Synthesis and Structure of Novel 4-Arylhexahydro-1H,3H-pyrido[1,2-c]pyrimidine Derivatives

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A series of new 4-aryl-hexahydro-1H,3H-pyrido[1,2-c]pyrimidine-1,3-dione derivatives **4a-k** were prepared by catalytic hydrogenation of 4-aryl-1H,2H-pyrido[1,2-c]pyrimidine-1,3-diones **3a-k**. The structures of compounds were determined by ^{1}H and ^{13}C nmr spectroscopy in solution. Steric hindrance caused twisting of the phenyl ring with respect to the pyridopyrimidine system, the effect was confirmed by X-ray diffraction.

As part of continuing studies focused on the synthesis of potentially pharmacologically-active heterocyclic compounds we became interested in the pyrido[1,2-c]pyrimidine system. Derivatives of pyrido[1,2-c]pyrimidine were first described by Winterfeld and Göbel [1,2], in subsequent publications [3-10] other interesting methods of synthesis were proposed. The pharmacological activity of these derivatives was tested more recently. Hunger and Hoffman [3] showed that the derivatives obtained were active on the blood circulatory system, Chorvat *et al.* [11-14] synthesized a series of hexahydro-3H-pyrido[1,2-c]pyrimidin-3-ones exhibiting high antiarrhythmic activity.

We report a synthesis of 4-arylhexahydro-1H,3H-pyrido-[1,2-c]pyrimidine-1,3-diones **4a-k**, Scheme 1. It seems that the derivatives developed could be used as an interesting starting material for the synthesis of numerous derivatives with the expected affinity for 5-hydroxytryptamine$_{1A}$ receptor.

Results and Discussion.

Chemical Synthesis.

The process of catalytic hydrogenation (using PtO$_2$ or Pd/C) of the derivatives of the 1H,2H- pyrido[1,2-c]pyrimidines **3a-k** was investigated in order to achieve selective saturation *i.e.* to obtain the hexahydropyrido[1,2-c]-pyrimidine and not the octahydropyrido[1,2-c]pyrimidine system. Compounds **4a-k** were obtained by catalytic hydrogenation of the 1H,2H-pyrido[1,2-c]pyrimidine-

1,3-diones **3a-k** and the best conditions for selective saturation are: 60 atmospheres, 50° and catalyst PtO$_2$. It is worth mentioning that further attempts at complete reduction, carried out under high (100 atmospheres) pressure with PtO$_2$ or Pd/C (10%) as the catalyst at 100° using acetic acid and trifluoroacetic acid as solvents, were unsuccessful. High stability and insensitivity to the catalytic reduction of the C4-C4a bond in both series **3a-k** and **4a-k** results from delocalization of the electron density and coupling with the π-electrons of the aromatic ring, as well as with π-electrons of the carbonyl group. The effects were confirmed by the analysis of nmr spectra. The physicochemical data for compounds **3a-k and 4a-k** are given in Table 1.

^{1}H and ^{13}C NMR Studies.

In the ^{1}H nmr spectra of compounds **3c,d,g** and **k** the multiplets of C5-H and C6-H are in the range 6.8-7.0 ppm and overlapped with other aromatic proton signals. It is interesting to note that in the spectra of **3b,e,h** and **j**, bearing an *ortho* substituent on the phenyl ring, the resonance of C5-H is shifted upfield by 0.12 to 0.34 ppm. Table 2. Molecular modeling (carried out by means of the semiempirical AM1 method) showed that even without *ortho* substituents the aromatic ring is almost perpendicular to the plane of pyridopyrimidine system. Due to the steric hindrance the rotation around Cl'-C4 is restricted and the twisting enables the location of the C5-H hydrogen to be in the shielding zone of the aromatic ring.

Scheme 1
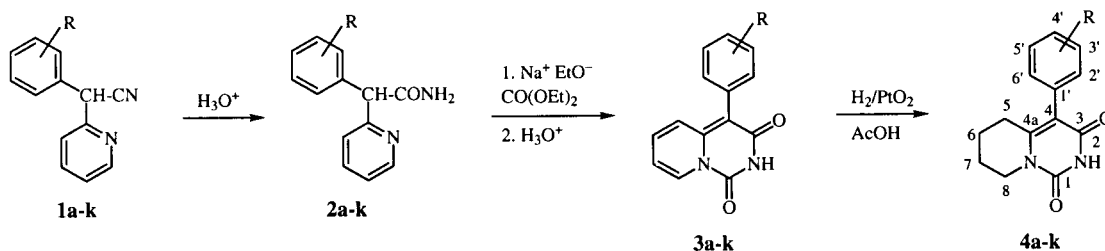
R = H, a; 2-Me, b; 3-Me, c; 4-Me, d; 2-MeO, e; 3-MeO, f, 4-MeO, g; 2-Cl, h; 4-Cl, i; 2F, j; 4-F, k.

Table I

Physical, Analytical and IR Spectroscopic Data of Compounds **3b-k** and **4a-k**

No.	R	Yield (%) Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found			IR (potassium bromide, cm^{-1})
				C	H	N	
3b	2-Me	83.7 220-221	$C_{15}H_{12}N_2O_2$	71.42/71.42	4.79/4.75	11.10/11.12	3120, 1730, 1630
3c	3-Me	88.0 246-248	$C_{15}H_{12}N_2O_2$	71.42/70.94	4.79/4.74	11.10/10.92	3110, 1740, 1630
3d	4-Me	82.0 260-262	$C_{15}H_{12}N_2O_2$	71.42/70.37	4.79/4.92	11.10/10.92	3130, 1730, 1630
3e	2-MeO	95.0 246-247	$C_{15}H_{12}N_2O_3$	67.16/67.10	4.51/4.48	10.44/10.40	3140, 1710, 1610
3g	4-MeO	89.3 224-225	$C_{15}H_{12}N_2O_3$	67.16/66.94	4.51/4.59	10.44/10.41	3100, 1740, 1640
3h	2-Cl	89.8 260-262	$C_{14}H_9ClN_2O_2$	61.67/60.64	3.33/3.36	10.27/10.28	3120, 1730, 1630
3j	2-F	64.8 271-272	$C_{14}H_9FN_2O_2$	65.62/65.70	3.54/3.49	10.93/10.85	3110, 1730, 1630
3k	4-F	73.3 298-299	$C_{14}H_9FN_2O_2$	65.62/65.71	3.54/3.56	10.93/10.88	3120, 1720, 1620
4a	H	74.4 278-280	$C_{14}H_{14}N_2O_2$	69.41/69.34	5.82/5.92	11.56/11.48	3149, 1712, 1650
4b	2-Me	80.2 218-219	$C_{15}H_{16}N_2O_2$	70.29/70.17	6.29/6.34	10.92/10.79	3148, 1710, 1640
4c	3-Me	78.2 217-218	$C_{15}H_{16}N_2O_2$	70.29/70.31	6.29/6.15	10.92/10.78	3146, 1705, 1643
4d	4-Me	88.5 272-275	$C_{15}H_{16}N_2O_2$	70.29/70.27	6.29/6.27	10.92/10.81	3147, 1710, 1649
4e	2-MeO	77.8 250-252	$C_{15}H_{16}N_2O_3$	66.16/66.10	5.92/5.95	10.28/10.20	3147, 1702, 1633
4f	3-MeO	80.3 224-227	$C_{15}H_{16}N_2O_3$	66.16/66.12	5.92/5.90	10.28/10.25	3146, 1706, 1646
4g	4-MeO	79.9 275-277	$C_{15}H_{16}N_2O_3$	66.16/66.20	5.92/5.90	10.28/10.22	3147, 1670, 1648
4h	2-Cl	90.2 251-252	$C_{14}H_{13}ClN_2O_2$	60.77/60.69	4.74/4.80	10.12/10.07	3149, 1712, 1657
4i	4-Cl	92.1 290-293	$C_{14}H_{13}ClN_2O_2$	60.77/60.82	4.74/4.77	10.12/10.10	3146, 1708, 1651
4j	2-F	97.2 291-293	$C_{14}H_{13}FN_2O_2$	64.61/64.54	5.03/5.10	10.76/10.68	3150, 1710, 1651
4k	4-F	70.0 294-296	$C_{14}H_{13}FN_2O_2$	64.61/64.67	5.03/5.12	10.76/10.87	3148, 1711, 1650

The proton-proton coupling constants exhibit some regularities and for all compounds the following sequence is valid : $^3J_{5,6} > {}^3J_{7,8} > {}^3J_{6,7}$; for example, the values for **3e** are: $^3J_{5,6}$ = 9.6 Hz > $^3J_{7,8}$ = 7.6 Hz > $^3J_{6,7}$ = 6.4 Hz, Table 2. Since there are neither geometrical changes nor the replacement of substituents with strong electronic effects within the aromatic pyrido pyrimidine system, the above sequence can be related to the bond lengths $R_{i,j}$ and/or bond orders. For aromatic six-member rings a linear relationship holds [15]: ^3J = $-35.1R_{ij} + 56.65$. The estimated bond lengths are 0.1340, 0.1397 and 0.1432 nm for C5-C6, C7-C8 and C5-C6 bonds, respectively. Shorter, *i.e.* with more double bond character, are the C5-C6 and C7-C8 bonds, in agreement with the structure shown in Scheme 1. The structures were initially characterized by routine ^{13}C nmr spectra. However, the discrimination between carbons C1'-C6' and those of the pyridopyrimi-

dine system was not straightforward at this stage, and therefore, the heteronuclear 2D experiments were required. The HETCOR $^1H/^{13}C$ spectrum of **3e** (2-OMe), such as that illustrated in Figure 1a, allowed the identification and assignment of all protonated carbons. The remainder was deduced from a gradient HMQC experiment.

The ^{13}C chemical shifts (see Table 3) of aromatic carbons C1'-C6' can be understood in terms of electron donor or electron acceptor properties of substituent R, located *ortho, meta* or *para* with respect to C1'. As mentioned above, steric hindrance caused twisting of the planes of the two aromatic systems, therefore the conjugation of the two π-systems is reduced. Thus substituents on the phenyl ring, which is linked to C4, have a minor influence on the chemical shifts of the carbonyl carbons and the C6-C8 carbons of the pyridopyrimidine skeleton.

Table 2

^{1}H NMR Chemical Shifts [δ, ppm, deuteriochloroform] and Coupling Constants (Hz) of Compounds **3b,c,d,e,g,h, j,k**

No.	R	N-2	C-5	C-6	C-7	C-8	C-4-Ph-R [a]
3b	2-Me	9.86 (bs, 1H)	6.58 (m,1H) $^4J_{5,8}=1.4$ $^3J_{5-6}=9.6$ $^4J_{5-7}=1.4$	6.92 (m, 1H) $^3J_{6-7}=6.3$ $^4J_{6-8}=1.6$	6.39 (m,1H) $^3J_{7,8}=7.4$	8.30(m,1H)	7.10-7.35 (m, 4H, Ph-H), 2.18 (s, 3H, CH$_3$)
3c	3-Me	9.08 (bs, 1H)	–	–	6.40 (m, 1H) $^4J_{5-7}=2.8$ $^3J_{6-7}=4.4$ $^3J_{7-8}=7.6$	8.27 (m, 1H) $^4J_{5-8}=1.0$ $^4J_{6-8}=1.0$	7.05-7.45 (m, 4H, Ph-H), 6.85-6.95 (m, 2H, C5-H + C6-H), 2.38 (s, 3H, CH$_3$)
3d	4-Me	9.13 (bs, 1H)	–	–	6.38 (m, 1H) $^4J_{5-7}=2.4$ $^3J_{6-7}=5.1$ $^3J_{7-8}=7.6$	8.26 (m., 1H) $^4J_{5-8}=1.0$ $^4J_{6-8}=1.0$	7.12-7.32 (m, 4H, Ph-H), 6.84-6.98 (m, 2H, C5-H + C6-H), 2.39 (s, 3H, CH$_3$)
3e	2-MeO	9.50 (bs, 1H)	6.65 (m, 1H) $^3J_{5-6}=9.6$ $^4J_{5-7}=1.2$ $^4J_{5-8}=1.2$	6.90 (m, 1H) $^3J_{6-7}=6.4$ $^4J_{6-8}=1.2$	6.38 (m, 1H) $^3J_{7-8}=7.6$	8.27 (m, 1H)	6.95-7.09 (m, 4H, Ph-H), 3.77 (s, 3H, OCH$_3$)
3g	4-MeO	9.01 (bs, 1H)	–	–	6.39 (m, 1H) $^4J_{5-7}=2.0$ $^3J_{6-7}=5.5$ $^3J_{7-8}=7.5$	8.26 (m, 1H) $^4J_{5-8}=1.0$ $^4J_{6-8}=2.0$	6.99 (m, 2H, C3'-H + C5'-H), 7.24 (m, 2H, C2'-H + C6'-H), J$_o$ = 8.5, 3.84 (s, 3H, OCH$_3$), 6.89-7.01 (m, 2H, C5-H + C6-H)
3h	2-Cl	9.45 (bs, 1H)	6.58 (m,1H) $^3J_{5-6}=9.5$ $^4J_{5-7}=1.2$ $^4J_{5-8}=1.2$	6.99 (m, 1H) $^4J_{6-8}=1.2$ $^3J_{6-7}=6.3$	6.45 (m, 1H) $^3J_{7-8}=7.5$	8.33 (m, 1H)	7.47-7.58 (m, 4H, Ph-H)
3j	2-F	8.65 (bs, 1H)	6.75 (m, 1H) $^3J_{5-6}=9.6$ $^4J_{5-7}=1.2$ $^4J_{5-8}=1.2$	7.02 (m, 1H) $^3J_{6-7}=6.4$ $^4J_{6-8}=1.2$	6.45 (m, 1H) $^3J_{7-8}=7.6$	8.31 (m, 1H)	7.08-7.50 (m, 4H, Ph-H)
3k	4-F	8.65 (bs, 1H)	–	–	6.42 (m, 1H) $^4J_{5-7}=1.8$ $^3J_{6-7}=6.0$ $^3J_{7-8}=7.6$	8.28(m, 1H) $^4J_{6-8}=1.2$ $^4J_{5-8}=1.2$	7.10-7.35 (m, 4H, Ph-H), J$_o$ = 9.0, 6.84-7.03 (m, 2H, C5-H + C6-H)

[a] Coupling constants for aromatic protons were described as J$_{ortho, meta, para}$ (J$_{o,m,p}$).

Table 3

^{13}C NMR Spectral Data of Compounds **3b,c,d,e,g,h,j,k** [a]

	3b	3c	3d	3e	3g	3h	3j	3k
C-1	145.4	145.5	145.4	145.6	145.5	145.8	145.5	144.6
C-3	148.3	148.0	148.0	148.3	148.0	148.1	148.6	148.0
C-4	**104.6**	**105.5**	**106.0**	**101.8**	**105.1**	**102.6**	**97.8**	**102.8**
C-4a	160.3	160.4	160.5	157.9	159.3	159.8	160.2	160.3
C-5	121.6	121.9	121.9	122.3	121.9	121.5	120.8	120.4
C-6	133.1	132.9	132.8	132.5	132.8	133.5	135.0	133.8
C-7	110.8	110.9	110.8	110.7	110.8	111.0	111.3	110.7
C-8	127.8	127.6	127.6	127.6	127.6	127.9	128.4	127.6
C-1'	**131.3**	**128.8**	**128.8**	**120.6**	**123.9**	**130.9**	**120.8**	**129.2**
C-2'	**138.6**	128.8	130.9	**160.4**	132.3	**135.7**	**161.9**	133.2
C-3'	126.4	**138.6**	129.6	111.6	114.4	130.1	124.9	115.3
C-4'	130.6	128.9	**137.9**	129.9	**160.5**	129.9	134.2	**162.2**
C-5'	128.5	128.1	129.6	121.0	114.4	127.4	116.3	115.3
C-6'	131.6	131.7	130.9	132.9	132.3	133.7	130.4	133.2
R	19.6	21.3	21.3	55.7	55.3	-	-	-

[a] [13]C Chemical shifts of the *ipso* carbon atoms of the pyridopyrimidine and phenyl rings are given in bold numbers δ, ppm, in deuteriochloroform, tetramethylsilane as the Internal Standard.

However, interesting shielding effects appear for compounds with *ortho* substituents. The changes in chemical shift (an increase in shielding) of proximate carbons C1', C4 and C4a result mainly from the steric effect of the R group. Since the steric Taft parameters (-E$_s$) for halogens, obtained in the ester hydrolysis model, are not reliable we used the Xi values (Ξ) [16] derived from the molecular graph structure, which encode only the information about shape. However, neither Taft nor Xi parameters yields a linear relationship:

R	-E$_s$	Ξ	δC1'	δC4	δC4a
Me	0.00	1.28	131.3	104.5	160.3
Cl	0.18	1.57	130.9	102.6	159.8
F	0.49	1.21	120.9	97.8	160.3
MeO	0.99	1.67	120.6	101.8	157.9

It would suggest that these compounds probably have a different twist angle and the larger steric effect of R is released by rotation of the phenyl ring around the C1'-C4 bond. The ^{1}H and ^{13}C nmr spectra of compounds **4a-k** are
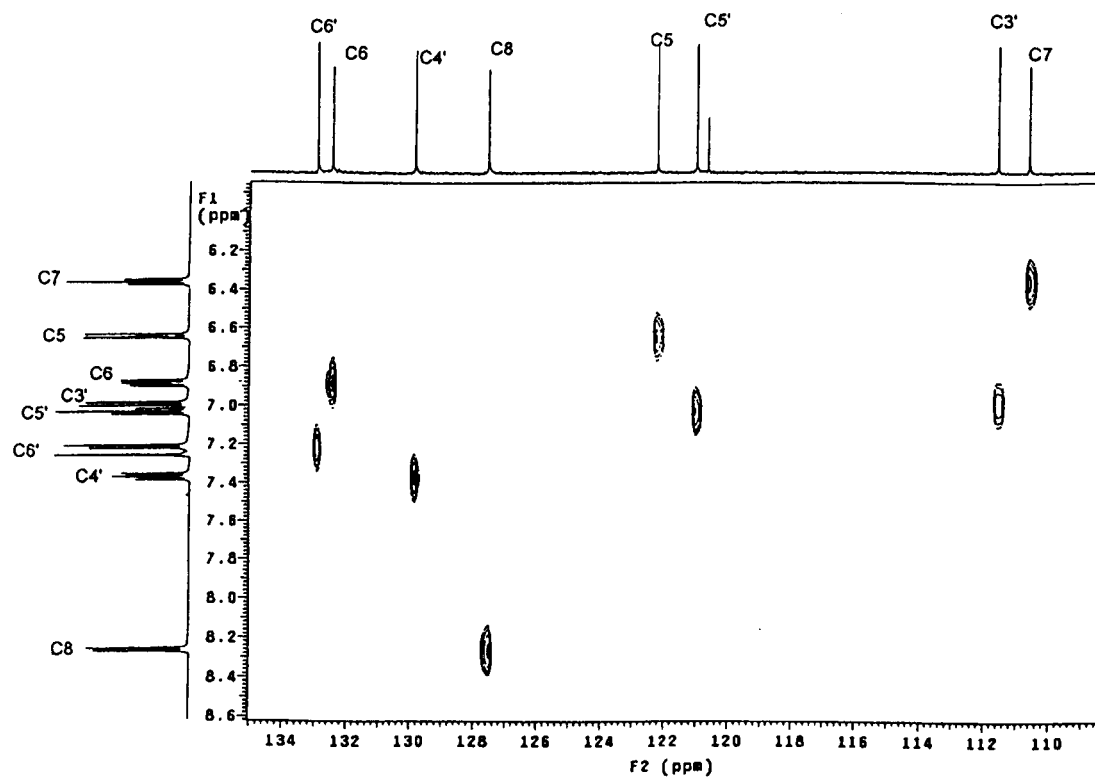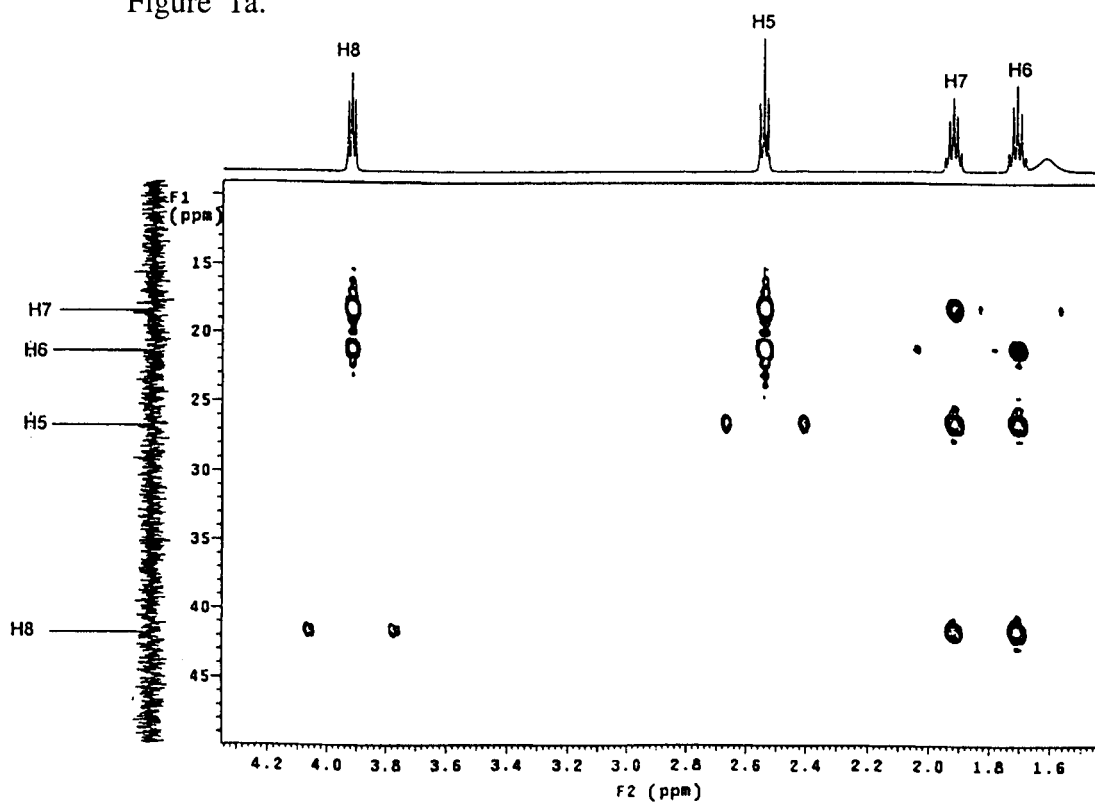
Figure 1a.

Figure 1b.

Figure 1. a) The HETCOR ^{1}H/^{13}C spectrum of **3e** (2-OMe), b) the GHMQC experiment for aliphatic carbons range for **4a**.

Table 4

^{1}H NMR Chemical Shifts [δ, ppm, deuteriochloroform] and Coupling Constants (Hz) of Compounds **4a-k**

No.	R	N-2	C-5	C-6	C-7	C-8	C-4-Ph-R [a]
4a	H	8.68 (bs, 1H)	2.55 (t, 2H) $^3J = 6.5$	1.71 (q, 2H) $^3J = 6.5$	1.92 (q, 2H) $^3J = 6.5$	3.93 (t, 2H) $^3J = 6.5$	7.41 (m, 2H, C2'-H, C6'-H); 7.34 (m, 1H, C4'-H) 7.21 (m, 2H, C3'-H, C5'-H)
4b	2-Me	9.20 (bs, 1H)	2.35 (m, 2H) $^2J = 17.5$ $^3J = 6.5$ $^4J = 1.5$	1.68 (m, 2H) $^2J = 13.5$ $^3J_{6-7} = 7$ $^3J_{5-6} = 6.5$	1.89 (m, 2H) $^2J = 21$ $^3J_{6-7} = 7$ $^3J_{7-8} = 6.5$	3.91 (m, 2H) $^3J = 14.5$ $^3J_{7-8} = 6.5$	7.26 (m, 2H, C4'-H, 6'-H) 7.20 (m, 1H, C5'-H) 7.04 (m, 1H, C3'-H) $J_o = 7.5$ 2.16 (s, 3H, CH$_3$)
4c	3-Me	9.32 (bs, 1H)	2.53 (t, 2H) $^3J = 6.6$	1.69 (q, 2H) $^3J = 6.6$	1.90 (q, 2H) $^3J = 6.6$	3.92 (t, 2H) $^3J = 6.6$	7.28 (m, 1H, C5'-H) 7.14 (m, 1H, C6'-H) 7.00 (m, 2H, C2'-H, C4'-H) $J_o = 7.8$ 2.36 (s, 3H, CH$_3$)
4d	4-Me	8.96 (bs, 1H)	2.55 (t, 2H) $^3J = 6.6$	1.70 (q, 2H) $^3J = 6.6$	1.91 (q, 2H) $^3J = 6.6$	3.92 (t, 2H) $^3J = 6.6$	7.21 (m, 2H, C2'-H, C6'-H) 7.09 (m, 2H, C3'-H, C5'-H) $J_o = 7.8$ 2.36 (s, 3H, CH$_3$)
4e	2-MeO	8.81 (bs, 1H)	2.44 (m, 2H) $^2J = 17.5$ $^3J = 6.7$	1.70 (m, 2H) $^2J = 13.5$ $^3J = 6.7$	1.90 (m, 2H) $^2J = 15.0$ $^3J = 6.7$ $^4J = 1.5$	3.91 (m, 2H) $^2J = 13.7$ $^3J = 6.7$	7.34 (m, 1H, C4'-H) 7.12 (m, 1H, C6'-H) 7.00 (m, 1H, C5'-H) 6.95 (m, 1H, C3'-H) $J_o = 7.5, J_m = 1.5$ 3.78 (s, 3H, OCH$_3$)
4f	3-MeO	8.42 (bs, 1H)	2.55 (t, 2H) $^3J = 6.6$	1,71 (q, 2H) $^3J = 6.6$	1.92 (q, 2H) $^3J = 6.6$	3.92 (t, 2H) $^3J = 6.6$	7.80 (t, 1H, C5'-H) 6.89 (m, 1H, C6'-H) $J_o = 7.8, J_m = 2.8$ 6.78 (m, 2H, C2'-H, C4'-H) 3.81 (s, 3H, OCH$_3$)
4g	4-MeO	8.40 (bs, 1H)	2.57 (t, 2H) $^3J = 6.4$	1.71 (q, 2H) $^3J = 6.4$	1.92 (q, 2H) $^3J = 6.4$	3.92 (t, 2H) $^3J = 6.4$	7.31 (m, 2H, C2'-H, C6'-H) 6.94 (m, 2H, C3'-H, C5'-H) $J_o = 8.8$ 3.82 (s, 3H, CH$_3$)
4h	2-Cl	9.01 (bs, 1H)	2.41 (m, 2H) $^2J = 17.3$ $^3J = 6.7$ $^4J = 1.0$	1.72 (m, 2H) $^2J = 13.0$ $^3J_{6-7} = 6.5$ $^3J_{5-6} = 6.7$	1.91 (m, 2H) $^2J = 15.0$ $^3J_{6-7} = 6.5$ $^4J = 1.5$ $^3J_{7-8} = 6.5$	3.92 (m, 2H) $^2J = 13.5$ $^3J_{7-8} = 6.5$ $^4J = 3.0$	7.46 (m, 1H, C6'-H) 7.3 (m, 2H, C4'-H, C-5'-H) 7.21 (m, 1H, C3'-H) $J_o = 5.5, J_m = 3.5$
4i	4-Cl	8.61 (bs, 1H)	2.54 (t, 2H) $^3J = 6.6$	1.72 (q, 2H) $^3J = 6.6$	1.93 (q, 2H) $^3J = 6.6$	3.92 (t, 2H) $^3J = 6.6$	7.39 (m, 2H, C2'-H, C6'-H) 7.15 (m, 2H, C3'-H, C5'-H) $J_o = 8.4, J_m = 2.4$
4j	2-F	8.44 (bs, 1H)	2.51 (m, 2H) $^2J = 17.0$ $^3J = 6.5$ $^4J = 1.0$	1.74 (m, 21-1) $^2J = 13.5$ $^3J = 6.5$	1.93 (m, 2H) $^2J = 13.5$ $^3J = 6.5$	3.92 (m, 2H) $^2J = 13.5$ $^3J = 6.5$	7.36 (m, 1H, C6'-H) 7.21 (m, 2H, C3'-H, C4'-H) 7.13 (t, 1H, C5'-H) $J_o = 8.5, J_m = 2.0, J_p = 1.0$
4k	4-F	8.41 (bs, 1H)	2.54 (t, 2H) $^3J = 6.4$	1.72 (q, 2H) $^3J = 6.4$	1.93 (q, 2H) $^3J = 6.4$	3.98 (t, 21-1) $^3J = 6.4$	7.00-7.24 (m, 4H, C2'-H, C3'-H, C5'-H, C6'-H)

[a] Coupling constants for aromatic protons were described as $J_{ortho, meta, para}$ $(J_{o,m,p})$.

complicated in the aliphatic region; the signals of the methylene protons of C5 and C8 for **4a** appeared as triplets, and those of C6 and C7 as slightly broadened quintets. Single frequency proton decoupling was used to differentiate between C6H$_2$ and C7H$_2$, the signal of C8H$_2$ at 3.93 ppm was irradiated and, as a result, the signal of C7H$_2$ at 1.92 ppm was reduced to a triplet. The assignment of the respective carbons required the use of heteronuclear

2D nmr methods and the GHMQC experiment for aliphatic carbons range for **4a** is shown in Figure 1b.

In the ^{1}H nmr spectra of compounds **4b,4e,4h** and **4j** bearing an *ortho* substituted aromatic ring, the methylene protons of the saturated ring are not equivalent. The resonance of C5H$_{A,B}$, C6H$_{A,B}$, C7H$_{A,B}$, C8H$_{A,B}$ appeared as multiplets with 9-14 lines. Proton chemical shifts, geminal and vicinal coupling constants given in Table 4 were obtained by

Table 5

^{13}C NMR Spectral Data of Compounds 4a-k [a]

	4a	4b	4c	4d	4e	4g	4h	4i	4j	4k
C-1	152.1	151.9	151.9	151.9	152.5	152.1	152.9	152.4	159.0	152.3
C-3	162.1	161.7	162.3	162.3	161.9	162.2	161.4	161.8	161.0	161.9
C-4	**113.0**	**112.4**	**113.1**	**112.9**	**109.2**	**112.6**	**110.6**	**111.8**	**120.9**	**112.0**
C-4a	**150.9**	**151.3**	**151.1**	**151.0**	**151.2**	**150.8**	**151.2**	**150.7**	**153.0**	**150.7**
C-5	26.8	26.6	26.7	26.8	26.4	26.8	26.5	26.8	26.0	26.8
C-6	21.4	21.5	21.4	21.4	21.5	21.5	21.5	21.4	20.8	21.4
C-7	18.5	18.5	18.4	18.5	18.4	18.5	18.3	18.4	17.7	18.5
C-8	41.9	42.6	41.8	41.8	42.1	41.9	42.2	41.9	41.1	41.9
C-1'	**132.5**	**132.1**	**132.4**	**129.4**	**121.2**	**124.5**	**131.6**	**130.9**	**150.8**	**128.4**
C-2'	128.6	**137.7**	128.6	129.3	**157.4**	131.8	**135.1**	132.1	**161.3**	132.5
C-3'	130.7	130.7	**138.1**	130.4	111.2	114.1	129.7	128.9	115.4	115.9
C-4'	127.9	128.3	128.4	**137.6**	129.7	**159.3**	129.7	**134.0**	129.9	**162.4**
C-5'	130.7	126.1	131.2	130.4	120.8	114.1	127.1	128.9	124.2	115.7
C-6'	128.6	130.3	127.6	129.3	132.3	131.8	132.6	132.1	133.2	132.4
R	-	19.6	21.4	21.3	55.6	55.3	-	-	-	-

[a] ^{13}C chemical shifts of the *ipso* carbon atoms of the pyridopyrimidine and phenyl rings are given in the bold numbers δ Values in deuteriochloroform, tetramethylsilane as Internal Standard.

computer simulation (RACOON program) of the respective spectral fragment. The non-equivalence of the methylene protons is from 0.0 15 to 0. 16 ppm and is smaller than typically observed *ca.* 0.5 ppm difference between axial and equatorial protons in the frozen chair conformation of cyclohexane. Fast (on the nmr time-scale) process of saturated ring inversion in 4a-k can be expected at room temperature. The free enthalpy of activation, a measure of the barrier to inversion, for the chair-to-chair process in structurally similar compounds is low and separate signals for axial and equatorial protons were observed [17] at temperatures far below room temperature. However, as in 3a-k, the steric hindrance results in the twisting of the aromatic ring and the effect is increased by the presence of an *ortho* substituent; there is not enough space for ring dynamics, especially the process of pseudorotation around C5-C6 should be restricted.

The ^{13}C chemical shifts of C5 are within 26.7-26.9 ppm but in compounds with *ortho* substituents the C5 carbons are more shielded and resonate at 26.0-26.6 ppm, Table 5. The dynamics of a saturated system are also influenced by electronic factors, the changes of electron density distribution within the pyridopyrimidine system; especially the delocalization of the free electron pair at the nitrogen atom in proximity to C8 and the likewise conjugation of the π electrons of carbonyl groups should be considered. Steric effect of an *ortho* substituent can be observed for carbons C4, C4a and C1' (see the discussion above, for 3a-k), the increase in the size of R results in the increase of shielding (2-F substituent is an exception). The ^{13}C chemical shifts of aromatic carbons C1'-C6' are influenced mainly by the properties of *ortho, meta* or *para* substituents.

It is of interest to compare chemical shifts of C1=O, C3=O and C4 carbons in the two series 3a-k and 4a-k. The presence of a saturated ring in place of an aromatic ring results in remarkable deshielding. The effect is most pronounced for C3=O (12.4-14.3 ppm) and *ca.* 6.8 ppm for C1=O (however

13.5 ppm for 4j with respect to 3j, bearing the 2F substituent) and *ca.* 7.8 ppm for C4 (again the compounds with 2-F exhibit 23.1 ppm difference).

X-ray Diffraction.

For the verification of our supposition concerning the twisting of the aromatic ring at C4 we finally determined the structure of the 4h derivative; of special interest were compounds with substituents R at the *ortho* position. Selected bond lengths, bond angles and torsion angles for the compound with R=2'-Cl are given in Table 6. The angle C4a-C4-C1'-C2' is 107°, which confirms the results of analysis of the nmr spectra. Hence, in the solid state, and probably also in solution, the aromatic ring is almost perpendicular to the plane of pyridopyrimidine system The comparison of carbon-nitrogen bond lengths reveals that

Table 6

Selected Bond Lengths [Å] and Angles [deg] for Compound 4h

N2-C1	1.361(7)	C7B-C8-N9	114.1(6) [a] 1 -x, -y, 2-z
N2-C3	1.374(6)	C7A-C8-N9	114.2(7) [b] 2-x, -y, 2-z
C4a-C4	1.348(7)	N2-C3-C4	114.6(5) [c] 2-x, 0.5+y, 2.5-z
C4a-N9	1.380(6)	C6A-C7A-C8	107(2) [d] 1-x, -y, 2-z
C4a-C5	1.500(7)	C6B-C7B-C8	110(1)
N9-C1	1.370(6)	C1-N9-C8	114.3(4)
N9-C8	1.482(7)	C7A-C6A-C5	113(2)
C8-C7A	1.49 (2)	O11-C3-C4-C4a	177.7(6)
C8-C7B	1.49(1)	O11 -C3 -C4-C1'	-1.9(9)
C7A-C6A	1.53 (3)	N2-C3-C4-C4a	-2.7(8)
C7B-C6B	1.55(2)	C4-C4a-N9-C8	-174.5(5)
C6A-C5	1.46(2)	C4a-C4-C1'-C2'	-107.6(7)
C1-N2-C3	127.3(5)		
C1-N2-H	113(4)		
C3-N2-H	120(4)	N2...O11 [a]	2.778(5)
C4a-C4-C3	119.9(4)	H...O11	2.01(5) [b]
C4a-C4-C1'	123.7(5)	N2-H...O11 [b]	166(5)
C3-C4-C1'	116.4(5)	Cl...Cl [d]	3.283(3)
C4-C4a-N9	121.3(5)	C8 010	3.269(7) [c]

N2-C1 is shorter than N2-C3. The bond C4-C4a is short, with significant double bond character. The C6 and C7 atoms were found to be disordered. The occupancies of the alternative positions were refined at 0.45(2) and 0.55(2) for the C6, C7 atoms, respectively. The packing arrangement of the molecules is shown in Figure 2. The molecules are linked by intermolecular hydrogen bonds C3=O...HN. The N2...O11 distance is 2.778(6). Neither static no dynamic proton disorder was observed; the proton is localized near the nitrogen atom. The second carbonyl group, C1=O, is involved in short intermolecular contacts with protons HC7 and HC8.
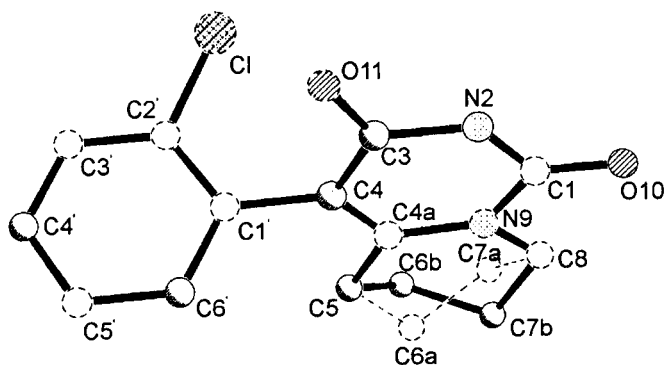

Figure 2. A drawing showing the molecular structure of **4h** with labeling scheme and showing disordered methylene groups.

Table 7

Crystal Data and Structure Refinement of **4h**

Molecular formula	$C_{14}H_{13}N_2O_2Cl$
Molecular weight	276.71
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a [Å]	11.146 (2)
b [Å]	8.328(1)
c [Å]	13.880 (2)
β [°]	94.47(2)
Volume [Å³]	1284.5 (3)
Z	4
Density (calcd.) [g cm³]	1.431
F (000) [e]	576
Wavelength [Å]	0.70926
μ [mm⁻¹]	0.296
Crystal size [mm]	0.6x0.25x0.2
Index ranges	-13≤h≤13
	0≤k≤9
	0≤l≤16
Reflection collected	2381
Independent reflection	2277
(R_int = 0.016)	
Parameters	195
Final R (F) [F² >2σ (F²)]	0.0717
wR (F²) (all data)	0.2324
S	1.391
max shift [e.s.d.]	<0.001
Max/min Δρ [e Å⁻³]	0.547/-0.352

EXPERIMENTAL

The ir spectra (potassium bromide pellets) were recorded on either a Specord IR-75 or a Bio-Rad FTS 13 5 spectrophotometer. The nmr spectra were recorded on a Varian Gemini 200 or a Unity plus 500 MHz spectrometers (200 MHz for ¹H, 50 MHz for ¹³C, and 500 MHz for ¹H, 125 MHz for ¹³C, respectively). Two-dimensional nmr experiments HETCOR (parameters: width 15791.6 Hz; and 3838.4 Hz, arrayed repetitions with 256 increments, FT size 2048 x 1024 points) and GHMQC (parameters: width 5134.8 and 25000.0 Hz, arrayed repetitions, 512 increments, FT size 2048 x 1024 points) were carried out on a Varian Unityplus spectrometer.

The single crystals suitable for X-ray analysis were grown from acetic acid by slow evaporation. The data were collected on a KM4 KUMA-diffractometer, with graphite monochromated MoKα radiation. The θ-2θ scan technique and a variable scan speed range from 1.2 to 18.0°/minute depending on reflection intensity were applied. Intensity data were corrected for Lorenz and polarization effects [28]. Both structures were solved by direct methods with the SHELXS86 program [29] and refined by full-matrix least squares method with SHELXL93 [30] on F². The function $\Sigma w(|Fo|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma(Fo)^2 + (0.0083P)^2 + 4.44P]$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined anisotropically. Weak constraints of the thermal parameters were applied to the disordered C6 and C7 atoms. Hydrogen atoms were placed in calculated positions and refined as "rigid model", *i.e.* they were restrained to move together with their carrier atoms in order to maintain the starting geometry. The isotropic thermal parameters of hydrogen atoms were set at 1.2 (1.5 for methyl groups) times U_eq of the bonded atom. Only for hydrogen atoms involved in hydrogen bonding positional and thermal parameters were refined. Crystal data together with the data collection and structure refinement details are listed in Table 7. All positional, geometric and thermal parameters are deposited as supplementary material (deposited at Cambridge Crystallographic Data Center).

The flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). The tlc were performed on the plates PSC-Fertigplatten Kieselgel 60 F254 of Merck, using a mobile phase chloroform, methanol and ethyl ether (7:2:1) and visualized using UV lamp or dyed with benzene solution of *p*-chloranil. Melting points were determined on a Boetius Micro PHMK Heiztisch instrument without corrections. Microanalytical data were obtained in the Department of Chemistry, Technical University of Warsaw.

The following compounds were prepared by the reported procedure: **1a** [18], **1b** [19] (Bp. 142-144, 0.8 mm.), **1c** [20], **1d** and **1j** [21], **1e** [22], **1f** [23], **1g** [24], **1h** and **1i** [25], **1k** [26] and compounds **3a, f** and **i** [3].

α-(Tolyl)-α-(2-pyridyl)acetamide (**2b**).

The α-(2-tolyl)-α-(2-pyridyl)acetonitrile (**1b**) 22.9 g (0.096 mole) was added successively to the stirred mixture of sulfuric and acetic acids (20 and 60 ml, respectively) and the solution was heated for 1 hour at 100°. The mixture was cooled down to 10°, and alkalized with ammonia to pH 9. The product was extracted with chloroform (3 x 60 ml), dried with magnesium sulfate and then the solvent was removed. The residue was recrystallized twice from acetonitrile and the yield of analytically pure **2b** was 17 g (78%), mp 134.4-135.0°; ir (potassium bromide pellets): cm⁻¹: 3270, 3110 (NH), 1660 (C=O); ¹H nmr (200 MHz, deuterio-

chloroform): δ, ppm 8.56 (m, 1H, pyridine H-6), 7.60 (m, 1H pyridine H-4), 7.3 8 (m, 1H pyridine H-3) 7.16 (in, 5H pyridine H-5 and Ph-H), 7.00 and 6.44 (bs, 2H, 2 x NH), 5.28 (s, 1H from CHCO), 2.33 (s, 3H, CH_3); coupling constants, Hz: $J_{5-6} = 5$, $J_{4-6} = 2$, $J_{3-6} = 1$, $J_{3-4} = 7.8$, $J_{4-5} = 7.8$; ^{13}C nmr (50 MHz, deuteriochloroform): δ, pyridine carbons 158.7 C-2, 137.0 C-3, 128.1 C-4, 130.7 C-5, 149.0 C-6, benzene ring carbons: 136.8 C-1, 136.8 C-2, 122.1 C-3, 126.4 C-4, 124.2 C-5, 127.4 C-6 and 173.7 C=O, 57.0 CH, 19.8 CH_3.

Anal. Calcd. For $C_{14}H_{14}N_2O$: C, 74.32; H, 6.24; N, 12.38. Found: C, 74.30; H, 6.24; N, 12.40.

The remaining amides **2a,c-k** were prepared in the same manner. The melting points for **2a** [18], **2f** and **i** [3], **2g** [27] were in agreement with literature data, mp for **2c** (97-98°), **2d** (109-110°), **2e** (127- 128°), **2h** (152-153°), **2j** (126-127°), **2k** (103-104°) [20] and in the reference [20] only the preparation mode was given, not the value of mp.

4-Aryl-1*H*,2*H*-pyrido[1,2-*a*]pyrimidine-1,3-diones **3a-k**.

General Procedure.

Sodium (0.18 gram atom) was dissolved in 30 ml of ethanol, then 0.17 mole of diethyl carbonate was added followed by 0.1 mole of the respective amide **2a-k**. The mixture was boiled for 6 hours to obtain **3b,c,d,e,g,h** and 14 hours to obtain **3j,k**, then ethanol was removed under vacuum. The residue was dissolved in 100 ml water and acidified with acetic acid to *p*H 4. The precipitate was filtered, washed with 2 x 20 ml of water and dried. The compounds obtained were crystallized from acetic acid **2a,e,f,g,i,j** and **k** or methanol **2b,c,d** and **h,** and finally, subjected to column chromatography (conducted on silica gel with chloroform-methanol, 97:3 v/v). The reaction yields, melting points, the results of elemental analysis and ir data are given in Table 1. The results obtained by nmr are collected in Table 2 (^1H nmr) and Table 3 (^{13}C nmr).

4-Aryl-hexahydro-1*H*,3*H*-pyrido[1,2-*a*]pyrimidine-1,3-diones **4a-k***

General Procedure for Hydrogenation.

The derivatives **3a-k** (0.01 mole) were hydrogenated in 100 ml of acetic acid with 0.1 g PtO_2, the catalytic reduction was carried out under 60 atmospheres of hydrogen pressure at 50° for 10 hours for **3a-i** or 15 hours for **3j,k**. The catalyst was removed by filtration and the solvent by evaporation *in vacuo*. The residue **4a,b** was recrystallized from ethanol, **4c,f,e,k** from acetic acid and **4d,g,h,i,j** from methanol. The compounds were purified by column chromatography (see above).

* The reduction of **3a,b,c,d,f,g,h,j** and **k** was carried out using 0.2 g of catalyst Pd/C (10%) for 0.01 mole of compound under the same conditions as described above. The yields were of 10% lower than those obtained using PtO_2 for **4a,b,c,d,f,g,h,j** and **k**. Compounds **3e** and **3j** did not undergo reduction under these conditions. The reaction yields, melting points, analytical and ir data are given in Table 1. The results of ^1H nmr analysis are collected in Table 4 and of ^{13}C nmr in Table 5.

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