

REACTION OF [1,4]BENZODIOXINOPYRIDAZINES WITH SODIUM METHOXIDE AND AMINES

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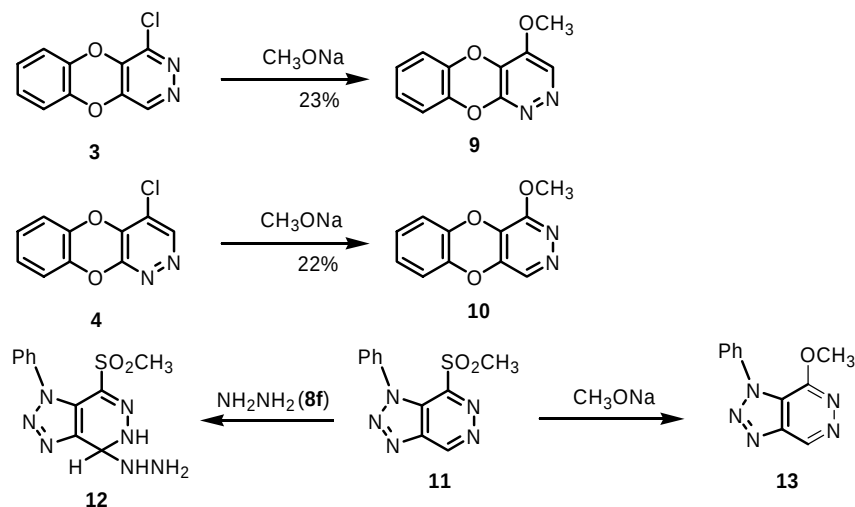
Abstract – The reaction of 1-chloro (**3**), 1-methylsulfonyl (**7**) [1,4]benzodioxino[2,3-*d*]pyridazine and 4-chloro[1,4]benzodioxino[2,3-*c*]pyridazine (**4**) with sodium methoxide afforded dioxin ring-opened pyridazines (**14** – **16**) and ring-cyclized pyridazines (**9**, **10**), while their reaction with amines [*n*-butylamine (**8a**), cyclohexylamine (**8b**), morpholine (**8c**), piperidine (**8d**), pyrrolidine (**8e**), hydrazine (**8f**) and aniline (**8g**)] afforded 1-substituted [1,4]benzodioxino[2,3-*d*]pyridazines (**18**), 4-substituted [1,4]benzodioxino[2,3-*c*]pyridazines (**19**) and/or 2-hydroxyphenoxypyridazines (**20** – **22**).

In our studies on the synthesis and reactivities of fused pyridazines,^{1a-c} our interest has been focused on the reactivity of [1,4]benzodioxinopyridazines with nucleophiles.

We have already presented the nucleophilic reactions of the fused pyridazine having electron-withdrawing substituent such as 7-methylsulfonyl-1-phenyl-1*H*-1,2,3-triazolo[4,5-*d*]pyridazine (**11**),^{1c} and reported that **11** reacts with nucleophiles in two ways, depending on the nature of the reagent, to afford either addition product (**12**) or substitution product (**13**). (Scheme 1)

It was reported by Ames and Chupp^{2a,b} that the treatment of 1-chloro[1,4]benzodioxino[2,3-*d*]pyridazine (**3**) and 4-chloro[1,4]benzodioxino[2,3-*c*]pyridazine (**4**) with boiling methanolic sodium methoxide results in the formation of 4-methoxy[1,4]benzodioxino[2,3-*c*]pyridazine (**9**) and 1-methoxy[1,4]benzodioxino[2,3-*d*]pyridazine (**10**), respectively. But only the reactivities of related chlorosubstituted benzodioxinopyridazines were reported.^{2c-h}

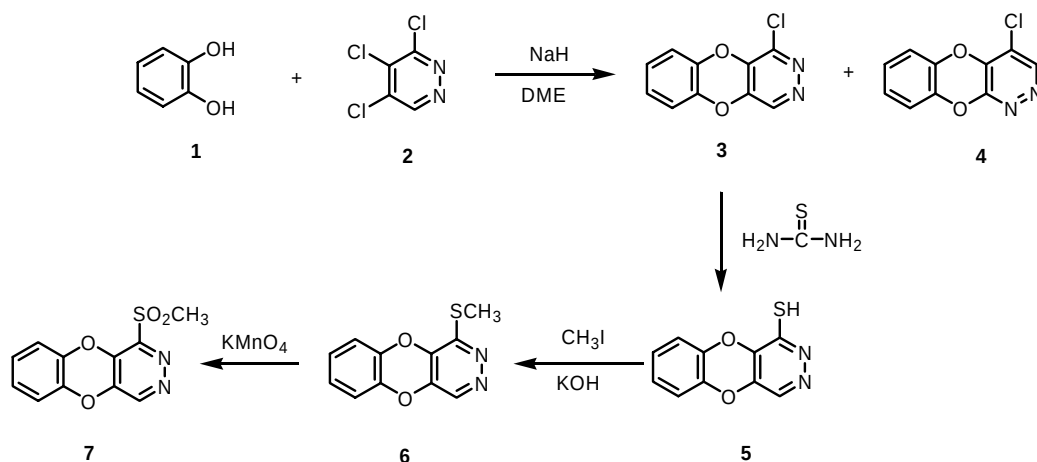
Scheme 1



In the expectation that similar substitution and addition reactions would take place, we prepared 1-methylsulfonyl[1,4]benzodioxino[2,3-*d*]pyridazine (**7**), and examined the reactions of **3**, **4** and **7** with sodium methoxide and amines [*n*-butylamine (**8a**), cyclohexylamine (**8b**), morpholine (**8c**), piperidine (**8d**), pyrrolidine (**8e**), hydrazine (**8f**) and aniline (**8g**)].

Condensation of **1** with **2**³ in the presence of NaH afforded a mixture of the isomeric benzodioxino-pyridazine (**3**) and (**4**). The isolated **3** was treated with thiourea to give the thiol (**5**), which was methylated to give **6**. Then the **6** was oxidized with KMnO_4 to give **7** in an overall yield of 66%. (Scheme 2)

Scheme 2



The Reaction of **7** with Sodium Methoxide

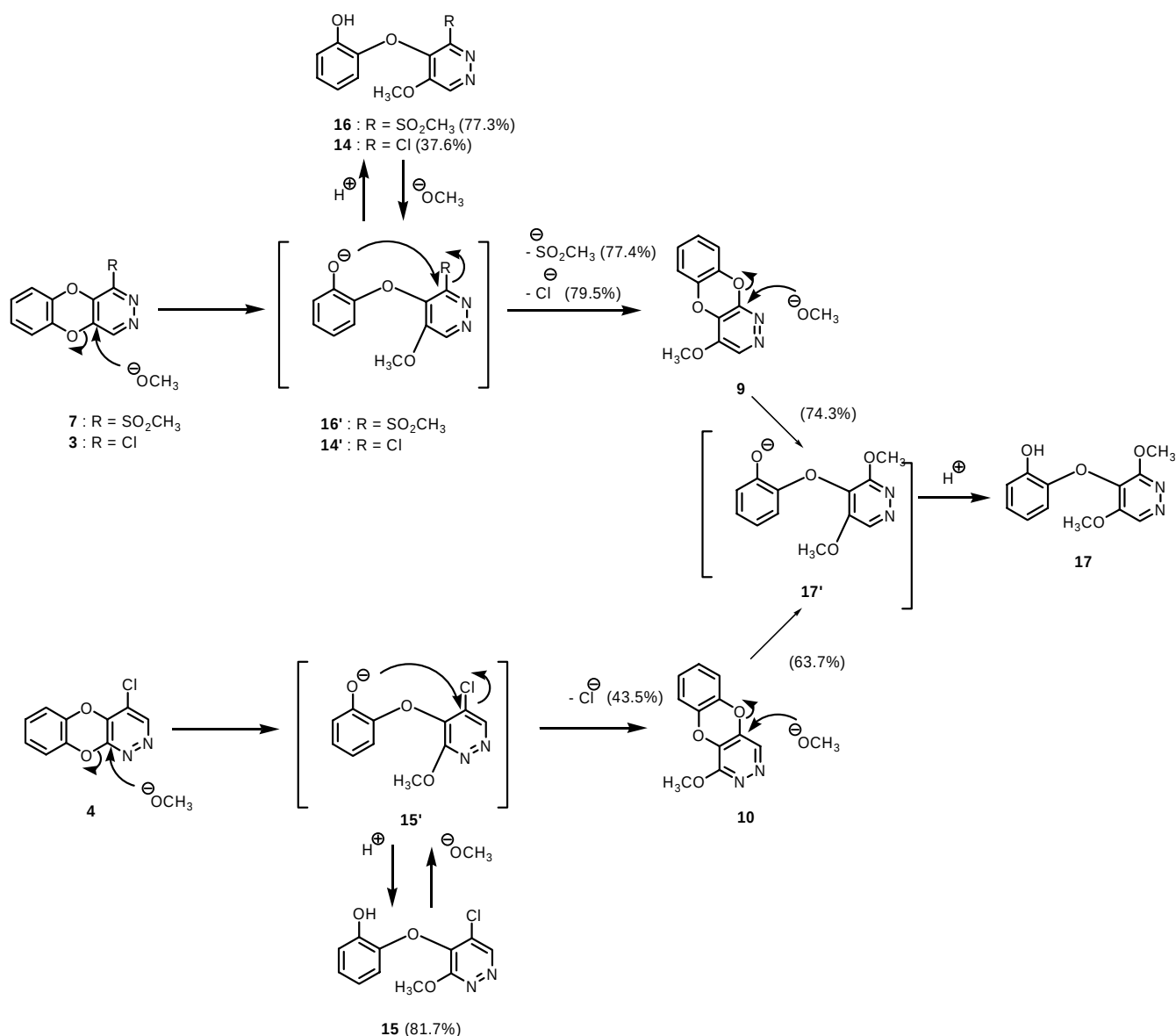
The reaction of **7** (1 equivalent) with sodium methoxide (1 equivalent) in MeOH at room temperature for 15 min gave 4-(2-hydroxyphenoxy)-5-methoxy-3-methylsulfonylpyridazine (**16**) in 77.3% yield.

Cyclization of **16**, in the presence of sodium methoxide (1 equivalent) in refluxing MeOH for 30 min, afforded **9** in 77.4% yield.

In the reaction of **3** and **4** with sodium methoxide, dioxin ring-opened pyridazines were not obtained under the reaction conditions employed by Ames *et al.*

We reexamined the reaction of **3** and **4** with sodium methoxide in the same manner described above and found that **3** and **4** (1 equivalent) reacted with sodium methoxide (1 equivalent) in MeOH at room temperature for 15 min to give dioxin ring-opened pyridazines, 3-chloro-4-(2-hydroxyphenoxy)-5-methoxypyridazine (**14**) and 5-chloro-4-(2-hydroxyphenoxy)-3-methoxypyridazine (**15**) in 37.6% (recovery of **3**: 30%) and 81.7% yields, respectively.

Scheme 3



Compound (**14**) and (**15**) reacted with one more equivalent sodium methoxide in refluxing MeOH for 30 min to give **9** and **10** in 79.5% and 43.5% yields, respectively. Compound (**9**) and (**10**) reacted with one

more equivalent sodium methoxide in refluxing MeOH for 30 min to afford the same product, 4-(2-hydroxyphenoxy)-3,5-dimethoxypyridazine (**17**) in 74.3% and 63.7% yields, respectively.

The nucleophilic displacement reactions of **3**, **7** and **4** with sodium methoxide first occurred on the C-4a ring carbon in **3** and **7**, and on the C-10a ring carbon in **4** to afford dioxin ring-opened pyridazines (**14**, **16** and **15**) respectively, and then the cyclizations of **14**, **16** and **15** proceeded to afford **9** and **10** respectively. The same reactions of **9** and **10** with methoxide ion proceeded both on the C-10a ring carbon in **9** and on the C-4a ring carbon in **10** to afford the same product (**17**). However, the direct replacement of chloro or methylsulfonyl substituent by methoxide ion did not take place.

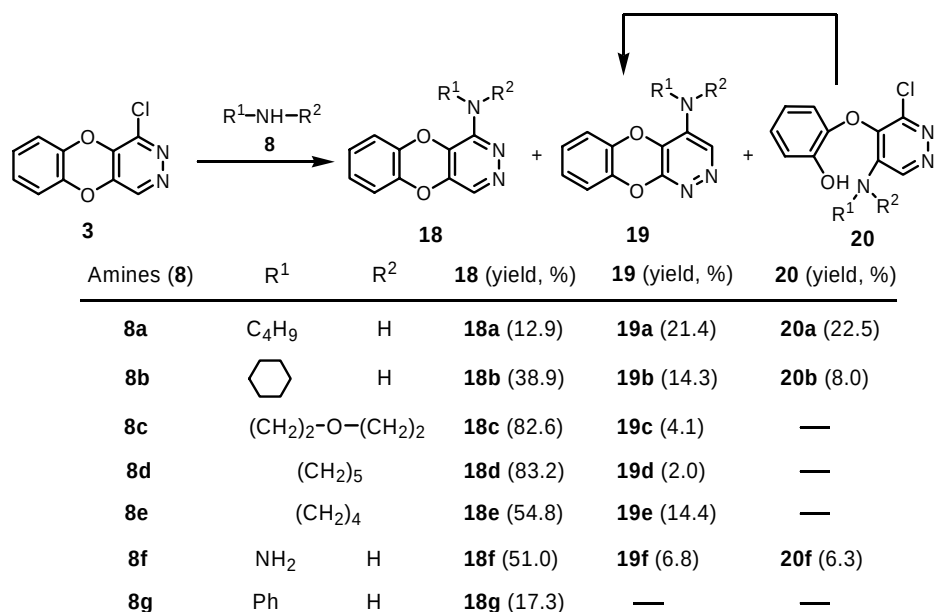
The structures of products (**14** – **17**) were confirmed by their elemental analyses, MS, IR, NMR spectral data (see EXPERIMENTAL) and ring closures of **14** – **16** to **9** or **10**. (Scheme 3)

The Reactions of **3**, **4** and **7** with Amines (**8a** – **g**)

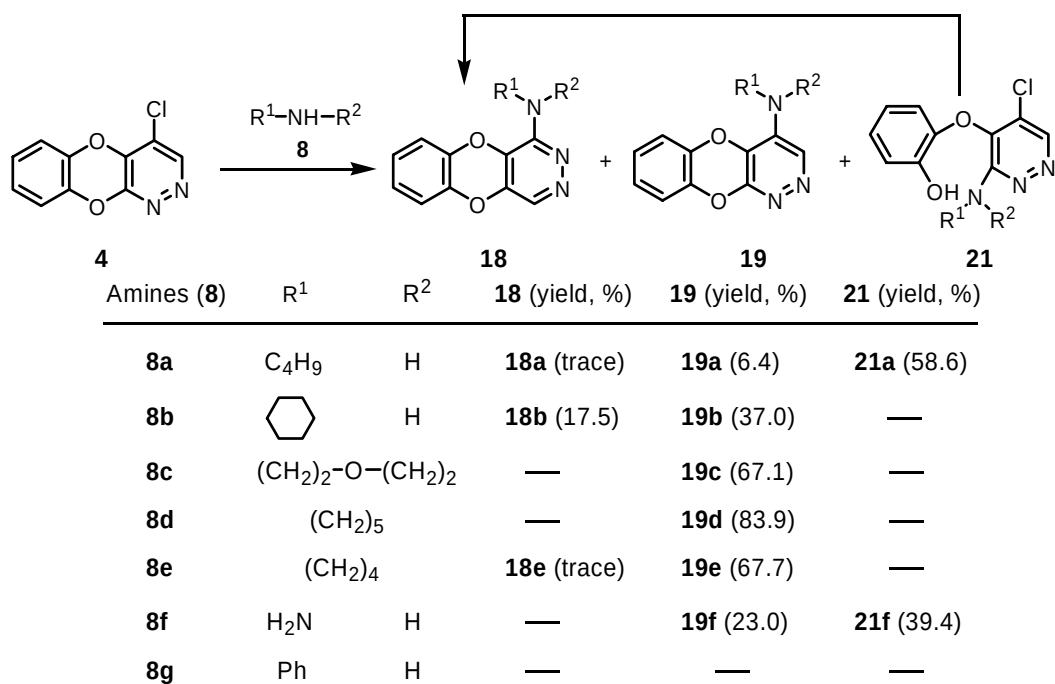
The reaction of **3**, **4** and **7** with excess amines (**8a** – **e**) at reflux temperature gave 1-substituted [1,4]benzodioxino[2,3-*d*]pyridazine (**18**), 4-substituted [1,4]benzodioxino[2,3-*c*]pyridazine (**19**) and dioxin ring-opened pyridazines (**20** – **22**). Their reaction with **8f** and **8g** was carried out in refluxing dioxane.

In the reaction of **7** with **8e**, 3-methylsulfonyl-4,5-dipyrrolidinopyridazine (**23**) was obtained together with **22e**. Compound (**23**) may be formed by the nucleophilic attack of pyrrolidine (**8e**) on the C-4 ring carbon in **22e** prior to the nucleophilic attack of phenol OH on the sterichindered C-3 ring carbon in **22e**. However, the nucleophilic addition of amines to carbon-nitrogen double bond in pyridazine moiety did not proceed. The results are summarized in Schemes 4 , 5 and 6.

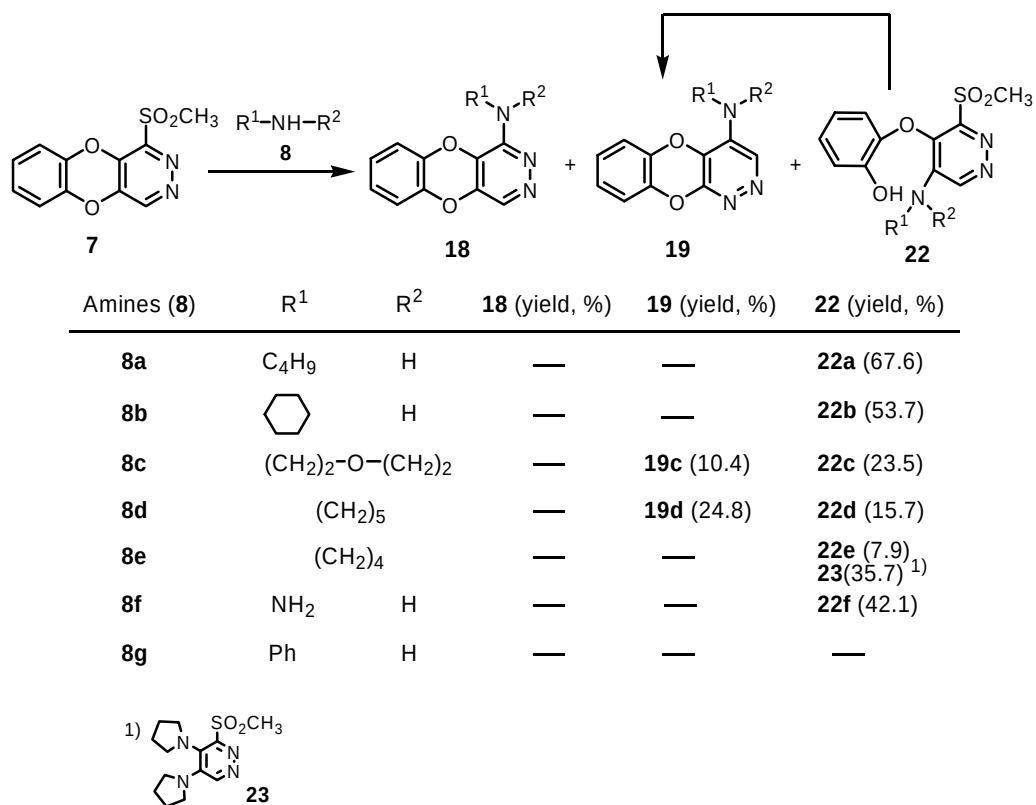
Scheme 4



Scheme 5



Scheme 6

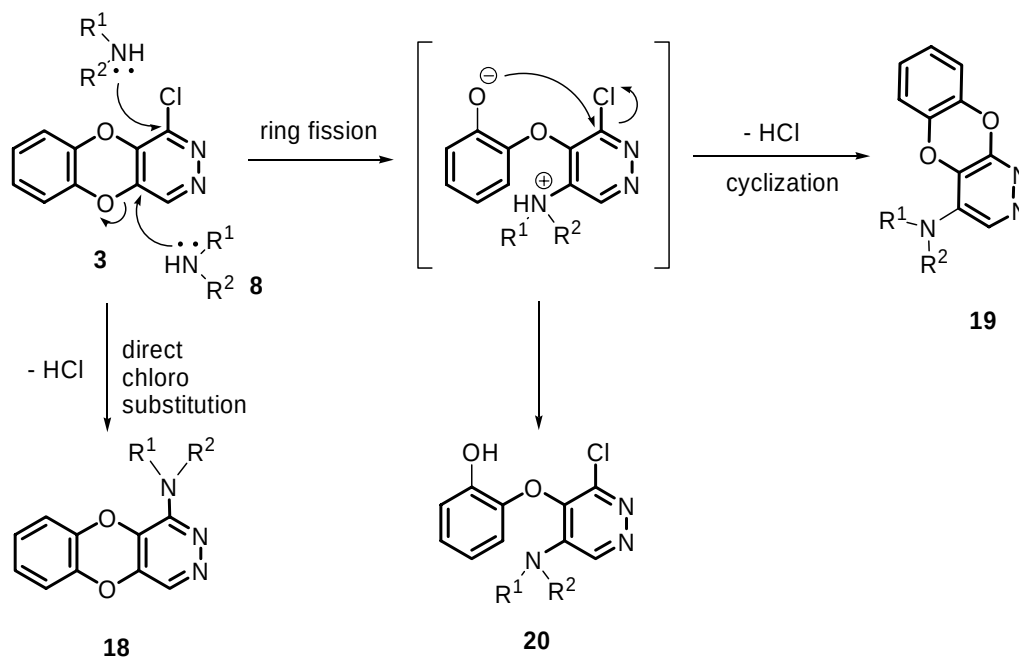


Amines (**8**) were found to react with [1,4]benzodioxinopyridazines (**3**, **4** and **7**) in three ways, depending on the amines used. The first one is the substitution of the chloro group in **3** and **4** by the reagent to give [1,4]benzodioxino[2,3-*d* and/or 2,3-*c*]pyridazines (**18** and **19**).

The second one is the ring fission of [1,4]benzodioxino moiety to afford 2-hydroxyphenoxy pyridazines (**20**, **21** and **22**).

The third one is the cyclization of 2-hydroxyphenoxy pyridazines (**20**, **22** and **21**) to produce **19** and **18**, respectively. The reactivity of amines (**8**) to **3** and **4** may be presumed to occur both due to the electron density of ring carbon bound to oxygen or chlorine atom and due to the bulk of amines. The secondary amines (**8c – e**) reacted with **3** and **4** to give direct chloro substituted products (**18** and **19**) in a 55 – 84% yields, but dioxin-ring opened products (**20** and **21**) and cyclization products (**19** and **18**) in a poor (trace – 14%) yields. However, the methylsulfonyl group in **7** was not directly replaced by amines, and the addition of amines to 3,4-double bond in **7** did not occur. This reactivity of **7** to amines (**8**) may be accounted for either by the presence of bulky methylsulfonyl group (steric effect) or by the relatively high electron density of C-4 ring carbon in **7** (electron-donating oxygen effect in catechol ring). Details of the reactivity of **7** are not clear yet. (Scheme 7)

Scheme 7



The structures of products (**18**, **19**, **20 – 22** and **23**) were confirmed both by their elemental analyses, MS, IR, and ¹H and ¹³C-NMR spectral data, as shown in Tables I - V.

TABLE I. Melting Points, Elemental Analyses and MS Data for **18 - 23**

Compd	mp (°C)	Appearance (Recryst. solvt. ^a)	Formula	Analysis (%) Calcd (Found)			MS
				C	H	N	
18a	170	colorless needles (c + e)	C ₁₄ H ₁₅ N ₃ O ₂	65.35 (65.06)	5.88 5.81	16.33 16.34)	257
18b	167	white needles (b + p.b)	C ₁₆ H ₁₇ N ₃ O ₂	67.82 (67.55)	6.05 6.09	14.83 14.72)	283
18c	168	white prisms (c)	C ₁₄ H ₁₃ N ₃ O ₂	61.98 (61.99)	4.83 5.03	15.49 15.44)	271
18d	105	white needles (b + p.b)	C ₁₅ H ₁₅ N ₃ O ₂	66.90 (66.83)	5.61 5.91	15.61 15.55)	269
18e	151	white needles (m)	C ₁₄ H ₁₅ N ₃ O ₂	65.87 (65.61)	5.13 5.02	16.46 16.18)	255
18f	214	white needles (m)	C ₁₀ H ₈ N ₄ O ₂	55.55 (55.27)	3.73 3.69	25.92 25.76)	216
18g	221	colorless scales (m)	C ₁₆ H ₁₁ N ₃ O ₂	69.30 (69.01)	4.00 3.92	15.16 15.04)	277
19a	191	colorless needles (c + e)	C ₁₄ H ₁₅ N ₃ O ₂	65.35 (65.09)	5.88 5.84	16.33 16.19)	257
19b	212	white needles (c + b)	C ₁₆ H ₁₇ N ₃ O ₂	67.82 (67.76)	6.05 5.97	14.83 14.66)	283
19c	207-8	white needles (b)	C ₁₄ H ₁₃ N ₃ O ₂	61.98 (61.87)	4.83 4.76	15.49 15.25)	271
19d	128	white needles (b + p.b)	C ₁₅ H ₁₅ N ₃ O ₂	66.90 (66.71)	5.61 5.60	15.61 15.48)	269
19e	223	white needles (m)	C ₁₄ H ₁₅ N ₃ O ₂	65.87 (65.64)	5.13 5.01	16.46 16.27)	255
19f	217	white needles (m)	C ₁₀ H ₈ N ₄ O ₂	55.55 (55.23)	3.73 3.62	25.92 25.72)	216
20a	145-6	colorless needles (c + m)	C ₁₄ H ₁₆ ClN ₃ O ₂	57.19 (57.33)	5.45 5.73	14.30 14.33)	293
20b	177 (decomp.)	white needles (b + m)	C ₁₆ H ₁₈ ClN ₃ O ₂	60.03 (60.27)	5.63 5.91	13.13 13.39)	319
20f	172-3 (decomp.)	pale brown needles (m)	C ₁₀ H ₉ ClN ₄ O ₂	47.49 (47.25)	3.56 3.71	22.16 22.30)	252
21a	112-4	white needles (c + e)	C ₁₄ H ₁₆ ClN ₃ O ₂	57.19 (57.34)	5.45 5.27	14.30 14.11)	293
21f	180 (decomp.)	pale brown needles (m)	C ₁₀ H ₉ ClN ₄ O ₂	47.49 (47.21)	3.56 3.35	22.16 22.01)	252
22a	170	white needles (m)	C ₁₅ H ₉ N ₃ O ₄ S	53.40 (53.31)	5.68 5.75	12.46 12.30)	337
22b	190-1	white needles (m)	C ₁₇ H ₂₁ N ₃ O ₄ S	56.21 (56.10)	5.78 6.05	11.57 11.30)	363
22c	193-4	white needles (c)	C ₁₅ H ₁₇ N ₃ O ₅ S	62.01 (62.08)	4.79 5.01	15.50 15.51)	351
22d	173	white needles (c + b)	C ₁₆ H ₁₉ N ₃ O ₄ S	55.02 (55.12)	5.44 5.40	12.03 11.81)	349
22e	206-7	white scales (m)	C ₁₅ H ₁₇ N ₃ O ₄ S	53.73 (53.52)	5.11 4.93	12.53 12.28)	335
22f	183-5	pale yellow needles (m)	C ₁₁ H ₁₂ N ₄ O ₄ S	44.60 (44.48)	4.08 3.88	18.91 18.72)	296
23	175	white scales (m)	C ₁₃ H ₂₀ N ₄ O ₂ S	52.69 (52.58)	6.80 6.57	18.91 18.65)	296

a) c: chloroform, b: benzene, p.b: petroleum benzine (bp 60 - 80°C), m: methanol,
e: ether, h: hexane

TABLE II IR, ¹H-NMR and ¹³C-NMR Spectral Data for **18**

Compd	IR ν_{max} KBr cm ⁻¹	¹ H-NMR (CDCl ₃) ppm	¹³ C-NMR (CDCl ₃) ppm
18a	3275 (NH)	8.20 (1H, s, H-4), 6.97 - 6.87 (4H, m, Ph-H), 4.54 (1H, br s, NH), 3.61 (2H, m, N-CH ₂), 1.69 (2H, m, CH ₂), 1.46 (2H, m, CH ₂), 0.98 (3H, t, CH ₃ , <i>J</i> = 7.5 Hz)	150.39 (C-1), 141.50, 141.42, 138.91 (C-4a, C-5a, C-9a), 135.14 (C-4), 127.91 (C-10a), 125.46, 125.11 (C-7, C-8), 117.38, 117.05 (C-6, C-9), 41.42 (N-CH ₂), 31.71 (CH ₂), 20.15 (CH ₂), 13.84 (CH ₃)
18b	3270	8.16 (1H, s, H-4), 6.96 - 6.84 (4H, m, Ph-H), 4.56 (1H, br s, NH), 4.14 (1H, m, NCH), 2.16 - 1.19 (10H, m, CH ₂ ×5)	149.74 (C-1), 141.49, 141.38, 138.95 (C-4a, C-5a, C-9a), 134.84 (C-4), 127.67 (C-10a), 125.42, 125.09 (C-7, C-8), 117.32, 117.07 (C-6, C-9), 49.77 (NHCH), 33.41, 25.78, 25.01 (-CH ₂ -)
18c		8.41 (1H, s, H-4), 6.98 - 6.90 (4H, m, Ph-H), 3.88 (4H, t, -OCH ₂ ×2, <i>J</i> = 5 Hz), 3.57 (4H, t, -NCH ₂ ×2, <i>J</i> = 5 Hz)	152.39 (C-1), 141.19, 141.11, 140.96 (C-4a, C-5a, C-9a), 138.06 (C-4), 132.53 (C-10a), 125.58, 125.51 (C-7, C-8), 117.17, 117.12 (C-6, C-9), 66.65 (-OCH ₂), 48.50 (-NH ₂)
18d		8.35 (1H, s, H-4), 6.97 - 6.86 (4H, m, Ph-H), 3.49 (4H, m, NCH ₂ ×2), 1.73 (6H, m, CH ₂ ×3)	153.33 (C-1), 141.44, 141.27, 140.74 (C-4a, C-5a, C-9a), 137.45 (C-4), 132.37 (C-10a), 125.33, 125.03 (C-7, C-8), 117.18, 117.02 (C-6, C-9)
18e		8.14 (1H, s, H-4), 6.93 - 6.80 (4H, m, Ph-H), 3.74 (4H, m, NCH ₂ ×2), 1.96 (4H, m, CH ₂ ×2)	150.65 (C-1), 141.77, 141.45, 140.39 (C-4a, C-5a, C-9a), 134.84 (C-4), 129.59 (C-10a), 125.13, 124.93 (C-7, C-8), 116.99, 116.92 (C-6, C-9), 49.07 (NCH ₂), 25.37 (CH ₂)
18f ^{a)}	3300 - 3100	8.29 (1H, s, H-4), 7.76 (1H, br s, NH), 7.06 - 6.96 (4H, m, Ph-H), 4.40 (2H, br s, NH ₂)	151.63 (C-1), 141.02, 140.87 (C-5a, C-9a), 138.15 (C-4a), 135.02 (C-4), 127.13 (C-10a), 125.48, 125.43 (C-7, C-8), 117.14 (C-6, C-9)
18g ^{a)}	3250	8.60 (1H, br s, NH), 8.49 (1H, s, H-4), 7.80 - 7.01 (9H, m, Ph-H)	148.07 (C-1), 140.98 (C-1'), 140.76, 139.93, 139.18 (C-4a, C-5a, C-9a), 136.13 (C-4), 127.55 (C-10a), 128.35 (C-3', C-5'), 125.53, 125.62 (C-7, C-8), 121.97 (C-4'), 119.94 (C-2', C-6'), 117.21, 117.15 (C-6, C-9)

a) NMR in (CD₃)₂SO

TABLE III IR, ¹H-NMR and ¹³C-NMR Spectral Data for **19**

Compd	IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}	¹ H-NMR (CDCl ₃) ppm	¹³ C-NMR (CDCl ₃) ppm
19a	3250 - 3000	8.38 (1H, s, H-3), 7.03 - 6.89 (4H, m, Ph-H), 4.24 (1H, br s, NH), 3.29 (2H, m, NHCH ₂), 1.68 (2H, m, CH ₂), 1.46 (2H, m, CH ₂), 0.99 (3H, t, CH ₃ , <i>J</i> = 7.5 Hz)	152.33 (C-10a), 141.54, 140.38 (C-5a, C-9a), 137.36 (C-3), 134.49 (C-4a), 125.92 (C-4), 125.06, 124.59 (C-7, C-8), 117.67, 116.19 (C-6, C-9), 42.66 (N-CH ₂), 31.44 (CH ₂), 19.95 (CH ₂), 13.70 (CH ₃)
19b	3250 - 3100	8.37 (1H, s, H-3), 7.02 - 6.90 (4H, m, Ph-H), 4.34 (1H, br s, NH), 3.41 (1H, m, NCH), 2.30 - 1.40 (10H, m, CH ₂ ×5)	152.47 (C-10a), 141.54, 140.43 (C-5a, C-9a), 137.66 (C-3), 133.69 (C-4a), 125.84 (C-4), 125.05, 124.62 (C-7, C-8), 117.62, 116.26 (C-6, C-9), 51.52 (NHCH), 33.22 (CH ₂ ×2), 25.43 (CH ₂ ×2), 24.71 (CH ₂)
19c		8.47 (1H, s, H-3), 7.07 - 6.91 (4H, m, Ph-H), 3.89 (4H, t, -OCH ₂ ×2, <i>J</i> = 5 Hz), 3.39 (4H, t, -NCH ₂ ×2, <i>J</i> = 5 Hz)	153.90 (C-10a), 142.11 (C-3), 141.33, 140.01 (C-5a, C-9a), 136.18 (C-4a), 131.07 (C-4), 125.46, 124.81 (C-7, C-8), 117.58, 116.32 (C-6, C-9), 66.45 (-OCH ₂), 48.88 (NCH ₂ ×2)
19d		8.46 (1H, s, H-3), 7.05 - 6.92 (4H, m, Ph-H), 3.36 (4H, m, NCH ₂ ×2), 1.72 (6H, m, CH ₂ ×3)	153.83 (C-10a), 142.81 (C-3), 141.52, 140.29 (C-5a, C-9a), 136.97 (C-4a), 130.41 (C-4), 125.17, 124.64 (C-7, C-8), 117.45, 116.36 (C-6, C-9), 50.01 (NCH ₂ ×2), 25.65 (CH ₂ ×2), 24.06 (CH ₂)
19e		8.17 (1H, s, H-3), 6.99 - 6.78 (4H, m, Ph-H), 3.60 (4H, m, NCH ₂ ×2), 1.98 (4H, m, CH ₂ ×2)	153.59 (C-10a), 141.81, 140.88 (C-5a, C-9a), 140.41 (C-3), 134.19 (C-4a), 126.12 (C-4), 126.12, 124.45 (C-7, C-8), 117.21, 116.10 (C-6, C-9), 49.64 (NCH ₂ ×2), 25.37 (CH ₂ ×2)
19f^{a)}	3300 - 3000	8.75 (1H, s, H-4), 7.77 (1H, br s, NH), 7.106 - 6.99 (4H, m, Ph-H), 4.45 (2H, br s, NH ₂)	151.41 (C-10a), 141.07, 140.18 (C-5a, C-9a), 138.52 (C-3), 137.03 (C-4a), 124.88, 124.84 (C-7, C-8), 123.21 (C-4), 117.12, 116.31 (C-6, C-9)

a) NMR in (CD₃)₂SO

TABLE IV IR, ¹H-NMR and ¹³C-NMR Spectral Data for **20**, **21**

Comp	IR ν_{max} ^{KBr} cm ⁻¹	¹ H-NMR (CDCl ₃) ppm	¹³ C-NMR (CDCl ₃) ppm
20a	3325, 2800 - 2400	8.11 (1H, s, H-6), 7.14 - 6.89 (4H, m, Ph-H), 4.80 (1H, br s, NH), 3.66 (2H, m, NCH ₂), 1.90 - 1.60 (1H, br s, OH), 1.63 (2H, m, CH ₂), 1.38 (2H, m, CH ₂), 0.92 (3H, t, CH ₃ , <i>J</i> = 7.5 Hz)	147.84 (C-2'), 144.60 (C-3), 141.88, 141.50 (C-4, C-1'), 141.07 (C-6), 134.64 (C-5), 126.59, 120.84 (C-4', C-5'), 119.82, 118.27 (C-3', C-6'), 45.28 (N-CH ₂), 33.12 (CH ₂), 19.76 (CH ₂), 13.71 (CH ₃)
20b	3400, 2850 - 2400	8.55 (1H, br s, OH), 8.11 (1H, s, H-6), 7.20 - 6.85 (4H, m, Ph-H), 4.71 (1H, br s, NH), 40.2 (1H, m, NCH), 2.04 - 1.25 (10H, m, CH ₂ ×5)	148.04 (C-2'), 144.99 (C-1), 141.52, 141.473 (C-4, C-1'), 140.70 (C-6), 135.57 (C-5), 126.7, 120.81, 120.62, 118.47 (Ph-C), 53.53 (NCH), 34.75 (CH ₂), 25.37 (CH ₂), 24.47 (CH ₂)
20f ^{a)}	3350,3250 2800 - 2450	8.17 (1H, s, H-6), 7.52 (1H, br s, NH), 5.00 (3H, br s, OH, NH, NH ₂), 7.22 - 6.89 (4H, m, Ph-H)	148.69 (C-2'), 142.43, 142.09, 140.18 (C-1', C-4, C-3), 140.41 (C-6), 126.46, 121.64, 119.70, 117.49 (Ph-C)
21a	3320, 2800 - 2400	8.20 (1H, s, H-6), 7.02 - 6.77 (4H, m, Ph-H), 5.24 (1H, br s, NH), 3.31 (2H, m, NCH ₂), 1.56 (2H, m, CH ₂), 1.46 (2H, m, CH ₂), 0.98 (3H, t, CH ₃ , <i>J</i> = 7.5 Hz)	155.24 (C-3), 148.63 (C-2'), 148.27 (C-6), 141.55, 134.67 (C-4, C-1'), 126.65, 122.11 (C-4', C-5'), 119.86, 118.59 (C-3', C-6'), 115.18 (C-5), 44.82 (NCH ₂), 33.17 (CH ₂), 19.75 (CH ₂), 13.77 (CH ₃)
21f	3400, 3350, 2800 - 2400	9.61 (1H, br s), 8.39 (1H, s, H-3), 7.84 (1H, br s), 7.13 - 6.81 (4H, m, Ph-H), 4.72 (2H, br s, OH, NH, NH ₂)	154.31 (C-3), 148.86 (C-2'), 140.94 (C-6), 139.59, 135.02 (C-4, C-1'), 125.95, 123.02, 119.06, 116.89 (Ph-O), 113.26 (C-6)

a) NMR in (CD₃)₂SO

TABLE V IR, ¹H-NMR and ¹³C-NMR Spectral Data for **22** and **23**

Compd	IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}	¹ H-NMR (CDCl ₃) ppm	¹³ C-NMR (CDCl ₃) ppm
22a	3350 3000 – 2500 1280, 1130	8.41 (1H, br s, OH), 8.07 (1H, s, H-6), 7.14 – 6.90 (4H, m, Ph-H), 6.80 (1H, br s, NH), 3.70 (2H, m, NCH ₂), 3.46 (3H, s, SO ₂ CH ₃), 1.64 (2H, m, CH ₂), 1.39 (2H, m, CH ₂), 0.91 (3H, t, CH ₃ , <i>J</i> = 7.5 Hz)	148.12 (C-2'), 146.70 (C-3), 144.35 (C-1'), 140.77 (C-6), 140.37 (C-4), 136.70 (C-5), 127.16, 121.04, 120.93, 118.43 (Ph-C), 45.82 (NCH ₂), 42.24 (SO ₂ CH ₃), 32.92 (CH ₂), 19.74 (CH ₂), 13.70 (CH ₃)
22b	3350, 3200 – 2550, 1295, 1100	8.07 (1H, s, H-6), 7.15 – 6.91 (4H, m, Ph-H), 6.83 (1H, br s, NH), 4.12 (1H, m, NCH), 3.46 (3H, s, SO ₂ CH ₃), 2.03 (CH ₂), 1.72 (CH ₂), 1.56 (1H, br s, OH), 1.34 (6H, m, CH ₂ ×3)	148.24 (C-2'), 146.99 (C-3), 144.12 (C-1'), 140.47 (C-6), 140.11 (C-4), 135.68 (C-5), 127.23, 121.06, 121.04, 118.52 (Ph-C), 54.02 (NCH ₂), 42.28 (SO ₂ CH ₃), 34.37 (CH ₂ ×2), 25.30 (CH ₂ ×2), 24.16 (CH ₂)
22c	3500 – 2600, 1300, 1130	8.41 (1H, s, H-4), 6.98 – 6.90 (4H, m, Ph-H), 3.88 (4H, t, -OCH ₂ ×2, <i>J</i> = 5 Hz), 3.57 (4H, t, -NCH ₂ ×2, <i>J</i> = 5 Hz)	159.02 (C-2'), 154.12 (C-3), 147.43 (C-1'), 143.74 (C-6), 140.38 (C-4), 136.63 (C-5), 127.70, 121.71, 121.41, 118.18 (Ph-C), 67.08 (OCH ₂ ×2), 51.55 (NCH ₂ ×2), 42.45 (SO ₂ CH ₃)
22d	3300 – 2700, 1310, 1100	8.35 (1H, s, H-4), 6.97 – 6.86 (4H, m, Ph-H), 3.49 (4H, m, NCH ₂ ×2), 1.73 (6H, m, CH ₂ ×3)	157.11 (C-2'), 153.01 (C-3), 147.92 (C-1'), 142.25 (C-6), 140.48 (C-4), 138.00 (C-5), 127.39, 121.36, 121.17, 118.27 (Ph-C), 52.97 (NCH ₂ ×2), 43.07 (SO ₂ CH ₃), 26.22 (CH ₂ ×2), 23.86 (CH ₂)
22e ^{a)}	3000 – 2500, 1300, 1098	8.14 (1H, s, H-4), 6.93 – 6.80 (4H, m, Ph-H), 3.74 (4H, m, NCH ₂ ×2), 1.96 (4H, m, CH ₂ ×2)	151.90 (C-3), 148.44 (C-6), 147.37 (C-2'), 140.94 (C-1'), 140.42 (C-4), 134.82 (C-5), 126.65, 121.46, 119.96, 117.58 (Ph-C), 53.33 (NCH ₂ ×2), 43.80 (SO ₂ CH ₃), 25.52 (CH ₂ ×2)
22f ^{a)}	3600 – 2500, 2800 – 2200, 1300, 1100	8.29 (1H, s, H-4), 7.76 (1H, br s, NH), 7.06 – 6.96 (4H, m, Ph-H), 4.40 (2H, br s, NH ₂)	148.74 (C-3), 146.38 (C-2'), 143.76, 137.64, 137.32 (C-4, C-5, C-1'), 127.04, 122.10, 119.65, 117.58 (Ph-C), 43.17 (SO ₂ CH ₃)
23	1300, 1130	8.63 (H-6), 3.45 (3H, SO ₂ CH ₃), 3.43 (4H, m, NCH ₂ ×2), 3.30 (4H, m, NCH ₂ ×2), 1.99 (8H, m, CH ₂ ×4)	161.73 (C-3), 147.26 (C-4), 142.76 (C-6), 128.60 (C-5), 52.83 (NCH ₂ ×2), 49.74 (NCH ₂ ×2), 42.47 (SO ₂ CH ₃), 26.19 (CH ₂ ×2), 25.43 (CH ₂ ×2)

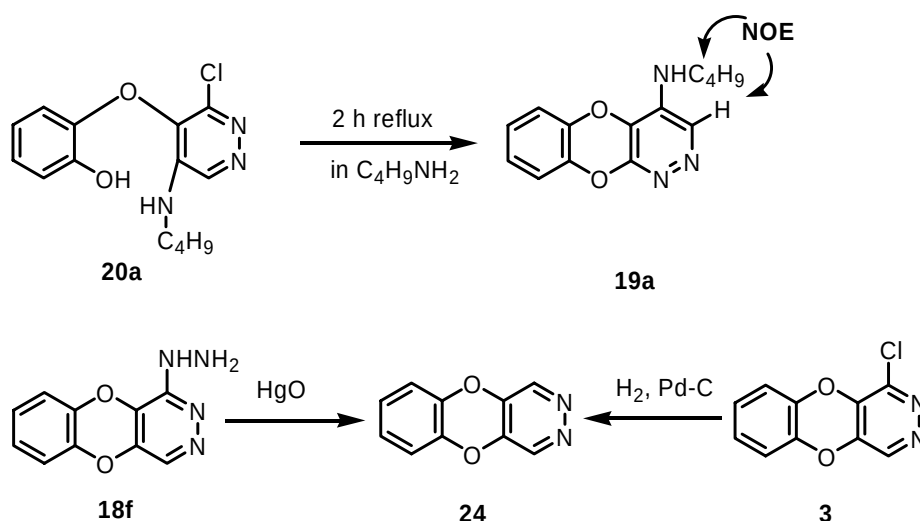
a) NMR in (CD₃)₂SO

In order to confirm the position of the 2-hydroxyphenoxy group for **20a**, a mixture of compound (**20a**) and butylamine was refluxed for 2h to afford **19a** in 41% yield, resulting in the recovery of **20a** in 48% yield. In the same manner, the cyclization of **22d** in refluxing piperidine afforded **19d** in 60% yield. The cyclization of **21a** with sodium methoxide in refluxing MeOH gave **18a** in 9.5% yield, resulting in the recovery of **21a** in 78% yield.

The structures of **19** were established by the nuclear overhauser effect (NOE) being observed between C³-H and C⁴-substituted amino group in their NMR spectrum.

Moreover, the structure of **18f** was determined by the oxidation of **18f** with HgO to give [1,4]benzodioxino[2,3-*d*]pyridazine (**24**) which is identical with the authentic specimen prepared from the reduction of **3**.^{2a, b} (Scheme 8)

Scheme 8

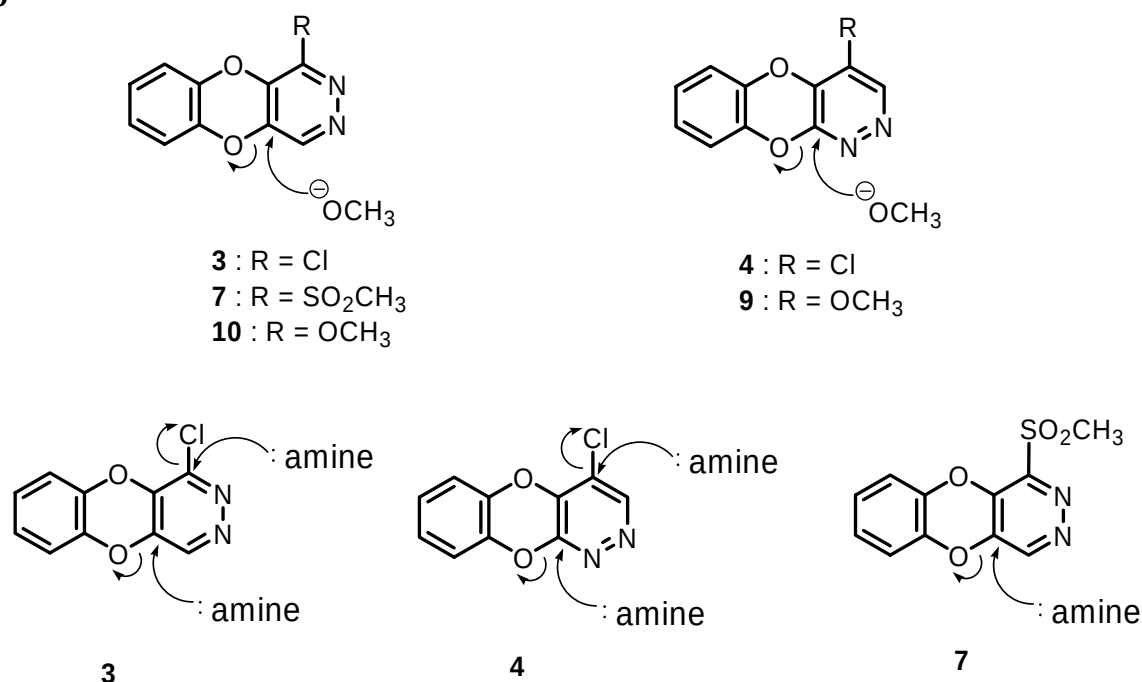


CONCLUSION

In the reaction of [1,4]benzodioxinopyridazines with methoxide ion, nucleophilic attack occurred both at the C-4a ring carbon in 1-substituted [1,4]dioxino[2,3-*d*]pyridazine (**3**, **7** and **10**) and at the C-10a ring carbon in 4-substituted [1,4]dioxino[2,3-*c*]pyridazine (**4** and **9**) to afford dioxin ring-opened pyridazines (**14** -**16** and **17**) followed by intramolecular ring closure to give **9** or **10**, respectively.

In their reaction with amines (**8**), **3** and **4** afforded dioxin ring-opened chloropyridazine (**20** and **21**), followed by ring closure to give aminobenzodioxinopyridazine (**19** and **18**) together with direct chloro-substituted aminobenzodioxinopyridazine (**18** and **19**), respectively. Compound (**7**) afforded dioxin ring-opened product (**22**) and ring closure product (**19**), but the direct substitution of methyl sulfonyl group did not proceed (Scheme 9).

Scheme 9



EXPERIMENTAL

All melting points are uncorrected. Infrared absorption spectra were recorded on a JASCO Report-100 diffraction grating ir spectrophotometer. ^1H -NMR and ^{13}C -NMR spectra were measured at 500 MHz on a JEOL instrument. Chemical shift are expressed in parts per million (ppm) with tetramethylsilane as an internal standard. ^1H -NMR spectral signal patterns are abbreviated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). MS were recorded with a JEOL JMS D-100 mass spectrometer. Column chromatography was carried out on silica gel (Merck Co. Ltd., 200 mesh).

1-Chloro[1,4]benzodioxino[2,3-d]pyridazine(3), and 4-Chloro[1,4]benzodioxino[2,3-c]pyridazine (4)

The following is a modified version of the method of Ames and Ward.^{2a, b} Catechol (**1**) (18.0 g, 164 mmol) was added to sodium hydride (60% dispersion; 13.2 g, 330 mmol) in dry 1,2-dimethoxyethane (DME, 200 mL). The suspension was stirred for 30 min, treated with 3,4,5-trichloropyridazine (**2**) (30.0 g, 164 mmol) in dry DME (50 mL), and then stirred under reflux for 2 h. After cooling, the precipitate was collected, treated with H_2O (200 mL) and extracted with CHCl_3 (100 mL $\times$ 3). The combined CHCl_3 solution was washed with H_2O and dried over Na_2SO_4 . The CHCl_3 solution was concentrated to give **3**, mp 203 – 204°C (from CHCl_3 – benzene), 13.6 g (37.2 %). ^1H -NMR (CDCl_3): 8.67 (1H, s, H-4), 7.04 – 6.91 (4H, m, Ar-H), ^{13}C -NMR (CDCl_3): 145.0 (s, C-1), 141.6 (d, C-4), 142.1, 140.9, 140.6, 139.0 (s, C-4a, C-5a, C-9a, C-10a), 126.2, 126.0 (d, C-7, C-8), 117.7, 117.3 (d, C-6, C-9).

The DME filtrate was treated in the same manner as described above to give the mixture of **3** and **4** (1 : 2), 15.0 g (41.0 %). The crystallization or column chromatography of SiO₂ with CHCl₃ failed to separate **3** and **4**, so the separation was achieved by the reaction of the mixture with thiourea. Compound (**3**) reacted with thiourea to give 1-mercapto[1,4]benzodioxino[2,3-*d*]pyridazine (**5**), but **4** did not react with thiourea to give the recovery of **4**. Thiourea (3.0 g) in MeOH (80 mL) was added to a solution of **3** and **4** mixture (1:2, 15.0 g) in CHCl₃ (100 mL) and the mixture was refluxed for 3.5 h. The solvent was concentrated to a volume of 50 mL to give 3.7 g of **5**. Filtrate was purified by SiO₂ column chromatography eluted with CHCl₃ to give 9.0 g of **4**, mp 156 - 157°C (from MeOH). ¹H-NMR (CDCl₃): 8.72 (1H, s, H-3), 7.08 – 7.03 (4H, m, Ar-H), ¹³C-NMR (CDCl₃): 151.1 (s, C-3), 154.3 (d, C-10a), 141.0, 139.7, 139.6 (s, C-4a, C-5a, C-9a), 126.5, 126.2 (d, C-7, C-8), 117.7, 116.9 (d, C-6, C-9), 122.2 (s, C-4).

1-Mercapto[1,4]benzodioxino[2,3-*d*]pyridazine (5**)**

A mixture of **3** (1.00 g, 6.6 mmol) in CHCl₃ (20 mL) and thiourea (0.54 g, 7 mmol) in MeOH (20 mL) was refluxed for 3.5 h. The solvent was evaporated. The residue was crystallized from MeOH to give slightly yellow powder of **5**, mp 245°C, in 78% yield (0.78 g). MS (*m/z*): 218 (M⁺). *Anal.* Calcd for C₁₀H₆N₂O₂S: C, 55.05; H, 2.77; N, 12.84; S, 14.67. Found: C, 54.79; H, 2.47; N, 12.76; S, 14.47. IR (cm⁻¹): 3100 – 2800 (SH).

1-Methylthio[1,4]benzodioxino[2,3-*d*]pyridazine (6**)**

Methyl iodide (4.69 g, 33 mmol) was added to a solution of **5** (3.69 g, 17 mmol) in 10% KOH (37 mL), and the mixture was shaken for 15 min at rt. The reaction mixture was extracted with CHCl₃ (60 mL×2). The extract was washed with H₂O, dried over Na₂SO₄, concentrated, and the residue was purified by a column chromatography on SiO₂ with CHCl₃. Crystallization from benzene gave **6**, pale yellow needles, mp 162 – 163°C, in 96% yield (3.76 g). *Anal.* Calcd for C₁₁H₈N₂O₂S: C, 56.79; H, 3.47; N, 12.07; S, 13.78. Found: C, 56.70; H, 3.41; N, 12.03; S, 13.65. MS (*m/z*): 232 (M⁺). ¹H-NMR (CDCl₃): 8.51 (1H, s, H-4), 7.00 – 6.85 (4H, m, Ar-H), 2.71 (3H, s, SCH₃). ¹³C-NMR (CDCl₃): 152.5 (s, C-1), 141.3, 141.2, 139.2, 138.5 (s, C-4a, C-5a, C-9a, C-10a), 139.3 (d, C-4), 125.7, 125.6 (d, C-7, C-8), 117.6, 117.3 (d, C-6, C-9), 12.7 (q, SCH₃).

1-Methylsulfonyl[1,4]benzodioxino[2,3-*d*]pyridazine (7**)**

A solution of 3% KMnO₄ (100 mL, 19 mmol) was added dropwise to a solution of **6** (1.0 g, 4.3 mmol) in AcOH (32 mL) over a period of 1 h under stirring at rt. The reaction mixture was decolorized with NaHSO₃ (3.7 g), diluted with H₂O (100 mL) and extracted with CHCl₃ (120 mL, 80 mL). The extract was washed with H₂O, dried over Na₂SO₄, and concentrated to dryness. The residue was recrystallized from

CHCl₃-benzene to give colorless needles, mp 218°C, in 88% yield (1.0 g). *Anal.* Calcd for C₁₁H₈N₂O₄S: C, 50.01; H, 3.05; N, 10.60; S, 12.14. Found: C, 50.08; H, 3.25; N, 10.66; S, 11.91. IR (cm⁻¹): 1320, 1140 (SO₂). ¹H-NMR (CDCl₃): 8.83 (1H, s, H-4), 7.10 – 6.93 (4H, m, Ar-H), 3.51 (3H, s, SO₂CH₃). ¹³C-NMR (CDCl₃): 150.0 (s, C-1), 144.1 (d, C-4), 143.2, 140.5, 140.4, 140.3 (s, C-4a, C-5a, C-9a, C-10a), 126.6, 126.4 (d, C-7, C-8), 118.3, 117.4 (d, C-6, C-9). MS (*m/z*): 264 (M⁺).

3-Chloro-4-(2-hydroxyphenoxy)-5-methoxypyridazine (14)

A mixture of **3** (500 mg, 2.27 mmol) and MeONa (prepared from Na 54 mg (2.35 mmol) and MeOH 6 mL) was stirred for 15 min at rt. The reaction mixture was diluted with H₂O (20 mL), acidified with AcOH and extracted with CHCl₃ (20 mL × 2). The extract was washed with H₂O, dried over Na₂SO₄, concentrated, and the residue was purified by a column chromatography on SiO₂ with CHCl₃, and then CHCl₃-MeOH (20:1). The first fraction gave recovery of **3** (150 mg, 30%) and the second fraction gave 3-chloro-4-(2-hydroxyphenoxy)-5-methoxypyridazine (**14**) in 37.6% yield (215 mg). Compound (**14**) was recrystallized from CHCl₃-benzene to give colorless needles, mp 141 °C (decomp). *Anal.* Calcd for C₁₁H₉N₂O₃: C, 52.29; H, 3.59; N, 11.09. Found: C, 52.01; H, 3.41; N, 10.82. IR (cm⁻¹): 3200 -2500 (OH). MS (*m/z*): 252 (M⁺). ¹H-NMR (DMSO-d₆): 10.13 (1H, br s, OH), 8.47 (1H, s, H-6), 7.26 – 6.93 (4H, m, Ar-H), 4.20 (3H, s, OCH₃). ¹³C-NMR (DMSO-d₆): 150.30 (C-3), 149.02, 148.69, 143.36, 140.77 (C-4, C-5, C-1', C-2'), 143.26 (C-6), 127.85, 122.46, 120.54, 118.13 (C-3', C-4', C-5', C-6'), 61.87 (OCH₃).

5-Chloro-4-(2-hydroxyphenoxy)-3-methoxypyridazine (15)

A mixture of **4** (500 mg, 2.27 mmol) and MeONa (prepared from Na 54 mg (2.35 mmol) and MeOH 6 mL) was stirred for 15 min at rt. The reaction mixture was treated in the same manner as described above to give 5-chloro-4-(2-hydroxyphenoxy)-3-methoxypyridazine (**15**) in 81.7% yield (468 mg). Compound (**15**) was recrystallized from MeOH to give colorless scales, mp 143 °C (decomp). *Anal.* Calcd for C₁₁H₉N₂O₃: C, 52.29; H, 3.59; N, 11.09. Found: C, 51.99; H, 3.35; N, 10.85. IR (cm⁻¹): 3100 -2500 (OH). MS (*m/z*): 252 (M⁺). ¹H-NMR (DMSO-d₆): 9.71 (1H, br s, OH), 8.97 (1H, s, H-6), 7.19 – 6.87 (4H, m, Ar-H), 4.21 (3H, s, OCH₃). ¹³C-NMR (DMSO-d₆): 159.10 (C-3), 149.37 (C-6), 148.83, 144.25, 140.78 (C-4, C-1', C-2'), 126.71 (C-5), 126.51, 122.92, 119.44, 117.12 (C-3', C-4', C-5', C-6'), 61.40 (OCH₃).

4-(2-Hydroxyphenoxy)-5-methoxy-3-methylsulfonylpyridazine (16)

A mixture of **7** (300 mg, 1.14 mmol) and MeONa (prepared from Na 27 mg (1.17 mmol) and MeOH 3 mL) was stirred for 15 min at rt. The reaction mixture was diluted with H₂O (5 mL), acidified with AcOH. The precipitate was collected and recrystallized from MeOH to give 4-(2-hydroxyphenoxy)-5-methoxy-3-methylsulfonylpyridazine (**16**) in 77.3% yield (260 mg), mp 165 °C (decomp), colorless

scales. *Anal.* Calcd for $C_{12}H_{12}N_2O_5S$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.36; H, 3.91; N, 9.25. IR (cm^{-1}): 3100 -2500 (OH), 1300, 1140 (SO_2). MS (m/z): 296 (M^+). 1H -NMR ($DMSO-d_6$): 9.15 (1H, br s, OH), 8.65 (1H, s, H-6), 7.31 – 6.94 (4H, m, Ar-H), 4.25 (3H, s, OCH_3), 3.52 (3H, s, SO_2CH_3). ^{13}C -NMR ($DMSO-d_6$): 155.19 (C-3), 149.17, 148.48, 144.30, 139.59 (C-4, C-5, C-1', C-2'), 144.80 (C-6), 127.62, 122.14, 120.07, 117.65 (C-3', C-4', C-5', C-6'), 61.87 (OCH_3), 41.77 (SO_2CH_3).

Reactions of **14**, **15** and **16** with Sodium Methoxide

A mixture of **14** (250 mg, 1.00 mmol) and MeONa [prepared from Na 24 mg (1.04 mmol) and MeOH 3 mL] was refluxed for 30 min. After cooling, the precipitate was collected, recrystallized from MeOH to give 4-methoxy[1,4]benzodioxino[2,3-*c*]pyridazine (**9**) in 79.5% yield (170 mg), mp 193-194 °C.

In the same manner as described above, **15** gave 1-methoxy[1,4]benzodioxino[2,3-*d*]pyridazine (**10**) in 43.5% yield (93 mg), mp 175-177 °C (from AcOEt).

16 gave compound (**9**) in 77.4% yield.

Reactions of **9** and **10** with Sodium Methoxide

A mixture of **9** (123 mg, 0.57 mmol) and MeONa [prepared from Na 14 mg (0.61 mmol) in MeOH 1.5 mL] was refluxed for 30 min. The reaction mixture was diluted with H_2O (5 mL), acidified with AcOH and extracted with $CHCl_3$ (5 mL $\times$ 2). The extract was washed with H_2O , dried over Na_2SO_4 . The solvent was evaporated. The residue was crystallized from benzene to give 4-(2-hydroxyphenoxy)-3,5-dimethoxypyridazine (**17**) in 74.3% yield (105 mg), colorless needles, mp 150 °C. *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.05; H, 4.87; N, 11.14. IR (cm^{-1}): 3100 -2500 (OH). MS (m/z): 248 (M^+). 1H -NMR ($CDCl_3$): 9.28 (1H, br s, OH), 8.24 (1H, s, H-6), 7.19 – 6.84 (4H, m, Ar-H), 4.14 (3H, s, OCH_3), 4.12 (3H, s, OCH_3). ^{13}C -NMR ($CDCl_3$): 160.46 (C-3), 148.44, 146.95, 141.81, 136.79 (C-4, C-5, C-1', C-2'), 140.75 (C-6), 126.76, 124.86, 120.71, 118.34 (C-3', C-4', C-5', C-6'), 61.17 (OCH_3), 55.76 (OCH_3).

In the same manner as described above, **10** gave compound (**17**) in 63.7% yield.

Reactions of **3**, **4** and **7** with Amines (**8**)

1) Standard Method: A mixture of **3**, **4**, **7** (2.72 mmol) and amines (**8a - e**) (3 mL) was refluxed for 2 h. After the removal of amines under reduced pressure, the residue was extracted with $CHCl_3$. The extract was washed with H_2O , dried over Na_2SO_4 , and concentrated to a volume of about 2 – 5 mL. The concentrated $CHCl_3$ solution was purified by a column chromatography on SiO_2 with $CHCl_3$, and then $CHCl_3$ -MeOH (20 : 1). The first and second fractions respectively gave **18**, and **19**, and the third fraction

gave **20** – **22**, which were purified by recrystallization from an appropriate solvent. The yield, elemental analysis, IR, MS, ¹H-NMR and ¹³C-NMR spectral data for **18** – **22** are summarized in Tables I - V.

The procedure for the reaction of **3** with butylamine (**8a**) is described in detail as a typical example.

A mixture of 1-chloro[1,4]benzodioxino[2,3-*d*]pyridazine (**3**) (600 mg, 2.72 mmol) and butylamine (**8a**) (3 mL, 30 mmol) was refluxed for 2 h. After the removal of butylamine under reduced pressure, the residue was extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄, and concentrated to a volume of about 2 – 5 mL. The concentrated CHCl₃ solution was purified by a column chromatography on SiO₂ with CHCl₃ and CHCl₃ – MeOH (20 : 1). The first fraction eluted with CHCl₃ gave 1-butylamino[1,4]benzodioxino[2,3-*d*]pyridazine (**18a**) in 12.9% yield (90 mg). Compound (**18a**) was recrystallized from CHCl₃-ether to give colorless needles, mp 170°C. The second fraction eluted with CHCl₃ gave 4-butylamino[1,4]benzodioxino[2,3-*c*]pyridazine (**19a**) in 21.4% yield (150 mg). Compound (**19a**) was recrystallized from CHCl₃ - hexane to give colorless needles, mp 191°C. CHCl₃ – MeOH (20 : 1) elution gave 5-butylamino-3-chloro-4-(2-hydroxyphenoxy)pyridazine (**20a**) in 22.5% yield (180 mg). Compound (**20a**) was recrystallized from CHCl₃ – MeOH to give colorless needles, mp 145 – 146°C.

The cyclization of **20a**, **22d** and **21a** was achieved as follows.

A mixture of **20a** (180 mg) and butylamine (**8a**) (2 mL, 20 mmol) was refluxed for 2 h. After removal of butylamine under reduced pressure, the residue was treated in the same manner as described above to give **19a** in 41.3% yield (65 mg) and recovery of **20a** (86 mg, 47.6%). In the same manner, **22d** (150 mg) gave **19d** (70 mg, 60.6%) and recovered **22d** (50 mg, 33.3%). A mixture of **21a** (180 mg, 0.6 mmol) and MeONa [prepared from Na 16 mg (0.7 mmol) and MeOH 2 mL] was refluxed for 1 h gave **18a** in 9.5% yield (15 mg) and the recovery of **21a** (140 mg, 78%).

2) A solution of **3** (600 mg, 2.72 mmol) and 80% hydrazine hydrate (**8f**) (544 mg, 10.9 mmol) in dioxane (6 mL) was refluxed for 2 h. After cooling, the separated crystals were collected by suction and recrystallized from MeOH (29 mL) to give **18f**, 257 mg (43.7%). The MeOH filtrate was concentrated to give a mixture of **18f** and **19f** (100 mg). The dioxane filtrate was evaporated to dryness. The residue was recrystallized from MeOH to give **20f**, 43 mg (6.3%). In the same manner as described above, the reaction of **4** with 80% hydrazine hydrate (**8f**) gave **19f**, 135 mg (23.0%) and **21f**, 270 mg (39.4%). The reaction of **7** (720 mg, 2.72 mmol) with **8f** gave **22f**, 340 mg (42.1%).

The separation of **18f** and **19f** from the reaction mixture was achieved as follows.

The mixture of **18f** and **19f** (100 mg) was added to acetone (0.6 mL) in MeOH (5 mL), refluxed for 2 h. After removal of acetone and MeOH under reduced pressure, the residue was extracted with CHCl₃. The CHCl₃ extract was purified by a column chromatography on SiO₂ with CHCl₃. The first fraction gave 4-isopropylidenehydrazino[1,4]benzodioxino[2,3-*c*]pyridazine (**19f-A**), colorless prisms, mp 210°C (from

benzene), 49 mg. The second fraction gave 1-isopropylidenehydrazino[1,4]benzodioxino[2,3-*d*]pyridazine (**18f-A**), pale yellow prisms, mp 148°C (from CHCl₃ – ether), 53 mg.

A solution of **18f-A** (53 mg, 0.21 mmol) and 80% hydrazine hydrate (35 mg, 0.88 mmol) in MeOH (1 mL) was refluxed for 10 min to give **18f** (43 mg, 7.3%). In the same manner as described above, **19f-A** (49 mg) gave **19f** (40 mg, 6.8%).

Likewise, **20f**, **21f**, and **22f** were purified by the conversion to their isopropylidenehydrazino derivatives respectively (**20f-A**, **21f-A** and **22f-A**). **20f-A**: pale brown prisms, mp 170°C (from MeOH). **21f-A**: pale brown needles, mp 191°C (from MeOH). **22f-A**: pale brown prisms, mp 185°C (from MeOH).

3) A solution of **3** (600 mg, 2.72 mmol) and aniline (**8g**) (1012 mg, 10.9 mmol) in dioxane (6 mL) was refluxed for 3 h. After cooling, the separated **18g** (130 mg, 17.3 %) was collected. **3** (370 mg, 61.7 %) was recovered from dioxane filtrate. The reaction of **4** or **7** with **8g** gave no product.

[1,4]Benzodioxino[2,3-*d*]pyridazine (**24**)

The finely ground 1-hydrazino[1,4]benzodioxino[2,3-*d*]pyridazine (**18f**) (500 mg, 2.3 mmol) was added during 20 min to a stirred suspension of yellow mercuric oxide (3.0 g, 13.9 mmol) in water (60 mL). The mixture was stirred a further 2 h at rt and filtered. The filtrate was extracted with CHCl₃ (40 mL×2). The combined extracts were washed with H₂O, dried over Na₂SO₄, and passed through a column of SiO₂ eluted with CHCl₃. Recrystallization from benzene-petr. benzine gave [1,4]benzodioxino[2,3-*d*]pyridazine (**24**) (colorless needles), mp 196°C (*lit.*,^{2a} 197 – 198°C) in 69.0% yield (297 mg).

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