Synthesis and Molecular Structure of Novel 4-Aryloctahydropyrido-[1,2-*c*]pyrimidine Derivatives

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A series of new 4-aryloctahydropyrido[1,2-*c*]pyrimidine-1,3-diones **6a,b,d-h** and **j** were synthesized by intramolecular cyclization of α-aryl-α-(1-ethoxycarbonyl-2-piperidyl)-acetamide derivatives **5a,b,d-h** and **j**. The structures of compounds were determined by ^{1}H and ^{13}C nmr spectroscopy. Nmr and X-ray diffraction data indicate that the configuration at the C4, C4a stereocenters constitute *RR* and *SS* pair.

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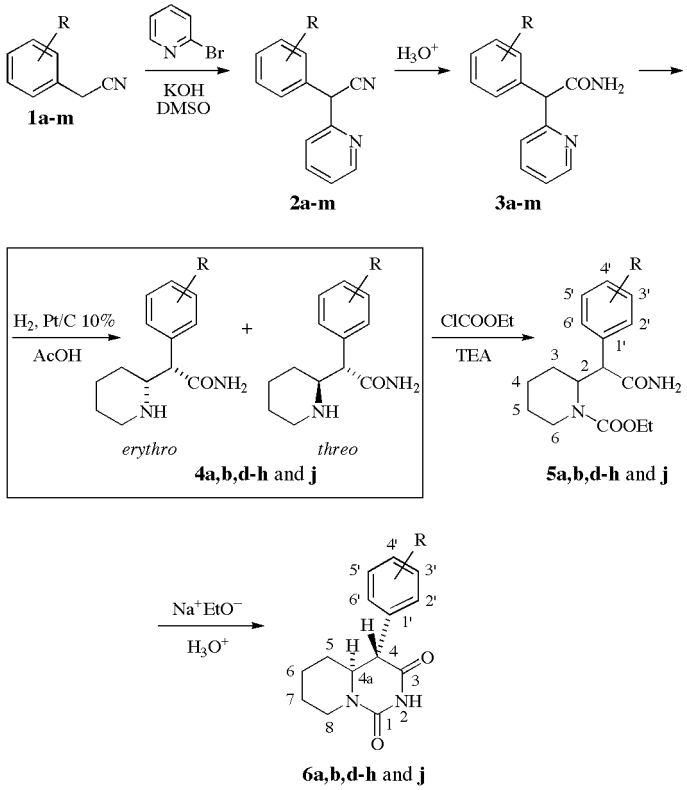
In continuation of our research on the synthesis of condensed heterocyclic compounds we focused our interest on the derivatives of octahydropyrido[1,2-*c*]pyrimidine [1,2]. Several methods of synthesis of such a heterocyclic ring system are described in the literature [3-18]. Numerous papers have been devoted to the synthesis and determination of pharmacological activity of these compounds. The differences in activity were related to the nature and position of substituents on the ring system [7,13-15]. In the present paper, the synthesis of a series of new derivatives of 4-aryl-octahydropyrido[1,2-*c*]pyrimidine (Scheme 1) is reported. The obtained compounds will be further applied as starting materials in the synthesis of new ligands of the $5HT_{1A}$ receptor. Due to the increased lipophilicity, the presence of imide group in their structure, and the elements providing a possibility of interaction with the $5HT_{1A}$ receptor, higher affinity for this receptor can be expected for octahydropyridopyrimidine series [19,20].

Results and Discussion.

Chemical Synthesis.

The derivatives of the octahydropyrido[1,2-*c*]pyrimidine **6a,b,d-h** and **j** were obtained according to the synthetic pathway given in Scheme 1. The respective nitriles **2a-m**, used as substrates, were synthesised by a new method. The reaction of C-arylation of the stabilised anion (Ar-CH-CN)$^-$ was carried out in the presence of 2-bromopyridine in aprotic polar solvent (with the addition of potassium hydroxide). This method in nitrile synthesis has some advantages: i) it avoids the use of expensive reagents for condensation (such as sodium amide, sodium hydride, potassium-*tert*-butoxide) and, therefore, strictly anhydrous conditions are not necessary, ii) the reaction temperature can be kept at 50 °C, which no need to use boiling benzene or toluene. The yields of the products were comparable with those described in [21-28]. As the next step in the synthesis, the nitriles **2a-m** were hydrolysed using a mixture of sulfuric and acetic acids, to obtain the amides **3a-m** in good yields. The catalytic reduction of the amides **3a,b,d-h** and **j** was performed in the presence of catalysts Pt/C(10%) or PtO_2. This reaction afforded the compounds **4a,b,d-h** and **j** as a mixture of *threo* and *erythro* forms (20/80) [28,29]. In the case of new compound **4b** the composition of its diastereomers (also: *threo* and *erythro* 20/80) was established by gas chromatography analysis. The crystallization of the isomeric mixture of hydrochlorides **4a**,**b**,**d-h** and **j** usually provided pure forms *erythro*, therefore mainly the *erythro* isomers were used for acylation. After acylation of compounds **4a,b,d-h** and **j**, their derivatives **5a,b,d-h** and **j** were obtained. The products **6a,b,d-h** and **j** were finally formed in the intramolecular cyclisation reaction (in the presence of sodium ethoxide) of **5a**,**b**,**d-h** and **j**.

Scheme 1



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

It is worth mentioning that dominanting forms *erythro* of compounds **4a**,**b**,**d-h** and **j** and **5a**,**b**,**d-h** and **j** (the absolute configuration *R*,*S*), which were used for cyclisation, underwent epimerisation since the compounds **6a**,**b**,**d-h** and **j** exhibited absolute configuration *R*,*R*.

The physicochemical data for compounds **5a,b,d-h** and **j** and **6a,b,d-h** and **j** are given in Table 1.

Table 1

Physical, Analytical and IR Spectroscopic Data of Compounds **5a, b, d-h, j** and **6a, b, d-h, j**

No.	R	Yield (%) Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	IR (potassium bromide, cm^{-1})
5a	H	68.0 107.8-111.8	$C_{16}H_{22}N_2O_3$	66.19 / 66.11	7.64 / 7.70	9.64 / 9.60	3372, 3170 1684, 1665
5b	2-Me	96.2 172.3-172.5	$C_{17}H_{24}N_2O_3$	67.08 / 66.95	7.95 / 7.95	9.20 / 9.18	3395, 3186 1689, 1669
5d	4-Me	72.0 201-202	$C_{17}H_{24}N_2O_3$	67.08 / 67.02	7.95 / 7.98	9.20 / 9.14	3369, 3159 1693, 1666
5e	2-F	65.0 172-173	$C_{16}H_{21}FN_2O_3$	62.32 / 62.27	6.86 / 6.64	9.08 / 9.00	3374, 3194 1691, 1665
5f	3-F	33.0 194.3-194.5	$C_{16}H_{21}FN_2O_3$	62.32 / 62.30	6.86 / 7.01	9.08 / 9.04	3385, 3192 1692, 1669
5g	4-F	46.0 160-161	$C_{16}H_{21}FN_2O_3$	62.32 / 62.28	6.86 / 6.80	9.08 / 9.10	3396, 3197 1687, 1664
5h	2-MeO	89.2 155.6-155.8	$C_{17}H_{24}N_2O_4$	63.73 / 63.66	7.55 / 7.59	8.74 / 8.59	3367, 3186 1687, 1665
5j	4-MeO	81.0 205-206	$C_{17}H_{24}N_2O_4$	63.73 / 63.49	7.55 / 7.50	8.74 / 8.67	3396, 3184 1692, 1658
6a	H	68.8 260-261	$C_{14}H_{16}N_2O_2$	68.83 / 68.79	6.60 / 6.55	11.46 /11.32	3170, 1714, 1676
6b	2-Me	94.3 185-186	$C_{15}H_{18}N_2O_2$	69.75 / 69.75	7.02 / 7.09	10.84 / 10.81	3218, 1708, 1692
6d	4-Me	74.0 253-254	$C_{15}H_{18}N_2O_2$	69.75 / 69.70	7.02 / 7.09	10.84 / 10.80	3190, 1713, 1681
6e	2-F	80.0 275-277	$C_{14}H_{15}FN_2O_2$	64.11 / 64.12	5.76 / 5.60	10.68 / 10.65	3178, 1714, 1676
6f	3-F	98.0 199.9-202	$C_{14}H_{15}FN_2O_2$	64.11 / 64.18	5.76 / 5.80	10.68 / 10.61	3180, 1715, 1681
6g	4-F	59.0 245-246	$C_{14}H_{15}FN_2O_2$	64.11 / 64.15	5.76 / 5.60	10.68 / 10.72	3187, 1714, 1681
6h	2-MeO	75.7 198-199	$C_{15}H_{18}N_2O_3$	65.68 / 65.49	6.61 / 6.61	10.21 / 10.14	3185, 1721, 1666
6j	4-MeO	75.7 273-274	$C_{15}H_{18}N_2O_3$	65.68 / 65.60	6.61 / 6.54	10.21 / 10.21	3192, 1704, 1687

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

In the ^{1}H nmr spectra of **4b** the signals of the two diastereomers *erythro* and *threo* were observed, best resolved in the spectrum of hydrochloride. Chemical shifts of the diagnostic protons for the two isomers were as follows: **4b** *erythro*: 4.13 (d, 1H, CHCO), 3.81 (m, 1H, C-2-H$_a$), 3.32 (m, 1H, C-6-H$_e$), 2.99 (m, 1H, C-6-H$_a$), 2.45 (s, 3H, CH$_3$). **4b** *threo*: 4.13 (d, 1H, CHCO), 3.73 (m, 1H, C-2-H$_e$), 3.50 (m, 1H, C-6-H$_e$), 3.03 (m, 1H, C-6-H$_a$), 2.40 (s, 3H, CH$_3$).

The above assignments were confirmed by the Overhauser effect observed in ^{1}H nmr spectrum of **4b**: the irradiation of the CH-CO signal at 4.13 ppm gave an increase in intensity of the C-2-H$_a$ resonance (for isomer *erythro*) at 3.81ppm.

The ^{1}H nmr data, which characterize the compounds **5a,b,d-h** and **j** are collected in Table 2. The chemical shift of the amino group, δ_{NH} is in the range of 5.7-6.7 ppm and the signals (even those of the ethyl group) are broader than 0.5-1 Hz, typically found in the ^{1}H spectra. The half width of the NH signal varies from 7.8 to 62.6 Hz, probably due to fast proton exchange (within intramolecular hydrogen bond and/or between tautomeric forms). ^{13}C nmr data for **5a,b,d-h** and **j** are given in Table 3.

The ^{1}H and ^{13}C nmr data of compounds **6a,b,d-h** and **j** are summarised in Tables 4, 5 and 6. The assignment of proton and carbon resonances was made on the basis of 2D ^{1}H-^{1}H COSY (see Figure 1a) and ^{1}H-^{13}C HECTOR (Figure 1b) correlations and comparison with literature data [30-33]. Most ^{1}H signals, which appear as multiplets, were attributed to the equatorial and axial methylene protons of the saturated ring. The largest separation of signals can be observed for H8$_e$ and H8$_a$ (δ_e- δ_a =1.72 ppm),

Table 2

^{1}H NMR Chemical Shifts [δ, ppm, deuteriochloroform] and Coupling Constants (Hz) of Compounds **5a,b,d-h** and **j** [a]

Compound No.	R	CO-N*H*$_2$ 2H	C*H*-CO 1H	C-2 1H	C-3 1H (*e*)	C-3 1H (*a*)	C-5 2H (*a*,*e*)	C-4 1H (*e*)	C-4 1H (*a*)	C-6 1H (*e*)	C-6 1H (*a*)	O-C*H*$_2$-CH$_3$ 2H	O-CH$_2$-C*H*$_3$ 3H	C-2-Ph-R [b]
5a	H	6.33 5.96 (bs) (bs) 12.5 12.5 [c]	3.99 (d) ^{3}J=11.5	5.00 (m)	1.83 (m)		1.69 (m)	1.61 (m)	1.40 (m)	3.68 (m)	2.69 (m)	3.85 (m)	1.09 (m)	7.35-7.41 (m, 2H, C-2'-H,C-6'-H), 7.17-7.25 (m, 3H, C-3'-H,C-4'-H, C-5'-H)
5b	2-CH$_3$	5.97 5.79 (s) (bs) 12.5 34.4 [c]	4.25 (d) ^{3}J=11.0	5.12 (m)	1.93 (m)	1.78 (m)	1.72 (m)	1.58 (m)	1.40 (m)	3.93 (m)	2.52 (m)	3.96 (k) ^{3}J=7.0	1.16 (m)	7.53 (m, 1H, C-6'-H), 7.11 (m, 3H, C-3'-H, C-4'-H, C-5'-H), 2.43 (s, 3H, CH$_3$)
5d	4-Me	5.83 5.73 (s) (s) 9.4 7.8 [c]	3.90 (m) ^{3}J=11.0	5.01 (m)	1.85 (m)		1.70 (m)	1.61 (m)	1.41 (m)	3.74 (m)	2.67 (t) ^{3}J=12.5	3.90 (m) ^{3}J=11.0	1.11 (m)	7.25 (pd, 2H, C-2'-H, C-6'-H), 7.05 (pd, 2H, C-3'-H, C-5'-H), J_o=8.0, 2.28 (s, 3H, CH$_3$)
5e	2-F	5.98 (bs) 15.6 [c]	^{3}J=11.0	4.41 (d)	5.06 (m)	1.85 (m)	1.71 (m)	1.60 (m)	1.39 (m)	3.81 (m)	2.71 (t) ^{3}J=13.5	3.89 (k) ^{3}J=7.0	1.12 (m)	7.66 (td, 1H, C-6'-H), J_o=7.5, J_m=1.5, 7.17 (m, 1H, C-4'-H), 7.05 (t, 1H, C-5'-H), 6.98 (t, 1H, C-3'-H)
5f	3-F	5.79 5.68 (s) (bs) 7.8 13.4 [c]	3.94 (d) ^{3}J=11.0	5.03 (m)	1.85 (m)		1.72 (m)	1.63 (m)	1.42 (m)	3.80 (m)	2.67 (m)	3.90 (m)	1.12 (m)	7.21 (m,1H, C-5'-H), 7.18 (m,1H, C-6'-H), 7.12 (m, 1H, C-2'-H), 6.93 (m,1H, C-4'-H)
5g	4-F	5.77 5.71 (s) (bs) 7.8 21.9 [c]	4.00 (m)	4.98 (m)	1.83 (t) ^{3}J=10.0		1.72 (m)	1.64 (m)	1.42 (m)	3.75 (m)	2.66 (t) ^{3}J=12.5	3.91 (m)	1.11 (m)	7.37 (m, 2H, C-2'-H, C-6'-H), 6.95 (m, 2H, C-3'-H, C-5'-H), J_o=8.5, J_m=2.5
5h	2-OCH$_3$	5.75 5.66 (bs) (s) 31.3 10.0 [c]	4.63 (d) ^{3}J=11.5	5.09 (m)	1.87 (m)		1.66-1.80 (m)	1.59 (m)	1.39 (m)	3.88 (m)	2.64 (m)	3.94 (k) ^{3}J=7.0	1.20 (m)	7.52 (dd, 1H, C-6'-H), J_o=7.5, J_m=1.5, 7.18 (m, 1H, C-4'-H), 6.89 (m, 1H, C-5'-H), 6.84 (d, 1H, C-3'-H), 3.87 (s, 3H, OCH$_3$), J_o=8.0
5j	4-MeO	6.75 5.72 (bs) (bs) 62.6	4.85 (dd) 43.8[c]	5.35 (m) ^{3}J=12.0	1.85 (m)	1.64 (m)	1.53 (m)	1.42 (m)	1.35 (m)	4.05 (m)	3.06 (t) ^{3}J=12.0	4.16 (k) ^{3}J=7.0	1.28 (t)	7.31 (m, 2H, C-2'-H, C-6'-H), 6.88 (m, 2H, C-3'-H, C-5'-H), 3.79 (s, 3H, OCH$_3$), J_o=9.0

[a] Abbreviations used bs = broad singlet, d = doublet, m = multiplet, t = triplet, pd = pseudodoublet, *a* = axial, *e* = equatorial. [b] Coupling constants for aromatic protons were described as J *ortho,meta* (J *o,m*). [c] The data of half width of the signal (Hz).

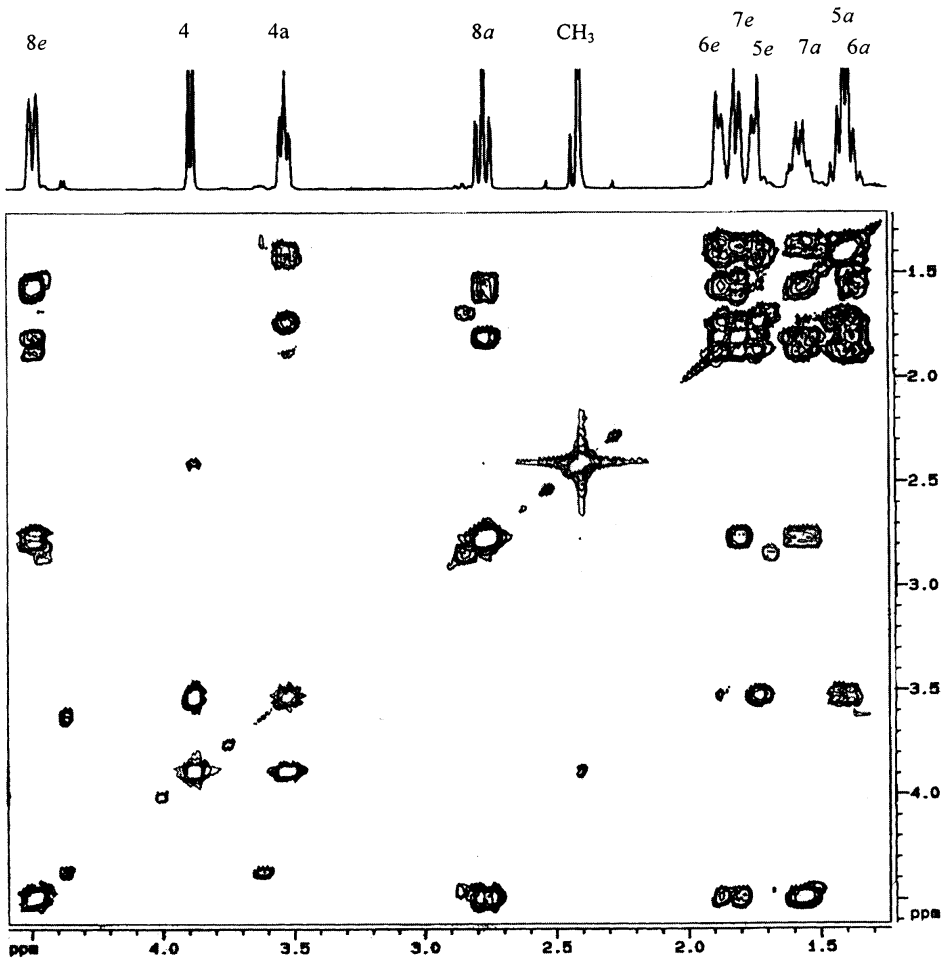


Figure 1. a) The COSY $^{1}H/^{1}H$ spectrum of **6b**.

Table 3

^{13}C NMR Spectral Data of Compounds **5a,b,d-h** and **j** [a]

	5a	**5b**	**5d**	**5e**	**5f**	**5g**	**5h**	**5j**
C-2	52.9	51.6	52.6	52.3	52.8	52.9	51.6	52.7
C-3	27.4	27.2	27.3	27.3	27.2	27.2	27.5	25.4
C-4	25.4	25.3	25.4	25.3	25.3	25.3	25.4	25.7
C-5	19.3	19.4	19.4	19.4	19.4	19.4	19.5	18.8
C-6	39.4	39.8	39.4	39.4	39.6	39.4	39.4	39.9
N-1-CO	155.5	155.4	155.5	155.3	155.4	155.4	155.4	156.5
C-H	51.2	47.2	50.9	42.3	51.1	50.5	41.8	52.3
$CONH_2$	174.4	174.4	174.4	173.5	173.3	173.9	174.5	174.5
$O\text{-}CH_2CH_3$	61.1	61.1	61.0	61.1	61.2	61.1	61.0	61.8
$O\text{-}CH_2CH_3$	14.5	14.5	14.5	14.5	14.4	14.5	14.7	14.7
C-1'	**136.6**	**135.9**	**137.3**	**123.4**[b]	**138.9**[b]	**132.2**[b]	**124.8**	**129.6**
C-2'	128.2	**134.7**	128.3	**160.7**[b]	115.4[b]	130.0[b]	**156.6**	129.1
C-3'	128.5	130.7	129.0	115.0[b]	**162.7**[b]	115.2[b]	110.4	114.5
C-4'	127.6	130.4	**133.5**	128.9	114.7[b]	**162.3**[b]	128.4	**159.2**
C-5'	128.5	127.0	129.0	124.1	129.8[b]	115.2[b]	120.9	114.5
C-6'	128.2	127.4	128.3	128.3	124.3	130.0[b]	129.3	129.1
R	-	CH_3 19.9	CH_3 21.0	-	-	-	OCH_3 55.6 [b]	OCH_3 55.3 [b]

[a] ^{13}C Chemical shifts of the *ipso* carbon atoms of the phenyl rings are given in bold numbers [δ, ppm], in deuteriochloroform compounds **5a,b,d-h** and **j**, tetramethylsilane as the Internal Standard. Coupling Constants $^{n}J(^{13}C\text{-}^{19}F)$ (Hz) for compounds: **5e** $^{1}J_{2'}$=243.6, $^{2}J_{1'}$=14.1 and $^{2}J_{3'}$=21.1; **5f** $^{1}J_{3'}$=246.0, $^{2}J_{2'}$=21.5, $^{2}J_{4'}$=19.7, $^{3}J_{5'}$=8.2 and $^{3}J_{1'}$=7.3; **5g** $^{1}J_{4'}$=245.8, $^{2}J_{3',5'}$=21.0, $^{3}J_{2',6'}$=7.8 and $^{4}J_{1'}$=3.3; **5h** ^{1}J=1.4 and **5j** ^{1}J=1.3 ($^{13}C\text{-}^{17}O$); [b] appear as doublet.

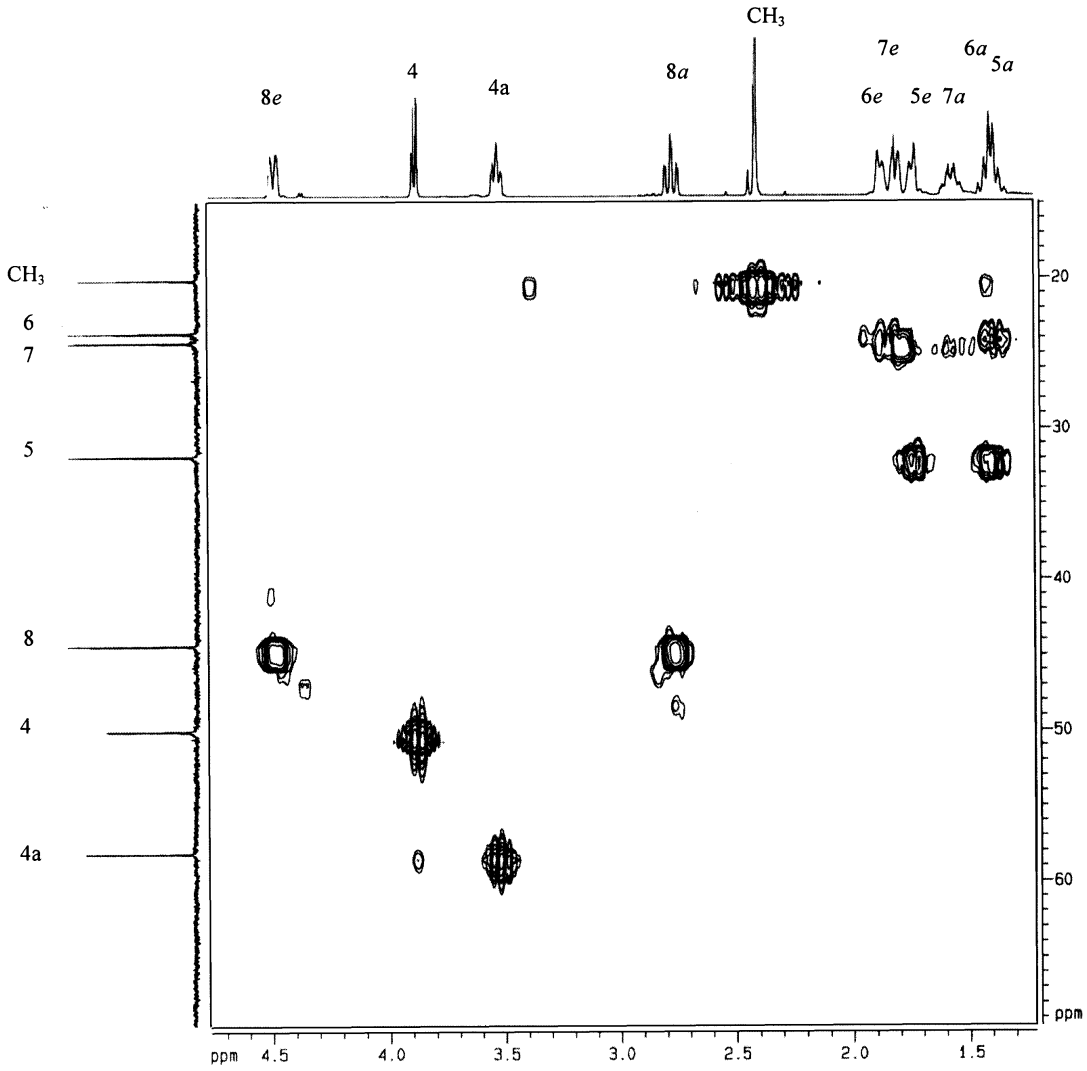


Figure 1. b) The HECTOR $^1H/^1H$ spectrum of **6b**.

whereas smaller separation of signals is observed for $H5_{e,a}$ (0.34 ppm), $H6_{e,a}$ (0.49 ppm) and $H7_{e,a}$ (0.24 ppm), as illustrated in Figure 1a,b for **6b** (2'-Me). The analysis of the splittings of signals of H4a, H4, $H8_a$, $H8_e$, $H7_a$ yielded a collection of coupling constants (Table 5). The problem of determination of stereochemistry around the chiral carbon C4 was of special interest. The coupling constants ^3J (H4/H4a) for **6a,b,d-h** and **j** are within the range 8.0-10.5 Hz, and are slightly higher (9.5-10.5 Hz) for the derivatives with 2'-R. According to Karplus and Conroy [30,31] the largest values of $^3JH_a/H_a$, of *ca*. 12-13.5 Hz, can be expected for planar *trans* arrangement (dihedral angle H4-C4-C4a-H4a, θ=180°). The ^3J H4a/H4 are smaller and indicate that the values of θ equal to 155-180° (included in Table 5) are probable. Such location of H4a and H4 hydrogens enabled an equatorial position of the aromatic ring, which is usually energetically more favoured.

The aryl substituent at C4 cannot be coplanar with the pyrido[1,2-*c*]pyrimidine system for steric reasons and the twisting reduces the electronic influence of substituents to the aromatic ring on the vicinal carbons C4, C4a and C1'. Nevertheless, an increased shielding of C4 (δ48.9-50.2 ppm) for 2'-substituted compounds is observed, as compared with 51.6-58.4 for other derivatives; a smaller effect can be noticed for C4a (Table 6). An increased shielding of C4 and C4a as well as higher values of the ^3JH-H coupling constants (mentioned above) result from a larger twist angle of the aromatic ring. A more hindered substituent at the *ortho* position makes the rotation around the C4-C1' bond particularly difficult to perform.

X-ray Diffraction.

The crystal structure of **6e** was determined by X-ray diffraction, the compound with the *ortho* substituent (2'-F)

Table 4
^{1}H NMR Chemical Shifts [δ, ppm, deuteriochloroform] of Compounds **6a,b,d-h** and **j** [a]

Compound No	R	N-2 1H (bs)	C-4 1H (d)	C-4a 1H[b] (m)	C-5 1H (m,*e*)	C-5,C-6 2H (m,*a*)	C-6 1H (m,*e*)	C-7 1H (m,*e*)	C-7 1H[c] (m,*a*)	C-8 1H[d] (m,*e*)	C-8 1H[e] (m,*a*)	C-4-Ph-R [*f*]
6a	H	7.73	3.56	3.49	1.65-1.70	1.33-1.40	1.82-1.91	1.73-180	1.53	4.43	2.75	7.31-7.40 (m, 3H, C-3'-H, C-4'-H, C-5'-H), 7.20-7.24 (m, 2H, C-2'-H, C-6'-H), J_o = 6.5 Hz
6b	2-CH_3	7.81	3.85	3.49	1.67-1.74	1.28-1.42	1.81-1.88	1.74-1.81	1.52	4.43	2.73	7.18-7.25 (m, 3H, C-3'-H, C-4'-H, C-5'-H), 7.11 (d, 1H, C-6'-H), 2.36 (s, 3H, CH_3), J_o = 7.0 Hz
6d	4- CH_3	7.95	3.52	3.46	1.64-1.72	1.29-1.42	1.80-1.88	1.72-1.79	1.52	4.43	2.74	7.17 (pd, 2H, C-3'-H, C-5'-H), 7.40 (pd, 2H, C-2'-H, C-6'-H), 2.34 (s, 3H, CH_3), J_o = 8.0 Hz
6e	2-F	7.62	3.81	3.50	1.64-1.70	1.23-1.39	1.76-1.88		1.51	4.40	2.73	7.34 (m, 1H, C-4'-H), 7.17 (m, 2H, C-5'-H, C-6'-H), 7.12 (m, 1H, C-3'-H),
6f	3-F	8.04	3.56	3.49	1.63-1.70	1.31-1.44	1.84-1.91	1.74-1.80	1.53	4.43	2.76	7.34 (m, 1H, C-5'-H), 7.00-7.06 (m, 2H, C-4'-H, C-6'-H), 6.95 (m, 1H, C-2'-H), J_o = 9.5 Hz, J_m = 2.0 Hz
6g	4-F	7.74	3.55	3.46	1.62-1.69	1.31-1.42	1.84-1.90	1.75-1.81	1.53	4.43	2.75	7.20 (m, 2H, C-2'-H, C-6'-H), 7.07 (m, 2H, C-3'-H, C-5'-H)
6h	2-OCH_3	8.32	3.71	3.51	1.64-1.71	1.20-1.35	1.72-1.82		1.48	4.41	2.69	7.30 (m, 1H, C-4'-H), 7.10 (dd,1H, C-6'-H), 6.92 (m, 2H, C-3'-H, C-5'-H), 3.80 (s, 3H, OCH_3) J_o = 7.5 Hz, J_m = 1.5 Hz
6j	4- OCH_3	10.38[g]	3.64	3.49	1.42-1.50	1.14-1.26	1.60-1.72		1.32	4.17	2.65	7.16 (pd, 2H, C-2'-H, C-6'-H), 6.90 (pd, 2H, C-3'-H, C-5'-H), 3.74 (s, 3H, OCH_3), J_o = 8.5 Hz

[a] Coupling constants and calculated dihedral angles are given in Table 5. Abbreviatious used: bs= broad singlet, d= doublet, m= multipled, pd= pseudo-dublet, *e*= equatorial, *a*= axial [b] Multipled (7 lines) from d t d pattern. [c] Multiplet (12 lines) from t t t t coupling pattern. [d] Multiplet (10 lines) from q q coupling pattern. [e] Multiplet (6 lines) from d d d coupling pattern. [f] Coupling constants for aromatic protons were discribed as *ortho, meta ($J_{o,m}$);* [g] Spectra in dimethyl-d_6 –sulfoxide.

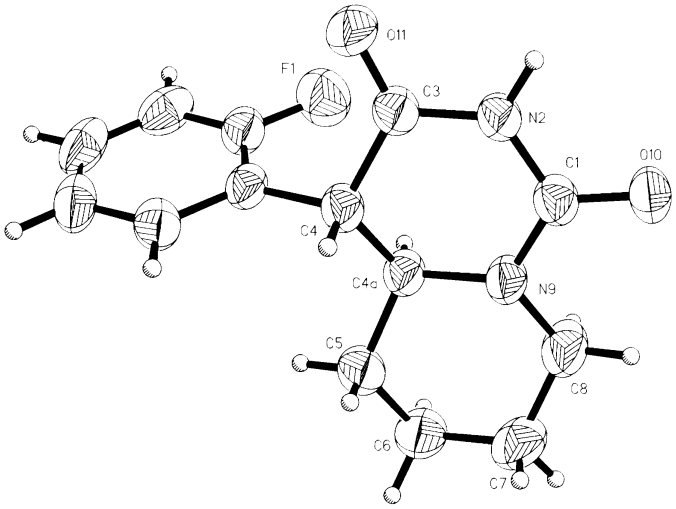


Figure 2. Ortep view of compound **6e** with 50% probability thermal elipsoides.

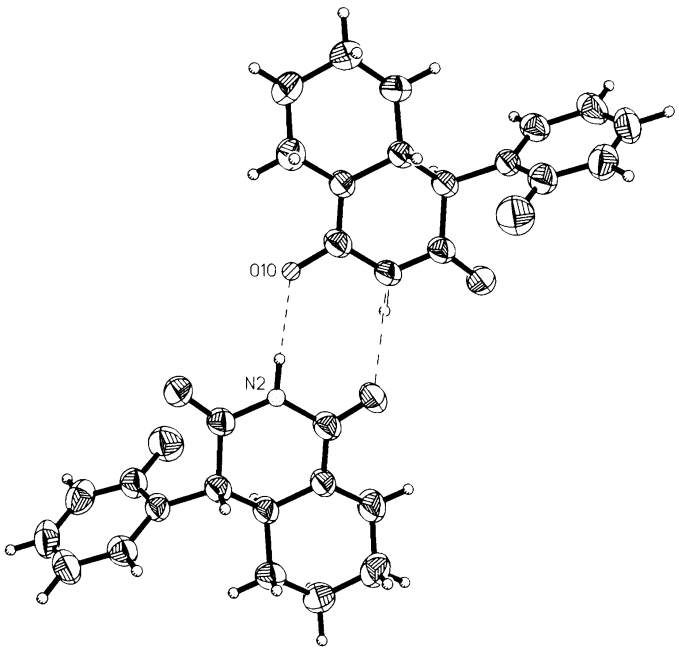


Figure 3. Hydrogen bonded dimer of **6e**.

was chosen. Of special interest was the configuration at the stereocenters (C4 and C4a) and the twisting of the aromatic ring at C4 with respect to the pyridopyrimidine skeleton.

Table 5

Coupling Constants [Hz] and Calculated Dihedral Angles [deg] of compounds **6a, b, d –h** and **j** [a]

Compound No	C-4-H		C-4a-H			C-7-H (*a*)				C-8-H (*e*)					C-8-H (*a*)	
	C-4a-H	C-5-H (*a*)	C-4-H	C-5-H (*e*)	C-7-H (*e*)	C-8-H (*a*)	C-6-H (*a*)	C-8-H (*e*)	C-6-H (*e*)	C-8-H (*a*)	C-7-H (*a*)	C-7-H (*e*)	C-6-H (*a*)	C-8-H (*e*)	C-7-H (*a*)	C-7-H (*e*)
Coupling Constant Dihedral Angles	^3J	^3J	^3J	^3J	^2J	^3J	^3J	^3J	^3J	^2J	^3J	^3J	^4J	^2J	^3J	^3J
6a	8.5	10.8	8.5	2.5	12.0	12.0	12.0	3.5	3.5	13.5	4.5	2.0	2.0	13.0	13.0	3.0
	155	180	155	55		180	180	40	45		40	55			180	50
6b	9.0	11.5	9.5	3.0	12.5	12.5	12.5	4.0	4.0	13.0	4.5	2.0	2.0	13.3	13.3	3.0
	160	180	160	50		180	180	40	40		40	55			180	50
6d	8.0	10.5	8.0	3.5	12.5	12.5	12.5	4.0	4.0	13.0	4.5	2.0	2.0	13.3	13.3	3.5
	150	180	150	40		180	180	40	40		40	55			180	45
6e	10.5	9.0	10.5	2.5	13.0	13.0	13.0	4.5	4.5	13.5	4.5	2.5	2.5	13.5	13.5	3.5
	180	180	180	55		180	180	40	40		40	55			180	45
6f	8.5	10.8	8.2	3.0	13.0	13.0	13.0	4.0	4.0	13.5	4.5	2.0	2.0	13.0	13.0	3.5
	150	180	150	50		180	180	40	40		40	55			180	45
6g	8.5	11.0	9.3	3.0	12.5	12.5	12.5	3.5	3.5	13.5	4.5	2.0	2.0	13.0	13.0	3.0
	155	180	160	50		180	180	40	45		40	55			180	50
6h	10.5	10.5	10.5	3.0	13.0	13.0	13.0	3.5	3.5	13.5	4.5	2.0	2.0	13.0	13.0	3.0
	180	180	180	50		180	180	40	45		40	55			180	50
6j	9.0	11.0	8.5	3.0	12.5	12.5	12.5	4.0	4.0	-	-	-	-	13.0	13.0	3.0
	160	180	155	50		180	180	40	40						180	50

[a] Abbreviations used : *a* = axial, *e* = equatorial.

Table 6

^{13}C NMR Spectral Data of Compounds **6a,b,d-h** and **j** [a]

	6a	**6b**	**6d**	**6e**	**6f**	**6g**	**6h**	**6j**
C-1	152.5	152.7	152.7	152.9	152.6	152.5	153.5	153.1
C-3	169.5	169.6	169.8	168.4	169.0	169.3	169.8	170.3
C-4	53.8	50.2	53.4	48.9	53.4[b]	53.1	50.2	51.6
C-4a	58.4	58.2	58.4	56.4	58.1	58.2	56.1	57.0
C-5	32.0	31.9	32.0	31.8	32.0	31.9	32.0	31.0
C-6	23.7	23.7	23.7	23.3	23.7	23.6	23.5	23.0
C-7	24.3	24.3	24.3	24.2	24.2	24.2	34.4	24.0
C-8	44.7	44.4	44.6	44.1	44.7	44.6	44.0	43.6
C-1’	**135.5**	**134.1**	**132.5**	**122.2**[b]	**137.7**[b]	**131.1**[b]	**123.9**	**128.6**
C-2’	129.1	**136.8**	128.6	**160.9**[b]	115.9[b]	130.4[b]	**157.0**	129.9
C-3’	128.7	131.1	129.7	116.0[b]	**163.0**[b]	116.1[b]	111.6	113.8
C-4’	128.2	128.0	**137.9**	130.1[b]	115.2[b]	**162.5**[b]	129.5	**158.4**
C-5’	128.7	126.7	129.7	124.6[b]	130.6[b]	116.1[b]	120.9	113.8
C-6’	129.1	128.3	128.6	131.1[b]	124.5[b]	130.4[b]	131.2	129.9
R	-	20.2	21.1	-		-	55.6 [b]	55.0 [b]

[a] ^{13}C Chemical shifts of the *ipso* carbon atoms of the phenyl rings are given in bold numbers [δ, ppm], in deuteriochloroform; compounds **6a,b,d-h** and compound **6j** in dimethyl-d_6-sufoxide, tetramethylsilane as the Internal Standard. Coupling Constants ^nJ (^{13}C – ^{19}F) (Hz) for compounds **6e** $^1J_{2'}$ = 247.2 , $^2J_{3'}$ = 22.0, $^2J_{1'}$ = 14.2 , $^3J_{4'}$ = 8.3, $^3J_{6'}$ = 4.0 and $^4J_{5'}$ = 3.6; **6f** $^1J_{3'}$=247.2, $^2J_{2'}$=22.4, $^2J_{4'}$=21.1, $^3J_{5'}$=8.7, $^3J_{1'}$=7.8, $^4J_{6'}$=3.2 and $^4J_{C\text{-}4}$=1.8; **6g** $^1J_{4'}$ = 247.2 , $^2J_{3',5'}$ = 22.0, $^3J_{2',6'}$ = 8.3 and $^4J_{1'}$ = 3.3; **6h** ^1J=1.2 and **6j** ^1J =1.4 Hz (^{13}C- ^{17}O); [b] appear as doublet.

The space group is centrosymmetric P2(1)c, therefore the configuration of the chiral molecule was determined as *RR* (*SS*) since the *RR* and *SS* pairs are present in the crystal unit. The compound forms cyclic dimers linked by C1=O...H-N hydrogen bonds (O...N distance of 2.81 Å) and the analysis of crystal packing does not show any strong intermolecular contact. An ORTEP view of the molecule **6e** (2'-F) is shown in Figure 2 and the hydrogen bonded dimer is illustrated in Figure 3. The 2'-fluorophenyl substituent at C4 is twisted with respect to the pyrido[1,2-*c*]pyrimidine system

Table 7

Selected Bond Lengths [Å] and Angles [deg] for Compound **6e**

C1-O10	1.210 (4)	N9-C1-N2	117.9 (3)
C1-N9	1.323 (4)	C3-N2-C1	127.6 (3)
C1-N2	1.357 (4)	O11-C3-N2	121.3 (3)
N2-C3	1.337 (4)	O11-C3-C4	123.8 (3)
C3-O11	1.190 (3)	N2-C3-C4	114.8 (3)
C3-C4	1.486 (4)	C1'-C4-C3	110.9 (3)
C4-C1'	1.482 (4)	C1'-C4-C4a	112.0 (2)
C4-C4a	1.503 (4)	C3-C4-C4a	113.2 (3)
C4a-N9	1.450 (4)	N9-C4a-C5	110.2 (3)
C4a-C5	1.479 (4)	N9-C4a-C4	111.1 (2)
C5-C6	1.496 (5)	C5-C4a-C4	110.7 (3)
C6-C7	1.480 (5)	C4a-C5-C6	113.5 (3)
C7-C8	1.461 (5)	C7-C6-C5	109.5 (3)
C8-N9	1.447 (4)	C8-C7-C6	111.9 (3)
C2'-F1	1.339 (4)	N9-C8-C7	112.6 (3)
O10-C1-N9	123.2 (3)	C1-N9-C8	116.3 (3)
O10-C1-N2	118.9 (3)	C1-N9-C4a	120.8 (3)
		C8-N9-C4a	116.5 (3)

Table 8

Crystal Data and Structure Refinement of **6e**

Molecular formula	$C_{14}H_{15}FN_2O_2$
Molecular weight	262.28
Temperature	293 (2) K
Wavelength	0.71073 Å
Crystal System	Monoclinic
Space Group	$P2_1 / n$
Unit Cell Dimensions	*a* = 5.8680 (10) Å *b* =18.083 (4) Å *c* =11.364 (2) Å β =101.82 (3) ^{0}
Volume, Z	1180.3 (4) Å ^{3}, 4
Density (Calculated)	1.476 Mg/m^3
Absorption Coefficient	0.111 mm^{-1}
F (000)	552
Crystal Size	0.3 x 0.25 x 0.22 mm
Θ Range for Data Collection	2.15 to 24.99 ^{0}
Index Ranges	$0 \le h \le 6$, $0 \le k \le 19$, $-12 \le 1 \le 12$
Reflections Collected	2094
Independent Reflections	1909 (R_{int} = 0.0160)
Refinement Method	Full-Matrix Least-Squares on F ^{2}
Data / Restraints / Parameters	1905 / 0 / 188
Goodness-of-Fit on F ^{2}	1.050
Final R Indices [I > 2 δ (I)]	R1= 0.0501, wR2 = 0.1288
R Indices (All Data)	R1= 0.0967, wR2 = 0.1775
Extinction Coefficient	0.000 (3)
Largest Diff. Peak and Hole	0.328 and – 0.375e Å $^{-3}$

and the torsion angle C4-C4a-C1'-C2' is 71°. Table 7 lists selected bond lengths and angles for **6e**, the structure refinement details are given in Table 8.

EXPERIMENTAL

The ir spectra (potassium bromide pellets) were recorded on either a Perkin-Elmer FT-IR spectrometer Spectrum 1000, PE AutoIMAGE System or a Bio-Rad FTS-135 spectrometer. The nmr spectra were recorded on a Varian Gemini 200 or a Unity plus 500 MHz spectrometers (200 MHz for ^{1}H, 50 MHz for ^{13}C, and 500 MHz for ^{1}H, 125 MHz for ^{13}C, respectively). Two-dimensional NMR ^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOR experiments were performed on a Bruker DRX 500 MHz spectrometer. The ^{1}H-^{13}C GHMQC correlations were run on a Varian UNITY plus 500 MHz spectrometer. For the two dimensional experiments the pulse sequences, acquisition and processing parameters were taken from standard Bruker and Varian software library.

The single crystal of **6e** (2'-F) suitable for X-ray analysis was grown from ethanol by slow evaporation. The data were collected on a KM 4 KUMA-diffractometer, with graphite monochromated Mo Kα radiation. The θ-2θ scan technique and a variable scan speed range from 1.2 to 18.0 °/minute were applied. Intensity data were corrected for Lorenz and polarization effects [34]. The structure was solved by direct method with SHELXS86 program [35] and refined by the full-matrix least-squares method with SHELXL93 [36] on F^2. All non-hydrogen atoms were refined anisotropically. The isotropic thermal parameters of hydrogen atoms were set at 1.2 times U_{eq} of the bonded atom. Only for hydrogen atoms involved in hydrogen bonding the positional and thermal parameters were refined. Crystal data together with the data collection and structure refinement details are listed in Table 8. All geometric and thermal parameters are as supplementary material (deposited at Cambridge Crystallographic Data Center No 178742).

The flash column chromatography was carried out on Merck Kieselgel 60 (230 – 400 mesh). TLC was performed on the plates DC-Platten Kieselgel 60 F_{254} of Merck, using a mobile phase $CHCl_3$, MeOH and Et_2O (7:2:1) and visualized using a UV lamp or dyed with benzene solution of *p*-chloranil.

Melting points were determined on an Electrothermal 9100 instrument without corrections.

Gas chromatography was performed on a Hewlett-Packard 5972A apparatus (HP-5MS column, 30m x 0.25mm, carrier gas helium). The analysis was carried out at 70 °C during the first 5 minutes with the increase of temperature 5 °C per minute up to 300 °C.

Microanalytical data were obtained on a Perkin Elmer Analyser CHN 2400 in the Department of Chemistry, Technical University of Warsaw.

The starting materials, substituted phenyl acetonitriles **1a-m** were purchased from Aldrich.

α-(*o*-Tolyl)- α-(2-pyridyl)acetonitrile (**2b**).

2-Methylbenzoacetonitrile (**1b**) 26.2 g (0.2 mole) was added dropwise for 0.5 hour, while stirring, to a solution of 56 g (1 mole) potassium hydroxide in 100 ml of dimethylsulphoxide. The stirring was continued for the next 0.5 hour. To the mixture obtained above 47.4 g (0.3 mole) of 2-bromopyridine was added dropwise. After 14 hours of stirring at 50 °C the cooled reaction mixture was poured into 500 ml of ice water. The reaction product was extracted twice with 100 ml portions of chloroform. The organic phase was washed twice with 100 ml of water, dried over anhydrous magnesium sulfate and evaporated. The residue obtained upon solvent evaporation was distilled at 165-170 °C at 0.1 mm to give **2b** 39 g (62 %); ir (potassium bromide pellets): cm^{-1}: 2230 (CN); ^{1}H nmr (200 MHz, deuteriochloroform): δ, ppm 8.61 (m, 1H, pyridine H-6), 7.68 (m, 1H, pyridine H-4), 7.46 (m, 1H, pyridine H-3), 7.26 (m, 5H, pyridine H-5 and Ph-H), 5.48 (s, 1H, CH-CN), 2.32 (s, 3H, CH_3); coupling constants, Hz: J_{5-6} =

4.9, J_{4-6} = 2.4, J_{3-4} = 7.7, J_{3-6} = 2.0; ^{13}C nmr (50 MHz, deuteriochloroform): δ, pyridine carbons 155.1 C-2, 122.0 C-3, 137.4 C-4, 128.6 C-5, 149.9 C-6, benzene ring carbons: 132.8 C-1, 136.2 C-2, 131.2 C-3, 128.7 C-4, 123.1 C-5, 126.9 C-6 and 119.1 C≡N, 42.8 CH, 19.6 CH_3.

Anal. Calcd. For $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.80; H, 5.79; N, 13.50.

The synthesis of the nitriles **2a** and **c-m** was performed using the method described above for compound **2b**. Compounds **2c,g,k** and **m** were oils and were isolated, as indicated above, by vacuum distillation (for compound **2c** at 150-152 °C at 1 mm, in the reference no data) [28]. Nitriles **2a,d,e,f,h,i,j** and **l** in ice water formed solids. Crude solids were purified by crystallization. Melting and boiling points were in agreement with literature data, the overall yields were equal to or higher than those described in the literature: **2a** (60,4 %) [21]; **2d** (60,8 %) [22]; **2e** (72,1 %) [22], **2f** (49,6 %) [22], **2g** (65,3 %) [23], **2h** (66.5 %) [24], **2i** (46,2 %) [25]**, 2j** (54.2 %) [26], **2k** (63,5 %) [27], **2l** (46,7 %) [28] and **2m** (40.3 %) [27].

α-Aryl-α-(2-pyridyl)acetamides **3 a-m**.

General Procedure.

The appropriate nitrile **2 a-m** (0.01 mole) was added portionwise, while stirring, to a solution composed of 60 ml acetic acid and 20 ml sulfuric acid. The mixture obtained above was stirred at 100 °C for 1 hour. After cooling to 5 °C the mixture was carefully made alkaline with ammonia to *p*H 9. The reaction product was extracted with chloroform (3 x 40 ml), dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized from the appropriate solvent, yielding analytically pure compounds **3a-m**. Melting points and yields were in agreement with literature data for **3a** [21], **3b** [1], **3i** and **m** [5], **3j** [29] and **3l** [28]. Melting points and yields for **3c** (97-98 °C; 64.5 %), **3d** (109-110 °C; 78.4 %), **2e** (126-127 °C; 80.3 %), **3f** (95.2-95.6 °C ; 76.4 %), **3g** (103- 104 °C; 68.2 %), **3h** (127-128 °C; 74.8 %) and **3k** (152-153 °C; 79.4 %) [28]. In reference [28] only the preparation mode was given, not the values of mp and yields.

(*Erythro* and *threo*) α-(2-Tolyl)- α-(2-piperidyl)acetamide (**4b**).

To a solution of 10 g (0.044 mole) of (**3b**) in 120 ml of acetic acid and 3 ml trifluoroacetic acid 1.3 g of 10 % Pt/C was added. The catalytic reduction was carried out under 10 atmospheres of hydrogen pressure at 35 °C for 30 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness (*in vacuo*). The oil was dissolved in methanol and then an excess of a solution of methanol saturated with hydrogen chloride was added. A white solid was obtained. The solid was stirred in 100 ml dichloromethane for 4 hours at room temperature and filtered off, yielding 11 g (93 %) **4b,** mp 221.2-221.4 °C, as a mixture of diastereomers *erythro* and *threo*. The precipitate was recrystallized from methanol, obtaining pure *erythro* form **4b**, mp 239.2-239.6 °C.

The hydrochloride 2.2 g obtained above was dissolved in water solution and then made alkaline to *p*H 9.5 using 20% solution of sodium hydroxide in an ice water bath. The base was extracted with chloroform (2 x 30ml). The organic phase was dried over anhydrous magnesium sulfate and evaporated. The crystalline residue was recrystallized from ligroin. Yielding 1.9 g (92.9 %) **4b**, mp 160.1- 160.3 °C of pure form *erythro* (mp 144.8-145.2 °C was established for the mixture of *threo*/*erythro*); ir (potassium bromide pellets): cm^{-1}: 3220, 3100 (NH), 1650 (C=O); ^{1}H nmr (500 MHz, deuteriochloroform): δ, ppm 7.50 (d, 1H C–6'–H, J_0=7.5), 7.18 (m, 3H, C–3'–H, C–4'–H, C–5'–H), 6.53 and 5.65 (bs, 2H, 2 x NH), 3.69 (d, 1H, CHCO, ^{3}J=7.5), 3.16 (m, 1H, C-2-H, 7 lines d t d coupling pattern, $^3J_{2\text{-}3a}$ =10.8, $^3J_{2-CH}$ =7.8, $^3J_{2-3e}$=2.5), 2.97 (m, 1H, C–6–H$_e$, 10 lines q q coupling pattern, $^2J_{6e\text{-}6a}$ =12.0, $^3J_{6e\text{-}5a}$ = 4.0, $^3J_{6e\text{-}5e}$ =2.0, $^3J_{6e\text{-}NH}$ = 2.0), 2.56 (m, 1H, C–6–H $_a$, 6 lines d d d coupling pattern, $^2J_{6a\text{-}6e}$= 12.0, $^3J_{6a\text{-}5a}$ =12.0, $^3J_{6a\text{-}5e}$ =2.5), 2.39 (s, 3H, CH_3), 1.55 (m, 1H, C–5–H $_e$), 1.42 (m, 1H, C–4–H$_e$, 12 lines t t t t coupling pattern, $^2J_{4e\text{-}4a}$ =12.5, $^3J_{4e\text{-}5e}$ = 12.5, $^3J_{4e\text{-}3e}$ =12.5, $^3J_{4e\text{-}5a}$ = 4.0, $^3J_{4e\text{-}3a}$ = 4.0), 1.84 (m, 3H, NH piperidine, C–3–H$_e$, C–3–H$_a$), 1.40 (m, 1H, C–5–H$_a$, 12 lines t t t t coupling pattern, $^2J_{5a\text{-}5e}$ = 12.5, $^3J_{5a\text{-}4a}$ = 12.5, $^3J_{5a\text{-}6a}$ = 12.5, $^3J_{5a\text{-}4e}$ = 4.0, $^3J_{5a\text{-}6e}$ = 4.0), 1.22 (m, 1H, C–4–H$_a$); ^{13}C nmr (125 MHz, deuteriochloroform): δ, piperidine carbons 58.8 C–2, 47.2 C–6, 30.7 C–3, 26.1 C–5, 24.7 C–4, benzene ring carbons: 137.3 C–1', 135.1 C–2', 130.9 C–3', 127.6 C– 4', 127.3 C–6', 126.6 C–5' and 174.8 C=O, 53.7 CH, 20.3 CH_3.

Anal. Calcd. For $C_{14}H_{20}N_2O$: C, 72.31; H, 8.61; N, 12.05. Found: C, 72.36; H, 8.71; N, 11.84.

Approximately 0.5 mg of **4b** hydrochloride, obtained before recrystallization, was derivatized with trifluoroacetic anhydride (0.25 ml in screw-cap vial, 100 °C, 0.5 hour) and subjected to gas chromatograph analysis: 80/20 *erythro-threo*; retention time: 33.9 and 34.4 minutes, respectively.

The amides **4a**,**d**,**e**,**f**,**g**,**h** and **j** were synthesized using the same procedure, only the trifluoroacetic acid was not added during the synthesis. After the evaporation of acetic acid, the residue was transformed into the base, which made the method much simpler. The melting point of the pure base **4a** was 158-159 °C (74.6%), and for the mixture of *erythro-threo* 172-173 °C was found in [21]; for compounds **4j** the melting point was 175.5-176 °C (81.3%), whereas for the salt it amounts to 222-223 °C [29]. For the other amides, such as **4d** (185-186 °C, 62.5 %), **4e** (163-164 °C, 71.2 %), **4f** (257.7-257.9 °C, 61.7 %) [b], **4g** (195-196 °C, 60.5 %) and **4h** (140-142 °C, 70.9 %), the method of synthesis was described, but without the analytical data, mp and yields of the compounds obtained [28] [a].

[a] Abbreviations used in ^{1}H nmr text: *e* = equatorial, *a* = axial.

[b] Melting point for hydrochloride.

α-Aryl-α-(1-ethoxycarbonyl-2-piperidyl) acetamide **5a**,**b**,**d–h** and **j**.

General Procedure.

The ethyl chloroformate 0.03 mole in 10 ml of chloroform was added dropwise, while stirring, to a mixture of 0.02 mole of appropriate acetamide **4a**,**b**,**d-h** and **j** dissolved in 50 ml of chloroform and 0.03 mole of triethylamine. The above-obtained mixture was refluxed for 12 hours, cooled to room temperature and washed with 30 ml of water. The organic phase was dried over anhydrous magnesium sulfate and then the solvent was removed. The residue was purified by flash column chromatography (with dichloromethane-methanol, 98:2 v⁄v) to afford the product as white solid. The purified compounds were crystallized from: **5a** from benzene-acetonitrile (3:1 v⁄v), **5b** from ligroin-absolute ethanol (4:1 v⁄v), **5d** and **j** from ethanol, **5e** from benzene and **5h** from toluene. 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 (^{1}H nmr) and Table 3 (^{13}C nmr).

4-Aryloctahydropyrido[1,2-*c*]pyrimidine-1,3-diones **6a**,**b**,**d-h** and **j**.

General Procedure.

To a mixture of 30 ml of absolute ethanol and 0.02 mole of metallic sodium, 0.01 mole of compounds **5a**,**b**,**d-h** and **j** was added. The cyclization was performed for 10 hours, under reflux. The reaction mixture was poured into ice water and was acidified with acetic acid to *p*H 5. The reaction product was extracted with chloroform (3 x 50 ml). The organic phase was dried over anhydrous magnesium sulfate and then the solvent was removed. The obtained residue was purified by flash column chromatography (with dichloromethane-methanol, 97:3 v/v) to provide compounds **6** as colorless solids. The compounds were crystallized: **6a**,**e** and **g** from acetonitrile [a]; **6b**,**d** and **h** from ethanol; **6f** from ethyl acetate-hexane (1:1 v/v) and **6j** from acetic acid. The reaction yields, melting points, analytical and ir data are given in Table 1. The results of ^{1}H nmr analysis are collected in Tables 4 and 5 and of ^{13}C nmr in Table 6.

[a] Compound **6a** was obtained by intermolecular condensation of methyl α-phenyl-α-(2-piperidyl)acetate hydrochloride and potassium isocyanate (mp 255 °C), however no nmr spectroscopic data were given [7].

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