Intramolecular Reactions of *N*-Nitrenes: Oxidation of 3-Amino-2-(arylalkyl)quinazolones

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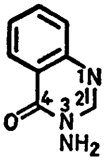
Summary Oxidation of the title compounds yields *N*-nitrenes which react intramolecularly with electron-rich aryl groups *via* 7-membered transition states; substituent effects are in accord with an electrophilic aromatic substitution rather than concerted addition.

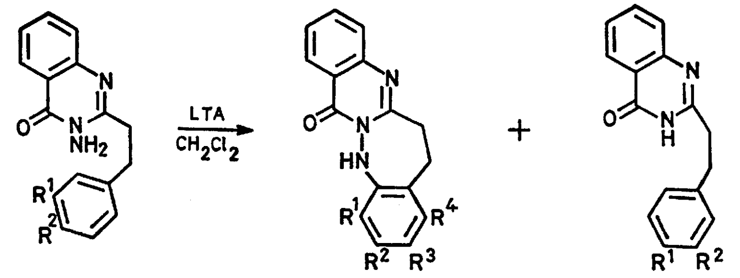
3-AMINOQUINAZOLONE (**1**) is one member of a family of *N*-aminoheterocyclic compounds from which *N*-nitrenes are generated by oxidation.[1] These nitrenes have singlet ground states and react stereospecifically with alkenes to give aziridines.[2] Electron-rich aryl rings are also able to intercept the *N*-nitrenes, and the isolated products are those resulting from further transformations of 7-azanorcaradienes.[3]



(**1**)

The quinazolone ring lends itself well to a study of the intramolecular reactions of *N*-nitrenes since a trap can readily be incorporated at position 2. Thus reaction of β-arylpropanoic acid chlorides with methyl anthranilate followed by treatment with hydrazine gave the 2-arylethylquinazolones, *e.g.* (**2**), in good yield.

Intramolecular trapping in the case of methoxyarylethylquinazolones is very sensitive to the location of the methoxy-group. Thus (**2**) on oxidation with lead tetraacetate (LTA) gave (**3**) (27%), m.p. 187—190 °C, ν_{max} (Nujol) 3285 and 1665 cm^{-1}; δ($CDCl_3$) 8·16 (1H, d, *J* 8·4 Hz, 5-H; numbering as in original quinazolone), 7·75 (1H, s, NH), 7·2—7·7 (3H, m, 6-, 7-, and 8-H), 7·10 (1H, d, *J ca.* 9 Hz, complicated by virtual coupling), 6·62 (1H, dd, *J ca.* 9, 2 Hz), 6·55 (1H, s, br), 3·68 (3H, s), and 3·1—3·6 (4H, AA′BB′) and (**4**) (32%), m.p. 155—157 °C, ν_{max} (Nujol) 3260 and 1680 cm^{-1}; δ($CDCl_3$) 9·08 (1H, s, NH), 8·20 (1H, d, *J* 8·4 Hz, 5-H), 7·2—7·8 (3H, m, 6-, 7-, and 8-H), 6·92 (1H, dd, *J* 8·1, 7·2 Hz), 6·70 (1H, dd, *J* 8·1, 1·7 Hz), 6·64 (1H, dd, *J* 7·2, 1·7 Hz), 3·97 (3H, s), and 3·2—3·7 (4H, AA′BB′), together with the deaminated product (**5**) (27%), m.p. 180—181 °C. (Deamination is commonly the fate of quinazolone *N*-nitrenes which escape trapping). Similarly, LTA oxidation of the dimethoxy-analogue (**6**) gave a mixture of (**7**) (21%), m.p. 167—170 °C, (**8**) (14%), m.p. 162—164 °C, and (**9**) (21%), m.p. 210—211 °C.



(**2**) $R^1 = OMe$, $R^2 = H$
(**6**) $R^1 = R^2 = OMe$
(**10**) $R^1 = H$, $R^2 = OMe$

(**3**) $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
(**4**) $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
(**7**) $R^1 = R^4 = H$, $R^2 = R^3 = OMe$
(**8**) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$

(**5**) $R^1 = H$, $R^2 = OMe$
(**9**) $R^1 = R^2 = OMe$
(**11**) $R^1 = OMe$, $R^2 = H$

In contrast, oxidation of the *p*-methoxyphenylethyl analogue (**10**) gave no products derived from trapping of the nitrene by the aromatic ring (n.m.r.): the only product isolated was the deaminated product (**11**) (38%). This substituent effect cannot easily be reconciled with a concerted reaction of the nitrenes with the aryl rings to form azanorcaradienes with subsequent acid-catalysed conversion into (**3**), (**4**), (**7**), and (**8**). Direct aryl C–H bond insertion is also unlikely (*N*-nitrenes do not insert into σ-bonds).

Examination of models suggests that the empty orbital of the nitrene (sp-hybridisation assumed) overlaps best with an aryl p(π) orbital in a 7-membered transition state (Figure 1). The resultant carbonium ion is stabilised by a *m*-OMe but not by a *p*-OMe substituent; loss of a proton and protonation on nitrogen give the products (in what is effectively an electrophilic aromatic substitution reaction).

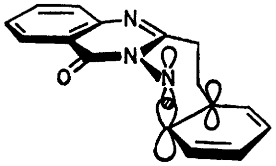
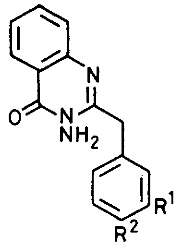
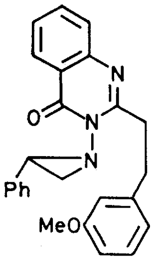


Figure 1



(**12**) $R^1 = OMe$, $R^2 = H$
(**13**) $R^1 = H$, $R^2 = OMe$



(**14**)

The preference for this 7-membered transition state over the corresponding 6- (or 5-) membered transition states is shown in the results from the oxidations of *m*- and *p*-methoxybenzylquinazolones (**12**) and (**13**), where only the corresponding deaminated products were obtained in both cases.†

Intramolecular reaction in the case of (**2**) can be diverted by the intermolecular reaction with styrene. Thus oxidation of (**2**) at a concentration of 11 mole % styrene in CH_2Cl_2 gave the aziridine (**14**) as the sole product, as shown by n.m.r. spectroscopy (57% isolated). Similar reaction of (**10**) in the presence of styrene gave 56% (isolated) of the corresponding aziridine. It appears, therefore, that the

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† The particular preference for a 7-membered transition state is also shown in intramolecular additions of these *N*-nitrenes to alkenes: R. S. Atkinson, J. R. Malpass, and K. L. Woodthorpe, unpublished work.

same species is reacting in both inter- and intra-molecular reactions, *i.e.* the latter reaction does not involve interception of an intermediate on the oxidation pathway to the nitrene. Moreover, oxidation of (**2**) using phenyl iodosodiacetate instead of LTA gives a virtually identical profile of reaction products (**3**), (**4**), and (**5**) which also supports a free nitrene intermediate.

N-Nitrenes differ at first sight from aryl nitrenes which invariably react intramolecularly *via* 5-membered transition states,[4] normally with electron-rich aromatic rings.‡ A rationalisation of this difference in behaviour can be obtained by assuming (a) sp-hybridisation of the nitrene nitrogen, (b) the presence in equilibrium of a 'conformation' of singlet aryl nitrene in which delocalisation of a lone pair into the aromatic ring occurs (Figure 2), and (c) the absence or unimportance of the analogous electron distribution in (b) in the case of *N*-nitrenes as a consequence of lone pair–lone pair repulsion (Figure 2).

This picture offers an explanation for the avoidance of a 6-membered transition state in both cases. For *N*-nitrenes, the ideal geometry in Figure 1 allows easy overlap of p-orbitals as shown and minimises eclipsing interactions in the ethano-linkage in contrast to the strain developed in forcing overlap in *ipso*-attack. In the case of aryl nitrenes the availability of an orthogonal empty p-orbital is ideal for the 5- (but not 6-) membered transition state observed in nucleophilic attack.§

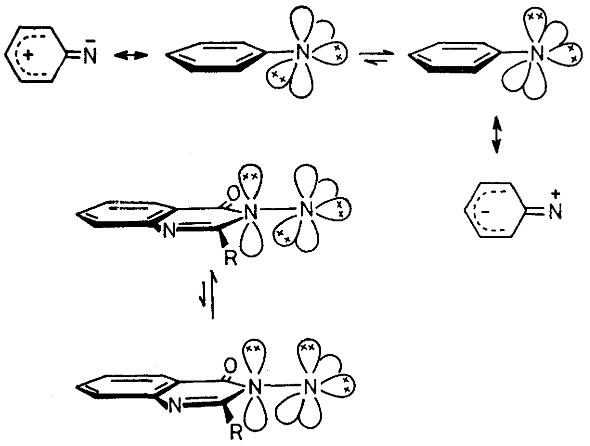

FIGURE 2

(*Received*, 24*th November* 1980; *Com.* 1250.)

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‡ For a recent example of addition to an electron-deficient aromatic ring see P. C. Hayes and G. Jones, *J. Chem. Soc., Chem. Commun.*, 1980, 844.

§ This model does not exclude the possibility that aryl nitrenes may also react preferentially *via* a 7-membered transition state given the opportunity.

[1] R. S. Atkinson and S. B. Awad, *J. Chem. Soc., Perkin Trans. 1*, 1977, 346 and references therein.
[2] R. S. Atkinson and C. W. Rees, *J. Chem. Soc. (C)*, 1969, 772; D. J. Anderson, T. L. Gilchrist, D. C. Horwell, and C. W. Rees, *ibid.*, 1970, 576.
[3] D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 1973, 67.
[4] J. I. G. Cadogan, *Acc. Chem. Res.*, 1972, **5**, 303; B. Iddon, O. Meth-Cohn, E. F. V. Scriven, H. Suschitzky, and P. T. Gallagher, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 900.