A Mechanistic Study of Quinoxaline Formation

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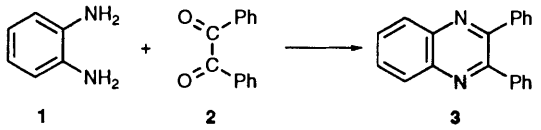
Benzil **2** reacts readily with 1,2-phenylenediamine **1** to give 2,3-diphenylquinoxaline **3**. By the use of ^{13}C NMR spectroscopy with a labelled substrate the course of the reaction has been determined. A parallel study of the reaction between benzil and 6-methoxy-2,4,5-triaminopyrimidine gave only an indication of the pathway because of the large number of possible intermediates.

The classical synthesis of quinoxalines is condensation of an aromatic 1,2-diamine with an α-dicarbonyl compound.[1] In particular, reaction of 1,2-phenylenediamine **1** with benzil **2** in boiling glacial acetic acid gives 2,3-diphenylquinoxaline **3** in high yield (Scheme 1).[2] Although the reaction is a simple one a



1 **2** **3**

Scheme 1

substantial number of bond breaking and making steps take place and the order in which the steps occur is not known. In an attempt to learn more about this reaction we carried out the synthesis using benzil with enhanced ^{13}C abundance in one carbonyl group and looked for the ^{13}C NMR spectra of transient intermediates.

Results and Discussion

One major difficulty in any experiment which attempts to detect the formation of transient intermediates by NMR spectroscopy is finding the experimental condition under which the reaction is slow enough to permit the accumulation of sufficient transients to give spectra of intermediates present at low concentrations. The reaction was examined first by UV spectroscopy to establish these conditions. This was possible because substantial spectral changes accompany the formation of **3**. The kinetics of this process have been examined previously[3] and it was shown that, with a mixture of chloroform and methanol (10:1) as solvent and reactant concentrations of 0.083 mol dm^{-3}, the reaction was complete in about 2 h. This is too fast for our purposes and we found that the reaction was even faster in neat methanol. However, with tetrahydrofuran as solvent and reactant concentrations of 0.2 mol dm^{-3} the reaction took about 18 h, which is suitable for NMR spectroscopic work. A spectrum was recorded every hour with an accumulation time of 15 min.

The variation of signal intensity with time for reactant and product is shown in Fig. 1. The signal due to the label in **2** at 195.50 ppm decreases more rapidly than that due to the corresponding signal in **3** at 154.47 ppm increases, indicating the accumulation of intermediate(s). This conclusion is confirmed by the appearance, and subsequent disappearance, of a cluster of signals around 84 ppm which is due to the transient intermediates. The cluster forms while the signal for benzil at 195.50 ppm is declining rapidly and it becomes too small for detection after 4 h. The chemical shifts and intensities of the signals in the cluster are displayed in Table 1. Our interpretation of the results is best understood by reference to the pathways shown in Scheme 2.

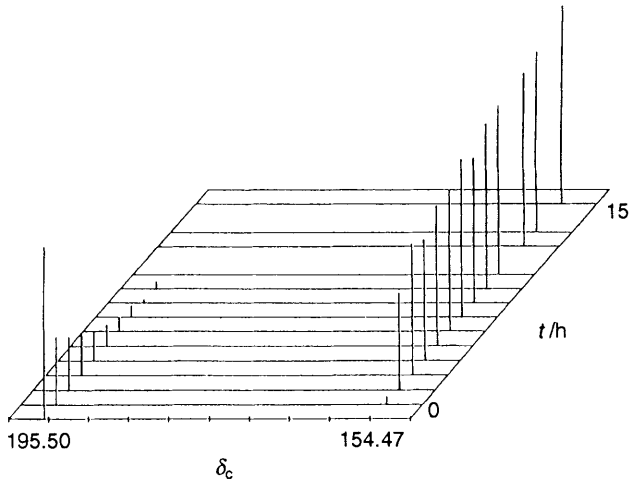


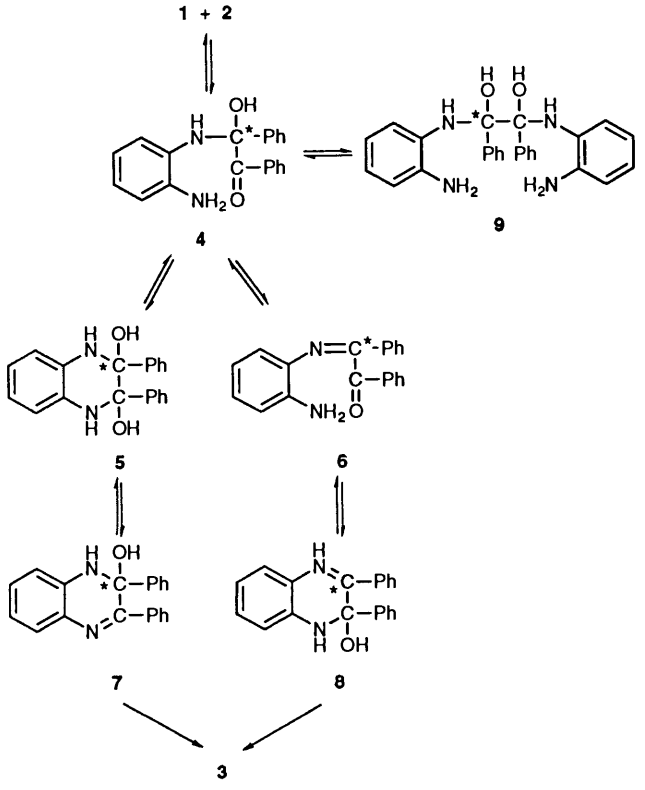
Fig. 1 Variation of signal intensity for reactant and product with time for the reaction of [^{13}C]benzil with 1,2-phenylenediamine

Table 1 Intensities of signals in the ^{13}C NMR spectra obtained during the reaction of 1,2-phenylenediamine with benzil

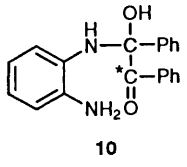
	Intensity (*t*/h)					
δ	0	1	2	3	4	5
84.55	0	14.16	5.90	1.37	0	0
84.40	0	3.55	3.34	2.25	1.24	0
84.29	0	15.81	7.35	2.98	1.85	1.27
84.21	0	8.04	4.81	1.21	0	0
84.07	0	5.80	1.60	0.90	0	0

In essence there are two routes for the conversion of **1** and **2** into **3** and they differ in whether the fully cyclised diol **5** is formed. There is, however, a further complication. In the initial step, as well as **4**, an equal amount of analogous intermediate with the label in the unreacted carbonyl group **10** will be formed but no transient signal in the expected part of the NMR spectrum (around 190 ppm) was observed. However, at low concentrations of **10** it is unlikely that a signal due to the nonhydrogen bearing carbon of the carbonyl group would be observed and so its absence is not inconsistent with the proposed reaction scheme. Alhough the carbinolamine carbon is also tertiary there are two hydrogens only two atoms away and so it is more likely to be seen in the NMR spectrum than the carbonyl carbon for which the nearest hydrogen is four atoms away. After reaction to give **4** or **10** the reaction may proceed *via* **5** and **7** or *via* **6** and **8**. Because the molecule is symmetrical, intermediate **5** is identical whether it is formed from **4** or **10**.

If the reaction went *via* **6** and **8** we would expect to see, as well as the signal from **4**, one transient signal around 84 ppm for **8**



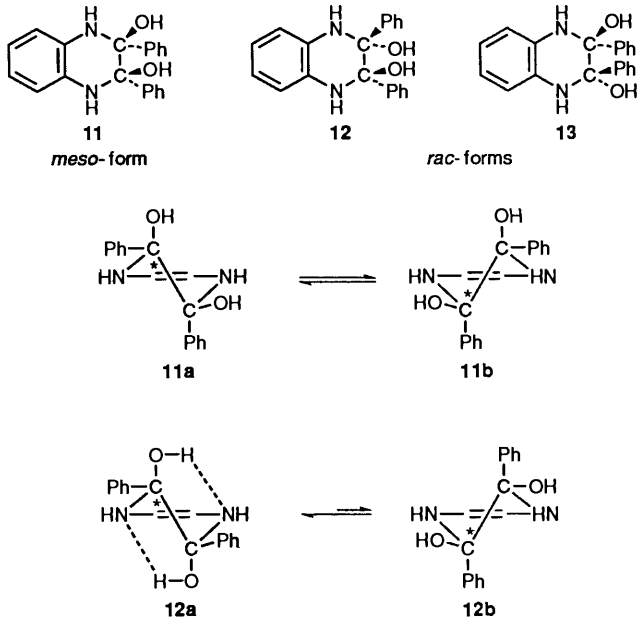
Scheme 2 The ^{13}C-labelled atom is marked by an asterisk



10

with the label at C-3 (the form of **8** obtained from **10** rather than **4** and which, because of the symmetry of the molecule, is identical with **5**) and two around 154 ppm corresponding to the C=N signals for **6** and **8**. The C=N signal for 2,3-diphenylquinoxaline is at 154.47 ppm and during the course of the reaction several new signals appeared around 154 ppm but they all remained even at the end of the reaction when the signal at 154.47 ppm had reached its maximum value. We assume that the new signals were due to by-products rather than **6** and **8**. Significantly none is transient. A reasonable explanation for the absence of transient signals is that, as with the unobserved carbonyl signal in **9**, those due to the C=N groups in **6** and **8** are too small to observe and so the absence of signals in this region does not eliminate reaction *via* **6** and **8**. However, this route is inconsistent with the number of signals around 84 ppm (Table 1) where there should be only two.

Our observations are more in accord with reaction *via* **5** and **7**. Intermediates **4** and **7** will each give rise to one signal around 84 ppm, while **5** will produce two signals, depending on its stereochemistry. The conformational analysis of heterocyclic rings has been discussed in detail by Riddell.[4] There are three isomers of **5**, *viz.* **11**, **12** and **13** (Scheme 3) and we make the assumption that all three are formed, although not necessarily in equal amounts. Compound **11** is the *meso*-form and will undergo ring inversion of the half-chair form *i.e.* **11a**⇌**11b** (Scheme 3). If that inversion were slow the labelled carbon would have two different chemical shifts and thus two NMR signals would be observed, but it is highly unlikely that inversion is slow enough on the NMR time scale for this to arise. Therefore, from **11** there will be one averaged NMR signal. The

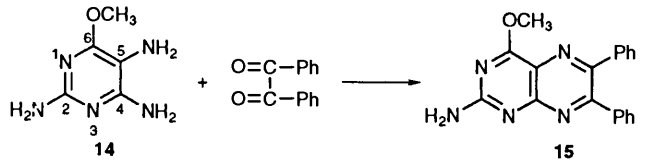


Scheme 3

rac-forms **12** and **13** are enantiomeric; in one the chiral centres are *R,R* and in the other *S,S*. They cannot be interconverted except by fission of a chemical bond but both will undergo ring inversion of the half-chair form *e.g.* **12a**⇌**12b**. The situation is rather different from that of **11** in that **12a** is greatly preferred to **12b** because of the hydrogen bonding as shown and the two pseudo-equatorial phenyl groups. Hydrogen bonding is known to affect the conformation of heterocyclic ring compounds.[5] As a consequence of the preference only one NMR signal will be obtained from **12**. A similar situation applies to **13** which again gives only one signal in the NMR spectrum but, because of the enantiomeric relationship, the chemical shift will be the same as the signal from **12**. This gives a total of two signals for the different forms of **5** and a grand total of four signals for **4**, **5** and **7**, one more than the observed number. The extra signal we ascribe to the intermediate (**9**) which does not lead to any isolable product. It is possible that there could also be reaction *via* **6** and **8** as this route has only one intermediate detectable by NMR spectroscopy which is identical with one intermediate formed in the **5**/**7** pathway but it is clear that reaction *via* **6** and **8** cannot be the only pathway.

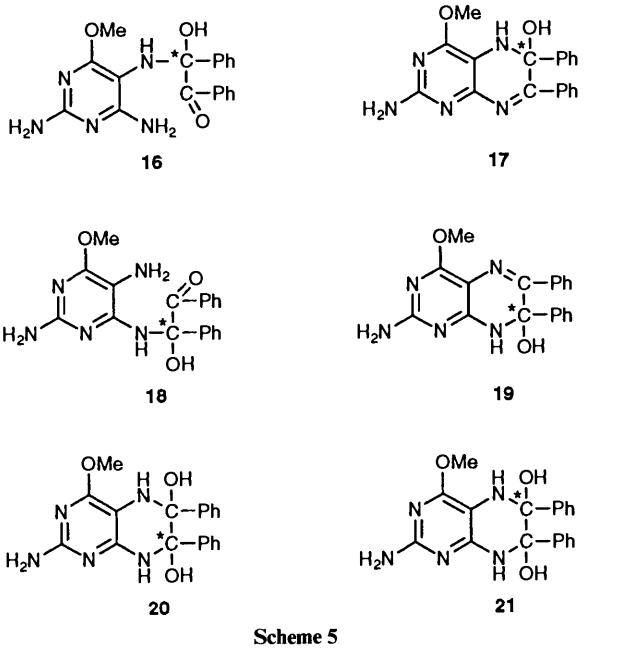
From the data in Table 1 it is seen that the intermediates form very quickly and, although they are shown as sequential in Scheme 2, all are present at the same time and the maximum concentration of all is achieved after 1 h, whereas product formation occurs over 13 h. Also, the signals corresponding to each intermediate decline more or less in parallel. All these observations are consistent with rapid formation at low concentrations of **4**, **5** and **7** in equilibrium processes, as we have observed in other systems.[6] The irreversible step, which is the driving force in product formation, is the conversion of **7** into **3**. We can also understand why the intermediates become undectable long before the reaction is complete. Conversion of **1** and **2** into **4** is a bimolecular process while all other processes are monomolecular and so the equilibria will adjust to favour the reactants as the reaction proceeds.

6-Methoxy-2,4,5-triaminopyrimidine **14** condenses readily with benzil to give 2-amino-4-methoxy-6,7-diphenylpteridine **15** (Scheme 4), in a process which is analogous to the production of quinoxaline.[7] Pteridines are notorously insoluble in all solvents but the 4-alkoxy group makes **15** quite soluble in most organic solvents. The nonsymmetrical nature of the pyrimidine means that there are more possible intermediates



Scheme 4

in this reaction than there are in the reaction considered above. For an NMR study methanol was used as solvent and a spectrum was obtained every hour over the course of 15 h. A further spectrum was run after 39 h, in which the signal for benzil had completely disappeared, indicating complete reaction. Two large new signals appeared in this spectrum at 152.4 and 162.1 ppm and these are assigned to the two C=N bonds in **15**. As displayed in Fig. 2 the intensities of these two signals increase in an identical manner and this suggests that initial attack can occur with equal facility at the 4-or 5-amino group. The final spectrum contained a number of other small signals which were not present in the spectra of the two reactants and these are assumed to be due to by-products. In the synthetic route to 4-methoxypteridine it was found[7] that by-products are formed and this has been confirmed by the NMR study. However, the proliferation of signals makes the detection and identification of transient intermediates rather difficult. The only region where there are signals which appear and disappear are, as with the formation of quinoxaline, around 84 ppm. If we assume that signals for C=N and C=O in transient intermediates will not be seen, we must equate the number of signals around 84 ppm with intermediates which contain a carbinolamine structure. The possibilities are **16–21** (Scheme 5). If the reaction pathway is analogous to that for the formation of quinoxaline all the above species will be present in the reaction mixture. Four NMR signals will be obtained from **16–19**. Both **20** and **21** have two chiral centres and, unlike those in **5**, they are different. The *meso*-form of **20** will provide one signal and, assuming that there is hydrogen bonding, the *rac*-forms of **20** will give another. Intermediate **21** will give two signals in the same way, making a total of eight for the carbinolamine intermediates in Scheme 5. More signals (up to a maximum of



Scheme 5

six) could be produced by intermediates analogous to **10** following reaction of the 2-, 4- and 5-amino-groups. After 3 h there were 13 signals in the range 81.99–85.36 ppm (81.99, 82.27, 82.60, 82.89, 83.56, 83.77, 83.97, 84.17, 84.39, 84.93, 85.04, 85.13, 85.36 ppm), all of which decreased to below the level of detection by 15 h and none of which showed in the final spectrum taken after 39 h. It has not been possible to assign the signals to any particular atom in the intermediates but the number does suggest that many, if not all, of the intermediates **16–21** are formed on reacting **14** with benzil. It would be difficult to account for all the signals if **20** and **21** were not formed. The final, irreversible step is the elimination of water to give **15** and this step is the driving force in the reaction. What has been observed in this work may be a general pattern for many organic reactions. A number of equilibria are established but somewhere along the reaction pathway there is one irreversible step which drives the reaction towards the products. It is not that there is one linear pathway which follows all the energy minima until a deep well is reached corresponding to the products. The multiplicity of equilibria established on mixing the reactants may explain the range of products obtained in one reaction, a characteristic of synthetic organic chemistry.

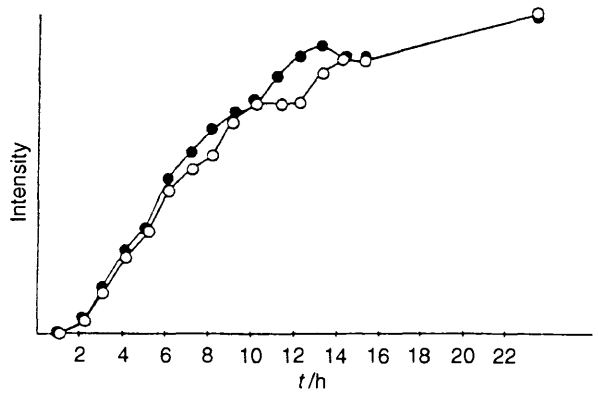


Fig. 2 Variation of signal intensities with time for the product of the reaction of [^{13}C]benzil with 6-methoxy-2,4,5-triaminopyrimidine; ○, signal at δ_C 162.06; ●, signal at δ_C 152.37

Experimental

Materials.—Benzil labelled with ^{13}C at one carbonyl was synthesised according to the method of Butler and Broan.[8] 1,2-Phenylenediamine was treated with charcoal and recrystallised from water before use. A sample of 6-methoxy-2,4,5-triaminopyrimidine was kindly supplied by Dr. Peter Boyle of Trinity College, Dublin. Deuteriated methanol and THF for use in ^{13}C NMR spectroscopy were obtained from MSD Isotopes.

Methods.—Preliminary experiments to determine approximate rates of reaction were carried out on a Pye-Unicam SP8-100 spectrophotometer with a cell holder thermostatted at 25 °C. Samples for NMR spectroscopy were made up in 5 mm tubes with Me_4Si as reference. The spectra were run on a Bruker AM-300 spectrometer at 25 °C. A spectrum was recorded every hour for 15 h. Each spectrum was accumulated for 15 min, resulting in 320 scans per spectrum, followed by a delay of 45 min before the next accumulation. The Me_4Si reference peak was used to normalise the peak intensities when the spectra were transformed. The data from the spectra were analysed on a Macintosh computer using a BASIC data handling program devised by Broan.[9]

Acknowledgements

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