Nitrogen Bridgehead Compounds. Part 79 [1]. Synthesis and Structure Elucidation of Benzimidazolo[2,1-*f*][1,6]naphthyridine Aza-derivatives

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6-Substituted 1,6-naphthyridine-5(6*H*)-ones were prepared from diethyl 2-[2-(dimethylamino)vinyl]-6-methylpyridine-3,5-dicarboxylate **1** [2] by ring closure with aromatic and heteroaromatic diamines (*o*-phenylenediamine, 2,3-diaminopyridine, 3,4-diaminopyridine and 4,5-diaminopyrimidine, respectively). 1,6-Naphthyridine-5(6*H*)-ones were cyclised in phosphoryl chloride to yield nitrogen bridgehead tetracycles **6-9**. The structure of the products was established by nOe difference spectroscopy. A complete ^1H and ^{13}C nmr assignment was achieved by different 2D carbon-proton correlation measurements.

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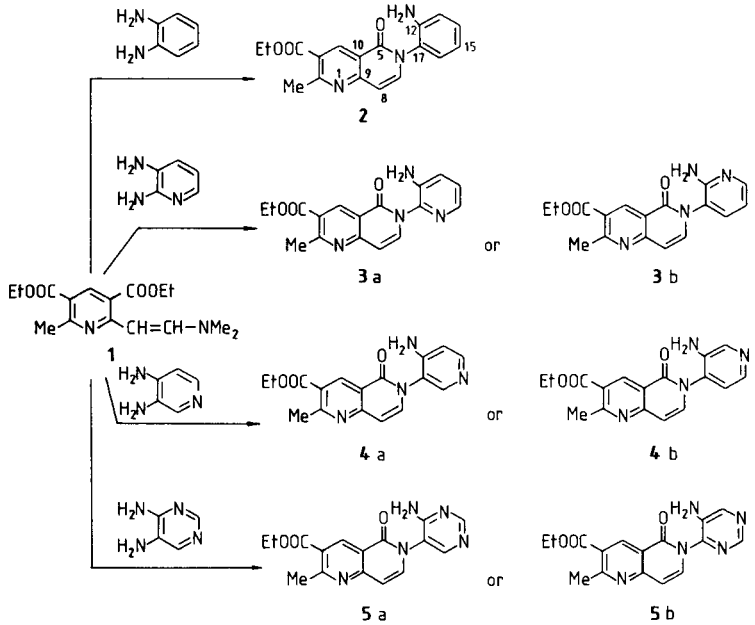
We recently reported the synthesis of ethyl 2-methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate and its 4-substituted and 6-substituted derivatives [2,3]. 1,6-Naphthyridin-5(6*H*)-ones display valuable biological properties *e.g.* antiinflammatory, anticonvulsant [4,5] antibacterial, antifungal [6] and Ca antagonistic activities [7].

Among other concepts for functionalization of the 1,6-naphthyridine ring our plan was to attach a new ring bridging at positions 5 and 6. For this purpose ethyl 6-(2-aminophenyl)-2-methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate **2** and its aminopyridine **3-4** and aminopyrimidine analogues **5** were cyclized in phosphoryl chloride to benzimidazo[2,1-*f*][1,6]naphthyridine **6**, a novel ring system and to the corresponding aza-derivatives **7-9**, respectively. Analogous systems were synthesized by Reddy *et al.* by condensation of benzaldehydes with amino-3-benzimidazo-substituted heterocycles [8,9].

Synthesis of 1,6-Naphthyridin-5(6*H*)-ones **2-5** and their Cyclization to the Corresponding Benzimidazo[2,1-*f*][1,6]-naphthyridines and their Aza Analogues **7-8**.

Diethyl 2-[2-(dimethylamino)vinyl]-6-methylpyridine-3,5-dicarboxylate **1** was reacted with an equimolar amount of an aromatic diamine in refluxing ethanol and dimethylformamide respectively to yield in approximately 60% yield 6-substituted 1,6-naphthyridines **2-5**. Depending on which of the two amino groups of the heteroaromatic diamine reacted, two isomers "**a**" or "**b**" could be formed (Scheme 1). The numbering of the carbon atoms for compounds **2-5** in Scheme 1 is not in accordance with IUPAC

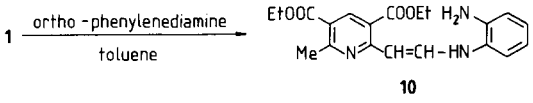
Scheme 1



nomenclature. This choice, however, facilitates the comparison of spectroscopically analogues atoms with **6-9**.

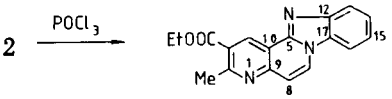
Condensation proved to be regioselective giving in every case a single isolable product. The reaction presumably proceeds *via* intermediate **10** and the corresponding heteroaromatic analogues respectively (Scheme 2). In the reaction of **1** with *o*-phenylenediamine in toluene this intermediate could be in fact isolated [3] and gave on further transformation **2**. When ethyl 6-(2-aminophenyl)-2-methyl-5-oxo-5,6-dihydro-1,6-naphthyridine-3-carboxylate **2** was boiled with phosphoryl chloride it gave in high yield benzimidazo[2,1-*f*][1,6]naphthyridine **6** (Scheme 3).

Scheme 2



10

Scheme 3



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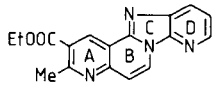
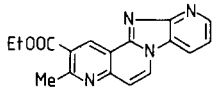
6-Substituted 1,6-naphthyridines obtained with heteroaromatic diamines gave in a similar ring closure reaction tetracyclic compounds, in which one or two CH groups of ring D were replaced by nitrogen atoms. Depending on whether the products are analogues of type "**a**" or type "**b**" isomers of naphthyridines **3-5**, two isomers can be envisaged for the tetracycles **7-9**. Elucidation of the structure of compounds **7-9** also settles the structure of the parent naphthyridines **3-5**, which was postulated [3] on our present investigations.

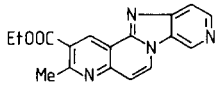
Scheme 4



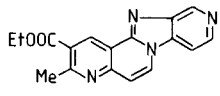
7 a



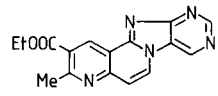
7 b



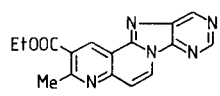
8 a



8 b



9 a



9 b

Structural Studies.

The structures of the 1,6-naphthyridines **2-5** was supported, apart from elementary analysis, by ir and nmr spectroscopy. Common features of their ir spectra are ν_{as} and ν_s NH_2 stretching bands in the range of 3500-3350 cm^{-1} as well as an amide-I band appearing at 1660-1670 cm^{-1}. Easily identifiable signals are the 2H signal of the amino group in the ^1H nmr spectra and the signal of the NC=O group at 165 ppm in the ^{13}C nmr spectra. After ring closure to **6-9** these signals disappear from the spectra.

Characteristic ^1H and ^{13}C signals and coupling constants for compounds **2-9** are compiled in Tables 1 and 2. Signal assignments were based on substituent effects [10] and on proton-proton [11] and carbon-proton [12] correlation spectra. Assignment of quaternary carbon atoms was assisted by COLOC [13] measurements optimized for J(C,H) = 6 Hz long-range coupling constants. Carbon-proton correlations found in this way are shown in Table 3.

A choice between "**a**" and "**b**" type structures for compounds **7-9** and the assignment of the signals for ring D protons was permitted by 1D proton-proton nOe experiments. Results are summarized in Table 4.

Reliability of the method was tested with compound **6**. Irradiation of the 7-H signal gave significant intensity enhancements both for 8-H and the sterically close 16-H. Conversely, when 16-H was irradiated, intensity of the 7-H and 15-H signals increased. Having assigned this way 16-H, the coupling pattern became clear and with the aid of a COSY-45 experiment the assignment of the other protons in ring D became possible. With compound **7** irradiation of 7-H gave intensity enhancement only at the 8-H signal, consequently the nitrogen atom was at position 16 (isomer "**a**"). In accordance with this, on irradiation of the proton in the *para* position to the nitrogen atom in ring D a nOe effect could only be observed for the signal at δ = 7.50 ppm (dd).

In case of **8** and **9** irradiation of 7-H not only affected the signal of 8-H but also a singlet signal, what proved that in position 16 there was a CH unit adjacent to a nitrogen atom, *i.e.* these compounds were also of type "**a**". By chemical correlation it also follows that compounds **3-5** are also of type "**a**".

Ring closure is associated with characteristic spectral changes. As compared with compounds **2-5** the ^1H signals of aromatic =CH groups in compounds **6-9** are significantly shifted downfield. This shift is the result of the anisotropic effect of the aromatic system, while with ring D it is a consequence of the conversion of an $-NH_2$ group to an -N=C group. A common feature of the proton spectra is a significant long-range coupling (^5J) between H-4 and H-8.

In compounds **2-5** the N-C(7)=C(8) moiety is essentially an enamine unit. This results in a high electron density in β-position and a strong shielding of C(8) (δC(8) ~ 108 ppm). As a consequence of ring closure ring B becomes

Table 1

^{1}H NMR Chemical Shifts and Characteristic Coupling Constants (Hz) of Compounds **2-9** in deuteriochloroform and 400 MHz

	2	**3a**	**4a**	**5a**	**6**	**7a**	**8a**	**9a**
4-H	8.90	9.14	9.03	9.12	9.30	9.52	9.55	9.53
7-H	7.26	7.66	7.33	7.30	8.17	8.77	8.55	8.54
8-H	6.63	6.82	6.78	6.86	7.05	7.33	7.40	7.45
13-H	6.73	7.26	6.68	–	7.85	8.27	7.86	–
14-H	7.10	7.23	8.21	8.64	7.39	7.50	8.67	9.26
15-H	6.72	8.00	–	–	7.28	8.54	–	–
16-H	7.01	–	8.17	8.27	7.62	–	9.29	9.32
2-CH_3	2.80	2.93	2.93	2.97	2.88	3.02	3.02	2.98
CH_3	1.31	1.39	1.39	1.42	1.40	1.45	1.45	1.46
OCH_2	4.28	4.38	4.37	4.40	4.37	4.45	4.45	4.42
NH_2	3.98	4.12	4.59	5.23	–	–	–	–
$J_{7,8}$	7.7	7.8	7.6	7.7	7.5	7.5	7.6	7.6
$J_{13,14}$	7.7	9.5	5.8	–	8.2	8.1	5.7	–
$J_{14,15}$	8.1	4.8	–	–	8.0	4.7	–	–
$J_{15,16}$	7.0	–	–	–	8.2	–	–	–
$J_{13,15}$		1.3			1.2	1.4		
$J_{14,16}$	1.3				1.2			
$J_{4,8}$	0.7	0.7	0.7	0.7	0.4	0.7 [a]	0.7 [a]	0.9
$J_{13,16}$							1.0 [a]	
$J_{4,2\text{-}CH_3}$					0.3			

[a] From decoupling.

Table 2

^{13}C NMR Chemical Shifts and Characteristic Coupling Constants (Hz) of Compounds **2-9** in deuteriochloroform

Carbon	**2** [a]	**3a** [a]	**4a** [a,c]	**5a** [b,c]	**6** [a]	**7a** [a,c]	**8a** [a,c]	**9a** [a]
2	160.7	160.6	161.1 d, 6	161.2 m	162.0	162.6 qi, 6.5	163.6 m	164.5
3	123.6	124.3	124.4	125.1	124.4	124.3	125.4	125.7
4	139.0	139.4	139.3 d, 170	139.2 d, 170	135.2	134.7 d, 168.5	136.2 d, 170	136.9
5	164.6 [d]	165.3 [d]	165.4	165.5	149.4	149.9 d, 9; d, 6	150.1 m	149.9
7	138.8	137.7	138.3 d, 183; d, 4	137.4 d, 182; d, 4	126.4	125.3 d, 187; d, 5	126.6 d, 185; d, 4	126.6
8	107.6	108.4	108.6 d, 173	109.2 d, 173	111.8	112.4 d, 171; d,3	113.6 d, 174; d, 3	114.6
9	154.5	154.9	154.7 d, 4	154.9	145.6	145.8 t, 5	148.4	149.9
10	119.3	119.3	119.5 d, 6	119.7	116.7	116.3 d, 5	116.7 d, 5	116.3
12	142.7	138.9	149.1 t, 6.5	159.1 d,12	143.7	135.8 d, 9	148.9 m	160.3
13	117.3	126.2	111.2 d, 164; t, 4	–	119.8	127.1 d, 160.5; d, 7	114.4 d, 163; d, 9	–
14	129.6	124.9	150.2 d, 177; d, 12	158.7 d, 201; d, 12	125.0	120.7 d, 161; d, 9; d 2	144.6 d, 182; d,12	155.6
15	118.7	139.4	–	–	122.5	143.2	–	–
16	127.7	–	148.5 d, 177; d, 12	154.2 d, 181; d, 10	109.7	–	133.6 d, 180; d, 13	139.9
17	126.8	140.2	123.8 d, 7; d, 3	120.7 d, 7	129.4	142.2 d, 13; d, 7	127.9 d, 4	121.7
C = O	165.1 [d]	165.6 [d]	165.4	165.5	165.4	165.0	165.4	165.1
OCH_2	61.2	61.5	61.6 t, 145; q, 3	61.7 t, 148; q, 4	61.5	61.4 t, 146; q, 5	61.8 t, 148; q, 9	61.9
CH_3	14.0	14.2	14.2 q, 127	14.3 q, 127	14.3	14.2 q, 130	14.3 q, 130	14.2
2-CH_3	25.3	25.6	25.5 q, 129	25.4 q, 129	25.4	25.3 q, 130	25.6 q, 130	25.7

[a] Measured at 100 MHz. [b] Measured at 25 MHz. [c] Proton-coupled spectrum measured at 25 MHz. [d] Tentative assignment d: dublet; t: triplet; q: quartet; qi: quintet, m: multiplet.

Table 3
Observed ^1H-^{13}C Long-Range Correlations for Compounds 6-8

	7a		8a		9a	
	^2J(C,H)	^3J(C,H)	^2J(C,H)	^3J(C,H)	^2J(C,H)	^3J(C,H)
2-C	2-CH_3, m		2-CH_3, s		2-CH_3, m	
3-C		2-CH_3, s		2-CH_3, w		2-CH_3, m
5-C		7-H, m		7-H, m		7-H, m
7-C	8-H, w					
9-C		7-H, m; 4-H,w				7-H, m
10-C		8-H, m				8-H, w
12-C		14-H, s		14-H, s		14-H, s
13-C		15-H, s	14-H, s			
14-C	15-H, w					16-H, m
15-C	14-H, w	13-H, m				
16-C						14-H, m
17-C		13-H, w; 15-H, m	16-H, w		16-H, m	
C=O		OCH_2, w 4-H, w				
OCH_2	CH_3, m		CH_3, m		CH_3, m	

w: weak; m: medium; s: strong.

Table 4
Results of Proton-Proton 1D NOE Difference Experiments on Compounds 6-9 Measued at 400 MHz

Compound	Proton irradiated	NOe observed (%)
6	7-H	16-H (7.4), 8-H (7.7)
	13-H	14-H (6.4)
	16-H	15-H (6.0), 7-H (7.6)
7a	13-H	14-H (4.2)
	7-H	8-H (5.2)
8a	7-H	16-H (6.5), 8-H (8.2)
	16-H [a]	7-H (8.0)
9a	7-H	16-H (4.5), 8-H (9.0)
	16-H [a]	7-H (18.0)

[a] Measured at 100 MHz.

part of a highly delocalised ring system, accordingly at C(7) an upfield (~ 12 ppm), at C(8) in turn a downfield shift (4-5 ppm) can be observed.

Assignments of the signals for the quaternary carbon atoms in the tetracyclic compounds required the recording of COLOC spectra optimized for the long-range coupling of J(CH) ~ 6 Hz. Signals for C=O (ester), C(2) and those for C(3), C(10) and C(17) are relatively close and therefore the evaluation of the substituent effects does not yield an unambiguous assignment. Characteristic cross peaks were recorded between the 2-CH_3 protons and C(2) and C(3) respectively, permitting the identification of the two carbon atoms. C(10) was correlated with H-8 and could be therefore assigned to the signal at 116 ppm. Assignment of C(17) became unequivocal by correlation with the D ring protons.

EXPERIMENTAL

All melting points are uncorrected. The uv spectra were obtained in ethanol on a UNICAM SP 800 spectrophotometer. The ir spectra were determined with potassium bromide disks on a ZEISS UR 20 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded in deuteriochloroform with JEOL FX-100 and Bruker AM-400 spectrometers at room temperature. Chemical shifts were determined on the δ scale, with tetramethylsilane (δ = 0) as internal standard. For homonuclear nOe experiments a delay time of 3 s and an irradiation time of 1.5 s was applied. The nOe difference and two-dimensional carbon-proton correlated experiments were recorded by using the Bruker software package. In the 2D experiments 1 K x 1 K data matrices were transformed.

Compounds **2-5** were prepared according to ref [3].

Ethyl 2-Methylbenzimidazo[2,1-*f*][1,6]naphthyridine-3-carboxylate **6**.

A mixture of **2** (3.23 g, 0.01 mole) and phosphoryl chloride (30 ml) was stirred at reflux temperature for 2 hours. After evaporation under reduced pressure water (100 ml) was added to the residue, *p*H was adjusted to 7 with 20% aqueous sodium carbonate solution and the precipitate was filtered off, washed with water (yield 2.99 g, 98%), mp 175-176° (from ethanol); uv: λ max 298 (log ε 4.63) and 237 (4.69); ir: 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 71.09; H, 4.94; N, 13.46.

Ethyl 2-Methylpyrido[3',2':4,5]imidazo[2,1-*f*][1,6]naphthyridine-3-carboxylate **7a**.

Compound **7a** was prepared similarly from **3a** (yield 2.8 g, 92%), mp 198-199° (from ethanol); uv: λ max 350 (infl), 330 (infl), 320 (infl), 296 (log ε 4.66), 245 (infl) and 228 (4.55); ir: 1725 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.40; H, 4.52; N, 18.10.

Ethyl 2-Methylpyrido[4',3':4,5]imidazo[2,1-*f*][1,6]naphthyridine-3-carboxylate **8a**.

Compound **8a** was prepared similarly from **4a** (yield 1.8 g, 59%), mp 253-255° (from ethanol); uv: λ max 353 (log ε 3.93), 337 (4.00), 325 (infl), 286 (4.66), 278 (infl), 240 (infl) and 233 (4.58); ir: 1695 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.32; H, 4.51; N, 18.06.

Ethyl 2-Methylpyrimido[4',5':4,5]imidazo[2,1-*f*][1,6]naphthyridine-3-carboxylate **9a**.

A mixture of **5a** (3.25 g, 0.01 mole) and phosphoryl chloride (60 ml) was stirred at reflux temperature for 6 hours. After evaporation under reduced pressure water (100 ml) was added to the residue, *p*H was adjusted to 8 with concentrated ammonium hydroxide solution, the aqueous mixture was extracted with chloroform (5 x 100 ml), then the organic phase was shaken with water (2 x 100 ml), dried (sodium sulfate) and evaporated to obtain **9a**. The crude product was purified by column chromatography (alumina) using chloroform as eluent (yield 1.63 g, 53%), mp 253-254° (from ethanol); uv: λ max 352 (log ε 3.93), 336 (4.04), 322 (infl), 305 (infl), 283 (4.77), 247 (infl), 234 (infl) and 226 (4.57); ir: 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.42; H, 4.19; N, 22.61.

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