincident, all compounds have three distinct methyl group signals: the signal for the 5-NMe group appears at 4.09 ± 0.09 ppm; the 2-NMe and the 3-NMe groups give rise to signals at *ca.* 3.75 and *ca.* 3.73 ppm, respectively, and the methoxy groups at the 1- and 4-positions produce signals at *ca.* 4.25 and *ca.* 4.15 ppm, respectively.

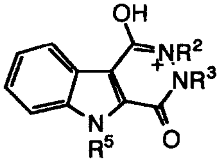
It is extremely difficult to draw any unambiguous conclusions from the electronic spectra of the neutral tautomeric system **1** and the fixed forms **5** - **8** (Table 1). The tautomeric systems **1** and **2** have closely similar spectra with only two major absorption bands and compound **3**, which can only exist as the monohydroxy mono-oxo or dioxo system, also has two major absorption bands, but the longer wavelength band has shifted bathochromically 10 nm relative to those for compounds **1** and **2**. This shift could reflect the difference in the composition of tautomeric equilibrium mixture or could arise from the electronic effect of the 2-methyl group (*cf.* an analogous absorption at 306 and 316 nm for the two corresponding 1-mono-oxygenated systems[3]). The spectral data for **1** - **3** are also similar to those for the neutral fixed dioxo system **5**, but differ from the spectra of the neutral forms of the other fixed forms systems **6** - **8**, all of which have four distinct absorption bands and show long wavelength absorption above 320 nm, which again could result from N-and O-methylation.

Table 1. Electronic Spectra of Neutral Species

	λ (nm)	log ε	λ (nm)	log ε	λ (nm)	log ε	λ (nm)	log ε	pH
1a-d	224	4.70			300	3.92			7.0
2a-d	233	4.65			305	3.90			7.0
3a,b	231	4.69			315	3.89			7.0
5	231	4.69			315	4.12			7.0
6	231	3.93	284	2.96	310	2.96	324	2.96	9.1
7	235	4.73	300	4.03	308	4.09	322	4.03	7.0
8	230	4.69	292	3.96	317	3.97	331	3.88	7.0

Normally, it is possible to obtain a quantitative estimate of the tautomeric equilibrium position from a comparison of the pK_a values of the conjugate acids of the tautomeric system and the fixed-form model compounds. The potentially tautomeric systems **1** and **2** can give rise, however, to four monocationic species **9a** - **9c**, **9g** and **10a** - **10c**, **10g**, respectively, while three possible monocationic species can be derived from the potentially tautomeric systems **3** and **4** (i.e. **11a** - **11c**, and **12a**, **12b** and **12g**, respectively).

1a, 2a, 3a, 4a, 5 ⇌



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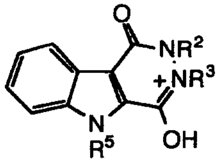
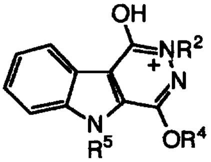


9a $R^2, R^3, R^5 = H$
10a $R^2, R^3 = H, R^5 = Me$
11a $R^2, R^5 = Me, R^3 = H$
12a $R^3, R^5 = Me, R^2 = H$
13a $R^2, R^3, R^5 = Me$

9b $R^2, R^3, R^5 = H$
10b $R^2, R^3 = H, R^5 = Me$
11b $R^2, R^5 = Me, R^3 = H$
12b $R^3, R^5 = Me, R^2 = H$
13b $R^2, R^3, R^5 = Me$

1b, 2b, 3b, 6 ⇌



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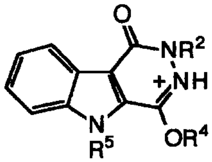
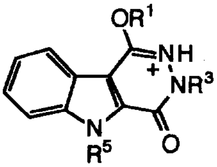


9c $R^2, R^4, R^5 = H$
10c $R^2, R^4 = H, R^5 = Me$
11c $R^2, R^5 = Me, R^4 = H$
14c $R^2, R^4, R^5 = Me$

9b $R^2, R^4, R^5 = H$
10b $R^2, R^4 = H, R^5 = Me$
11b $R^2, R^5 = Me, R^4 = H$
14d $R^2, R^4, R^5 = Me$

1c, 2c, 4c, 7 ⇌



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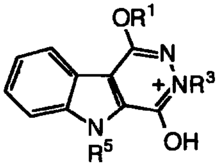
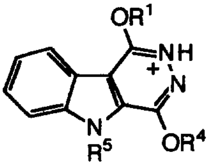


9a $R^1, R^3, R^5 = H$
10a $R^1, R^3 = H, R^5 = Me$
12a $R^3, R^5 = Me, R^1 = H$
15f $R^1, R^3, R^5 = Me$

9g $R^1, R^3, R^5 = H$
10g $R^1, R^3 = H, R^5 = Me$
12g $R^3, R^5 = Me, R^1 = H$
15g $R^1, R^3, R^5 = Me$

1d, 2d, 8 ⇌



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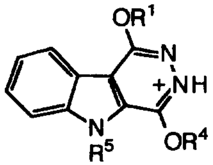


9c $R^1, R^4, R^5 = H$
10c $R^1, R^4 = H, R^5 = Me$
16h $R^1, R^4, R^5 = Me$

9g $R^1, R^4, R^5 = H$
10g $R^1, R^4 = H, R^5 = Me$
16i $R^1, R^4, R^5 = Me$

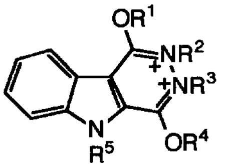
Similarly there is potential for the fixed-form compounds to each have two monocationic forms (**5** $\rightleftharpoons$ **13a** or **13b**, **6** $\rightleftharpoons$ **14c** or **14d**, **7** $\rightleftharpoons$ **15f** or **15g**, **8** $\rightleftharpoons$ **16h** or **16i**).

Table 2. Electronic Spectra of Monocationic Species

	λ (nm)	log ε	λ (nm)	log ε	λ (nm)	log ε	λ (nm)	log ε	λ (nm)	log ε	H_0^a
9a-c, g	214	4.39	238	4.45					312	3.95	-4.80
10a-c, g			245	4.55					311	3.98	-4.80
11a-c	214	4.51	244	4.65					314	4.23	-4.52
13a,b	218	4.49	247	4.68					320	4.29	-4.80
14c,d			237	3.68	248	3.73	301	3.11			+0.97
15f,g	222	4.43	252	4.60			306	4.01			-4.80
16h,i	219	4.46	242	4.63					312	4.17	-4.80

[a] acidity of solution used for measurement

The electronic spectra for the monocations **14c**, **d** and **15f**, **g**, derived from the two fixed-form monohydroxy mono-oxo compounds **6** and **7**, are similar to each other but differ from the spectra of the protonated forms **9a** - **c**, **g** and **10a** - **c**, **g** derived from the potentially tautomeric systems **1** and **2**, and also from the spectra of the monoprotonated dihydroxy and dioxo fixed form systems **13a**, **b** and **16h**, **i**, respectively (Table 2). These observations indicate that a monocation of common structure is not formed by the potentially tautomeric systems and the fixed form systems. Consequently, a direct measure of the tautomeric equilibrium constant between the four tautomeric forms of **1** cannot be obtained from the respective pK_a values of the conjugate acids of the fixed forms **5** - **8**. Recourse therefore has to be made to data obtained from further protonation of the monocationic species to produce a single dicationic salts having the common electronic structure **17**.



17a R^1, R^2, R^3, R^4, R^5 = H
17b R^5 = Me, R^1, R^2, R^3, R^4 = H
17c R^2, R^5 = Me, R^1, R^3, R^4 = H
17d R^2, R^3, R^5 = Me, R^1, R^4 = H
17e R^2, R^4, R^5 = Me, R^1, R^3 = H
17f R^1, R^3, R^5 = Me, R^2, R^4 = H
17g R^1, R^4, R^5 = Me, R^2, R^3 = H

Evidence for the commonalty of the diprotonated structures is provided by the electronic spectra (Table 3). The small variations in the positions of the maxima are consistent with the expected effects of N- and O-methylation.

Table 3. Electronic Spectra of Dicationic Species

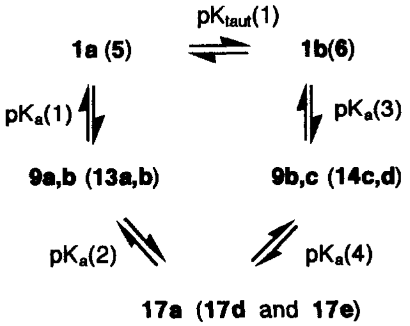
	λ (nm)	log ε	λ (nm)	log ε	λ (nm)	log ε	H_0[a]
17a	233	4.66	266	4.38	342	4.12	-8.8
17b	238	4.37	266	4.34	344	4.11	-8.8
17c	240	4.40	266	4.36	346	4.08	-8.8
17d	246	4.43	265	4.33	352	4.07	-8.8
17e	239	4.39	268	4.42	343	4.09	-8.8
17f	241	4.46	271	4.26	345	3.99	-8.8
17g	240	4.43	267	4.42	345	4.16	-8.8

[a] acidity of solution used for measurement

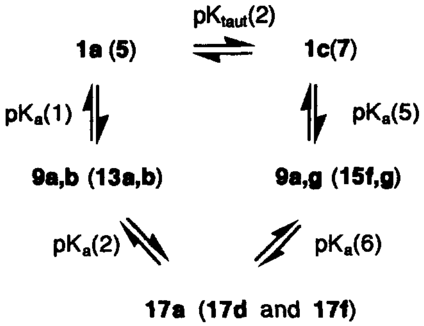
Table 4. pK_a Values of Monoprotonated and Diprotonated Forms of 4-Oxygenated Pyridazino[4,5-*b*]indoles

	Monoprotonation	Diprotonation
1a - d ⇌ 9a - c, g	-0.10 ± 0.03	
2a - d ⇌ 10a - c, g	0.00 ± 0.01	
3a - b ⇌ 11a - c	-1.60 ± 0.001	
5 ⇌ 13a,b ⇌ 17d	-2.31 ± 0.02	-2.61 ± 0.002
6 ⇌ 14c,d ⇌ 17e	2.06 ± 0.04	-2.05 ± 0.16
7 ⇌ 15f,g ⇌ 17f	-1.36 ± 0.01	-6.66 ± 0.001
8 ⇌ 16h,i ⇌ 17g	-0.83 ± 0.004	-2.77 ± 0.001

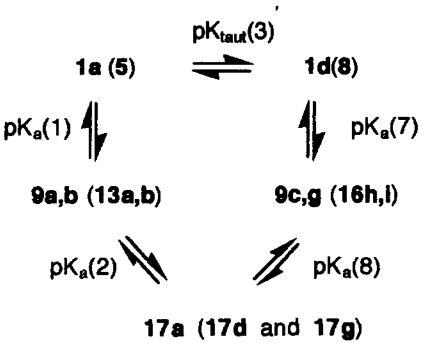
From the pK_a values (Table 4) for the mono- and di-protonation of **5** and **6** corresponding to the 1,4-dioxo and 4-hydroxy-1-oxo forms (Scheme 2), it is possible to estimate that the monohydroxy mono-oxo form **1b** is favoured over the dioxo form **1a** to the extent of $10^{3.10}$:1 [$pK_{taut}(1) = (pK_a1 + pK_a2) - (pK_a3 + pK_a4)$]. Similarly, from the pKa values for monoprotonation and diprotonation of **5** and **7**, the ratio of dioxo form **1a** to the 1-hydroxy-4-oxo form **1c** can be estimated to be $10^{1.30}$:1 [$pK_{taut}(2) = (pK_a1 + pK_a2) - (pK_a5 + pK_a6)$] (Scheme 3), and a comparison of the pKa values for mono- and di-protonation of **5** and **8** shows that dihydroxy form **1d** is the minor component of the equilibrium mixture and that it exists in equilibrium with the dioxo system **1a** to the extent of 1:$10^{4.93}$ [$pK_{taut}(3) = (pK_a1 + pK_a2) - (pK_a7 + pK_a8)$] (Scheme 4). Combining these data, it is apparent that the 4-hydroxy-1-oxopyridazino[4,5-*b*]indole is the predominant tautomeric system in the equilibrium mixture of **1** and that the ratio of **1a**:**1b**:**1c**:**1d** is $10^{4.93}$:$10^{8.03}$:$10^{3.63}$:1. The greater stability of the 4-hydroxy system **1b**, compared with the 1-hydroxy system **1c**, is consistent with the earlier observation[3] that 4-hydroxy-5*H*-pyridazino[4,5-*b*]indole exists to a greater extent in equilibrium with 3,4-dihydro-4-oxo-5*H*-pyridazino[4,5-*b*]indole than does the 1-hydroxy isomer in equilibrium with the 1-oxopyridazinoindole. These observations reflect the predictably greater conjugative stabilisation of the 1-oxo group by the indolic system, compared with the conjugative interaction of the indole ring with the 4-oxo group.



Scheme 2



Scheme 3



Scheme 4

EXPERIMENTAL

Electronic spectra of the neutral species, monocationic and dicationic species were measured for *ca.* 10^{-5}M solutions in an aqueous buffer at pH 7.0, and in sulphuric acid at H_0 values of *ca.* -2.8 and -8.8, respectively using a Pye Unicam SP8-200 spectrophotometer. The pK_a values for the conjugate acids of the pyridazinoindole derivatives were determined spectrophotometrically using buffered aqueous phosphate solutions or sulphuric acid solutions of known H_0. Infrared spectra were recorded for mulls in Nujol using a Perkin Elmer 295 spectrometer and ^{1}H NMR spectra at 60 and 90 MHz were measured for *ca.* 30% solutions in the solvents indicated using a JEOL PMX-60SI or EX-90Q spectrometer, respectively. All chemical shifts are expressed relative to Me_4Si.

Ethyl 3-cyano-1-methylindole-2-carboxylate: Ethyl 3-formyl-1-methylindole-2-carboxylate[9] (30 g, 0.13 mol) and hydroxylamine hydrochloride (11.72 g, 0.17 mol) in formic acid (100 ml) were refluxed for 30 min. and then allowed to cool to room temperature. The mixture was diluted with ice-water (500 g), neutralised with aqueous sodium hydroxide (5 %), and extracted with diethyl ether (3 x 250 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was crystallised from ethanol to give *ethyl 3-cyano-1-methylindole-2-carboxylate* (28 g, 94%), m.p. 128 - 129°C (Found: C, 68.0; H, 5.2; N, 12.2 $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%). δ_H ($CDCl_3$) 1.51 (t, 3H), 4.12 (s, 3H), 4.48 (q, 2H), 7.20 - 7.60 (m, 3H), 7.60 - 7.92 (m, 1H); ν_{max} 2210 and 1715 cm^{-1}.

1-Methylindole-2,3-dicarboxylic acid. Method A: A suspension of ethyl 3-cyano-1-methylindole-2-carboxylate (10.0 g, 43.6 mmol) in aqueous sodium hydroxide (10M, 75 ml) was heated under reflux for 7h. The solution was cooled to -5°C, diluted with crushed ice (300 g), and taken to pH 7.5 by the addition of hydrochloric acid (12M). The solution was extracted with ethyl acetate (3 x 150 ml) and the pH of the aqueous phase was adjusted to 2.0 by the addition of hydrochloric acid (2M) at 5°C. The precipitated product was collected and recrystallised from propan-2-ol to give 1-methylindole-2,3-dicarboxylic acid (5.0 g, 52%), m.p. 208°C (lit.,[10,11] 218°C, 208 - 209°C).

Method B: Dimethyl 1-methylindole-2,3-dicarboxylate[11,12] (2.0 g, 8.09 mmol) in ethanolic potassium hydroxide (0.5M, 100 ml) was heated under reflux for 2h. The mixture was cooled to 0°C and the precipitated potassium salt was collected and redissolved in water (20 ml). The solution was acidified to pH 2.0 with hydrochloric acid (5M). to give the dicarboxylic acid (1.6 g, 90%), m.p. 209°C.

1-Methylindole-2,3-dicarboxylic acid anhydride: 1-Methylindole-2,3-dicarboxylic acid (3.0 g, 1.37 mmol) in acetic anhydride (50 ml) was heated under reflux for 2h. The reaction mixture was cooled to yield the crystalline anhydride, which was recrystallised from acetic anhydride to give 1-methylindole-2,3-dicarboxylic acid anhydride (2.6 g, 94%), m.p. 208°C (lit.,[11] m.p. 209 - 212°C).

1,4-Dioxo-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole (**1**): Hydrazine hydrate (5.0 g, 0.1 mol) was added dropwise to dimethyl indole-2,3-dicarboxylate[12] (5.0 g, 21 mmol) in a minimal amount of refluxing ethanol and the reaction mixture was refluxed for 10h. The reaction mixture was cooled to room temperature and the precipitated product was collected and redissolved in warm aqueous ammonium hydroxide (10 %, 25 ml) at 60°C. The product was reprecipitated by the addition of hydrochloric acid (1 M) and was washed successively with hydrochloric acid, (1 M, 5 x 20 ml), water (5 x 20 ml), and warm ethanol (5 x 20 ml). Recrystallisation from aqueous DMF gave 1,4-dioxo-1,2,3,4-tetrahydro-*5H*-pyridazino[4,5-*b*]indole (3.0 g, 71%), m.p. >330°C (lit.,[7,8] m.p. 330°C, 360°C) (Found: C, 59.5; H, 3.5; N, 20.9 Calc. for $C_{10}H_7N_3O_2$ requires C, 59.7; H, 3.5; N, 20.9%). δ_H (DMSO-d_6) 7.30 - 7.90 (m, 3H), 8.15 - 8.30 (m, 1H), 10.45 (br s, 2H); ν_{max} 2600 - 3300, 1660 and 1630 cm^{-1}.

1,4-Dioxo-5-methyl-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole (**2**): Hydrazine hydrate (10.0 g, 0.2 mol) was added dropwise to dimethyl 1-methylindole-2,3-dicarboxylate[11,12] (3.0 g, 12.1 mmol) in refluxing propan-2-ol (50 ml) and the reaction mixture was refluxed for 10h. Concentrated hydrochloric acid (5 ml) was then added to the reaction mixture and the mixture was refluxed for a further 24 h. The reaction mixture was cooled to room temperature and the precipitated product was collected, washed successively with water (5 x 20 ml) and ethanol (5 x 20 ml). Recrystallisation from DMF gave *1,4-dioxo-5-methyl-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole* (2.1 g, 81%), m.p. >325 °C (Found: C, 61.2; H, 4.2; N, 19.5 $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%). δ_H (DMSO-d_6) 4.20 (s, 3H), 7.20 - 7.80 (m, 3H), 8.00 - 8.28 (m, 1H); ν_{max} 3170 (br), 1655 and 1625 cm^{-1}.

2,5-Dimethyl-1,4-dioxo-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole (**3**): 1,2-Dihydro-2,5-dimethyl-4-methoxy-1-oxo-*5H*-pyridazino[4,5-*b*]indole (0.15 g, 0.62 mmol) in concentrated hydrochloric acid (30 ml) and methanol (10 ml) was refluxed for 24h. Volatile material was removed under reduced pressure and water was added to the residue. The precipitated product was collected and recrystallised from aqueous ethanol to give *2,5-dimethyl-1,4-dioxo-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole* (0.09 g, 63 %), m.p. 305 - 307°C (Found: C, 62.9; H, 5.0; N, 17.5 $C_{12}H_{11}N_3O_2$ requires C, 62.9; H, 4.8; N, 18.3%). δ_H (CF_3CO_2H) 4.10 (s, 3H), 4.38 (s, 3H), 7.60 - 7.90 (m, 3H), 8.30 - 8.60 (m, 1H); ν_{max} 3300 - 3400, 1630 and 1615 cm^{-1}.

3,5-Dimethyl-1,4-dioxo-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole (**4**): 3,4-Dihydro-3,5-dimethyl-1-methoxy-4-oxo-*5H*-pyridazino[4,5-*b*]indole (0.15 g, 0.62 mmol) in concentrated hydrochloric acid (30 ml) and methanol (10 ml) was refluxed for 12h. The mixture was concentrated under reduced pressure and water was added to the residue. The precipitated product was collected and recrystallised from DMF-ethanol to give *3,5-dimethyl-1,4-dioxo-1,2,3,4-tetrahydro-5H-pyridazino[4,5-b]indole* (0.1 g, 70%), m.p. 305°C (decomp.) (Found: C, 62.9; H, 4.7; N, 18.3 $C_{12}H_{11}N_3O_2$ requires C, 62.9; H, 4.8; N, 18.3%). δ_H (CF_3CO_2H) 3.92 (s, 3H), 4.36 (s, 3H), 7.40 - 7.80 (m, 3H), 8.12 - 8.36 (m, 1H); ν_{max} 1640 and 1620 cm^{-1}.

1,4-Dioxo-1,2,3,4-tetrahydro-2,3,5-trimethyl-5H-pyridazino[4,5-b]indole (**5**): 1-Methylindole-2,3-dicarboxylic acid anhydride (1.0 g, 5.0 mmol), 1,2-dimethylhydrazine dihydrochloride (6.61 g, 49.7 mmol), and sodium acetate (8.15 g, 0.1 mol) in 2-ethoxyethanol-water mixture (1:1, 50 ml) were refluxed for 24 h. The reaction mixture was cooled to room temperature and the precipitated product was collected, washed with water (4 x 25 ml) and recrystallised from 2-ethoxyethanol-ethanol to give *1,4-dioxo-1,2,3,4-tetrahydro-2,3,5-trimethyl-5H-pyridazino[4,5-b]indole* (0.6 g, 50%), m.p. 222°C (Found: C, 64.3; H, 5.5; N, 17.3

$C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.4; N, 17.3%). δ_H ($CDCl_3$) 3.70 (s, 6H), 4.20 (s, 3H), 7.20 - 7.60 (m, 3H), 8.20 - 8.48 (m, 1H); ν_{max} 1640 cm^{-1}.

1,2-Dihydro-2,5-dimethyl-4-methoxy-1-oxo-5H-pyridazino[4,5-b]indole (**6**): 4-Methoxy-5-methyl-5*H*-pyridazino [4,5-*b*]indole[3] (0.6 g, 2.81 mmol) and iodomethane (0.8 g, 5.64 mmol) in methanol (50 ml) were refluxed for 1h. Volatile material was removed under reduced pressure and the residue was taken up in dioxane:water (1:1, 60 ml) containing potassium hydroxide (5.84 g, 0.104 mol) and potassium ferricyanide (2.32 g, 7.05 mmol). The mixture was heated under reflux for 5h and then cooled to room temperature and diluted with water (100 ml). The precipitated product was collected, washed with water (3 x 25 ml), and recrystallised from ethanol to give *1,2-dihydro-2,5-dimethyl-4-methoxy-1-oxo-5H-pyridazino[4,5-b]indole*, (0.35 g, 51%), m.p. 198°C (Found: C, 64.05; H, 5.4; N, 17.2 $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.4; N, 17.3%). δ_H ($CDCl_3$) 3.80 (s, 3H), 4.00 (s, 6H), 7.20 - 7.60 (m, 3H), 8.30 - 8.60 (m, 1H); ν_{max} 1640 and 1620 cm^{-1}.

3,4-Dihydro-3,5-dimethyl-1-methoxy-4-oxo-5H-pyridazino[4,5-b]indole (**7**).*Method A*: 1-Methoxy-5-methyl-5*H*--pyridazino[4,5-*b*]indole[3] (0.4 g, 1.876 mmol) and iodomethane (0.53 g, 3.73 mmol) in methanol (50 ml) were refluxed for 1h. Volatile material was removed under reduced pressure and the residue was taken up in dioxane:water (1:1, 60 ml) containing potassium hydroxide (3.89 g, 69 mmol) and potassium ferricyanide (1.54 g , 4.68 mmol). The mixture was heated under reflux for 5h and then cooled to room temperature and diluted with water (100 ml). The precipitated product was collected, washed with water (3 x 25 ml), and recrystallised from ethanol to give *3,4-dihydro-3,5-dimethyl-1-methoxy-4-oxo-5H-pyridazino[4,5-b]indole*, (0.4 g, 87.6%), m.p. 189 - 190°C (Found: C, 64.0; H, 5.4; N, 17.1 $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.4; N, 17.3%). δ_H ($CDCl_3$) 3.72 (s, 3H), 3.98 (s, 3H), 4.20 (s, 3H), 7.00 - 7.60 (m, 3H), 7.85-8.20 (dd, 1H); ν_{max} 1645 cm^{-1}.

Method B: 2,5-Dimethyl-1,4-dioxo-1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole (0.95 g, 4.14 mmol), anhydrous potassium carbonate (15.6 g, 61.2 mmol), and dimethyl sulphate (1.7 g, 13.5 mmol) in acetone (50 ml) was refluxed with stirring for 3h. An excess of aqueous ammonium hydroxide (10 %) was then added to the cooled reaction mixture and the acetone was removed under reduced pressure. Water (50 ml) was added to the residue and the aqueous mixture was extracted with dichloromethane (3 x 50 ml). The dried ($MgSO_4$) organic phase was evaporated under reduced pressure and the residue was crystallised from 2-ethoxyethanol to give 3,4-dihydro-3,5-dimethyl-1-methoxy-5*H*-pyridazino[4,5-*b*]indole, (0.9 g, 89%), m.p. 189 - 191°C. All spectral data were identical to those of the product obtained by method A.

1,4-Dichloro-5-methyl-5H-pyridazino[4,5-b]indole: 1,4-Dioxo-5-methyl-1,2,3,4-tetra-hydro-5*H*-pyridazino-[4,5-*b*]indole (2.0 g, 9.29 mmol) was suspended in phosphorus oxychloride and the mixture was refluxed for 6 h. The reaction mixture was cooled to room temperature and the precipitated product was collected, washed successively with water (5 x 20 ml), ethanol (5 x 50 ml), diethyl ether (5 x 50 ml), and recrystallised from DMF-ethanol to yield *1,4-dichloro-5-methyl-5H-pyridazino[4,5-b]indole* (1.8 g, 77%), m.p. 224 - 225°C (Found: C, 52.2; H, 2.6; N, 16.7; Cl, 27.8 $C_{11}H_7Cl_2N_3$ requires C, 52.4; H, 2.8; N, 16.7; Cl, 28.1%). δ_H (CF_3CO_2H) 4.64 (s, 3H), 7.80 - 8.20 (m, 3H), 8.56 - 8.80 (dd, 1H).

1,4-Dimethoxy-5-methyl-5H-pyridazino[4,5-b]indole (**8**). *Method A*: 1,4-Dichloro-5-methyl-5*H*-pyridazino[4,5-*b*]indole (1.0 g, 3.97 mmol) and sodium methoxide (4.0 g, 74 mmol) in methanol (100 ml) was heated under reflux for 5 days. The reaction mixture was cooled, filtered, and the solid was washed methanol (100 ml). The combined organic phases were evaporated under reduced pressure and water (100 ml) was added to the residue. The precipitated product was collected, washed with water (3 x 25 ml), and recrystallised from aqueous methanol to give *1-chloro-4-methoxy-5-methyl-5H-pyridazino[4,5-b]indole*, (0.6 g, 61%), m.p. 153 - 154°C (Found: C, 58.4; H, 4.1; N, 16.9; Cl, 14.3 $C_{12}H_{10}ClN_3O$ requires C, 58.2; H, 4.1; N, 17.0; Cl, 14.3%). δ_H ($CDCl_3$): 4.08 (s, 3H), 4.28 (s, 3H), 7.20 - 7.80 (m, 3H), 8.24 - 8.50 (m, 1H); ν_{max} 1620 cm^{-1}.

Method B: 1,4-Dichloro-5-methyl-5*H*-pyridazino[4,5-*b*]indole (1.0 g, 3.97 mmol) and sodium methoxide (4.0 g, 74 mmol) in methanol (100 ml) were heated under reflux for 10 days. The mixture was cooled to room temperature, filtered, and the solid was washed methanol (100 ml). The combined organic phases were evaporated and water (100 ml) was added to the residue. The precipitated product was collected, washed with water (3 x 25 ml), and the product was purified by column chromatography from silica gel, using ethyl acetate as the eluant, to give 1-chloro-4-methoxy-5-methyl-5*H*-pyridazino[4,5-*b*]indole (0.8 g, 81.6 %), which is identical with that obtained in Method A, and *1,4-dimethoxy-5-methyl-5H-pyridazino[4,5-b]indole*, (50 mg, 5.2%), recrystallised from ethanol-water, m.p. 178 - 179 °C (Found: C, 64.1; H, 5.4; N, 16.9 $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.4; N, 17.3%). δ_H ($CDCl_3$) 4.12 (s, 3H), 4.24 (s, 3H), 4.28 (s, 3H), 7.20 - 7.60 (m, 3H), 8.08 - 8.32 (m, 1H); ν_{max} 1620 cm^{-1}.

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