Benzocarbacephems from quinolines

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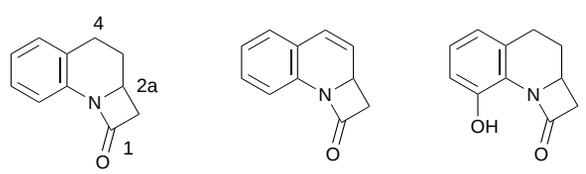
The azetidinones 1, 2 and 3 have been prepared from simple quinoline derivatives. 2,2a,3,4-Tetrahydro-1*H*-azeto[1,2-*a*]quinolin-1-one 1 has been synthesised from quinoline *N*-oxide and, more efficiently, in three steps from 2-methylquinoline. In both routes 1,2,3,4-tetrahydroquinoline-2-acetic acid 7 is prepared as an intermediate and this is then cyclised to the azetidinone 1. The 8-hydroxyazetidinone 3 has been synthesised by analogous routes, the hydroxy group being protected as an isopropyl ether during the intermediate steps. An X-ray crystal structure of compound 3 has been obtained and this reveals intramolecular hydrogen bonding between the hydroxy and carbonyl groups. The unsaturated azetidinone 2 has been prepared from 1 by stereoselective radical bromination at C-4 followed by dehydrobromination with DBU.

In the preceding paper we described the preparation of several benzocarbapenems from indoles.[1] The compounds, especially those unsubstituted in the four-membered ring, were susceptible to nucleophilic attack and unstable at room temperature. In the expectation that analogous compounds with a fused six-membered ring would be much less strained we have investigated routes to the tetrahydroazeto[1,2-*a*]quinolin-1-one (benzocarbacephem) ring system from quinolines and describe the results in this paper.

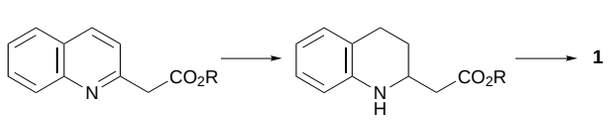
The parent compound **1** was recently reported by Schwenninger and Ongania.[2] They used an intramolecular Wittig reaction to construct the six-membered ring from an appropriately substituted β-lactam. This gave the unsaturated compound **2** from which **1** was obtained by reduction. Both **1** and **2** were



1 **2** **3**

obtained as crystalline solids, although compound **2**, which is formally an adduct of ketene and quinoline, is sensitive to light and to acids. Derivatives of the ring system **1** have been prepared from monocyclic β-lactams by other methods, including radical cyclisation[3] and intramolecular aromatic substitution[4] reactions. The four-membered ring has been constructed by intramolecular rhodium(II) catalysed carbenoid C–H bond insertion.[5] The only other derivative of the unsaturated ring system **2** was reported by Hegedus *et al.* as a product of the reaction of quinoline with the chromium carbene complex $(CO)_5CrC(OMe)Me$.[6]

We set out to establish a route to compound **1** from quinoline-2-acetic acid, as outlined in Scheme 1, and then to extend



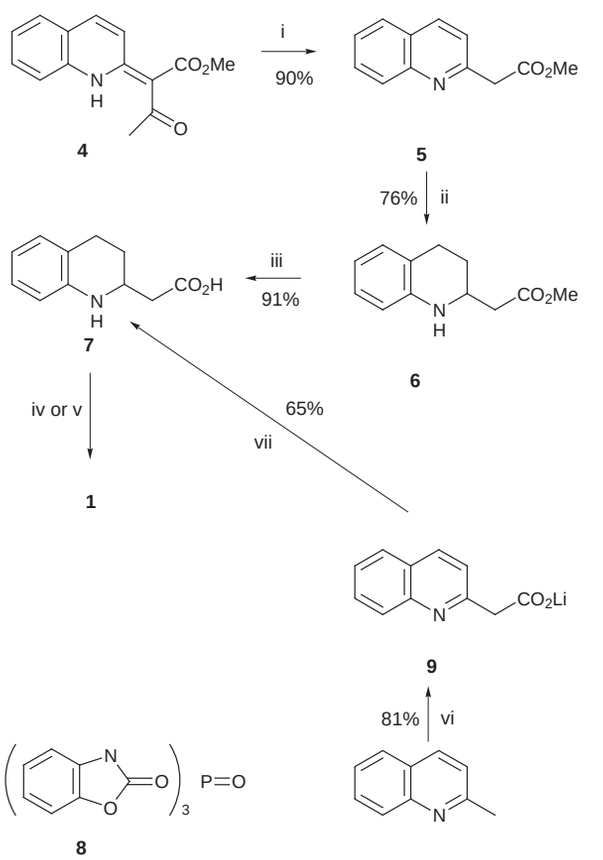
Scheme 1

it to the synthesis of the phenol **3**. As discussed in the preceding paper, the 8-hydroxy function is intended to provide a mimic of the carboxy function in biologically active β-lactams. This requires a method of preparation of quinoline-2-acetic acid or of one of its esters that can readily be applied to the corresponding 8-hydroxyquinoline. Previous routes to quinoline-2-acetic acid derivatives have used quinoline *N*-oxide,[7] 2-methylquinoline[8] and 2-chloromethylquinoline[8] as starting materials. Methyl 1,2,3,4-tetrahydroquinoline-2-acetate has been prepared by extension of the side chain of methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate; both enantiomers of the ester were also separately synthesised by this method from homochiral starting materials.[9] We have used both quinoline *N*-oxides and 2-methylquinolines as precursors to quinoline-2-acetic acid derivatives. A short and efficient route to the azetidinone **1** has been devised that starts from 2-methylquinoline and this has been extended to provide a synthesis of the phenol **3**.

Synthesis of the azetidinone 1

The routes used to prepare this compound are illustrated in Scheme 2. The quinolinylidene ester **4** was prepared in 42% yield from quinoline *N*-oxide and methyl acetoacetate by the literature procedure,[7] and this was cleaved by HCl to give methyl quinoline-2-acetate **5**. The heterocyclic ring was selectively reduced by catalytic hydrogenation over platinum[8,10] and the tetrahydroquinoline ester **6** was hydrolysed to the corresponding acid **7**. The acid was then cyclised to the azetidinone **1** in moderate yield by tris(2-oxobenzoxazol-3-yl)phosphine oxide **8**, a cyclising agent that had been used successfully in the indole series.[1] After attempting the cyclisation with several other reagents we found that methanesulfonyl chloride, when used under the conditions described by Loewe *et al.*,[11] proved to be a better cyclising agent for this acid; it was simpler to use and the yield of the azetidinone **1** was higher.

A more direct route to the ester **5** from 2-methylquinoline was investigated. 2-Methylquinoline was deprotonated with LDA and the anion was acylated with methyl chloroformate and with dimethyl carbonate. As Jones and Wood had reported earlier,[8] this procedure proved to be unsatisfactory because of unidentified side reactions. When carbon dioxide was used as the electrophile, however, the lithium salt **9** was isolated cleanly and in good yield. Attempts to reduce the lithium salt by hydrogenation over platinum gave unsatisfactory results. The reduction, which had to be carried out in water or in aqueous methanol, was extremely slow and 2-methylquinoline (formed by decarboxylation of quinoline-2-acetic acid *in situ*) was observed as a significant side product. These difficulties were overcome by reduction over Raney nickel. The strongly basic conditions of the reaction prevented the formation of quinoline-2-acetic acid and hence of 2-methylquinoline, and



Scheme 2 *Reagents:* i, aq. HCl; ii, H_2, PtO_2; iii, aq. KOH then citric acid; iv, **8**, Et_3N (44%); v, $MeSO_2Cl$, $NaHCO_3$ (77%); vi, LDA then CO_2; vii, Ni–Al, KOH then acetic acid

the β-amino acid **7** was isolated in 65% yield from the lithium salt **9**. This reaction sequence thus provides a three step synthesis of the azetidinone **1** in 40% overall yield from 2-methylquinoline.

Synthesis of the azetidinone 3

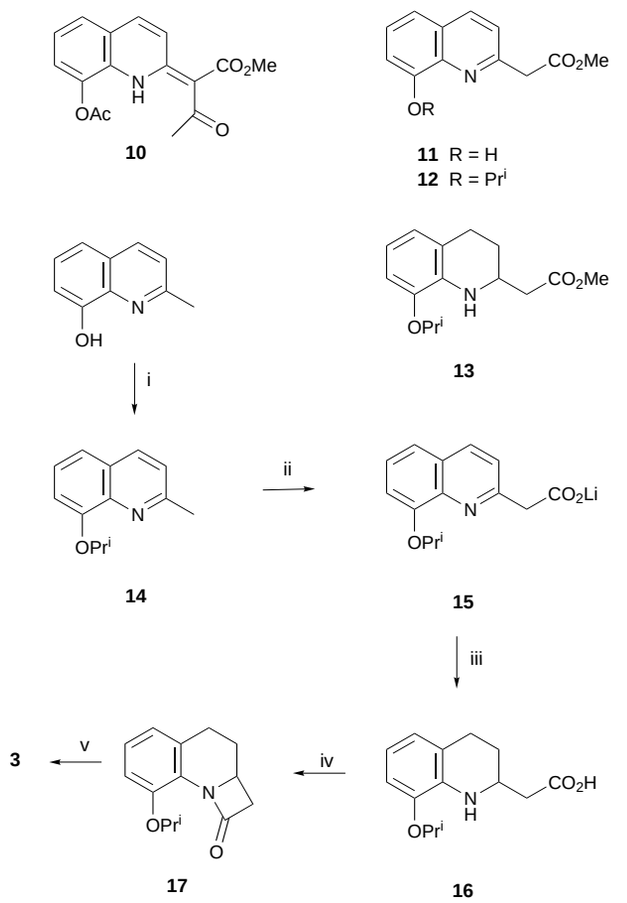
We first investigated a route to the azetidinone **3** starting from the commercially available 8-hydroxyquinoline *N*-oxide. The reaction sequence is analogous to that shown in Scheme 2 from quinoline *N*-oxide. Reaction with methyl acetoacetate and acetic anhydride gave the 8-acetoxyquinolinylidene ester **10** in 53% yield. This was hydrolysed to methyl 8-hydroxyquinoline-2-acetate **11** (62%). The 8-hydroxy function was protected (56%) by reaction with 2-bromopropane and the resulting 8-isopropoxy ester **12** was hydrogenated to the tetrahydroquinoline ester **13** (95%). Although this was taken on to the azetidinone **3** on a small scale, a better procedure, based on 8-hydroxy-2-methylquinoline, was developed and is illustrated in Scheme 3. 8-Hydroxy-2-methylquinoline is also commercially available and relatively inexpensive. The reaction sequence is analogous to that starting from 2-methylquinoline in Scheme 2, with two additional steps for protection and deprotection of the 8-hydroxy function. The azetidinones **17** and **3** were both isolated as stable crystalline solids.

An X-ray crystal structure of the azetidinone **3** was obtained (Fig. 1) in order to compare it with an analogous compound **18** for which a crystal structure was available.[1] Selected bond lengths and bond angles are listed in Table 1.† The most important difference between the two structures is that the crystal of compound **3** shows the presence of an internal hydrogen bond between the hydroxy group and carbonyl functions whereas that of compound **18** does not. Hydrogen bonding is also revealed by the unusually low IR carbonyl stretching frequency of 1701 cm^{-1} (in comparison, the carbonyl stretching frequency of its precursor **17** is at 1761 cm^{-1}).

Table 1 Selected bond lengths and bond angles for **3**[a]

Bond lengths (Å)		Bond angles (°)	
N1–C7	1.479(4)	C7–N1–C11	94.7(3)
N1–C6	1.412(4)	N1–C11–C10	92.5(3)
N1–C11	1.354(4)	C7–C10–C11	85.9(3)
C1–C6	1.388(4)	N1–C7–C10	86.9(3)
C7–C10	1.540(5)	N1–C6–C1	121.1(3)
C10–C11	1.518(5)	H10–C10–H11	108.62
O1–C1	1.372(4)	O1–C1–C6	123.0(3)
O2–C11	1.221(4)	N1–C11–O2	130.3(3)

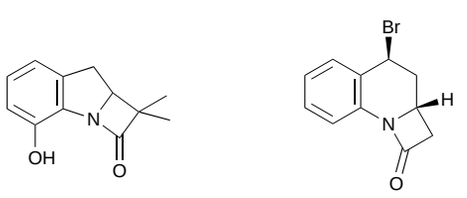
[a] Atom numbering corresponds to that in Fig. 1.



Scheme 3 *Reagents:* i, Pr^iBr, K_2CO_3; ii, LDA then CO_2; iii, Ni–Al, KOH then citric acid; iv, $MeSO_2Cl$, $NaHCO_3$; v, $TiCl_4$

Synthesis of the azetidinone 2

The unsaturated azetidinone **2** was prepared from compound **1** in two steps. The bromoazetidinone **19** was produced cleanly and in good yield by radical bromination using *N*-bromo-



† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http//www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/195.

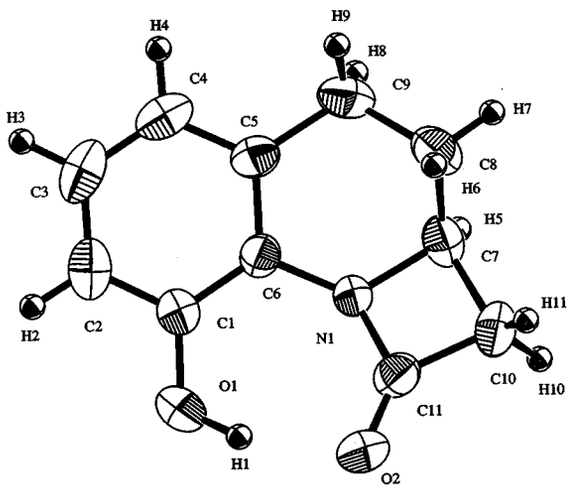


Fig. 1 Crystal structure of the azetidinone **3**

succinimide. The (2a*S*,4*S*)-stereochemistry of **19** was established from the coupling constants in the NMR spectrum and from a COSY spectrum. If the six membered ring in **19** adopts a half chair conformation the bromine atom and the bridgehead hydrogen (2a-H) lie in axial positions; the observed coupling constants are then consistent with this structure. This isomer is the one that would result from the attack of bromine on the less hindered *exo* face of the azetidinone **1**. The bromoazetidinone **19** was then cleanly dehydrobrominated to give **2** by reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) below room temperature. A similar low temperature dehydrobromination, but using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), has been carried out on a chrysene derivative.[12] An attempt to carry out a similar reaction sequence on the azetidinone **17** was unsuccessful because the bromination did not proceed cleanly. This may be because of competitive radical bromination of the isopropyl group, and we are planning to carry out the synthesis with a different protecting group on oxygen.

Azetidinones such as **2** are potentially useful because a range of further transformations could be carried out on the double bond. Since they are formally adducts of quinoline and ketenes, we briefly investigated the reaction of several ketenes, generated *in situ*, with quinoline, but obtained no evidence for the formation of azetidinones. The addition of a chromium carbene complex, as reported by Hegedus *et al.*,[6] remains the only successful reaction of this type.

Experimental

General

^{1}H NMR spectra were recorded on Bruker AC 200 (200 MHz) or Varian Gemini 2000 (300 MHz) spectrometers. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). *J* Values are in Hz. Infrared spectra were recorded either on a Perkin-Elmer 298 or on a Perkin-Elmer 1720-X FTIR spectrometer. Solid samples were run as Nujol mulls, and liquids as thin films. Mass spectra were recorded on a VG Micromass 7070E machine as electron impact spectra (70 eV). Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. Melting points (mp) were determined on a Kofler block and are uncorrected. Flash chromatography was carried out using Kieselgel 60 and water-pump vacuum. Thin layer chromatography (TLC) was carried out on Merck 10 × 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 F_{254}. Light petroleum refers to the fraction bp 60–80 °C and ether refers to diethyl ether.

Methyl 2-(1,2-dihydroquinolin-2-ylidene)-3-oxobutanoate 4

Methyl acetoacetate (4.99 g, 0.043 mol) was added in portions to a solution of quinoline *N*-oxide hydrate (4.96 g, 0.034 mol) in acetic anhydride (22 cm^3) at 40 °C. The reaction mixture was stirred at 40 °C for 9 h then poured into ice–water. The yellow precipitate was filtered off, washed with water and recrystallised to give the ester (3.50 g, 42%), mp 103–104 °C (from methanol) (lit.,[7] 119.5–120.5 °C) (Found: C, 69.3; H, 5.4; N, 5.75. Calc. for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.4; N, 5.8%); ν_{max}(Nujol)/cm^{-1} 3394, 1693 and 1632; δ_H(200 MHz; $CDCl_3$) 2.43 (3 H, s), 3.83 (3 H, s), 7.31–7.39 (1 H, m), 7.51–7.64 (3 H, m), 7.87 (1 H, d, *J* 9.3) and 7.93 (1 H, d, *J* 9.3); *m*/*z* 243 (M$^+$, 71%) and 169 (100).

Methyl quinoline-2-acetate 5

The ester **4** (1.46 g, 6.00 mmol) was added slowly with stirring to 10% aq. HCl (10 cm^3). After 10 min the solution was basified to pH 9 with aq. sodium carbonate then extracted with dichloromethane. Flash chromatography gave (with ether) the ester **5** (1.08 g, 90%) as an orange oil; ν_{max}(film)/cm^{-1} 1736; δ_H(200 MHz; $CDCl_3$) 3.71 (3 H, s), 4.04 (2 H, s), 7.40 (1 H, d, *J* 8.2, 3-H), 7.46–7.53 (1 H, m), 7.63–7.80 (2 H, m), 8.04 (1 H, d, *J* 8.2) and 8.10 (1 H, d, *J* 8.2, 4-H); *m*/*z* 201 (M$^+$, 26%) and 143 (100).

Methyl 1,2,3,4-tetrahydroquinoline-2-acetate 6

The ester **5** (1.08 g, 5.37 mmol) in methanol (10 cm^3) and platinum(IV) oxide (50 mg) were stirred under hydrogen at 1 atm for 3 h. The mixture was then filtered through kieselguhr and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give (with ethyl acetate) the *ester* **6** (0.84 g, 76%) as a yellow oil (Found: C, 70.0; H, 7.3; N, 7.0. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); ν_{max}(film)/cm^{-1} 1731; δ_H(200 MHz; $CDCl_3$) 1.60–1.80 (1 H, m), 1.89–2.08 (1 H, m), 2.49 (2 H, d, *J* 6.0), 2.54–2.81 (2 H, m), 4.44 (1 H, br s), 6.45–6.62 (2 H, m) and 6.85–7.21 (2 H, m); *m*/*z* 205 (M$^+$, 26%) and 132 (100).

1,2,3,4-Tetrahydroquinoline-2-acetic acid 7

(a) By hydrolysis of the ester 6. To the ester **6** (0.84 g, 4.10 mmol) in methanol (1 cm^3) was added aqueous potassium hydroxide (0.86 g) dissolved in the minimum amount of water; the resulting emulsion was stirred for 12 h. The methanol was distilled off and the residue diluted with water and washed with ethyl acetate. The aqueous solution was then acidified to pH 2 by the addition of 10% aq. citric acid. Extraction with ethyl acetate gave the acid **7** (0.71 g, 91%) as a brown amorphous solid (Found: M$^+$, 191.095. $C_{11}H_{13}NO_2$ requires *M*, 191.095). The amino acid was characterised as its *hydrochloride* by bubbling hydrogen chloride gas through a solution of the acid in ethyl acetate at 0 °C, mp 134–135 °C (from methanol–ether) (Found: C, 58.0; H, 6.2; N, 6.1. $C_{11}H_{14}ClNO_2$ requires C, 58.0; H, 6.2; N. 6.2%) ν_{max}(Nujol)/cm^{-1} 1734.

(b) By reduction of the lithium salt 9. Aqueous potassium hydroxide (1 M, 100 cm^3) was added to a solution of the salt **9** (1.00 g, 5.18 mmol) in methanol (100 cm^3). Nickel–aluminium alloy (4.0 g) was added in portions over 4 h. The mixture was stirred for 18 h and then filtered through kieselguhr. The filtrate was acidified to pH 9 with acetic acid and the solution then reduced *in vacuo* to approx. 10 cm^3. The pH was adjusted to 6 and the amino acid **7** (0.64 g, 65%) was precipitated.

2,2a,3,4-Tetrahydro-1*H*-azeto[1,2-*a*]quinolin-1-one 1

(a) Phosphine oxide method. The amino acid **7** (0.20 g, 1.05 mmol), tris(2-oxobenzoxazolin-3-yl)phosphine oxide **8** (0.47 g, 1.05 mmol) and triethylamine (0.51 cm^3, 3.6 mmol) in acetonitrile (100 cm^3) were stirred under reflux for 6 h. The solvent was then removed *in vacuo* and the resulting crude product purified by flash chromatography [dichloromethane–hexane (1 : 1)] to yield the azetidinone (0.08 g, 44%) as a colourless crystalline solid, mp 97–98 °C (after sublimation) (lit.,[2] 107 °C) (Found: C, 76.3; H, 6.4; N, 8.1. Calc. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4, N, 8.1%); ν_{max}(Nujol)/cm^{-1} 1749; δ_H(200 MHz; $CDCl_3$) 1.57 (1 H, m, 3-H), 2.31 (1 H, dq, *J* 12.6 and 3.8, 3-H), 2.81 (1 H, dd, *J* 15.4 and 2.7, 2-H), 2.83–2.89 (2 H, m, 4-H),

3.29 (1 H, dd, *J* 15.4 and 4.9, 2-H), 3.73–3.84 (1 H, m, 2a-H), 6.95–7.03 (1 H, m), 7.11–7.26 (2 H, m) and 7.47 (1 H, d, *J* 8.2); *m*/*z* 173 (M^+, 22%) and 130 (100).

(b) Methanesulfonyl chloride method. To a stirred suspension of sodium hydrogen carbonate (2.16 g, 25.7 mmol) in dry acetonitrile (20 cm^3) was added methanesulfonyl chloride (0.33 cm^3, 4.29 mmol). The mixture was stirred under N_2 at 60 °C and a solution of the amino acid **7** (0.82 g, 4.29 mmol) in dry acetonitrile (20 cm^3) was added. The mixture was stirred at RT for 2 h, then it was cooled to 0 °C and filtered. The filtrate was evaporated to dryness and the residue was subjected to flash chromatography which gave [with ether–hexane (1 : 1)] the azetidinone **1** (0.57 g, 77%).

Quinoline-2-acetic acid lithium salt 9

LDA was prepared from diisopropylamine (10.60 cm^3, 75.8 mmol) and butyllithium (1.6 M, 44.7 cm^3, 71.6 mmol) in ether (20 cm^3) at −60 °C under N_2. 2-Methylquinoline (5.00 g, 34.9 mmol) in ether (20 cm^3) was added and the mixture was stirred for 10 min at −60 °C. It was poured on to a suspension of solid carbon dioxide in dry ether. This was then allowed to evaporate and the residual solid was then washed with ether and dried *in vacuo* to yield the lithium salt **9** (5.43 g, 81%); δ_H(300 MHz; D_2O) 3.91 (2 H, s), 7.51 (1 H, d, *J* 8.4, 3-H), 7.64 (1 H, approx. t, *J* 7.5), 7.82 (1 H, dt, *J* 1.2 and 7.5), 7.99 (2 H, approx. t, *J* 7.5) and 8.34 (1 H, d, *J* 8.4, 4-H).

Methyl 2-(8-acetoxy-1,2-dihydroquinolin-2-ylidene)-3-oxobutanoate 10

8-Hydroxyquinoline 1-oxide (5.00 g, 31.0 mmol) was dissolved in acetic anhydride at 40 °C and methyl acetoacetate (4.50 g, 38.8 mmol) was added. After 36 h the reaction mixture was then poured into ice–water. The yellow precipitate was filtered off, washed with water and recrystallised to give the *ester* **10** (4.95 g, 53%), mp 103–104 °C (from dichloromethane–hexane) (Found: C, 63.8; H, 5.1; N, 4.6. $C_{16}H_{15}NO_5$ requires C, 63.8; H, 5.0; N, 4.65%); ν_{max}(Nujol)/cm^{-1} 3400, 1765, 1678 and 1637; δ_H(200 MHz; $CDCl_3$) 1.56 (1 H, s), 2.47 (3 H, s), 2.62 (3 H, s), 3.86 (3 H, s) and 7.33–8.00 (5 H, m); *m*/*z* 301 (M^+, 47%) and 185 (99).

Methyl 8-hydroxyquinoline-2-acetate 11

A solution of the ester **10** (0.20 g, 0.67 mmol) in 10% aq. HCl (15 cm^3) was stirred for 3 h. It was then neutralised with aq. sodium hydrogen carbonate. Extraction with dichloromethane gave the ester (0.09 g, 62%) as a viscous orange oil; ν_{max}(film)/cm^{-1} 3403 and 1735; δ_H(200 MHz; $CDCl_3$) 3.70 (3 H, s), 3.98 (2 H, s), 7.12–7.44 (4 H, m) and 8.04 (1 H, d, *J* 8.2); *m*/*z* 217 (M^+, 100%) and 157 (96).

Methyl 8-isopropoxyquinoline-2-acetate 12

The ester **11** (3.01 g, 13.8 mmol) and potassium carbonate (3.44 g, 24.9 mmol) in dry DMF (100 cm^3) were heated and stirred under N_2 at 80 °C for 5 min and 2-bromopropane (2.60 cm^3, 27.7 mmol) was added. The mixture was then stirred for a further 2 h. It was poured into water and extracted with dichloromethane. The organic solution was washed with 5% aq. KOH (100 cm^3) and then with water, dried and evaporated. Flash chromatography gave [with hexane–ether (4 : 1)] the *ester* **12** (2.17 g, 60%) as an oil (Found: C, 69.2; H, 6.6; N, 5.4. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); ν_{max}(film)/cm^{-1} 1739; δ_H(200 MHz; $CDCl_3$) 1.47 (6 H, approx. t, *J* 6.0), 3.73 (3 H, s), 4.11 (2 H, s), 4.75–4.86 (1 H, m), 7.05–7.41 (4 H, m) and 8.06 (1 H, d, *J* 8.3); *m*/*z* 259 (M^+, 8%) and 157 (95).

Methyl 8-isopropoxy-1,2,3,4-tetrahydroquinoline-2-acetate 13

A solution of the ester **12** (0.57 g, 2.20 mmol) in methanol (10 cm^3) was hydrogenated over platinum(IV) oxide. The crude product was purified by flash chromatography which gave [with ether–hexane (1 : 1)] the *ester* **13** as a yellow oil (0.55 g, 95%) (Found: C, 68.2; H, 8.1; N, 5.4. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.0; N, 5.3%); ν_{max}(film)/cm^{-1} 3404 and 1735; δ_H(200 MHz; $CDCl_3$) 1.39 (6 H, dd, *J* 1.6 and 6.0), 1.68–1.86 (1 H, m), 1.95–2.09 (1 H, m), 2.59 (2 H, d, *J* 5.5), 2.70–2.95 (2 H, m), 3.76 (3 H, s), 4.47–4.59 (1 H, m), 4.88 (1 H, s) and 6.56–6.71 (3 H, m); *m*/*z* 263 (M^+, 52%) and 148 (100).

8-Isopropoxy-2-methylquinoline 14

To a flame-dried flask was added 8-hydroxy-2-methylquinoline (5.00 g, 31.4 mmol) and potassium carbonate (7.8 g, 56.5 mmol) followed by DMF (100 cm^3). The reaction mixture was stirred under N_2 at 80 °C and 2-bromopropane (5.90 cm^3, 62.8 mmol) was added. After 2 h the reaction mixture was poured into water and extracted with dichloromethane. The organic solution was washed with 5% aq. potassium hydroxide (100 cm^3) and then with water until the washings were no longer alkaline. The solution was dried and evaporated and the residue subjected to flash chromatography which gave [with hexane–ether (4 : 1)] the quinoline **14** (4.81 g, 76%) as an orange oil (Found: C, 77.2; H, 7.6; N, 7.3. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%); ν_{max}(film)/cm^{-1} 1599, 1570 and 1507; δ_H(200 MHz; $CDCl_3$) 1.53 (6 H, dd, *J* 6.0), 2.77 (3 H, s), 4.82 (1 H, septet, *J* 6.0), 7.04–7.09 (1 H, m), 7.23–7.41 (3 H, m) and 7.98 (1 H, dd, *J* 8.8 and 1.6); *m*/*z* 201 (M^+, 2%) and 159 (100).

8-Isopropoxyquinoline-2-acetic acid lithium salt 15

The salt was prepared from the quinoline **14** (2.00 g, 9.9 mmol) by the same procedure as was described for the lithium salt **9**. It was isolated (1.79 g, 72%) as a colourless powder; δ_H(300 MHz; D_2O) 1.35 (6 H, d, *J* 6.0), 4.87–4.95 (1 H, m), 7.13 (1 H,dd, *J* 7.1 and 1.6), 7.36 (1 H, d, *J* 8.2, 3-H), 7.40–7.46 (2 H, m) and 8.15 (1 H, d, *J* 8.2, 4-H).

8-Isopropoxy-1,2,3,4-tetrahydroquinoline-2-acetic acid 16

The amino acid **16** was prepared by reduction of the lithium salt **15** (1.79 g, 7.12 mmol) by the same procedure as described for the conversion of the salt **9** into the acid **7**. It was isolated (1.04 g, 58%) as a pale yellow oil; *m*/*z* 249 (M^+, 23%) and 148 (100). The amino acid was characterised as its *hydrochloride*, mp 182–183 °C (from methanol–ether) (Found: C, 58.7; H, 7.1; N, 4.9. $C_{14}H_{21}ClNO_3$ requires C, 58.8; H, 7.1; N, 4.9%); ν_{max}(Nujol)/cm^{-1} 1718.

8-Isopropoxy-2,2a,3,4-tetrahydro-1*H*-azeto[1,2-*a*]quinolin-1-one 17

To a stirred suspension of sodium hydrogen carbonate (0.99 g, 11.8 mmol) in dry acetonitrile (20 cm^3) was added methanesulfonyl chloride (0.15 cm^3, 1.97 mmol). A solution of the β-amino acid **16** (0.49 g, 1.97 mmol) in dry acetonitrile (20 cm^3) was added and the mixture was stirred for 2 h at 60 °C. It was then cooled to 0 °C and filtered. The filtrate was evaporated to dryness. Flash chromatography of the residue gave [with ether–hexane (1 : 1)] the *azetidinone* **17** (0.27 g, 59%), mp 94–95 °C (from ether–hexane) (Found: C, 73.0; H, 7.5; N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6%); ν_{max}(Nujol)/cm^{-1} 1761; δ_H(200 MHz; $CDCl_3$) 1.38 (6 H, approx. t, *J* 6.2), 1.49–1.67 (1 H, m, 3-H), 2.20–2.32 (1 H, m, 3-H), 2.60 (1 H, dd, *J* 15.4 and 2.2, 2-H), 2.79–2.91 (2 H, m, 4-H), 3.28 (1 H, dd, *J* 15.4 and 4.9, 2-H), 3.57–3.68 (1 H, m, 2a-H), 4.59 (1 H, septet), 6.66 (1 H, dd, *J* 7.7 and 1.1), 6.76 (1 H, br d, *J* 8.3) and 6.94 (1 H, dd, *J* 8.3 and 7.7); *m*/*z* 231 (M^+, 24%) and 147 (100).

8-Hydroxy-2,2a,3,4-tetrahydro-1*H*-azeto[1,2-*a*]quinolin-1-one 3

The azetidinone **17** (0.40 g, 1.73 mmol) was dissolved in dry dichloromethane (100 cm^3) and the solution was stirred under N_2 at −78 °C. Titanium(IV) chloride (1 M in dichloromethane, 9.70 cm^3, 9.70 mmol) was added and the mixture was stirred at −78 °C for a further 1.5 h then at −10 °C for 12 h. Ice-cold HCl (2 M, 200 cm^3) was added. Extraction with ethyl acetate and flash chromatography gave (with dichloromethane) the *azetidinone* **3** (0.21 g, 64%), mp 103–104 °C (after sublimation)

(Found: C, 69.8; H, 5.85; N,7.4. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%); ν_{max}(Nujol)/cm^{-1} 3104 (br) and 1701; δ_H(200 MHz; $CDCl_3$) 1.54–1.76 (1 H, m, 3-H), 2.27–2.39 (1 H, m, 3-H), 2.91 (1 H, dd, *J* 15.4 and 2.7, 2-H), 2.86–2.95 (2 H, m, 4-H), 3.28 (1 H, dd, *J* 15.4 and 4.6, 2-H), 3.78–3.89 (1 H, m, 2a-H), 6.66 (1 H, br d, *J* 7.8), 6.83 (1 H, br d, *J* 8.2), 6.96 (1 H, dd, *J* 8.2 and 7.8) and 8.83 (1 H, s); *m*/*z* 189 (M^+, 40%) and 147 (100).

(2a*S*,4*S*)-4-Bromo-2,2a,3,4-tetrahydro-1*H*-azeto[1,2-*a*]quinolin-1-one 19

N-Bromosuccinimide (0.17 g, 0.98 mmol) was added to a solution of the azetidinone **1** (0.17 g, 0.98 mmol) in dry tetrachloromethane (100 cm^3) and the solution was stirred under N_2 while it was irradiated with a sunlamp until the starting material had been consumed (6 h). Succinimide was filtered off and the filtrate was evaporated to dryness. Flash chromatography gave [with ether–hexane (1 : 1)] the *azetidinone* **19** (0.19 g, 77%), mp 98–99 °C (from ether–hexane) (Found: C, 52.6; H, 4.0; N, 5.6. $C_{11}H_{10}BrNO$ requires C, 52.4; H, 4.0; N, 5.6%); ν_{max}(Nujol)/cm^{-1} 1764; δ_H(200 MHz; $CDCl_3$) 2.05 (1 H, ddd, $J_{2a,3}$ 11.5, $J_{3,3'}$ 14.3, and $J_{3,4}$ 3.3, 3-H), 2.70 (1 H, dt, $J_{2a,3'}$ 2.7, $J_{3,3'}$ 14.3, and $J_{3',4}$ 2.7, 3′-H), 2.93 (1 H, dd, $J_{2,2'}$ 15.4 and $J_{2,2a}$ 2.7, 2-H), 3.44 (1 H, dd, $J_{2,2'}$ 15.4 and $J_{2',2a}$ 4.9, 2′-H), 4.37–4.48 (1 H, m, 2a-H), 5.46 (1 H, dd, $J_{3,4}$ 3.3 and $J_{3',4}$ 2.7, 4-H), 7.04 (1 H, dd, *J* 7.4 and 1.1), 7.24–7.32 (2 H, m) and 7.47 (1 H, br d, *J* 8.2); *m*/*z* 253/251 (M^+, 5%), 172 (51) and 130 (100).

2,2a-Dihydro-1*H*-azeto[1,2-*a*]quinolin-1-one 2

A solution of the azetidinone **18** (72 mg, 0.29 mmol) and DBU (0.044 cm^3, 0.29 mmol) in dry THF (10 cm^3) under N_2 was stored at −10 °C for 16 h and then at 0 °C for 2 h. Ethyl acetate (20 cm^3) was added and the organic layer was washed with water (2 × 20 cm^3), 1 M HCl (2 × 30 cm^3), 5% aq. sodium hydrogen carbonate (20 cm^3) and water (20 cm^3). The organic layer was then dried and evaporated to leave the azetidinone **2** (28 mg, 57%), mp 52–54 °C (lit.,[2] 57 °C); δ_H(200 MHz; $CDCl_3$) 3.17 (1 H, dd, *J* 15.1 and 2.7, 2-H), 3.47 (1 H, dd, *J* 15.1 and 4.8, 2-H), 4.56–4.62 (1 H, m, 2a-H), 5.89 (1 H, dd, *J* 10.0 and 1.8, 3-H), 6.36 (1 H, dd, *J* 10.0 and 2.2, 4-H), 6.95–7.00 (2 H, m) and 7.09–7.13 (2 H, m); *m*/*z* 171 (M^+, 23%) and 129 (100).

Crystal data for 3

$C_{11}H_{11}NO_2$, $M = 189.21$. Monoclinic, $a = 8.368(5)$, $b = 14.024(5)$, $c = 8.492(7)$ Å, $\beta = 115.12(5)°$, $V = 902(1)$ Å^3, $F(000)$ 400, $\lambda = 0.710\,69$ Å, $T = 294$ K, space group $P2_1/n$ (no. 14), $Z = 4$, $D_c = 1.393$ g cm^{-3}, colourless prism, 0.15 × 0.10 × 0.30 mm.

Data collection and processing. Rigaku AFC6S diffractometer, graphite-monochromated Mo-Kα radiation, $\omega - 2\theta$ scans to a maximum 2θ value of 50.0° with ω scan width $(1.15 + 0.30 \tan \theta)°$; 1773 reflections collected of which 1658 were unique ($R_{int} = 0.047$). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection; no decay correction was applied.

Structure solution and refinement. Automatic direct methods[13] (all non-H atoms). Non-H atoms were refined either anisotropically or isotropically. The final cycle of full-matrix least-squares refinement was based on 752 observed reflections [$I > 3.00\sigma(I)$] and 127 variable parameters and converged (largest parameter shift was 0.01 times its esd) with weighted and unweighted agreement factors of:

$$R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.042$$

$$R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2)]^{\frac{1}{2}} = 0.042$$

The standard deviation of an observation of unit weight was 1.36. The weighting scheme was based on counting statistics and included a factor ($\rho = 0.03$) to downweight the intense reflections. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and −0.21 e Å^{-3}, respectively. All calculations were performed using the TEXSAN crystallographic structure package of the Molecular Structure Corporation.[14]

Acknowledgements

We thank the EPSRC for a Studentship (to A. R.) and Mr J. V. Barkley (University of Liverpool) for determining the X-ray crystal structure of **3**.

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Paper 8/00280K
Received 9*th January* 1998
Accepted 5*th February* 1998