

Novel Synthesis Modes and Properties of  
[1,4]Benzodioxinopyridazines[1]  
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A simple synthesis involving fusion of catechol and derivatives with 3,4,5-trichloropyridazine has furnished 4-chloro[1,4]benzodioxino[2,3-*c*]pyridazines **5** for the first time. This new method complements the previously reported base promoted procedure for preparing 4-chloro[1,4]benzodioxino[2,3-*d*]pyridazines **3**. Employing both methods, 4-(trifluoromethyl)catechol was converted to the four regio isomers **3b,c** and **5c,d**. Structure assignment of these four was aided by the remarkably consistent influence of the pyridazine 4-chlorine substituent and diazo-linkage in inducing <sup>1</sup>H nmr downfield shifts of their nearest neighbor phenyl ring protons. Finally, contrary to what might be expected from previously reported results, reaction of methoxide with either **3** or **5**, gave chlorine substitution with formation of methoxybenzodioxinopyridazines **6** and **7** respectively. However, these reactions both give what appears to be an unprecedented rearrangement, with conversion of [2,3-*c*]pyridazine to [2,3-*d*]pyridazine, and *vice versa*.

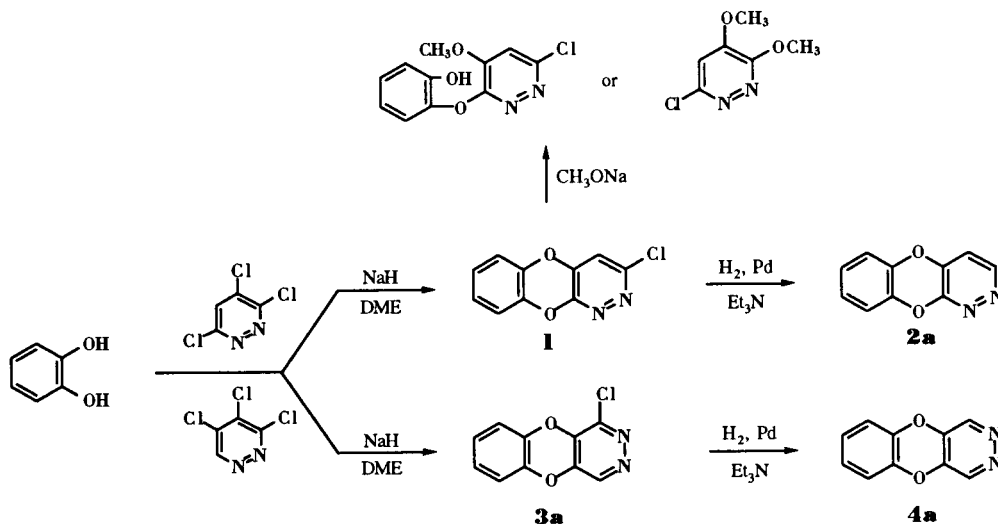
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There appears to be only one definitive reference to the reaction of trichloropyridazines with catechol [2]. These investigators reacted catechol with 3,4,6-trichloropyridazine under basic conditions (as the disodium salt, or the free phenol in the presence of potassium carbonate) to give 3-chloro[1,4]benzodioxino[2,3-*c*]pyridazine **1**. Structure proof was offered by catalytic hydrodechlorination to the parent heterocycle **2a**, where <sup>1</sup>H nmr clearly showed vicinal coupling of the lowest field proton (*i.e.* adjacent to the ring nitrogen). Similar reaction of 3,4,5-trichloropyridazine gave 1-chloro[1,4]benzodioxino[2,3-*d*]pyridazine **3a**, which could be hydrodechlorinated to **4a**, the latter characterized by an <sup>1</sup>H singlet of two identical, uncoupled lowest field protons. Further, these authors were able to replace the chlorine in **1** and **3a** only with strong amine nucleophiles such as *N*-

methylpiperazine; reaction of **1** with methoxide did not give chlorine replacement, but rather ring-opened compounds, the structure depending upon the reaction temperature. The authors did not comment however on the reaction of **3a** with alcohols. These results are summarized in Scheme I.

It is apparent from examining Scheme I that there is no reported method for preparing 4-substituted analogs possessing a fused[2,3-*c*]pyridazine system. Consequently it became of first concern to devise a route to 4-chloro[1,4]benzodioxino[2,3-*c*]pyridazine **5**. Examination of the literature [3] reveals that under most circumstances reactivity of the three halogens in 3,4,5-trichloropyridazine is of the order 4 = 5 > 3. There are exceptions to this, and also examples from studies in tetrafluoropyridazines that changes in conditions, particularly base *vs.* acid environments, can change the position of methanol attack [4,5]. It

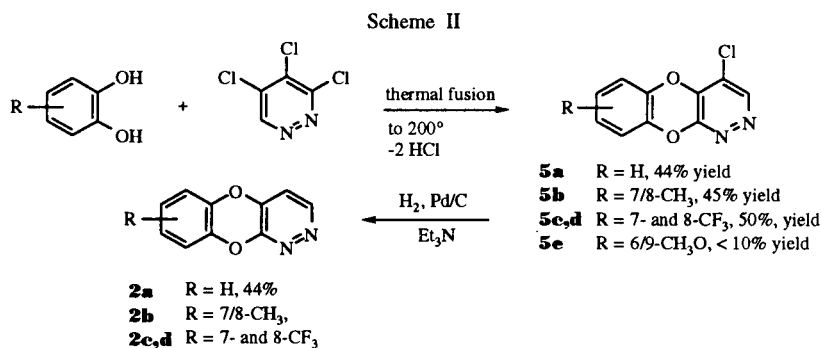
Scheme I



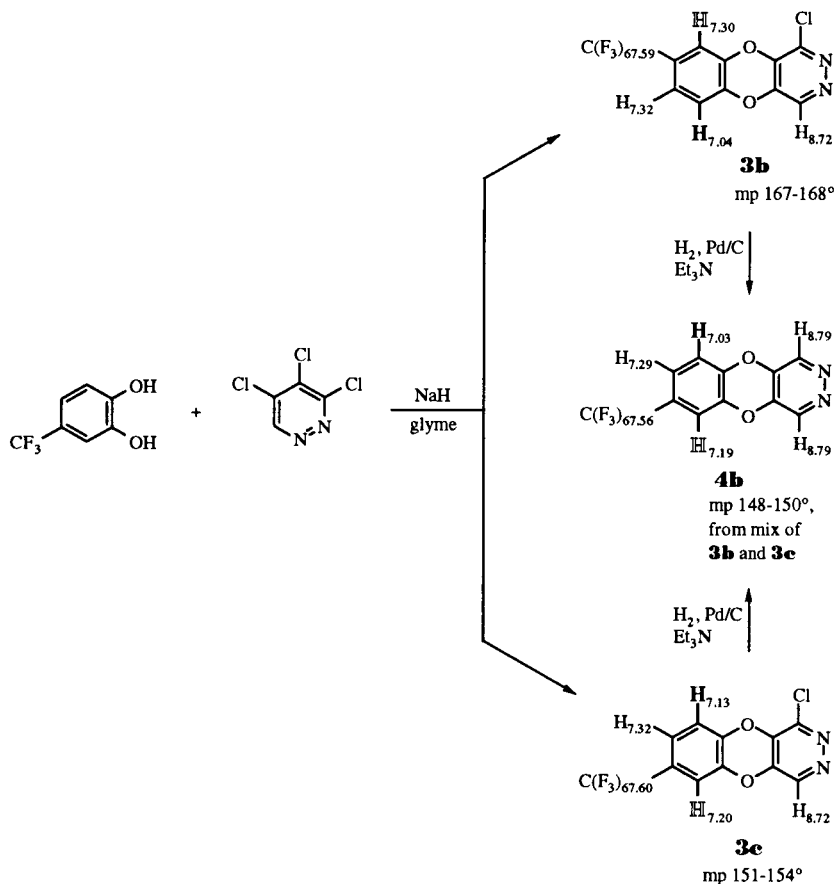
thus seemed reasonable to expect that reaction of catechol with 3,4,5-trichloropyridazine could be carried out by a simple thermal fusion reaction, since the first chlorine in this latter reagent is quite reactive. The high propensity to form a 6-membered dioxin ring might then provide the basis for reaction of the second chlorine. In this fashion a chloro[1,4]benzodioxinopyridazine could be formed, perhaps even including the [2,3-*c*]isomer from 3-chlorine participation.

Consequently these two reagents were fused together in equimolar amounts, allowing gaseous hydrogen chloride evolution as the temperature (oil bath) was

raised slowly from 120° to 200°. After cooling to room temperature weight loss from the contents amounted to nearly 2 equivalents of hydrogen chloride. Recrystallization of the crude or bulb-to-bulb distillation gave an acceptable yield of a single[2,3-*c*]isomer, **5a**. This material had different properties from **3a** and moreover, could be converted by hydrodechlorination to **2a**, identical with that from its previous source [2] (I, Scheme I). Moreover, <sup>13</sup>C nmr of **5a** clearly indicates an upfield (122 ppm) <sup>13</sup>C-Cl; the carbon holding the chlorine in **3a** would be expected to be further downfield because it is also adjacent to a ring nitrogen.



Scheme III



The fusion reaction appears to be general with 3,4,5-trichloropyridazine and certain catechols, since 4-methylcatechol, 4-(trifluoromethyl)catechol, and 3-methoxycatechol behave similarly, although the last gave a very poor yield (Scheme II). Although only the fused [2,3-*c*] as opposed to [2,3-*d*] isomer is formed, with *substituted* catechols mixtures of regional isomers arising from the position of the catechol substituent do arise.

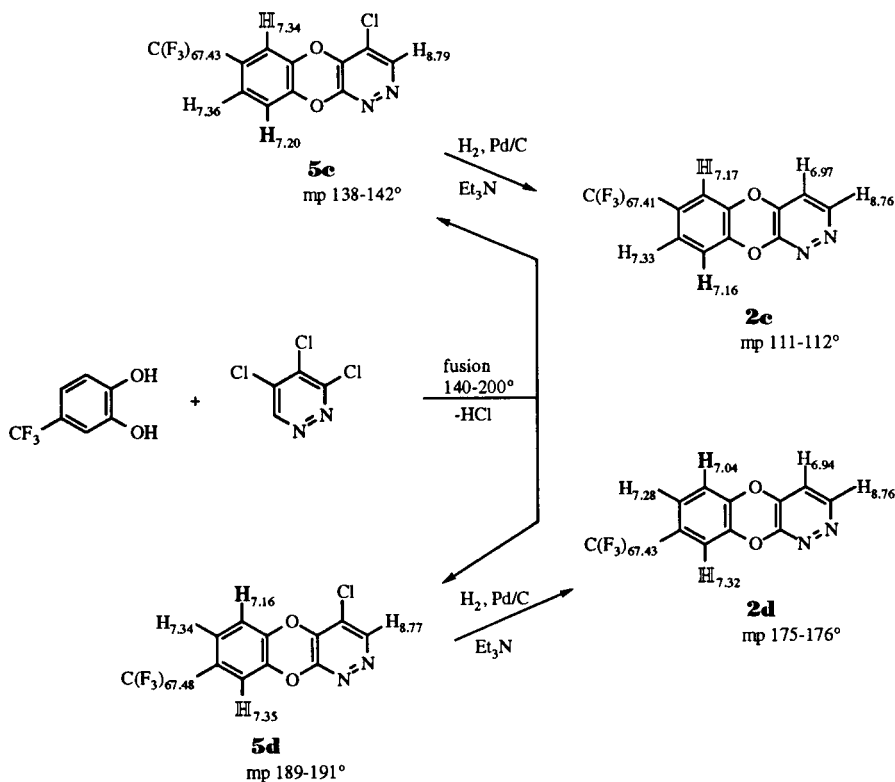
It became of interest to sort out the regional isomers of **3b,c** and **5e,d**, when 4-(trifluoromethyl)catechol was reacted with 3,4,5-trichloropyridazine under both base and thermal fusion conditions. The chemistry along with certain identifying physical constants for each of these isomeric materials and their hydrodechlorination products are shown in Schemes III and IV.

The two base generated regio isomers **3b** and **3c** shown in Scheme III are both converted to the *same* hydrodechlorinated product **4b**, clearly indicating both substrates to be of the [2,3-*d*] configuration. Coincidental chemical shifts are registered for the two pyridazine protons in **4b** at  $\delta$  8.79. In contrast as shown in Scheme IV, the two regio-isomers **5c** and **5d** arising from the fusion method are converted to *different* hydrodechlorination isomers **2c** and **2d** respectively. In the latter two products the two pyridazyl protons are vicinally coupled to each other, with only one proton at lower field the  $\delta$  8.0. These

results likewise clearly indicate that the four compounds in Scheme IV are of the [2,3-*c*] configuration.

Remaining then is to assign to each pair of chloro isomers the regio position of the CF<sub>3</sub> (*i.e.* 7- or 8-). Unfortunately, a full blown connectivity table with <sup>13</sup>C-<sup>13</sup>C and/or <sup>1</sup>H-<sup>13</sup>C coupling is obviated, or at least made unduly complicated by the intervening dioxo oxygens. Consequently, in lieu of more rigorous methods, regio CF<sub>3</sub> assignments were made on the basis of what was observed, as discussed below, to be a remarkably consistent pattern of <sup>1</sup>H chemical shifts. Fortunately, *within* each respective phenyl and pyridazine ring, the protons are easily assigned by chemical shifts, and *ortho/meta* coupling multiplicity (see Experimental for detailed descriptions of nmr including *J* values). Thus the pyridazine ring protons are furthest downfield when next to nitrogen, and where *ortho* coupled in the hydrodechlorinated products, possess identical *J* values. The ring protons in the phenyl ring are easily distinguishable also. The two *vicinal* protons show the usual *ortho* coupling value, while the *downfield* partner (next to trifluoromethyl) shows *meta* coupling to the proton on the other side of the trifluoromethyl moiety. This last proton displays only *meta* coupling. Thus all three phenyl protons are easily differentiated from each other and the pyridazine protons, permitting assignment of chemical shifts to each proton.

Scheme IV



The only dioxin in Schemes III and IV whose structure can be unequivocally assigned with respect to the CF<sub>3</sub> group is the (pyridazine) symmetrical **4b**. It is apparent that both the H and H type phenyl hydrogens in this material are at higher field (*i.e.*  $\delta$  7.03 and 7.19 respectively) than found for these particular nuclei in some of the other dioxins in Schemes III and IV. This observation suggested that there might be validity in assigning all the structures in these two Schemes such that the high field H and H always face a pyridazine hydrogen, while low field H and H would be assigned to those facing a deshielding nitrogen or chlorine. On this basis then similar groupings are shown in Table Ia, where the differences between low and high field H and H are consistently 0.09 ppm or greater. In contrast, assignment of the reverse CF<sub>3</sub> regio structure to each compound gives the *inconsistent* results shown in Table Ib, where there are *both* low and high field absorptions within each category of H and H. If there is a certain legitimacy to assigning structure on the basis of consistent substituent influence upon chemical shift, then the above case appears to be an interesting and perhaps novel application thereof. The basis for this consistent variance in chemical shift between chlorine and nitrogen *vs.* hydrogen is not clear. Perhaps the chlorine and nitrogen are too far distant to directly influence H and H, but exert their influence by reinforcing the deshielding of the more proximate oxygen.

As noted above, previous investigators [2] had not mentioned reaction of **3a** with methoxide while reporting that **1** gave only ring-opened products with this reagent. Having the compounds **3** and the new chloro types **5** in hand, it was therefore deemed appropriate to investigate the reaction of both with methoxide. Although the yield was something less than quantitative, replacement of chlorine by methoxide in **3a** and **5a,b** did indeed take place to produce cyclic products **6a** and **7a,b** respectively.

Inspection of the spectral data from these products however indicated that *direct* replacement of chlorine by methoxide did not take place from either starting chloro isomer, but rather rearrangement occurred, in effect converting [2,3-*c*] to [2,3-*d*] and similarly [2,3-*d*] to the [2,3-*c*] system (Scheme V). Suspicions concerning the course of the replacement reaction were aroused with examination of the *e.i.* ms of the products. Thus **7a** and **7b** displayed a strong  $m/z-1$  peak, while **6a** registered no such peak. Since it was highly unlikely that any of these compounds were *N*-substituted, the results indicated that the methoxy group in the first two compounds was *adjacent* to

nitrogen, as is generally known [6] for *alpha*-methoxy cyclic aza compounds.

Table Ia

 $\delta$  [a] H and H from Assigned Structures in Schemes III and IV

High field		Low Field			
	$\delta H < > H$		$\delta H < > Cl$	$\delta H < > N$	
<b>2d</b>	7.04	<b>3c</b>	7.13	<b>2c</b>	7.16
<b>3b</b>	7.04	<b>5d</b>	7.16	<b>5c</b>	7.20
<b>4b [b]</b>	7.03				
	$\delta H < > H$		$\delta H < > Cl$	$\delta H < > N$	
<b>2c</b>	7.17	<b>3b</b>	7.30	<b>2d</b>	7.32
<b>3c</b>	7.20	<b>5c</b>	7.34	<b>5d</b>	7.35
<b>4b</b>	7.19				

Table Ib

 $\delta$  H and H from Reverse Assignment of CF<sub>3</sub> Regio Isomers [c]

	$\delta H < > H$		$\delta H < > Cl$		$\delta H < > N$
<b>2c'</b>	7.16	<b>3b'</b>	7.04	<b>2d'</b>	7.04
<b>3c'</b>	7.13	<b>5c'</b>	7.20	<b>5d'</b>	7.16
<b>4b [b]</b>	7.03				
	$\delta H < > H$		$\delta H < > Cl$		$\delta H < > N$
<b>2d</b>	7.32	<b>3c'</b>	7.20	<b>2c'</b>	7.17
<b>3b'</b>	7.30	<b>5d'</b>	7.35	<b>5c'</b>	7.34
<b>4b</b>	7.19				

[a] Referenced internally to the proton in chloroform. [b] Note that **4b** is common to *both* Tables and structure assignments. [c] An illustrative example of the difference between the assigned structures as given in Schemes III and IV (Table Ia) and the reverse CF<sub>3</sub> (primed) materials referred to in Table Ib, is as follows: Material **3c** is converted to structure **3c'** by moving the CF<sub>3</sub> from the 7- to the 8-position, which in effect shifts H from the 9- to the 6-position, and H from the 6- to the 9-position. Thus **3c'** has the physical constants of **3c**, while assigned the structure of **3b**.

This prompted a detailed look at the <sup>13</sup>C and <sup>1</sup>H nmr. The "J scaled HETCOR" (version SUPHC2, see Table II and Experimental), a program designed to measure C-H coupling constants from two dimensional nmr was employed. This confirmed the rearranged structures of **6a** and **7a**. The interpretation relies in part on the usual observation that the magnitude of <sup>13</sup>C-<sup>1</sup>H coupling is generally: 1 bond > 3 bond > 2 bond > 4 bond [7]. Note also that the most downfield carbon in each compound is predictably attached to both a nitrogen and oxygen nuclei. In **7a** this C<sub>1</sub> is coupled to CH<sub>3</sub> and minimal (4 bond) coupling to ArH. In contrast the most downfield carbon in **6a** is C<sub>10a</sub>, which displays only minimal (4 bond) coupling to ArH. Finally, a single crystal X-ray determination completely confirmed the new inversion sequence for **7a** (see Experimental for data).

It is not clear why this rollover takes place, particularly from both directions. It may be under-

Scheme V

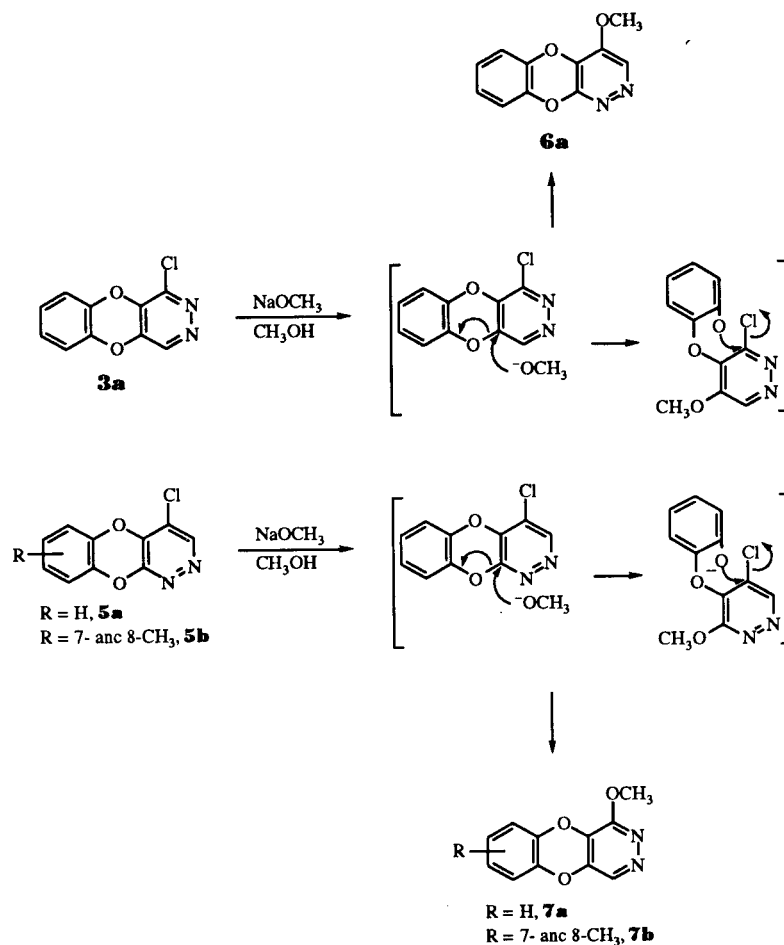
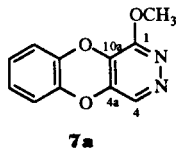
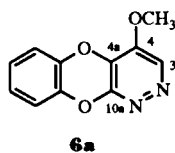


Table II

2 D HETCOR Derivation of <sup>13</sup>C-<sup>1</sup>H Coupling Constants [a]

Ring Carbon	δ(ppm)	J <sub>C-ArH</sub> (Hz)	J <sub>C-CH<sub>3</sub></sub> (Hz)	Ring Carbon	δ(ppm)	J <sub>C-ArH</sub> (Hz)	J <sub>C-CH<sub>3</sub></sub> (Hz)
3	139	182		1	157	1	3
4	145	4.2	4	4	140	187	
4a	131	6.4		4a	143	2.8	
10a	154	2.4		10a	132	5.5	

[a] Only nuclear carbons making up the pyridazine ring are shown.

standable when considering only **3a**. The position adjacent to the nitrogen (as in 3,4,5-trichloropyridazine) as alluded to earlier, is generally regarded as the least reactive, while the 4 and 5 positions have greater activity [3,8]. By reason of analogy therefore, it might be supposed that methoxide would prefer to open the

C<sub>4a</sub>-O bond in **3a** to initiate rearrangement, rather than direct replacement *via* the more inert C<sub>1</sub>-Cl bond. Attack of methoxide at the comparatively reactive C<sub>10a</sub>-O position in **3a** would in fact not be productive of any new fused ring system.

On the other hand, the chlorine in compounds **5a** and **5b** presumably would be more labile (being equivalent to the 4- or 5-chlorine in pyridazine), and therefore would precede bond breakage of the more inert C<sub>10a</sub>-O bond to give product without rearrangement. This does not happen, and in both the chloro [2,3-*c*] and [2,3-*d*] isomers reaction apparently is initiated at the C-O bond. Perhaps the driving force is formation of the catechololate anion. As observed in reaction of **1** with methoxide [2] only ring-opened products were found without initial elimination of chlorine. Apparently the two rearrangements depicted in Scheme V represent systems wherein there is still sufficient energy remaining at the catechololate anion stage to cause at least some ring closure to the (more stable?) inversion products observed (the yields of **7a**, **7b**, and **6a** are not quantitative, and ring-opened

Table III  
Atomic Coordinates and Equivalent Isotropic Displacement Coefficients of Material 7a [a]

Atom type [b]	Fractional Coordinates			Equivalent Isotropic Thermal Parameter [c], B
	10 <sup>4</sup> x	10 <sup>4</sup> y	10 <sup>4</sup> z	
O1	3007(2)	2451(7)	2500d	39(1)
O2	3431(2)	6558(7)	641(5)	43(1)
O3	1792(2)	1824(7)	2776(6)	39(1)
C1	1976(3)	3709(11)	1853(8)	35(2)
N2	1573(2)	5155(10)	1128(7)	39(1)
N3	1766(2)	7063(10)	236(8)	44(2)
C4	2381(3)	7493(10)	75(9)	37(2)
C5	2802(3)	6005(11)	855(8)	34(2)
C6	2615(2)	4050(11)	1721(8)	33(1)
C7	3628(2)	2865(10)	2180(7)	32(1)
C8	3832(2)	4842(12)	1317(7)	35(2)
C9	4459(2)	5207(12)	1027(8)	40(2)
C10	4873(3)	3520(120)	1645(9)	50(2)
C11	4663(2)	1488(12)	2508(9)	46(2)
C12	4047(2)	1188(10)	2812(9)	37(2)
C13	1151(2)	1249(12)	2720(10)	44(2)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms are labeled in agreement with Figure 1. [c]  $\text{Å} \times 10^3$ . This is one-third of the trace of the orthogonalized Bij tensor. [d] This coordinate was used to fix the origin of the unit cell along the c axis and is therefore listed without an estimated standard deviation.

Table IV  
Bond Lengths In Material 7a [a]

Type [b]	Length, Å	Type [b]	Length, Å
O1-C6	1.373(7)	C1-C6	1.399(7)
O1-C7	1.389(6)	C4-C5	1.376(8)
O2-C5	1.406(7)	C5-C6	1.345(9)
O2-O8	1.394(7)	C7-C8	1.364(8)
O3-C1	1.336(7)	C7-C12	1.391(8)
		C9-C10	1.383(9)
C1-N2	1.317(8)	C10-C11	1.394(9)
C4-N3	1.360(8)	C11-C12	1.364(7)
N2-N3	1.339(8)		

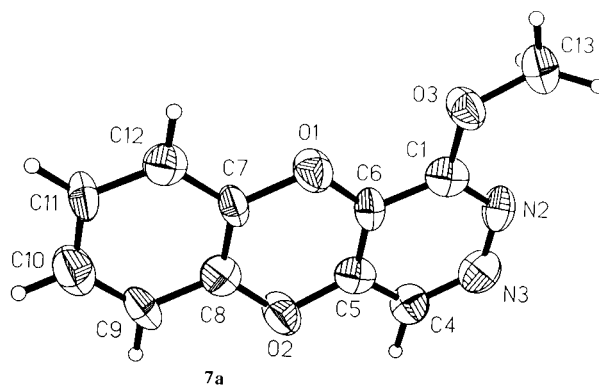
[a] The numbers in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms are labeled in agreement with Figure 1.

Table V  
Bond Angles In Material 7a [a]

Type [b]	Angle, degrees	Type [b]	Angle, degrees
O6-O1-C7	114.2(4)	C1-N2-N3	120.2(4)
C5-O2-C8	114.1(4)	N2-N3-C4	119.6(5)
C1-O3-C13	116.5(5)		
O3-C1-N2	121.1(5)	O1-C7-C8	122.5(5)
O3-C1-C6	116.2(5)	O1-C7-C12	117.1(5)
N2-C1-C6	122.7(5)	C8-C7-C12	120.3(5)
N3-C4-C5	120.1(6)	O2-C8-C9	116.4(5)
O2-C5-C4	117.2(5)	O2-C8-C9	116.4(5)
O2-C5-C6	121.9(5)	C7-C8-C9	121.0(5)
C4-C5-C6	120.8(5)	C8-C9-C10	118.3(6)
O1-C6-C1	119.3(5)	C9-C10-C11	120.5(5)
O1C6C5	124.3(5)	C10-C11-C12	120.3(6)
C1-C6-C5	116.4(5)	C7-C12-C11	119.4(6)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit. [b] Atoms are labeled in agreement with Figure 1.

Figure 1



products akin to those observed previously [2] are apparent from gcms).

The role of the catecholate anion however can be overwhelming. Thus, when benzodioxinopyridazines are derived from 4-(trifluoromethyl)catechol, such as **5c** and **5d**, all attempts to replace the chlorine while preserving a fused ring system failed. Presumably, the increased stability of the (trifluoromethyl)catecholate anion over those derived from methyl or unsubstituted catechol. Although leading to facile cleavage of the C-O bond, inhibits further reaction of this anion at the C-Cl bond.

## EXPERIMENTAL

Melting points were determined on a Haake Buchler apparatus and are uncorrected. The <sup>13</sup>C, <sup>1</sup>H, and <sup>19</sup>F nmr

spectra were recorded on an XL300 (300 MHz), XL360 (360 MHz), or XL400 (400 MHz) with instruments referenced internally. Mass spectra (ms) were measured by a direct probe *e.i.* isobutane chemical ionization (c.i.), and gcms. Parent molecular ion (*m/z*) is expressed in all cases as molecular weight. Liquid chromatography purification was achieved on a Rainin reverse phase, C-18 Prep lc with variable uv detector, or by Chromatotron™ (rotary tlc) on silica plates. Unless otherwise noted, boiling and sublimation points are recorded as oven temperatures during bulb-to-bulb (Kugelrohr) distillations. All microanalyses were performed by Atlantic Microlab Inc., P.O. Box 2288, Norcross, Georgia 30091.

#### 4-(Trifluoromethyl)-1,2-benzenediol.

Although the title compound is indexed there appears no description of its properties or preparation. 4-(Trifluoromethyl)-2-nitrophenol (Aldrich) (6 g, 29 mmoles) was dissolved in 60 ml of ethanol with 0.2 g 5% Pd/C, and hydrogenated on the Parr shaker. The reduction proceeded well to give after workup by filtration and solvent removal, 4.9 g of 4-(trifluoromethyl)-2-aminophenol. This material was converted to the title product by adapting a method from the literature for the preparation of 3,5-dihydroxybenzotrifluoride [9]. The 4.9 g aminophenol described above was dissolved in a mixture of 19 ml of water and 20 ml of concentrated sulfuric acid, and the solution cooled to 0° and treated with 1.9 g of sodium nitrite in 10 ml of water. After excess nitrous acid was destroyed with urea, the solution was added to a boiling saturated solution of copper sulfate in 250 ml of water, with care taken that nitrogen evolution did not lead to excessive foaming. The cooled solution was extracted with 4 x 100 ml of ether, and the combined extracts dried over magnesium sulfate. Upon evaporation of solvent the dark colored residue which showed only one gc peak was bulb-to-bulb distilled at 120° (1.5 mm) to give 2.3 g (45%), mp 26-28°. The residue weighed 0.2 g. The hygroscopic product is best safely stored in a plastic (Caution! not soft glass [10]) container sealed with parafilm in the refrigerator; <sup>1</sup>H nmr (deuteriochloroform): δ 5.64 and 5.77 (2s, 2H, 2 OH), 6.92 and 7.10 (2d [or AB q], 2H, 5- and 6-H), 7.11 (s, 1H, 3-H); <sup>19</sup>F nmr: δ -63.33; gcms: *m/z* = 178.

*Anal.* Calcd. for C<sub>7</sub>H<sub>5</sub>F<sub>3</sub>O<sub>2</sub>•0.3H<sub>2</sub>O: C, 45.81; H, 3.08. Found: C, 45.90; H, 3.19.

#### [1,4]Benzodioxino[2,3-*c*]pyridazine (2a).

Material 5a (0.77 g, 3.5 mmoles) was dissolved in ethyl acetate, 5% Pd/C added with 1 g of triethylamine, and the mixture hydrogenated on the Parr shaker. Upon filtration and vacuum evaporation of solvent the residue was triturated with water, and air dried to give 0.5 g (77%), with a portion recrystallized from ethyl acetate, mp 142-144° (lit [2] mp 137-138°); <sup>1</sup>H nmr (deuteriochloroform): δ 6.84 and 8.66 (2d, J = 5.3 Hz, 2 H, 4- and 3-H), 6.86-7.01 (m's 4 H, 6,7,8,9-H); gcms: *m/z* = 186.

*Anal.* Calcd. for C<sub>10</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.40; H, 3.27 N, 14.95.

#### 7-(and 8-)Methyl[1,4]benzodioxino[2,3-*c*]pyridazine (2b).

Material 5b (1 g, 4.3 mmoles) was dissolved in 20 ml of ethyl acetate, containing 1 ml of triethylamine, and 0.3 g of 5% Pd/C. The contents were hydrogenated on the Parr shaker, filtered and the filtrate vacuum treated to remove solvent. After washing with water, and air drying, a portion of the 0.69 g (80%) product was recrystallized from ethyl acetate, mp 128-130°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.21 and 2.22 (2s, 3 H, 7- and 8 CH<sub>3</sub>), 6.82 and 8.63 (2d, J = 5.3 Hz, 2 H, 4- and 3-H), 6.65-6.90 (m's, 3 H, 6-,9- and either 7- or 8-H); gcms: *m/z* = 200.

*Anal.* Calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.80; H, 4.04; N, 13.94.

#### 7-(Trifluoromethyl)[1,4]benzodioxino[2,3-*c*]pyridazine (2c).

A mixture of 5c and 5d, (0.55 g, 1.9 mmoles) was derived from the methanol filtrate portion of the fusion reaction between 3,4,5-trichloropyridazine and 4-(trifluoromethyl)-catechol (see preparations of both of these materials below). This mixture was combined with 1 ml of triethyl amine, 0.2 g of 5% Pd/C, in 25 ml of ethyl acetate, and hydrogenated on the Parr shaker at *ca* 50 psi. Workup by filtration, evaporation of the solvent, water washes, and air drying gave a mixture of the two hydrodechlorinated isomers 2c and 2d. The title compound was isolated in pure form from the ethyl acetate filtrate, after crystallization of 2d. Of 0.125 g from this filtrate charged to the Chromatotron™, elution with 30-40% ethyl acetate in cyclohexane gave 30 mg of pure 2c, mp 111-112°; <sup>1</sup>H nmr (deuteriochloroform): δ 6.97 (d [J<sub>4,3</sub> = 5.28 Hz], 1 H, 4-H), 7.16 (d [J<sub>9,8</sub> = 8.46 Hz], 1 H, 9-H), 7.17 (d [J<sub>6,8</sub> = 2.01 Hz], 1 H, 6-H), 7.33 (d [J<sub>8,9</sub> = 8.39 Hz, also with smaller 6-H and CF<sub>3</sub> coupling], 1 H, 8-H), 8.76 (d [J<sub>3,4</sub> = 5.26 Hz], 1 H, 3-H); <sup>19</sup>F nmr: δ -67.41 (s).

*Anal.* Calcd. for C<sub>11</sub>H<sub>5</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 51.98; H, 1.98; N, 11.02. Found: C, 51.92; H, 2.18; N, 10.76.

#### 8-(Trifluoromethyl)[1,4]benzodioxino[2,3-*c*]pyridazine (2d).

Material 5d (0.4 g, 1.4 mmoles) was placed in 10 ml of ethyl acetate with 1 g of triethylamine, 0.2 g of 5% Pd/C, and hydrogenated on the Parr shaker at 50 psi. The contents were filtered (2x filter paper), the filtrate vacuum treated to remove solvent, then the residue triturated with water to give 0.3 g of yellow solid. The material was recrystallized from cold ethyl acetate to give 200 mg (56%) of colorless crystals, mp 175-176°; <sup>1</sup>H nmr (deuteriochloroform): δ 6.94 (d [J<sub>4,3</sub> = 5.29 Hz], 1 H, 4-H), 7.04 (d [J<sub>6,7</sub> = 8.44 Hz], 1 H, 6-H), 7.28 (d [J<sub>7,6</sub> = 8.48 Hz] [also with smaller 9-H and CF<sub>3</sub> coupling], 1 H, 7-H), 7.32 (d [J<sub>9,7</sub> = 1.81 Hz], 1 H, 9-H), 8.76 (d [J<sub>3,4</sub> = 5.29 Hz], 1H, 3-H); <sup>19</sup>F nmr: δ -67.43 (s); gcms: *m/z* = 254.

*Anal.* Calcd. for C<sub>11</sub>H<sub>5</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 51.98; H, 1.98; N, 11.02. Found: C, 51.92; H, 1.96; N, 10.99.

#### 1-Chloro[1,4]benzodioxino[2,3-*d*]pyridazine (3a).

This known material was prepared according to literature procedure [2] as follows: Catechol (9 g, 82 mmoles) was added to 6.6 g (165 mmoles) of 60% sodium hydride in oil, contained in 100 ml of dry 1,2-dimethoxyethane (glyme). The suspension was stirred for 30 minutes, then 15 g (82 mmoles) of 3,4,5-trichloropyridazine dissolved in glyme was added, and the mixture heated at reflux for 2.15 hours. After standing 2 days the material was treated with water

(resultant pH = 5.5), filtered, and air dried to give 20.2 g of crude material, which by gcms showed 2 peaks *m/z* 220. The second, *minor* peak had an *e.i.* ms identical to **5a**. A portion of the crude material recrystallized 2x from methanol to give a product identical with that described in the literature, mp 197-201° (lit mp 198-200°). Final yield of pure **3a** from methanol recrystallization was 5.0 g (28%); <sup>1</sup>H nmr (deuteriochloroform): δ 6.87-6.95, and 6.97-7.15 (2 m's, 1 and 3 H respectively, 6,7,8,9-H), 8.67 (s, 1 H, 4-H); gcms: *m/z* = 220.

*Anal.* Calcd. for C<sub>10</sub>H<sub>5</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 54.44; H, 2.28; Cl, 16.07; N, 12.70. Found: C, 54.46; H, 2.36; Cl, 16.01; N, 12.67.

1-Chloro-8-(trifluoromethyl)[1,4]benzodioxino[2,3-*d*]pyridazine (**3b**).

Fraction 7 obtained from the chromatography procedure described in the preparation of **3c** (see below) proved to be **3b**. Recrystallization from methanol gave 18 mg, mp 167-168°; <sup>1</sup>H nmr (deuteriochloroform): δ 7.04 (d [J<sub>6,7</sub> = 8.72 Hz], 1 H, 6-H), 7.30 (s [small 7-H and/or CF<sub>3</sub> coupling], 1 H, 9-H), 7.32 (d [J<sub>7,6</sub> = ca 8-9 Hz, and smaller coupling with 9-H and/or CF<sub>3</sub>], 1 H, 7-H), 8.72 (s, 1 H, 4-H); <sup>19</sup>F nmr: δ -67.59 (s); gcms: *m/z* = 288.

*Anal.* Calcd. for C<sub>11</sub>H<sub>4</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 45.78; H, 1.40; Cl, 12.28; N, 9.71. Found: C, 45.81; H, 1.41; Cl, 12.17; N, 9.71.

1-Chloro-7-(trifluoromethyl)[1,4]benzodioxino[2,3-*d*]pyridazine (**3c**).

4-(Trifluoromethyl)catechol (3.3 g, 18 mmoles), contained in 10 ml of dry glyme was added to a slurry of 1.5 g 60% sodium hydride in 20 ml of dry glyme. The suspension was stirred for 30 minutes, then 3.4 g of 3,4,5-trichloropyridazine was added, and the contents refluxed for 2 hours, cooled and most of the solvent glyme removed by vacuum evaporation. The residue was washed with water, filtered, and the resulting solid washed with water having pH > 8.5. A total of 0.7 g was thereby isolated. This was charged to the Chromatotron™, and elution performed with 20% ethyl acetate in cyclohexane. Fractions 3-5 after evaporation of the elution solvent and recrystallization from cold methanol, gave 140 mg, mp 151-154°; <sup>1</sup>H nmr (deuteriochloroform): δ 7.13 (d [J<sub>9,8</sub> = 8.45 Hz], 1 H, 9-H), 7.20 (d [J<sub>6,8</sub> = 2.3 Hz], 1 H, 6-H), 7.32 (d [J<sub>8,9</sub> = 8.47 Hz], 1 H, 8-H), 8.72 (s, 1 H, 4-H); <sup>19</sup>F nmr: δ -67.60 (s).

*Anal.* Calcd. for C<sub>11</sub>H<sub>4</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 45.78; H, 1.40; Cl, 12.28; N, 9.71. Found: C, 45.74; H, 1.41; Cl 12.19; N, 9.60.

[1,4]Benzodioxino[2,3-*d*]pyridazine (**4a**).

Material **3a** (1.0 g 4.5 mmoles) was dissolved in 20 ml of ethyl acetate with 1 ml of triethylamine, and 0.3 g of 5% Pd/C, then hydrogenated on the Parr shaker at ca 50 psi. The mixture was subsequently filtered (2x filter paper), the filtrate vacuum treated to remove solvent, then triturated with water to give 0.5 g (60%), mp 200-201° (lit [2] mp 197-198°); <sup>1</sup>H nmr (deuteriochloroform): δ 6.87-6.93 and 6.95-7.01 (2 m's, 2H each, 6,7,8,9-H), 8.72 (s, 2H, 1- and 4-H); gcms: *m/z* = 186.

*Anal.* Calcd. for C<sub>10</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub>: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.56; H, 3.27; N, 15.00.

7-(Trifluoromethyl)[1,4]Benzodioxino[2,3-*d*]pyridazine (**4b**).

A mixture of 115 mg of **3b** and 130 mg of **3c** (total charge 0.85 mmole) was placed in 20 ml of ethyl acetate with 1 g of triethylamine, with 50 mg of 10% Pd/C, and hydrogenated on the Parr shaker at ca 50 psi. The contents were filtered through double filter paper, the filtrate evaporated to remove solvent, and the residue triturated with water. The filtered, air dried solid weighed 110 mg (51% yield), which proved by nmr to be only one compound. Recrystallization from ethyl acetate gave mp 148-150°; <sup>1</sup>H nmr (deuteriochloroform): δ 7.03 (d, [J<sub>9,8</sub> = 8.50 Hz], 1 H, 9-H), 7.19 (d, [J<sub>6,8</sub> = 2.01 Hz], 1 H, 6-H), 7.29 (d, [J<sub>8,9</sub> = 8.50 Hz, and smaller 6-H and/or CF<sub>3</sub> coupling], 1 H, 8-H), 8.79 (s, 2 H, 1- and 4-H); <sup>19</sup>F nmr: δ -67.56.

*Anal.* Calcd. for C<sub>11</sub>H<sub>5</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>•0.3H<sub>2</sub>O: C, 50.91; H, 2.17; N, 10.79. Found: C, 51.34; H, 2.51; N, 10.64.

4-Chloro[1,4]benzodioxino[2,3-*c*]pyridazine (**5a**).

After several preliminary runs, a preferred procedure is represented as follows: Catechol (2.2 g, 20 mmoles) was mixed with 3.7 g (20 mmoles) of 3,4,5-trichloropyridazine, and the intimate mixture heated slowly to 195° (oil bath). At ca 135° gaseous hydrogen chloride started to evolve, becoming copious at 150-160°. The liquid formed a solid, which melted again as the temperature was raised. The material was cooled to give a crude weight at slightly greater than quantitative yield (4.3 g). The solid was then vacuum bulb-to-bulb sublimed to give a product that was recrystallized from methanol, with initial crystals forming at room temperature. A second recrystallization from methanol gave pure **5a** mp 162-164°, yield from an 87 mmole run gave upon recrystallization, 8.54 g (44%); <sup>1</sup>H nmr (deuteriochloroform): δ 7.09-7.13 (m's, 4 H, 6,7,8,9-H), 8.79 (s, 1H, 3-H); <sup>13</sup>C nmr: δ 116.8, 117.7, 125.5, 126.1 (6-9 CH), 122 (4-C-Cl), 139.5, 139.7, 140.96 (4a,5a,9a C-O), 151.1 (3-CH), 154 (10a C-O); gcms: *m/z* = 220.

*Anal.* Calcd. for C<sub>10</sub>H<sub>5</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 54.44; H, 2.28; Cl, 16.07; N, 12.70. Found: C, 54.11; H, 2.23; Cl, 16.08; N, 12.67.

4-Chloro-7-(and 8-)methyl[1,4]benzodioxino[2,3-*c*]pyridazine (**5b**).

A mixture of 5.42 g (44 mmoles) of 4-methylcatechol (Aldrich) and 8 g (44 mmoles) of 3,4,5-trichloropyridazine was ground intimately by mortar and pestle, then placed in a flask fitted with a magnetic stirrer, and this in turn partially immersed in a stirred oil bath. The material was slowly heated. The material melted and evolved hydrogen chloride between 140-180°. Hydrogen chloride evolution then diminished, although the mixture was momentarily heated to an oil bath temperature of 197°. On cooling the mixture weighed 9.15 g. Of this material, 8.2 g was vacuum bulb-to-bulb distilled to give 4.6 g (45%) yield. Both the distillate and crude material could be recrystallized from methanol to give white crystals, mp 206-209°; <sup>1</sup>H nmr (deuteriochloroform): δ 2.29 (s, 3H, CH<sub>3</sub>), 6.83-6.93 (m's, 3H, ArH), 8.70 (s, 1H, 3-H). From the complexity of the ArH, the product appeared to be a mixture of the 7- and 8-isomers; gcms: *m/z* = 234.



*Anal.* Calcd. for  $C_{11}H_7ClN_2O_2$ : C, 56.31; H, 3.01; Cl 15.11; N, 11.94. Found: C, 56.38; H, 2.96; Cl, 15.01; N, 11.93.

4-Chloro-7-(trifluoromethyl)[1,4]benzodioxino[2,3-*c*]pyridazine (**5c**).

The methanol filtrate from the preparation of **5d** (see below) was found to contain the title product, plus apparently some byproducts from 4-(trifluoromethyl)catechol and trichloropyridazine. Chromatotron™ treatment with 10% ethyl acetate in cyclohexane gave separation, with 50 mg isolated as pure **5c** in fraction 10 mp 138-142°;  $^1H$  nmr (deuteriochloroform):  $\delta$  7.20 (d, [ $J_{9,8} = 8.37$  Hz], 1H, 9-H), 7.34 (s, [with small 8-H and  $CF_3$  coupling], 1H, 6-H), 7.36 (d, [ $J_{8,9} = 8.40$  Hz], 1H, 8-H), 8.79 (s, 1H, 3-H);  $^{19}F$  nmr:  $\delta$  -67.43 (s); gcms:  $m/z = 288$ .

*Anal.* Calcd. for  $C_{11}H_4ClF_3N_2O_2$ : C, 45.78; H, 1.40; Cl, 12.28; N, 9.71. Found C, 45.83; H, 1.41; Cl, 12.22; N, 9.70.

4-Chloro-8-(trifluoromethyl)[1,4]benzodioxino[2,3-*c*]pyridazine (**5d**).

4-(Trifluoromethyl)catechol (2.85 g, 16 moles) and 2.93 g of 3,4,5-trichloropyridazine, (16 moles) were heated together slowly in an oil bath to 200°. The material recovered was bulb-to-bulb distilled to 200° (1 mm) to give 3.58 g of distillate (77% yield as a mixture of 7- and 8- trifluoromethyl isomers), and 1.0 g of residue. The distilled material was recrystallized twice from methanol to give 0.6 g of white lustrous plates as pure **5d**, mp 189-191°;  $^1H$  nmr (deuteriochloroform):  $\delta$  7.16 (d, [ $J = 8.12$  Hz], 1H, 6-H), 7.34 (d, [ $J = ca$  8 Hz, and small coupling to  $CF_3$ ], 1H, 7-H), 7.35 (s, [with small coupling to  $CF_3$ ], 1H, 9-H) 8.77 (s, 1H, 3-H);  $^{19}F$  nmr:  $\delta$  -67.48 (s); gcms:  $m/z = 288$ .

*Anal.* Calcd. for  $C_{11}H_4ClF_3N_2O_2$ : C, 45.78; H, 1.40; Cl, 12.28; N, 9.71. Found: C, 45.55; H, 1.47; Cl, 12.31; N, 9.66.

4-Chloro-6/9-methoxy[1,4]benzodioxino[2,3-*c*]pyridazine (**5e**).

3-Methoxycatechol (Aldrich) (6.1 g, 50 mmoles) was mixed with 8 g (43.6 mmoles) of 3,4,5-trichloropyridazine, and heated to 130-140° to start hydrogen chloride evolution. The reaction was finished at 190°. On cooling a tarry resinous mixture was obtained that weighed 10.2 g. Upon bulb-to-bulb distillation at 160-200° (1 mm), only 0.17 g was distilled. This material, recrystallized from methanol, mp 177-183° was presumably the title product, although unlike other materials **5**, this was not subjected to hydrodechlorination to **2** for rigorous structure proof;  $^1H$  nmr (deuteriochloroform):  $\delta$  3.90 (s, 3H,  $OCH_3$ ) 6.62-6.72 (m's, 2H, 6,8-H/7,9-H), 6.96 and 6.99 (2t [ $J = 8.40$ ], 1H, 7/8-H), 8.72 (s, 1H, 3-H); gcms:  $m/z = 250$  (1 Cl).

*Anal.* Calcd. for  $C_{11}H_7ClN_2O_3$ : C, 52.71; H, 2.82; N, 11.18. Found: C, 52.54; H, 2.80; N, 11.13.

4-Methoxy[1,4]Benzodioxino[2,3-*c*]pyridazine (**6a**).

Material **3a** (2.3 g, 10 mmoles), was placed in 25 ml of methanol with 0.7 g of sodium methoxide and heated to boiling. After reflux for 4 hours the material was cooled and the solid collected by filtration. This material was triturated with water that was kept basic by the addition of 2 drops of

10% sodium hydroxide. A final filtration, water wash, and air drying gave 0.5 g (23%) of pure product, mp 193-194°;  $^1H$  nmr (deuteriochloroform): (see also Table II for HETCOR data)  $\delta$  4.06 (s, 3H,  $OCH_3$ ), 6.97-7.04 (m's, 4H, ArH), 8.67 (s, 1H, 3-H); *e.i.* gcms:  $m/z = 216$ ; no  $m/z-1$  peak at 215.

*Anal.* Calcd. for  $C_{11}H_8N_2O_3$ : C, 61.11; H, 3.73; N, 12.96. Found: C, 61.33; H, 3.75; N, 12.82.

The  $^1H$ - $^{13}C$  coupling constants reported for **6a** and **7a** in Table I were measured from 2 dimensional nmr spectra produced by a HETCOR sequence which had a J scaling element [11,12] in the labeling period. The parameters were set so that the splitting due to coupling were scaled by 10x relative to the chemical shifts. Consequently, the reported couplings are corresponding splittings in the 2 dimensional nmr spectrum divided by ten.

1-Methoxy[1,4]Benzodioxino[2,3-*d*]pyridazine (**7a**).

Material **5a** (1.5 g, 6.8 mmoles), bulb-to-bulb distilled, but not recrystallized from methanol, was dissolved in methanol to which 0.37 g of sodium methoxide had been added. The gc and gcms indicated only partial reaction of **5a** with prolonged heating. More sodium methoxide was added (total 0.53 g, 9.8 mmoles), and the mixture heated several hours longer, then permitted to stir at room temperature over 2 days. It appeared from gcms that more **7a** was formed, along with dioxin ring opening. The material was mixed with water, made basic with sodium hydroxide, then the solid remaining filtered. After water trituration and air drying, the solid was recrystallized from ethyl acetate to give 0.33 g (22%) glistening crystals, mp 175-177°;  $^1H$  nmr (deuteriochloroform): (see also Table II for HETCOR data)  $\delta$  4.20 (s, 3H,  $OCH_3$ ), 6.85-6.92, and 6.95-7.0 (2 m's, 1 and 3H resp, 6,7,8,9-H), 8.49 (b, 1H, 4-H); direct probe and *e.i.* gcms:  $m/z$  216, strong  $m/z-1$  at 215.

*Anal.* Calcd. for  $C_{11}H_8N_2O_3$ : C, 61.11; H, 3.73; N, 12.96. Found: C, 61.03; H, 3.74; N, 12.96.

Single Crystal X-ray Determination (from Crystalytics Company, Lincoln Nebraska). Single crystals of  $C_{11}H_8N_2O_3$  are, at  $20 \pm 1^\circ$ , orthorhombic, space group  $Pca2_1-C5_2v$  (No, 29) with  $a = 21.648$  (3)Å,  $b = 5.526$  (1)Å,  $c = 7.975$  (2)Å,  $V = 954.1$  (3)Å<sup>3</sup>, and  $Z = 4$  { $d_{calcd} = 1.505$  gcm<sup>-3</sup>;  $\mu_a$  (CuK $\alpha$ ) = 0.90 mm<sup>-1</sup>}. A total of 769 independent reflections having  $2\theta$  (CuK $\alpha$ ) < 120.0° (the equivalent of 0.65 limiting CuK  $\alpha$  spheres) were collected on a computer-controlled Nicolet autodiffractometer using  $\theta-2\theta$  scans and nickel-filtered CuK $\alpha$  radiation. The structure was solved using Direct Methods techniques with the Siemens SHELXTL-PLUS software package modified at Crystalytics Company. The resulting structural parameters have been refined to convergence { $R_1$  (unweighted, based on F) = 0.045 for 654 independent reflections having  $2\theta$ (CuK  $\alpha$ ) < 120° and  $I > 3\sigma(I)$ } using counter-weighted full-matrix least-squares techniques and a structural model which incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The methyl group was included in the refinement as an idealized sp<sup>3</sup>-hybridized rigid rotor and gave final values for the O-C-H angles which ranged from 97° to 131°. Hydrogen atom H<sub>4</sub> was located

from a difference Fourier map and refined as an independent isotropic atom. The remaining hydrogen atoms were fixed at idealized  $sp^2$ -hybridized positions with a C-H bond length of 0.96 Å. Atomic coordinates, bond lengths, and bond angles involving the non hydrogen atoms in material **7a** are given respectively in Tables 3,4 and 5 with atom numbering in these cases as given in the ortep model representation of Figure 1.

1-Methoxy-7-(or 8-)methyl[1,4]benzodioxino[2,3-*c*]pyridazine (**7b**).

Material **5b** (2.35 g, 10 mmoles), was placed in 30 ml of methanol, to which 0.7 g of sodium methoxide had been added. The reaction on reflux was followed by gc and lc. After 4 hours, 0.12 g more methoxide was added, and the mixture refluxed another 2 hours. The contents were cooled and stirred overnight, yielding a solid precipitate. This was filtered off, triturated with water (resultant pH = 5), which was then made strongly basic with 2 drops of 10% sodium hydroxide. The material was filtered, washed with water, then air dried to give 0.5 g (22%), which by gc showed the absence of **5b**. A portion could be recrystallized from ethyl acetate to give a pure isomeric product, mp 168-170°;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.24 (s, 3H,  $\text{CH}_3$ ), 4.18 (s, 3H,  $\text{CH}_3\text{O}$ ), 6.68-6.85 (m's, 3H, ArH), 8.45 (s, 1H, 4-H); e.i. ms:  $m/z = 230$ , strong  $m/z-1$  peak at 229.

Anal. Calcd. for  $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3$ : C, 62.61; H, 4.38; N, 12.17. Found: C, 62.61; H, 4.36; N, 12.20.

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