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AMINATION WITH 3-ACETOXYAMINOQUINAZOLIN-4-(3H)ONES: PREPARATION OF α-AMINOACID ESTERS BY REACTION WITH SILYL KETENE ACETALS FOLLOWED BY N-N BOND CLEAVAGE

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Abstract: Solutions of 3-acetoxyaminoquinazolinone (5) react with enol ethers and silyl ketene acetals to give α-aminoaldehyde α-aminoketone or α-aminoacid derivatives. Acylation of the exocyclic nitrogen in these derivatives, as a preliminary to reductive N-N bond cleavage, could only be accomplished by indirect means. Samarium diiodide, however, effected the reduction of this N-N bond without the necessity for N-acylation. Solutions of the corresponding enantiopure 3-acetoxyaminoquinazolinone (34) brought about the diastereoselective amination of the prochiral silyl ketene acetal (15) and reductive N-N bond cleavage of the major diastereoisomer lead to enantiopure 2-phenylalanine methyl ester.

INTRODUCTION

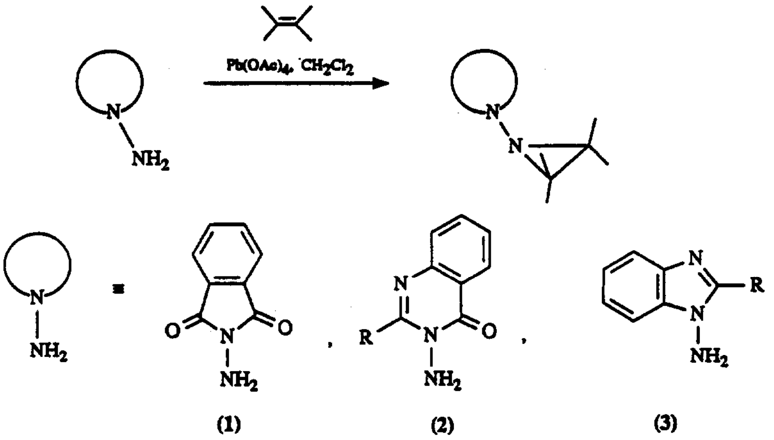
There is a dearth of general methods available for direct and efficient conversion of alkenes into aziridines—aziridination.[1] Consequently, relatively little use is made of aziridines as relay intermediates by comparison with that made of epoxides.

Epoxidation of double bonds by the use of peracids or by the use of hydroperoxides in the presence of metal salts are important methods particularly where they are accompanied by high levels of diastereo- or enantioselection.[2] By contrast, aziridination of double bonds using the nitrogen analogues of these reagents is unknown (see however, below). Although the existing methods for aziridination are frequently stereospecific with retention of the double bond configuration in the 3-membered ring,[3] examples of high diastereo- or enantiofacial selection in these reactions are few.

One of the most successful and expedient methods for aziridinating double bonds is still that discovered by C. W. Rees and his coworkers in the late 1960's.[4] This method uses the oxidative addition of various N-aminoheterocycles e.g. (1)—(3) to alkenes (Scheme 1).

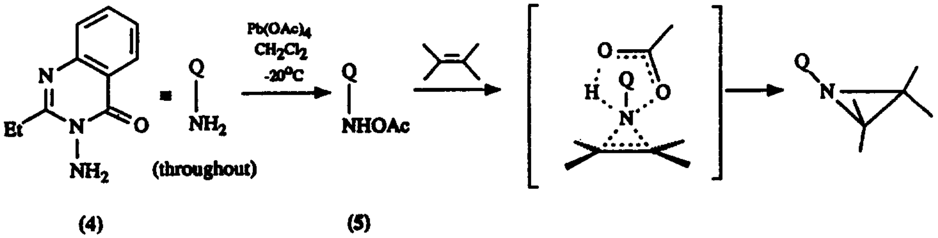
Both electron-rich alkenes (e.g. styrene) and electron-deficient ones (e.g. α,β-unsaturated esters or ketones) can be aziridinated in good yields (70%) by this method using a modest excess of the alkene.[5]

The identities of the intermediates in these oxidative aziridinations were assumed to be the corresponding N-nitrenes but, at least for the case of 3-aminoquinazolinones e.g. (4), are now known to be the 3-acetoxyaminoquinazolinones e.g. (5)[6]



Scheme 1

(Scheme 2).* Aziridination of alkenes by (5), therefore, resembles epoxidation of alkenes by peracids.[7]



Scheme 2

Previously, aziridination was carried out (Scheme 1) by oxidation of the N-aminoheterocycle in the presence of the alkene. Our ability to prepare stable solutions of 3-acetoxyaminoquinazolinones e.g. (5) at <-10 °C and to use these solutions to aziridinate alkenes is advantageous since the lead tetra-acetate (LTA) is consumed before the alkene is added.[6] Consequently aziridination of alkenes can be attempted which would otherwise be attacked by lead tetra-acetate.

The use of 3-acetoxyamino-derivatives of 3-aminoquinazolinones (2) as aziridinating agents has additional advantages. Firstly, a chiral centre can be incorporated into the R group in position 2 which can then be used to bring about high asymmetric induction in addition to prochiral alkenes (Scheme 3).[8]

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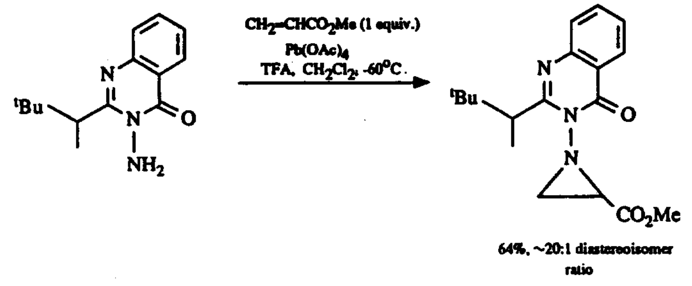
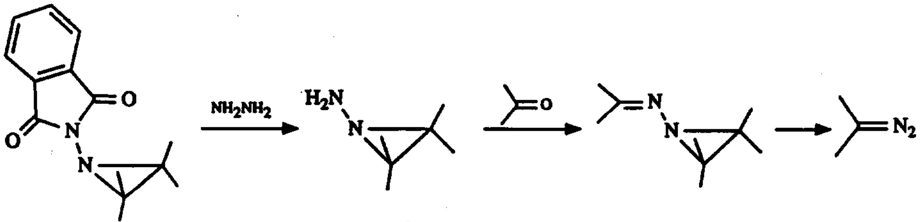
* Interestingly the earlier presumed N-phthalimidonitrene intermediate from oxidation of (1) has been generated by other means and appears to have a reactivity profile which is different from, but similar to, the N-acetoxyaminophthalimide (analogous to (5)) which is now believed to be intermediate in oxidative addition of (1) to alkenes (see R. S. Atkinson and D. W. Jones J.C.S. Perkin Trans. 1, 1991 1344).



Scheme 3

Secondly, addition of trifluoroacetic acid catalyses aziridinations using 3-acetoxyaminoquinazolinones e.g. (5) and facilitates the reaction with otherwise unreactive alkenes (or enables a smaller excess of reactive alkene to be used (see Scheme 3)).[9] Thirdly, the ready assembly of 3-aminoquinazolinones in which the 2-substituent contains an alkene has proved useful for the study of intramolecular aziridinations.[10]

For the aziridination procedure in Scheme 1 to be useful in synthesis some means for removal of the superfluous heterocyclic ring is required. For the case of N-phthalimidoaziridines, Eschenmoser et al have shown that the aziridine ring is sufficiently stable to conditions which allow removal of the phthalimide ring by hydrazinolysis.[11] (Scheme 4)

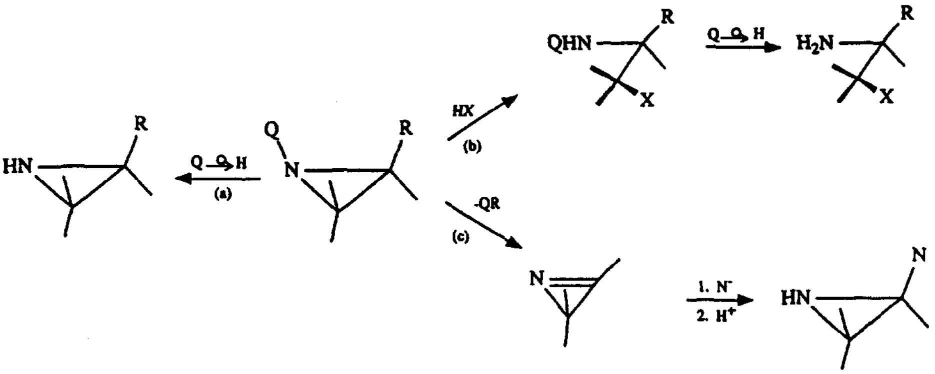


Scheme 4

The hydrazones obtained from reacting these N-aminoaziridines with ketones are useful as latent diazoalkanes and hence carbenes (Scheme 4).

Since other heterocyclic rings in this family of N-amino compounds in Scheme 1 are more robust than phthalimide, we have examined other methods for their removal. Because of the advantages which the use of quinazolinones afford, we have concentrated on methods for removal of this ring from the derived aziridines or their ring-opened derivatives (Scheme 5).

Whilst the availability of N(H)-substituted aziridines, and particularly enantiopure ones, from the reductive cleavage (a) in Scheme 5 is highly desirable, there are advantages in delaying this reduction until after aziridine ring-opening (Scheme 5(b)) (in which the quinazolinone ring might play a useful role). Route (c) in Scheme 5 is an alternative means by which the quinazolinone ring could be lost whilst retaining the aziridine ring intact which we have recently shown to be practicable.[12]

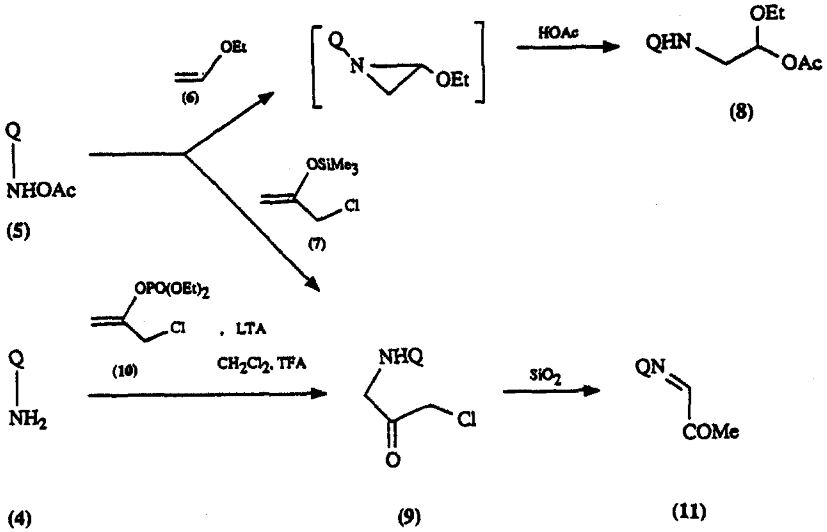


Scheme 5

In this paper we give details of our attempts to bring about reductive cleavage of the N-N bond in substrates which are formed by ring-opening of 3-aminoquinazolinone-derived aziridines (Scheme 5 route (b)).

RESULTS

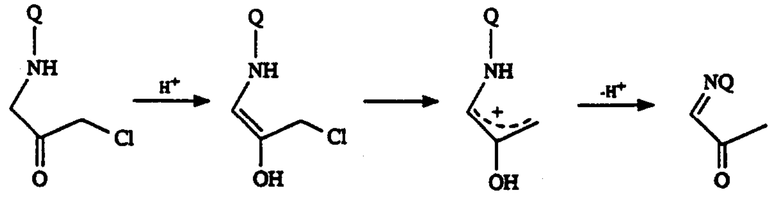
Reductive cleavage of the N-N bond according to pathway (b) in Scheme 5 is also the only one which is relevant for those cases in which the intermediate aziridines cannot be isolated because they suffer ring-opening in the aziridination. This is the case with addition of 3-acetoxyaminoquinazolinone (5) to enol ethers (6) and (7) (Scheme 6).[13]



Scheme 6

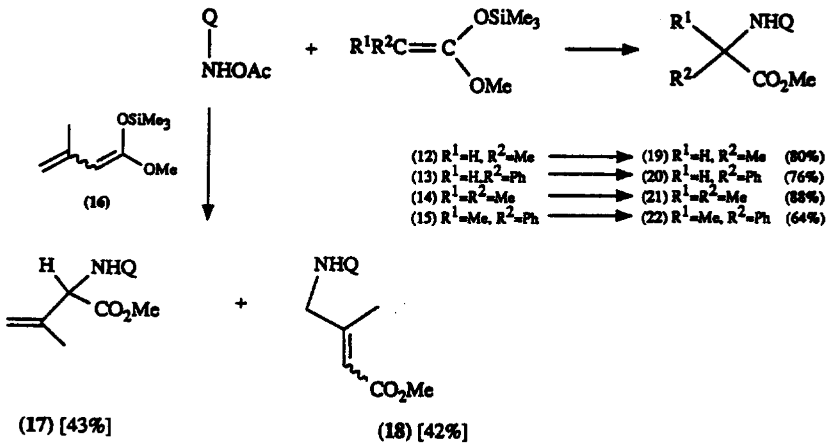
In both cases the isolated products (8) and (9), respectively, are those which are presumed to arise from ring-opening of aziridine intermediates by reaction with acetic acid which was either present in the *in situ* formation of (5) or generated in the aziridination itself. The chloroketone (9) was identical with a sample previously obtained by aziridination of the 2-diethoxyphosphoryloxyallyl chloride (10) with (5) in the presence of TFA.[9]

Attempted chromatography of (9) over silica brought about its conversion to the imine (11) presumably *via* a Favorskii-type rearrangement (Scheme 7).



Scheme 7

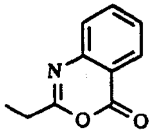
Likewise, reaction of solutions of the 3-acetoxyaminoquinazolinone (5) with silyl ketene acetals (12)-(16) gave products (17)-(22) from ring-opening of the presumed intermediate aziridines (Scheme 8).



Scheme 8

In these reactions in Scheme 8, excess ketene acetal was used to scavenge the acetic acid which is present (see above). With the use of 2,6-di-*t*-butyl-4-methylpyridine (2 equiv.) as the base and using only 1.5 mol equiv. of the silyl ketene acetal (12), amino acid ester (19) was isolated in 63% yield.

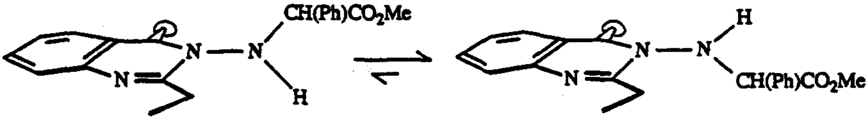
When only 1.5 equiv. of the silyl ketene acetal is used in this reaction, the yield of (19) drops to 22%: a by-product in this case is the benzoxazinone (23)(11%).



(23)

Addition to both double bonds of 1-methoxy-1-trimethylsilyloxy-3-methylbutadiene (16) (Scheme 8) occurred: one of the double bond isomers of (18) (of unknown configuration) was isolated in pure form from the mixture of the two by fractional crystallisation.

The structures of the products in Scheme 8 follow from their spectroscopic data. In the n.m.r. spectra of some of the products and notably in that of (20), some of the signals are broadened indicating the onset of some dynamic process which is slow on the n.m.r. time-scale. At -90°C in CD_2Cl_2, separate signals are visible from the two species (3:1 ratio) whose dynamic interconversion is responsible for the broadening of signals in the n.m.r. spectrum of (20) at room temperature. We assign the relationship between these two species as N-N bond rotamers. (Scheme 9)



(20a) **(20b)**

Scheme 9

At -90°C, rotation around the N-N bond becomes sufficiently slow that the N-N bond constitutes a chiral axis. Separate signals from (20a) and (20b) then become visible because of their diastereoisomeric relationship.

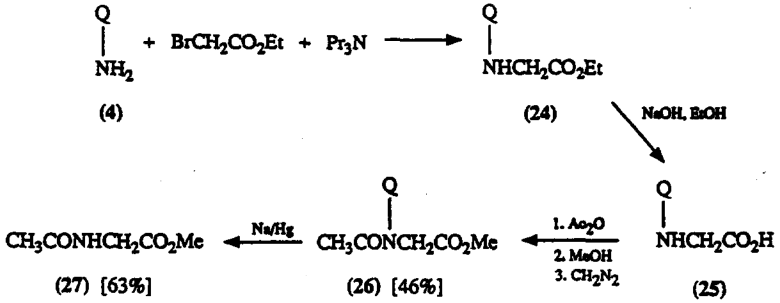
It is assumed in (20a) and (20b) that the exocyclic nitrogen is sp^3-hybridised and, in principle, therefore, the observable dynamic process could be attributable to retarded inversion at this nitrogen. However, the magnitude of the barrier in this case (~11.3 kcal/mole) we believe is too high to be attributable to an N-inversion barrier. Not surprisingly, the barrier to rotation around the N-N bond can be dramatically raised by additional substitution on the exocyclic nitrogen in compounds resembling (20) to the point where the molecule is chiral and resolvable at room temperature solely by virtue of lack of rotation around the N-N bond.[14]

Reduction of N-N bonds in N-(quinazolinone-3-yl)aminoacid esters

The products in Scheme 8 are 'protected' amino acid esters. Attempts to reductively cleave the *N*-*N* bond of the phenylglycine derivative (20) by catalytic reduction, aluminium amalgam, Raney nickel or by sodium in liquid ammonia were unsuccessful although the latter two methods in particular have been successfully used to cleave *N*-*N* bonds previously.[15]

Reductive cleavage of *N*-*N* bonds has been shown to be facilitated by the presence of carbonyl or sulphonyl substituents on *both* nitrogens.[16] Since the quinazolinone ring nitrogen already bears a carbonyl substituent, acylation or sulphonylation of the exocyclic nitrogen in e.g. (19) would, accordingly, be expected to facilitate the *N*-*N* bond reduction. However, our attempts to acylate or sulphonylate this exocyclic nitrogen of (19) and of all other 3-(substituted)alkylaminoquinazolinones have been unsuccessful using a variety of reagents and conditions.

Failure of attempts to bring about this intermolecular acylation lead us to consider the possibility of carrying out this conversion intramolecularly. For this purpose we prepared the *N*-quinazolinone-substituted glycine derivative (24) by alkylation of 3-aminoquinazolinone (4) with ethyl α-bromoacetate (Scheme 10).

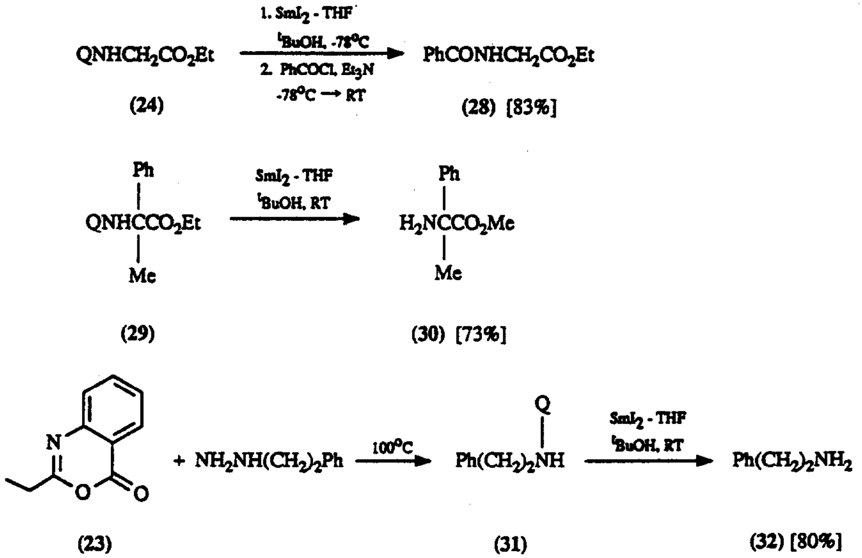


Scheme 10

When the derived acid (25) was heated in acetic anhydride under closely controlled conditions, the product, isolated as its methyl ester, was the required *N*-acetylated glycine methyl ester derivative (26). This product, presumably formed *via* intramolecular acylation *via* a mixed anhydride, has an n.m.r. spectrum in which the two protons of the *N*-methylene group are diastereotopic and resonate at widely different chemical shifts (δ3.68 and 5.02 *J* 17Hz). A minor *amide* rotamer is also visible in which these CH$_2$ groups are also diastereotopic (δ4.22 and 4.85 J 18Hz). It is well known that the barrier to rotation around the *N*-*N* bond is greatly increased when both nitrogen are acylated.[17] In the present case this rotation is slow, at least on the n.m.r. time-scale, and the chiral element which gives rise to diastereotopic protons in the methylene group is the *N*-*N* chiral axis.

Gratifyingly, reduction of the N-N bond in (26) with aluminium amalgam gave methyl N-acetylglycinate (27), identical with authentic material, in 63% yield.

Unfortunately, attempts to extend the procedure outlined in Scheme (10) to the more substituted N-quinazolinone-substituted products (17)-(22) in Scheme 8 were less successful. After examining a number of reducing agents, we attempted reduction of the N-quinazolinone-substituted glycine ester (24) with samarium diiodide in tetrahydrofuran in the presence of t-butanol (Scheme (11)) and isolated ethyl glycinate as its N-benzoyl derivative (ethyl hippurate) (28) in 83% yield.

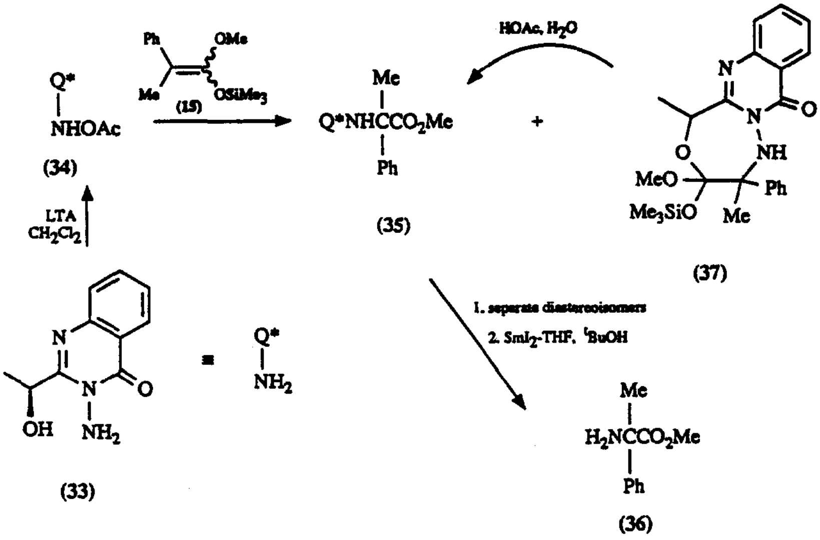


Scheme 11

This reduction with samarium iodide was tolerant of substituents on the carbon adjacent to the N-N bond ((29)→(30)) and was also successful for 3-alkyaminoquinazolinones e.g. (31)→(32). 3-(Phenylethylamino)-2-ethylquinazolin-4(3H)one (31) was conveniently prepared by heating benzoxazinone (23) with phenylethylhydrazine.

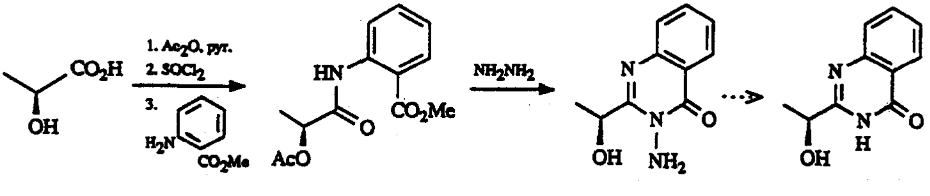
Synthesis of an enantiopure α-amino ester

We have synthesised the 2-hydroxyethyl-3-aminoquinazolone (33) in enantiopure form from (S)(+)-lactic acid and have used its derived 3-acetoxyamino derivative (34) to aminate the silyl ketene acetal (15) diastereoselectively. N-N bond cleavage of the major diastereoisomer (35) has lead to the α-aminoacid ester (36) in enantiopure form (Scheme 12).



Scheme 12

Synthesis of the enantiopure 3-aminoquinazolinone (33) was accomplished by the route shown in Scheme 13.



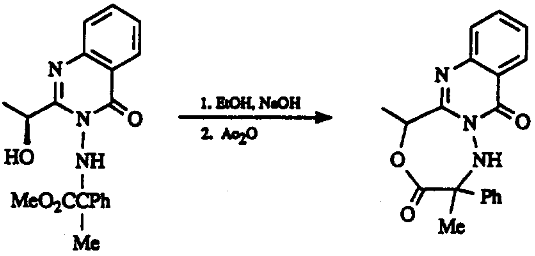
Scheme 13

Protection of the hydroxyl group by acetylation is expedient since treatment of the intermediate anthranilate with hydrazine not only brings about formation of the 3-aminoquinazolinone but also de-acetylates the hydroxyl group.

The optical purity of (33) was confirmed by its reaction with Mosher's acid chloride and by comparison of the n.m.r. spectrum of the product with that obtained from a racemic sample.[18] Acetylation of (33) with this acid chloride takes place largely if not exclusively on the hydroxyl group. 2-(1-Hydroxyethyl)quinazolin-4(3H)-one (38) is a natural product, chrysogine, isolated as metabolite from strains of Penicillium chrysogenum and Alternaria citri.[19] De-amination of 3-aminoquinazolinones is a competitive pathway by which the derived 3-acetoxyamino derivatives (e.g. (5) and (34)) react in attempted aziridination of unreactive alkenes. Samples of (38) obtained from such reactions of (33) have been found to have a rotation $[\alpha]_D = -35.5°$ (c 2 EtOH) identical in sign to that of this natural product $[\alpha]_D = -41°$ (c 2.5 EtOH).[20]

Oxidation of the 3-aminoquinazolinone (33) at -20°C with LTA followed by addition of the silyl ketene acetal (15)(3.5 equiv.) gave a mixture of the O-silylorthoester (37) and a mixture of two diastereoisomeric N-(quinazolinone-3-yl)aminoacid esters (35). (Scheme 12). The O-silylorthoester (37) appeared to be a single diastereoisomer and was converted into the less polar of the two aminoacid ester diastereoisomers (35) which were separated in part by crystallisation and then by chromatography.

The more polar of the two esters (35) was hydrolysed to the corresponding acid and heated with acetic anhydride under the conditions which successfully brought about N-acetylation of (25). In this case, however, the only product isolated was the lactone (39).



(35) (39)

Fortunately, samarium diiodide reduction of the major (less polar) diastereoisomer of ester (35) gave a methyl ester of α-phenylalanine (36) (Scheme 12) whose enantiopurity was shown to be complete by comparison of its derived Mosher amide with that of racemic material prepared earlier (Scheme 11). From its sign of rotation this recovered enantiomer of (36) has the (S) configuration by comparison with that reported in the literature for its enantiomer.[21]

Nitroso compounds[22] diazonium salts[23] and nitrenes,[24] have been used as sources of electrophilic nitrogen in the conversion of silyl ketene acetals into aminoacids There have also been a number of syntheses of enantiopure aminoacids using attack by dialkyl azodicarboxylate as an NH_2^+synthon on silyl ketene acetals.[25] In each case, the diastereoselectivity is substrate-controlled with the presence of a chiral auxiliary on the silyl ketene acetal directing attack on one diastereoface preferentially. In the present case, the diastereoselectivity is reagent-controlled with the inducing chiral centre contained in the NH_2^+ synthon and eventually removed as an accompaniment to the required unmasking of the amino group.

EXPERIMENTAL

I.r. spectra were determined as Nujol mulls using Perkin Elmer 298 or 1605 (FTIR) spectrometers. ^{1}H n.m.r. spectra at 90MHz were obtained using Varian EM 390 or JEOL FX 90 spectrometers. ^{1}H, ^{13}C and ^{19}F n.m.r. higher field spectra were obtained using a Bruker AM-300 spectrometer in deuteriochloroform solutions with trimethylsilane (^{1}H, ^{13}C) or trifluoracetic acid (^{19}F) as internal standards. The low temperature spectrum of (20) was obtained using a Bruker WH-400 spectrometer (University of Warwick). Mass spectra were obtained using a Micromass 16B spectrometer and in addition to the molecular ion, M^{+}, peaks of $\geqslant$40% of the base peak are quoted.

Flash chromatography was carried out according to the method of Still[26] using silica gel (supplied by Merck & Co) Kieselgel 60, 230-400 mesh. Lead tetra-acetate was freed from acetic acid by transferring the solid to a desiccator and evacuating the latter using a water pump for 15min. Trimethylsilylchloride was distilled immediately prior to use from tributylamine. Light petroleum refers to the fraction 60-80°C. Phenethylhydrazine, *n*-butyllithium, and samarium diiodide (0.1M in tetrahydrofuran) were supplied by Aldrich and used as received.

Solutions of 3-acetoxyamino-2-ethylquinazolin-4(3H)-one (5) in dichloromethane at -20°C were prepared from the corresponding 3-aminoquinazolinone (4) by the method given in Ref. 6 immediately prior to use and maintained at -20°C.

The following methyl trimethylsilyl ketene acetals were prepared by literature methods: 1-methoxy-1-trimethylsilyloxypropene (12) (57%) b.p. 46-48°C/22mm Hg (lit.[27] b.p. 46°C/23mm Hg); 1-methoxy-1-trimethylsilyloxy-2-phenylethene (13) (80%) b.p. 92-95°C/0.5mm Hg (lit.[28] 95°C/0.5mm Hg); 1-methoxy-2-methyl-1-trimethylsilyloxypropene (14) (80%) b.p. 30-35°C/15mm Hg (lit.[28] 35°C/15mm Hg); 1-methoxy-3-methyl-1-trimethylsilyloxybuta-1,3-diene (16) (90%) b.p. 45-49°C/0.5mm Hg (lit.[29] b.p. not given); 1-methoxy-1-trimethylsilyloxy-2-phenylpropene (15) (82%) b.p. 74-78°C/2mm Hg (lit.[28] 76°C/0.1mm Hg).

Reaction of ethyl vinyl ether with (5).— To a solution of (5) prepared from *N*-aminoquinazolinone (4) (0.255g), and LTA (0.628g) in dichloromethane (2.5ml) at -20°C was added ethyl vinyl ether (0.146g, 1.5 equiv.) with stirring and the temperature of the solution allowed to rise to ambient. After separation of the insoluble lead di-acetate, the reaction mixture was washed with sodium hydrogen carbonate solution, water, then dried and evaporated. Chromatography of the residue over silica using ethyl acetate-light petroleum (1:1) as eluant gave the *acetal* (8) as colourless crystals (0.281g, 69%) m.p. 53-54°C (from diethylether-light petroleum) (Found: C, 60.3; H, 6.8; N, 12.7 $C_{16}H_{21}N_{3}O_{4}$ requires C, 60.2; H, 6.6; N, 13.1%); δ(300MHz) 8.23 (ddd, *J* 8, 1.5, and 0.6 Hz, quinaz. H-5), 7.74 (ddd, *J* 8.1, 7.3, and 1.5 Hz, quinaz. H-7), 7.67 (ddd, *J* 8.1, 1.3, and 0.6 Hz, quinaz. H-8), 7.45 (ddd, *J* 8.0, 7.3, and 1.3 Hz quinaz. H-6), 6.02 (t, *J* 5 Hz, $CH_2C\underline{H}$(OAc), 5.74 (t, *J* 7.1 Hz (exch. D_2O), NH), 3.82 (dq, *J* 9 and 7 Hz, $CH_3\underline{H}CHO$-), 3.65 (dq, *J* 9 and 7 Hz $CH_3HC\underline{H}O$-), 3.21 (br m, $NH\underline{H}CH$), 3.17 (br m, $NHHC\underline{H}$), 3.03 (br q, *J* $C\underline{H_2}Me$), 2.11 (s, OCOMe), 1.38 (t, *J* Hz, $CH_2\underline{Me}$), and 1.23 (t, *J* 7Hz, $OCH_2\underline{Me}$); $\nu_{max.}$ 3290s, 1740s, 1675s, and 1595s cm^{-1}; m/z 319(M^{+}), 259, 202, 175, 174 (base), and 173.

Preparation of 3-chloro-2-(trimethylsilyloxy)prop-1-ene and its reaction with (4).— 3-Chloro-1-(trimethylsilyl)propan-2-one was prepared from trimethylsilylmethylmagnesium chloride and chloracetic anhydride[30] and converted into the title enol silyl ether (7) by isomerisation with tetra(triphenylphosphine)palladium as previously described.[31] This enol silyl ether (7) (0.762g, 3.5 equiv.) was added in one portion to a stirred solution of (5) prepared from 3-aminoquinazolone (4) (0.25g) and LTA (0.616g) in dry dichloromethane (2.5 ml) at -20°C and the temperature allowed to rise to ambient. After separation of the lead diacetate, the solution was washed with sodium hydrogen carbonate solution, water, then dried and evaporated. Trituration of the residual oil with warm light petroleum and crystallisation of the resulting solid from ethanol gave 58% of the chloroketone (9) m.p. 116-119°C identical to a sample isolated previously.[9]

Chromatography of the above chloroketone over silica and elution with ethyl acetate-light petroleum (1:2) resulted in conversion to the *imine* (11) (64%) which was obtained as colourless crystals m.p. 76-78°C (from ethanol) (Found: C, 64.25; H, 5.45; N, 17.2.

$C_{13}H_{13}N_3O_3$ requires C, 64.2; H, 5.5; N, 17.25%); δ(300MHz) 9.07 (s, N=CH), 8.23 (ddd, J 8.1, 1.4, and 0.6 Hz, quinaz. H-5), 7.75 (ddd, J 8, 7.3, and 1.4 Hz, quinaz. H-7), 7.66 (ddd, J 8.0, 1.5, and 0.6 Hz, quinaz. H-8), 7.45 (ddd, J 8.1, 7.3, and 1.5 Hz, quinaz. H-6), 3.04 (q, J 7.5 Hz, CH_2Me), 2.52 (s, COMe), and 1.40 (t, J 7.5 Hz, CH_2Me); $\delta(^{13}C)$ (75MHz) 198.3(s), 159.8(s), 157.7(s), 155.8(d), 145.7(s), 134.8(d), 127.3(d), 127.2(d), 126.8(d), 121.3(s), 28.6(t), 24.7(q), and 11.2(q), $\nu_{max.}$ 1695s, 1620s, 1605m, and 1580s cm^{-1}; m/z 243(M^+), 201, 200, 174 (base), 173, 146, and 119.

Methyl 2-(2-ethylquinazolin-4(3H)one-3-yl)aminopropanoate (19).— To a solution of (5) prepared from 3-aminoquinazolinone (4) (0.25g) and LTA (0.616g) in dichloromethane (2.5ml) at -20°C was added silyl ketene acetal (12) (0.317g, 1.5 equiv.) and the solution allowed to warm to ambient. After separation of lead di-acetate, the dichloromethane solution was washed with water, dried, and evaporated. Chromatography of the residue over silica using ethyl acetate-light petroleum (1:2) gave the benzoxazinone (23) (25mg, 11%) identical with an authentic sample.[32] Further elution with the same solvent gave the title *aminoacid ester* (19) as colourless crytals (79mg, 22%) m.p. 64-67°C (from light petroleum) (Found: C, 61.15; H, 6.3; N, 15.25. $C_{14}H_{17}N_3O_3$ requires C, 61.05; H, 6.2, N, 15.25); δ(300MHz) 8.21 (ddd, J 8.1, 1.5, and 0.6 Hz, quinaz. H-5), 7.73 (ddd, J 8.1, 7.2, and 1.5 Hz, quinaz. H-7), 7.66 (ddd, J 8.1, 1.4, and 0.6 Hz, quinaz. H-8), 7.43 (ddd, J 8.1, 7.2, and 1.4 Hz, quinaz. H-6), 5.79 (br d, J 4.1 Hz (exch. D_2O), NH, 3.97 (dq, J 6.9 and 4.1 Hz, NHCH), 3.73 (s, CO_2Me), 3.1(dq, J 17 and 7.4 Hz, HCHMe), 3.01 (dq, J 17 and 7.4 Hz, HCHMe), 1.4 (d, J 6.9 Hz, NHCHMe), and 1.35 (t, J 7.4 Hz, CH_2Me); $\nu_{max.}$ 3280m, 1740s, 1675s, and 1595s cm^{-1}; m/z 275 (M^+), 174 (base), and 173.
The above experiment was repeated twice with the following modifications.
i) Before addition of silyl ketene acetal, the dichloromethane solution was stirred for 15min. at -20°C with 2,6-di-t-butyl-4-methylpyridine (0.54g, 2 equiv.). Work up as described above gave (19) (63%) after chromatography. ii) Addition of excess silyl ketene acetal (0.74g, 3.5 equiv.) followed by the same work up gave (19) (80%) after chromatography. In neither of the above modifications was any benzoxazinone (23) isolated.

Methyl 2-(2-ethylquinazolin-4(3H)-one-3-yl)amino-2-phenylacetate (20) was prepared similarly from a solution of (5) obtained from 3-aminoquinazolinone (4) (0.305g), LTA (0.717g), and dichloromethane (5ml) with addition of silyl ketene acetal (13) (1.26g 3.5 equiv.). After chromatography, *the aminoacid ester* (20) (0.42g, 76%) was obtained as colourless crystals m.p. 86-88°C (from ethanol) (Found: C, 67.6; H, 5.8; N, 12.4. $C_{19}H_{19}N_3O_3$ requires C, 67.6; H, 5.7; N, 12.5%); δ(300MHz) 8.24 (ddd, J 8, 1.5 and 0.6 Hz, quinaz. H-5), 7.73 (ddd, J 8.1, 7.4, and 1.5 Hz, quinaz. H-7), 7.63 (ddd, J 8.1, 1.3, and 0.6 Hz, quinaz. H-8), 7.45 (ddd, J 8, 7.4, and 1.3 Hz, quinaz. H-6), 7.45-7.3 (m, 5 x PhH), 6.08 (br s (exch. D_2O), NH), 4.94 (d, J 2 Hz, PhCH), 3.72 (s, CO_2Me), 2.77 (br m, CH_2Me), and 1.17 (t, J 7 Hz, CH_2Me); at -90°C in CD_2Cl_2 two rotamers around the N-N bond are distinguishable (ratio 3:1) with δ(400MHz) major rotamer 8.17 (ddd, J 8, 1.5 and 0.6 Hz, quinaz. H-5), 7.76 (ddd, J 8.1, 7.4 and 1.5 Hz, quinaz. H-7), 7.63-7.2 (m, 5 x PhH, quinaz. H-8 and H-6), 6.41 (d J 2 Hz, NH), 4.79 (d, J 2 Hz, PhCH), 3.7 (s, CO_2Me), 2.7 (dq, J 17 and 7.5 Hz, HCHMe), 1.96 (dq, J 17 and 7.5 Hz, HCHMe), and 0.98 (t, J 7.5 Hz, CH_2Me); minor rotamer 8.1 (dd, J 8 and 1.5 Hz, quinaz. H-5), 7.76-7.20 (m, 5 x PhH, quinaz. H-7, H-8, and H-6), 5.6 (s, NH or PhCH (other signal obscured)), 3.62 (dq, J 17 and 7.5 Hz, HCHMe), 3.48 (s, CO_2Me), 3.33 (dq, J 17 and 7.5 Hz, HCHMe), and 1.28 (t, J 7.5 Hz, CH_2Me); $\nu_{max.}$ 3290m, 1745s, 1670s, and 1600s cm^{-1}; m/z 338(M^++1), 175, 174(base), and 104.

Methyl 2-(2-ethylquinazolin-4(3H)-one-3-yl)amino-2-methylpropanoate(21) was prepared similarly from a solution of (5) obtained from 3-aminoquinazolinone (4) (0.3g), LTA (0.739g) and dry dichloromethane (3ml) with addition of silyl ketene acetal (14) (0.968g, 3.5 equiv.). After chromatography the *aminoacid ester* (21)(0.4g, 88%) was obtained as colourless crystals, m.p. 87-89°C (from light petroleum) (Found: C, 62.5; H, 6.55; N, 14.55. $C_{15}H_{19}N_3O_3$ requires C, 62.25; H, 6.6; N, 14.5%); δ(300MHz) 8.19 (ddd, J 8.0, 1.5, and 0.6 Hz, quinaz. H-5), 7.72 (ddd, J 8.1, 7.4, and 1.5 Hz, quinaz. H-7), 7.65 (ddd, J 8.1, 1.3, and 0.6 Hz, quinaz. H-8), 7.41 (ddd, J 8, 7.4, and 1.3 Hz, quinaz. H-6), 5.87 (br s (exch. D_2O), NH), 3.81 (s, CO_2Me), 3.01 (br m, CH_2Me), 1.35

(t, *J* 7.5 Hz, CH_2Me), and 1.32 (br s, Me_2C); $\nu_{max.}$ 3300m, 1740s, 1680s, and 1600s cm^{-1}; m/z 289(M^+) and 230 (base).

Methyl 2-(2-ethylquinazolin-4(3H)-one-3-yl)amino-2-phenylpropanoate(22) was prepared similarly from a solution of (5) prepared from 3-aminoquinazolinone (4) (1g), LTA (2.46g), and dry dichloromethane (10ml) with addition of silyl ketene acetal (15) (4.37g, 3.5 equiv.). After chromatography the *aminoacid ester* (22) (1.2g, 64%) was obtained as colourless crystals, m.p. 159-162°C (from ethanol-ethylacetate) (Found: C, 68.1; H, 6.1; N, 12.0. $C_{20}H_{21}N_3O_3$ requires C, 68.35; H, 6.0; N, 11.95%); δ(90MHz) 8.20 (d, *J* 8 Hz, quinaz. H-5), 7.85-7.25 (m, 3 x quinaz. H and C_6H_5), 6.51 (s, NH), 3.82 (s, CO_2Me), 2.91 (2 x dq, (ABX_3), J_{AB} 16 J_{AX} 7 J_{BX} 7 Hz, CH_2Me), 1.41 (s, MeCPh), and 1.35 (t, *J* 7 Hz, CH_2Me); $\nu_{max.}$ 3304m, 1737s, and 1684s cm^{-1}.

Reaction of silyl ketene acetal (16) with 3-acetoxyaminoquinazolinone(5).—A solution of (5) was prepared from 3-aminoquinazolinone (4) (0.5g) and LTA (1.23g) in dry dichloromethane (5ml) with addition of silyl ketene acetal (16) (1.72g, 3.5 equiv.). After the same work up, chromatography over silica yielded the *aminoacid ester* (17) (43%) as colourless crystals, m.p. 59-61°C (from light petroleum) (Found: 64.0; H. 6.5; N, 13.6, $C_{16}H_{19}N_3O_3$ requires C, 63.8; H, 6.4; N, 13.9%); δ(300MHz) 8.22 (ddd, *J* 8, 1.6, and 0.6 Hz, quinaz. H-5), 7.74 (ddd, *J* 8.1, 7.3, and 1.6 Hz, quinaz. H-7), 7.66 (ddd, *J* 8.1, 1.5, and 0.6 Hz, quinaz. H-8), 7.44 (ddd, *J* 8, 7.3, and 1.5 Hz, quinaz. H-6), 6.00 (d, *J* 3 Hz (exch. D_2O), NH), 5.03 (m, HCH=CMe), 4.94 (m, HCH=CMe), 4.27 (d, *J* 3 Hz, NHCH), 3.81 (s, CO_2Me), 3.1 (dq, *J* 16 and 7.5 Hz, HCHMe) 2.89 (dq, *J* 16 and 7.5 Hz, HCHMe), 1.86 (m, CH_2=CMe), and 1.34 (t, *J* 7.5 Hz, CH_2Me); $\nu_{max.}$ 3280m, 1745s, 1680s and 1595s cm^{-1}; m/z 301 (M^+), 174 (base), and 173.
Further elution with ethyl acetate-light petroleum (1:2) afforded the *aminoacid ester* (18) (0.33g, 42%) as a mixture of double bond isomers. Fractional crystallisation (from ethanol) gave a single double bond isomer m.p. 104-107°C (Found: C, 63.8; H, 6.35; N, 13.95. $C_{16}H_{19}N_3O_3$ requires C, 63.75; H, 6.35; N, 13.95%); δ(300MHz) 8.24 (ddd, *J* 8.1, 1.5, and 0.6 Hz, quinaz. H-5), 7.75 (ddd, *J* 8.1, 7.2, and 1.5 Hz, quinaz. H-7), 7.67 (ddd, *J* 8.1, 1.4, and 0.6 Hz, quinaz. H-8), 7.45 (ddd, *J* 8.1, 7.2, and 1.4 Hz, quinaz. H-6), 6.04 (m, $CHCO_2Me$), 5.59 (t, *J* 7 Hz (exch. D_2O), NH), 4.10 (br m, $NHCH_2$), 3.72 (s, CO_2Me), 3.00 (br q, CH_2Me), 2.27 (d *J* 1.4 Hz, vinylic Me), and 1.39 (t, *J* 7.3 Hz, CH_2Me); $\nu_{max.}$ 3260s, 1710s, and 1595s cm^{-1}; m/z 302 (M^++1), 175, 174 (base), and 173; the second double isomer was not obtained pure but was identifiable by signals at δ(300MHz) 3.59 (s, CO_2Me), 2.12 (d, *J* 1.4 Hz, vinylic Me), and 1.38 (t, *J* 7.3 Hz CH_2Me).

Alkylation of 3-aminoquinazolinone (4) with ethyl bromoacetate.—3-Aminoquinazolinone (4) (10g), ethyl bromoacetate (11.8 ml) and dry tripropylamine (12 ml) were heated with stirring under nitrogen for 4½h. at 140-150°C (oil-bath temp.). After cooling to room temperature, the solid-liquid reaction mixture was triturated with dry ether (*ca* 80 ml) and the ether separated. The gummy orange residue obtained after evaporation of the ether was crystallised from ethanol to give the *ester* (24) (8.87g, 60%) as a colourless solid, m.p. 89-92°C (Found: C, 60.9; H, 6.3; H, 15.25. $C_{14}H_{17}O_3N_3$ requires C, 61.1; H, 6.2; N, 15.25); δ(90MHz) 8.2 (d, *J* 8 Hz, quinaz. H-5), 7.8-7.2 (m, 3 x quinaz. H), 5.85 (t, *J* 7 Hz, NH), 4.22 (q, *J* 8 Hz, OCH_2CH_2), 3.76 (d, *J* 7 Hz, CH_2N), 3.0 (q, *J* 8 Hz, quinaz. CH_2Me), 1.37 (t, *J* 8 Hz, CH_2Me), and 1.28 (t, *J* 8 Hz, CH_2Me); $\nu_{max.}$ 3296m, 1741s, and 1673s cm^{-1}.

Preparation of ethyl N-acetyl-N-(2-ethylquinazolin-4(3H)-one-3-yl)glycinate(26).— The ester (24) prepared above (4g) was dissolved in aqueous ethanol (30 ml), (50%), ethanol (70 ml) and sodium hydroxide solution (1M, 14.5 ml) were added and the solution stirred for 1h. at room temperature. After removal of the ethanol under reduced pressure, the aqueous solution was extracted with ethyl acetate to remove non-acidic material, acidified with hydrochloric acid (2M) to pH 3-4 and then extracted with ethyl acetate (3 x 20 ml). The combined ethyl acetate extracts were dried and evaporated and the acid (25) (2.72g) was obtained as a colourless solid which was heated with acetic anhydride (14 ml) for precisely 14 min. at 130°C (bath temp.) with stirring under nitrogen. After allowing to cool, methanol (40 ml) was added, the solution stirred for 10 min., then evaporated to dryness under reduced pressure. The residue was dissolved in methanol (20 ml), cooled to 0°C and treated dropwise with a solution of diazomethane in methanol until no effervescence was observed on addition. Excess diazomethane was destroyed with acetic acid then the solvent removed under reduced pressure. Crystallisation of the residue from ethanol gave the title *glycinate* (1.40g, 35%) m.p. 129-132°C (Found: C, 59.25; H, 5.65; N, 13.75. $C_{15}H_{17}N_3O_4$ requires C, 59.4; H, 5.65; N, 3.85%); δ8.2 (d, *J* 8 Hz, quinaz. H-5), 7.8-7.4 (m, 3 x quinaz. H), 5.02 (d, *J* 17 Hz, *H*CHCO$_2$Me), 3.77 (s, CO$_2$Me), 3.68 (d, *J* 17 Hz, HC*H*CO$_2$Me), 3.4-2.8 (structured m, C*H*$_2$Me), 1.92 (s, COMe), and 1.41 (t, *J* 7 Hz, CH$_2$*Me*); in addition, signals from the minor rotamer around the NH-CO bond were visible at 4.85 (d, *J* 18 Hz *H*CHCO$_2$Me), 4.22 (d, *J* 18 Hz, HC*H*CO$_2$Me), 3.81 (s, CO$_2$Me), and 2.34 (s, COMe); δ^{13}C 10.8, 19.9, 26.7 52.1, 52.5, 120.8, 127.2 127.7, 135.5, 146.8, 158.5, 160.2, 168.1 and 173.2. Additional signals were visible at δ10.5, 20.9, 25.8, 52.8, 53.7, 126.5, 126.9, 127.5 and 134.9; $\nu_{max.}$ 1740s, 1700s and 1600 cm^{-1}.

Aluminium amalgam reduction of (26).—The glycinate prepared above (278mg) was dissolved in dry methanol (50 ml), aluminium amalgam (prepared from aluminium turnings (2g)) was added and the solution stirred in a flask immersed in water at ambient temperature for 22h. The solution was centrifuged, the methanol decanted, the solid re-suspended in methanol (~20 ml) and again centrifuged and the methanol separated. Evaporation of the combined methanol extracts and chromatography of the residue over silica, eluting with ethyl acetate gave 2-ethylquinazolin-4(3*H*)-one and its reduction products. Further elution with methanol-ethyl acetate (3:1) gave methyl *N*-acetyl glycinate (83 mg, 63%), after combination of those fractions Rf 0.3 (methanol-ethyl acetate 3:1), evaporation, and kugelrohr distillation of the residue. The n.m.r. spectrum of this material was identical with that of an authentic sample prepared by acetylation of methyl glycinate.

Preparation of 2-ethyl-3-(phenethylamino)quinazolin-4(3H)-one(31).— Phenethylhydrazine (6.76g) (Aldrich) and benzoxazinone (23) (8.79g)^{32} were heated together at 100°C for 1h. The product was dissolved in dichloromethane (100 ml) and this solution washed successively with dilute hydrochloric acid (twice), sodium hydrogen carbonate solution, then water. After drying and evaporation, a yellow oil was obtained which was dissolved in ethyl acetate-chloroform and passed through a short column of silica, the solvent removed and the residue distilled (b.p. 180°C/4 x 10^{-4} mm Hg) to give *amine* (31) (5.75g 35%) as an oil which crystallised on standing. Recrystallisation gave a colourless solid m.p. 63-65°C (from diethylether at -78°C)(Found: C, 73.45; H, 6.7; N, 14.1: $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.55; N, 14.35%); δ(90MHz) 8.21 (d *J* 8 Hz, quinaz. H-5), 7.73-7.2 (m, 3 x quinaz. H), 7.28 (s, C_6H_5), 5.53 (t, *J* 7 Hz, NH), 3.36-3.1 (m, CH$_2$), 2.92 (t, *J* 7 CH$_2$) superimposed on 2.88 (q, *J* 7 Hz, C*H*$_2$CH$_3$), and 1.32 (t, *J* 7 Hz); $\nu_{max.}$ 3261m and 1656s cm^{-1}.

Procedure for reduction with samarium diiodide.— The amine (1-2 mmol), dry *t*-butanol (1 ml) and tetrahydrofuran (10 ml; dried by distillation from lithium aluminium hydride) were added to a two-necked flask equipped with a stirring bar, a septum cap and connected *via* a 3-way tap to an argon supply and an oil-pump. The flask was alternately evacuated and filled with argon several times whilst stirring, taking care to avoid excessive bumping by limiting the evacuation time. Samarium iodide (0.1M in tetrahydrofuran 2.2 equiv.) (Aldrich) was added *via* the septum cap by syringe with stirring. The following (quinazolin-4(3*H*)-one-3-yl)amines were reduced in this way with the work up as described in each case.

Reduction of (22).—The above procedure was carried out using ester (22) (122 mg), *t*-butanol (1 ml), and tetrahydrofuran (5 ml) with addition of samarium diiodide (10.5 ml). After ~20 min., the colour of the solution had changed from deep blue to green. Stirring was continued for a further 2h, the bulk of the tetrahydrofuran was removed under reduced pressure and the residue dissolved in dichloromethane. The solution was washed with sodium carbonate solution, then with water, dried and evaporated. The residual solid was triturated with ethyl acetate-light petroleum (1:1) and the insoluble material (largely 2-ethylquinazolin-4(3H)-one) separated. Evaporation of the residue gave 2-phenyalanine methyl ester (46 mg, 73%) b.p. 120°C/0.5mm Hg (lit.^{33} b.p. 138-142°C/15 mm Hg; δ(90 MHz) 7.54-7.25 (m, C_6H_5), 3.70 (s, CO$_2$Me), 2.08 (s, NH$_2$), and 1.70 (s, C-Me).

Reduction of (24).—The ester (275 mg) was dissolved in dry tetrahydrofuran (10 ml) containing dry t-butanol (1 ml) in a two-necked flask as described above but the flask was then cooled to -78°C and maintained at this temperature whilst samarium diiodide (24 ml) was added through the septum cap. After stirring for 40 min. at -78°C a solution of acetic acid (114 μl, 2 equiv.) in tetrahydrofuran (5 ml) was injected by syringe followed by triethylamine (2.80 ml) and benzoylchloride (2.32 ml) before the flask was removed from the cooling bath and allowed to warm to ambient temperature. All volatile material was removed under reduced pressure and the residue dissolved in dichloromethane, washed twice with sodium carbonate solution, then water, dried and evaporated to give a yellow oil. Flash chromatography of this oil over silica using light petroleum-ethyl acetate (2:1) and combination of those fractions Rf 0.2 in this solvent gave ethyl N-benzoylglycinate (28) (170 mg, 82%) whose n.m.r. spectrum was identical to that of an authentic sample prepared from glycine ethylester and benzoylchloride.

Reduction of (31).—The procedure above was applied to the amine (31) (293 mg), dissolved in dry tetrahydrofuran (10 ml) containing dry t-butanol (1 ml) and using samarium diiodide (20 ml). After 1½h., the bulk of the tetrahydrofuran was removed under reduced pressure and the residue dissolved in dichloromethane and extracted with sodium carbonate solution. The organic layer was then extracted with hydrochloric acid (2M, 2 x 30 ml), and then combined aqueous acid extracts basified to pH 10 with sodium hydroxide solution. The aqueous layer was extracted with dichloromethane, the dichloromethane solution dried and evaporated to give 2-phenylethylamine (97 mg, 80%) as a yellow oil, b.p. 105°C/10mm Hg (kugelrohr)(lit.[34] 92-98°C/19mm Hg); δ(90MHz) 7.2 (m, C_6H_5), 3.05-2.66 (m, including peaks at 2.96, 2.90, 2.81, and 2.75,$(CH_2)_2$), and 2.24 (s, NH) identical with that of an authentic sample.

Preparation of (S)(-)-3-amino-2-(1-hydroxyethyl)quinazolin-4(3H)-one(33).—(S)(+)-lactic acid (89.3g) was dissolved in dry pyridine (100 ml) and acetic anhydride (93 ml) added with stirring at 0°C. After setting aside for 24h, the solution was poured into ice-water (500 ml), stirred for ½h, and extracted with ethyl acetate (3 x 100 ml), the combined ethyl acetate layers washed with hydrochloric acid (1M) and then with water before drying and evaporating. The residual oil was distilled to give 2-acetoxypropanoic acid (b.p. 106-110°/0.8 mm Hg) (58.1g, 55%) (lit.[35] b.p. 127°C/10mm Hg) which was added to thionyl chloride (75ml, previously distilled from triphenylphosphite) and the solution heated at 50°C for 2h. Excess thionyl chloride was removed under reduced pressure and the residual acid chloride dissolved in dry ether (50 ml) and added briskly with stirring to a solution of methyl anthranilate (200g, 3 equiv.) in dry ether (1l). The resulting thick suspension was mixed as thoroughly as possible with addition of further dry ether as necessary and then the insoluble methyl anthranilate hydrochloride separated and washed with ether. The ether solution was washed five times with dilute hydrochloric acid (2M), then with water, dried and evaporated to give methyl 2-acetoxypropanoylanthranilate (60g, 52%); δ(90MHz) 8.71 (d, J 8 Hz, ArH adj. to NH), 8.0 (dd, J 8 and 2 Hz, ArH adj. to CO_2Me), 7.52 (structured m, ArH), 7.12 (structured m, ArH), 5.35 (q, J 7 Hz, CHOAc), 3.9 (s, CO_2Me), 2.25 (s, OCOMe), and 1.58 (d, J 7 Hz, CHMe). This amide was heated with ethanol (150 ml) and hydrazine (56g) under reflux for 3h. On cooling, the bulk of the product (22g) crystallised: a further quantity (14g) (total 36g, 81%) was obtained by evaporation of the bulk of the ethanol and addition of water. After crystallisation the product (33) had m.p. 118-120°C (from ethanol) (lit.[18] 108-110°C (racemic)) $[\alpha]_D^{18}$ -29.3° (c 1.09, MeOH).

Mosher ester of (33).—The above optically active 3-aminoquinazolinone (33) (42 mg) was dissolved in dry pyridine (0.5 ml) and treated with (S)(-)-α-methoxy-α-(trifluoromethyl)phenylacetylchloride (65 mg) and the solution set aside for 2h. After addition of water, the solution was extracted with ether, the ether layer separated and washed successively with hydrochloric acid (1M)(twice), dilute sodium carbonate solution and water, dried and evaporated. Repetition of the above procedure was carried out using racemic 3-aminoquinazolinone (33) prepared according to ref. 18. Examination of the crude product from derivatization of the racemic compound (33) by n.m.r. shows *inter alia* δ^1H(300MHz) 3.64 (q, J ~1 Hz, OMe), and 3.67 (q, J ~1 Hz, OMe); $\delta^{19}F$(282.4 Hz) 69.53 (s, CF_3), and 68.92 (s, CF_3). The crude product from derivatization of the optically active material showed only the corresponding signals at δ^1H 3.67 and $\delta^{19}F$ 69.53.

Preparation of ester(35).—The optically pure 3-aminoquinazolinone (33) above was converted to the corresponding 3-acetoxyaminoquinazolinone (34) by oxidation with LTA as described for the conversion of (4) into (5). To the solution of (35) maintained at -20°C, the ketene silyl acetal (15) (8.26g) was added with stirring and the temperature then allowed to rise to ambient. After 30 min., the precipitated lead diacetate was separated, the filtrate washed with sodium hydrogen carbonate, dried and evaporated to give a yellow oil. Crystallisation from light petroleum gave a solid (3.01g) from which a more polar ester (35) (438 mg) was obtained as a colourless solid m.p. 188-189°C by crystallisation from ethanol (Found: C, 65.15; H, 5.9; N, 11.32. $C_{20}H_{21}N_3O_4$ requires C, 65.4; H, 5.75; N, 11.45%): δ8.19 (d, J 7 Hz, quinaz. H-5), 7.9-7.25 (m, 3 x quinaz. H and C_6H_5), 6.61 (s, NH), 5.07 (quint, J 7 Hz, MeCH), 4.07 (d, J 7 Hz, OH), 3.84 (s, OMe), 1.59 (s, MeCPh), and 1.45 (d, J 7 Hz, MeCH); $\nu_{max.}$ 3475m, 3324m, 1716s, and 1683s cm^{-1}.

Flash chromatography using 2:1 light petroleum-ethyl acetate of the combined residues, after evaporation of the light petroleum ethanol solutions above, removed the bulk of methyl 2-methylphenylacetate and gave a mixed fraction (1.18g) containing the O-silyl orthoester (37) and the less polar ester (34) closely followed by a further mixed fraction (1.62g) containing both ester diastereoisomers (34); (total recovery of O-silylorthoester (37) and esters (35) was 85%). Further flash chromatography gave the O-silylorthoester (37) (216 mg) as an oil δ(90MHz) 8.1 (d, J 7 Hz, quinaz. H-5), 7.8-7.2 (m, 3 x quinaz. H, C_6H_5), 6.46 (s, NH), 5.25 (q, J 6 Hz, CHMe), 3.76 (s, OMe), 1.61 (d, J 6 Hz, CHMe), 1.39 (s, MeCPh), and 0.05 (s, Me_3Si) which was converted directly into the less polar ester (35) as described below. Further elution gave the less polar ester (714 mg) followed by the more polar ester (217 mg). Crystallisation of the less polar ester (35) gave a colourless solid m.p. 145-147°C (from ethanol) (Found: C, 65.35; H, 5.9; N, 11.35. $C_{20}H_{21}N_3O_4$ requires C, 65.4; H, 5.75; N, 11.45%); δ(90 MHz) 8.2 (d, J 7 Hz, quinaz. H-5); 7.8-7.26 (m, 3 x quinaz. H and C_6H_5), 6.47 (s, NH), 4.95 (q, J 6.5 Hz, MeCH), 4.29 (d, J Hz, OH), 3.84 (s, OMe), 1.65 (d, J 6.5 Hz, MeCH), and 1.39 (s, MeCPh); $\nu_{max.}$ 3455w, 3305w, 1744s and 1689s cm^{-1}. The O-silylorthoester (37) from the reaction above (107 mg) was dissolved in glacial acetic acid (1 ml) and water (0.1 ml) added. After setting aside for 5h, the solvent was removed under reduced pressure using an oil pump and the residual material (95 mg) was found to be identical with the less polar ester (35) isolated above.

Hydrolysis and lactonisation of ester(35).—The more polar ester (35) (2.3 mg) was dissolved in ethanol (36 ml) and sodium hydroxide solution (1M, 2.9 ml (2 equiv.)) added. After stirring at room temperature for 10 min, the bulk of the ethanol was removed under reduced pressure and the residue dissolved in water and extracted with ethyl acetate. The aqueous layer was separated, acidified to pH 4 and re-extracted with ethyl acetate. After separation, this latter ethyl acetate layer was washed with water, dried and evaporated to give the corresponding acid as a solid (192 mg) δ(d^5 pyridine) 8.26 (d, J 7 Hz, quinaz. H-5), 8.1-7.1 (m, 3 x quinaz. H, C_6H_5), 5.55 (q, J 6 Hz, CHMe), 1.81 (s, MeCPh), and 1.63 (d J 6 Hz, MeCH)) which was heated in acetic anhydride (2 ml) at 150°C (oil-bath temp.) with stirring for 5 min. under nitrogen. After allowing to cool, all volatile material was removed under reduced pressure. Crystallisation of the residual solid gave the lactone (39) (129 mg) as a colourless solid m.p. 138-141°C (from ethanol-water) (Found: C, 68.15; H, 5.25; N, 12.4. $C_{19}H_{17}N_3O_3$ requires C, 68.05, H, 5.1, N, 5.1%); δ(90 MHz) 8.28 (d, J 7 Hz, quinaz, H-5) 7.9-7.1 (m, 3 x quinaz. H, C_6H_5), 6.51 (q, J 6 Hz, CHMe), 6.42 (s, NH), 1.87 (d, J 6 Hz, MeCH), and 1.84 (s, MeCPh); $\nu_{max.}$ 3320w, 3293w, 1738s, 1673s and 1607m cm^{-1}; m/z 335(M^+), 292, 276, 188, 173, 119, 104, and 77 (base).

Reduction of (35).—The less polar ester (35) m.p. 145-147°C prepared as described above (190 mg) was dissolved in dry tetrahydrofuran (5 ml) containing dry t-butanol (1 ml) and reduced with samarium diiodide (11 ml, 0.1M in THF) using the procedure given above. After ½h. the bulk of the tetrahydrofuran was removed under reduced pressure and the residue dissolve in dichloromethane (40 ml) and washed with sodium carbonate solution. The organic layer was dried, evaporated, and the residue distilled (b.p. 120°C/0.5 mm Hg) (lit.[33] b.p. 138-142°C/15 mm Hg) to give (+)-methyl 2-amino-2-phenylpropionate (81 mg, 87%) $[\alpha]_D$= +27.8° (c=5, MeOH) (lit.[36] $[\alpha]_D$ (-)-methyl 2-amino-2-phenylpropionate -7.1° (neat 1 1dm).

Mosher ester of (36).—This aminoacid ester (35 mg) was dissolved in dry pyridine (0.5 ml) and (S)(-)-α-methoxy-α-(trifluoromethyl)phenylacetylchloride (65 mg) was added and the solution set aside for 2h. After addition of water, the solution was extracted with ether, the ether layer separated and washed successively with hydrochloric acid (1M, twice), sodium carbonate solution, water, then dried and evaporated. The same procedure as that described above was carried out using racemic α-phenylalanine methyl ester (35 mg). For the product from racemic material δ(300 MHz) ^{1}H 3.41 (q, J ~1Hz, OMe) and 3.56 (q, J ~1 Hz, OMe), δ^{19}F -69.23 (s, CF_3), and -69.32 (s, CF_3); for the product from the optically active material prepared above δ^1H 3.41 (q, J ~1 Hz, OMe, δ^{19}F- 69.32 (s, CF_3) only.

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