Pyridazines with Heteroatom Substituents in Position 3 and 5. 3 [1]. 2-Aryl-5-hydroxypyridazin-3(2*H*)-ones as Potential Herbicides: Synthesis and Some Reactions

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Dedicated to Professor Hans Funek on the occasion of his 60th birthday.

The coupling of dimethyl acetonedicarboxylate **1** with a variety of aryldiazonium salts **2a-i** produces the hydrazones **3a-i** which can be cyclized in boiling dichlorobenzene to yield the pyridazone esters **4a-i**, or in sodium hydroxide solution to give the pyridazone acids **5a-f,h,i**, which can be decarboxylated at elevated temperatures. The hydroxy group in **4a,d** can be acylated, sulfonated or alkylated yielding compounds **8a-n**. Condensation of **4a,d** with magic malonates **9a-d** produces the pyronopyridazinones **10a-f**. The reaction of **4a** with hydrazine yields the hydrazide **12** *via* the salt **11**, and with ammonia the amide **14**.

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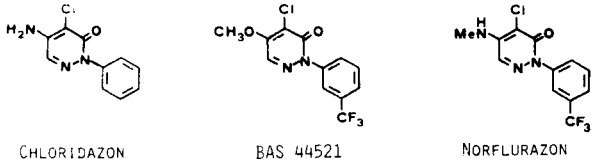
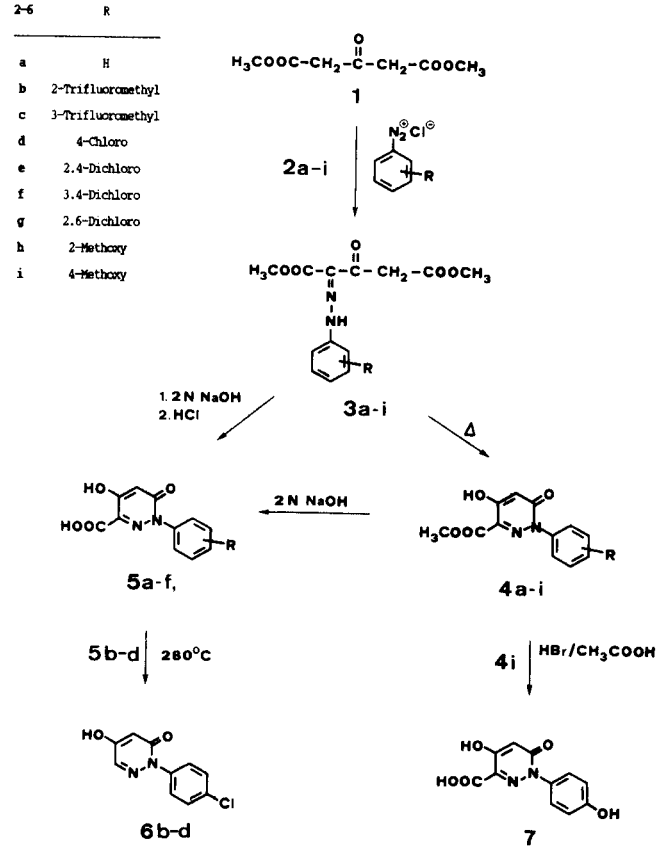


Figure 1

Some pyridazin-3(2*H*)-ones with heteroatoms in position 5 show herbicidal activity, especially those with aryl substituents at N-2, such as "Chloridazon" [4,5], "BAS 44521" [6], and "Norflurazon" [7,8] are worth mentioning (Figure 1). In the synthesis of these compounds mostly mucochloric acid and the corresponding arylhydrazines serve as starting materials. However, there is another entry to this class of *N*-arylpyridazin-3(2*H*)-ones. In 1901 Bülow and Höpfner [9] already had studied the coupling reaction of diethyl acetonedicarboxylate with benzenediazonium chloride **2a** and subsequent treatment with sodium hydroxide solution, and in 1935 Sonn [10] established the structure of the compound obtained with **2a** as 5-hydroxy-2-phenyl-3-oxo-2.3-dihydropyridazine-6-carboxylic acid **5a**. We have now adopted this method to synthesize a number of new *N*-arylpyridazin-3(2*H*)-ones.

According to the ir and ^{1}H-nmr data the coupling products **3a-i** exist predominantly in the hydrazone form. This structure is stabilized by a hydrogen bridge between NH and CO, resulting in a six-membered ring system. We found a direct approach to **4a-i** from **3a-i** by thermal ring closure performed in bromo benzene or better 1.2-dichloro benzene yielding **4a-i** in very good yields, while Sonn [10] obtained **4a** only from esterification of **5a** with methanol. The hydrazones **3b,e,g,h**, substituted in the *ortho*-position, require more time to react which can be explained by steric hindrance. There is no such difference between the hydrazones **3** in the reaction with alkali leading directly to the carboxylic acids **5a-f,h,i**.

Scheme 1



Decarboxylation of **5b-d** can be performed without solvent at 280°, there is no need to use concentrated sulfuric

Table 1

1-Arylhydrazono-2-oxopropane-1.3-dicarboxylates **3a-i**

No.	R	Formula (Molecular weight)	Yield (%)	mp (recrystallization solvent)	Analysis (Calcd./Found) C	H	N	Cl	IR (cm^{-1})
3a	H	$C_{13}H_{14}N_2O_5$ (278.2)	98	86-89° (ethanol/water)					3120 w, 2929 w, 1720 s, 1715 s, 1680 s 1665 s, 1640 sh, 1635 sh, 1625 sh, 1590 sh, 1585 w, 1520 s, 1500 s, 1490 sh
3b	2-Trifluoro-methyl	$C_{14}H_{13}F_3N_2O_5$ (346.3)	99	101-103° (ligroin)	48.56 48.80	3.78 3.99	8.09 8.23		1750 s, 1740 sh, 1700 sh, 1690 s, 1675 sh, 1590 w, 1540 sh, 1525 s,
3c	3-Trifluoro-methyl	$C_{14}H_{13}F_3N_2O_5$ (346.3)	95	94-95° (ligroin)	48.56 48.42	3.78 3.98	8.09 8.08		2970 w, 2750 s, 1690 s, 1680 sh, 1610 w, 1525 s, 1500 sh
3d	4-Chloro [a]	$C_{13}H_{13}ClN_2O_5$ (312.7)	94	108-109° (methanol)	49.93 50.03	4.19 4.13	8.96 8.85		3160 w, 2960 w, 1730 s, 1700 s, 1680 sh, 1595 w, 1530 s, 1500 m
3e	2.4-Dichloro	$C_{13}H_{12}Cl_2N_2O_5$ (347.2)	92	123-124° (ligroin)	44.97 44.87	3.49 3.61	8.07 8.01	20.43 20.82	3600-3000 b, 2960 w, 1740 s, 1700 s, 1685 sh, 1670 m, 1640 sh, 1570-1550 m, 1520 s, 1510 s
3f	3.4-Dichloro	$C_{13}H_{12}Cl_2N_2O_5$ (347.2)	86	120-122° (ligroin)	44.97 44.85	3.49 3.55	8.07 8.04	20.43 20.26	3140-3070 w, b, 3000 sh, 2960 w, 1750 sh, 1735 s, 1705 sh, 1695 s, 1680 sh, 1575 m, 1540 sh, 1520 s
3g	2.6-Dichloro	$C_{13}H_{12}Cl_2N_2O_5$ (347.2)	88	69-72° (ligroin)	44.97 44.76	3.49 3.60	8.07 8.05		3080 w, 3000 w, 2960 w, 1780 sh, 1750 s, 1710 sh, 1690 s, 1675 sh, 1660 sh, 1570 m, 1560 sh, 1540 s, 1500 sh, 1495 m
3h	2-Methoxy	$C_{14}H_{16}N_2O_6$ (308.3)	69	110-112° (ligroin)	54.54 54.30	5.23 5.32	9.09 8.99		3200 sh, 3170 w, 2970 sh, 2950 w, 1735 s, 1710 sh, 1690 s, 1660 sh, 1640 sh, 1530-1520 s, b, 1510 sh
3i	4-Methoxy	$C_{14}H_{16}N_2O_6$ (308.3)	100	70-72° (ethanol/water)	54.54 54.19	5.23 4.96	9.09 8.96		2940 w, 2840 w, 2380 w, 1780 s, 1700 s, 1680 sh, 1650 w, 1620 w, 1540 sh, 1510 s

[a] The diethyl ester of **3d** was also obtained: $C_{15}H_{17}ClN_2O_5$ (340.8), yield 80%, mp 83-84° (methanol).

Table 2

^{1}H-NMR Spectral Data of **3**
(measured in deuteriochloroform)

3a: δ = 3.7 (s, CH_3), 3.9 (s, CH_2), 3.95 (s, CH_3), 7.4 (s, 5 ArH)

3b: δ = 3.7 (s, CH_3), 3.85 (s, CH_2), 3.9 (s, CH_3), 7.1-8.0 (m, 4 ArH)

3c: δ = 3.7 (s, CH_3), 3.9 (s, CH_2), 4.0 (s, CH_3), 7.4-7.7 (m, 4 ArH), 13.1-13.3 (b, NH)

3d: δ = 3.7 (s, CH_3), 3.85 (s, CH_2), 3.9 (s, CH_3), 7.3 (s, 4 ArH)

3e: δ = 3.7 (s, CH_3), 3.9 (s, CH_2), 4.0 (s, CH_3), 7.1-7.9 (m, 3 ArH), 13.2-13.4 (s, b, NH)

3i: δ = 3.7 (s, ester-CH_3), 3.8-4.0 (m, CH_2, ester-CH_3 and methoxy-CH_3), 6.9-7.5 (m, 4 ArH), 13.2-13.3 (s, b, NH)

acid at 240° as it was described by Sonn [10].

Some attempts to cleave the (4-methoxy)phenyl group in **4i** by reaction with ceric ammonium nitrate in acetonitrile/water as it was described for some 4-membered lactames [11] were performed without success. This cleavage should be preceeded by demethylation [12], but also the 4-hydroxy-derivative **7**, obtained from **4i** by reaction with hydrobromic acid in glacial acetic acid, failed to react with ceric ammonium nitrate.

Scheme 2

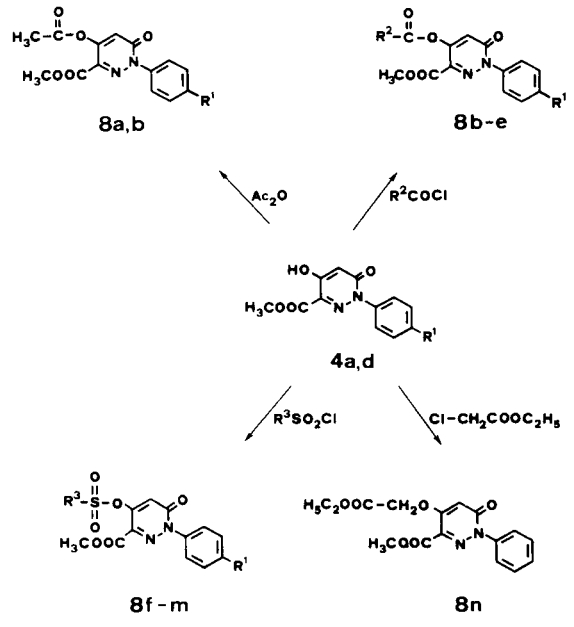


Table 3

2-Aryl-5-hydroxy-3-oxo-2.3-dihydropyridazine-6-carboxylates (**4a-i**)

No.	R	Formula (Molecular weight)	Yield (%)	mp (recrystallization solvent)	Analysis (Calcd./Found) C	H	N	Cl	IR (cm^{-1})
4a	H	$C_{12}H_{16}N_2O_4$ (246.2)	94	129-130° [a] (ethanol/water)					3200-2200 w, b, 1740 s, 1690 sh, 1670 s, 1630 m, 1570-1550 m, b, 1510 m, 1500 sh, 1480 m
4b	2-Trifluoro-methyl	$C_{13}H_9F_3N_2O_4$ (314.2)	85	151-152° (ligroin)	49.69 49.37	2.88 2.79	8.92 8.82		3200-2900 w, b, 1770 sh, 1720 sh, 1690 s, 1680 s, 1620 w, 1610 w, 1525 m
4c	3-Trifluoro-methyl	$C_{13}H_9F_3N_2O_4$ (314.2)	73	120-121° (methanol)	49.69 49.29	2.88 2.83	8.92 8.84		3300-3100 w, b, 1720 sh, 1700 s, 1680 m, 1620 w, 1520 w, 1510 w, 1500 w
4d	4-Chloro	$C_{12}H_9ClN_2O_4$ (280.7)	97	161-162° (methanol)	51.34 51.14	3.23 3.18	9.98 9.80	12.63 12.35	3360-3200 w, b, 1715 s, 1690 s, 1520 m, 1500 m
4e	2.4-Dichloro	$C_{12}H_8Cl_2N_2O_4$ (315.1)	70	126-127° (toluene)	45.74 46.09	2.56 2.70	8.89 8.73		3260 m, 3100 w, 1765 sh, 1700-1690 sh, s, b, 1680 s, 1650 sh, 1510 m
4f	3.4-Dichloro	$C_{12}H_8Cl_2N_2O_4$ (315.1)	89	176-178° (toluene)	45.74 45.72	2.56 2.71	8.89 8.73		3300-3160 w, b, 1760 sh, 1720 sh, 1700 s, 1690 sh, 1650 sh, 1510 m
4g	2.6-Dichloro	$C_{12}H_8Cl_2N_2O_4$ (315.1)	72	196-198° (toluene)	45.74 45.71	2.56 2.74	8.89 8.83	22.51 22.74	3200-2600 m, b, 1755 s, 1740 sh, 1680 sh, 1660 sh, 1640 s, 1580-1560 s, b, 1545 sh, 1520 m, 1500 sh
4h	2-Methoxy	$C_{13}H_{12}N_2O_5$ (276.3)	91	171-172° (toluene)	56.52 56.80	4.38 4.39	10.14 10.02		3240-2600 m, b, 1755 s, 1740 sh, 1660 sh, 1645 s, 1605 m, 1570-1560 s, b, 1550 sh, 1530 s, 1500 s
4i	4-Methoxy	$C_{13}H_{12}N_2O_5$ (276.3)	82	183-184° (ethanol)	56.52 56.42	4.38 4.52	10.14 9.92		3260 w, 3080 w, 1740 sh, 1720 sh, 1690 s, 1660 sh, 1610 m, 1510 s

[a] Lit [10] 138°.

According to the structure of Pyridate, a selective herbicide [13-15], the esters **8a-m** and the *O*-acetate **8n** were of interest. The synthesis was performed by three methods:

Table 4

^{1}H-NMR Spectral Data of **4**
(measured in deuteriochloroform unless otherwise stated)

4a: (hexadeuteriodimethyl sulfoxide): δ = 3.7 (s, CH_3), 6.2 (s, H at C-4), 7.4 (s, 5 ArH)

4b: (hexadeuteriodimethyl sulfoxide): δ = 3.8 (s, CH_3), 6.3 (s, H at C-4), 7.4-8.0 (m, 4 ArH)

4c: δ = 4.0 (s, CH_3), 6.4 (s, H at C-4), 7.5-7.9 (m, 4 ArH), 10.3 (s, OH)

4d: δ = 3.9 (s, CH_3), 6.3 (s, H at C-4), 7.4 (s, 4 ArH)

4e: (hexadeuteriodimethyl sulfoxide): δ = 3.8 (s, CH_3), 6.3 (s, H at C-4), 7.5-7.9 (m, 3 ArH)

4f: δ = 4.0 (s, CH_3), 6.4 (s, H at C-4), 6.5-6.8 (m, 3 ArH), 10.3-10.5 (b, OH)

4g: δ = 4.1 (CH_3), 6.9 (s, H at C-4), 7.5 (s, 3 ArH)

4h: (hexadeuteriodimethyl sulfoxide): δ = 3.7 (s, methoxy-CH_3), 3.8 (s, ester-CH_3), 6.2 (s, H at C-4), 7.0-7.6 (m, 4 ArH), 11.4-11.9 (b, OH)

4i: δ = 3.8 (s, methoxy-CH_3), 4.0 (s, ester-CH_3), 6.3 (s, H at C-4), 6.8-7.6 (m, 4 ArH)

Scheme 3

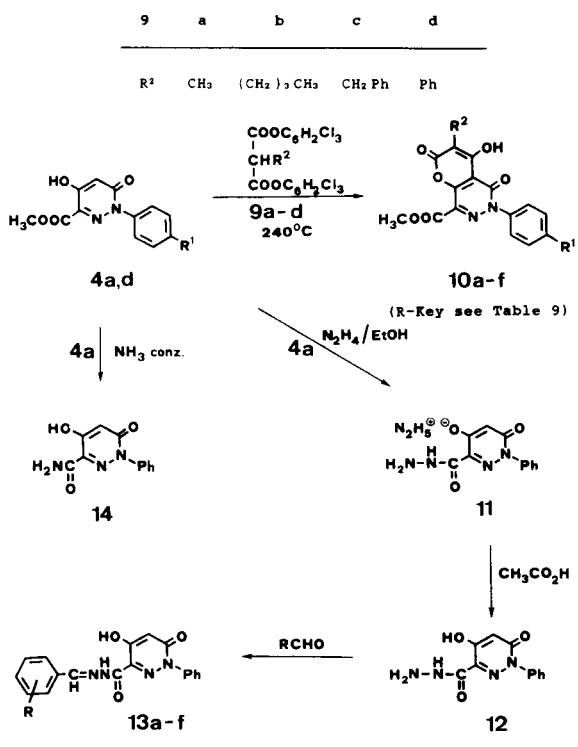


Table 5

2-Aryl-5-hydroxy-3-oxo-2,3-dihydropyridazine-6-carboxylic Acids **5a-f,h,i**

No.	R	Formula (Molecular weight)	Yield (%)	mp (recrystallization solvent)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
5a	H	$C_{11}H_8N_2O_4$ (232.2)	89	251-253° [a] (methanol)				3300-2300 m, b, 1720 s, 1640 sh, 1625-1615 sh, s, b, 1610 s, 1600 sh, 1580 sh, 1560 sh, 1510 m, 1490 sh
5b	2-Trifluoro-methyl	$C_{12}H_7F_3N_2O_4$ (300.2)	92	258-259° (acetone)	48.02 47.62	2.35 2.34	9.33 9.17	3500-2300 m, b, 1710 s, 1660 sh, 1650 s, 1620 m, 1605 sh, 1520 m, 1500 m
5c	3-Trifluoro-methyl	$C_{12}H_7F_3N_2O_4$ (300.2)	81	262-263° (methanol)	48.02 47.95	2.35 2.40	9.33 9.25	3350-2400 m, b, 1730 s, 1660 sh, 1640 s, 1625 s, 1605 sh, 1520 m, 1500 w
5d	4-Chloro	$C_{11}H_7ClN_2O_4$ (266.7)	85	269-271° (methanol)	49.54 49.30	2.65 2.40	10.50 10.35	1720 s, 1710 sh, 1695 sh, 1630 s, 1600 s, 1585 s, 1520 m, 1495 s
5e	2.4-Dichloro	$C_{11}H_6Cl_2N_2O_4$ (301.1)	77	240° (methanol)	43.88 43.52	2.01 2.13	9.31 9.06	3500-2200 m, b, 1720 s, 1700 sh, 1685 sh, 1620 s, 1585 m, 1570 sh, 1510 m, 1480 m
5f	3.4-Dichloro	$C_{11}H_6Cl_2N_2O_4$ (301.1)	99	266-268° dec (methanol)	43.88 43.68	2.01 2.21	9.31 9.22	3300-2700 w, b, 1725 m, 1710 sh, 1690 sh, 1660 sh, 1635 s, 1610 sh, 1560 sh, 1510 m
5h	2-Methoxy	$C_{12}H_{10}N_2O_5$ (262.2)	76	232° dec (methanol)	54.96 54.89	3.84 3.83	10.69 10.58	3080-2780 w, b, 1720 sh, 1690-1670 m, b, 1605 s, 1600-1560 sh, s, b, 1500 s
5i	4-Methoxy	$C_{12}H_{10}N_2O_5$ (262.2)	95	238° dec (1-butanol)	54.96 54.60	3.84 3.95	10.69 10.50	3200 m, 3100 m, 3000-2600 w, b, 1720 s, 1640 sh, 1620 s, 1590 sh, 1510 s, 1500 sh

[a] Lit [9] 251°; Lit [10] 244-255°.

Table 6

^{1}H-NMR Spectral Data of **5**
(measured in hexadeuteriodimethyl sulfoxide)

5b: δ = 6.3 (s, H at C-4), 7.4-8.1 (m, 4 ArH), 10.0 (s, OH and COOH)

5c: δ = 6.2 (s, H at C-4), 7.4-8.0 (m, 4 ArH)

5d: δ = 6.1 (s, H at C-4), 7.5 (s, 4 ArH)

5e: δ = 6.2 (s, H at C-4), 7.5-7.9 (m, 3 ArH), 11.7 (s, OH and COOH)

5f: δ = 6.2 (s, H at C-4), 7.5-8.0 (m, 3 ArH), 12.0-12.3 (s, b, OH and COOH)

5h: δ = 3.8 (s, CH_3), 6.2 (s, H at C-4), 6.9-7.7 (m, 4 ArH), 10.9-11.2 (s, b, OH and COOH)

5i: δ = 3.7 (s, CH_3), 6.2 (s, H at C-4), 6.8-7.5 (m, 4 ArH), 10.1-10.3 (s, b, OH and COOH)

refluxing in acetic anhydride (**8a,b**), reaction with the suitable acid chlorides in dimethylformamide with trimethylamine and 4-dimethylamino-pyridine as catalyst (**8b-m**), or reaction with ethyl chloroacetate in dimethylformamide with dry potassium carbonate (**8n**).

The synthesis of condensed 4-hydroxypyran-2-ones using phenols and dialkyl malonates has been known for a long time [16-18]. The use of 5-hydroxypyridazin-3(2*H*)-ones leads to the little known pyrano[2,3-*d*]pyridazine system [19,20]. Kos [20] was able to show that the reaction of the corresponding 6-phenylpyridazines can be performed with dialkyl malonates at very high temperatures whereas the active malonates **9a-d** [21] afford the desired products at much lower temperatures. Starting from **4a,d** we had to use the reactive malonates **9a-d** to obtain **10a-f** because increasing of the reaction temperature led to decomposition (the esters **10a-f** are much more instable than the products obtained by Kos).

The ester **4a** undergoes hydrazinolysis leading first to the hydrazinium salt **11** which can be isolated. The 6-hydrazinocarbonyl compound **12** was obtained from **11** in aqueous solution by acidification with acetic acid. The Schiff-bases **13a-f** are easily obtained from **12** and the corresponding aldehydes in ethanolic solution.

Finally, **14** was obtained by reaction of **4a** with aqueous ammonia.

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus Model MFB-595 and are uncorrected. The ir spectra were recorded on a Perkin Elmer 298 spectrophotometer using samples in potassium bromide disks. The ^{1}H-nmr spectra were recorded in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) and with TMS as an internal standard; the instrument used was the Varian EM 360 at 60 MHz. Elemental analyses were performed with a C,H,N-automat Carlo Erba 1106.

Table 7

Esters **8a-m**

No.	R^1	R^2	R^3	Formula (Molecular weight)	Method	Yield (%)	mp (recrystallization solvent)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
8a	H	CH_3	-	$C_{14}H_{12}N_2O_5$ (288.3)	A	83	121-122° (ethanol)	58.33 58.20	4.20 4.30	9.72 9.73	3380 w, 3100 w, 2980 w, 1780 m, 1760 m, 1730 s, 1690 s, 1660 sh, 1600 w, 1580 sh, 1515 m, 1500 m
8b	Cl	CH_3	-	$C_{14}H_{11}ClN_2O_5$ (322.7)	A B	99 58	129-132° (ethanol)	52.10 52.15	3.44 3.60	8.68 8.45	3100-3070 w, 2960 w, 1780 s, 1735 s, 1690 sh, 1680 s, 1655 sh, 1490 s
8c	H	$(CH_3)_2N$	-	$C_{15}H_{15}N_3O_5$ (317.3)	B	74	144-146° (ethanol)	56.78 56.81	4.77 4.71	13.24 13.25	3040 w, 2950 w, 1740 s, 1730 s, 1685 sh, 1680 s, 1610 w, 1490 m
8d	Cl	$(CH_3)_2N$	-	$C_{15}H_{14}ClN_3O_5$ (351.7)	B	85	118-120° (cyclohexane)	51.22 51.26	4.01 4.17	11.95 11.90	3100 w, 3070 m, 2960 w, 1740 s, 1720 s, 1685 sh, 1680 s, 1650 sh, 1610 m, 1510 sh, 1490 m
8e	Cl	$(C_2H_5)_2N$	-	$C_{17}H_{18}ClN_3O_5$ (379.8)	B	47	95-97° (ligroin)	53.76 53.69	4.78 4.76	11.06 11.01	3080 w, 2980 w, 1740 s, 1720 s, 1685 s, 1655 sh, 1620 w, 1490 m
8f	H	-	$(CH_3)_2N$	$C_{14}H_{15}N_3O_6S$ (353.3)	B	74	130-131° (ligroin)	47.59 47.80	4.28 4.35	11.89 11.90	3100 w, 2960 w, 1740 s, 1680 s, 1600 sh, 1510 sh, 1490 sh, 1480 w
8g	Cl	-	$(CH_3)_2N$	$C_{14}H_{14}ClN_3O_6S$ (378.8)	B	78	140-142° (ethanol)	43.36 43.44	3.64 3.81	10.84 10.65	3060 w, 2950 w, 1745 s, 1685 s, 1610 w, 1510 sh, 1490 m
8h	H	-	Ph	$C_{18}H_{14}N_2O_6S$ (386.4)	B	62	131-133° (ethanol)	55.95 55.73	3.65 3.80	7.25 7.21	3060 w, 2960 w, 1735 s, 1690 s, 1670 sh, 1650 sh, 1500 m, 1490 m
8i	Cl	-	Ph	$C_{18}H_{13}ClN_2O_6S$ (420.9)	B	62	136-138° (ligroin)	51.37 51.53	3.11 3.17	6.66 6.77	1775 sh, 1735 s, 1705 sh, 1695 s, 1690 sh, 1660 sh, 1605 w, 1490 m
8j	H	-	4-CH_3Ph	$C_{19}H_{16}N_2O_6S$ (400.4)	B	92	120-121° (ethanol)	56.98 56.68	4.03 3.86	7.00 6.99	3100 w, 2960 w, 1740 s, 1690 s, 1670 sh, 1650 sh, 1595 m, 1490 m
8k	Cl	-	4-CH_3Ph	$C_{19}H_{15}ClN_2O_6S$ (434.9)	B	92	118-120° (ethanol)	52.48 52.34	3.48 3.47	6.44 6.25	3090-3060 w, 3000 w, 2950 w, 1740 s, 1690 s, 1605 w, 1590 w, 1490 m
8l	H	-	4-BrPh	$C_{18}H_{13}BrN_2O_6S$ (465.3)	B	49	126-128° (ethanol)	46.46 46.42	2.82 2.94	6.02 6.01	3070 sh, 3050 m, 2960 w, 1735 s, 1700 sh, 1685 s, 1650 sh, 1600 sh, 1590 m, 1585 m, 1500 m, 1490 m
8m	Cl	-	4-BrPh	$C_{18}H_{12}BrClN_2O_6S$ (499.8)	B	56	144-145° (ethanol)	43.26 43.19	2.42 2.51	5.61 5.60	3100 w, 3080 sh, 1740 s, 1685 sh, 1680 s, 1650 sh, 1610 w, 1570 m, 1510 w, 1490 m

Table 8

^{1}H-NMR Spectral Data of **8a-m**
(measured in deuteriochloroform)

8a: δ = 2.3 (s, acetyl-CH_3), 3.8 (s, ester-CH_3), 6.7 (s, H at C-4), 7.3-7.7 (m, 5 ArH)

8b: δ = 2.4 (s, acetyl-CH_3), 3.9 (s, ester-CH_3), 6.8 (s, H at C-4), 7.4-7.7 (m, 4 ArH)

8c: δ = 3.0 (s, N-CH_3), 3.1 (s, N-CH_3), 3.9 (s, ester-CH_3), 6.9 (s, H at C-4), 7.2-7.9 (m, 5 ArH)

8d: δ = 3.1 (s, N-CH_3), 3.2 (s, N-CH_3), 4.0 (s, ester-CH_3), 6.9 (s, H at C-4), 7.5-7.6 (d, J = 7 Hz, 4 ArH)

8e: δ = 1.1-1.5 (2 t, J = 7 Hz, 2 ethyl-CH_3), 3.2-3.7 (2 q, J = 7 Hz, 2 N-CH_2), 3.9 (s, ester-CH_3), 6.9 (s, H at C-4), 7.5-7.7 (d, J = 7 Hz, 4 ArH)

8f: δ = 3.1 (s, 2 N-CH_3), 3.9 (s, ester-CH_3), 7.1 (s, H at C-4), 7.4-7.7 (m, 5 ArH)

8g: δ = 3.1 (s, 2 N-CH_3), 4.0 (s, ester-CH_3), 7.1 (s, H at C-4), 7.5-7.6 (m, 4 ArH)

8h: δ = 3.8 (s, CH_3), 6.9 (s, H at C-4), 7.5 (s, 5 ArH of N-phenyl), 7.5-8.2 (m, 5 ArH of SO_2-phenyl)

8j: δ = 2.5 (s, tosyl-CH_3), 3.9 (s, ester-CH_3), 6.8 (s, H at C-4), 7.3-8.0 (m, 9 ArH)

8k: δ = 2.5 (s, tosyl-CH_3), 3.9 (s, ester-CH_3), 6.9 (s, H at C-4), 7.2-8.1 (m, 8 ArH)

8l: δ = 3.9 (s, CH_3), 6.9 (s, H at C-4), 7.3-7.6 (m, 5 ArH of N-phenyl), 7.7-7.9 (m, 4 ArH of 4-Br-phenyl)

8m: δ = 3.9 (s, CH_3), 6.9 (s, H at C-4), 7.5-7.7 (m, 4 ArH), 7.8-8.0 (m, 4 ArH)

Table 9

6-Aryl-4-hydroxy-8-methoxycarbonylpyrano[2,3-*d*]pyridazine-2.5(6*H*)-diones **10a-f**

No.	R^1	R^2	Formula (Molecular weight)	Yield (%)	mp (recrystallization solvent)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
10a	H	CH_3	$C_{16}H_{12}N_2O_6$ (328.3)	66	187-188° (ligroin)	58.54 58.80	3.69 3.94	8.54 8.57	1750 s, 1735 sh, 1690 sh, 1675 s, 1655 sh, 1610 w, 1590 w, 1520 w, 1490 w
10b	H	$(CH_2)_3CH_3$	$C_{19}H_{18}N_2O_6$ (370.4)	37	134-136° (ligroin)	61.61 61.63	4.90 4.65	7.57 7.88	2960 w, 2930 w, 2860 w, 1750 s, 1730 s, 1720 sh, 1690 sh, 1670 s, 1650 sh, 1610 w, 1590 w, 1490 w
10c	H	CH_2Ph	$C_{22}H_{16}N_2O_6$ (404.4)	76	173-175° (ligroin)	65.34 65.37	3.99 4.16	6.93 6.86	1750 s, 1740 sh, 1680 s, 1600 w, 1590 sh, 1490 w
10d	H	Ph	$C_{21}H_{14}N_2O_6$ (390.3)	81	192-194° (ligroin)	64.61 64.88	3.61 3.80	7.18 7.13	1780 sh, 1750 s, 1735 s, 1720 sh, 1690 sh, 1670 s, 1650 sh, 1600 w, 1490 w
10e	Cl	CH_3	$C_{16}H_{11}ClN_2O_6$ (362.7)	83	206° (ligroin)	52.98 52.99	3.06 3.26	7.72 7.75	1760 s, 1735 s, 1720 sh, 1685 sh, 1670 s, 1650 sh, 1610 w, 1490 w
10f	Cl	Ph	$C_{21}H_{13}ClN_2O_6$ (424.8)	70	196-197° (ligroin)	59.37 59.14	3.08 3.27	6.60 6.56	1780 m, 1750 s, 1730 s, 1720 sh, 1670 s, 1650 sh, 1490 m

Table 10

^{1}H-NMR Spectral Data of **10**
(measured in deuteriochloroform)

10a: δ = 2.1 (s, CH_3 at C-3), 4.0 (s, ester-CH_3), 7.5 (s, 5 ArH), 11.7 (s, OH)

10b: δ = 0.7-1.1 (m, *n*-butyl-CH_3), 1.1-1.8 (m, 2 *n*-butyl-CH_2), 2.3-2.7 (m, CH_2 at C-3), 4.0 (s, ester-CH_3), 7.5 (s, 5 ArH), 11.7 (s, OH)

10c: δ = 3.9 (s, CH_2), 4.0 (s, CH_3), 7.1-7.6 (m, 10 ArH), 11.8-11.9 (s, b, OH)

10d: δ = 4.1 (s, CH_3), 7.4-7.8 (m, 10 ArH), 12.1-12.3 (s, b, OH)

10e: δ = 2.2 (s, CH_3 at C-3), 4.1 (s, ester-CH_3), 7.3 (s, OH), 7.6 (m, 4 ArH)

10f: δ = 4.1 (s, CH_3), 7.3-7.9 (m, 4 ArH)

General Procedure for Dimethyl 1-Arylhydrazono-2-oxopropane-1.3-dicarboxylates **3a-i**.

A mixture of 10 ml of concentrated hydrochloric acid, 20 ml of water, and 20 mmoles of the aniline **2a-i** was treated with a solution of 1.38 g (20 mmoles) of sodium nitrite in 15 ml of water at temperatures below 5°. When the diazotation reaction was finished this solution was poured into a mixture of 3.48 g (20 mmoles) of dimethyl acetonedicarboxylate in 12 ml of ethanol and 12 g of sodium acetate in 40 ml of water with vigorous stirring. The product started to precipitate almost immediately, but the mixture was stirred for another 30 minutes before filtration.

General Procedure for Methyl 2-Aryl-5-hydroxy-3-oxo-2.3-dihydropyridazine-6-carboxylates **4a-i**.

A solution of 10 mmoles of **3a,c,d,f,i** in 10 ml of 1.2-dichlorobenzene was refluxed for 45 minutes; using 2-substituted hydrazones **3b,e,g,h** three hours of refluxing were required. The solvent was removed under reduced pressure and the oily residue crystallized by the addition of cyclohexane.

General Procedures for 2-Aryl-5-hydroxy-3-oxo-2.3-dihydropyridazine-6-carboxylic Acids **5a-f,h,i**.

A) The hydrazones **3a-f,h,i** (40 mmoles) were dissolved in 200 ml of 2 *N* sodium hydroxide, filtered and the solution was acidified by addition of concentrated hydrochloric acid with vigorous stirring. The product precipitated immediately. The yields are in Table 5.

B) The pyridazine esters **4c,d,i** (10 mmoles) were refluxed in 20 ml of 2 *N* sodium hydroxide for 30 minutes. After cooling the solution was acidified with concentrated hydrochloric acid.

The yields following Method B are **5c**, 93%; **5d**, 85%; **5i**, 95%.

5-Hydroxy-2-(2-trifluoromethyl)phenylpyridazin-3(2*H*)-one (**6b**).

The carboxylic acid **5b** (2.0 g) was heated to 280°. When the evolution of carbon dioxide was completed, the residue was cooled, dissolved in 30 ml of 2 *N* sodium hydroxide, filtered and acidified by the addition of concentrated hydrochloric acid. The yield was 1.0 g (59%), mp 205-207° (acetonitrile); ir: 3200-2200 w, b, 1645 s, 1620 w, 1600 sh, 1585 sh, 1570 s, 1550 s, 1505 w cm^{-1}; ^{1}H-nmr: δ = 6.0 (d, J = 2 Hz, H at C-4), 7.3-8.0 (m, 4 ArH and H at C-6).

Anal. Calcd. for $C_{11}H_7F_3N_2O_2$: C, 51.57; H, 2.75; N, 10.94. Found: C, 51.38; H, 2.76; N, 10.84.

5-Hydroxy-2-(3-trifluoromethyl)phenylpyridazin-3(2*H*)-one (**6c**).

The carboxylic acid **5c** (1.0 g) was treated as described for **6b**. The yield was 0.55 g (64%), mp 199-201° (acetonitrile); ir: 1650 m, 1615 sh, 1600 sh, 1580-1565 sh, m, 1560 s, 1500 sh cm^{-1}; ^{1}H-nmr: δ = 6.05 (d, J = 2 Hz, H at C-4), 7.5-8.0 (m, 4 ArH and H at C-6), 11.3-12.0 (b, OH).

Anal. Calcd. for $C_{11}H_7F_3N_2O_2$: C, 51.57; H, 2.75; N, 10.94. Found: C, 51.48; H, 2.63; N, 10.88.

2-(4-Chloro)phenyl-5-hydroxypyridazin-3(2*H*)-one (**6d**).

The carboxylic acid **5d** (1.0 g) was treated as described for **6b**. The yield was 0.50 g (60%), mp 312-313° (methanol); ir: 3200-2300 m, b, 1685 sh, 1675 sh, 1660 m, 1645 m, 1610 s, 1595 s, 1580 s, 1550 m, 1500 m cm^{-1}; ^{1}H-nmr: δ = 5.95 (d, J = 2 Hz, H at C-4), 7.5 (s, 4 ArH), 7.7 (d, J = 2 Hz, H at C-6).

Anal. Calcd. for $C_{10}H_7ClN_2O_2$: C, 53.96; H, 3.15; N, 12.59. Found: C, 53.71; H, 3.12 N, 12.40.

5-Hydroxy-2-(4-hydroxy)phenyl-3-oxo-2.3-dihydropyridazine-6-carboxylic Acid (**7**).

The pyridazine **4i** (15.7 g) was refluxed in 120 ml of hydrobromic acid (33% in glacial acetic acid) for three hours. Upon cooling **7** started to precipitate and water was added to complete the precipitation to afford 11.82 g (84%), mp 245-248° dec (1-butanol); ir: 3500 w, b, 1740 sh, 1720

Table 11

6-Arylidenhydrazinocarbonyl-5-hydroxy-2-phenylpyridazin-3(2*H*)-ones **13a-f**

No.	R	Formula (Molecular weight)	Yield (%)	mp (recrystallization solvent)	Analysis (Calcd./Found) C	H	N	IR (cm^{-1})
13a	H	$C_{18}H_{14}N_4O_5$ (334.3)	95	184-186° (ethanol)	64.66 64.65	4.22 4.23	16.76 16.76	3600-3340 w, b, 3240-3120 w, b, 3080-2960 w, b, 1680 s, 1650 s, 1635 sh, 1610 s, 1530 m, 1490 w
13b	2-Chloro	$C_{18}H_{13}ClN_4O_2$ (368.8)	72	207-208° (ethanol)	58.62 58.20	3.55 3.62	15.19 15.16	3300 w, 3240-3120 w, b, 3100-3000 w, b, 1740-1720 sh, b, 1700 sh, 1690 s, 1680 s, 1660 s, 1640 sh, 1610 sh, 1595 m, 1570-1540 sh, b, 1530 m
13c	4-Methoxy	$C_{19}H_{16}N_4O_4$ (364.4)	90	189-190° (ethanol)	62.63 62.25	4.43 4.72	15.38 15.03	3530 m, 3460-3320 m, b, 3260-3100 w, b, 1690 s, 1660 sh, 1650 s, 1605 s, 1580 sh, 1515 s, 1500 sh
13d	2.5-Dimethoxy	$C_{20}H_{18}N_4O_5$ (394.4)	88	216-220° (ethanol)	60.91 60.60	4.60 4.60	14.21 14.07	3260-3100 w, b, 3080-3020 w, b, 2980 w, 2940 w, 1680 s, 1660 s, 1650 sh, 1600 m, 1540 m, 1490 m
13e	4-Hydroxy-3-methoxy	$C_{19}H_{16}N_4O_5$ (380.4)	97	202-204° (ethanol)	59.99 59.62	4.24 4.46	14.73 14.56	3600-2700 w, b, 1690 s, 1660 s, 1650 sh, 1640 sh, 1600 sh, 1580 s, 1570 sh, 1520 s, 1490 m
13f	4-N,N-Dimethylamino	$C_{21}H_{19}N_5O_2$ (377.4)	84	135-137° (ethanol)	63.65 63.72	5.07 4.97	18.56 18.28	3490 m, 3420-3320 w, b, 1710 sh, 1685 m, 1655 sh, 1650 s, 1640 sh, 1595 s, 1580 sh, 1560 sh, 1535 sh, 1525 s, 1510 sh, 1490 w

Table 12

^{1}H-NMR Spectral Data of **13**
(measured in hexadeuteriodimethyl sulfoxide unless otherwise stated)

13a: δ = 6.2 (s, H at C-4), 7.3-7.8 (m, 10 ArH), 8.4 (s, CH=N), 11.9 (s, NH)

13b: (trifluoroacetic acid): δ = 6.9 (s, H at C-4), 7.3-7.8 (m, 9 ArH), 8.8 (s, CH=N)

13c: δ 3.8 (s, CH_3), 6.3 (s, H at C-4), 6.8-7.1 (m, 2 ArH), 7.3-7.8 (m, 7 ArH), 8.4 (s, CH=N), 11.8 (s, NH)

13d: (trifluoroacetic acid): δ = 3.9 (s, CH_3), 4.3 (s, CH_3), 6.9 (s, H at C-4), 7.2-7.7 (m, 8 ArH), 10.7 (s, CH=N)

13e: δ = 3.8 (s, CH_3), 6.2 (s, H at C-4), 6.8-7.6 (m, 8 ArH), 8.3 (s, CH=N), 11.8 (s, NH)

13f: δ = 2.9 (s, 2 CH_3), 6.2 (s, H at C-4), 6.6-6.9 (m, 2 ArH), 7.3-7.7 (m, 7 ArH), 8.3 (s, CH=N), 11.5-11.7 (b, NH)

s, 1700 sh, 1650 sh, 1640 sh, 1630 sh, 1620 s, 1600 sh, 1560 sh, 1525 sh, 1510 s, 1500 sh, 1490 sh cm^{-1}; ^{1}H-nmr: δ = 6.2 (s, H at C-4), 6.7-7.5 (m, 4 ArH), 10.1-10.5 (b, OH and COOH).

Anal. Calcd. for $C_{11}H_8N_2O_6$: C, 53.22; H, 3.25; N, 11.29. Found: C, 53.55; H, 3.65; N, 10.91.

General Procedures for the Esters **8a-m**.

A) A solution of 5 mmoles of the 5-hydroxypyridazine **4a,d** in 15 ml of acetic anhydride was refluxed for one hour. After cooling the solution was poured into 100 ml of ice water and stirred for 18 hours before filtration.

B) To a solution of 10 mmoles of **4a,d** in 40 ml of dry dimethylformamide 15 mmoles of the corresponding acid chloride, 30 mmoles of triethylamine and about 10 mg 4-dimethylaminopyridine as catalyst were added and the mixture was stirred at 60° for 6 hours. The mixture was allowed to cool and then it was poured into 300 ml of ice water. The precipitate was filtered.

Ethyl (6-Methoxycarbonyl-3-oxo-2-phenyl-2.3-dihydropyridazin-5-yloxy)-acetate (**8n**).

A suspension of 2.46 g (10 mmoles) of **4a**, 1.35 g (11 mmoles) of ethyl chloroacetate and 3.50 g (25 mmoles) of dry potassium carbonate in 20 ml of dry dimethylformamide was stirred at room temperature for 16 hours. Then the inorganic salt was filtered off and the solvent was removed under reduced pressure at 60°. The residue was crystallized by the addition of cyclohexane. The yield was 2.21 g (67%), mp 138-139° dec (cyclohexane); ir: 3580-3300 w, b, 1740 s, 1730 s, 1720 sh, 1680 sh, 1670 s, 1650 sh, 1635 w, 1605 sh, 1590 m, 1510 w, 1495 w cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.4 (t, J = 7 Hz, ethyl-CH_3), 3.9 (s, methyl-CH_3), 4.3 (q, J = 7 Hz, ethyl-CH_2), 4.7 (s, acetic CH_2), 6.2 (s, H at C-4), 7.2-7.9 (m, 4 ArH).

Anal. Calcd. for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 58.26; H, 5.03; N, 8.14.

General Procedure for 3-Substituted 6-Aryl-4-hydroxy-8-methoxycarbonylpyrano[2,3-*d*]pyridazine-2.5(6*H*)-diones **10a-f**.

A mixture of 5 mmoles of **4a,d** and 5 mmoles of the corresponding active malonate **9a-d** was heated to 240° for 15 minutes. The oily product crystallized by the addition of cyclohexane.

Hydrazinium 6-Hydrazinocarbonyl-3-oxo-2-phenyl-2.3-dihydropyridazin-5-olate (**11**).

A solution of 2.46 g (10 mmoles) of **4a** and 1.50 g (30 mmoles) of hydrazinium hydrate in 50 ml ethanol was refluxed for one hour. After cooling **11** crystallized very slowly (within 16 hours) in large yellow prisms. The yield was 1.81 g (65%), mp 190-191° dec (ethanol); ir: 3340 s, 3320 sh, 3300-2500 m, b, 1670 sh, 1650 sh, 1640 sh, 1630-1600 s, b, 1580-1570 s, b, 1560 sh, 1530-1510 s, b, 1490 s cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 6.8 (s, H at C-4), 7.3-7.7 (m, 5 ArH).

Anal. Calcd. for $C_{11}H_{14}N_6O_3$: C, 47.48; H, 5.07; N, 30.20. Found: C, 47.58; H, 4.84; N, 30.36.

6-Hydrazinocarbonyl-5-hydroxy-2-phenylpyridazin-3(2*H*)-one (**12**).

A solution of 9.84 g (40 mmoles) of **4a** and 6.00 g (120 mmoles) of hydrazinium hydrate in 200 ml ethanol was refluxed for one hour. The precipitated salt **11** was filtered off, dissolved in 100 ml of water, stirred with charcoal for 15 minutes, filtered again and acidified by addition of acetic acid to afford 6.00 g **12** (61% corresponding to **4a**), mp 224° (ethanol); ir: 3300 m, 3280-3180 m, b, 1670 m, 1650 sh, 1645 s, 1640 sh, 1620 sh, 1600 sh, 1530-1520 m, b, 1490 w cm^{-1}; ^{1}H-nmr: δ = 5.6-6.7 (b, 3 NH), 6.2 (s, H at C-4), 7.3-7.7 (m, 5 ArH).

Anal. Calcd. for $C_{11}H_{10}N_4O_3$: C, 53.66; H, 3.77; N, 20.96. Found: C, 53.37; H, 4.11; N, 21.33.

General Procedure for 6-Arylidenehydrazinocarbonyl-5-hydroxy-2-phenylpyridazin-3(2*H*)-ones **13a-f**.

Compound **12** (1.23 g, 5 mmoles) was dissolved in 100 ml of boiling ethanol and 7.5 mmoles of the corresponding aldehyde in 5 ml of ethanol was added. The solution was refluxed for 30 minutes and the volume was reduced to 30 ml. The product usually started to precipitate at reflux temperature and was allowed to complete crystallization at room temperature for 15 hours.

6-Amidocarbonyl-5-hydroxy-2-phenylpyridazin-3(2*H*)-one (**14**).

A solution of 5.0 g of **4a** in 100 ml of concentrated ammonia was refluxed for three hours. After cooling it was acidified by addition of acetic acid to yield 3.84 g (82%), mp 183-185° (methanol); ir: 3360-3340 m, b, 3200 m, 1690 sh, 1670 s, 1655 sh, 1640 sh, 1630 sh, 1600 sh, w, 1530 m, 1490 w cm^{-1}; ^{1}H-nmr: δ = 6.3 (s, H at C-4), 7.3-7.8 (m, 5 ArH), 8.2-8.6 (m, 2 NH).

Anal. Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.08; H, 4.03; N, 18.04.

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