Total Synthesis of Aaptamine of Potent α-Blocking Activity *via* Thermal Cyclization of 1-Azahexatriene Systems

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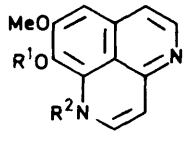
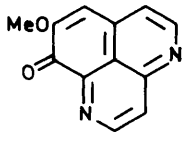
The total synthesis of the marine alkaloid aaptamine (**1**), 1*H*-benzo[*de*][1,6]naphthyridine, has been completed, based on the thermal cyclization of the 1-azahexatriene system, the key intermediate for the construction of the isoquinoline moiety. 5-Nitroveratraldehyde (**7**) is converted, *via* a Wittig reaction, into the nitrostyrene (**8**). Reduction of (**8**) to the aniline (**9**) and subsequent treatment of (**9**) with ethyl 2-formylacetate gives the enamino ester (**10**). Preparation of the quinolone nucleus is achieved by heating compound (**10**) in diphenyl ether, which affords the *N*-benzylquinolone (**12**) along with the quinoline (**13**). Treatment of an inseparable mixture of (**12**) and (**13**) with hydroxylamine gives the debenzylated quinolone oxime (**11**), methylation of which affords a separable mixture of the *N,O*-dimethyl quinolones (**14**) and (**15**). The methyloxime (**14**) (the 1-azahexatriene system) when heated in *o*-dichlorobenzene gives the unnatural 1-methylaaptamine (**3**). In a similar way, benzylation of (**15**) affords the *N,O*-dibenzyl quinolone derivatives (**16**) and (**17**). The benzyloxime (**16**) when heated in *o*-dichlorobenzene affords *N*-benzylaaptamine (**18**). Subsequent cleavage of the *N*-benzyl protecting group with concentrated hydrochloric acid gives aaptamine hydrochloride (**1**).

Aaptamine (**1**), demethylaaptamine (**2**), and demethyl(oxy)-aaptamine (**4**) isolated from the Okinawan sea sponge *Aaptos aaptos* are of interest because of their remarkable pharmacological properties and for the novel 1*H*-benzo[de][1,6]-naphthyridine ring system.[1] We were interested in the total synthesis of this unique heterocyclic natural product (**1**). To



(**1**) R^1 = Me, R^2 = H
(**2**) R^1 = R^2 = H
(**3**) R^1 = R^2 = Me



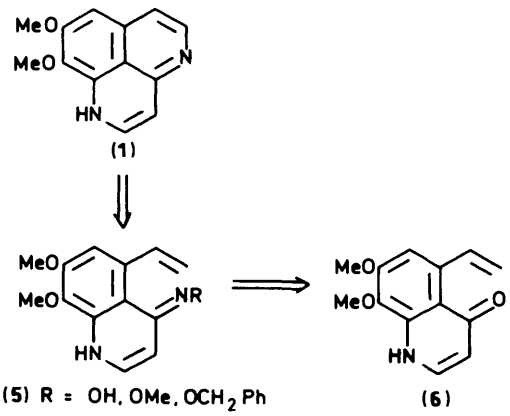
(**4**)

date, four synthetic efforts have been reported by Cava,[2] Kelly,[3] Yamanaka,[4] and Tollari.[5] The total synthesis of aaptamine (**1**) by Kelly involved using a Pomeranz–Fritsch-type reaction for the construction of the isoquinoline moiety. The other three groups have established the total synthesis of (**1**) *via* the construction of the quinoline part.

We have developed the synthesis of condensed heteroaromatics based on the thermal cyclization of intramolecular hexa-1,3,5-triene[6,7] or monoazahexa-1,3,5-triene systems.[8] We now describe the total synthesis of aaptamine (**1**) *via* the construction of the isoquinoline nucleus using this methodology.

As shown in retrosynthetic pathway (Scheme 1), the *o*-iminostyrene-type intermediate (**5**) derived from the breakage of the 4, 5-bond of (**1**), that is 1-azahexatriene system, was envisaged as the key intermediate in this synthesis. We also considered that the R substituents (OH, OMe, OCH_2Ph) attached to the nitrogen of *o*-iminostyrene intermediate (**5**) would contribute to the stability of the intermediate and would act as a good leaving group thus facilitating the final aromatization.

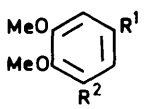
Initially we aimed at deriving the intermediate (**5**) and its precursor (**6**) from 5-nitroveratraldehyde (**7**).[9] For the



(**1**)

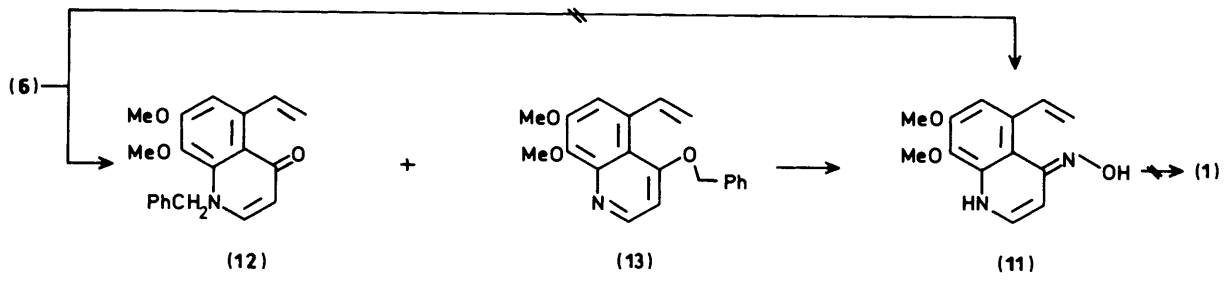
(**5**) R = OH, OMe, OCH_2Ph (**6**)

Scheme 1.

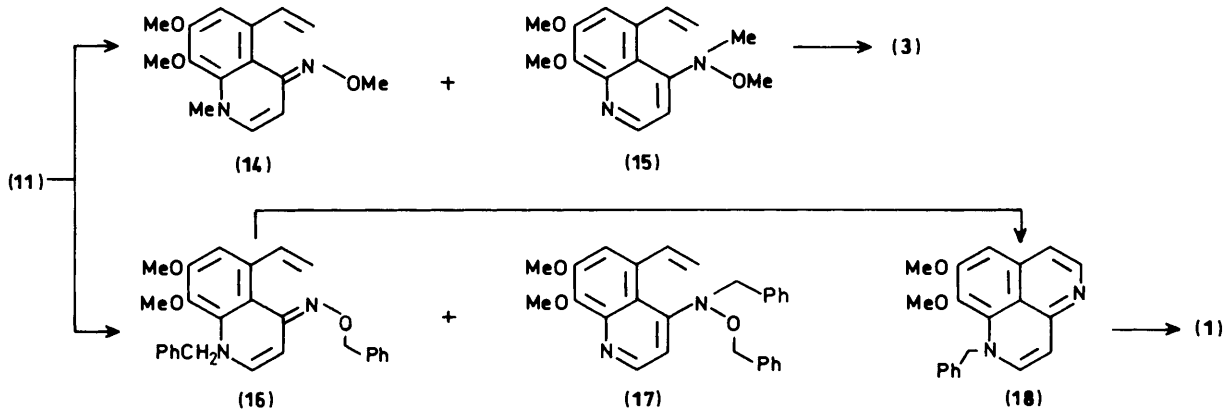


(**7**) R^1 = CHO, R^2 = NO_2
(**8**) R^1 = $CH{=}CH_2$, R^2 = NO_2
(**9**) R^1 = $CH{=}CH_2$, R^2 = NH_2
(**10**) R^1 = $CH{=}CH_2$, R^2 = $NHCH{=}CHCO_2Et$

synthesis of quinolone ring system (**6**), the readily available 5-nitroveratraldehyde (**7**) was treated with methylenetriphenylphosphorane to give the nitrostyrene (**8**) (70%). Reduction of compound (**8**) with sodium dithionite in aqueous methanol provided the aminostyrene (**9**) in 42% yield. This product was treated with ethyl 2-formylacetate[10] in ethanol at room temperature to give the enamino ester (**10**) (62%). Subsequent cyclization of (**10**) in diphenyl ether at reflux, for 40 min afforded the appropriate quinolone ring system (**6**) in 30% yield. The conversion of quinolone (**6**) into the oxime intermediate (**11**) was unsuccessful. No products could be



Scheme 2.



Scheme 3.

detected, and a near quantitative amount of the starting material was recovered. It was assumed that the failure to obtain oxime (**11**) under the various conditions used was a result of the vinylogous amide.

The protection of the nitrogen function in the quinolone (**6**) with benzyl bromide and sodium hydride in dimethylformamide gave an inseparable mixture of the *N*-benzylquinolone (**12**) and the quinoline (**13**) (1:1). When the mixture of (**12**) and (**13**) was refluxed with hydroxylamine hydrochloride and sodium acetate for 1 h in ethanol, the debenzylated quinolone oxime (**11**) was obtained in 33% yield from (**6**) (Scheme 2). Subsequent thermal cyclization of the quinolone oxime (**11**) was unsuccessful in various solvents such as xylene and *o*-dichlorobenzene. It seems to us that the failure of the thermal cyclization is a result of the tautomerism between the quinolone and quinoline forms.

Our attention was then turned to the alkylation of quinolone oxime (**11**) in order to prevent the aromatization of quinolone (**11**) and to investigate the final cyclization process. Methylation of (**14**) with methyl iodide and sodium hydride in dimethylformamide gave the *N*-methylated quinolone methyloxime (**14**) (19%) along with the quinoline (**15**) (41%). Compound (**14**) was then heated to 180 °C in *o*-dichlorobenzene to afford 1-methylaaptamine (**3**) in 73% yield. Similarly, benzylation of (**14**) with benzyl bromide and sodium hydride in dimethylformamide gave the *N*-benzylated quinolone benzyloxime (**16**) (13%) and the unexpected quinoline (**17**) (21%). Thermal cyclization of the 1-azahexatriene intermediate (**16**) afforded the aaptamine derivative (**18**) in 67% yield. Finally, treatment of (**18**) with concentrated hydrochloric acid at reflux provided aaptamine hydrochloride (**1**) in 90% yield, which was identified by direct comparison with an authentic sample.

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were measured with a Shimadzu IR-408 spectrometer. Proton nuclear magnetic resonance spectra were taken with JEOL PMX-60 and JEOL JNM-GX 400 instruments with $SiMe_4$ as an internal standard unless otherwise stated. Mass spectra and high-resolution mass spectra (e.i.) were recorded on Shimadzu GC-MS 6020 and Hitachi M-80 spectrometers, respectively. Silica gel (60—100 mesh, Merck Art 7734) and Iatrobeads (Iatron Chem. Prod.) were used for column chromatography.

3,4-*Dimethoxy*-5-*nitrostyrene* (**8**).—A solution of BuLi 1.56M in hexane; (38.5 ml, 60.5 mmol) was added to a stirred suspension of methyl triphenylphosphonium bromide (21.7 g, 60.5 mmol) and anhydrous THF (100 ml) at 0 °C under N_2. After the ylide had been formed (*ca.* 30 min), a solution of the aldehyde (**7**) (10.6 g, 50.4 mmol) in anhydrous THF (100 ml) was added dropwise under the same conditions. The stirring was continued for 14 h at room temperature whereupon it was worked up with water and extracted with benzene. The benzene layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; 150 g) with 1% EtOAc–hexane as the eluant to give the styrene (**8**) (7.4 g, 70%), m.p. 54—56 °C (EtOH) (Found: C, 57.4; H, 5.35; N, 6.8. $C_{10}H_{11}NO_4$ requires C, 57.41; H, 5.30; N, 6.70%); $\nu_{max.}$(KBr) 1 530 and 1 335 cm^{-1} (NO_2); δ_H(60 MHz; $CDCl_3$) 3.90 (6 H, s, OMe × 2), 5.23 (1 H, d, *J* 10 Hz, vinyl-H), 5.58 (1 H, d, *J* 17 Hz, vinyl-H), 6.52 (1 H, dd, *J* 10 and 17 Hz, vinyl-H), 7.00 (1 H, d, *J* 2 Hz, 2-H), and 7.17 (1 H, d, *J* 2 Hz, 6-H); *m/z* 209 (M^+).

3-*Amino*-4,5-*dimethoxystyrene* (**9**).—A solution of $Na_2S_2O_4$ (41 g, 235 mmol) in aqueous MeOH (200 ml; 1:1) was added to a solution of the nitro compound (**8**) (7.07 g, 33.8 mmol) in MeOH (50 ml) and the reaction was stirred for 10 min. After the solvent had been removed, brine (200 ml) was added. This mixture was extracted with $CHCl_3$ (200 ml × 3). The combined $CHCl_3$ layers were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was distilled to give amine

(**9**), b.p. 125 °C/1 Torr (2.52 g, 42%) (Found: C, 67.05; H, 7.2; N, 7.2. $C_{10}H_{13}NO_2$ requires C, 67.02; H, 7.31; N, 7.82%); δ_H(60 MHz; $CDCl_3$) 3.73 (3 H, s, OMe), 3.77 (3 H, s, OMe), 5.07 (1 H, dd, *J* 11 and 2 Hz, vinyl-H), 5.48 (1 H, dd, *J* 17 and 2 Hz, vinyl-H), 6.03 (2 H, br s, 2- and 6-H), and 6.47 (1 H, dd, *J* 17 and 11 Hz, vinyl-H); *m/z* 179 (M^+).

(Z)-Ethyl 3-(2,3-Dimethoxy-5-ethenylanilino)acrylate (**10**).—A solution of the aniline (**9**) (1.9 g, 10.6 mmol) and ethyl 2-formylacetate (1.5 g, 13.1 mmol) was stirred at room temperature for 14 h under N_2. After the solvent had been removed, the crude material was recrystallized from EtOH to give the enamino ester (**10**) (1.8 g, 62%), m.p. 92—93 °C (Found: C, 65.15; H, 7.0; N, 5.05. $C_{15}H_{19}NO_4$ requires C, 64.96; H, 6.91; N, 5.05%); $\nu_{max.}$(KBr) 1 720 cm^{-1} (ester); δ_H(60 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7 Hz, OCH_2Me), 3.83 (6 H, s, OMe × 2), 4.10 (2 H, q, *J* 7 Hz, OCH_2Me), 4.72 (1 H, d, *J* 8 Hz, CH=C*H*CO), 5.10 (1 H, d, *J* 10 Hz, vinyl-H), 5.48 (1 H, d, *J* 18 Hz, vinyl-H), 6.28—6.57 (3 H, m, C*H*=CHCO, ArH × 2), and 7.12 (1 H, dd, *J* 18 and 10 Hz, vinyl-H); *m/z* 277 (M^+).

5-Ethenyl-7,8-dimethoxy-4-quinolone (**6**).—A solution of the enamino ester (**10**) (1.5 g, 0.545 mmol) in diphenyl ether (15 ml) was added to boiling diphenyl ether (30 ml) and the solution was refluxed for 40 min under N_2. After the solvent had been removed, the residue was purified by column chromatography (silica gel; 100 g) with 3% MeOH–$CHCl_3$ as the eluant to give the quinolone (**6**) (0.63 g, 30%), m.p. 176—178.5 °C (EtOH–Et_2O) (Found: 67.8; H, 5.75; N, 6.2. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06%); δ_H(60 MHz; $CDCl_3$) 3.93 (3 H, s, OMe), 3.98 (3 H, s, OMe), 5.23 (1 H, dd, *J* 8 and 2 Hz, vinyl-H), 5.47 (1 H, dd, *J* 15 and 2 Hz, vinyl-H), 6.17 (1 H, d, *J* 7 Hz, 3-H), 6.97 (1 H, s, 6-H), 7.62 (1 H, br m, 2-H), 8.25 (1 H, dd, *J* 15 and 8 Hz, vinyl-H), 10.22 (1 H, br s, exchangeable with D_2O, NH); *m/z* 231 (M^+).

1-Benzyl-5-ethenyl-7,8-dimethoxy-4-quinolone (**12**) *and 4-Benzyloxy-5-ethenyl-7,8-dimethoxyquinoline* (**13**).—A solution of the quinolone (**6**) (140 g, 0.609 mmol) in dimethylformamide (DMF) (2 ml) was added to a solution of NaH (60% dispersion in oil; 30 mg, 0.75 mmol) in DMF (1 ml) at room temperature under N_2. The reaction was stirred for 0.5 h when a solution of benzyl bromide (130 mg, 0.76 mmol) in DMF (2 ml) was added dropwise. The reaction mixture was stirred for 2 h, worked up with brine (50 ml), and extracted with $CHCl_3$ (50 ml × 3). The combined $CHCl_3$ layers were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was separated by column chromatography (silica gel; 40 g) with EtOAc–benzene (2:3) as the eluant to give an inseparable 1 : 1 mixture of 1-benzylquinolone (**12**) and quinoline (**13**) (30 mg, 65.5%), which was used in the next reaction.

5-Ethenyl-7,8-dimethoxy-4-quinolone Oxime (**11**).—A stirred solution of a 1:1 mixture of the quinolones (**12**) and (**13**) (30 mg), hydroxylamine hydrochloride (150 mg, 2.2 mmol) and NaOAc (180 mg, 2.2 mmol) in EtOH (5 ml) was refluxed for 1 h. After the solvent had been removed the residue was purified by column chromatography (silica gel; 15 g) with 2% MeOH–$CHCl_3$ as the eluant to give the oxime (**11**) [54.3 mg; 33% from (**6**)], m.p. 168—170 °C (decomp.) (benzene) (Found: C, 63.15; H, 5.9; N, 11.4. $C_{13}H_{14}N_2O_3$ requires C, 63.40; H, 5.73; N, 11.38%); δ_H(60 MHz; $CDCl_3$) 3.87 (3 H, s, OMe), 3.92 (3 H, s, OMe), 5.15 (1 H, dd, *J* 10 and 2 Hz, vinyl-H), 5.40 (1 H, dd, *J* 18 and 2 Hz, vinyl-H), 6.33 (1 H, d, *J* 8 Hz, 3-H), 6.77 (1 H, s, 6-H), 6.87 (1 H, d, *J* 8 Hz, 2-H), and 7.63 (1 H, dd, *J* 18 and 10 Hz, vinyl-H); *m/z* 246 (M^+).

5-Ethenyl-7,8-dimethoxy-1-methyl-4-quinolone O-Methyloxime (**14**) *and 5-Ethenyl-7,8-dimethoxy-4-[methoxy(methyl)amino]quinoline* (**15**).—A solution of the oxime (**11**) (70 mg, 0.285 mmol) in DMF (2 ml) was added to a mixture of NaH (60% dispersion in oil; 25 mg, 0.625 mmol) and DMF (2 ml) with ice cooling. The reaction was stirred for 0.5 h, whereupon a solution of CH_3I (90 mg, 0.643 mmol) in DMF (1 ml) was added. Stirring was continued for 1 h at room temperature and worked up with brine (50 ml), which was extracted with $CHCl_3$ (50 ml × 3). The $CHCl_3$ layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; 25 g) with 5% EtOAc–hexane as the eluant to give the faster-moving oxime ether (**14**) (14.8 mg, 19%) and then with 20% EtOAc–hexane as the eluant to give the slower-moving quinoline (**15**) (32 mg, 41%).

Compound (**14**) had m.p. 58—61 °C (hexane) (Found: C, 65.25; H, 6.7; N, 10.35. $C_{15}H_{18}N_2O_3$ requires C, 65.07; H, 6.61; N, 10.21%); δ_H(60 MHz; $CDCl_3$) 3.63 (3 H, s, NMe), 3.73 (3 H, s, OMe), 3.93 (6 H, s, OMe × 2), 5.10 (1 H, dd, *J* 10 and 2 Hz, vinyl-H), 5.35 (1 H, dd, *J* 17 and 2 Hz, vinyl-H), 6.17 (1 H, d, *J* 8 Hz, 3-H), 6.45 (1 H, d, *J* 8 Hz, 2-H), 6.87 (1 H, s, 8-H), and 7.67 (1 H, dd, *J* 17 and 10 Hz, vinyl-H); *m/z* 274 (M^+).

Compound (**15**) had m.p. 108—110 °C (Et_2O–hexane) (Found: C, 65.3; H, 6.8; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.07; H, 6.61; N, 10.21%); δ_H(60 MHz; $CDCl_3$) 2.83 (3 H, s, NMe), 3.67 (3 H, s, NMe), 4.02 (3 H, s, OMe), 4.07 (3 H, s, OMe), 5.23 (1 H, dd, *J* 10 and 2 Hz, vinyl-H), 5.52 (1 H, dd, *J* 18 and 2 Hz, vinyl-H), 7.28 (1 H, s, 6-H), 7.33 (1 H, d, *J* 5 Hz, 3-H), 7.77 (1 H, dd, *J* 18 and 10 Hz, vinyl-H), and 8.73 (1 H, d, *J* 5 Hz, 2-H); *m/z* 274 (M^+).

8,9-Dimethoxy-1-methylbenzo[de][1,6]*naphthyridine* (*1-Methylaaptamine*) (**3**).—A mixture of the *O*-methyloxime (**14**) (10 mg, 0.036 mmol) and *o*-dichlorobenzene (5 ml) was refluxed for 2 h. After the solvent had been removed, the residue was purified by column chromatography (silica gel; 10 g) with 3% MeOH–$CHCl_3$ as the eluant to give 1-methylaaptamine (**3**) (5.8 mg, 73%), m.p. 186 °C (decomp.) (EtOH–Et_2O) (Found: M^+, 242.1052. $C_{14}H_{14}N_2O_2$ requires *M*, 242.1054); δ_H(400 MHz; $CDCl_3$) 3.76 (3 H, s, NMe), 3.97 (3 H, s, OMe), 3.98 (3 H, s, OMe), 6.33 (1 H, d, *J* 7.56 Hz, 3-H), 6.91 (1 H, d, *J* 7.08 Hz, 6-H), 7.18 (1 H, s, 7-H), 7.48 (1 H, d, *J* 7.08 Hz, 5-H), and 7.81 (1 H, d, *J* 7.56 Hz, 2-H); *m/z* 242 (M^+).

1-Benzyl-5-ethenyl-7,8-dimethoxy-4-quinolone O-Benzyloxime (**16**) *and 4-[Benzyl(benzyloxy)amino]-5-ethenyl-7,8-dimethoxyquinoline* (**17**).—A solution of the oxime (**11**) (220 mg, 0.9 mmol) in DMF (10 ml) was added to a suspension of NaH (60% dispersion in oil; 80 mg, 2 mmol) and DMF (10 ml). The reaction was stirred for 0.5 h at room temperature, whereupon a solution of benzyl bromide (350 mg, 2.05 mmol) in DMF (10 ml) was added. The mixture was stirred for a further 1 h, then was worked up with brine (50 ml) and extracted with $CHCl_3$ (50 ml × 3). The $CHCl_3$ layer was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; 70 g) with benzene as the eluant to give the faster-moving quinolone benzyloxime (**16**) (50.2 mg, 13%) and then with 5% EtOAc–benzene as the eluant to give the slower-moving quinoline (**17**) (84.2 mg, 21%).

Compound (**16**) was an oily product (Found: M^+, 426.1942. $C_{27}H_{26}N_2O_3$ requires *M*, 426.1942); δ_H(60 MHz; $CDCl_3$) 3.43 (3 H, s, OMe), 3.80 (3 H, s, OMe), 4.87—5.40 (2 H, m, vinyl-H), 5.10 (2 H, s, NC*H*Ph), 5.17 (2 H, s, $NOCH_2Ph$), 6.30 (1 H, d, *J* 8 Hz, 3-H), 6.53 (1 H, d, *J* 8 Hz, 2-H), 6.70 (1 H, s, 6-H), and 6.97—7.63 (11 H, m, Ph × 2 and vinyl-H); *m/z* 426 (M^+).

Compound (**17**) had m.p. 94—96 °C (Et_2O–hexane) (Found: C, 76.15; H, 6.23; N, 6.33. $C_{27}H_{26}N_2O_3$ requires C, 76.03; H,

6.15; N, 6.57%); δ_H(60 MHz; $CDCl_3$) 4.02 (3 H, s, OMe), 4.07 (3 H, s, OMe), 4.68 (2 H, s, $NOCH_2Ph$), 5.17 (1 H, dd, *J* 10 and 2 Hz, vinyl-H), 5.53 (1 H, dd, *J* 17 and 2 Hz, vinyl-H), 7.10—7.27 (12 H, m, Ph × 2, 3-H and 6-H), 7.73 (1 H, dd, *J* 17 and 10 Hz, vinyl-H), and 8.63 (1 H, d, *J* 5 Hz, 2-H); *m/z* 426 (M^+).

1-*Benzyl*-8,9-*dimethoxy*[de][1,6]*naphthyridine* (1-*Benzylaaptamine*) (**18**).—A solution of the quinolone benzyloxime (**16**) (20 mg, 0.047 mmol) and *o*-dichlorobenzene (5 ml) was refluxed for 2 h. After the solvent had been removed, the residue was purified by column chromatography (silica gel; 30 g) with 3% MeOH–$CHCl_3$ as the eluant to give 1-benzylaaptamine (**18**) (9.7 mg, 67%), m.p. 167—169 °C (Et_2O) (Found: M^+, 318.1372. $C_{20}H_{18}N_2O_2$ requires *M*, 318.1367); δ_H[400 MHz; $(CD_3)_2SO$] 3.52 (3 H, s, OMe), 3.92 (3 H, s, OMe), 5.59 (2 H, s, CH_2Ph), 6.41 (1 H, d, *J* 6.96 Hz, 3-H), 6.97 (1 H, d, *J* 6.59 Hz, 6-H), 7.15—7.36 (6 H, m, Ph and 7-H), 7.57 (1 H, d, *J* 6.59 Hz, 5-H), and 7.92 (1 H, d, *J* 6.96 Hz, 2-H); *m/z* 318 (M^+).

Aaptamine Hydrochloride (**1**).—A solution of 1-benzylaaptamine (**18**) (9 mg, 0.028 mmol) in concentrated HCl was refluxed for 2 h. After the solvent had been removed, the residue was purified by column chromatography (Iatrobeads, 10 g), with 4% MeOH–$CHCl_3$ as the eluant, to give aaptamine hydrochloride (**1**) (3.9 mg, 61%), m.p. 105—107 °C (MeOH–acetone) (lit.,[1] 105—106 °C) [Found: (M^+ − HCl), 228.6893 $C_{13}H_{12}N_2O_2$ requires (*M* − HCl), 228.6897]; δ_H[400 MHz; $(CD_3)_2SO$] 3.82 (3 H, s, OMe), 3.99 (3 H, s, OMe), 6.44 (1 H, d, *J* 6.96 Hz, 3-H), 6.89 (1 H, d, *J* 7.33 Hz, 6-H), 7.13 (1 H, s, 7-H), 7.43 (1 H, d, *J* 7.33 Hz, 5-H), and 7.85 (1 H, d, *J* 6.96 Hz, 2-H); *m/z* 228 (M^+ − HCl).

Acknowledgements

We wish to thank Professor Hiroshi Yamanaka, Pharmaceutical Institute, Tohuku University, for sending us a sample of synthetic aaptamine hydrochloride. We also thank Mr. Hideaki Kondo, Department of Analytical Chemistry, Research Centre, Taisho Pharmaceutical Co. Ltd., and Professor Takushi Kurihara, Osaka Pharmaceutical University for the measurement of 400 MHz n.m.r. spectra and high resolution mass spectra, respectively.

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Received 7th December 1987; *Paper* 7/2140