Nitrogen Bridgehead Compounds. Part 80 [1]. Unusual Reaction of Ethyl 9-Bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and *N*-Methylaniline

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The acid-catalysed intramolecular nucleophilic addition of the phenyl ring to the C(9a)=N(1) double bond of ethyl 9-(*N*-methyl-*N*-phenyl)-4-oxotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates, formed in the reactions of ethyl 9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylates and *N*-methylaniline, gave the first examples of a new tetracyclic pyrimido[1′,2′:1,2]pyrido[3,2-*b*]indole ring system (**7**). X-ray diffraction analysis of **7a** revealed that the annelation of the pyrimidine and piperidine rings is transoid, while that of the piperidine and pyrroline rings is *cis*, the piperidine ring adopts an unusual $^{6}T_{8}$ twisted boat conformation, while the pyrroline ring has a $^{9}T_{8a}$ conformation.

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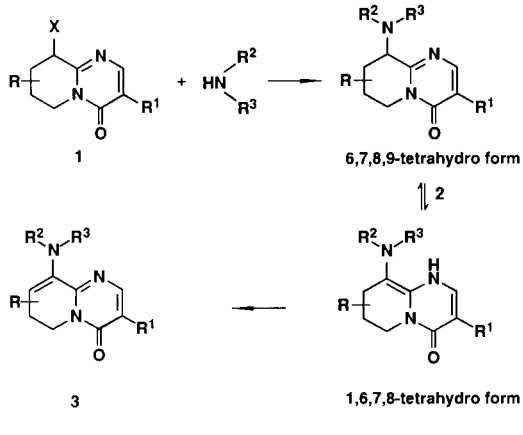
Of the pharmacologically active 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [2], the antiallergic, antiasthmatic 9-aminopyrido[1,2-*a*]pyrimidin-4-ones [3-6] are prepared in the reactions of 9-halo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones with *N*-nucleophiles (*e.g.* amines [6-9], hydrazines [5] or sodium azide [10]). Amines yield 9-aminotetrahydropyridopyrimidinones **2** [6,8] or 9-amino-6,7-dihydropyridopyrimidinones **3** [6,9] when the reactions are carried out in the absence or the presence of air, respectively (Scheme 1). 9-Amino-6,7-dihydropyridopyrimidinones **3** are obtained by the autooxidation of the primarily formed 9-aminotetrahydropyridopyrimidinones **2**, which exhibit a solvent-dependent tautomerism [8] (as 6,7,8,9-tetrahydro- and 1,6,7,8-tetrahydropyridopyrimidinones, see Scheme 1), in a free-radical electron-transfer process with the oxygen of the air [9].

Scheme 1



The present paper reports an unusual reaction of *N*-methylaniline and ethyl 9-bromo-4-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidine-3-carboxylate (**4a**). Whereas the 6-methyl derivative of pyridopyrimidinecarboxylate **4b** in boiling ethanol for 8 hours under nitrogen afforded the expected 9-(*N*-methyl-*N*-phenylamino)-6-methyltetrahydropyridopyrimidinecarboxylate **5b** [6], the desmethyl derivative **4a** gave a product with different chromatographic behaviour from that of **5b** [tlc: Rf ≈ 0.69 for **5b** *vs.* Rf ≈ 0.46 for this product on a Kieselgel plate (Merck) with the developing system: methanol-benzene = 1:4].

Accurate mass measurement of the molecular ion indicates the elementary composition $C_{18}H_{21}N_3O_3$ for the reaction product, which is identical with that for the corresponding tetrahydropyridopyrimidinecarboxylate **5a**, and in the ir spectrum (potassium bromide) the NH vibrational band at 3200 cm^{-1} might suggest the presence of the 1,6,7,8-tetrahydro tautomer of 9-anilinotetrahydropyridopyrimidinecarboxalate **5a**. However, the shape of the ethanolic uv spectrum of the product **7**, and its longest wavelength maximum (312 nm, log ε = 3.97) do not resemble those of either the 6,7,8,9-tetrahydro or the 1,6,7,8-tetrahydro tautomer (298 ± 6 nm [7,8,11] and 359 ± 4 nm [7,8], respectively), but are very similar to those of 4-oxo-1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid derivatives **8** (314 ± 5 nm) [12].

In the ^{1}H nmr spectrum (deuteriochloroform), the doublet at the 2 position of the pyridopyrimidine moiety indicates that the neigbouring N-1 bears a hydrogen, the intensities of the aromatic protons point to the presence of four protons only, instead of five, and their pattern suggests the presence of an *ortho*-substituted phenyl ring. The chemical shift of C(13b) of the pyridopyrimidine moiety can be identified at 78.7 ppm in the aliphatic region, as a singlet in the "off-resonance" ^{13}C nmr spectrum (deuteriochloroform-DMSO-d_6, 1:1), demonstrating that it must be a quaternary carbon (see Table 1).

On the basis of the above-mentioned data, we assumed

Table 1

^{1}H and ^{13}C NMR Data on Pyrimidopyridoindoles 7 (δ_{TMS} = 0 ppm)

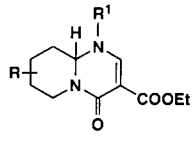
^{1}H NMR	7a [a]	[b]	7b [c]	^{13}C NMR	7a [b]	7b [c]
1-H	6.65-6.90 [d]	8.35 d	9.25 br	C-2	150.5 d	149.5 d
2-H	7.85 d	7.95 d	7.62 br	C-3	92.6 s	93.5 s
6_{eq}-H	4.25-4.65 m	4.30-4.70 m	4.25-4.70m	C-4	160.9 s	161.0 s
6_{ax}-H	2.10-2.55 m	2.20-2.50 m	-	C-6	34.9 t	43.4 d
7-H_2 and 8-H_2	1.30-2.10 m	1.45-2.15 m	1.30-2.05	C-7	18.4 t	24.8 t
				C-8	20.8 t	18.3 t
8a-H	3.35-3.65 m	3.40-3.60 m	3.30-3.65	C-8a	69.2 d	69.4 d
10-H, 11-H, 12-H, 13-H	6.40-6.80 m [d] and 7.08-7.35 m	6.45-6.85 m and 7.15-7.45 m	6.45-6.75 m and 6.95-7.35 m	C-9a	150.4 s	149.0 s
				C-10	108.1 d	108.0 d
				C-11	122.9 d	122.7 d
				C-12	118.0 d	117.5 d
N-Me	2.75 s	2.80 s	2.80 s	C-13	130.8 d	131.7 d
6-Me	-	-	0.80 d	C-13a	128.7 s	130.7 s
O-CH_2	4.18 q	4.22 q	4.05 q	C-13b	78.7 s	76.0 s
CH_2CH_3	1.28 t	1.30 t	1.20 t	3-CO	164.3 s	164.2 s
J_{NH-H}	7.1 Hz	7.5 Hz		O-CH_2	58.6 t	58.5 t
$J_{6a,6e}$	13.0 Hz			N-CH_3	31.9 q	31.3 q
$J_{6a,7a}$	4.8 Hz			6-CH_3	-	18.3 q
$J_{6a,7e}$	2.1 Hz			CH_2CH_3	14.4 q	14.5 q

[a] In deuteriochloroform. [b] In deuteriochloroform: DMSO-d_6 = 1:1. [c] In DMSO-d_6. [d] Overlapping signals.

that the product was a derivative of a new tetracyclic nitrogen bridgehead ring system (**7**), pyrimido[1′,2′:1,2]-pyrido[3,2-*b*]indole, in which one of the *ortho* carbons of the phenyl ring and C(9a) of the pyridopyrimidine moiety are linked by a valence bond, and the hydrogen atom of the phenyl ring has migrated to N(1). This structure was fully justified by X-ray investigations, which also revealed the stereochemistry at the ring junctions.

X-ray Diffraction Studies.

X-ray analysis of **7a** was carried out on single-crystals of the racemic compound. Figure 1 depicts the solid-state structure for the 8a-*R* enantiomer, and shows endocyclic torsion angles. The signs of the torsion angles of the junction at the N(5)-C(13b) bond are opposite, corresponding to a transoid ring junction. The puckering amplitude (Table 2) and the endocyclic torsion angles show that the pyrimidine ring is rather flat, in accordance with similar hexahydro derivatives (compound **8**, R = 6-Me, R^1 = H;



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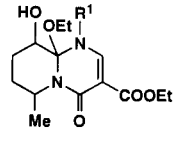

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Table 2

Puckering Parameters in 7a (for the 8a-*R* Enantiomer) [a]

Piperidine ring N(5)C(6)C(7)C(8)C(8a)C(13b)

Q, Å	θ, [b] deg	Φ, [c] deg
0.738 (6)	92.0 (4)	204.3 (4)

Pyrimidine ring N(1)C(2)C(3)C(4)N(5)C(13b)

Q, Å	θ, [b] deg	Φ, [c] deg
0.220 (4)	112 (1)	125 (1)

Pyrrole ring N(9)C(9a)C(13a)C(13b)C(8a)

Q, Å	Φ, [c] deg
0.202 (5)	334 (1)

[a] Esd's are given in parentheses. [b] $\theta_{mirror} = 180° \pm \theta$. [c] $\Phi_{mirror} = \Phi \pm 180°$.

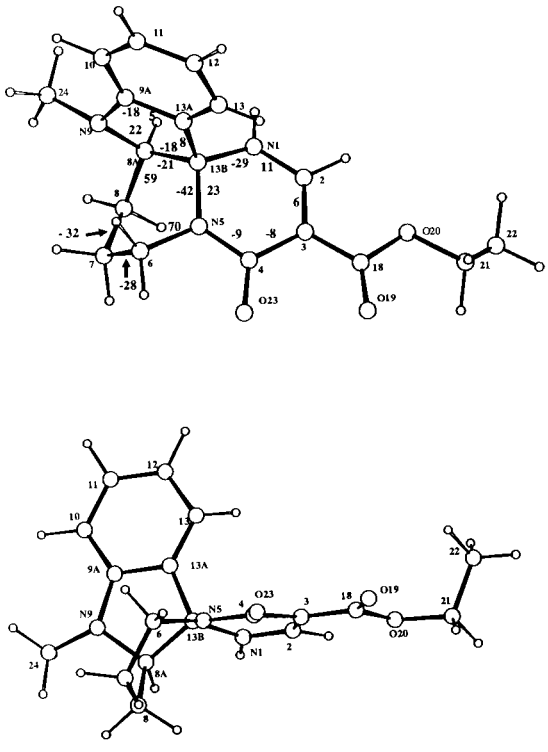

Figure 1. Molecular diagrams for the 8a-*R* enantiomer of compound **7a** with atomic numbering. The endocyclic torsion angles are given in the upper diagram where the N(5)-C(13b) bond is at an angle of 75° to the plane of the drawing whereas in the lower diagram the same angle is 10°.

and compound **9**, in refs [12] and [16]) with a transoid junction.

The piperidine ring has a high puckering amplitude (Q = 0.738 Å), and the angular parameters indicate a $^{6}T_{8}$ twisted conformation. The five-membered ring has a $^{6}T_{8a}$ conformation due to the attached phenyl ring. On the basis of the sign sequence of the endocyclic torsion angles [13] C(13a) is in the axial position relative to the pyrimidine ring, and in the isoclinal position relative to the piperidine ring above the pyridopyrimidine bicycles. N(9) is also above the pyridopyrimidine bicycles, in the axial position. The pyramidality parameters (χ) [14,15] reveal that N(1), C(2), C(4) and N(5) are sp^2 in character (Table 3), the latter atom exhibits significant pyramidality in other hexahydro derivatives [12]. H(1) forms bifurcated hydrogen bonds with two symmetry-transformed carbonyl oxygens: H(1)...0(19) [x,-y,1/2+z] = 2.12 Å, N(1)...0(19) = 1.853 Å, N(1)-H(1)....0(19) = 129°, H(1)...0(23) [x,-1/2-y,1/2+z] = 2.07 Å, N(1)...0(23) = 2.868 Å, and N(1)-H(1)....0(23) = 135°.

Table 3

Conformational Parameters for the Amide and Enamine Groups [a], [14,15]

$\chi_N = \omega_2 - \omega_3 + 180° = \omega_4 - \omega_1 + 180°$

$\chi_C = \omega_1 - \omega_3 + 180° = \omega_4 - \omega_2 + 180°$

$\tau'_{CN} = \omega_1 + \omega_2 + \omega_3 + \omega_4$

Amide group (A)

$\chi_{N(5)}$ 6.1; $\tau'_{N(5)C(4)}$ -6.6, $\chi_{C(4)}$ -4.3

Enamine group (E)

$\chi_{C(2)}$ 0.2; $\tau'_{C(2)N(1)}$ 25.0, $\chi_{N(1)}$ -1.9

[a] Torsion angles (ω values) are given in Table 7.

Tables 4-7 contain atomic coordinates, U(eq) values, bond lengths, bond angles and torsion angles for **7a**.

Discussion.

In a previous paper [12] on the hexahydropyrido[1,2-*a*]-pyrimidin-4-ones, we analysed the influence of the interactions of the 1,4,6,9 substituents on the type of junctions of the hexahydropyrido[1,2-*a*]pyrimidine ring. A transoid

Scheme 2

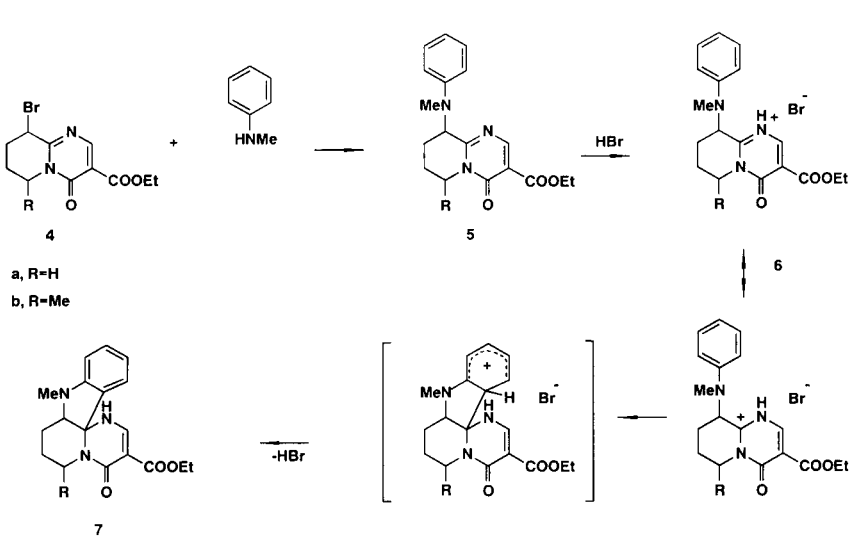

Table 4

Atomic Coordinates and U(eq) Values with e.s.d's for **7a**

	x/a	y/b	z/c	U(eq)
N1	.7818(3)	-.1760(3)	.7925(2)	.036(1)
C2	.7612(3)	-.2800(4)	.7329(3)	.033(2)
C3	.7571(3)	-.2881(4)	.6246(3)	.030(2)
C4	.7876(3)	-.1810(4)	.5765(3)	.032(2)
N5	.8051(3)	-.0750(3)	.6391(2)	.037(1)
C6	.8404(4)	.0368(4)	.6013(3)	.044(2)
C7	.9602(4)	.0750(5)	.6885(4)	.060(2)
C8	.9831(4)	.0306(5)	.8089(4)	.053(2)
C8A	.8740(4)	.0272(4)	.8275(3)	.039(2)
N9	.8185(3)	.1465(3)	.8125(3)	.046(2)
C9A	.7001(4)	.1294(4)	.7632(3)	.041(2)
C10	.6135(4)	.2109(5)	.7543(4)	.057(2)
C11	.5007(4)	.1741(5)	.6946(4)	.068(3)
C12	.4722(4)	.0591(6)	.6474(4)	.063(3)
C13	.5587(4)	-.0246(5)	.6549(4)	.048(2)
C13A	.6710(3)	.0130(4)	.7133(3)	.036(2)
C13B	.7812(3)	-.0573(4)	.7408(3)	.033(2)
C18	.7339(3)	-.4034(4)	.5650(3)	.040(2)
O19	.7287(3)	-.4222(3)	.4700(2)	.050(1)
O20	.7206(3)	-.4957(3)	.6284(2)	.050(1)
C21	.7022(5)	-.6174(4)	.5764(4)	.060(2)
C22	.5778(6)	-.6406(6)	.5062(5)	.082(3)
O23	.8048(2)	-.1821(3)	.4886(2)	.044(1)
C24	.8735(5)	.2405(5)	.8980(4)	.071(3)
H1	.8007	-.1800	.8767	.0389
H2	.7467	-.3626	.7727	.0400
H61	.8412	.0230	.5184	.0467
H62	.7805	.1096	.5945	.0467
H71	1.0243	.0377	.6617	.0609
H72	.9676	.1743	.6896	.0609
H81	1.0202	-.0632	.8202	.0643
H82	1.0478	.0878	.8730	.0643
H8A	.0952	-.0057	.9162	.0463
H10	.6339	.3023	.7927	.0573
H11	.4311	.2386	.6823	.0680
H12	.3817	.0318	.6025	.0681
H13	.5430	-.1094	.6250	.0593
H211	.7481	-.6273	.5228	.0585
H212	.7343	-.6870	.6437	.0585
H221	.5626	-.7303	.4669	.0867
H222	.5438	-.5724	.4370	.0867
H223	.5299	-.6322	.5579	.0867
H241	.9662	.2379	.9252	.0728
H242	.8557	.2271	.9719	.0728
H243	.8426	.3301	.8615	.0728

Table 5

Bond lengths (Angstrom) with e.s.d's for **7a**

Including Hydrogen Atoms

N1-C2	1.334(5)	C7 -H72	1.089(6)	C12 -H12	1.099(4)
N1-C13B	1.457(5)	C8 -C8A	1.519(4)	C13 -C13A	1.378(5)
N1-H1	1.006(3)	C8 -H81	1.114(5)	C13 -H13	.991(5)
C2-C3	1.374(5)	C8 -H82	1.088(5)	C13A-C13B	1.516(5)
C2-H2	1.092(4)	C8A-N9	1.459(5)	C18 -O19	1.213(4)
C3-C4	1.454(5)	C8A-C13B	1.547(5)	C18 -O20	1.352(5)
C3-C18	1.440(6)	C8A-H8A	1.098(4)	O20 -C21	1.463(6)
C4-N5	1.374(5)	N9 -C9A	1.390(4)	C21 -C22	1.487(6)
C4-O23	1.241(4)	N9 -C24	1.452(6)	C21 -H211	1.086(4)
N5-C6	1.457(5)	C9A-C10	1.391(5)	C21 -H212	1.093(5)
N5-C13B	1.477(4)	C9A-C13A	1.403(6)	C22 -H221	1.082(6)
C6-C7	1.531(5)	C10-C11	1.382(5)	C22 -H222	1.100(6)
C6-H61	1.082(4)	C10-H10	1.096(5)	C22 -H223	1.084(5)
C6-H62	1.085(4)	C11-C12	1.377(8)	C24 -H241	1.090(4)
C7-C8	1.528(6)	C11-H11	1.097(5)	C24 -H242	1.077(5)
C7-H71	1.097(4)	C12-C13	1.410(6)	C24 -H243	1.087(5)

Table 6

Bond Angles (deg) with e.s.d's for **7a**

C2	-N1	-C13B	122.4(5)	N9	-C9A	-C10	129.3(6)
N1	-C2	-C3	123.4(5)	N9	-C9A	-C13A	111.1(6)
C2	-C3	-C4	118.5(5)	C10	-C9A	-C13A	119.6(6)
C2	-C3	-C18	120.4(5)	C9A	-C10	-C11	118.3(7)
C4	-C3	-C18	120.8(5)	C10	-C11	-C12	122.1(8)
C3	-C4	-N5	115.9(5)	C11	-C12	-C13	120.5(7)
C3	-C4	-O23	124.3(5)	C12	-C13	-C13A	117.1(7)
N5	-C4	-O23	119.6(5)	C9A	-C13A	-C13	122.4(6)
C4	-N5	-C6	120.6(5)	C9A	-C13A	-C13B	108.1(5)
C4	-N5	-C13B	125.9(5)	C13	-C13A	-C13B	129.4(6)
C6	-N5	-C13B	113.3(5)	N1	-13B	-N5	108.9(5)
N5	-C6	-C7	110.0(5)	N1	-C13B	-C8A	110.5(5)
C6	-C7	-C8	111.1(6)	N1	-C13B	-C13A	112.5(5)
C7	-C8	-C8A	111.8(6)	N5	-C13B	-C8A	109.4(5)
C8	-C8A	-N9	112.9(5)	N5	-C13B	-C13A	112.5(5)
C8	-C8A	-C13B	112.4(5)	C8A	-C13B	-C13A	102.9(5)
N9	-C8A	-C13B	104.7(5)	C3	-C18	-O19	126.5(6)
C8A	-N9	-C9A	108.6(5)	C3	-C18	-O20	112.5(5)
C8A	-N9	-C24	118.6(6)	O19	-C18	-O20	120.9(6)
C9A	-N9	-C24	121.9(6)	C18	-O20	-C21	116.1(5)
				O20	-C21	-C22	110.9(6)

junction was found only in the case of the 1-desmethyl derivative. However, a study [16] of the crystal structure of ethyl 1,6-dimethyl-4-oxo-9-hydroxy-9a-ethoxy-1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**9**) indicated that the transoid junction was favoured even in the 1-methyl derivative when a relatively bulky substituent was present in the 9a position. In the latter case, an unfavourable interaction would occur between the N(1) substituent and the C(9a) substituent if the bicycle adopted a cisoid ring junction (C_B) [12]. In compounds **7**, both effects (the absence of a 1-methyl group and a substituent on the bridgehead carbon C(13b)) favour a transoid junction. The unusual $^6T_8$ twisted boat conformation of the piperidine ring shifts C(13a) in the isoclinal position toward the piperidine ring, permitting a relatively small C(13a)-C(13b)-C(8a)-N(9) torsion angle of -17.9°, while in **9** the corresponding H(9)-C(9)-C(9a)-O(20) torsion angle is 53.6°. Such a large torsion angle would be impossible in a five-membered ring fused to a 1,2-phenyl group. In **7b**, the 6-methyl group should be in the axial position, on the same side of the ring as N(9) and C(13a).

For the formation of the tetracyclic ring system **7**, the following mechanism seems to be plausible (see Scheme 2): In the first step, nucleophilic substitution of the bromine

Table 7

Torsion Angles (deg.) with e.s.d's for 7a Including H1 and H2 Atoms and the Definition of ω Values (see Table 3)

C4	-C3	-C2	-N1	6.2(5)	C13A	-C9A	-C10	-C11	-.8(7)
C4	-N5	-C13B	-N1	23.0(6)	C13A	-C13	-C12	-C11	1.6(7)
N5	-C4	-C3	-C2	-7.5(5)	C13A	-C13B	-N1	-C2	101.4(6)
N5	-C13B	-N1	-C2	-24.0(5)	C13A	-C13B	-N5	-C4	-102.4(6)
C6	-N5	-C4	-C3	177.6(6) ω_{4a}	C13A	-C13B	-N5	-C6	71.9(5)
C6	-N5	-C13B	-N1	-162.7(5)	C13A	-C13B	-C8A	-C8	-140.9(6)
C7	-C6	-N5	-C4	-115.7(6)	C13A	-C13B	-C8A	-N9	-17.9(4)
C8	-C7	-C6	-N5	-27.9(5)	C13B	-N1	-C2	-C3	11.4(5) ω_{2E}
C8	-C8A	-C13B	-N1	98.8(6)	C13B	-N5	-C4	-C3	-8.5(6) ω_{1A}
C8	-C8A	-C13B	-N5	-21.1(5)	C13B	-N5	-C6	-C7	69.6(5)
C8A	-C8	-C7	-C6	-32.1(6)	C13B	-C8A	-C8	-C7	59.0(6)
C8A	-C13B	-N1	-C2	-144.2(6)	C13B	-C8A	-N9	-C9A	21.9(5)
C8A	-C13B	-N5	-C4	143.8(6)	C13B	-C13A	-C9A	-N9	5.0(5)
C8A	-C13B	-N5	-C6	-41.8(5)	C13B	-C13A	-C9A	-C10	-177.5(6)
N9	-C8A	-C8	-C7	-59.2(6)	C13B	-C13A	-C13	-C12	176.6(8)
N9	-C8A	-C13B	-N1	-138.2(5)	C18	-C3	-C2	-N1	-179.7(7)
N9	-C8A	-C13B	-N5	101.9(5)	C18	-C3	-C4	-N5	178.4(6)
C9A	-N9	-C8A	-C8	144.6(6)	O19	-C18	-C3	-C2	-179.5(8)
C9A	-C13A	-C13B	-N1	127.3(6)	O19	-C18	-C3	-C4	-5.5(6)
C9A	-C13A	-C13B	-N5	-109.3(6)	O20	-C18	-C3	-C2	-1.4(5)
C9A	-C13A	-C13B	-C8A	8.4(5)	O20	-C18	-C3	-C4	172.6(6)
C10	-C9A	-N9	-C8A	165.4(9)	C21	-O20	-C18	-C3	-177.1(6)
C11	-C10	-C9A	-N9	176.1(8)	C21	-O20	-C18	-O19	1.1(6)
C12	-C11	-C10	-C9A	2.1(8)	C22	-C21	-O20	-C18	-88.6(7)
C12	-C13	-C13A	-C9A	-.4(6)	O23	-C4	-C3	-C2	168.0(7)
C13	-C12	-C11	-C10	-2.5(7)	O23	-C4	-C3	-C18	-6.1(6)
C13	-C13A	-C9A	-N9	-177.4(8)	O23	-C4	-N5	-C6	1.9(5) ω_{2A}
C13	-C13A	-C9A	-C10	.1(7)	O23	-C4	-N5	-C13B	175.8(7) ω_{3A}
C13	-C13A	-C13B	-N1	-50.1(7)	C24	-N9	-C8A	-C8	-70.5(7)
C13	-C13A	-C13B	-N5	73.4(7)	C24	-N9	-C8A	-C13B	166.9(7)
C13	-C13A	-C13B	-C8A	-169.0(8)	C24	-N9	-C9A	-C10	21.9(7)
C13A	-C9A	-N9	-C8	-17.5(5)	C24	-N9	-C9A	-C13A	-161.0(7)
H1	-N1	-C2	-C3	-166.7(6) ω_{3E}	H2	-C2	-N1	-C13B	-168.4(7) ω_{4E}
H1	-N1	-C13B	-N5	154.1(6)	H2	-C2	-N1	-H1	13.6(5) ω_{1E}
H1	-N1	-C13B	-C8A	33.9(5)	H2	-C2	-C3	-C4	-174.0(7)
H1	-N1	-C13B	-C13	-80.5(5)	H2	-C2	-C3	-C18	.1(5)

atom by *N*-methylaniline takes place, and N(1) of the bicycle is then protonated by the hydrogen bromide formed. After the protonation, a new bond develops between the electron-deficient C(9a) and one of the relatively electron-rich *ortho* carbons of the phenyl ring. Finally, aromatization of the phenyl ring occurs through elimination of the *ortho* hydrogen atom, to give the tetracyclic heterocycle **7**.

In other words, the formation of the tetracyclic ring system is a proton-catalysed intramolecular nucleophilic addition of the phenyl ring to the C(9a)=N(1) double bond.

According to this mechanism, the tetracyclic derivative should be obtained from the 6-methyl derivative too if the reaction is carried out under more acidic conditions. When a solution of 9-substituted 6-methyltetrahydropyridopyrimidinecarboxylate **5b** in acetic acid was left to stand at room temperature for 3 days, no reaction occurred.

However, when the acetic acid contained 85% orthophosphoric acid, the expected tetracyclic compound **7b** was obtained in 40% yield. A better yield (60%) could be achieved when **5b** was dissolved in ethanolic hydrogen chloride and left to stand for 3 days at ambient temperature.

As a consequence of the presence of a further asymmetric center at position 6 of the bicycle **5b**, two diastereomeric tetracyclic derivatives might form, depending upon the side of the C(9a)=N double bond on which the new bond formation occurs. However the new bond formation between C(9a) and one of the *ortho* positions of the phenyl ring must be highly stereospecific [17]. If it took place on the side opposite to the 6-methyl group, a severe $A^{1,3}$-type allylic strain [18,19] would develop between the 6-methyl and 4-carbonyl groups, leading to an unfavourable transition state with a much higher energy than in the other case.

There is only one set of signals in the nmr spectrum of **7b**, proving that only one diastereomer is formed.

As concerns the ^1H and the ^{13}C nmr data on **7a** and **7b** (Table I), the similar chemical shifts indicate that the

stereochemistry of the ring junctions and the conformation of the four-ring system are the same in both compounds.

The axial position of the 6-methyl group in **7b** is indicated both by the downfield shift of 6-H (around 4.5 ppm, see Table I) in consequence of the diamagnetic anisotropy of the adjacent carbonyl group in the ^{1}H nmr spectrum, and by the upfield shift of C-8 (18.3 ppm) caused by the γ_{gauche} steric effect [20-22] of the 6-methyl group (-2.5 ppm on C-8) in the ^{13}C nmr spectrum. Therefore, the methyl group and the condensed pyrrolidine ring are on the same side of the piperidine ring in **7b** too. This arrangement is confirmed by the upfield chemical shift of the 6-methyl group in the ^{1}H nmr spectrum as compared to the values measured for similar bicyclic-hexahydropyridopyrimidine derivatives [12], which is due to the shielding at aromatic ring.

The difference in the reactivities of 9-bromotetrahydropyridopyrimidinecarboxylates **4a** and **b** could be interpreted as follows in the case of the 6-desmethyl derivative **4a**, both steps in the formation of the tetracyclic derivative **7a** (nucleophilic substitution and addition) proceed relatively easily, while in the case of the 6-methyl derivative **4b**, a steric interaction between the quasi-axial methyl group and the phenyl ring in **5b** makes the addition step in the formation of the tetracyclic ring system more difficult. In the latter case, therefore, both pyridopyrimidine **5b** and pyrimidopyridoindole **7b** could be isolated.

EXPERIMENTAL

Melting points were determined in capillary tubes and are not corrected. Yields were not maximized. Ultraviolet (uv) spectra were taken in ethanol on a Pye Unicam SP 8-200 instrument. Infrared (ir) spectra were obtained with potassium bromide disks on a Zeiss UR-20 spectrophotometer. The ^{1}H and ^{13}C nmr spectra were recorded at 80.0 and 20.1 MHz, respectively, using a Bruker WP-80 spectrometer. The ^{1}H and ^{13}C chemical shifts were determined on the scale by using tetramethylsilane (δ = 0) as internal standard. Mass spectral analyses were carried out with a JEOL JMS-D300 spectrometer, (ionization potential 70 eV) with a direct sample inlet.

Crystallography.

Compound **7a** crystallizes in the monoclinic $P2_1/c$ space group, with a = 12.843(6), b = 10.935(4), c = 12.860(3) Å, β = 114.98(3), and Z = 4.2863 unique reflections were collected on an Enraf-Nonius CAD 4 diffractometer. The structure was solved by means of direct methods, and refinement was carried out with the Enraf-Nonius structure determination package. All hydrogen atoms could be found in the difference electron density map following anisotropic refinement, but their calculated positions were taken in the final cycles of refinement, which concluded with R = 0.071 and R_w = 0.090 for the reflections used in the refinement [$I > 2x\ \sigma(I)$]. The weighting scheme was $w = 1/[\sigma^2(F_o) + 0.01F_o^2]$. Atomic coordinates with averaged temperature factors are given in Table 4, while bond length and bond angles are to be found in Tables 5 and 6.

Ethyl 9-Bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**4a**).

A solution of ethyl 4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxylate [23] (12.0 g, 5.4 mmoles) and NBS (9.6 g, 5.4 mmoles) in chloroform (100 ml) was stirred at ambient temperature for 24 hours. The reaction mixture was extracted with water (3 x 30 ml), then dried (sodium sulphate) organic layer was evaporated to dryness, and the residue was crystallized from ethanol to give 12.6 g of **4a**, mp 110-110°.

Anal. Calcd. for $C_{11}H_{13}N_2O_3Br$: C, 43.87; H, 4.35; N, 9.30; Br, 26.53. Found: C, 43.94; H, 4.32; N, 9.16; Br, 26.82.

Ethyl 9-Methyl-4-oxo-6,7,8,8a-tetrahydro-1*H*,9*H*-pyrimido[1',2':1,-2]pyrido[3,2-*b*]indole-3-carboxylate (**7a**).

A solution of ethyl 9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidine-3-carboxylate (**4a**) (2 g, 6.6 mmoles) and *N*-methylaniline (1.32 g, 12.3 mmoles) in ethanol (20 ml) was refluxed for 8 hours under nitrogen. To the brownish reaction mixture, 5% aqueous hydrochloric acid (10 ml) was added, and the aqueous mixture was extracted with methylene chloride (3 x 5 ml). The combined and dried (sodium sulphate) organic layer was evaporated to dryness under reduced pressure. The residue was crystallized from methanol to yield 0.9 g (37%) of **7a**, mp 250°; ms: (m/e) 327 (35.8%, M^+), 298 (41), 281 (48.5), 270 (19.4), 254 (12), 226 (49.2), 186 (100), 185 (61.2), 171 (29.9), 158 (56), 143 (17.9); uv (ethanol): λ max 312 nm, 230i, 216; ir (potassium bromide): ν max 3200 (NH), 1715 (3-CO), 1620 cm^{-1} (C(4)=O).

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.46; N, 12.84. Found: C, 66.13; H, 6.55; N, 12.51.

Ethyl 6,9-Dimethyl-4-oxo-6,7,8,8a-tetrahydro-1*H*,9*H*-pyrimido[1',-2':1,2]pyrido[3,2-*b*]indole-3-carboxylate (**7b**).

a) A solution of ethyl 9-(*N*-methyl-*N*-phenylamine)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**5b**) [8] (0.5 g, 1.46 mmoles) in a mixture of glacial acetic acid (5 ml) and 85% orthophosphoric acid (2 ml, Fluka) was left to stand at ambient temperature for 3 days under nitrogen. The reaction mixture was diluted with water (20 ml), and the precipitated crystals were filtered off and recrystallized from acetonitrile to give 0.2 g (40%) of **7b**, mp 215-217°.

b) A solution of compound **5b** [8] (0.5 g, 1.46 mmoles) in ethanol (5 ml) containing 20% hydrogen chloride was left to stand at ambient temperature for 3 days. The red solution was then diluted with water (20 ml), and the *p*H of the aqueous reaction mixture was adjusted to 7 with sodium hydrogen-carbonate. The precipitated crystals were filtered off and recrystallized from acetonitrile to give 0.3 g (60%) of **7b**, mp 215-217°; uv (ethanol): λ max 311 nm, 231i, 216.

Anal. Calcd. for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.82; H, 7.02; N, 12.33.

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