Synthesis of Novel Benzo[*h*][1,6]naphthyridines *via* a Rearrangement of Hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines

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Heating of hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione in boiling phosphoryl chloride led to a rearranged product like 3,5-dichlorobenzo[*h*][1,6]naphthyridine. This structure was established from X-ray diffraction analysis.

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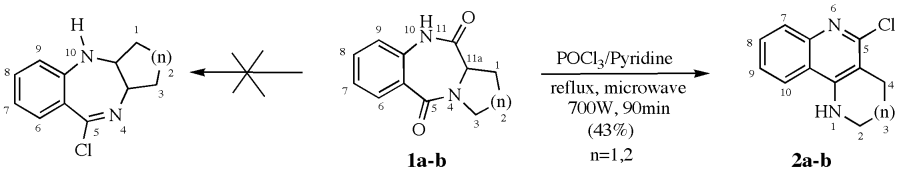
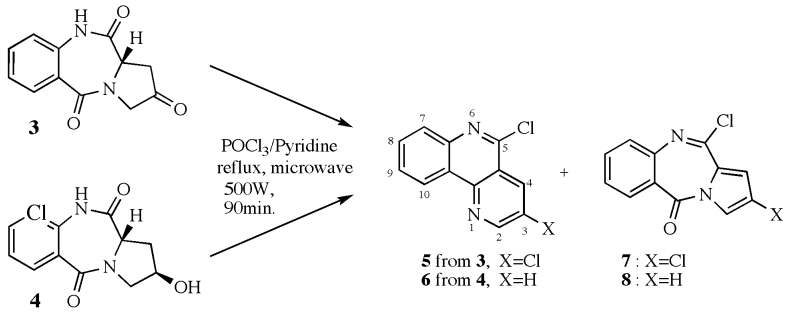
Carrying on with the study of rearrangement and aromatization reactions in the benzodiazepine series [1-4], we wish to report here the reinvestigation of rearrangement of 2-substituted pyrrolo[2,1-*c*][1,4]benzodiazepines. We have established that hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-dione **1a** and octahydropyrido-[2,1-*c*][1,4]benzodiazepine-6,12-dione **1b** rearranged respectively into 5-chlorotetrahydrobenzo[*h*][1,6]naphthyridine **2a** and 6-chlorotetrahydro-1*H*-azepino[3,2-*c*]-quinoline **2b**, and not into cyclopenta[*b*][1,4]benzodiazepine as described in a preliminary note [1] (Scheme 1). The structures were elucidated from X-ray diffraction analysis [5].

Scheme 1



Scheme 2



Taking account of the originality and the potentiality of these new structures in medicinal chemistry, we interested herein in the investigation of further tricyclic derivatives. We applied this rearrangement in pyrrolo[2,1-*c*]-[1,4]benzodiazepine-2,5,11-trione **3** and 2-hydroxypyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione **4**. Analytical data (IR, ^{1}H, ^{13}C NMR, MS and elemental analysis) and X-ray diffraction studies led us to ascertain with conviction benzo[*h*][1,6]naphthyridines **5** and **6** and not cyclopenta[*b*][1,4]benzodiazepines as we first claimed [4] (Scheme 2). In contrary of **1a-b**, the rearrangement of compounds **3** and **4** in the same conditions is not complete since we could observe the formation of pyrrolobenzodiazepine structures **7** (mixture with **5**) and **8** (mixture with **6**) in a 40/60 ratio at the end of the reaction.

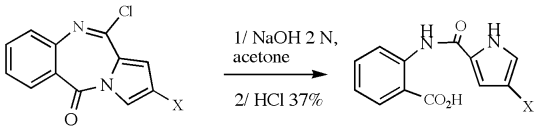
This rearrangement was performed in boiling phosphoryl oxychloride in the presence of pyridine under microwave heating conditions. Conversion of starting material was obtained in 90 min *versus* 8 h under thermal conditions but no difference in yields or selectivity of the reaction was observed.

The structure of compound **8** was undoubtedly confirmed by unequivocal synthesis from **4** following a previously reported procedure [2].

Even if it appeared that the rearrangement occurred with aromatization of the tricycle leading to benzo[*h*][1,6]naphthyridine, the structure of compounds **5** and **6** had to be confirmed. Compound **5** was separated from **7** by aqueous sodium hydroxide treatment in acetone of the mixture. In

these conditions, the pyrrolobenzodiazepine **7** opened in anthranilic derivative **9** which could have been easily isolated in the form of its soluble sodium salt in the solvent (Scheme 3). The same treatment applied to the mixture of **6** and **8** led to an open-derivative **10** separated from **6**. We have not isolated the compounds **7** and **8**.

Scheme 3



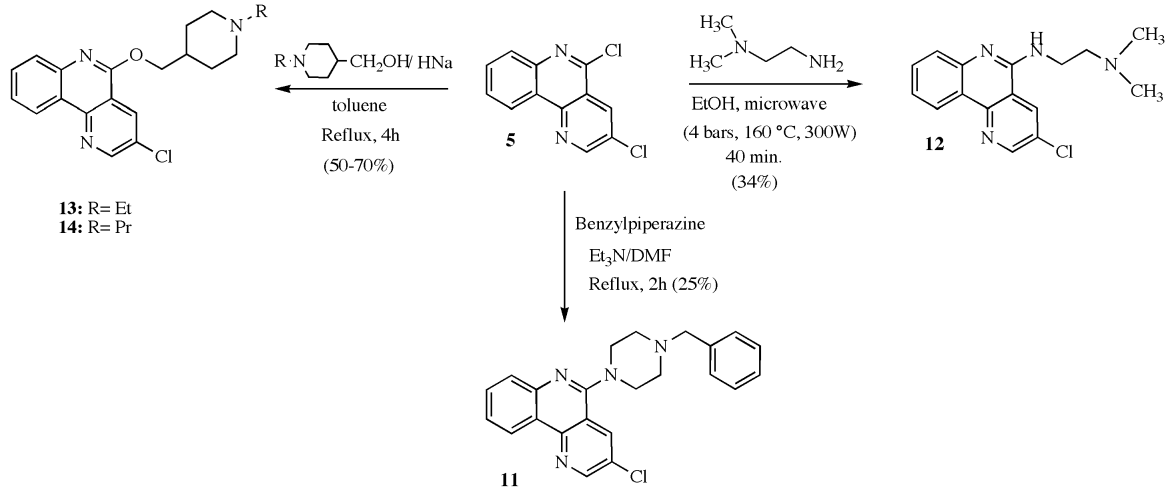
7: X = Cl
8: X = H

9: X = Cl
10 : X = H

The presence of the two chlorine atoms in the napthyridine **5** made us to consider its reactivity towards nucleophilic substitutions. Thus, by warming the compound **5** with one equivalent *N*-benzylpiperazine in refluxing dimethylformamide in the presence of triethylamine for 2 hours, we obtained the 3-chloro-5-*N*-benzylpiperazinobenzo[*h*][1,6]naphthyridine **11**.

Reaction of **5** with an excess of *N*,*N*-dimethylaminoethylamine in ethanol in a sealed tube under microwave heating conditions (160 °C, 4 bars, 300 W) gave more rapidly with a global better yield the monosubstituted derivative **12** without trace of a possible disubstituted one (Scheme 4). This compound was crystallised from diethyl ether to give good single crystals that permit us to confirm its structure from X-ray analysis (Figure 1), and the structure of **5** as 3,5-dichloro benzo[*h*][1,6]naph-

Scheme 4



13: R= Et
14: R= Pr

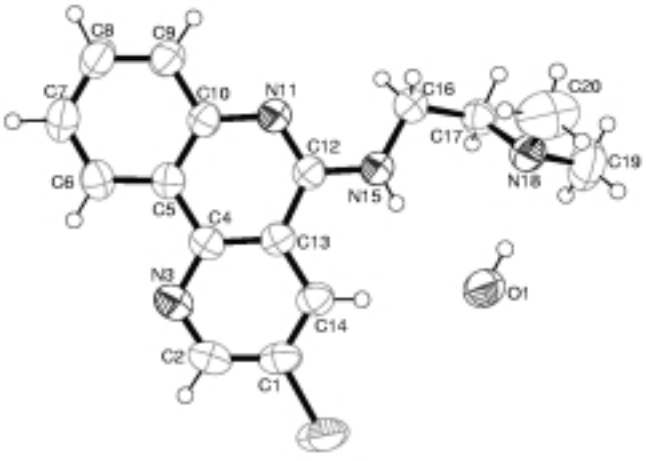


Figure 1. Ortep diagram of crystal structure of **12**. Displacement ellipsoids are shown at 50% probability levels and H atoms are drawn as small circles of arbitrary radii.

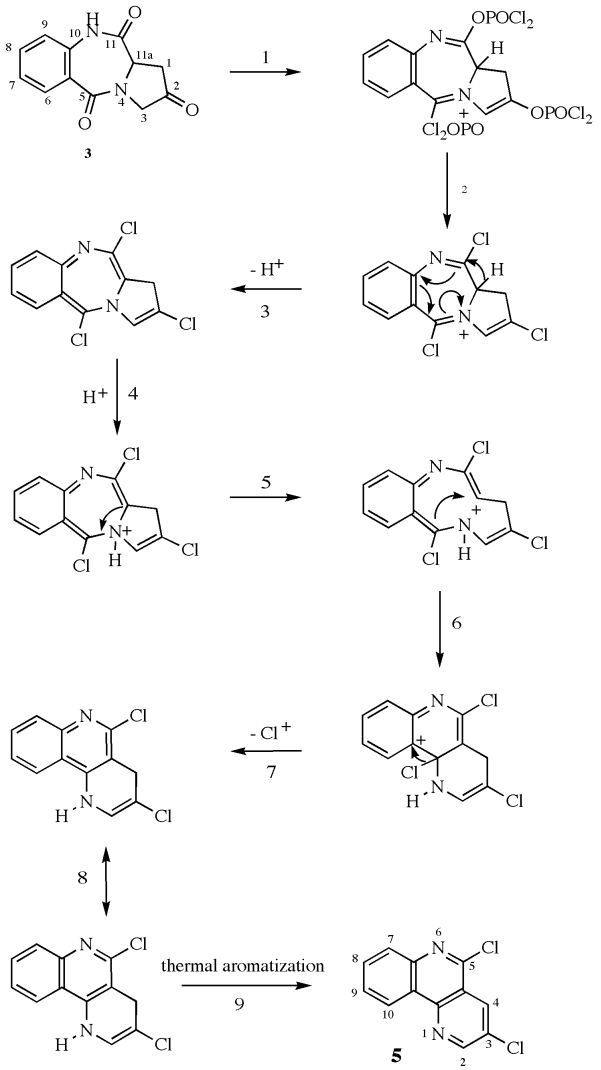
thyridine. The compound **6** would be by analogy 5-chlorobenzo[*h*][1,6]naphthyridine.

The substitutions with *N*-alkylpiperidine methyl alcohols required preliminary formation of alcoholate anions that react in refluxing toluene for 4 h [6,7].

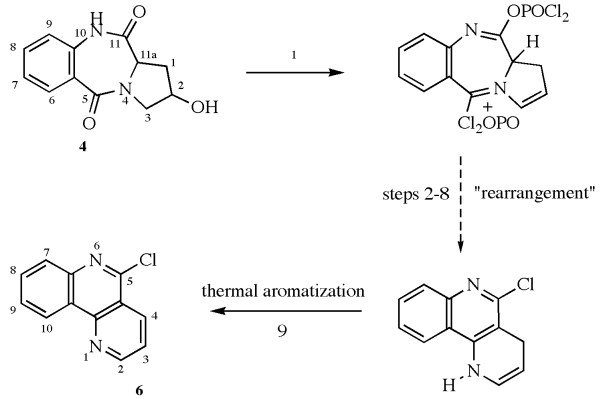
The hypothetical mechanism of this rearrangement could be transposed with a related process that we previously described [1]. We supposed a chlorodehydroxylation of the starting compound **3** (steps 1-2) leading to a chloroalkene that is then rearranged (steps 3-8) to give after a final thermal aromatization (step 9) the expected dichlorobenzonaphthyridine **5** (Scheme 5). This mechanism applied to the hydroxylated compound **4** would give a dehydrated intermediate before the reaction of rearrangement (Scheme 6).

In conclusion, this rearrangement was a new method to synthesise aromatic benzo[*h*][1,6]naphthyridines [8-13] and these new tricyclic structures appeared as promising scaffolds in medicinal chemistry with potential anti-tumor

Scheme 5



Scheme 6



effect particularly for the amidine **11**. Recent biological results (binding with leucemic cells : L-1210) showed a micromolar affinity (IC_{50} = 4.1µM) for this amidine. In the light of this encouraging result, and taking into account an hypothetical intercalating property for these new aromatic systems, a pharmacomodulation of the aromatic ring will be further developed.

EXPERIMENTAL

Melting points were determined on a Köfler melting point apparatus and are uncorrected. The infrared spectra were taken with a Genesis Series FT-IR spectrometer. ^{1}H nmr (400 MHz) and ^{13}C nmr (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts were expressed in parts per million downfield from TMS as the internal standard. Mass spectra (MS) were obtained on a JEOL JMS GCMate spectrometer at an ionizing potential of 70eV. Elemental analyses were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen). Reaction times were monitored by TLC until no starting material remained. Thin-layer chromatography (TLC) were performed on 0.2-mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light. All solvents and reagents were purchased from Acros and Aldrich Chimie and used without further purification.

General Procedure for the Reaction of Rearrangement of Benzodiazepinones (**3,4**).

Method A.

A solution of hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-2,5,11-trione **3** (9 g, 39 mmol) in $POCl_3$ (80 ml) and pyridine (2 ml) was heated with stirring under microwave irradiation (500 W) for 90 min. in a Normatron® apparatus. After elimination of phosphoryl chloride under reduced pressure, the residue was taken up in water, basified (pH 11) with 28% aqueous ammonia solution and extracted with diethyl ether. The organic layer was evaporated to give a mixture of **5** and **7**. This mixture was dissolved in acetone and treated with a saturated aqueous sodium hydroxide solution for ten minutes at 50 °C (approx.) in order to separate the two compounds (see Scheme 3). After filtration, 1.2 g of a beige solid **5** (12%) crystallized from methanol was isolated, whereas the filtrate was acidified (pH 1) with 37% aqueous hydrochloric acid solution. The resulting brown precipitate was washed with water then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, treated with charcoal and evaporated to dryness to give 0.6 g of a yellow powder **9** (6%) crystallized from diethyl ether.

Method B.

The reaction was carried out under conventional heating for 8 h.

3,5-Dichlorobenzo[*h*][1,6]naphthyridine (**5**).

This compound was obtained as a beige solid (methanol), mp 174 °C; ir (potassium bromide): CN 1600, 1575, 1510, 1450, 1390, 1330, 1290, 1180, 1115, 990, 780 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 9.30 (s, 1H, 2-H), 8.95 (d, 1H, 10-H, *J*= 8.1 Hz), 8.79 (s, 1H, 4-H), 8.08 (d, 1H, 7-H, *J*= 7.8 Hz), 7.96 (t, 1H, 8-H, *J*= 6.9 Hz), 7.86 (t, 1H, 9-H, *J*= 6.9 Hz). ^{13}C nmr (DMSO-d_6): δ

153.4, 148.3, 147.1, 144.4, 133.6, 131.6, 130.7, 128.6, 128.3, 124.0, 123.6, 120.3; ms: m/z 252 (M^+, +4), 250 (M^+, +2), 249 (100), 213 (85), 179 (26).

Anal. Calcd. for $C_{12}H_6N_2Cl_2$: C, 57.86; H, 2.43; N, 11.25. Found: C, 57.66; H, 2.25; N, 11.45.

2-[(Chloro-1*H*-pyrrole-2-carbonyl)-amino]benzoic Acid (**9**).

This compound was obtained as a yellow powder (ether), mp > 260 °C; ir (potassium bromide): OH 3259, CO 1677, CO 1630, 1601, 1535, 1449, 1415, 1240 cm^{-1}. ^1H nmr (DMSO-d_6): δ 12.25 (s, 1H, NH pyrrole), 11.88 (s, 1H, NH lactam), 8.59 (d, 1H, phenyl, *J*= 8.2 Hz), 8.03 (d, 1H, phenyl, *J*= 7.8 Hz), 7.63 (t, 1H, phenyl, *J*= 7.5 Hz), 7.16 (m, 2H, H phenyl and H pyrrole), 6.72 (s, 1H, pyrrole); ms: m/z 264 (M^+, 22), 230 (25), 169 (22), 137 (62).

Anal. Calcd. for $C_{12}H_9N_2ClO_3$: C, 54.46; H, 3.43; N, 10.58. Found: C, 54.62; H, 3.39; N, 10.29.

5-Chlorobenzo[*h*][1,6]naphthyridine (**6**).

The same procedure as for **5** from the 2-hydroxypyrrolobenzodiazepine **4** (10 g, 43 mmol) gave a mixture of **6** and **8**. This mixture was dissolved in acetone and treated with a saturated aqueous sodium hydroxide solution for ten minutes at 50 °C (approx.) in order to separate the two compounds (see Scheme 3). After filtration, 1.0 g of a beige solid **6** (11%) crystallized from diethyl ether was isolated, whereas the filtrate was acidified (pH 1) with 37% aqueous hydrochloric acid solution. The resulting precipitate was washed with water then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, treated with charcoal and evaporated to dryness to give 0.5 g of a white powder **10** (6%) crystallized from diethyl ether. Compound **6**: mp 100 °C; ^1H nmr (DMSO-d_6): δ 9.30 (d, 1H, 2-H, *J*= 8.1 Hz), 9.02 (d, 1H, 3-H, *J*= 8.1 Hz), 8.77 (t, 1H, 2-H, J= 8.1 Hz), 8.08 (d, 1H, 10-H, *J*= 7.8 Hz), 7.96-7.85(m, 2H, 7-H, 8H), 7.85 (t, 1H, 9-H, *J*= 7.8 Hz). ^{13}C nmr (DMSO-d_6): δ 154.6, 149.4, 148.8, 144.4, 135.1, 131.2, 128.2, 128.1; 124.6, 124.3, 123.6, 119.7; ms: m/z 216 (M^+,+2, 37), 214 (M^+, 100).

Anal. Calcd. for $C_{12}H_7N_2Cl$: C, 67.15; H, 3.29; N, 13.05. Found: C, 67.43; H, 3.28; N, 12.95.

2-[(1*H*-Pyrrole-2-carbonyl)-amino]benzoic Acid (**10**).

This compound has Mp>260 °C; ^1H nmr (DMSO-d_6): δ 13.8 (s, 1H, COOH), 11.9 (s, 1H, NH), 8.69 (d, 1H, Hphenyl, *J*=7.5Hz), 8.03 (d, 1H, Hphenyl, *J*=7.5Hz), 7.63 (t, 1H, Hphenyl, *J*=7.5Hz), 7.14 (t, 1H, Hphenyl, J=7.5Hz), 7.03 (m, 1H, Hpyrrole), 6.78 (m, 1H, Hpyrrole), 6.24 (m, 1H, Hpyrrole). ^{13}C nmr (DMSO-d_6): δ 170.1, 158.7, 141.7, 134.3, 131.3, 126.2, 123.5, 122.0, 119.2, 115.3, 110.3, 109.4; m/z 230 (M^+,80).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.39; N, 12.17. Found: C, 62.54; H, 4.46; N, 12.19.

3-Chloro-5-*N*-benzylpiperazinobenzo[*h*][1,6]naphthyridine, (Fumarate Salt) (**11**).

N-Benzylpiperazine (0.1 ml, 0.57 mmol) was added to a solution of 3,5-dichlorobenzo[*h*][1,6]naphthyridine **5** (0.12 g, 0.48 mmol) and triethylamine (0.07 ml, 0.53 mmol), in *N*,*N*-dimethylformamide (5 ml). After stirring for 2 hours under reflux, the solvent was removed. The residue was crystallised in water, filtered, and purified by chromatography on silicagel with chloroform-methanol (99:1 v/v) as eluent to give a yellow solid. After dissolution in isopropanol (3 ml) with fumaric acid (0.08 g, 0.66 mmol), the mixture was warmed under reflux for 3 min, then cooled to furnish a yellow powder **11**, which was crystallized from isopropanol to yield 0.06 g (25%), mp 228 °C; ir (potassium bromide): CO fumarate 1707, 1571, 1453, 1424, 1376, 1299, 1151 cm^{-1}. ^1H nmr (DMSO-d_6): δ 9.16 (s, 1H, 2-H), 8.82 (d, 1H, 10-H *J*= 8.4 Hz), 8.45 (s, 1H, 4-H), 7.83 (d, 1H, 7-H, *J*= 8.4 Hz), 7.76 (t, 1H, 8-H, *J*= 8.2 Hz), 7.58 (t, 1H, 9-H, *J*= 7.1 Hz), 7.37-7.28 (m, 5H, phenyl), 6.62 (s, 2H, 2CH fumarate), 3.62 (s, 2H, CH_2 benzyl), 3.45 (m, 4H, $2CH_2$), 2.70 (m, 4H, $2CH_2$); ms: m/z 389 (M+, 16), 242 (100), 213 (42), 159 (70), 146 (66), 91 (50).

Anal. Calcd. for $C_{27}H_{25}N_4O_4Cl$: C, 64.22; H, 4.99; N, 11.1. Found: C, 64.44; H, 5.02; N, 11.32.

3-Chloro-5-(*N*,*N*-dimethylaminoethylamino)benzo[*h*][1,6]naphthyridine, (Fumarate Salt) (**12**).

N,*N*-Dimethylaminoethylamine (4.4 ml, 40 mmol) was added to a solution of 3,5-dichlorobenzo[*h*][1,6]naphthyridine **5** (0.5 g, 2 mmol) in ethanol (10 ml). The solution was stirred for 40 minutes under pressure (4 bars) at 160 °C in a sealed tube under microwave heating conditions (300 W). The solvent and excess of reactive were removed under reduced pressure and the resulting residue was taken up in water (50 ml). After stirring for 20 minutes (approx.), the precipitate was collected by filtration and dried to give a beige powder. The resulting solid was dissolved in isopropyl alcohol (6 ml), fumaric acid (0.23 g, 2 mmol) was added and the mixture was warmed at reflux for 35 minutes. After cooling, the precipitate was collected by filtration and dried to afford a white powder **12** which was crystallized from isopropanol to yield 0.36 g (34%), mp 190 °C; ir (potassium bromide): NH 3407, CO fumarate 1693, 1584, 1536, 1360, 1256, 1208 cm^{-1}. ^1H nmr (DMSO-d_6): δ 9.09 (s, 1H, 2-H), 8.92 (s, 1H, 4-H), 8.69 (d, 1H, 10-H, *J*=7.8 Hz), 8.13 (s, 1H, NH), 7.62 (m, 2H, 7-H and 8-H), 7.36 (m, 1H, 9-H), 6.52 (s, 4H, 4CH fumarate), 3.86 (m, 2H, CH_2), 3.13 (m, 2H, CH_2), 2.64 (s, 6H, $2CH_3$); ms: m/z 300 (M^+, 21), 254 (60), 242 (100), 230 (56), 213 (52), 178 (46), 151 (48).

Anal. Calcd. for $C_{24}H_{25}N_4ClO_8$: C, 54.09; H, 4.73; N, 10.51. Found: C, 54.24; H, 4.93; N, 10.92.

X-ray.

Suitable crystals of the title compound (**12**) were obtained by slow evaporation from diethyl ether at room temperature. Examined crystal reveals a monoclinic system (the space group C2/c) with the following unit cell dimensions: a=23.216(5)Å, b=9.060(7)Å, c=11.268(1)Å, β= 128.79(1)°.

Intensity data for compound **12** were collected on an Enraf-Nonius - CAD4 diffractometer with Mo K_α radiation (λ= 0.71073 Å) at room temperature. The data treatment, polarisation and decay corrections, was carried out with JANA98 programme [14] The crystal structure was solved by direct methods using SHELX97 package [15]. All non-hydrogen atoms were refined anisotropically. The H atoms were determined *via* difference Fourier maps and refined with isotropic atomic displacement parameters.

The crystal packing in **12** consists of 3-chlorobenzo[*h*]-[1,6]naphthyridine pairs made up through two symmetry-equivalent stacking interactions of the aromatic rings that form across inversion centre. The interplanar spacing of the parallel rings in the pair is 3.5 Å. The base-pair dimers lies between them *via* a water molecule, present in the crystal, through a network of four

hydrogen bonds, two from a molecule of one base-pair dimer and two symmetry-equivalent from a molecule of another base-pair dimer.

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