Intramolecular Reactions of *N*-Nitrenes: Oxidation of 3-Amino-2-(2,4-dimethoxyphenylethyl)quinazolin-4(3*H*)-ones

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Oxidation of the *N*-aminoquinazolones (**5**) and (**6**) gave the 1*H*-azepines (**7**) and (**10**) respectively. Boat-to-boat flipping of the azepine ring in compound (**7**) is slow on the n.m.r. time-scale even at 140 °C. Heating of compound (**10a**) in chlorobenzene at 135 °C brings about interconversion with the stereoisomer (**10b**) with a minimum free energy barrier of 30 kcal mol^{-1}. Possible reasons for this high barrier to azepine ring inversion are examined.

A study of the intramolecular reactions of *N*-nitrenes has revealed unsuspected features of the reactivity of these transitory species. We have previously described the reaction of *N*-nitrenes derived from the oxidation of *N*-aminoquinazolones, *e.g.* (**1**), and have rationalised the results in terms of an electrophilic aromatic substitution by the *N*-nitrene *via* a seven-membered transition state[1] (Scheme 1). Thus, whereas oxidation of the *m*-methoxy-substituted quinazolone (**1**) gave rise to the substitution products (**2**) and (**3**), oxidation of the corresponding *p*-methoxy analogue gave no products from attack on the aromatic ring.

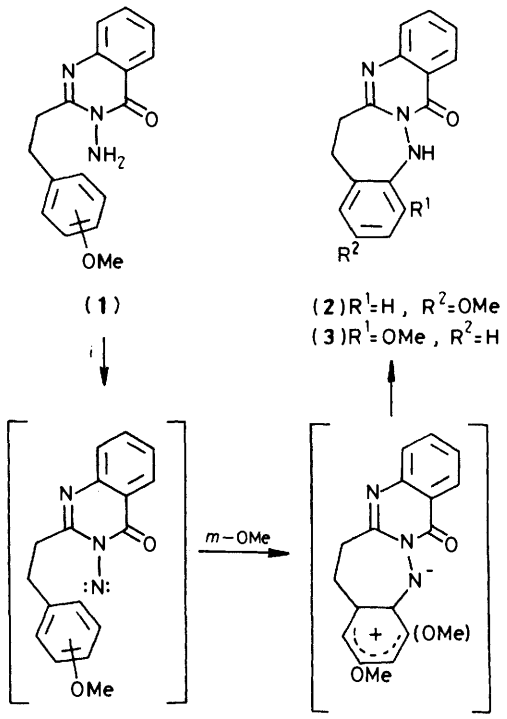
In order to encourage attack on the aromatic ring to take place *via* a six-membered transition state, and to determine what the products from the spiro-intermediate (**4**) resulting from such an attack might be, we have synthesised and oxidised the 2-(2,4-dimethoxyphenylethyl)-substituted quinazolone (**5**).[2]

The synthesis of compound (**5**) was carried out by the familiar route outlined in Scheme 2 and the crystalline *N*-aminoquinazolone was oxidised by the addition of small quantities of the solid, intimately mixed with dry lead tetra-acetate (LTA), to a stirred chloroform solution as previously described. The major product (70%), m.p. 150—153 °C, from this oxidation was identified as the 1*H*-azepine (**7**).

The azepine ring protons [δ 6.54 (d, *J* 11.5 Hz, 7-H), 5.95 (dd, *J* 11.5 and 2.9 Hz, 6-H), and 5.52 (d, *J* 2.9 Hz, 4-H)] confirm the substitution pattern shown in structure (**7**); in particular, the size of the coupling constant (11.5 Hz) between the azepine ring protons at C-6 and C-7 shows them to be vicinal on a double bond (an alternative substitution pattern with methoxy at C-5 and C-7 would put the two vicinal protons at C-3 and C-4, separated by a single bond with an expected coupling constant of *ca.* 5 Hz).[3]

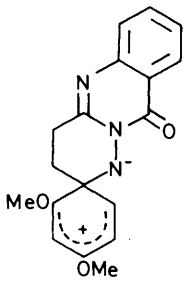
The most striking feature of the ^{1}H n.m.r. spectrum of compound (**7**) was the non-equivalence of the protons within each of the two methylene groups of the reduced pyridazine ring. Although an *X*-ray structure determination of *N*-*p*-bromophenylsulphonyl-1*H*-azepine (**9**) had shown the azepine ring to have a shallow boat shape in the crystalline state,[4] the temperature invariance of the n.m.r. spectra of other 1*H*-azepines down to −90 °C[5] indicated that the barrier for boat-to-boat conversion in this ring was <5 kcal mol^{-1}.† The surprising thermal stability of compound (**7**), compared with *N*-alkyl, N-unsubstituted,[6,3] or *N*-phthalimido-1*H*-azepines,[7] allowed us to monitor the protons in its methylene groups; even at 140 °C their non-equivalence persisted (the onset of decomposition was evident at this temperature).

The simplest explanation for the chirality in compound (**7**) which must be present to account for the non-equivalence of these protons is that the azepine ring is not undergoing boat-to-boat interconversion, even at 140 °C, at a rate which is fast on the n.m.r. time-scale. Clearly there is a gross difference between the apparent barrier for ring-inversion in compound (**7**) and that for other 1*H*-azepines. An examination of the three-dimensional representations (**7a**) and (**7b**) for the two enantiomeric boat forms of the azepine (**7**) reveals the origin of this grossly inflated barrier. The lack of sufficient conformational mobility within (**7a**) or (**7b**) means that the inversion of the azepine boat requires simultaneous inversion at the azepine ring nitrogen. Thus, at this point of inversion of both the boat and the ring nitrogen, the whole molecule must be very close to planarity [structure (**7c**)]. In consequence the barrier to inversion of the azepine ring nitrogen is unusually high as the eclipsing of the lone pairs of electrons on adjacent nitrogens with sp^2 hybridisation is an added contribution. This factor is equivalent to the barrier to rotation about such an N–N bond, which is known to have a value of 21 ± 2 kcal/mole;[8] this is considerably in excess of the normal value for inversion at a similar pyramidal–planar (hydrazine) nitrogen (7—8 kcal mol^{-1}).[9]

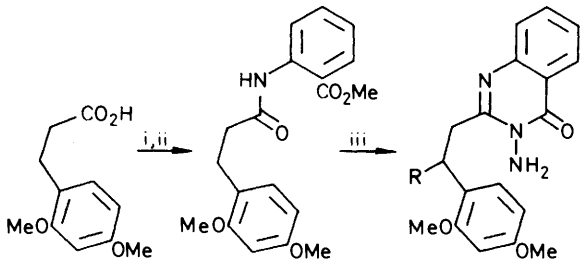


Scheme 1. *Reagents:* i, LTA

† 1 cal = 4.184 J.

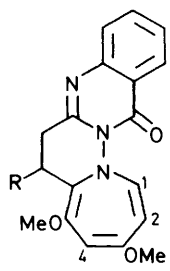


(4)

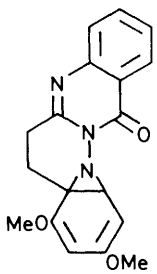


(5) R = H
(6) R = Me

Scheme 2. *Reagents:* i, $(COCl)_2$ + Na^+ Salt; ii, methyl anthranilate; iii, NH_2NH_2–EtOH



(7) R = H
(10) R = Me



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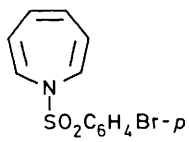
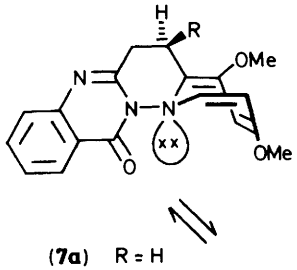


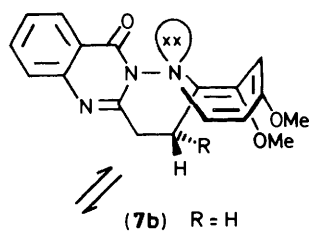
(9)

In an attempt to quantify the barrier separating the conformers (**7a**) and (**7b**), we synthesised the *N*-aminoquinazolone (**6**) by the route outlined in Scheme 2 and, from its oxidation in chloroform, obtained the azepine (**10**), m.p. 169—171 °C, in 45% yield.

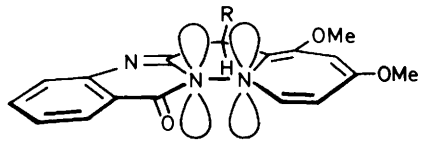
A spectroscopic examination of compound (**10**) reveals that it has structure (**10a**) with the methyl group *endo*; the attack of the nitrene derived from the oxidation of compound (**6**) on the aromatic ring appears to be stereospecific as none of the stereoisomer with this methyl group *exo* (see below) appears to be present. Proof of this *endo*-configuration (**10a**) is derived from the observation of a small nuclear Overhauser enhancement (n.O.e.) between this methyl group and the azepine ring hydrogen at C-7; this observation also supports the orientation of the methoxy substitution shown in structure (**10a**), and the similarities between the chemical shifts and coupling constants of conformers (**7a**) and (**10a**) indicate that both have the same substitution pattern in the azepine ring.



(**7a**) R = H
(**10a**) R = Me



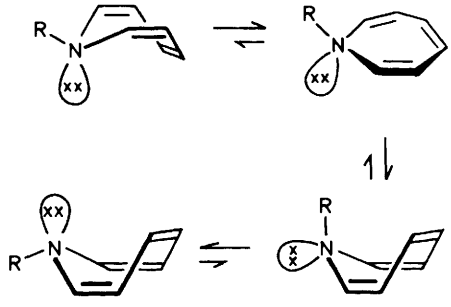
(**7b**) R = H
(**10b**) R = Me



(**7c**) R = H
(**10c**) R = Me

When this *endo*-isomer (**10a**) is warmed in chloroform, rapid equilibration with the *exo*-isomer (**10b**) occurs. At equilibrium the ratio of (**10a**):(**10b**) is 2:1 and at 400 MHz all the signals in the n.m.r. spectrum of the mixture (except for some of those in the quinazolone ring) were clearly separated.

It was of considerable interest to us to measure the thermodynamic parameters for the conversion (**10a**)⇌(**10b**) as, in the transition state (**10c**) for this process, the azepine ring is constrained to be planar with the electrons on its ring nitrogen contained a p orbital. This presents a unique opportunity to probe the effect of overlap of 8π electrons in a planar azepine ring. Previous attempts to gauge the effect of anti-aromaticity on the azepine ring inversion barrier have never excluded the possibility of ring inversion succeeded by nitrogen inversion where the planar 8π system is by-passed (Scheme 3).*

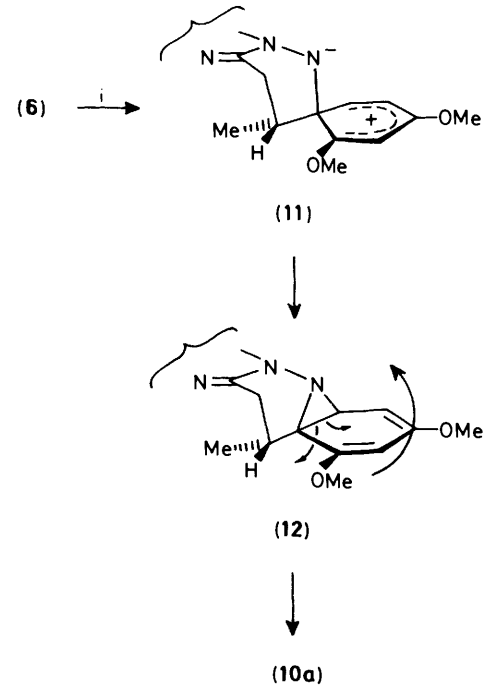


Scheme 3.

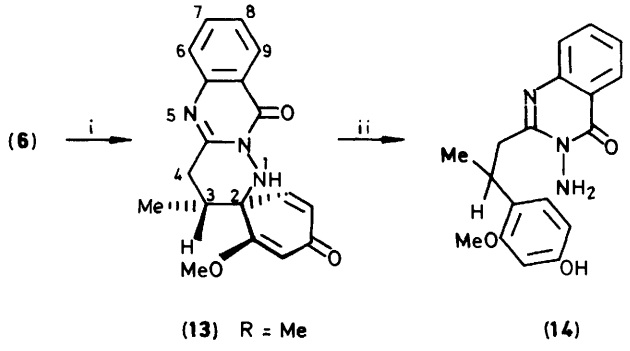
Unfortunately our attempts to measure the kinetics for the conversion (**10a**)⇌(**10b**) were plagued by non-reproducibility: in chlorobenzene the highest temperature at which the interconversion took place at a measurable rate [with reasonable reversible first-order kinetics ($k = 8.5 \times 10^{-4}$ s^{-1}) for the forward reaction] was 135 °C. We suspect that the alternative pathway for this interconversion possibly involves azepine ring protonation at C-2 followed by rapid ring inversion and then proton loss, but attempts to eliminate this route have so far been unsuccessful.

From the measured rate constant at 135 °C discussed above, a minimum value for the energy barrier separating the con-

* In 1*H*-Azepines bearing a *N*-ethoxycarbonyl group, the nitrogen atom is probably sp^2 hybridised; however, delocalisation of electrons from this ring nitrogen will effectively reduce any anti-aromaticity.



Scheme 4. *Reagents:* i, LTA

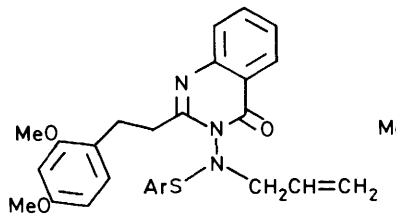


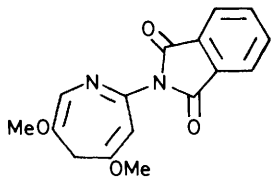
Reagents: i, LTA, MeOH; ii, Zn/H^+

formers (**10a**) and (**10b**) can be estimated to be 30 kcal mol^{-1} which we believe to comprise three components: (*a*) the azepine ring inversion barrier; (*b*) the azepine nitrogen inversion barrier; and (*c*) a contribution from eclipsing in the saturated portion of the reduced pyridazine ring. In principle, therefore (using, perhaps, a less acid-sensitive azepine ring), the value of component (*a*) could be determined.

The stereospecific formation of conformer (**10a**) on *N*-nitrene addition can be rationalised by attack of the latter moiety on the phenyl ring, as shown in structure (**11**) (Scheme 4) (where interaction between the benzylic methyl and *o*-methoxy groups is minimised) followed by benzeneimine formation, and then by disrotatory ring-opening to the azepine accompanied by boat formation as indicated by the arrows in structure (**12**). Nitrogen inversion in the benzeneimine (**12**) is not likely because this would generate a *trans*-fused diazabicyclo[4.1.0]-heptane as well as putting three substituents *cis* on the aziridine ring.[10]

Although in the proton spectra of both compounds (**7**) and (**10a**) there was no evidence for the presence of the isomeric benzeneimine valence structure [*cf.* (**12**)], the assigned chemical shifts of the azepine quaternary carbons C-2 in these compounds at δ 82.8 and 85.8 respectively were at first sight anomalously far upfield. Although this could be interpreted as evidence for a contribution from the benzeneimine structure, the upfield shift of the azepine C-7 resonances that would be expected is less obvious and we prefer to attribute this shift of the C-2 signal to the exceptional local environment of this carbon.





The oxidation of the quinazolone (**6**) with LTA in *methanol* yielded none of the previously described azepine (**10a**). Instead a more polar compound (40%), m.p. 228—230 °C (decomp.) was obtained to which the dienone structure (**13**) was assigned. (This material was also obtained as a minor product in the oxidation in chloroform of compound (**6**). The spectroscopic data for this compound did not distinguish between the *ortho* and *para* dienone structures; however, it was reduced by zinc in methanol–hydrochloric acid to the corresponding phenol (**14**) whose substitution was unambiguously determined using the known empirical shielding increments for *ortho* and *para* ring protons in methoxy-substituted sodium phenolates in Me_2SO by comparison with the free phenol.[11] Thus the *ortho* protons in compound (**14**) were shifted upfield by 0.42 p.p.m. (expected shift, 0.42—0.59 p.p.m.) whereas the expected value for a *para* proton would have been 0.71—0.79 p.p.m. The configuration of compound (**13**) at the benzylic position is assigned on the assumption that it is derived by protonation of the intermediate (**11**) (Scheme 4) with methanol. We are unable to exclude the possibility that compound (**13**) may be formed by ring-opening of the benzeneimine (**12**) by methanol followed by demethylation.

An ever-present possibility in intramolecular reactions of reactive intermediates is that the intramolecular reaction may, in fact, be occurring with a precursor of the reactive intermediate—in the present case an amine–lead^{IV} acetate derived species. To eliminate this possibility, we oxidised compound (**5**) in the presence of five mole equivalents of allyl *p*-chlorophenyl sulphide, a highly nitrenophilic trap; the product was shown to be the sulphenamide (**16**) (50%), m.p. 100—102 °C, formed by the expected [2,3]-sigmatropic rearrangement of the initial sulphilimine.[12] It appears therefore that the dimethoxyphenyl ring is not intercepting an intermediate *en route* to the nitrene.

The conclusion from this work is, therefore, that although *N*-nitrenes derived from oxidation of 3-aminoquinazolones have a preference for intramolecular reaction *via* a seven-membered transition state, increased nucleophilicity in the trap can allow reaction *via* a six-membered transition state. It is also clear that intramolecular nitrene addition can result in unexpectedly stable structures: the intermolecular addition of phthalimido-nitrene to 1,3-dimethoxybenzene yields the 4*H*-azepine (**16**) presumably by rearrangement of an initially formed 1*H*-azepine.[7]

Experimental

N.m.r. spectra were determined on a Bruker WH-400 or a Varian EM390 spectrometer in deuteriochloroform with

trimethylsilane as internal standard unless otherwise stated. I.r. spectra of crystalline compounds were determined for Nujol mulls and those of other compounds for thin films. Mass spectra were obtained using an A.E.I. MS9 spectrometer. Ether refers to diethyl ether.

General Procedure for the Synthesis of 3-Amino-2-(2,4-dimethoxyphenylalkyl)quinazolin-4(3H)-ones: Methyl N-[3-(2,4-dimethoxyphenyl)alkanoyl]anthranilates.—The 2,4-dimethoxyphenylalkanoic acid (0.01 mol) was added to a solution of sodium (0.01 mol) in dry methanol (50 ml). After evaporation of the methanol, the residue was triturated with dry ether and the insoluble sodium salt filtered off and dried at 100 °C for 1 h. This sodium salt (0.01 mol) was converted into its acid chloride by suspending it in dry benzene (20 ml), treating the suspension with 4 drops of dry pyridine and then, whilst cooling it in ice, adding oxalyl chloride (3 ml).[13] After the mixture had been stirred for 5 min, the benzene and excess of oxalyl chloride were removed under reduced pressure and a solution of methyl anthranilate (0.02 mol) in dry ether (50 ml) was added to the residue with stirring. The mixture was set aside for 3 h and then the crystalline methyl anthanilate hydrochloride and sodium chloride were filtered off and washed with dry ether. The combined ether filtrates were washed four times with hydrochloric acid (2M) and then with water before being dried and evaporated. The following amides were obtained by the above procedure: methyl *N*-[3-(2,4-dimethoxyphenyl)propanoyl]-anthranilate (75%) as a colourless solid, m.p. 76—78 °C (from ethanol); δ 10.9br (s, NH), 8.62 (d, *J* 8 Hz, H *ortho* to NH), 7.99 (dd, *J* 7 and 2 Hz, H *ortho* to CO_2Me), 7.51 (ddd, *J* 8, 8 and 2 Hz, H *meta* to NH), 7.09 (m, H *meta* to CO_2Me, Ar 6-H), 6.45—6.2 (m, Ar 3-H and Ar 5-H), 3.92, 3.84, 3.79 (3 × s, 2 × OMe + CO_2Me), and 3.2—2.5 (m, CH_2CH_2); $\nu_{max.}$ 3 300w, 1 687s, and 1 603 cm^{-1}; methyl *N*-[3-(2,4-dimethoxyphenyl)butanoyl]-anthranilate (80%) [from 3-(2,4-dimethoxyphenyl)butyric acid] as a pale yellow oil, δ 10.9br (s, NH), 8.7 (d, *J* 8 Hz, H *ortho* to NH), 7.9 (dd, *J* 7 and 2 Hz, H *ortho* to CO_2Me), 7.45 (ddd, *J* 8, 8 and 2 Hz, H *meta* to NH), 7.0 (m, H *meta* to CO_2Me, Ar 6-H), 6.6—6.3 (m, Ar 3-H and 5-H), 3.85, 3.76, 3.70 (3 × s, 2 × OMe + CO_2Me), 2.90—2.47 (m, CH_2CH_2), and 1.40 (d, *J* 7 Hz, Me); $\nu_{max.}$ 3 300w, 1 685s, and 1 595s cm^{-1}.

3-*Amino*-2-[2-(2,4-*dimethoxyphenyl*)*ethyl*]*quinazolin*-4(3H)-*one* (**5**).—The corresponding amide prepared as above (0.01 mol) and hydrazine hydrate (95%, 0.05 mol) were dissolved in ethanol (10 ml) and heated for 2 h under reflux. Cooling in ice gave the *product* (**5**) as a colourless solid (60%), m.p. 139—140 °C (from ethanol) (Found: C, 66.6; H, 5.9; N, 12.8. $C_{18}H_{19}N_3O_3$ requires C, 66.45; H, 5.9; N, 12.9%); δ 8.17 (d, *J* 8 Hz, quinaz. 5-H), 7.7—7.2 (m, quinaz. 6-, 7-, and 8-H), 7.02 (d, *J* 9 Hz, Ar 6-H), 6.42—6.26 (m, Ar 3-H and Ar 5-H), 4.73 (s, NH_2), 3.74 (s, OMe), 3.67 (s, OMe), and 3.4—2.7 (m, CH_2CH_2); $\nu_{max.}$ 3 310w, 1 673s, 1 619m, and 1 529s cm^{-1}.

3-*Amino*-2-[2-(2,4-*dimethoxyphenyl*)*propyl*]*quinazolin*-4(3H)-*one* (**6**).—The corresponding amide prepared as above (2 g), hydrazine hydrate (95%, 5 ml), and ethanol (10 ml) were heated in a degassed sealed tube at 120 °C overnight. The reaction mixture was poured into water, extracted with ether, and the ether layer separated, dried and evaporated to give an oil which crystallised on standing (65%). Crystallisation from ethanol gave the quinazoline (**6**), m.p. 95—97 °C (Found: C, 67.1; H, 6.0; N, 12.2. $C_{19}H_{21}N_3O_3$ requires C, 67.25; H, 6.2; H, 12.3%); δ 8.17 (d, *J* 8 Hz, quinaz. 5-H), 7.7—7.2 (m, quinaz. 6-, 7-, and 8-H), 7.1 (d, *J* 9 Hz, Ar 6-H), 6.4 (dd, *J* 9 and 2 Hz, Ar 5-H), 6.3 (d, *J* 2 Hz, Ar 3-H), 4.71 (s, NH_2), 3.72 (s, OMe), 3.6 (s, OMe), 3.35—3.05 (m, CH_2CHMe), and 1.53 (d, *J* 7 Hz, Me); $\nu_{max.}$ 3 320w, 3 210w, 1 680s, and 1 600s cm^{-1}.

Oxidation of 2-Substituted 3-aminoquinazolin-4(3H)-ones with Lead Tetra-acetate.—The general procedure is exemplified in the case of compound (**5**): the solid quinazoline (**5**) (100 mg) and dry LTA (109 mg) were intimately mixed in a small sample tube (**CAUTION**: this procedure has not been carried out on more than a total of 600 mg of solid) and then added continuously in very small portions to chloroform (50 ml; dried immediately before use by distillation from P_2O_5) with vigorous magnetic stirring. After stirring for an additional 5 min, insoluble lead diacetate was separated and the chloroform solution washed with sodium hydrogen carbonate solution, dried and evaporated to give an oil (76 mg). Crystallisation from ethanol gave the 6,7-*dihydro*-3,5-*dimethoxyazepino*-[1′,2′:1,6]*pyridazo*[3,2-b]*quinazolin*-13-*one* (**7**) (19 mg), m.p. 150—153 °C (Found: C, 66.6; H, 5.35; N, 12.85. $C_{18}H_{17}N_3O_3$ requires C, 66.85; H, 5.3; N, 13.0%); δ 8.33 (dd, *J* 8.0 and 1.5 Hz, quinaz. H *ortho* to C=O), 7.74 (ddd, *J* 7.2, 8.1, and 1.5 Hz, quinaz. H *meta* to N), 7.66 (d, *J* 8.1 Hz, quinaz. H *ortho* to N), 7.45 (ddd, *J* 7.2, 8.0, and 1.3 Hz, quinaz. H *meta* to C=O), 6.54 (d, *J* 11.5 Hz, azep. 1-H), 5.95 (dd, *J* 11.5 and 2.9 Hz, azep. 2-H), 5.52 (d, *J* 2.9 Hz, azep. 4-H), 3.69 (s, OMe), 3.54 (s, OMe), 3.19 (ddd, *J* 17, 11, and 9 Hz, azep. CH_2HCH), 2.99 (ddd, *J* 17, 9, and 3 Hz, azep. CH_2HCH), 2.81 (ddd, *J* 13, 9, and 3 Hz, azep. $HCHCH_2$), and 2.18 (ddd, *J* 13, 11, and 9 Hz, azep. $HCHCH_2$); δ_C 163.8(s), 160.5(s), 158.8(s), 158.7(s), 148.8(s), 138.0(d), 133.9(d), 126.6(d), 126.4(d), 125.8(d), 122.0(d), 121.9(s), 96.3(d), 82.8(s), 54.8(q), 31.3(t), and 29.9(t); $\nu_{max.}$ 1 680s, 1 650s, and 1 610s cm^{-1}; *m/z* 323 (M^+) (base), 308, 198, 197, 185, 184, and 140.

Oxidation of Compound (**6**) *in Chloroform.*—Using the procedure above on compound (**6**) (100 mg) and LTA (130 mg) in chloroform (60 ml), and crystallisation of the product, gave the 6,7-*dihydro*-3,5-*dimethoxy*-6-*methylazepino*[1′,2′:1,6]-*pyridazo*[3,2-b]*quinazolin*-13-*one* stereoisomers (**10a**) (45%) as a colourless solid, m.p. 169—171 °C (from methanol–water) (Found: C, 67.25; H, 5.7; N, 12.45. $C_{19}H_{19}N_3O_3$ requires C, 67.65; H, 5.7; N, 12.45%); δ 8.23 (dd, *J* 8 and 1.5 Hz, quinaz. H *ortho* to C=O), 7.65 (ddd, *J* 8, 7.5 and 1.5 Hz, quinaz. H *meta* to N), 7.57 (d, *J* 7.5 Hz, quinaz. H *ortho* to N), 7.36 (ddd, *J* 8, 7, and 1.3 Hz, quinaz. H *meta* to C=O), 6.40 (d, *J* 11.7 Hz, azep. 1-H), 5.98 (dd, *J* 11.7 and 2.8 Hz, azep. 2-H), 5.42 (d, *J* 2.8 Hz, azep, 4-H), 3.36 (dd, *J* 16.5 and 7.4 Hz, $MeCHCHH$), 2.84 (quintet, *J ca.* 7 Hz, $MeCHCH_2$), 2.59 (dd, *J* 16.5 and 0.7 Hz, $MeCHCHH$), and 0.90 (d, *J* 7.2 Hz, Me); δ_C (−50 °C) 163.6(s), 161.2(s), 158.8(s), 158.8(s), 148.1(s), 134.9(d), 134.2(d), 126.5(d), 126.1(d), 126.0(d), 122.3(d), 121.7(s), 95.6(d), 85.8(s), 55.0(q), 53.9(q), 38.0(dd), 34.3(d), and 18.1(q); $\nu_{max.}$ 1 678s and 1 600s cm^{-1}. When the sample was warmed briefly in chloroform solution, the following additional signals due to the conformer (**10b**) appeared in solution: δ (400 MHz) 8.19 (dd, *J* 8 and 1.5 Hz, quinaz. *ortho* to C=O), 7.63 (ddd, *J* 8, 7.5 and 1.5 Hz, quinaz. *meta* to NH), 7.56 (d, *J ca.* 7 Hz, quinaz. *ortho* to N), 7.34 (ddd, *J* 8, 7, and 1.3 Hz, quinaz. *meta* to C=O), 5.95 (d, *J* 12.2 Hz, azep. 1-H), 5.85 (dd, *J* 12.2 and 2.9 Hz azep. 2-H), 5.26 (d, *J* 2.9 Hz, azep. 4-H), 3.04 (dd, *J* 16.5 and 8.0 Hz, $MeCHCHH$), 2.97 (dd, *J* 16.5 and 9.8 Hz, $MeCHCHH$), 2.95 (m, $MeCHCH_2$), and 1.07 (d, *J* 7.1 Hz, Me).

Oxidation of Compound (**6**) *in Methanol.*—The procedure above the following except that dry methanol (60 ml) was used instead of chloroform. After the solution had been stirred for the additional 5 min, the bulk of the methanol was removed under reduced pressure and chloroform was added. This solution was washed with sodium hydrogen carbonate solution, the organic layer was separated, dried, and evaporated. Crystallisation of the residue from ethyl acetate–light petroleum gave 1,2,3,4-*tetrahydro*-2′-*methoxy*-3-*methylpyridazo*[3,2-b]-*quinazoline*-2-*spirocyclohexa*-2′,5′-*diene*-4′,10-*dione* (**13**) (40%), m.p. 228—230 °C (decomp.) (Found: C, 66.6; H, 5.35; N, 12.9.

$C_{18}H_{17}N_3O_3$ requires C, 66.7; H, 5.3; N, 13.0%); δ 8.23 (dd, *J* 8 and 1.5 Hz, quinaz. H *ortho* to C=O), 7.75—7.25 (m, quinaz. 6-, 7-, and 8-H), 7.2 (s, NH, exch. D_2O), 6.7 (d *J* 10 Hz, C*H*=CHCO), 6.25 (dd, *J* 10 and 2 Hz, CH=C*H*CO), 5.5 (d, *J* 2 Hz, MeOC=C*H*CO), 3.55 (s, OMe), 3.05—2.4 (m, C*HCH*$_2$), and 1.08 (d, *J* 7.2 Hz, Me); $\nu_{max.}$ 3 238s, 1 668s, and 1 605s cm^{-1}; *m/z* 323 (M^+), 164 (base).

Reduction of Compound (**13**) *with Zinc–Methanol–Acid.*—The dienone (**13**) (20 mg) was heated under reflux and vigorously stirred with methanol (20 ml), hydrochloric acid (5 drops; 2M), and zinc powder (30 mg) for 2.5 h. After the solution had cooled and the zinc separated, the methanol was evaporated under reduced pressure, the product extracted into chloroform, and the chloroform solution washed with sodium hydrogen carbonate solution, dried and evaporated. Trituration of the oily residue with ether gave a colourless solid (90%) which crystallised from ethyl acetate–light petroleum to give 3-*amino*-2-[2-(4-*hydroxy*-2-*methoxyphenyl*)*propyl*]*quinazolin*-4(3H)-*one* (**14**) as a colourless solid, m.p. 174—175 °C (Found: C, 66.15; H, 5.9; N, 12.8. $C_{18}H_{19}N_3O_3$ requires C, 66.45; H, 5.9; N, 12.9%); δ 9.18 (s, OH), 8.09 (dd, *J* 8 and 1.4 Hz, quinaz. H *ortho* to C=O), 7.76 (ddd, *J* 7, 8, and 1.5 Hz, quinaz. H *meta* to N), 7.59 (d, *J* 8 Hz, quinaz. H *ortho* to N), 7.47 (ddd, *J* 7, 7 and 1.1 Hz, H *meta* to C=O), 7.04 (d, *J* 8.8 Hz ArH *meta* to OH), 6.30 (m, 2 × ArH *ortho* to OH), 8.68 (s, NH_2), 3.79 (m, C*H*Me), 3.61 (s, OMe), 3.18 (dd, *J* 14.7 and 8.4 Hz, *H*CHCHMe), 3.08 (dd, *J* 14.7 and 6.1 Hz, HC*H*CHMe), and 1.21 (d, *J* 6.9 Hz, Me); $\nu_{max.}$ 3 321w, 3 263w, 1 682s, and 1 608s cm^{-1}.

Oxidation of Compound (**5**) *in the Presence of Allyl* p-*Chlorophenyl Sulphides.*—An intimate solid mixture of compound (**5**) (250 mg) and LTA (300 mg) was added in small amounts to a solution of allyl *p*-chlorophenyl sulphide (567 mg) in chloroform (4 ml). The precipitated lead diacetate was separated and the chloroform washed with sodium hydrogen carbonate solution, dried, and evaporated under reduced pressure. Chromatography of the crude product using Kieselgel and elution with ethyl acetate–light petroleum (1:4) gave 3-*allyl*(p-*chlorophenylthio*)*amino*-2-[2-(2,4-*dimethoxyphenyl*)*ethyl*]*quinazolin*-4(3H)-*one* (**15**) (50%), m.p. 100—102 °C (from ether) (Found: C, 63.9; H, 5.2; N, 8.2. $C_{27}H_{26}ClN_3O_3S$ requires C, 63.85; H, 5.1; N, 8.25%), δ 8.21 (d, *J* 8 Hz, quinaz. H *ortho* to C=O), 7.8—7.1 (m, 3 × quinaz. H, 4 × SC_6H_4Cl) 6.82 (d, *J* 8 Hz, Ar 6-H), 6.35 (m, Ar 3- and 5-H), 6.2—5.7 (m, C*H*=CH_2), 5.2 [d, *J* 16 Hz, HC=C*H*H (*trans*)], 5.16 [d, *J* 10 Hz, HC=CH*H* (*cis*)], 4.30 (m, *J* 6 Hz, CH_2CH=CH_2), 3.78 (s, OMe), 3.64 (s, OMe), and 2.9 (m, CH_2CH_2); $\nu_{max.}$ 1 680s, 1 615m, and 1 602s cm^{-1}.

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