First Synthesis and X-ray Crystal Structure of Hexahydrobenzo[*b*]pyrido[3,4,5-*de*]-1,6-naphthyridines

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The reaction of 10-carboxamido tetrahydrobenzo[*b*][1,6]naphthyridines **1-3** with activated terminal alkynes in DMF/methanol resulted with the formation of hexahydrobenzo[*b*]pyrido[3,4,5-*de*]-1,6-naphthyridines **7-10**– representatives of a new heterocyclic system.

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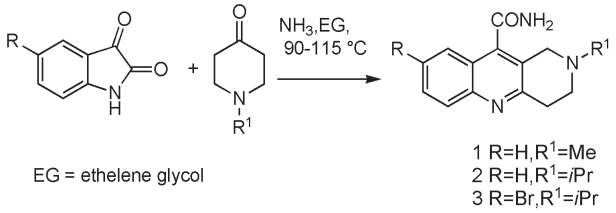
Introduction.

The reactivity of hydrogenated benzonaphthyridines has not been the focus of much interest probably due to the lack of efficient methods to make them. On the other hand, the naphthyridine and hydronaphthyridine skeletons are found in some bioactive compounds [1,2] and more recently have been proved to be effective lithium [3] or copper [4,5] complexing agents or designed as chiral biomimetic NADH models [6]. We have recently reported tetrahydropyridine (THP) ring enlargement in tetrahydropyrrolo[3,2-*c*]pyridines (THPP) under the action of dimethyl acetylene dicarboxylate (DMAD) or ethyl propiolate (EP) in aprotic solvents to form annulated azocines [7]. THPP as well as tetrahydropyridoindole derivatives were also demonstrated to undergo cleavage process under the action of DMAD or EP in protic solvents [8]. Hence, it seemed to us of interest to investigate the reactivity of another THP-containing substrate toward activated alkynes.

Results and Discussions.

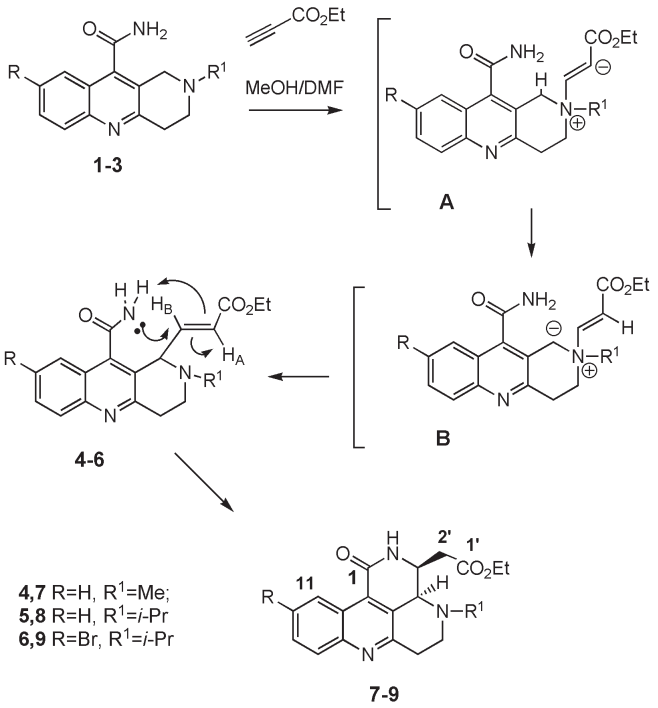
Compounds **1-3** were synthesized according to the protocol previously described by condensation of isatine with γ-piperidones in the presence of gaseous ammonia (Pfitzinger reaction)(Scheme 1) [9].

Scheme 1



Due to the very low solubility of the carboxamides **1-3** in previously used organic solvents (methanol, acetonitrile), the reaction was carried out in 1:5 DMF /methanol mixture. The reaction of DMAD with compounds **1**-**3** was not successful, leading to the isolation of only small amounts of tarring products and almost complete recovery of the unreacted starting materials. Very surprisingly, the reaction of **1** - **3** with EP proceeded smoothly, affording hexahydrobenzo[*b*]pyrido[3,4,5-*de*]-1,6-naphthyridines **7-9** as the main products. The structure of **8** was unambiguously elucidated by means of X-ray analysis (Figure 1) [10]. According to the NMR data compounds **7-9** have been obtained as single diastereomeres having *cis*-oriented protons at C_3 and C_{3a} positions. The isolation of acrylates **4**-**6** from the reaction mixtures allowed us to offer the following reaction mechanism (Scheme 2).

Scheme 2



We presume, that the reaction starts with the formation of the zwitter-ionic intermediate **A**, the anionic part of which than cleaves one proton from the C_1 methelene group, thus producing ylide B, Stevens rearrangement [11] of which affords compounds **4**-**6**. Subsequent intramolecular Michael addition of the amide NH_2 group to the activated alkene moiety results with the formation of hexahydrobenzo[*b*]pyrido[3,4,5-*de*]-1,6-naphthyridines **7-9**. The low reactivity of DMAD in this reaction is consistent with the proposed mechanism, as the anionic part of the corresponding zwitter-ion A in this case should be less reactive (more stable) due to the stabilization by the additional COOMe- group and (or) due to the steric hindrance. To see, whether this reaction is general for activated terminal alkynes, we studied the reaction of but-3-yn-2-one with benzo[*b*][1,6]naphthyridine **2** under the same reaction conditions. The reaction proceeded smoothly and the corresponding tetracyclic derivative **10** was isolated with 33 % yield (Scheme 3).

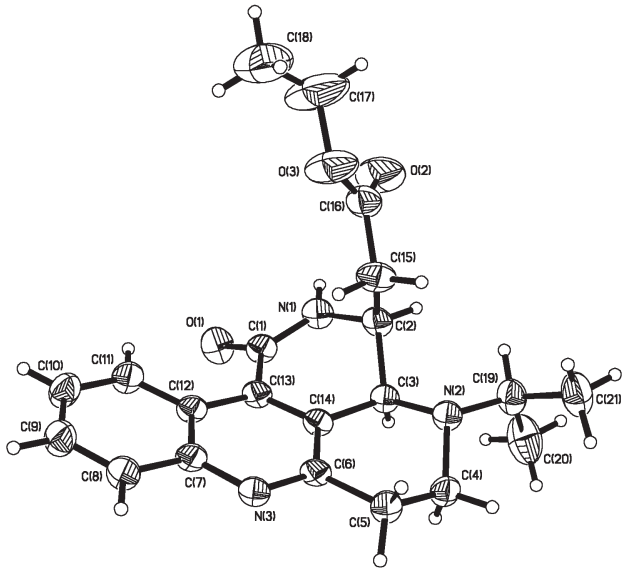
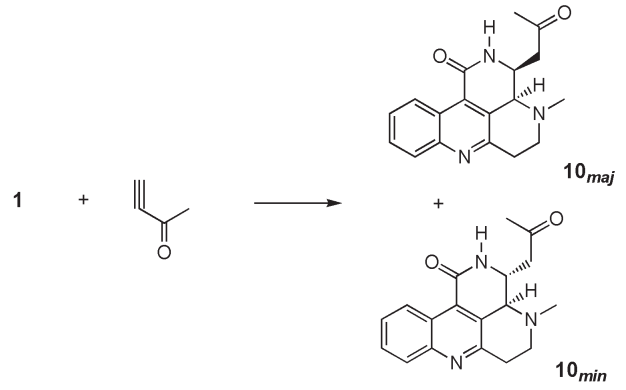


Figure 1. Crystal structure of **8** with atom-numbering scheme and 50% probability displacement ellipsoids.

Scheme 3



According to the NMR data, compound **10** has been obtained as diastereomeric mixture, the major isomer (80%) having *cis* -oriented protons at C_3 and C_{3a} positions as well.

Conclusion.

In conclusion, we have elaborated an effective synthetic scheme towards previously unknown heterocyclic system - 2,3,3a,4,5,6-hexahydro-1*H*-benzo[*b*]pyrido[3,4,5-*de*][1,6]naphthyridine *via* the cascade Michael addition – Stevens rearrangement – Michael addition reaction of activated terminal alkynes with tetrahydrobenzo[*b*]naphthyridines. To the best of our knowledge, this is also the first example of the Stevens rearrangement of ylides formed *via* Michael addition of alkynes to saturated tertiary amines.

EXPERIMENTAL

All solvents were distilled and dried before use, DMAD, EP and but-3-yn-2-one were purchased from Lancaster Synthesis Ltd. and were used without any additional purification. Column chromatography was performed with alumina oxide 60 from Fluka. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, at 25 °C or in DMSO-d_6 solutions at 40 °C, using a Bruker WM 400 NMR spectrometer operating at 400 and 100 MHz correspondingly, peak positions are given in parts per million (δ) with tetramethylsilane used as the internal standard. ^{1}H-^{13}C COSY experiment was used for the assignment of signals in the spectrum of compound **7**. Mass-spectra were obtained by the EI technique (Finnigan-MAT 95 XL engine) or ESI method (Agilent 1100 Series LC/MSD Trap System VL). Melting points were determined in a capillary tube and are uncorrected.

Preparation of Tetrahydrobenzo[*b*][1,6]naphthyridines.

General Procedure [9].

Through a vigorously stirred solution of the corresponding isatine and piperidone in 200 ml of ethylene glycol at 90-115 °C, gaseous ammonia was bubbled for 3 hours. The reaction mixture was cooled to room temperature. Addition of 200 ml of cold water caused precipitation of compounds **1-3**, which were collected by filtration, dried and recrystallised from *i*PrOH/DMF mixture.

2-Methyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine-10-carboxamide (**1**).

The reagents used were: 10.0 g (68.0 mmol) of isatine, 8.5 g (75.2 mmol) of *N*-methylpiperidone-4. Reaction temperature 100 °C. Dark-yellow crystals with mp 226-228 °C. Yield 6.7 g (41%). ^{1}H nmr (DMSO-D_6): δ 8.15 (bs, 1H, NH), 7.99 (bs, 1H, NH), 7.88 (d, 1H, $J_{H9\text{-}H8}$ = 8.6 Hz, H9), 7.67(d, 1H, $J_{H6\text{-}H7}$ = 8.4 Hz, H6), 7.63 (m,1H, H7), 7.45(m,1H, H8), 3.82 (s, 2H, CH_2-1), 3.34 (m, 2H, CH_2-3), 2.82 (s, 3H, N-CH_3), 2.67 (m, 2H, CH_2-4); ESI MS 242 (M^++1).

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41; O, 6.63. Found: C, 69.32; H, 6.12; N, 17.14.

2-Isopropyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine-10-carboxamide (**2**).

The reagents used were: 10.0 g (68.0 mmol) of isatine, 10.6 g (75.2 mmol) of *N*-isopropylpiperidone-4. Reaction temperature 95-100 °C. Brown crystals with mp 218-220 °C. Yield: 11.4 g (62 %). ^{1}H nmr (DMSO-D_6): δ 8.00 (bs, 1H, NH), 7.96 (bs, 1H, NH), 7.85 (d, 1H, $J_{H9\text{-}H8}$ = 8.4 Hz, H9), 7.64(d, 1H, $J_{H6\text{-}H7}$ = 8.2 Hz, H6), 7.60 (m, 1H, H7), 7.45(m,1H, H8), 3.82 (s, 2H, CH_2-1), 3.34 (m, 2H, CH_2-3), 3.00 (spt, 1H, J=6.2 Hz, CH-*i*Pr), 2.67 (m, 2H, CH_2-4), 1.10 (d, 6H, J= 6.2 Hz, 2×CH_3- *i*Pr); ESI MS 270 (M^++1).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71,35; H, 7.11; N, 15.60; O, 5.94. Found: C, 71.14; H, 7.44; N, 15.53.

8-Bromo-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine-10-carboxamide (**3**).

The reagents used were: 5 g (22.1 mmol) of 5-bromoisatine, 3.7 g (26.5 mmol) of *N*-isopropylpiperidone-4. Reaction temperature 115 °C. Brown crystals with mp 235-237 °C. Yield: 5 g (65%). ^{1}H nmr (DMSO-D_6): δ 8.30 (bs, 1H, NH), 8.10 (bs, 1H, NH), 7.88-7.80(m, 3H, H9,H8,H7), 3.79(s, 2H, CH_2-1), 3.07 (m, 2H, CH_2-3), 2.94 (spt, 1H, J=6.0 Hz, CH-*i*Pr), 2.86 (m, 2H, CH_2-3), 1.05 (d, 6H, J= 6.0 Hz, 2×CH_3- *i*Pr); ESI MS 348(M^++1), 350(M^++1).

Anal. Calcd. for $C_{16}H_{18}BrN_3O$: C, 55.18; H, 5.21; Br, 22.95; N, 12.07; O, 4.59. Found: C, 55.34; H, 5.53; N, 12.04.

General Procedure for the Reaction of Tetrahydrobenzo[*b*][1,6]-naphtyridines **1-3** with Activated Alkynes.

To a stirred solution of tetrahydrobenzo[*b*][1,6]naphtyridines **1-3** in methanol/DMF mixture, the corresponding alkyne was added in one portion and the reaction mixture was stirred at 50° C for 3 hours. After being cooled to room temperature, the mixture was stirred overnight. The resultant acrylates **4-6** were filtered and the filtrate was evaporated *in vacuo* to give an oily residue. The residue was dissolved in ethyl acetate and percolated through a short column (alumina oxide, ethyl acetate) to give **7-10** respectively.

Ethyl (2*E*)-3-[10-(Aminocarbonyl)-2-methyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridin-1-yl]acrylate (**4**); Ethyl [(3*S**,3a*R**)-4-Methyl-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*b*]pyrido[3,4,5-*de*]-1,6-naphthyridin-3-yl]acetate (**7**).

The reagents and solvents used were: 1.10 g (4.56 mmol) of tetrahydrobenzo[*b*][1,6]naphthyridine (**1**), absolute methanol 10 ml, absolute DMF 30 ml, 0.64 g (6.48 mmol) of EP. Compound (**4**) was isolated as orange crystals (0.22 g, 14%), mp 205-207 °C (ethyl acetate). ^{1}H nmr (DMSO-D_6): δ 8.45 (bs, 1H, NH), 8.13 (bs, 1H, NH), 8.00 (d, 1H, $J_{H9\text{-}H8}$ = 8.4 Hz, H9), 7.89(d, 1H, $J_{H6\text{-}H7}$ = 8.3 Hz, H6), 7.65 (m, 1H, H7), 7.54(m, 1H, H8), 7.02 (dd, 1H, $J_{HB\text{-}H1}$ = 5.4 Hz, $J_{HB\text{-}HA}$ = 15.1 Hz, H_B), 5.90 (dd, 1H, $J_{HA\text{-}HB}$ = 15.1 Hz, $J_{HA\text{-}H1}$ = 1.5 Hz, H_A), 4.93 (m, 1H, H1), 4.12(q, 2H, J = 7.3 Hz, O-CH_2), 3.10-2.90 (m, 4H, CH_2-3+CH_2-4), 2.72 (s, 3H, N-Me) 1.17(t, 3H, J = 7.3 Hz, CH_3-ethyl); ESI MS 340(M^++1)

Anal. Calcd. for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38; O, 14.14. Found: C, 67.32; H, 6.43; N, 12.00.

Compound (**7**) was isolated as white crystals (0.48 g, 31 %), mp 172-173° C (hexane/ethyl acetate). ^{1}H nmr ($CDCl_3$): δ 9.34 (dd, 1H, $J_{H11\text{-}H9}$ = 1.6 Hz, $J_{H11\text{-}H10}$ = 8.6 Hz, H11), 8.06 (dd, 1H, $J_{H8\text{-}H10}$ = 1.7 Hz, $J_{H8\text{-}H9}$ = 8.4 Hz, H8), 7.76 (m, 1H, H9), 7.64 (m, 1H, H10), 7.00 (d, 1H, J= 5.6 Hz, NH), 4.35 (m,1H, H3), 4.15 (q, 2H, J = 7.1 Hz, O-CH_2), 3.87 (d, 1H, $J_{H3a\text{-}H3}$ = 5.4 Hz, $H3_a$), 3.41(m, 1H, H-6), 3.24 (m, 2H, H6+H5), 2.83 (dd, 1H, $J_{H2'\text{-}H3}$ =3.0 Hz, ^{2}J =17.1 Hz, H2'), 2.80 (dd, 1H, $J_{H5\text{-}H6}$ = 4.0 Hz, ^{2}J=13.6 Hz, H5), 2.48 (s, 3H, N-Me), 2.21 (dd, 1H, $J_{H2'\text{-}H3}$ =10.9 Hz, ^{2}J=17.1 Hz, H2'), 1.25 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C nmr ($CDCl_3$): δ 171.9, 163.6, 155.2, 148.1, 129.7, 129.0, 128.7, 127.7, 127.0, 126.4, 123.6, 62.6, 60.9, 52.6, 48.8, 43.3, 33.6, 33.0, 14.1. EI MS m/z, (I %) 339 (M^+,10), 224 (32), 196 (100), 153 (41), 42 (20).

Anal. Calcd]. for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38; O, 14.14. Found: C, 66.98; H, 6.10; N, 12.44.

Ethyl (2*E*)-3-[10-(Aminocarbonyl)-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridin-1-yl]acrylate (**5**); Ethyl 2-[(3*S**,3a*R**)-4-isopropyl-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*b*]pyrido[3,4,5-*de*][1,6]naphthyridin-3-yl]acetate (**8**).

The reagents and solvents used were: 0.91 g (3.38 mmol) of tetrahydrobenzo[*b*][1,6]naphthyridine (**2**), absolute methanol 10 ml, absolute DMF 30 ml, 0.395 g (4.04 mmol) of EP. Compound (**5**) was isolated as yellow crystals (0.4 g, 32 %), mp 143-145 °C (ethyl acetate). ^{1}H nmr (DMSO-D_6): δ 8.32 (bs, 1H, NH), 8.06 (bs, 1H, NH), 7.94 (d, 1H, $J_{H9\text{-}H8}$ = 8.2 Hz, H9), 7.85(d, 1H, $J_{H6\text{-}H7}$ = 8.0 Hz, H6), 7.74 (m, 1H, H7), 7.59(m,1H, H8), 6.99 (dd, 1H, $J_{HB\text{-}H1}$ = 5.4 Hz, $J_{HB\text{-}HA}$ = 15.5 Hz, H_B), 5.87 (dd, 1H, $J_{HA\text{-}HB}$ = 15.4 Hz, $J_{HA\text{-}H1}$ = 1.5 Hz, H_A), 5.00 (m, 1H, H1), 4.06(q, 2H, J = 7.1 Hz, O-CH_2), 3.20 (m, 1H, CH-*i*Pr), 3.10-2.90 (m, 4H, CH_2-3+CH_2-4), 1.17(t, 3H, J = 7.1 Hz, CH_3-ethyl), 1.05 (d, 6H, J = 6.4 Hz, CH_3-*i*Pr); ^{13}C nmr (DMSO-D_6): δ 168.0, 165.9, 157.9, 151.5, 150.0, 149.3, 146.5, 142.3, 129.9, 126.7, 125.6, 125.4, 123.3, 60.4, 51.4, 41.5, 40.8, 34.2, 20.7, 20.7, 14.5; EI MS m/z, (I %) 367 (M^+, 22), 323 (63), 278 (100), 268 (50), 235 (41), 226 (40), 181 (35), 84 (50), 56 (82), 43 (61).

Anal. Calcd. for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44; O, 13.06. Found: C, 68.54; H, 6.75; N, 11.33.

Compound (**8**) was isolated as white crystals (0.30 g ,24 %), mp 118-120° C (hexane/ethyl acetate). ^{1}H nmr ($CDCl_3$): δ 9.25 (d, 1H, $J_{H11\text{-}H10}$ = 8.5 Hz, H11), 8.00 (d, 1H, $J_{H8\text{-}H9}$ = 8.4 Hz, H8), 7.70 (m, 1H, H9), 7.58 (m, 1H, H10), 7.05 (d, 1H, J= 4.2 Hz, NH), 4.33 (m, 2H, H3+H3a), 4.09 (q, 2H, J = 7.2 Hz, O-CH_2), 3.13-3.03 (m, 4H, $CH_2$6+H5+CH-*i*Pr), 2.63 (m, 2H, H2'+H5), 2.10 (dd, 1H, $J_{H2'\text{-}H3}$ =10.9 Hz, ^{2}J=18.0 Hz, H2'), 1.21 (t, 3H, J = 7.2 Hz, CH_3-ethyl), 1.21 (d, 3H, J = 6.3 Hz, CH_3-*i*Pr), 1.08 (d, 3H, J = 6.3 Hz, CH_3-*i*Pr) , ESI MS 368 (M^++1).

Anal. Calcd. for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44; O, 13.06. Found: C, 68.29; H, 6.99; N, 11.46.

Ethyl (2*E*)-3-[10-(Aminocarbonyl)-8-bromo-2-isopropyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridin-1-yl]acrylate (**6**); Ethyl [(3*S**,3a*R**)-10-Bromo-4-isopropyl-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*b*]pyrido[3,4,5-*de*]-1,6-naphthyridin-3-yl]acetate (**9**).

The reagents and solvents used were: 0.50 g (1.12 mmol) of tetrahydrobenzo[*b*][1,6]naphthyridine (**3**), absolute methanol 5 ml, absolute DMF 20 ml, 0.16 g (1.61 mmol) of EP. Compound (**6**) was isolated as yellow crystals (0.16 g, 32 %), mp 143-145 °C (ethyl acetate). ^{1}H nmr ($CDCl_3$): δ 8.05 (d, 1H, $J_{H9\text{-}H7}$ = 2.0 Hz, H9), 7.85(d, 1H, $J_{H6\text{-}H7}$ = 9.4 Hz, H6), 7.74 (dd, 1H, $J_{H7\text{-}H9}$ = 2.0 Hz, $J_{H7\text{-}H8}$ = 9.4 Hz, H7), 7.06 (dd, 1H, $J_{HB\text{-}H1}$ = 5.4 Hz, $J_{HB\text{-}HA}$ = 15.4 Hz, H_B), 6.32 (bs, 1H, NH), 6.11 (bs, 1H, NH), 5.77 (d, 1H, $J_{HA\text{-}HB}$ = 15.4 Hz, H_A), 5.77 (d, 1H, $J_{H1\text{-}HB}$ = 5.4 Hz, H1), 4.12(q, 2H, J = 6.7 Hz, O-CH_2), 3.29-3.09 (m, 4H, CH_2-

3+CH_2-4), 2.98 (spt, 1H, J = 5.4 Hz, CH-*i*Pr), 1.24(t, 3H, J = 6.7 Hz, CH_3-ethyl), 1.23 (d, 3H, J = 5.4 Hz, CH_3-*i*Pr), 1.21 (d, 3H, J = 5.4 Hz, CH_3-*i*Pr); ESI MS 446(M^++1), 448(M^++1).

Anal. Calcd. for $C_{21}H_{24}BrN_3O_3$: C, 56.51 H, 5.42; Br, 17,90; N, 9.41; O, 10.75. Found: C, 56.34; H, 5.45; N, 9.46.

Compound **(9)** was isolated as pale-yellow crystals (0.12 g, 24%), mp 107-109 °C (ethyl acetate/ hexane). ^{1}H nmr ($CDCl_3$): δ 9.48 (d, 1H, J_{H11-H9} = 2.0 Hz, H11), 7.88 (d, 1H, J = 8.7 Hz, H8), 7.76 (dd, 1H, J_{H9-H11} = 2.0 Hz, J_{H9-H8} = 8.7 Hz, H9), 6.70 (d, 1H, J= 5.4 Hz, NH), 4.33-4.30 (m, 2H, H3+H3a), 4.13 (q, 2H, J = 7.4 Hz, O-CH_2), 3.30(m, 1H, H-6), 3.16 (m, 3H, H6+H5+CH-*i*Pr), 2.62 (m, 2H, H2'+H5), 2.11 (dd, 1H, $J_{H2'-H3}$ =10.7 Hz, ^{2}J=17.6 Hz, H2'), 1.23 (t, 3H, J = 7.3 Hz, CH_3-ethyl), 1.21 (d, 3H, J = 6.7 Hz, CH_3-*i*Pr), 1.07 (d, 3H, J = 6.7 Hz, CH_3-*i*Pr); ^{13}C nmr ($CDCl_3$): δ 173.8, 168.2, 149.1, 145.3, 135.2, 134.3, 132.6, 128.4, 125.3, 122.1, 120.7, 62.3, 50.4, 48.2, 47.3, 44.2, 40.1, 32.6, 20.0, 20.0, 15.3; ESI MS 446(M^++1), 448(M^++1).

Anal. Calcd. for $C_{21}H_{24}BrN_3O_3$: C, 56.51 H, 5.42; Br, 17,90; N, 9.41; O, 10.75. Found: C, 56.50; H, 5.15; N, 9.68.

4-Methyl-3-(2-oxopropyl)-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*b*]-pyrido[3,4,5-*de*]-1,6-naphthyridin-1-one (**10**).

The reagents and solvents used were: 0.60 g (2.49 mmol) of tetrahydrobenzo[*b*][1,6]naphthyridine (**1**) , absolute methanol 10 ml, absolute DMF 30 ml, 200 mg (2.9 mmol) of but-3-yn-2-one . Compound (**10**) was isolated as white crystals (0.25 g, 32.5 %), mp 171-173 °C (ethyl acetate/hexane). ^{1}H-NMR ($CDCl_3$): δ 9.34 (d, 0.2H, $J_{H11-H10}$ = 9.3 Hz, $H11_{min}$), 9.27 (d, 0.8H, $J_{H11-H10}$ = 8.6 Hz, $H11_{maj}$), 8.00 (d, 0.8H, J_{H8-H9} = 8.3 Hz, $H8_{maj}$), 7.92 (d, 0.2H, J_{H8-H9} = 7.9 Hz, $H8_{min}$), 7.68 (m, 1H, H9), 7.56 (m, 1H, H10), 7.40 (bs, 0.2 H, NH_{min}), 7.05 (d, 0.8H, J= 5.4 Hz, NH_{maj}), 4.35 (m, 0.8H, $H3_{maj}$), 4.17 (m, 0.2H, $H3_{min}$), 4.03 (d, 0.2H, J = 11 Hz, $H3a_{min}$), 3.79 (d, 0.8H, J = 5.4 Hz, $H3a_{maj}$), 3.41-3.02 (m, 3H, CH_2-6+ H-5), 2.86-2.73 (m, 2H, H2'+H5), 2.42 (s, 2.25H, N-$CH_{3\ maj}$), 2.33 (m, 1H, H2'), 2.28 (s, 0.75H, N-$CH_{3\ min}$), 2.05 (s, 2.25H, O=C-$CH_{3\ maj}$), 2.00(s, 0.75H, O=C-$CH_{3\ maj}$); ^{13}C nmr ($CDCl_3$): δ maj(min): 207.1(206.2), 163.4(162.9), 154.9(154.7), 147.0, 129.6(129.5), 128.7(128.6), 127.6, 127.2, 126.4, 124.3, 123.4, 62.4(60.6), 52.5(50.5), 47.5(49.3), 43.2(47.9), 42.5(45.0), 33.0(30.6), 30.4(25.9); ESI MS 310(M^++1).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58; O, 10.34. Found: C, 69.76; H, 6.15; N, 13.88.

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[10] Crystal structure analysis for **8**: $C_{21}H_{25}N_3O_3$, M_r=367.44 g mol^{-1}, monoclinic, space group $P2_1/c$, a=8.092(10), b=17.392(3), c=14.225(2) Å, β=106.23(3)°, V=1922.2(5) $Å^3$, Z=4, ρ=1.270 g cm^{-3}, μ=0.086 cm^{-1}, F(000)=784, crystal size: 0.70 x 0.50 x 0.40 mm . Crystal data was collected on a Cad-4 diffractometer (λMoK_α radiation, graphite monochromator; ω scaning). A total of 4514 reflections ($1.9<\theta<26.97°$) were collected of which 4187 were unique (R(int)= 0.0177). The structure was solved with the program SHELXS-97 [12] and refined using SHELXL-97 [13] to R_1=0.0510 and wR(F^2)= 0.1652 for 2996 reflections with $I>2\sigma(I)$; max.\min. residual electron density 0.497 and –0.252 e $Å^{-3}$. All nonhydrogen atoms were refined with anisotropic thermal parameters. Crystallographic data (excluding structure factors) for compound **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258224.

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