Synthesis of (±)-Actinidine by an Intramolecular Cycloaddition Process

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A new synthesis of (±)-actinidine (1), which relies on intramolecular cycloaddition of an acetylene across a pyrimidine ring, is described. Preparation of 5-(hept-5-yn-2-yl)-4,6-dihydroxypyrimidine (2) followed by thermolysis afforded 1-hydroxyactinidine (13), which could be converted into (±)-actinidine by chlorination and hydrogenation.

ACTINIDINE (1) is a member of the comparatively rare group of monoterpene alkaloids.[1] It occurs in a number of plants and as a constituent of the defensive secretion in certain ants, and has been described as a potent cat attractant. Several syntheses have been described previously.[2] Herein we describe a new route which incorporates, in a key step, the thermal intramolecular cycloaddition of the substituted pyrimidine (2).

RESULTS AND DISCUSSION

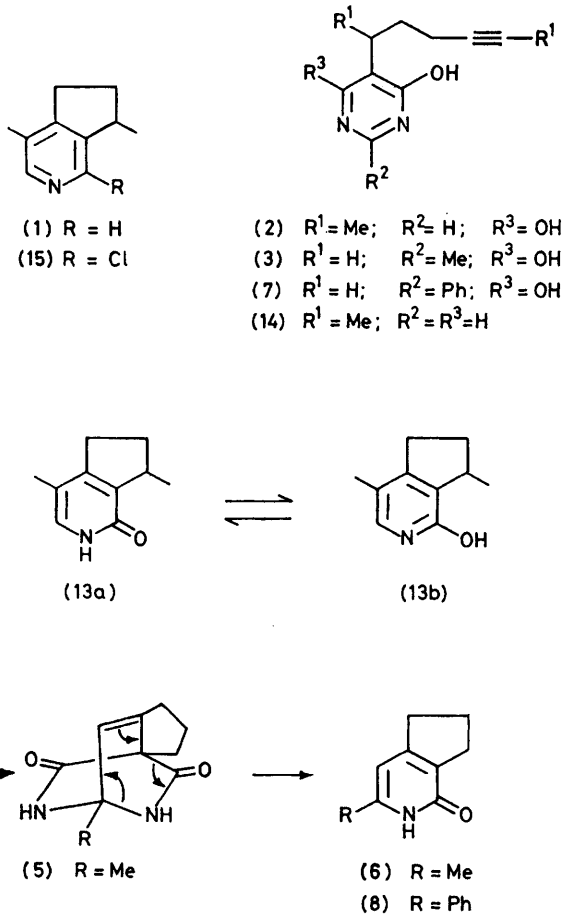
Earlier work had revealed the possibility of intramolecular cycloaddition of olefins across such dihydroxypyrimidines [3] and, in order to extend the scope of these reactions, the addition of the acetylene derivative (3) was attempted.[4] Preparation of the pyrimidine (3) was achieved by reacting the alkylated malonic ester (4) with acetamidine in ethanol under the influence of base; the ester (4) was itself made by alkylation of diethyl malonate with 5-bromopent-1-yne.[5]

Upon thermolysis of the pyrimidine (3) at 200 °C in a sealed tube, using dimethylformamide as solvent, intramolecular cycloaddition occurred leading directly to the known [3] substituted pyridone (6) by rapid loss of one of the amide bridges from the expected intermediate (5), which was too unstable for detection (Scheme 1). By condensation of the malonic ester (4) with benzamidine the phenyl-substituted pyrimidine (7) was produced, thermolysis of which afforded the phenyl-substituted pyridine (8), thus illustrating the generality of this method.

The projected route to (±)-actinidine, through the intermediate pyrimidine (2), depends on availability of the appropriately substituted malonate (9). After attempting several routes the most effective method, outlined in Scheme 2, was adopted. Alkylation of the t-butyl ester of acetoacetic acid with propargyl bromide afforded mainly the monoalkylated derivative (10). When this was heated to 200 °C a smooth decarboalkoxylation occurred to produce the hexynone (11). Application of more classical routes involving ethyl acetoacetate gave much lower yields.

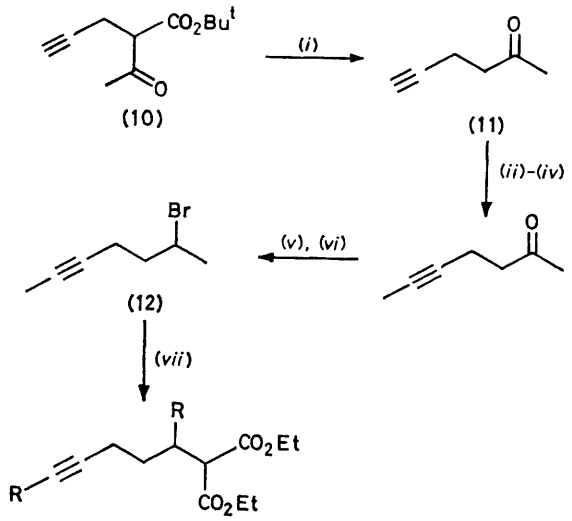
Protection of the ketone group with ethylene glycol, to give the acetal, was followed by alkylation of the acetylene function with methyl iodide using butyl-lithium as base. Use of sodamide as base gave a much lower yield of the required heptyne. Deprotection of the ketone group, followed by its reduction with sodium borohydride to give the corresponding alcohol, and then bromination with carbon tetrabromide–triphenylphosphine,[6] produced the bromide (12). Alkylation of (12) with diethyl malonate afforded the monosubstituted ester (9). Subsequent condensation of the ester (9) with formamidine was more difficult than analogous reactions involving acetamidine; moderate yields of the desired pyrimidine (2) were only obtained using prolonged reaction times in refluxing ethanol.

On heating the acetylenic pyrimidine (2) at its melting point (203 °C) a smooth cycloaddition reaction occurred, rapidly followed by elimination of isocyanic acid to produce the fused pyridone (13). In principle, actinidine



SCHEME 1

could be produced directly by intramolecular cycloaddition across a monohydroxypyrimidine, *e.g.* (14), a process known to produce fused pyridines.[3] However, there is a lack of efficient routes to the appropriately substituted pyrimidines and hence the conversion of 1-hydroxyactinidine, *i.e.* the pyridone (13), into actinidine



SCHEME 2 (*i*) Heat, 200 °C; (*ii*) $HOCH_2CH_2OH$–H^+; (*iii*) BuLi, MeI; (*iv*) H_3O^+; (*v*) $NaBH_4$; (*vi*) Ph_3P, CBr_4; (*vii*) $NaCH(CO_2Et)_2$, EtOH

was pursued. Conversion of the pyridone (13) into the chloropyridine (15) was effected with phosphoryl chloride; reduction, with 10% palladium–charcoal in the presence of alkali, afforded the racemic alkaloid (1).

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus apparatus and are uncorrected. ^{1}H N.m.r. spectra were recorded on a JEOL MH100 or Perkin-Elmer R32 instrument for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal reference. U.v. spectra were recorded, for solutions in ethanol, on a Unicam SP800A spectrometer, i.r. spectra on either a Perkin-Elmer 157G or 297 spectrometer on Nujol mulls, unless otherwise stated, and mass spectra were obtained with A.E.I. MS902 and MS25 instruments. Solvents were purified and, where necessary, dried before use. T.l.c. was carried out on silica gel GF_{254}, and the thermolysis of compounds was generally performed by sealing samples in Pyrex tubes under vacuum and heating in baths of the appropriate refluxing solvents.

Preparation of Substituted Pyrimidines (3) *and* (7).—5-Bromopent-1-yne [5] was prepared from the corresponding alcohol [7] by reaction with phosphorus tribromide in pyridine. Diethyl malonate (5.4 g) and the bromide (4.85 g) were added successively to a solution of sodium (0.77 g) in absolute ethanol (50 ml). The mixture was refluxed for 1 h and allowed to stand at room temperature for a further 18 h. The solvent was evaporated, water (30 ml) added to the residue, and the product extracted with ether (3 × 25 ml). The extracts were combined, dried ($MgSO_4$), and evaporated to yield diethyl 2-(pent-4-ynyl)malonate (4) (3.9 g, 52%); $\nu_{max.}$ 2 930, 2 878, 2 118, 1 720, 1 626, 1 440, 1 364, 1 092, 1 024, and 852 cm^{-1}; δ 4.17 (4 H, q, *J* 7 Hz), 3.34 (1 H, t, *J* 6.5 Hz), 2.60—1.48 (7 H, m), and 1.24 (6 H, t, *J* 7 Hz).

The ester (4) (2.85 g) and acetamidine hydrochloride (1.18 g) were added to a solution of sodium (0.86 g) in ethanol (50 ml), the mixture refluxed for 18 h, cooled, evaporated, and the residue taken up in water (50 ml). The solution was neutralised with concentrated HCl to pH 7. Upon cooling a white precipitate formed which was collected, washed, and dried to afford 4-*hydroxy*-2-*methyl*-5-(*pent*-4-*ynyl*)*pyrimidin*-6(1H)-*one* (3) (0.80 g, 33%), sublimed with decomp. at 200 °C; $\nu_{max.}$ 2 610, 2 115, 1 628, 1 560, 1 238, 1 208, and 1 153 cm^{-1}; δ (trifluoroacetic acid) 2.86 (3 H, s) and 2.40—1.80 (7 H, m); $\lambda_{max.}$ 248 (ε 4 600) and 263 nm (6 550) (Found: M^+, 192.0904; $C_{10}H_{12}N_2O_2$ requires *M*, 192.0899).

Benzamidine hydrochloride (2.77 g) and the ester (4) (4.0 g) were successively added to a solution of sodium (0.82 g) in ethanol (30 ml) and the mixture refluxed for 6 h, cooled, and the solvent distilled off. The residue was dissolved in water (50 ml), neutralised to pH 7 with concentrated HCl, and the precipitate collected, washed, and dried to give 4-*hydroxy*-5-(*pent*-4-*ynyl*)-2-*phenylpyrimidine*-6(1H)-*one* (7) as a pale yellow solid (1.6 g, 36%), m.p. 220 °C (with sublimation and decomposition); $\nu_{max.}$ 2 640, 2 116, 1 612, 1 582, 1 374, 1 176, and 1 110 cm^{-1}; $\lambda_{max.}$ 232 (ε 25 000) and 306 nm (9 800); δ (trifluoroacetic acid) 7.92—7.15 (5 H, m) and 2.50—1.10 (6 H, m) (Found: M^+, 254.1047; $C_{15}H_{14}N_2O_2$ requires *M*, 254.1055).

Thermolysis of the Pyrimidines (3) *and* (7).—The methylpyrimidine (3) (0.15 g) was heated in dimethylformamide (5 ml) at 200 °C in a sealed tube for 6 h. Removal of the solvent left a crystalline mass which, after treatment with charcoal in ethyl acetate, afforded 4-methyl-3-azabicyclo-[4.3.0]nona-1(6),4-dien-2-one (6) (72 mg, 46%), m.p. (EtOAc) 160—161 °C, identical in all respects to an authentic sample.[3] In a similar manner the phenyl-substituted derivative (7) (0.11 g) was heated in dimethylformamide (5 ml) at 200 °C for 18 h. Work-up gave 4-phenyl-3-azabicyclo[4.3.0]nona-1(6),4-dien-2-one (8) (42 mg, 40%), m.p. (EtOAc) 210—211 °C, identical in all respects to an authentic sample.[3]

Preparation of Hex-5-*yn*-2-*one* (11).—To a stirred solution of sodium ethoxide [from sodium (4.6 g) in ethanol (85 ml)] was added, dropwise over 30 min at 0 °C, t-butyl acetoacetate (31.6 g), followed by propargyl bromide (23.7 g in toluene 6 g) in ether (30 ml) over a further 30 min. The temperature was allowed to rise to ambient overnight with stirring. The mixture was filtered, the solid washed with absolute ethanol, and the combined filtrates evaporated to small bulk before adding water and extraction with ether. The organic layer was washed with brine, dried (K_2CO_3), evaporated, and the residue distilled under reduced pressure to give t-butyl propargylacetoacetate (10) (31 g, 77%) (contaminated with a little of the dialkylated material), boiling range 110—132 °C/17 mmHg; $\nu_{max.}$ 3 290, 2 120, 1 740, and 1 720 cm^{-1}.

Heating the ester (10) (44 g), under nitrogen, for 18 h at 200 °C caused decarboalkoxylation. The residue (14.7 g, 69%) was distilled on a spinning-band column to afford, as a colourless liquid, hex-5-yn-2-one (11), b.p. 150—154 °C/760 mmHg; 50—50.5 °C/16 mmHg (lit.,[8] b.p. 50—60 °C/15 mmHg), $n_D^{19.5}$ 1.4376 (lit.,[8] n_D^{25} 1.4315—1.4339); $\nu_{max.}$ ($CHCl_3$) 3 315, 2 120, and 1 720 cm^{-1} (Found: C, 74.5; H, 8.6. Calc. for C_6H_8O: C, 74.95; H, 8.4%).

Preparation of 2-*Bromo-hept-5-yne* (12).—Hex-5-yn-2-one (11) was converted into its ethylene acetal (74%) [8] with ethylene glycol in benzene under the influence of a catalytic amount of toluene-*p*-sulphonic acid. The acetal, b.p. 71—72 °C/15 mmHg (lit.,[8] 72—80 °C/17 mmHg) (15.1 g) in dry tetrahydrofuran (130 ml) at 0 °C was sequentially treated with a hexane solution of n-butyl-lithium (1.5M, 75 ml) and methyl iodide (19.3 g, excess) in tetrahydrofuran (10 ml). The mixture was stirred for 1 h at 0 °C and then for 18 h at room temperature. Saturated ammonium chloride solution (10 ml) and water (20 ml) were added, the aqueous layer was separated and extracted with ether, and the combined organic layers washed with brine, dried ($MgSO_4$), and filtered. After evaporation of solvent the residue was distilled to produce the heptyne acetal, b.p. 83.5—86 °C/8 mmHg (lit.,[8] 93—94 °C/17 mmHg). The acetal (57 g) was deprotected by stirring vigorously overnight with ether (200 ml) and 2M hydrochloric acid (200 ml). The aqueous layer was separated and re-extracted with ether and the combined ether layers washed with a small amount of sodium hydrogencarbonate solution, dried ($MgSO_4$), filtered, and distilled to give hept-5-yn-2-one (67% from the hexynone), b.p. 57.59 °C/7.5 mmHg (lit.,[8] 67—70 °C/19 mmHg). The ketone was reduced with ethanolic sodium borohydride to produce *hept-5-yn-2-ol* (82%), b.p. 69.5—70 °C/8 mmHg, n_D^{22} 1.4555 (Found: C, 75.1; H, 10.7. $C_7H_{12}O$ requires C, 75.0; H, 10.7%).

To a stirred ice-cold solution of freshly distilled hept-5-yn-2-ol (27.3 g) in dichloromethane (350 ml) was added carbon tetrabromide (102 g) followed, in portions over 30 min, by freshly powdered triphenylphosphine (97 g).[6] The mixture was stirred whilst being allowed to attain room temperature overnight. The mixture was evaporated almost to dryness under reduced pressure, ether (200 ml) was added, and the solution was filtered, the solid residue being washed with more ether (2 × 100 ml). The filtrate was evaporated to give a pale yellow liquid which was vacuum-distilled on a spinning-band column to give the title bromide (34 g, 64%), b.p. 56—59 °C/7.5 mmHg.

Preparation of 5-(*Hept-5-yn-2-yl*)-4,6-*dihydroxypyrimidine* (2).—Malonic ester (46.9 g) was added dropwise to a stirred suspension of sodium hydride (60% w/w dispersion in oil; 10.0 g) in freshly distilled tetrahydrofuran (120 ml). After hydrogen evolution ceased, hept-5-yn-2-yl bromide (30.0 g) in dimethylformamide (100 ml) was added and the mixture refluxed for 22 h; after cooling, water (200 ml) was added and the mixture extracted several times with dichloromethane (total volume, 450 ml). The organic extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and filtered. Evaporation and distillation afforded *diethyl* 2-(*hept-5-yn-2-yl*)*malonate* (9) (21 g, 61%), b.p. 135—138 °C/0.15 mmHg, n_D^{22} 1.4534; $\nu_{max.}$ 1 730—1 760 cm^{-1} (Found: C, 65.95; H, 8.6. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.8%).

Formamidinium acetate (2.5 g) was added to a stirred ice-cooled solution of sodium ethoxide [from sodium (1.38 g) in ethanol (40 ml)]. After 20 min the filtered solution was added to heptynylmalonate (9) (5.15 g) in dry ethanol (10 ml) and the solution refluxed for 20 h. The mixture was evaporated to dryness, the residue dissolved in water (10 ml), and concentrated hydrochloric acid (*ca.* 2.5 ml) added until the pH was below 6 to produce a white precipitate. Water (10 ml) was added and the pH adjusted to 6 by the careful addition of a saturated sodium hydrogencarbonate solution. The solid was collected, washed with water, and dried to give the title *pyrimidine* (2) (4.0 g, 96%). A sample, crystallised from ethanol–dimethylformamide (4 : 1), showed m.p. 210 °C (decomp.); $\nu_{max.}$ 1 635 and 1 570 cm^{-1}; $\lambda_{max.}$ (EtOH) 246 and 263 nm; δ ([$^2H_6$]DMSO) 1.15 (3 H, d, *J* 7 Hz), 1.7 (3 H, t, *J* 2 Hz), 1.8—2.2 (4 H, m), 2.0—3.2 (1 H, m), 7.9 (1 H, s), *ca.* 5.9 (2 H, br, NH and OH); *m/e* 206 (M^+), 191, 163, and 148 (Found: C, 64.25; H, 6.75; N, 13.35. $C_{11}H_{14}N_2O_2$ requires C, 64.0; H, 6.8; N, 13.6%).

Preparation of 5,9-*Dimethyl*-3-*azabicyclo*[4.3.0]*nona*-1(6),-6-*dien*-2-*one* (13).—The heptynylpyrimidine (2) was heated in a sublimation apparatus to 200 °C. Vigorous gas evolution occurred, and a condensate formed on the upper part of the apparatus. The residual brown liquid was heated for a further few minutes after gas evolution ceased (total heating time being *ca.* 10 min at 200 °C) and then cooled, when it solidified. The solid residue was sublimed *in vacuo* at 150—169 °C/0.1 mmHg to afford the crystalline *pyridone* (13) (87%), m.p. 180—183 °C; $\nu_{max.}$ 1 660, 1 625, and 1 550 cm^{-1}, $\lambda_{max.}$ 236 and 302 nm; δ ([$^2H_6$]DMSO) 1.25 (3 H, d, *J* 7 Hz), 2.0 (3 H, br s), 1.4—3.4 (5 H, m), *ca.* 3.8 (1 H, br, N*H*), and 7.0 (1 H, s) (Found: C, 72.35; H, 7.75; N, 8.2. $C_{10}H_{13}NO$ requires C, 73.6; H, 8.0; N, 8.6%).

Preparation of (±)-*Actinidine* (1).—The pyridone (13) (1.2 g) and phosphoryl chloride (5 ml) were heated in a sealed tube at 195 °C for 3.5 h. After cooling and opening the tube the excess of phosphoryl chloride was removed by vacuum distillation and ice added, followed by solid K_2CO_3, followed by dichloromethane. The resulting mixture was filtered through Celite and the aqueous layer re-extracted with more dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed through silica gel, eluting with dichloromethane, then ethyl acetate–dichloromethane (1 : 4) to give the *chloropyridine* (15), b.p. 120 °C/0.12 mmHg, as a colourless liquid (0.5 g, 39%); $\nu_{max.}$ (film) 1 730, 1 580, 1 430, 1 380, and 1 170 cm^{-1}; $\lambda_{max.}$ 225, 268, and 275 nm; δ 1.25 (3 H, d, *J* 7 Hz), 2.2 (3 H, s), 0.8—4.3 (5 H, m), and 7.97 (1 H, s); *m/e* 163 (M^+) and 148 (Found: C, 66.65; H, 7.05; N, 8.05. $C_{10}H_{12}NCl$ requires C, 66.1; H, 6.6; N, 7.7%).

Reduction of the chloropyridine (15) (0.4 g) was achieved by hydrogenation in a Parr bomb over 10% palladium–charcoal (0.2 g) in methanol (50 ml) containing 1M methanolic potassium hydroxide (2 ml) at 18 atm over 80 h. The mixture was filtered through Celite, washed with MeOH, and the filtrate acidified with dilute HCl, then basified with NH_4OH, evaporated under reduced pressure (in the cold, product volatile), and the residue extracted into dichloromethane and washed with brine. After drying and concentrating the organic extract was chromatographed through silica gel to remove traces of the starting chloropyridine. The product was eluted with dichloromethane–ethyl acetate mixture to afford (±)-actinidine (1) as an oil (0.1 g, 34%), b.p. 105—116 °C/11.5 mmHg (lit.,[2a] 100—103 °C/9 mmHg); $\nu_{max.}$ (film) 1 590 cm^{-1} (lit.,[2b] 1 587 cm^{-1}); $\lambda_{max.}$ (EtOH) 262 (ε 1 800) and 270 nm (1 600) [lit.,[2e] 261.5 (2 620) and 269.5 nm (2 420)]; δ 1.3 (3 H, d, *J* 7 Hz), 2.25 (3 H, s), 0.8—3.5 (5 H, m), 8.2 (1 H, s), and 8.3 (1 H, s); *m/e* 147 (54%, M^+), 146 (35%), 132 (100%), and 117 (18%) (Found: M^+, 147.104 74. $C_{10}H_{13}N$ requires *M*, 147.104 79).

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