Aziridination of alkenes using 3-acetoxyamino-2-trifluoromethylquinazolin-4(3*H*)-one

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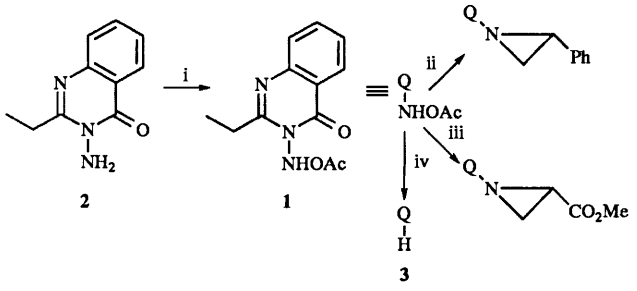
Oxidation of 3-amino-2-trifluoromethylquinazolin-4(3*H*)-one 6 with lead tetraacetate in dichloromethane gives the title 3-acetoxyamino derivative 7 which is isolable at room temperature and considerably more stable than the corresponding 2-alkyl substituted analogues. Compound 7 aziridinates alkenes in yields which are consistently higher than those from the 2-alkyl substituted analogues. Aziridinations using 3-acetoxyaminoquinazolinones bearing other electron-withdrawing groups on the 2-position of the quinazolinone ring have been examined.

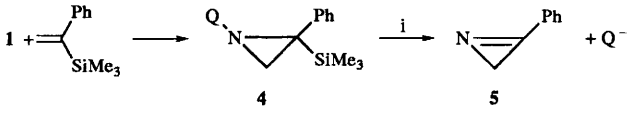
3-Acetoxyaminoquinazolinones, *e.g.* **1** (QNHOAc), are aziridinating agents for alkenes of widely different electron demand.[1] Thus, styrene and methyl acrylate are aziridinated in good yields using only modest excesses of the alkenes (Scheme 1).



Scheme 1 *Reagents and conditions:* i, LTA, CH_2Cl_2, −20 °C; ii, CH_2=CHPh; iii, CH_2=$CHCO_2Me$; iv, > 5 °C

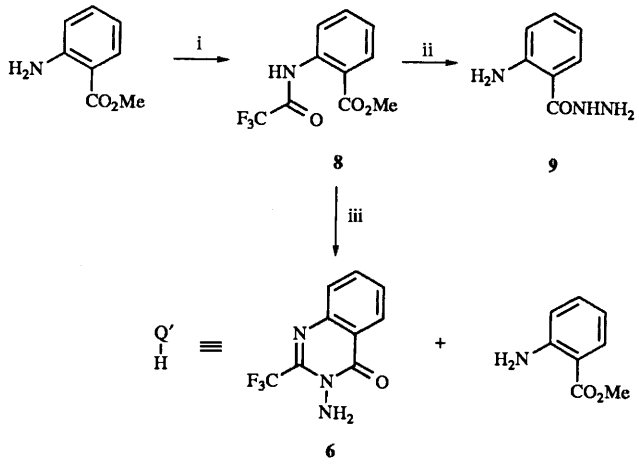
QNHOAc **1** is produced in solution in excellent yield by oxidation of the corresponding 3-aminoquinazolinone **2** with lead tetra-acetate in dichloromethane at −20 °C. Aziridinations are conducted by addition of the alkene at −20 °C to this solution and then warming to ambient temperature. If a solution of QNHOAc **1** prepared as above is maintained at 5 °C for a few minutes before addition of the alkene, yields of aziridine are reduced and the major product is the 3*H*-quinazolinone **3**. This product **3** is also the major one in attempted aziridinations of unreactive alkenes.

In exploring the chemistry of the *N*-(oxoquinazolinyl)aziridines derived from QNHOAc **1** and alkenes, we became aware of the ability of the quinazolinone (Q) ring to function as a leaving group. An example was the finding that the 2-trimethylsilyl-substituted aziridine **4** on treatment with fluoride anion, gives the azirine **5** by loss of Q^- (Scheme 2).[2]



Scheme 2 *Reagents:* i, CsF, DMF

Reactions in which the N–Q bond is broken as in Scheme 2 are of particular interest because if the aziridines or their ring-opened products derived from *e.g.* QNHOAc **1** and alkenes are to be useful in synthesis, ways must be found for cleavage of this N–Q bond.[3] In this paper[4] we describe the synthesis of 3-amino-2-trifluoromethylquinazolinone **6** ($Q'NH_2$) (Scheme 3)



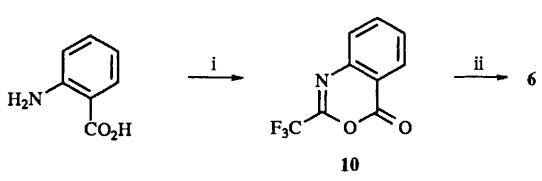
Scheme 3 *Reagents:* i, $(CF_3CO)_2O$; ii, NH_2NH_2 (×5); iii, NH_2NH_2 (1 equiv.)

and the properties of the 3-acetoxyamino derivative **7** (Q'NHOAc). It was expected that the presence of the strongly electron-withdrawing trifluoromethyl group would markedly increase the ability of the quinazolinone ring to function as a leaving group and facilitate reactions such as that in Scheme 2.

Synthesis of 3-amino-2-trifluoromethylquinazolinone 6

Surprisingly, the synthesis of this compound **6** ($Q'NH_2$) had not been reported. Initially, attempts were made to follow the standard procedure for synthesis of 2-substituted 3-aminoquinazolinones (Scheme 3). Reaction of methyl anthranilate with trifluoroacetic anhydride gave the corresponding *N*-trifluoroacetylanthranilate **8** but attempts to convert this into the required 3-aminoquinazolinone **6** with an excess of hydrazine failed and anthranilohydrazide **9** was the only product identified. The formation of this product **9** indicated that the trifluoroacetyl carbonyl group underwent nucleophilic attack. However, by the addition of only 1 equiv. of hydrazine, a small quantity (~5%) of the required product $Q'NH_2$ **6** was recovered although the major product in this case was methyl anthranilate, confirming that attack on the trifluoroacetyl group was preferred over attack on the ester group of anthranilate **8**.

A more efficient route to $Q'NH_2$ **6** was eventually devised *via* the 2-trifluoromethylbenzoxazinone **10** (Scheme 4) which had been prepared previously.[5] Treatment with 1 equiv. of hydrazine in ethanol gave the required product $Q'NH_2$ **6** in 64% yield after crystallisation.



Scheme 4 *Reagents:* i, $(CF_3CO)_2O$; ii, NH_2NH_2 (1 equiv.)

Aziridinations of alkenes using 3-acetoxyamino-2-trifluoromethylquinazolinone 7 (Q'NHOAc)

Initially, this 3-acetoxyamino derivative **7** was prepared in dichloromethane solution at −20 °C by *N*-acetoxylation of the 3-aminoquinazolinone **6** as described earlier for preparation of QNHOAc **1**. Aziridination of methyl cinnamate (1.8 mol equiv.) using a solution of Q'NHOAc **7** was found to give the corresponding aziridine **11** in superior yield (60%) to that obtained using QNHOAc **1** under the same conditions (42%) (Scheme 5).

A more impressive demonstration of the superior yields in aziridination of alkenes using Q'NHOAc **7** was obtained using hex-1-ene. Using this alkene (3.6 mol equiv.) and QNHOAc **1** (1 mol equiv.) the yield of the corresponding aziridine is only 10–15% but using Q'NHOAc **7** under the same conditions, the isolated yield of aziridine **12** was 50.5%. In this latter reaction none of the 2-trifluoromethyl-3*H*-quinazolinone **13** (see Scheme 5), corresponding to the analogous 3*H*-quinazolinone **3** in Scheme 1, was isolated. Instead an insoluble crystalline by-product, identified as the *N*,*N*-bis(4-oxoquinazolin-3-yl)amine **14** (Q'NHQ'), was separated. The structure of this by-product **14** was deduced from the low field NH proton signal in its NMR spectrum which integrated to half of the signal which could be assigned to the Q'H-5 protons.

Mass spectrometry (FAB) confirmed the molecular mass as $M^+ = 442$ and confirmation of the structure assignment comes from an X-ray crystal structure determination (Fig. 1).

In the crystal, compound **14** has N-2 as a tetrahedral centre. The non-orthogonality of the two planes containing the two quinazolinone rings means that the two carbonyl groups have different environments. It appears that the carbonyl oxygen O(1a) of one quinazolinone ring in Fig. 1 is interacting with the carbonyl carbon C-4 of the other quinazolinone ring. The O(1a)–C(4)–O(1) angle is 87° and the O(1a)–C(4) distance at 2.806 Å is less than the sum of the Van de Waals radii of these atoms (~3 Å). In support of a nucleophilic O(1a)–electrophilic C(4) interaction, O(1) is behind the averaged (least squares) plane of the heterocyclic ring of the quinazolinone ring by 0.16

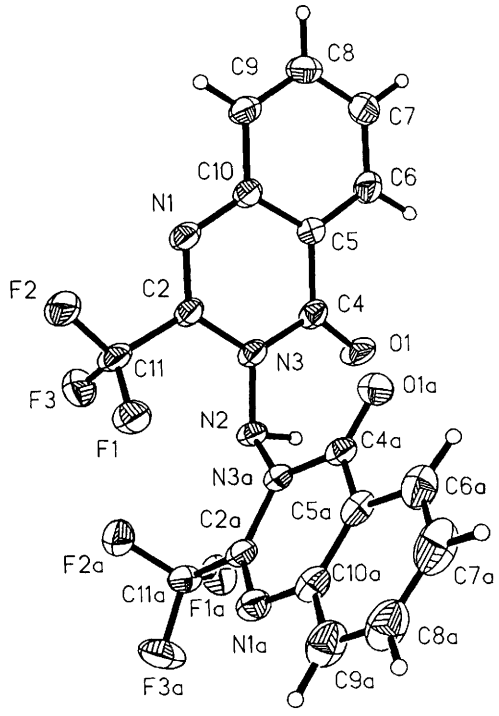


Fig. 1 X-Ray crystal structure of **14** (Q'NHQ')

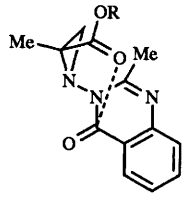
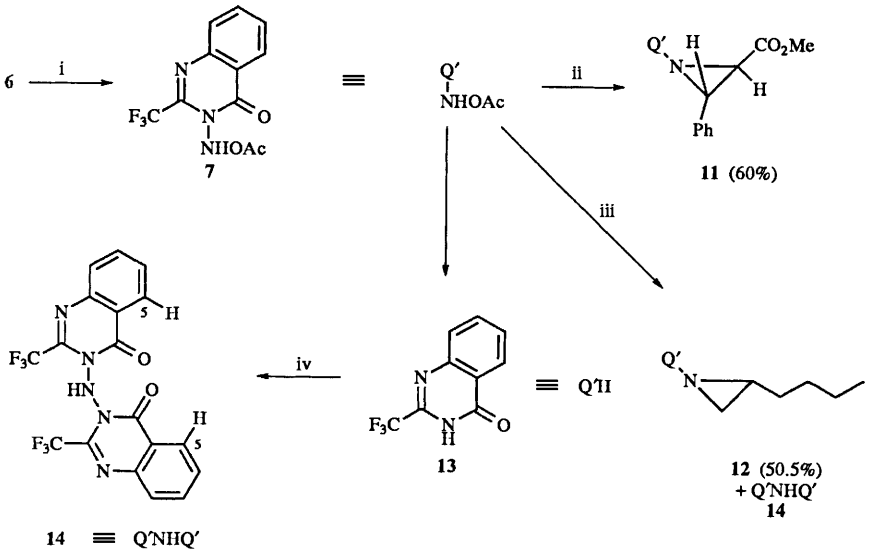


Fig. 2 Previously proposed interaction (- - - -) to account for the unexpected effect on *N*-invertomer ratio with increase in the size of R

Å, when viewed from the perspective in Fig. 1. An attractive interaction between O(1a) and C(4) is analogous to that in Fig. 2, which was previously proposed by us to account for some unexpected trends in aziridine ester invertomer ratios with changes in the size of the ester group R.[6]

Fig. 3 shows the intermolecular hydrogen bonding between O(1)/O(1b) and H(2a)/H(2) which again distinguishes these carbonyl oxygen atoms from those O(1a)/O(1aa) interacting with C(4)/C(4b) as indicated above. There appears to be an



Scheme 5 *Reagents and conditions:* i, LTA, CH_2Cl_2, −20 °C; ii, PhCH=CHCO$_2$Me; iii, CH_2=CH$(CH_2)_3CH_3$; iv, **7**

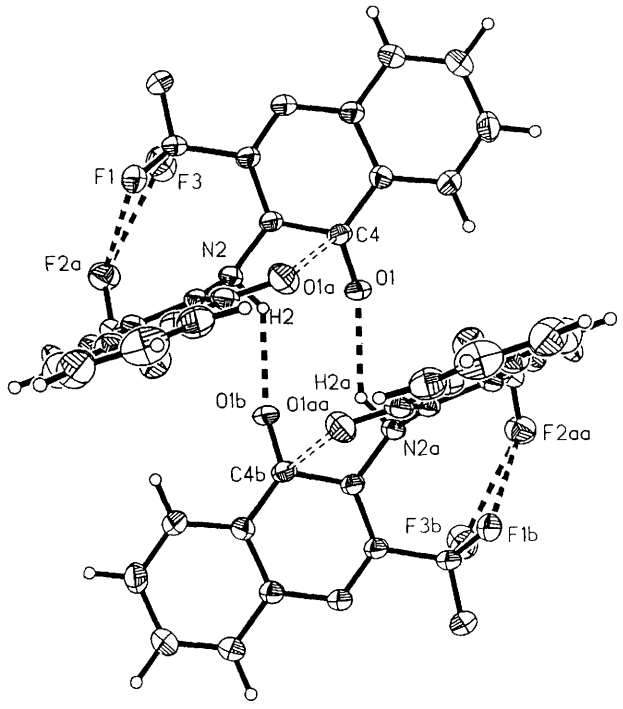


Fig. 3 X-Ray crystal structure of **14** (Q'NHQ') showing intermolecular interactions between two molecules and the dissimilarity of the environments of O(1)/O(1b) and O(1a)/O(1aa). Selected distances: F(1)···F(2a) = 2.814 Å, F(3)···F(2a) = 2.659 Å, O(1b)···H(2) = 2.227 Å and O(1a)···C(4) = 2.806 Å.

attractive interaction between the pairs of trifluoromethyl groups with the F–F bond distances indicated within the sum of their Van de Waals radii.

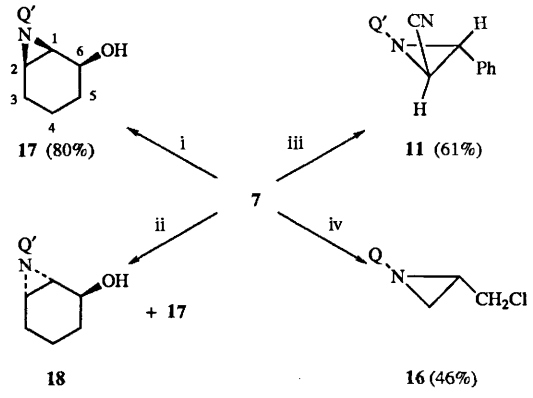
Presumably this interaction above between O(1a) and C(4) is not sufficiently strong to prevent a small rotation around the N–N bond and hence to allow an identical interaction between O(1) and C(4a) since there is no evidence for non-identity of the two quinazolinone rings by NMR spectroscopy at room temperature.†

The presence of Q'NHQ' **14** and the absence of Q'H **13** can be ascribed to the acidity of the NH proton in the latter and attack of the conjugate anion on Q'NHOAc **7**. This absence of Q'H **13** in the crude reaction mixture was confirmed by comparison with an authentic sample obtained by treatment of the benzoxazinone **10** with ammonia in ethanol. The lowfield NH proton signal in the NMR spectrum (δ 13.6) of Q'H **13** was absent from the spectra of the crude products from alkene aziridinations using Q'NHOAc **7**. As expected, Q'H **13** was soluble in aqueous sodium hydrogen carbonate.

It soon became apparent that the aziridinating agent Q'NHOAc **7** in Scheme 5 was appreciably more stable in solution than QNHOAc **1** and all other 3-acetoxyaminoquinazolinones prepared hitherto. In fact, this compound **7** was obtained as a crystalline solid from ethyl acetate–light petroleum [contaminated with only a small quantity (~ 7%) of Q'NHQ' **14**], was stable for several days at room temperature and unaffected by boiling in chloroform for a short period. Aziridinations using Q'NHOAc **7** could, therefore, be carried out by *N*-acetoxylation of the 3-aminoquinazolinone **6** at room temperature followed by addition of the alkene with no loss in yield.

Aziridinations of other alkenes using Q'NHOAc **7** which were examined included cinnamonitrile, allyl chloride and cyclohexenol (Scheme 6).

† The insolubility of compound **14** has prevented further investigation of this barrier to interconversion, by NMR spectroscopy at low temperature.



Scheme 6 *Reagents:* i, cyclohex-2-enol; ii, cyclohex-2-enol, CH_2Cl_2, $NaHCO_3$, water; iii, PhCH=CHCN; iv, CH_2=$CHCH_2Cl$

Attempted aziridination of allyl chloride with QNHOAc **1** yields < 15% of the required product but using Q'NHOAc **7** a 46% yield of the corresponding aziridine **16** was obtained.

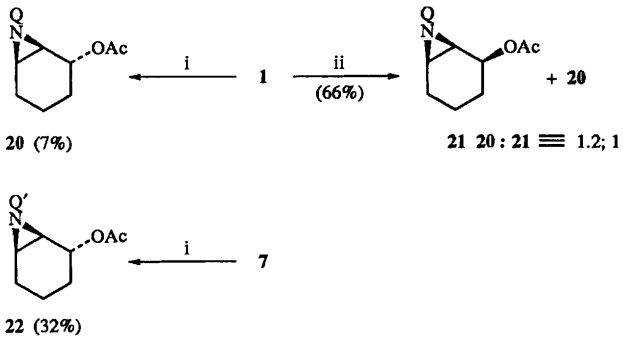
The mechanism for aziridination of double bonds by 3-acetoxyaminoquinazolinones, *e.g.* **1** and **7**, may be considered analogous to that by which peroxyacetic acid brings about the epoxidation of double bonds.[7] Like the epoxidation of cyclohexenol using peroxy acids which gives the *cis*-epoxide/alcohol stereoselectively, aziridination of cyclohexenol with QNHOAc **1** gives the *cis*-aziridine/alcohol stereoselectively (ratio *cis*:*trans* 20:1). Using Q'NHOAc **7** brought about an increase of the stereoselectivity in this aziridination: only signals from the *cis*-aziridine **17** (Scheme 6) were visible in the NMR spectrum of the crude reaction mixture and this aziridine **17** was isolated in 80% yield. Assignment of the *cis*-configuration was made from the magnitude of the coupling constant *J* between 1-H and 6-H (4.2 Hz) and its similarity with that between the same protons in the NMR spectrum of the *cis*-aziridine obtained from QNHOAc and cyclohexenol (4.0 Hz).

Confirmation of the absence of signals from the aziridine *trans*-stereoisomer **18** in the NMR spectrum of the crude aziridination mixture above was possible when it was found that aziridination of cyclohexenol in a two-phase system of dichloromethane and aqueous sodium hydrogen carbonate gave a mixture of *cis*- and *trans*-stereoisomers (1.3:1) (43%). The signal from the C*H*OH proton in the *trans*-aziridine **18** at δ 4.30 was downfield of that in the *cis*-stereoisomer **17**; it was clearly absent in the crude mixture from aziridination of cyclohexenol in the absence of aqueous sodium hydrogen carbonate. As expected,[7] the magnitude of the coupling constant between the aziridine ring proton 1-H and C*H*OH in aziridine **18** was small (< 2 Hz). It appears that in aziridination using the two-phase system above, the hydrogen bonding, which is believed to direct the *syn*-aziridination in dichloromethane alone, is disrupted and non-stereoselective aziridination results.

Aziridination of cyclohexenyl acetate **19** with QNHOAc **1** was previously shown[7] to give only the *trans*-stereoisomer **20** although the yield was very low (7%) (Scheme 7).

We have previously shown that increased yields in aziridinations of unreactive alkenes, *e.g.* hex-1-ene (see above) with QNHOAc **1** can be accomplished by the addition of trifluoroacetic acid (TFA) to the dichloromethane solution in which aziridination is taking place.[8] The presence of TFA, however, does bring about some ring-opening of the aziridine product **12** in the reaction mixture. Likewise, in the presence of trifluoroacetic acid, the yield of aziridination product using QNHOAc **1** and cyclohexenyl acetate **19** is raised (Scheme 7). Here, however, the complete stereoselectivity which is obtained in the absence of TFA is lost and a mixture of *cis*- and *trans* aziridine acetates **20** and **21** is formed.

Using Q'NHOAc **7** (in the absence of TFA) in the



Scheme 7 *Reagents:* i, cyclohex-2-enyl acetate **19**, CH_2Cl_2; ii, cyclohex-2-enyl acetate **19**, CH_2Cl_2, TFA; iii, cyclohex-2-enyl acetate **19**, CH_2Cl_2

aziridination of cyclohexenyl acetate **19**, a 32% yield of *trans*-aziridine **20** is obtained and complete stereoselectivity is conserved.

Aziridinations of alkene using 3-acetoxyaminoquinazolinones 2-substituted with other electron-withdrawing groups

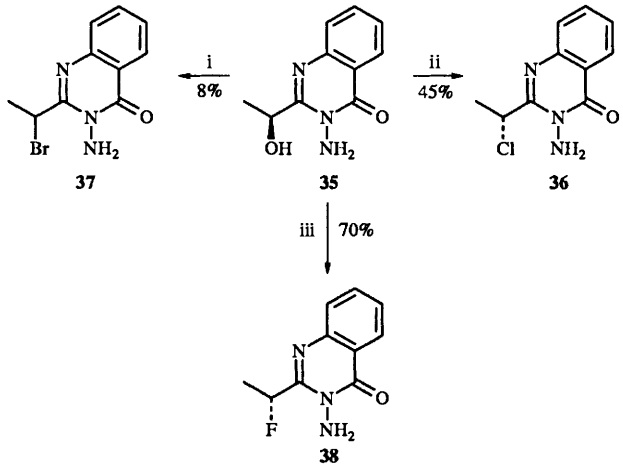
The 3-aminoquinazolinones **23–27** and **36–39** were prepared to determine whether their 3-acetoxyamino derivatives showed the same stability and efficiency in aziridination of alkenes as Q'NHOAc **7** above. 3-Amino-2-ethoxycarbonylquinazolinone **23** was available by a literature method:[9] **24–27** were obtained by reaction of the corresponding acid chlorides with methyl anthranilate followed by treatment with hydrazine (Scheme 8). For the case of compound **24**, the corresponding anthranilate **28** was converted into the corresponding hydrazide **29** and then converted into the 3-aminoquinazolinone **24** by heating in ethanol at 170 °C (in the absence of hydrazine).

The acid chloride $F_2CHCOCl$ required for the synthesis of 3-aminoquinazolinone **25** has a boiling point of 25 °C at atmospheric pressure. Conversion of the acid into the acid chloride was expediently accomplished using triphenylphosphine and carbon tetrachloride in chloroform solution and the acid chloride was co-distilled from the reaction mixture with chloroform and treated directly with methyl anthranilate to form compound **30**. It was subsequently found that the yield of this anthranilate **30** was much improved by heating a mixture of the acid, carbon tetrachloride, triphenylphosphine and methyl anthranilate under reflux.

A problem in the synthesis of the 3-amino-2-fluoromethylquinazolinone **26** was the non-availability of the (hazardous) fluoroacetic acid. To circumvent the use of this acid, an attempt was made to bring about exchange of the bromide by fluoride in methyl *N*-bromoacetylanthranilate **31** using caesium fluoride in dimethylformamide (Scheme 8): the only product isolated, however, was the compound **34**, presumably as a result of a base-induced dimerisation.

The required halogen exchange was successfully achieved when anthranilate **31** was treated with a slurry of calcium fluoride and potassium fluoride (5 : 1) in sulpholane at 180 °C;[10] conversion of the methyl *N*-fluoroacetylanthranilate **32** into the required 3-aminoquinazolinone **26**, was carried out using hydrazine in 77% yield.

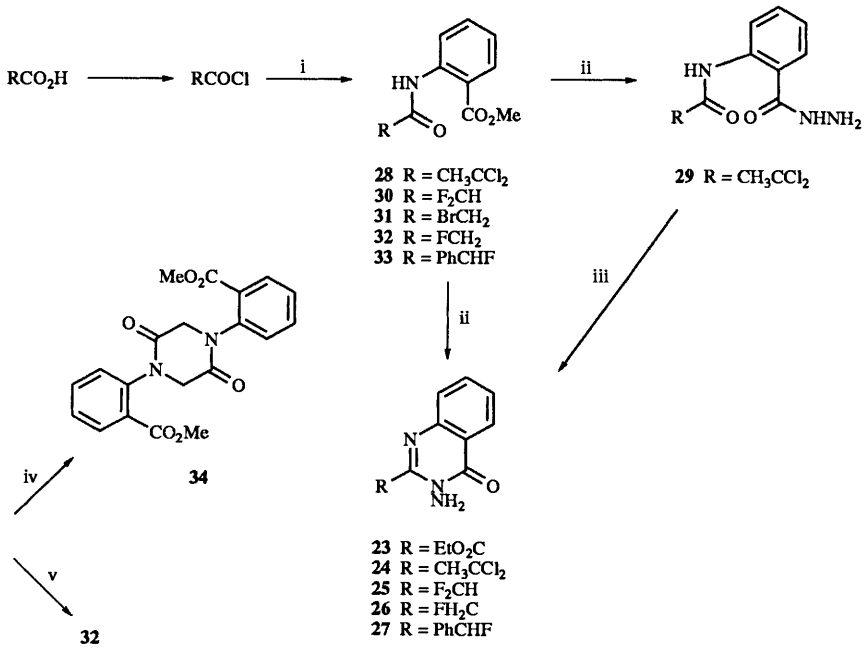
3-Amino-2-(1-chloroethyl)quinazolinone **36** was obtained from the corresponding enantiopure (*S*)-alcohol **35**[3] by the action of triphenylphosphine and carbon tetrachloride in 45% yield (Scheme 9).



Scheme 9 *Reagents:* i, PPh_3, CBr_4; ii, PPh_3, CCl_4; iii, DAST

This substitution of hydroxy by chloride is assumed to proceed with inversion and the configuration of the chiral centre in compound **36** is then *R*. This compound is optically active, $[\alpha]_D$ −39.4 (*c* 0.1, $CHCl_3$),‡ but its enantiopurity is

‡ $[\alpha]_D$ Values given in units of 10^{-1} deg cm^2 g^{-1} throughout.

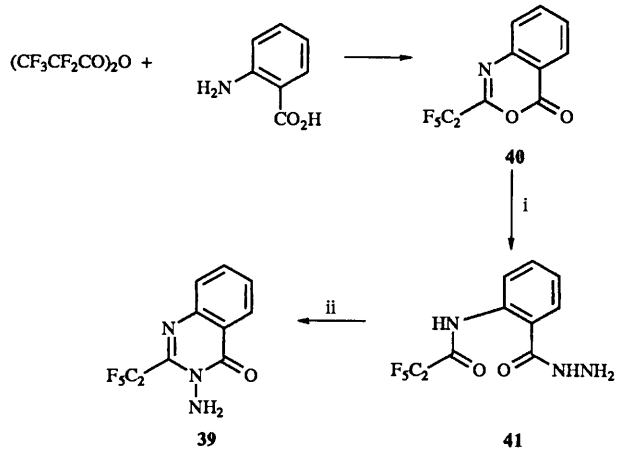


Scheme 8 *Reagents and conditions:* i, methyl 2-aminobenzoate; ii, NH_2NH_2; iii, heat; iv, CsF, DMF; v, CaF, KF, sulfolane

unknown. Interestingly, the analogous conversion of the alcohol **35** into the 3-amino-2-(1-bromoethyl)quinazolinone **37**, gave a product (in low yield) whose optical rotation was zero and it is likely that in this case, racemisation has occurred under the reaction conditions.

Attempts to prepare 3-amino-2-(1-fluoroethyl)quinazolinone **38** by exchange of chlorine or bromine in compounds **35** and **37**, respectively, were unsuccessful but it was obtained by reaction of the alcohol **35** with diethylaminosulfur trifluoride (DAST) in good yield (70%). This product **38** was also optically active $[\alpha]_D$ −1.04 ($CHCl_3$) but of unknown enantiopurity.

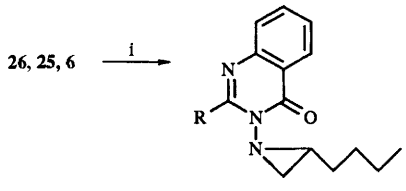
Finally, 3-amino-2-pentafluoroethylquinazolinone **39** (Scheme 10) was obtained from the commercially available



Scheme 10 *Reagents and conditions:* i, NH_2NH_2; ii, heat

anhydride by the method successfully used to prepare the 2-trifluoromethyl analogue **6**, except that in this case the anthranilate **40** was first converted into the hydrazide **41** and then into the required product **39** by heating.

Each of the 3-aminoquinazolinones **23–27** and **36–39** was *N*-acetoxylated with LTA in dichloromethane at −20 °C, as described previously for the preparation of QNHOAc **1** and Q'NHOAc **7**. The efficiency of the derived *N*-acetoxyaminoquinazolinones as aziridinating agents by comparison with Q'NHOAc **7** was assayed by addition of hex-1-ene (3 mol equiv.) and by determination of the yields of the corresponding 2-butyl-1-(4-oxoquinazolinyl)aziridine in the crude reaction product by NMR spectroscopy. A comparison of yields of the aziridines obtained from the mono-, di- and tri-fluoromethyl-substituted quinazolinones **26** (< 13% from NMR), **25** (37% isolated) and **6** (50.5% isolated) (Scheme 11) suggests that the



42 R = FCH_2 (< 13%)
43 R = F_2CH (37%)
12 R = F_3C (50%)

Scheme 11 *Reagents and conditions:* i, CH_2=$CH(CH_2)_3CH_3$, LTA, CH_2Cl_2, −20 °C

aziridinating efficiency of Q'NHOAc **7** falls off as the number of fluorine substituents on the 2-methyl substituent is reduced.

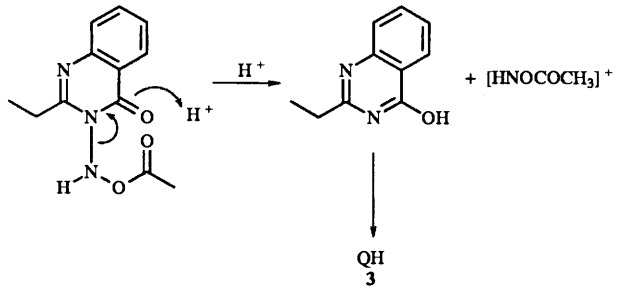
Apart from the 2-pentafluoro-substituted compound **39** whose 3-acetoxyamino derivative showed some stability at room temperature and aziridination yields with alkenes comparable with those of Q'NHOAc **7**, none of the 3-acetoxyaminoquinazolinone derivatives of compounds **23–27** and **36–38** showed a thermal stability comparable with Q'NHOAc **7**: with the exception of compound **25** above, none showed any significantly increased yield over that obtained using the 2-alkyl-substituted analogue QNHOAc **1** in aziridination of hex-1-ene.

Origin of the stability of Q'NHOAc 7 and the increased yields associated with its use in aziridination of alkenes

It was pointed out earlier that the decomposition of these 3-acetoxyaminoquinazolinones, *e.g.* **1**, gives 3*H*-quinazolinones **3** (Scheme 1). The increased yields of aziridines obtained using Q'NHOAc **7**, therefore, could be the result not of an inherently greater reactivity of this 3-acetoxyaminoquinazolinone but of its slower rate of decomposition to the corresponding 3*H*-quinazolinone Q'H **13** (and thence to Q'NHQ' **14**: see Scheme 5). The reduction in yields of aziridines with a reduction in the number of fluorines in the quinazolinone 2-substituent (Scheme 11) suggests that the enhancement of yield using the trifluoromethyl group may be the result of its electron-withdrawing effect although it is surprising that there was no comparable effect from other electron-withdrawing substituents.

We have now shown that the decomposition of QNHOAc **1** is accelerated by the acetic acid which is co-produced in its formation from 3-aminoquinazolinone **2** and LTA. A dichloromethane solution of QNHOAc **1**, prepared in the usual way at −20 °C and freed from lead diacetate, was divided into two parts one of which was washed with an aqueous sodium hydrogen carbonate. The decomposition of QNHOAc **1** in both solutions was monitored at 10 °C by IR spectroscopy by disappearance of the acetoxy carbonyl absorption at 1760 cm^{-1}. In the solution which retained acetic acid, decomposition of QNHOAc **1** was complete within 15 min, whereas in the base-washed solution at least 2 h were required for complete decomposition.

Presumably the effect of acid on the decomposition of QNHOAc **1** and other 3-acetoxyaminoquinazolinones is the result of protonation of the quinazolinone ring thus converting it into a better leaving group (Scheme 12): the fate of the acetoxyamino group in this decomposition is unknown.



Scheme 12

A plausible explanation for the increased stability of Q'NHOAc **7** *and* the increased yields of aziridines obtained in its reactions with alkenes, therefore, is that the trifluoromethyl group reduces the basicity of the quinazolinone ring and, consequently, the rate of its decomposition in the presence of acid. If this interpretation is correct it should be possible to obtain the same augmented yields of aziridines using 3-acetoxyaminoquinazolinones lacking the 2-trifluoromethyl substituent: this will require removal not only of the 1 mol equiv. of acetic acid co-produced in LTA oxidation but also the 1 mol equiv. produced in the aziridination itself.

Experimental

For general experimental details see ref. 3. Ether refers to diethyl ether. Light petroleum refers to the fraction bp 60–80 °C. Sodium sulfate was used as the drying agent for

organic solutions. Brine refers to saturated aqueous sodium chloride. The following were commercially available and used as received: 2,2-dichloropropionic acid, pentafluoropropionic acid anhydride, difluoroacetic acid, α-fluorophenylacetic acid and diethylaminosulfur trifluoride. Unless otherwise indicated, NMR spectra were run at 90 MHz in $CDCl_3$ solutions using tetramethylsilane as an internal standard. For mass spectral data, with the exception of the M^+ peak, only fragment peaks > 20% of the base peak are given.

Methyl *N*-trifluoroacetylanthranilate 8

To methyl anthranilate (27.7 g, 0.18 mol) was added trifluoroacetic anhydride (37.18 g, 0.18 mol) with stirring and with exclusion of moisture. The mixture was heated under reflux for 1 h and then set aside for 1 h. The resulting solid mass was dissolved in ethyl acetate (100 cm^3) and this solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3) and brine (50 cm^3), dried and evaporated to yield the anthranilate **8** as a colourless solid (36 g, 80%), mp 63–65 °C (from light petroleum) (lit.,[11] mp 62.5–64 °C).

Reaction of the anthranilate 8 with an excess of hydrazine

To a solution of the amide **8** (15 g, 0.061 mol) in ethanol (30 cm^3) was added hydrazine monohydrate (15.45 g, 0.31 mol) and the solution was heated under reflux for 6 h. After being set aside overnight, the mixture was evaporated under reduced pressure and the residue dissolved in ethyl acetate (50 cm^3). The solution was washed with water (5 × 50 cm^3), dried and evaporated under reduced pressure. The product was crystallised from ethanol to give anthranilohydrazide **9** (4 g, 43%), mp 119–121 °C (lit.,[12] mp 118–121 °C).

2-Trifluoromethylbenzoxazinone 10

To a suspension of anthranilic acid (500 mg, 3.6 mmol) in chloroform (15 cm^3) was added trifluoroacetic anhydride (2.2 g, 10.8 mmol) dropwise with stirring and the mixture was then heated under reflux for 1 h. After evaporation of the reaction mixture to dryness under reduced pressure, the residue was crystallised from light petroleum to yield the benzoxazinone **10** as colourless crystals (306 mg, 40%), mp 48–49 °C (lit.,[5] 51–52 °C).

3-Amino-2-trifluoromethylquinazolin-4(3*H*)-one 6

The benzoxazinone **10** (12.7 g, 0.059 mol) was dissolved in ethanol (50 cm^3) containing hydrazine monohydrate (3.03 g, 0.062 mol) and the mixture stirred for 1 h. After concentration of the mixture by evaporation of the bulk of the ethanol, the residual solid was dissolved in ethyl acetate (100 cm^3) and the solution washed with dilute hydrochloric acid (2 mol dm^{-3}; 2 × 50 cm^3) and brine (2 × 50 cm^3), dried and evaporated to give 3-*aminoquinazolinone* **6** as colourless crystals (from methanol) (64%), mp 150–151 °C (Found: C, 47.25; H, 2.65; N, 18.4. $C_9H_6F_3N_3O$ requires C, 47.15; H, 2.65; N, 18.35%); δ_H 8.3 (d, *J* 9, 5-Q'H), 7.7–7.3 [m, 3 × CH (Q')] and 4.9 (s, NH_2); δ_F −67.53; ν_{max}/cm^{-1}, 3320w, 3200w, 1675s and 1630s; *m/z* (%) 229 (97) (M^+), 200 (66), 180 (39), 130 (100), 91 (36), 77 (68), 70 (37) and 64 (30).

2-Trifluoromethylquinazolin-4(3*H*)-one 13

The benzoxazinone **10** (774 mg, 3.6 mmol) was dissolved in ethanol (10 cm^3) and an ethanol solution of ammonia (62 mg, 3.6 mmol) was added directly to it with stirring. After the mixture had been stirred for a further 2 h, the *quinazolinone* **13** separated (316 mg, 41%) as colourless crystals, mp 204–206 °C (from methanol) (Found: C, 50.15; H, 2.3; N, 13.4. $C_9H_5F_3N_2O$ requires C, 50.45; H, 2.35; N, 13.15%); δ_H([$^2H_6$]-DMSO, 300 MHz) 13.6 (s, NH), 8.1 (d, *J* 6 5-Q'H) and 8.10–7.80 [m, 3 × CH(Q')]; ν_{max}/cm^{-1} 3020br, 1725s and 1675s; *m/z* (%) 214 (100) (M^+), 145 (87), 117 (20), 91 (69), 70 (24) and 64 (42).

3-Acetoxyamino-2-trifluoromethylquinazolin-4(3*H*)-one 7

To a well-stirred solution of LTA (400 mg, 0.9 mmol) in dichloromethane (2 cm^3) was added 3-aminoquinazolinone **6** (200 mg, 0.87 mmol) continuously in very small portions over a period of 10 min. After addition, the mixture was stirred for a further 10 min before the insoluble lead salts were separated and the dichloromethane solution washed with saturated aqueous sodium hydrogen carbonate (2 × 5 cm^3) and brine (5 cm^3), dried and evaporated under reduced pressure. The residual oil was dissolved in ethyl acetate and crystallised by the addition of light petroleum with ice cooling to give the title compound **7** as an off-white solid (167 mg, 67%), mp 126–127 °C; δ_H 10.7 (s, N*H*OAc), 8.3 (d, *J* 6, 5-Q'H), 7.9–7.5 [m, 3 × CH (Q')] and 2.0 (s, $OCOCH_3$); δ_F −67.010; ν_{max}/cm^{-1} 3680w, 1760s, 1720s, 1630s and 1610s. This compound was contaminated with a small quantity (~7%) of the bis(4-oxoquinazolin-3-yl)amine **14** (detected by the presence of the signal δ_F −66.712).

Methyl 3-phenyl-1-(4-oxo-2-trifluoromethyl-3,4-dihydroquinazolin-3-yl)aziridine-2-carboxylate 11

To a stirred solution of methyl cinnamate (1.3 g, 8 mmol) in dichloromethane (10 cm^3) held at −17 to −20 °C was added alternately, continuously and in very small portions LTA (1.94 g, 4.37 mmol) and 3-aminoquinazolinone **6** (1 g, 4.3 mmol) in small portions over a period of 15 min, with addition of LTA always ahead of that of compound **6**. After the temperature of the solution had been allowed to rise to ambient, the insoluble lead salts were separated and the dichloromethane solution was washed with saturated sodium hydrogen carbonate (2 × 20 cm^3) and then brine (2 × 20 cm^3), dried and evaporated under reduced pressure. Trituration of the residual yellow oil with ice-cold ethanol (2 cm^3) and crystallisation of the solid separated gave the *aziridine* **11** as a colourless solid (1.04 g, 60%), mp 119–121 °C (from ethanol) (Found: C, 58.55; H, 3.75; N, 10.75. $C_{19}H_{14}F_3N_3O_3$ requires C, 58.6; H, 3.6; N, 10.8%); δ_H 8.3 (d, *J* 9 5-Q'H), 7.8–7.5 [m, 3 × CH(Q')], 7.3 [s, 5 × CH(Ph)], 4.9 (d, *J* 6, azir. 3-H), 3.7 (s, CO_2Me) and 3.6 (d, *J* 6, azir. 2-H); ν_{max}/cm^{-1} 1730s, 1670s and 1600s; *m/z* (%) 389 (3) (M^+), 330 (100) and 116 (43).

Standard procedure for aziridination using Q'NH_2 6 (for alkenes stable to LTA)

To a stirred solution of LTA (2 g, 4.5 mmol) and alkene in dichloromethane (10 cm^3) was added the 3-aminoquinazolinone **6** (1.03 g, 4.5 mmol) in small portions over 10 min. The mixture was stirred for a further 30 min before the lead salts were separated and washed with dichloromethane (~2 cm^3). The combined dichloromethane solutions were washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3) and brine (2 × 20 cm^3), dried and evaporated under reduced pressure.

3-Cyano-2-phenyl-1-(4-oxo-2-trifluoromethyl)-3,4-dihydroquinazolin-3-yl)aziridine 15

Using the general procedure above with cinnamonitrile (3.08 g, 24 mmol) gave an oil which solidified and gave the *aziridine* **15** (986 mg, 61%) as colourless crystals, mp 143–144 °C (from ethanol) (Found: C, 60.55; H, 3.25; N, 15.8. $C_8H_{11}F_3N_4O$ requires C, 60.65; H, 3.1; N, 15.75%); δ_H 8.3 (d, *J* 9, 5-Q'H), 7.9–7.5 [m, 3 × CH(Q')], 7.3 [s, 5 × CH(Ph)], 6.0 (d, *J* 6, azir. 2-H) and 3.2 (d, *J* 6, azir. 3-H); ν_{max}/cm^{-1} 2240s, 1690s and 1600s; *m/z* (%) 356 (3.1) (M^+) 143 (100), 116 (51) and 76 (24).

2-Butyl-1-(4-oxo-2-trifluoromethyl-3,4-dihydroquinazolin-3-yl)-aziridine 12

Using the procedure above, hex-1-ene (1.07 g, 3 mmol) was aziridinated using 3-aminoquinazolinone **6** (830 mg, 3.6 mmol) and LTA (1.62 g, 3.6 mmol) in dichloromethane (8.5 cm^3). After work-up, flash chromatography using light petroleum–ethyl acetate (5:1) as eluent gave *aziridine* **12** as an oil (556 mg, 50.5%) (R_F 0.75) (Found: M^+, 311.124. $C_{15}H_{16}F_3N_3O$ requires M^+, 311.124); δ_H(300 MHz) 8.22 (d, *J* 7.9, 5-Q'H), 7.81 [m, 2 × CH(Q')], 7.6–7.5 [m, CH(Q')], 3.61 (m, azir. ring 2-H), 3.33 (d, *J* 7.5 azir. 3-H *trans* to Bu), 2.16 (structured d, *J* 6, azir. 3-H *cis* to Bu), 1.46–1.36 (3 × CH_2) and 0.99 (t, *J* 7, CH_3); ν_{max}/cm^{-1} 1680s and 1600s; *m/z* (%) 311 (17) (M^+) 242 (33), 240 (24), 215 (100), 214 (80), 146 (42), 145 (25), 117 (25) and 104 (25).

2-Chloromethyl-1-(4-oxo-2-trifluoromethyl-3,4-dihydroquinazolin-3-yl)aziridine 16; bis(4-oxo-2-trifluoromethyl-3,4-dihydroquinazolin-3-yl)amine 14

Allyl chloride (1.88 g, 24.6 mmol) was aziridinated using 3-aminoquinazolinone **6** (1.03 g, 81 mmol) and LTA (3.6 g, 8.1 mmol) in dichloromethane (18 cm^3) using the general procedure above except that the reaction mixture was stirred overnight before separation of the lead salts. After work-up, flash chromatography using light petroleum–ethyl acetate (4:1) as eluent gave the *aziridine* **16** as colourless crystals (2.46 g, 46%), mp 159–160 °C (from light petroleum) (Found: C, 47.65; H, 3.0; N, 13.85. $C_{12}H_9ClF_3N_3O$ requires C, 47.45; H, 3.0; N, 13.85%); δ_H(300 MHz) 8.2 (d, *J* 7.9, 5-Q'H), 7.8–7.5 [m, 3 × CH(Q')], 4.14 (m, azir. 2-H), 3.8 (dd, *J* 11.5, 6.2, C*H*HCl and d, *J* 7.6, azir. 3-H *trans* to OH_2Cl), 3.55 (dd, *J* 11.5, 6.2, CH*H*Cl) and 2.29 (d, *J* 4.2 azir. 3-H *cis* to CH_2Cl); ν_{max}/cm^{-1} 1680s and 1620s; *m/z* (%) 305 (15), 303 (48) (M^+), 268 (63), 240 (43), 214 (100), 145 (28), 130 (35), 104 (53), 90 (61) and 76 (49). Further elution with light petroleum–ethyl acetate (1:1) gave bis(4-oxo-2-trifluoromethyl-3,4-dihydroquinazolin-3-yl)-amine **14** (788 mg, 22%) as colourless crystals (from ethanol), mp 178 °C (decomp.) (Found: C, 49.05; H, 2.15; N, 15.95. $C_{18}H_9F_6N_5O_2$ requires C, 49.0; H, 2.05; N, 15.85%); δ_H(300 MHz) 10.3 (s, NH), 8.2 (d, *J* 8, 2 × 5-Q'H), 7.9 [m, 4 × CH(Q')] and 7.6 [m, 2 × CH(Q')]; δ_F 66.633; ν_{max}/cm^{-1} 3400br, 1700s and 1610s; *m/z* (%) 229 (17), 214 (100), 145 (78), 130 (25), 117 (23), 104 (21), 91 (91), 76 (43) and 64 (46); *m/z* (FAB) 442 ($M + H^+$). A sample of this compound suitable for an X-ray crystal structure determination was obtained by slow evaporation of an ethanol solution.

Aziridination of cyclohexenol with 7

Cyclohex-2-enol (1 g, 10.2 mmol) was aziridinated using the general procedure above with 3-aminoquinazolinone **6** (775 mg, 3.38 mmol) and LTA (1.57 g, 3.54 mmol) in dichloromethane (8 cm^3) except that the solution was stirred overnight before separation of the lead salts. After work-up, flash chromatography and elution with light petroleum–ethyl acetate (1:1) gave the *aziridine* **17** (886 mg, 80%) (R_F 0.25) as colourless crystals, mp 133–135 °C (from diethyl ether) (Found: C, 55.2; H, 4.35; N, 12.85. $C_{15}H_{14}F_3N_3O_2$ requires C, 55.4; H, 4.35; N, 12.9%); δ_H(300 MHz) 8.24 (d with additional fine coupling, *J* 8, 5-Q'H), 7.83 [m, 2 × CH(Q')], 7.63 [m, CH(Q')], 4.13 (m, br, C*H*OH), 3.79 (d, *J* 6.4, H), 3.73 [dd, *J* 4.2, 7.9, azir. 1-H (see **17**)], 3.62–3.57 (m, br, azir. 2-H), 1.97–1.87 (m, 2 H) and 1.76–1.15 (m, 4 H); ν_{max}/cm^{-1} 3480br, 1680s and 1660s; *m/z* (%) 215 (79) and 145 (41).

Aziridination of cyclohexenol in the presence of aqueous sodium hydrogen carbonate

A solution of 3-acetoxyamino-2-trifluoromethylquinazolinone **7** in dichloromethane (16 cm^3) was prepared as described above from **6** (1.6 g, 6.9 mmol) and LTA (3.2 g, 6.9 mmol). An equal volume of saturated aqueous sodium hydrogen carbonate was added to the rapidly stirred emulsion followed by cyclohex-2-enol (1 g) and stirring continued for 10 min. After separation of the organic layer and work-up as described for the general aziridination procedure, the product was purified by flash chromatography and elution with ethyl acetate–light petroleum (1:6) gave the *cis*-aziridine **17** above (560 mg) (R_f 0.25) followed by the *trans*-aziridine **18** (420 mg) (R_f 0.2) which was obtained as colourless crystals, mp 121–122 °C (from diethyl ether) (Found: C, 54.85; H, 4.35; H, 12.8. $C_{15}H_{14}F_3N_3O_2$ requires C, 55.4; H, 4.35; N, 12.9%); δ_H(300 MHz) 8.2 (d, *J* 8, 5-Q'H), 7.79 [2 × CH(Q')], 7.61 [m, CH(Q')], 4.30 (m, C*H*OH), 3.78–3.74 (m, br, azir. 3-H), 3.70 (d, br, *J* 7.3, azir. 2-H), 2.31 (s, br, OH), 2.15–2.07 (m, 1 H), 1.92–1.75 (m, 3 H) and 1.38–1.21 (m, 2 H); ν_{max}/cm^{-1} 3300br, 1680s and 1610s.

Aziridination of cyclohex-2-enyl acetate with 7

Cyclohex-2-enyl acetate (900 mg, 6.4 mmol) was aziridinated with the 3-aminoquinazolinone **6** (734 mg, 3.2 mmol) and LTA (1.42 g, 3.2 mmol) in dichloromethane (7 cm^3) following the general procedure above. After work-up, flash chromatography using ethyl acetate–light petroleum (4:1) gave *aziridine* **22** (377 g, 32%) as colourless crystals, mp 130–132 °C (from diethyl ether) (Found: C, 55.35; H, 4.4; N, 11.35. $C_{17}H_{16}F_3N_3O_3$ requires C, 55.6; H, 4.4; N, 11.45%); δ_H(300 MHz) 8.18 (dd, *J* 7.9 and 0.8, 5-Q'H), 7.81 [m, 2 × CH(Q')], 7.61 [m, CH(Q')], 5.22 (m, br C*H*OH), 4.11–4.07 (m, azir. 2-H), 4.04 (d, *J* 7.1, azir. 1-H), 2.09–1.89 (m, 4 H including OAc), 1.87–1.74 (m CH_2) and 1.52–1.30 (m, 2 × CH_2); ν_{max}/cm^{-1} 1730s, 1670s and 1610s; *m/z* (%) 368 ($M^+ + H$), 309 (25), 308 (32), 216 (44), 215 (100), 145 (47) and 112 (24).

3-Amino-2-ethoxycarbonylquinazolin-4(3*H*)one 23

This compound, prepared by a literature procedure, was obtained as colourless crystals (40%), mp 134–136 °C (lit.,[11] mp 138 °C).

3-Amino-2-(1,1-dichloroethyl)quinazolin-4(3*H*)one 24

To 2,2-dichloropropionic acid (8.5 g, 38.5 mmol) was added thionyl chloride (9.79 g, 82.3 mmol) and DMF (0.1 cm^3) and the mixture heated under reflux for 3 h. It was then distilled through a column packed with Raschig rings until the temperature at the top of the column exceeded 80 °C. The liquid remaining in the column was washed back into the flask with dry ether (50 cm^3) and the contents of the flask, dissolved in this ether, was then added dropwise *via* a dropping funnel to a stirred solution of methyl anthranilate (17.5 g, 116 mmol) in dry ether (100 cm^3). After the mixture had been stirred for 16 h, hydrochloric acid (2 mol dm^{-3}; 100 cm^3) was added to dissolve the thick precipitate of methyl anthranilate hydrochloride. The organic layer was separated, washed with further hydrochloric acid (2 mol dm^{-3}; 5 × 50 cm^3) and then aqueous sodium hydrogen carbonate (50 cm^3) and brine (50 cm^3), dried and evaporated under reduced pressure to yield methyl *N*-(2,2-dichloropropionyl)anthranilate **28** (9.07 g, 85%) as colourless crystals, mp 44–46 °C (from light petroleum) (Found: C, 47.85; H, 4.0; H, 5.0. $C_{11}H_{11}Cl_2NO_3$ requires C, 47.85; H, 4.0; N, 5.05%); δ_H 12.2 (s, br, CONH), 8.7 (d, *J* 9, 3-H), 8.1 (d, *J* 9, 6-H), 7.5 and 7.3 (2 × t, *J* 9, 4-H and 5-H), 3.9 (s, CO_2CH_3) and 2.3 (s, CH_3CCl_2); ν_{max}/cm^{-1} 3180w, br, 1700s and 1620s; *m/z* (%) 277 (1.3) (M^+), 178 (31) and 146 (100). To a solution of the anthranilate above (6 g, 0.02 mol) in ethanol (20 cm^3) was added hydrazine hydrate (56 g, 5 mol equiv.) and the solution heated under reflux for 3 h. The bulk of the ethanol was removed under reduced pressure and the residue dissolved in ethyl acetate (50 cm^3) and the solution washed with brine (30

cm^3), dried and evaporated under reduced pressure to give the anthranilohydrazide **29**. This was characterised by dissolution in propanone (excess) and then evaporation of the excess of propanone under reduced pressure to give the hydrazone as colourless crystals, mp 184–186 °C (from ethanol) (Found: C, 49.55; H, 4.85; N, 13.3. $C_{13}H_{15}Cl_2N_3O_2$ requires C, 49.4; H, 4.8; N, 13.3%); δ_H 11.9 (s, NH), 8.8 (s, br, NH), 8.5 [d, *J* 9, CH(Ar)], 7.6–7.0 [m, 3 × CH(Ar)], 2.3 (s, CH_3CCl_2) and 2.1 and 1.9 (2 × s, CH_3CH_3); ν_{max}/cm^{-1}, 3240s br, 1690s and 1600s.

A solution of the above anthranilohydrazide **29** (1.46 g, 5.2 mmol) in ethanol (30 cm^3) was heated to 180 °C in a thick-walled Young's tube for 5 h. After cooling to ambient temperature, the mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane (50 cm^3). The solution was washed with brine (2 × 30 cm^3), dried and evaporated to give the 3-aminoquinazolinone **24** as colourless crystals, mp 138–140 °C (from ethanol) (Found: C, 46.6; H, 3.55; N, 16.2. $C_{10}H_9Cl_2N_3O$ requires C, 46.55; H, 3.5; N, 16.3%); δ_H 8.2 (d, *J* 9, 5-Q'H), 7.7–7.3 [m, 3 × CH(Q)], 5.2 (s, NH_2) and 2.6 (CH_3CCl_2); ν_{max}/cm^{-1} 3320s, 3220w, 1670s and 1630w; *m/z* (%) 261 (6.8) (M^+), 159 (41), 257 (64), 222 (100), 192 (28), 130 (21) and 76 (24).

3-Amino-2-difluoromethylquinazolinone 25

To triphenylphosphine (4.2 g, 16 mmol) and methyl anthranilate (4.9 g, 32 mmol) was added difluoroacetic acid (1.52 g, 16 mmol) and carbon tetrachloride (10 cm^3). The mixture was heated under reflux for 1 h with intermittent addition of further carbon tetrachloride to maintain mobility. After cooling of the mixture to ambient temperature, the insoluble material was separated and the organic solution was washed with dilute hydrochloric acid (2 mol dm^{-3}; 5 × 30 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3) and brine (2 × 30 cm^3), dried and evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the solution filtered through a column of silica to remove triphenylphosphine oxide. Evaporation of the ethyl acetate under reduced pressure gave the *anthranilate* **30** (2.97 g, 80%), mp 78–79 °C (from light petroleum) (Found: C, 52.35; H, 4.0; N, 6.1. $C_{10}H_9F_2NO$ requires C, 52.4; H, 3.95; N, 6.1%); δ_H 12.1 (s, br, CONH), 8.8 (d, *J* 9, 3-ArH), 8.1 (*J* 9, 6-ArH), 7.6 (t, *J* 9, ArH), 7.2 (t, *J* 9, ArH), 6.6 (t, $J_{H,F}$ 54, CHF_2) and 4.0 (s, CO_2Me); ν_{max}/cm^{-1} 3500w, 3200m, 2280w, 1690s and 1610m. To a stirred solution of the anthranilate **30** above (2.17 g, 9.5 mmol) in ethanol was added hydrazine hydrate (2.58 g, 51 mmol) and the solution heated under reflux for 2 h. The bulk of the ethanol was removed under reduced pressure and the residue triturated with ether to give the 3-*aminoquinazolinone* **25** as colourless crystals (1.1 g, 55%), mp 162–163 °C (from ethanol) (Found: C, 51.0; H, 3.4; N, 19.8. $C_9H_7F_2N_3O$ requires C, 51.2; H, 3.35; N, 19.9%); δ_H([$^2H_6$]acetone) 7.5 (d, *J* 9, 5-QH), 7.2 [m, 3 × CH(Q)], overlapping 6.4 (t, $J_{H,F}$ 54, CHF_2) and 4.0 (s, CO_2Me); ν_{max}/cm^{-1} 3310m, 3200m, 1680s and 1640m; *m/z* (%) 211 (100), 182 (55), 134 (20) and 132 (24).

Reaction of methyl *N*-bromoethanoylanthranilate 31 with caesium fluoride

Caesium fluoride (1.76 g, 12 mmol) was dried *in vacuo* at ~ 150 °C for 5 min in a flask equipped with a magnetic stirring bar. A solution of the anthranilate **31**[13] (1.22 g, 4.48 mmol) in dry DMF (3 cm^3) was added *via* a syringe through a septum cap. The mixture was stirred for 3 h and then decanted into water (3 cm^3) and extracted with ethyl acetate (25 cm^3). The extract was washed with brine (5 × 25 cm^3), dried and evaporated under reduced pressure to give a solid, crystallisation of which from ethyl acetate–light petroleum and then from ethanol afforded the dihydropyridazine-2,5-dione **34** as a colourless solid (675 mg, 39%), mp 168–170 °C (Found: C, 62.7; H, 4.8; N, 7.3. $C_{20}H_{18}N_2O_6$ requires C, 62.8; H, 4.75; N, 7.35%); δ_H 8.2 [d, *J* 6, 2 × CH(Q)], 7.7–7.3 [m, 6 × CH(Q)], 4.5 (s, 2 × CH_2) and 3.9 (s, 2 × CO_2Me); ν_{max}/cm^{-1} 1715s and 1670s; *m/z* (%) 383 (23) (M^+ + H), 382 (100) (M^+), 351 (27), 350 (52), 149 (35), 148 (40), 132 (51), 105 (27) and 77 (35).

Reaction of compound 31 with sodium hydride

To a dried flask containing sodium hydride (25 mg, 1.04 mmol) and a magnetic stirrer bead, was added, *via* a septum cap, the anthranilate **31** (250 mg, 0.92 mmol) as a solution in dry DMF (3 cm^3). The solution was stirred for 3 h and then worked up as described above to give pyridazine-2,5-dione **34** (202 mg, 57%) identical (mixed mp comparison) with the sample obtained as described above.

3-Amino-2-fluoromethylquinazolinone 26

Methanol (100 cm^3) was added to a flask containing caesium fluoride (9.8 g) and potassium fluoride (2.7 g) and the mixture heated under reflux until the solids were thoroughly dispersed in the solution; this was then evaporated to dryness under reduced pressure. This procedure of addition of methanol (100 cm^3), heating under reflux and evaporation under reduced pressure was repeated three times. The flask was then equipped with a magnetic stirring bar and the anthranilate **31** (3.42 g, 13.3 mmol) added as a solution in sulfolane (30 cm^3). The stirred reaction mixture was heated to 150 °C for 2 h under a nitrogen atmosphere, cooled to room temperature, diluted with ethyl acetate (100 cm^3), filtered to remove insoluble material and then washed successively with brine (5 × 50 cm^3), hydrochloric acid (2 mol dm^{-3}; 5 × 50 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3) and water (2 × 50 cm^3), dried and evaporated under reduced pressure. Methyl *N*-fluoroethanoylanthranilate **32** was obtained as a colourless solid (1.93 g, 78%) by sublimation (21 °C, 2 mmHg) of the residue and crystallised from light petroleum, mp 120–122 °C (Found: M^+, 211.064. $C_{10}H_{10}FNO_2$ requires M^+, 211.064); δ_H 11.7 (s, br, CONH) 8.7 (d, *J* 9, 3-ArH), 8.0 (d, *J* 9, 6-ArH), 7.6 (t, *J* 6, CHAr), 7.2 (dd, *J* 6, CHAr), 5.1 (d, $J_{H,F}$ 48, CH_2F) and 3.8 (s, CO_2Me); ν_{max}/cm^{-1} 3180w, 1710s and 1680s; *m/z* (%) 211 (58) (M^+) and 146 (100).

A solution of the anthranilate **32** above (395 mg, 1.87 mmol) in ethanol (5 cm^3) containing hydrazine (0.103 g, 2 mmol) was heated under reflux for 3 h. The bulk of the solvent was removed under reduced pressure and the solid residue crystallised from water to give 3-aminoquinazolinone **26** (281 mg) as a colourless solid, mp 158–159 °C (lit.,[13] mp 163 °C).

3-Amino-2-[fluoro(phenyl)methyl]quinazolinone 27

Fluoro(phenyl)acetic acid (1 g, 6.5 mmol) and thionyl chloride (8.15 g, 69 mmol) were heated under reflux for 2 h after which the excess of thionyl chloride was removed under water pump pressure at room temperature. The residue was added to a solution of methyl anthranilate (2.39 g, 15 mmol) in ether (30 cm^3) and the mixture stirred for 1 h. The resulting thick suspension was treated with hydrochloric acid (2 mol dm^{-3}; 30 cm^3) after which the organic layer was separated and washed with further hydrochloric acid (2 mol dm^{-3}; 2 × 30 cm^3), saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3) and brine (30 cm^3), dried and evaporated to dryness under reduced pressure. Crystallisation of the residue from light petroleum gave the anthranilate **33** (1.29 g, 69%) as a colourless solid, mp 81–83 °C; δ_H 11.9 (s, br, NH), 8.7 (d, *J* 9, 3-ArH), 8.1 [d, *J* 9, CH(Ar)], 7.6–7.1 [m, 2 × CH(Ar) and 5 × CH(Ph)], 6.1 (d, $J_{H,F}$ 48, PhCHF) and 3.9 (s, CO_2Me); ν_{max}/cm^{-1} 3250w, 1710s and 1690; *m/z* (%) 287 (12) (M^+), 178 (39) and 146 (100). To a solution of this anthranilate **33** (1 g, 3.48 mmol) in ethanol (5 cm^3) was added hydrazine hydrate (1.03 g, 20 mmol) as a

solution in ethanol (5 cm^3) and the mixture heated under reflux for 3 h. After cooling, the solution was diluted with ethyl acetate (50 cm^3), washed with brine (5 × 50 cm^3), dried and evaporated to dryness under reduced pressure. The residual solid was crystallised from ethanol to give the *3-aminoquinazolinone* **27** (755 mg, 80%) as colourless crystals, mp 137–141 °C (Found: C, 67.0; H, 4.6; N, 15.6. $C_{15}H_{12}FNO_3$ requires C, 66.9; H, 4.5; N, 15.6%); δ_H 8.2 (d, *J* 9, 5-QH), 7.7–7.3 [m, 3 × CH(Q) and 5 × CH(Ph)], 7.1 (d, $J_{H,F}$ 48, PhCHF) and 4.6 (s, NH_2); ν_{max}/cm^{-1} 3320w, 3280w, 1680s and 1610; *m/z* (%) 269 (20, M^+), 255 (98), 253 (47), 250 (35), 249 (100), 248 (50), 236 (26), 235 (50), 220 (56), 119 (24), 109 (59), 105 (37), 91 (24) and 90 (31).

3-Amino-2-(1-chloroethyl)quinazolinone 36

To a stirred solution of the 3-aminoquinazolinone **35** (1 g, 4.9 mmol) in carbon tetrachloride (50 cm^3) was added triphenylphosphine (1.3 g, 5.0 mmol) and DMF (5 cm^3) and the mixture stirred for 2 h. After separation of insoluble material, the solution was evaporated to dryness under reduced pressure, adsorbed onto silica and chromatographed with light petroleum–ethyl acetate (4:1) as eluent to remove the more polar triphenylphosphine oxide. Evaporation of the eluent under reduced pressure gave the title compound 3-aminoquinazolinone **36** as a colourless low-melting solid (509 mg, 54%), $[\alpha]_D$ −39.4 (*c* 1.0, $CHCl_3$) (Found: M^+, 223.050. $C_{10}H_{10}N_3ClO$ requires M^+, 223.051); δ_H 8.2 (d, *J* 9, 5-QH), 7.6 [m, 2 × CH(Q)], 7.5–7.2 [m, CH(Q)], 5.7 (q, *J* 6, CH_3CHCl), 5.0 (s, br, NH_2) and 1.9 (d, *J* 6, CH_3CHCl); ν_{max}/cm^{-1} 3340w, 3220w, 1675s and 1600s; *m/z* (%) 225 (18) (M^+, ^{37}Cl), 223 (63) (M^+, ^{35}Cl), 188 (100) and 171 (21).

3-Amino-2-(1-bromoethyl)quinazolinone 37

Following the above procedure but substituting carbon tetrabromide (1.62 g, 4.88 mmol) for carbon tetrachloride gave, after a similar work-up, the title 3-aminoquinazolinone **37** (170 mg, 8%) as colourless crystals, mp 170–171 °C (from ethanol), $[\alpha]_D$ 0 (Found: C, 44.95; H, 3.85; N, 15.55. $C_{10}H_{10}BrN_3O$ requires C, 44.8; H, 3.75; N, 15.65%); δ_H 8.2 (d, *J* 9, 5-QH), 7.7 [m, 2 × CH(Q)], 7.6–7.2 [m, CH(Q)], 5.9 (q, *J* 6, MeC*H*Br), 5.0 (s, br, NH_2) and 2.2 (d, *J* 6, CH_3CHBr); ν_{max}/cm^{-1} 3340w, 3280w and 1680s; *m/z* (%) 269 (39) (M^+, ^{81}Br), 267 (39) (M^+, ^{79}Br), 188 (100) and 173 (49).

3-Amino-2-(1-fluoroethyl)quinazolinone 38

To an ice-cold stirred solution of 3-aminoquinazolinone **35** (1 g, 4.9 mmol) in dichloromethane (20 cm^3) was added diethylaminosulfur trifluoride (1 cm^3, 1.21 g, 7.5 mmol) dropwise. The solution was stirred for 1 h at 0 °C and then diluted with methanol (20 cm^3), washed with saturated aqueous sodium hydrogen carbonate (5 × 20 cm^3) and saturated brine (5 × 50 cm^3), dried and evaporated under reduced pressure. Flash chromatography of the residue using ethyl acetate gave the title *3-aminoquinazolinone* **38** as a low-melting solid (714 mg, 70%), $[\alpha]_D$ −9.04 (*c* 1.0, $CHCl_3$) (Found: M^+, 207.080. $C_{10}H_{10}FN_3O$ requires M^+, 207.080); δ_H 8.3 (d, *J* 9, 5-QH), 7.8 [m, 2 × CH(Q)], 7.5–7.2 [m, CH(Q)], 6.5 (dq, *J* 6, $48_{H,F}$, MeC*H*F), 5.2 (s, NH_2), 2.9 [dd, *J* 6, 24 (HF) and CH_3CHF]; *m/z* (%) 207 (100) (M^+), 192 (25), 186 (41), 158 (24) 130 (35), 119 (30), 90 (25) and 76 (22).

3-Amino-2-pentafluoroethylquinazolinone 39

To anthranilic acid (2 g, 15 mmol) as a stirred suspension in dry dichloromethane (50 cm^3) was added pentafluoropropionic anhydride (14.4 g, 47 mmol) and the mixture heated under reflux for 1 h. The reaction mixture was evaporated to dryness under reduced pressure and to the residual solid mass was added hydrazine hydrate (0.75 g, 15 mmol) as a solution in ethanol (50 cm^3). After the mixture had been stirred for 1 h, the volatile material was removed under reduced pressure and the residual hydrazine **41** was characterised by dissolving a little in an excess of propanone and then removing the excess of the latter under reduced pressure to give the corresponding *hydrazone* as colourless crystals, mp 188–190 °C (from ethanol) (Found: C, 46.15; H, 3.6; N, 12.4. $C_{13}H_{12}F_5N_3O_2$ requires C, 46.3; H, 3.6; N, 12.45%). A solution of the hydrazine **41** (2.88 g, 9.7 mmol) prepared above in ethanol (50 cm^3) was heated to 180 °C for 5 h in a thick-walled Young's tube. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure and the resultant solid crystallised from ethanol to give *3-aminoquinazolinone* **39** as a colourless solid (1.73 g, 64%), mp 123–124 °C (from ethanol) (Found: C, 42.95; H, 2.25; N, 15.0. $C_{10}H_6N_3F_5O$ requires C, 43.0; H, 2.15; N, 15.0%); δ_H 8.2 (d, *J* 9, 5-QH), 7.8 [m, 2 × CH(Q)], 7.6 [m, CH(Q)] and 5.0 (s, NH_2); ν_{max}/cm^{-1} 3320w, 3220w, 1690s and 1610s: *m/z* (%) 279 (100) (M^+), 250 (83), 230 (21) and 187 (21).

2-Butyl-1-(2-difluoromethyl-4-oxo-3,4-dihydroquinazolin-3-yl)-aziridine 43

The aziridination procedure described earlier (for 3-aminoquinazolinone **6**) was followed using hex-1-ene (396 mg, 4.02 mmol), 3-aminoquinazolinone **25** (300 mg, 1.42 mmol) and LTA (600 mg, 1.59 mmol) in dichloromethane (3 cm^3). After a similar work-up procedure, flash chromatography of the residue over silica gave the title *aziridine* **43** as a colourless oil (155 mg, 37%) (Found: M^+, 293.133. $C_{15}H_{17}F_2N_3O$ requires M^+, 293.133); δ_H(300 MHz) 8.21 (dd, *J* 8.4 and 0.8, 5-QH), 7.79 (m, 7-QH and 8-QH), 7.56 (m, 6-QH), 7.30 (t, *J* 53.4, CHF_2), 3.51 (m, azir. 2-H), 3.22 (d, br, *J* 7.6, azir. 3-H *trans* to Bu), 2.24 (dd, *J* 5.3, 1.5, azir. 3-H *cis* to Bu), 2.07–1.89 (m, 2C*H*), 1.50 (m, br, 4CH) and 0.96 (t, *J* 7.1, CH_3CH_2), ν_{max}/cm^{-1} 1740s, 1680s and 1610s; *m/z* (%) 293 (12) (M^+), 224 (23), 222 (26), 197 (85), 196 (100), 146 (21), 145 (32), 129 (25), 98 (41) and 76 (29).

Aziridination of hex-1-ene using 3-amino-2-fluoromethylquinazolinone 26

The aziridination procedure described above was followed using hex-1-ene (156 mg, 1.85 mmol). After work-up, an oily product (77 mg) was obtained whose NMR spectrum after addition of anisole (47 mg) as internal standard showed a maximum yield of the aziridine **42** to be not greater than 13% from integration comparison of the resonances at δ 1.55–0.80 (butyl) to δ 3.79 (OCH_3).

Crystal data

$C_{18}H_9F_6N_5O_2$, M = 441.3, tetragonal, space group $P4n2$, a = 14.426(1), c = 17.258(2) Å, U = 359.17(7) $Å^3$, Z = 8, D_c = 1.632 g cm^{-3}, Mo-Kα radiation, λ = 0.710 73 Å, μ(Mo-Kα) = 0.152 mm^{-1}, $F(000)$ = 1776, crystal dimensions 0.54 × 0.52 × 0.26 mm. Accurate unit cell dimensions were determined by least-squares refinement of omega angles for 28 centred reflections with 10 < 2θ < 25°. Data were measured on a Siemens P4 diffractometer with Mo-Kα radiation using omega scans. 3739 Reflections were measured over the range 2θ < 50° with −1 < *h* < 15, −1 < *k* < 17, −1 < *l* < 20. The reflections were corrected for Lorentz and polarisation effects and merged to give 2866 independent reflections (R_{int} = 0.013) with 2093 having $I > 2\sigma(I)$ regarded as observed.

The structure was solved by direct methods using the program SHELXTL-pc.[15] The hydrogen atom on N-2 was located from difference Fourier maps and refined as a normal atom. All other hydrogen atoms were included in calculated positions (C–H = 0.96 Å), with a common isotropic thermal

parameter. All other atoms were refined with anisotropic thermal parameters. Final cycles of refinement gave $R = 0.041$, $R_w = 0.056$ $[w^{-1} = \sigma^2 F + 0.0026F^2]$. The maximum and minimum residual electron densities in the final ΔF map were 0.36 and -0.27e Å^{-3}, respectively. The mean and maximum shift/error in the final refinement cycle were 0.000 and 0.002.

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