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A SYNTHESIS OF AAPTAMINE

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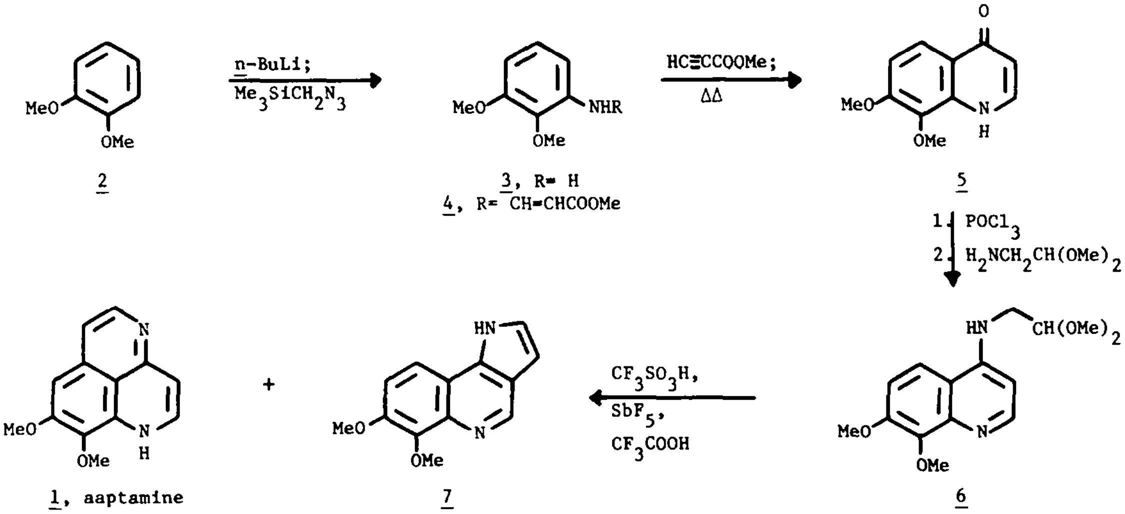
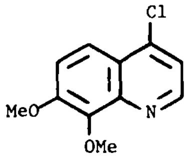
Abstract: A five-step synthesis of the unusual marine alkaloid aaptamine (1) from veratrole is described (Scheme 1).

Fractionation of the methanol extract from a sea sponge (*Aaptos aaptos*) collected off the island of Okinawa afforded a bright yellow substance christened aaptamine and assigned structure 1.[1] In addition to having remarkable α-adrenoceptor blocking activity, aaptamine is the first[2,3] known example of the 1*H*-benzo[*de*]-1,6-naphthyridine ring system. We now report a simple synthesis[4] of aaptamine which not only makes available useful quantities of the material but should also provide a flexible route for the preparation of analogs. The synthesis is outlined in Scheme 1.

Scheme 1



Thus ortho-lithiation[5] of veratrole (2) followed by reaction with trimethylsilylmethyl azide[6] affords 2,3-dimethoxyaniline (3).[7] Michael addition[8] of 3 to methyl propiolate in methanol (→4), followed by replacement of the methanol with diphenyl ether and thermal cyclization[8] at reflux provides quinolone 5. Chlorination[9] of 5 gives the 4-chloroquinoline 8, which reacts[10] with the dimethyl acetal of aminoacetaldehyde to afford the key intermediate 6.



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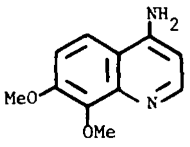

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We had anticipated that 6 might be induced to undergo an intramolecular, Pomeranz-Fritsch type[11] reaction to yield aaptamine directly. For although closure to the 1H-pyrrolo-[3,2-c]quinoline 7 appears favored by the entropic factors attending formation of a 5-membered (as opposed to a 6-membered) ring, the carbocyclic aromatic ring appears, on the basis of mechanistic considerations, to be the ring more susceptible to electrophilic attack, especially under acidic conditions. In practice, reaction along these two conflicting pathways occurs to a similar extent, giving approximately equal amounts of aaptamine and 7.[12] Best results were achieved using a mixture of triflic acid and antimony pentafluoride in trifluoroacetic acid.[13] The identity of the aaptamine was established by direct comparison with a sample of naturally derived material.

EXPERIMENTAL

NMR spectra were recorded on a Varian FT-80A spectrometer with chemical shifts reported in ppm downfield of internal Me_4Si. IR spectra were recorded on a Perkin-Elmer Model 599B spectrophotometer; UV spectra on a Perkin-Elmer Model 575 spectrophotometer. Flash column chromatography was conducted using silica gel 60 (particle size 0.040-0.063 mm, EM reagents). Column chromatography was also conducted on Activity I acidic alumina (ca. 150 mesh, Aldrich Chem. Co.). Pet. ether refers to the fraction boiling from 40-60°C. Melting points were determined in Pyrex capillaries and are uncorrected. Anhydrous ether used in moisture-sensitive reactions was purchased from Mallinckrodt and used directly. Elemental analyses were performed by Robertson Laboratory Inc.

2,3-Dimethoxyaniline (3). To a stirred solution of 30 ml (234 mmol) of veratrole and 35.4 ml (234 mmol) of N,N,N',N'-tetramethylethylenediamine in 240 ml of ether cooled to 0°C under an N_2 atmosphere was added dropwise over 15 min 94.8 ml (234 mmol) of 2.47 M n-butyllithium in hexane. The resulting suspension was stirred at 22° for 18.5 h and then recooled to 0°C. A solution of 33.6 ml (234 mmol) of trimethylsilylmethyl azide[6] (CAUTION[6]) in 120 ml of ether was added dropwise over 10 min into the mixture. The resulting brown solution was warmed to 22°C, stirred for an additional 3.5 h, and poured into 200 ml of water. The organic layer was extracted with 1M HCl (5 x 100 ml), and the combined aqueous extracts were made basic to litmus with 3M NaOH and extracted with ether (5 x 100 ml). The combined ether extracts were washed with 150 ml of water, 150 ml of brine and then dried ($MgSO_4$). Evaporation of the solvent followed by kugelrohr distillation gave 28.25 g (78%) of 3, bp 137°C (15 torr) [lit.[7] bp: 129-136°C (7 torr)]. The product exhibits ^1H NMR and IR spectra identical to those of a sample of 3 prepared by literature[7] methods.

7,8-Dimethoxy-4(1H)-quinolone (5).

a) One-pot preparation from 3. To a solution of 8.6 g (56 mmol) of 3 in 21 ml of MeOH under a nitrogen atmosphere was added 5.0 ml (56 mmol) of methyl propiolate in one portion. After the reaction was stirred for four days at 22°C, the MeOH was evaporated at aspirator vacuum and the residue (^1H NMR spectroscopy indicated it to be a mixture of cis- and trans-4) was dissolved in 25 ml of diphenyl ether. This solution was added over a 3 min period to 175 ml of boiling diphenyl ether. After heating at reflux without protection from air for an additional 25 min, the mixture was cooled to room temperature, poured into 250 ml of pet. ether, and left overnight. The solvent was decanted and the solid residue recrystallized from EtOAc/MeOH to give 8.3 g (72%) of 5. An analytical sample, mp 187-190°C, was prepared by sublimation (180°C/0.1 torr) and recrystallization from EtOAc/MeOH; IR (KBr) 3300-2700, 1610, 1558 cm^{-1}; ^1H NMR (DMSO-d_6) δ11.19 (br s, 1H), 7.83 (d, J=9.1 Hz, 1H), 7.74 (dd, J=6.0, 7.4 Hz, 1H), 7.15 (d, J=9.1 Hz, 1H), 5.94 (br d, J=7.4 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H).

Anal. calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.41; N, 6.82. Found: C, 64.40; H, 5.46; N, 6.63.

b) With Isolation of Methyl 3-(2,3-Dimethoxyanilino)acrylate (4). To a solution of 27.7 g (181 mmol) of 3 in 65 ml of dry MeOH under an N_2 atmosphere, was added 15.2 g (181 mmol) of methyl propiolate in one portion. The solution was stirred for 3 days at 22°. After cooling to 0° overnight, 24.9g of crystals of pure cis-4 (mp 76-77°C) were obtained. Concentration of the mother liquor gave an additional 6.3 g of a mixture of cis- and trans-4 for a total of 31.2g (73%) of 4;

IR (of cis-4) (KBr) 3304, 1680, 1626, 1604, 1590 cm^{-1}; ^{1}H NMR (of cis-4) (DMSO-d_6) δ10.25 (d, J=13.1 Hz, 1H), 7.68 (dd, J=8.3, 13.1 Hz, 1H), 6.61-7.05 (m, 3H), 4.86 (d, J=8.3 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H).

Anal. calcd for $C_{12}H_{15}NO_4$: C, 60.74; H, 6.38; N, 5.90. Found: C, 60.56; H, 6.51; N, 5.89.

To 600 ml of boiling diphenyl ether was added 22.09 g (94.0 mmol) of 4. The solution was heated at reflux for 25 min, cooled to room temperature, and poured into 500 ml of pet. ether. After standing overnight, the product was filtered off and washed with Et_2O to give 17.3 g (91%) of 5, suitable for use in the next step.

4-Chloro-7,8-dimethoxyquinoline (8). To 100 ml of $POCl_3$ was added 12.9 g of 5; after a few minutes a yellow precipitate formed and the mixture was stirred at 22° for 24 h under an N_2 atmosphere. Excess $POCl_3$ was removed by distillation at aspirator vacuum, and the residual solid was dissolved in 100 ml of 1M HCl. The aqueous solution was washed with 50 ml of ether, made basic to litmus with 3M NaOH, and extracted with CH_2Cl_2 (3 x 75 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give 12.5 g of crude 8. The crude material was chromatographed through 110 g of flash-column silica gel using 1:99 dimethylethylamine/ethyl acetate to give 12.1 g (86%) of 8. An analytical sample, mp 80-81.5°C, was prepared by recrystallization from ether; IR (KBr) 2930, 1610, 1502, 1475 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ8.78 (d, J=4.7 Hz, 1H), 7.99 (d, J=9.3 Hz, 1H), 7.44 (d, J=9.3 Hz, 1H), 7.37 (d, J=4.7 Hz, 1H), 4.12 (s, 3H), 4.05 (s, 3H).

Anal. calcd for $C_{11}H_{10}NO_2Cl$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.94; H, 4.39; N, 6.27.

7,8-Dimethoxy-4-(2,2-dimethoxyethylamino)quinoline (6). To a solution of 6.00 g (26.8 mmol) of 8 in 120 ml of DMSO was added 3.21 ml (29.5 mmol) of aminoacetaldehyde dimethyl acetal under an N_2 atmosphere. After stirring for 5 days at 95°C, DMSO and excess acetal were removed by distillation at reduced pressure (1 mm, 100°C). The resulting crude residue was mixed with 100 ml of 5% aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give 5.92 g of a solid, shown by ^{1}H NMR spectroscopy to be an otherwise pure 21:79 mixture of 8 and 6. Separation of 6 was accomplished by recrystallization from EtOH/Et_2O to give 4.1 g (52%) of 6. An analytical sample, mp 142-143°C, was prepared by recrystallization from EtOAc/MeOH. IR (KBr) 3245, 2830, 1585, 1485, 1292 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ8.36 (d, J=5.3 Hz, 1H), 7.95 (d, J=9.4 Hz, 1H), 7.31 (d, J=9.4 Hz, 1H), 7.12 (br t, J=5.9 Hz, 1H; exch. with D_2O), 6.42 (d, J=5.3 Hz, 1H), 4.63 (t, J=5.3 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.37 (m, 2H), 3.33 (s, 6H).

Anal. calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.59. Found: C, 61.84; H, 7.08; N, 9.73.

Aaptamine hydrochloride (1·HCl), 6,7-Dimethoxy-1H-pyrrolo(3,2-c)quinoline (7) and 4-Amino-7,8-dimethoxyquinoline (9). A solution of 20 ml of trifluoroacetic acid, 4 ml of trifluoromethanesulfonic acid, and 0.74 g (3.41 mmol) of antimony pentafluoride was prepared and heated to 75-80°. To this solution, which was open to the air, was added 1.0 g (3.4 mmol) of 6 in small portions over a three-minute period. Heating was continued for an additional 30 sec and the mixture was poured into 100 ml of water. The aqueous solution was made slightly basic (pH 7.5-8.0) with 2M NaOH and *immediately*[14] extracted into CH_2Cl_2 (3 x 50 ml). A small amount of methanol was used to transfer into the CH_2Cl_2 extract some gummy insoluble material remaining in the separatory funnel. The organic extracts were quickly[14] washed with 50 ml of brine and extracted into 0.15M HCl (4 x 50 ml). The combined HCl extracts were evaporated under reduced pressure (*ca.* 5 torr) and the residue was chromatographed through acidic alumina. After 7·HCl (300 mg, 33%) was eluted with 1:99 MeOH/$CHCl_3$, the solvent polarity was increased to 2.5:97.5 MeOH/$CHCl_3$ to elute 308 mg (34%) of aaptamine hydrochloride (1·HCl); elution with 1:19 MeOH/$CHCl_3$ then gave 200 mg (24%) of 9·HCl. A sample of aaptamine hydrochloride (1·HCl), mp 114-121°C[15] [lit.[1] mp (natural): 110-113°C; lit.[4] mp (synthetic): 107°C; mixture mp with natural aaptamine hydrochloride which melted at 113-117°C: 113-121°C], was prepared by rechromatography and three recrystallizations from methanol/acetone. The synthetic 1 exhibits tlc behavior identical to natural 1 in a variety of systems.[16]

An analytically pure sample of 7, mp 209-211°C (dec), was obtained by rechromatography of its hydrochloride, generating the free base by partitioning between CH_2Cl_2 and 5% Na_2CO_3, and two recrystallizations from MeOH/EtOAc; IR (KBr) 3400-2400, 1628, 1572, 1503, 1467 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ12.32 (br s, 1H), 9.05 (s, 1H), 8.12 (d, J=9.1 Hz, 1H), 7.49 (d, J=9.1 Hz, 1H), 7.45 (m, 1H), 6.72 (dd, J=1.7, 3.0 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H).

Anal. calcd for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.28. Found: C, 68.36; H, 5.14; N, 12.17.

Analytically pure 9 [mp 199-201°C (dec)], identical to material synthesized independently (see below), was secured by rechromatography of its hydrochloride, generation of the free base (as with 7), and two recrystallizations from MeOH/EtOAc; IR (KBr) 3435, 3405, 1650, 1618, 1588 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ8.25 (d, J=5.2 Hz, 1H), 7.88 (d, J=9.3 Hz, 1H), 7.26 (d, J=9.3 Hz, 1H), 6.68 (br s, 2H), 6.42 (d, J=5.2 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H).

Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.56; H, 5.97; N, 13.58.

4-Amino-7,8-dimethoxyquinoline (9). A solution of 50.0 mg (0.224 mmol) of 8 in 1 ml of phenol[10] was prepared and heated to 180°C. A slow stream of ammonia was passed through the solution for 2 h. The mixture was cooled and partitioned between 30 ml of CH_2Cl_2 and 30 ml of 5% Na_2CO_3. The organic layer was washed with 20 ml of 1M NaOH, 20 ml of brine, and dried (Na_2SO_4). Evaporation of the CH_2Cl_2, followed by silica gel chromatography (1:7:92 dimethylethylamine/methanol/chloroform) gave 28 mg (61%) of 9, identical to 9 isolated from the cyclization of 6 (see above).

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12. For other routes to 1*H*-pyrrolo[3,2-*c*]quinolines see, *inter alia*, J. Parrick and R. Wilcox, *J.C.S. Perkin I*, 2121 (1976) and M.A. Khan and J.F. da Rocha, *J. Heterocyclic Chem.*, 15, 913, (1978).

13. A variety of other reagents (including CF_3CO_2H, H_2SO_4, polyphosphoric acid, CH_3SO_3H, $POCl_3$, CF_3SO_3H/CH_3CO_2H, $ClSO_3H/CF_3CO_2H$, $TiCl_4/CH_2Cl_2$, and CF_3SO_3H alone) was examined. None gave 1 to the exclusion of 7 and yields of 1 were, at best, much lower: in most cases 9 became the major reaction product. Use of acids which can also function as oxidizing[14] agents (e.g. H_2SO_4) seems particularly deleterious to the formation of 1.

14. The free base of aaptamine is sensitive to air oxidation.

15. The value and range of the mp are sensitive to the length of time the material is dried; the mp also tends to become lower upon storage.

16. The ^1H NMR spectrum is in agreement with reported values.[1,4b] In the UV spectrum [λ_{max} (ϵ) (H_2O): 214 (18,700), 236 (20,300), 255 (24,400), 309 (4,800), 381 (6,700) nm] the positions of the maxima agree with those reported earlier[1,4] but "our" extinction coefficients are 10-20% higher. Qualitative experiments indicate that the magnitude of the ϵ's varies with the precise pH of the solution.