SYNTHESIS AND ^{13}C-NMR STUDIES OF QUINOXALINE SPIRANS AND CARBOXYUREIDES

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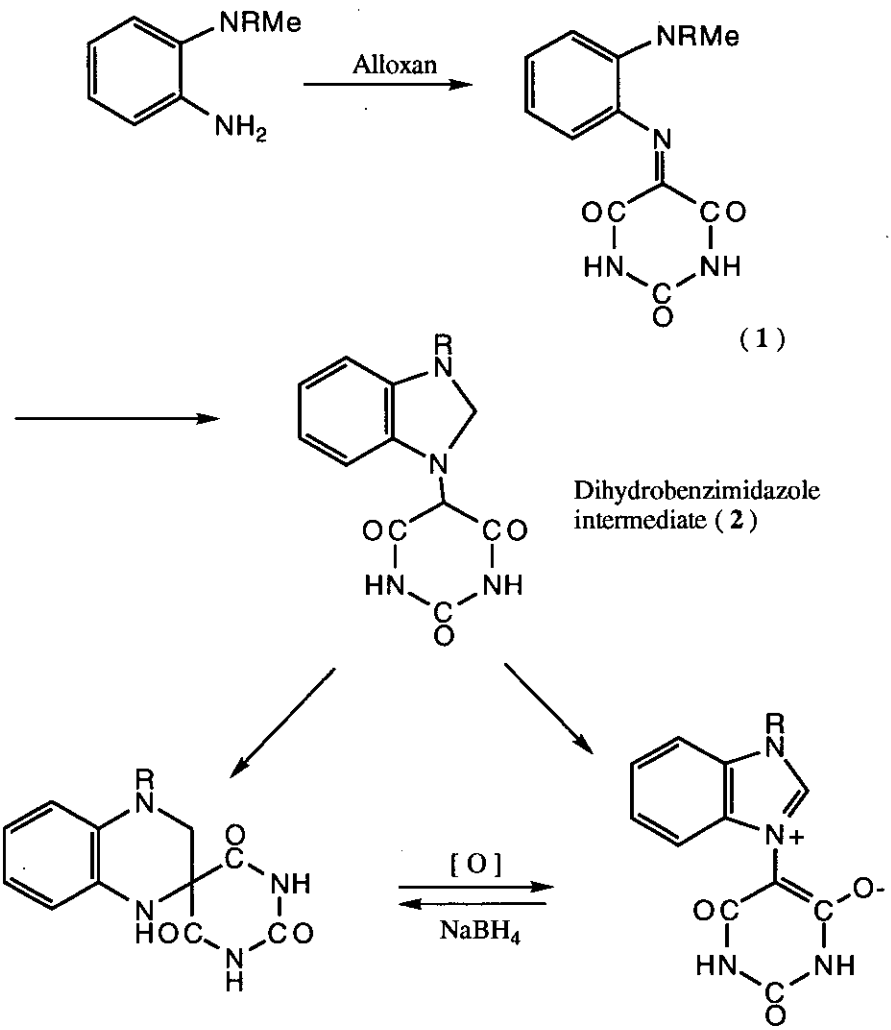
Abstract - New quinoxaline spirans were synthesised by the condensation reaction between alloxan and a series of 2-amino-*N,N*-dimethylanilines derived from substituted nitrophenols. The spiro compounds were then subjected to treatment with hydrogen peroxide in acidic media. This procedure leads to the formation of coloured compounds which were previously proposed to be parabanic acid imines. This study shows the compounds to be quinoxaline carboxyureides.

Heterocyclic spiro compounds are of considerable interest to the chemical and pharmaceutical industries as they have exhibited antibiotic,[1] herbicidal [2] and anti-inflammatory [3] properties. The formation of heterocyclic products from the interaction between aromatic amines and barbituric acid derivatives was reported as early as the last century.[4,5] The reaction of 2-amino-*N,N*-dimethylaniline with alloxan in aqueous ethanolic solution gives a product which was originally proposed as an imine (**1**) [6] but which was later shown [7,8] to be 1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro(hexahydro-2,4,6-trioxo-pyrimidine). This spiro quinoxaline (**3**), henceforth referred to as the "spiran", is formed *via* a dihydrobenzimidazole (**2**) obtained by participation of the *N*-methyl group in a unique ring closure as first reported by Pinnow.[9] This ring formation, termed the " *tert*- amino effect " by Meth-Cohn [10] was observed to be a generalized cyclization of certain *ortho*-substituted-*N,N*-dialkylanilines. The dihydrobenzimidazole is a common intermediate to both the spiran and the benzimidazole betaine (**4**) as shown in Scheme 1. Formation of the latter is favoured under conditions of enhanced hydride lability of the 2-proton in the intermediate, while formation of the spiran requires the presence of an acidic proton at the rearrangement site. For example, reaction between alloxan and 2-amino-*N*-ethyl-*N*-methylaniline

gives only the betaine while reaction with 2-amino-*N*-mesityl-*N*-methylaniline gave only the corresponding spiran.[11,12]

Scheme 1

Proposed overall scheme [10,11] for the formation of quinoxaline spiran (**3**) *via* a dihydrobenzimidazole intermediate (**2**).



Surprisingly, the effect of the presence of other substituent groups in the precursor 2-amino-*N,N*-dimethylanilines, on the formation of spirans has received little attention. The focus of the present

research is two fold. Firstly, the attempted synthesis of substituted quinoxaline spirans to ascertain the electronic and steric effect of a substituent in the aromatic ring on the formation of the spiran. Secondly, the structural elucidation of the red product found on treatment of the unsubstituted spiran with hydrogen peroxide in acidic solution.

RESULTS AND DISCUSSION

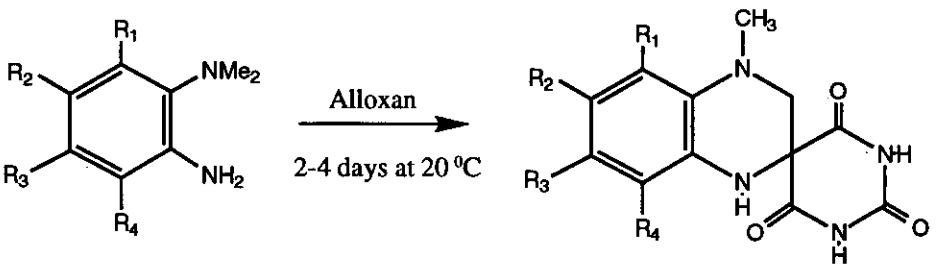
This study followed the procedure for spiran synthesis described by King and Clark-Lewis [7] with the 2-amino-*N,N* -dimethylanilines derived from the corresponding phenols. For evaluation of electronic effects substituents were introduced mainly at the position para to the NMe_2 position, as it was deemed necessary for the substituent to be far removed from the reaction centre in order to eliminate any steric bias. The steric influence was evaluated by the presence of a Me group at position R_1 or R_4. Figure 1 gives a summary of the anilines which have been condensed with alloxan and the spirans obtained. When indicated in Figure 1 that no spiran was formed, no spiran product was isolated after the usual work-up procedure and no evidence was found by mass spectrometry for an ion corresponding to the spiran.

The addition of electron donating alkyl groups (+I) in the 2-amino-*N,N*-dimethylaniline was expected to enhance formation of the spiran. This is based on the likelihood that it would enhance the amine nucleophilicity leading to formation of the intermediate (2). Once formed, the presence of the alkyl group would lower the tendency for hydride ion loss lowering oxidation and hence favour formation of the spiran. The influence of an alkyl group was found to be variable and dependent on the nature and position of the group. Rudy and Cramer [6b] gave a yield of 50 % spiran for R_2=Me and R_3=Me and 51% when both R_2 and R_3=Me. In our hands the yield was less than 30 % in each case. When either R_1=Me or R_4=Me no spiran was formed. For these compounds it is most likely that a steric factor is dominating the reaction pathway. The steric inhibition to the formation of the spiran with a methyl at R_1 is also evident by the inability of the amine with a methyl at R_1 and R_3 to form a spiran. It may also be argued that a methyl group (R_1=Me) ortho to the NMe_2 of the diamine acts as an electron donor in a similar way to the effect of the presence of the extra methylene group in *N*-ethyl-*N*-methylaniline. This enhances the hydride lability in the oxidation leading to the betaine. Reaction of this amine with alloxan gives exclusively a betaine.[12] The highest yield of spiran found in this study is when R_3=*t*-Bu, this being the strongest inductive electron donating group tested. The yield of spiran obtained when R_3=Et was lower than might have been predicted based on the other alkyl groups at R_3, as this compound was

more difficult to isolate and crystallise using the aqueous pyridine work up procedure.

Figure 1

Attempted synthesis of quinoxaline spirans from substituted 2-amino-*N,N*-dimethylanilines and alloxan in aqueous ethanol at room temperature.



(3)

R1	R2	R3	R4	Spiran*	Betaine**	Ref
H	H	H	H	21 %	11 %	8
Me	H	H	H	Nil	Nil	
H	Me	H	H	50 %		6b
H	H	Me	H	50 %		6b
H	H	H	Me	Nil	Nil	
Me	H	Me	H	Nil	Nil	
H	H	Et	H	15 %	12 %	
H	H	tBu	H	35 %	Nil	
H	H	F	H	3 %	15 %	
H	H	Cl	H	15 %	18 %	
H	H	Br	H	Nil	19 %	11a
H	H	I	H	9 %	14 %	
H	H	OMe	H	Nil		
H	H	CH_2OH	H	Nil		
H	H	COMe	H	Nil		
H	H	CN	H	Nil		
H	H	CF_3	H	2 %	10 %	
H	Me	Me	H	51 %		6b
H	Cl	Cl	H	Nil	40 %	11b

Spiran* refers to the amount of spiran isolated after the usual work up procedure.

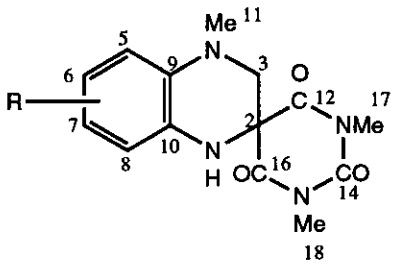
Betaines ** were not isolated and characterised in all cases.

All other substituent groups tested at R_3 showed a decreased tendency for the formation of the spiran. (Figure 1). For the halogenated compounds the pattern of reactivity for the formation of the halogenated spirans is : Cl > I > F > Br. Only the chloro spiran was formed in good yield, with a small yield of iodo

spiran and a very small yield of fluoro spiran. No bromo spiran was formed as has previously been reported.[11]

Figure 2

^{13}C-Nmr of the dimethylquinoxaline spirans (**5**) after methylation with diazomethane, ppm down field from TMS.



Sub.	C-2	C-3	C-5	C-6	C-7	C-8	C-9
H	63.74	57.88	113.14	119.97	119.89	116.18	134.27
6Me	63.71	58.16	113.93	129.21	120.46	116.72	134.33
7Me	63.95	58.29	113.30	120.54	129.45	116.85	132.05
7Et	64.03	58.24	113.33	119.40	135.98	115.78	131.69
7tBu	64.14	58.13	112.98	117.12	142.94	113.77	131.77
7F	63.82	58.18	114.27(d)	105.51(d)	155.89(d)	102.72(d)	130.32(d)
			J=9 Hz	J=22 Hz	J=236 Hz	J=26 Hz	J=0.8 Hz
7Cl	63.36	57.69	113.96	119.45	124.57	115.55	132.75
7I	63.11	57.48	114.85	128.45	81.37	123.95	133.86
7CF_3	62.68	57.10	112.36	117.11(q)	121.42(q)	112.77(q)	136.57
				J=4 Hz	J=33 Hz	J=4 Hz	

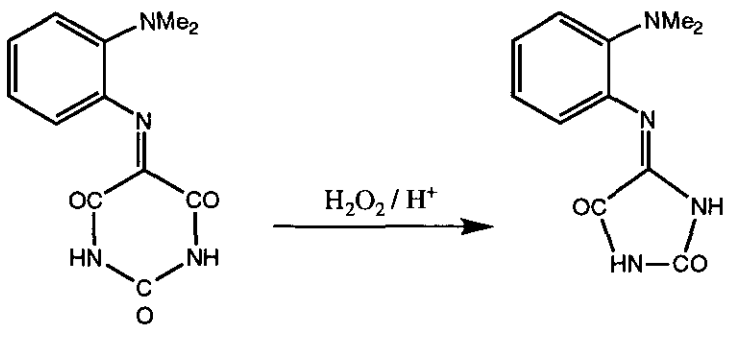
Sub	C-10	C-11	C-12/16	C-14	C-17/18	R	R
H	131.89	39.49	168.23	151.01	29.42		
6Me	129.64	39.55	168.18	151.01	29.39	21.07	
7Me	131.78	39.60	168.32	151.04	29.42	20.64	
7Et	132.24	39.60	168.26	150.98	29.42	28.06	15.60
7tBu	132.05	39.49	168.32	151.01	29.44	33.94	31.47
7F	133.10(d)	39.93	167.99	150.93	29.52		
	J=10 Hz						
7Cl	132.94	39.57	167.91	150.85	29.49		
7I	133.54	39.38	167.83	150.82	29.47		
7CF_3	131.91	39.33	167.89	150.82	29.47	124.32(q)	
						J=272 Hz	

The other halogenated aniline tested was the trifluoromethyl. A small amount of trifluoromethyl spiran was formed but this proved difficult to isolate as it decomposed during the work-up procedure. All other substituent groups tested, which are in essence electron withdrawing groups (except the -OMe which

may also donate electrons mesomerically) gave no isolable yield of spiran. Formation of the spiran has been shown to be sensitive to electronic influences as demonstrated by the introduction of a substituent group in the aromatic amine. It appears that for the case of electron withdrawing groups the primary influence may be the reduction of the amine nucleophilicity leading to a reduction in the formation of the initial imine. Secondly, inductive electron withdrawal or mesomeric electron donation of the substituent para to the NMe_2 group in the intermediate imine may inhibit formation of the dihydrobenzimidazoline (**2**). Formation of the spiran has also been shown to influenced by steric factors as demonstrated by methyl substituents at R_1 and R_4. For ^{13}C-nmr studies the substituted quinoxaline spirans formed were methylated with diazomethane to give the dimethyl compounds (**5**). These are more readily purified and crystallised and are more soluble in $CDCl_3$. The ^{13}C-nmr spectra of the methyl derivatives were recorded and spectral assignments were made based on signal intensities, substituent chemical shifts (SCS) referenced to the starting anilines and the use of HETCOR and DEPT techniques and long range C-H coupling. The values are shown in Figure 2.

Peroxide Treatment of the Spirans

Rudy and Cramer [6] originally proposed the condensation product to be alloxan-5-(2-dimethylamino)-imine (**1**) based on previous condensation products with 2-amino-*N*-methylanilines. When these authors subjected the condensation product to hydrogen peroxide under acidic conditions it afforded a deep red product which they referred to as parabanic acid-4-(2-dimethylaminoanil) and to which they assigned structure (**6**).



(**1**) (**6**)

Since the original structure of the condensation product was incorrectly assigned by these authors, it is further proposed that they had also incorrectly assigned the structure (**6**) to the peroxide treatment product. In this study treatment of the unsubstituted spiran with hydrogen peroxide following the

procedure of Rudy and Cramer [6] gave an almost quantitative yield of a red compound. Spectroscopic analysis in the ir region shows the presence of two absorbance peaks at 3430 cm^{-1} and 3400 cm^{-1} for two N-H groups and two peaks at 1740 cm^{-1} and 1710 cm^{-1} for two carbonyl absorptions. This ir evidence could be used to support the structure proposed by Rudy and Cramer but the further evidence presented in this study makes this structure unlikely. The uv spectrum is significantly different from that of the spirans in having a strong absorption band extending well into the visible spectrum and with a λ_{max} of 458 nm. All the quinoxaline compounds prepared in this study, with the exception of the tan coloured iodo spiran, were yellow compounds with a uv absorption maximum in the 350 nm region. If the structure for the condensation product is the imine as proposed by Rudy and Cramer, the contraction of the six membered barbiturate ring to a five membered ring would not be expected to involve such a large bathochromic shift of 100 nm.

^{1}H-Nmr analysis of the compound showed the presence of three proton signals at δ: 9.35, 8.00 and 5.40 which were exchangeable with D_2O. A sharp 2 proton singlet was found at δ 4.20 and also a sharp three proton singlet for an *N*-methyl at δ 2.90. Each of these signals argues against the structure proposed by Rudy and Cramer but is consistent with the structure being 3,4-dihydro-4-methylquinoxaline-2-carboxyureide (**7**) the formation of which is outlined in Scheme 2.

Geometry optimisation of this structure by the AM1 procedure of MOPAC V6.0 [13,14] shows the likelihood of an intra-molecular H-bond of the terminal N-H group. This would account for the presence of three different N-H signals in the ^{1}H-nmr. Similar H-bonding is present in the 3-keto derivative of the quinoxaline-carboxyureide formed by the condensation reaction between alloxan and 2-amino-*N*-methyl-aniline, the structure of which has been previously assigned.[7]

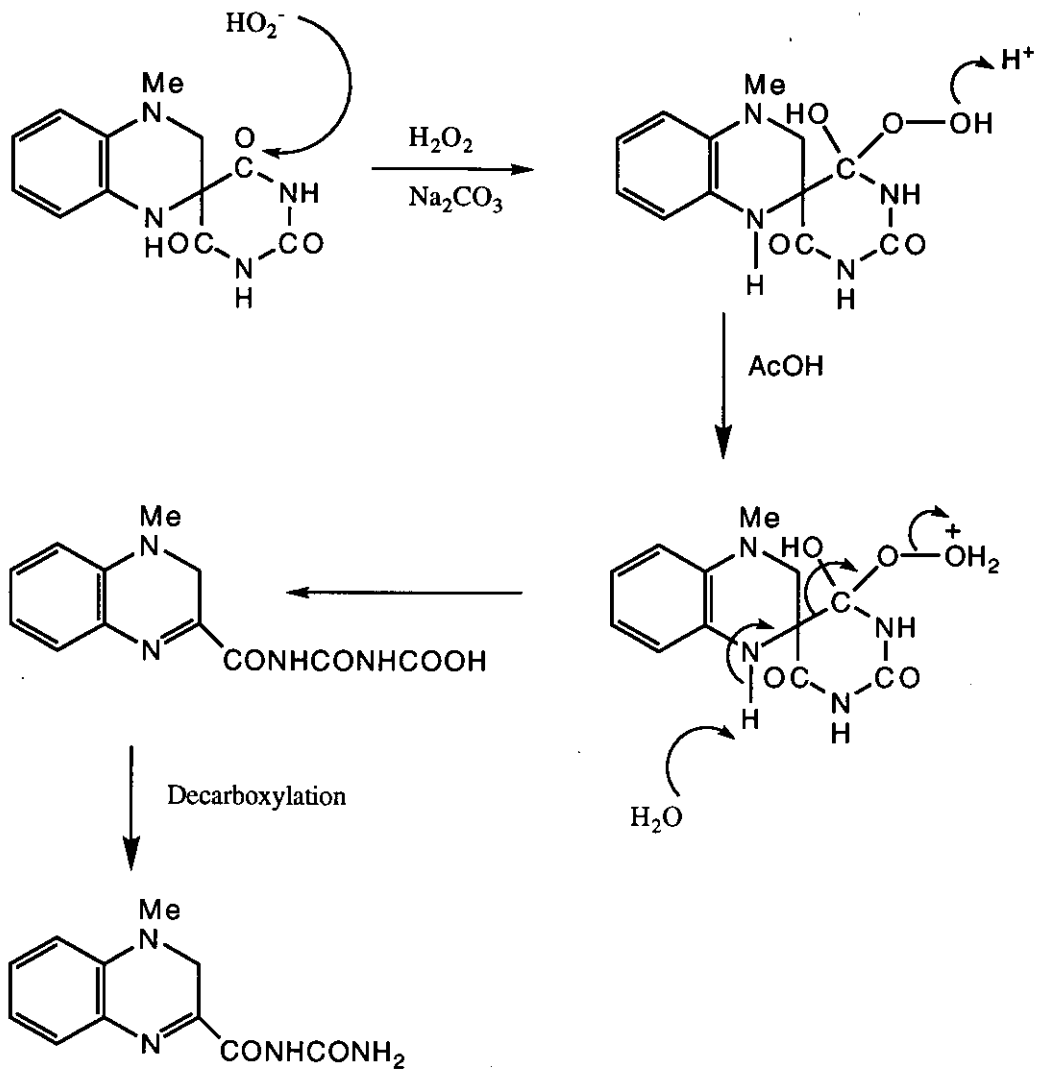
Synthesis and ^{13}C-nmr studies of other carboxyureides

^{13}C-Nmr of the red carboxyureide at 75 MHz was accomplished in dilute solution in $CDCl_3$. Spectral assignment was initially made less certain due to the inability to obtain other substituted carboxyureides of sufficiently high purity for comparison purposes. Attempted peroxide treatment of several of the other quinoxaline spirans resulted in one of two possible outcomes. Either no reaction occurred due to the insolubility of the spiran in the aqueous basic medium (R = 7-tBu, 7-Et, 7-I and 7-CF_3) or formation of a complex mixture of products due partly to decomposition and/or oxidation of the starting material (R= 6-Me, 7-Me, 7-F, and 7-Cl). In the latter cases some evidence was found by mass spectrometry for the

presence of the red carboxyureide but it was not isolable. The main product for this latter group appeared by mass spectral analysis to be the tetrahydroquinoxaline, resulting from complete decomposition of the pyrimidine ring, and the betaine which forms by oxidation.

Scheme 2

The proposed mechanism for the conversion of the quinoxaline spiran (**3**) into the quinoxaline carboxyureide (**7**) by the action of H_2O_2 in acidic solution.



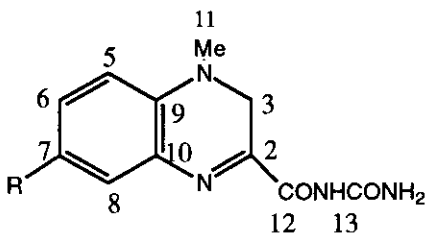
3,4-dihydro-4-methylquinoxaline-2-carboxyureide (**7**)

In two cases (6-Me and 7-Cl) one of the other products detected in the product mixture appeared to be the corresponding 2-carbamyl-1,4-dihydro-4-methylquinoxaline, resulting from partial decomposition

of the pyrimidine ring. In neither case were the products able to be isolated and characterised.

Figure 3

^{13}C-Nmr values for 3,4-dihydro-4-methylquinoxaline-2-carboxyureides (**7**) in $CDCl_3$, ppm down field from TMS.



	H	7-Me	7-tBu
C-2	148.60	148.79	148.57
C-3	46.61	46.50	46.47
C-5	111.07	111.01	110.72
C-6	132.39	132.93	129.30
C-7	118.63	127.99	141.45
C-8	129.91	129.93	126.53
C-9	140.88	138.70	138.45
C-10	132.23	132.33	131.86
C-11	36.88	36.86	37.02
C-12	163.17	163.15	163.00
C-13	152.96	153.06	152.85
R		20.07	36.61 31.14

Other co-solvents (ethanol, methanol, acetonitrile, butylamine, pyridine, acetone, DMSO and DMF) were used in an attempt to increase the solubility of the spirans in the aqueous base. DMF was found to be the only co-solvent to increase the spiran solubility and which was sufficiently miscible with the base (2M Na_2CO_3 or K_2CO_3) and 15% peroxide solution and which did not lead to decomposition. In this solvent system the 7-tBu spiran and 7-Me spiran were converted to the red carboxyureide but the yield was less than 20%. No conversion to the carboxyureide was successful for any of the other spirans tested.

^{13}C-Nmr of the two substituted carboxyureides in dilute solution in $CDCl_3$ enabled the unambiguous spectral assignment of all three compounds, based on peak intensity, SCS values based on the parent aniline and HETCOR and DEPT procedures. The chemical shifts for C9 and C10 were the most difficult

to distinguish with long range C-H coupling constants proving to be the best guide. In particular C9 showed 3 bond coupling to the NMe group at position 4 . The chemical shift values are shown in Figure 3.

SUMMARY AND CONCLUSIONS

This study has shown that substituted quinoxaline spiran compounds can be synthesised by condensation reaction between alloxan and 2-amino-*N,N*-dimethylanilines which in turn are derived from simple phenol precursors. The formation of the spiran does not appear to be the common rule as yields are generally low. Subtle electronic and steric influences of a substituent in the aniline have a considerable effect in determining the nature and amounts of the products. We have further shown that the red compound obtained from spirans by treatment with hydrogen peroxide under acidic conditions is a quinoxaline carboxyureide. Formation of this type of compound in appreciable amounts from spirans appears to be variable, though this may reflect the inability to find suitable reaction conditions. Further studies are in progress looking in more detail at the range of condensation products and in particular the competition between the formation of the spiran and its oxidation product the benzimidazoline betaine.

EXPERIMENTAL

All melting points are uncorrected. Micro-analyses were performed by the Australian Microanalytical Service. Infra-red spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotomer. Ultraviolet-visible spectra were recorded on a Hewlett-Packard 8452a diode array spectrophotometer. Routine ^{1}H-nmr were recorded in $CDCl_3$ solution on an Hitachi 1200 (60 MHz) spectrometer with shifts relative to TMS internal standard. ^{13}C-Nmr were recorded on a Varian Gemini 300 MHz spectrometer operating at 75.46MHz. Mass spectra were recorded on a Kratos MS25RF spectrometer with an ionising energy of 70 eV.

Synthesis of quinoxaline spirans:

The quinoxaline spirans were prepared following the procedure described by King and Clark-Lewis.[7]

1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6-trioxo-pyrimidine) **(3)** R_1, R_2, R_3, R_4=H. The following represents a typical procedure.

2-Amino-*N,N*-dimethylaniline (7.50 g, 50 mmol) in ethanol (50 ml) was added to alloxan monohydrate (15.0 g, 90 mmol) in water (30 ml). After 3 days at room temperature the total solid (6.70 g) was collected. The solid was triturated with hot water (50 ml) and the water insoluble portion crystallised

from aqueous pyridine to afford the spiran as bright yellow plates, 3.0 g (21 %), mp 248 °C (lit.,7 mp 250 °C). Eims : m/z 260.0910. Calcd for $C_{12}H_{12}N_4O_3$ 260.0907. Anal. Calcd for $C_{12}H_{12}N_4O_3$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.62; H, 4.89; N, 21.35.

1,2,3,4-Tetrahydro-7-ethyl-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxo-pyrimidine) **(3)** R_3=Et This compound was obtained as bright yellow plates, 0.50 g (15 %), mp 255 °C. Eims : m/z 288.1223. Calcd for $C_{14}H_{16}N_4O_3$: 288.1222. Anal. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43 Found: C, 58.10; H, 5.90; N, 19.70.

1,2,3,4-tetrahydro-7-t-butyl-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) **(3)** R_3=tBu This compound was obtained as a pale yellow solid, 1.15 g (35 %), mp 295 °C. Eims : m/z 316.1535. Calcd for $C_{16}H_{20}N_4O_3$: 316.1521. Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N,17.71. Found: C, 60.80; H, 6.30; N, 17.95.

1,2,3,4-Tetrahydro-7-chloro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) **(3)** R_3=Cl. This compound was obtained as a pale yellow solid, 0.33 g (15 %), mp 250 °C. Eims : m/z 296.0464/294.0509. Calcd for $C_{12}H_{11}N_4O_3Cl$: 296.0490/294.0519. Anal. Calcd for $C_{12}H_{11}N_4O_3Cl$: C, 48.91; H, 3.76; N,19.01. Found: C, 49.10; H, 3.95; N, 19.00.

1,2,3,4-Tetrahydro-7-fluoro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) **(3)** R_3=F. This compound was obtained as a pale green solid, 0.10 g (3 %), mp=250 °C (decomp) Eims: m/z 278.0826. Calcd for $C_{12}H_{11}N_4O_3F$: 278.0815. Anal. Calcd for $C_{12}H_{11}N_4O_3F$: C, 51.86; H, 3.98; N, 20.13. Found: C, 51.50; H, 4.10; N, 20.35.

1,2,3,4-Tetrahydro-7-iodo-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) **(3)** R_3=I . This compound was obtained as a pale tan solid, 0.20 g (9 %), mp 225 °C (decomp) Eims : m/z 385.9888. Calcd for $C_{12}H_{11}N_4O_3I$: 385.9877. Anal. Calcd for $C_{12}H_{11}N_4O_3I$: C, 37.33; H, 2.87; N, 14.51. Found: C, 37.10; H, 3.00; N, 14.70.

1,2,3,4-Tetrahydro-7-trifluoromethyl-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) **(3)** R_3=CF_3 This compound was obtained as a pale yellow solid, 0.13 g (2 %), mp 205 °C (decomp) Eims : m/z 328.0810. Calcd for $C_{13}H_{11}N_4O_3F_3$: 328.0783. Anal. Calcd for $C_{13}H_{11}N_4O_3F_3$: C, 47.57; H, 3.38; N, 17.07. Found: C, 47.30; H, 3.30; N,17.45.

Synthesis of Dimethylspirans:1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** The general procedure for the methylation of the spirans is described below. In each case the yield was almost quantitative.

1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) (0.050 g, 0.185 mmol) was methylated with a large excess of ethereal diazomethane and left for 12 h at 4 °C. The ether solution was filtered and the solvent was removed to afford the dimethylspiran, which crystallised from ethanol as yellow needles, 0.05 g (91 %), mp 193 °C. Eims : m/z 288.1231. Calcd for $C_{14}H_{16}N_4O_3$: 288.1222. Anal. Calcd for $C_{13}H_{11}N_4O_3$: C, 58.35; H, 3.38; N, 17.07. Found: C, 58.60; H, 5.45; N,17.45. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.85 (br s, 4H), 3.35 (s, 6H), 3.30 (s, 2H), 2.95 (s, 3H).

1,2,3,4-Tetrahydro-4,6-dimethylquinoxaline-2-spiro-5'-(hexahydro-1,3,-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_2=Me. This compound was obtained as yellow needles, 0.05 g (91 %), mp 176 °C. Eims : m/z 302.1352. Calcd for $C_{15}H_{18}N_4O_3$: 302.1379 ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.82 (s, 1H), 6.7 (d, J = 8 Hz; 2H), 4.50 (br s, 1H), 3.43 (s, 6H), 3.35 (s, 2H), 2.95 (s, 3H), 2.30 (s, 3H).

1,2,3,4-Tetrahydro-4,7-dimethylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_3=Me. This compound was obtained as yellow needles, 0.052 g, (92 %), mp 177 °C. Eims : m/z 302.1390. Calcd for $C_{15}H_{18}N_4O_3$: 302.1379. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.65 (br s, 3H). 4.20 (br s, 1H), 3.35 (s, 6H), 3.25 (s, 2H), 2.95 (s, 3H), 2.25 (s, 3H).

1,2,3,4-Tetrahydro-7-ethyl-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_3 = Et. This compound was obtained as yellow needles, 0.049 g (91 %), mp 200 °C. Eims : m/z 316.1521. Calcd for $C_{16}H_{20}N_4O_3$: 316.1535. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.65 (br s 3H), 3.90 (br s, 1H), 3.35 (s, 6H), 3.20 (s, 2H), 2.90 (s, 3H), 2.5 (q, J = 7 Hz; 2H), 1.20 (t, J = 7 Hz; 3H).

1,2,3,4-Tetrahydro-7-t-butyl-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_3 =tBu. This compound was obtained as bright yellow needles, 0.053 g (95 %), mp 210 °C. Eims : m/z 344.1870. Calcd for $C_{18}H_{24}N_4O_3$: 344.1848. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.90 (br s, 1H), 6.75 (d, J = 7 Hz; 2H), 3.90 (br s, 1H), 3.35 (s, 6H), 3.25 (s, 2H), 2.90 (s, 3H), 1.30 (s, 9H).

1,2,3,4-Tetrahydro-7-chloro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_3=Cl. This compound was obtained as pale orange needles, 0.048 g (88 %), mp 190 °C. Eims : m/z 322.0844 Calcd for $C_{14}H_{15}N_4O_3Cl$: 322.0832.

^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.80 (d, J = 2 Hz; 1H), 6.60 (d, J = 7 Hz; 2H), 3.35 (s, 6H), 3.25 (s, 2H), 2.85 (s, 3H).

1,2,3,4-Tetrahydro-7-fluoro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_3=F. This compound was obtained as a pale green solid, 0.05 g (90 %), mp 212 °C. Eims : m/z 306.1142. Calcd for $C_{14}H_{15}N_4O_3F$: 306.1128.^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 6.55 (m, 3H), 4.60 (s, 1H), 3.35 (s, 6H), 3.25 (s, 2H), 2.90 (s, 3H).

1,2,3,4-Tetrahydro-7-iodo-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** R_3=I. This compound was obtained as pale yellow solid, 0.051 g (95 %), mp 225 °C (decomp) Eims : m/z 414.0203. Calcd for $C_{14}H_{15}N_4O_3I$: 414.0197. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 7.14 (m, 2H), 6.44 (d, J = 8 Hz; 1H), 4.63 (br s, 1H), 3.35 (s, 6H), 3.30 (s, 2H), 2.90 (s, 3H).

1,2,3,4-Tetrahydro-7-trifluoromethyl-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) **(5)** $R_3 = CF_3$. This compound was obtained as a pale yellow solid, 0.048 g (89 %), mp 185 °C (decomp) Eims : m/z 356.1106. Calcd for $C_{15}H_{15}N_4O_3F_3$: M=356.1096. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 7.06 (d, J = 9 Hz; 1H), 7.03 (s, 1H), 6.75 (d, J = 10 Hz, 1H), 4.80 (br s, 1H), 3.34 (s, 6H), 3.325 (s, 2H), 2.96 (s, 3H).

Quinoxaline carboxyureides

The procedure of Rudy and Cramer [6] was followed for the peroxide treatment of the spirans.

3,4-Dihydro-4-methylquinoxaline-2-carboxyureide (7)

1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) (1.0 g, 3.8 mmol), was dissolved in 20 % Na_2CO_3 (20 ml) with gentle warming. After cooling 15 % H_2O_2 solution (5 ml) was added and the solution weakly acidified with acetic acid. After 1 h a dark red solid was isolated which crystallised from ethanol as red plates (0.65 g, 74 %) , mp 168 °C. Eims : m/z 232.0990 Calcd for $C_{11}H_{12}N_4O_2$: 232.0982. Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.60; H, 5.35; N, 24.30. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.30 (br s, 1H), 8.00 (br s, 1H), 7.2 (t, J = 9 Hz; 2H), 6.75 (m, 2H), 5.40 (br s, 1H), 4.20 (s, 2H), 2.90 (s, 3H).

3,4-Dihydro-4,7-dimethylquinoxaline-2-carboxyureide (7) 7-Me.

This compound was obtained as red plates (0.04 g, 22 %) , mp 175 °C. Eims : m/z 246.1079. Calcd for $C_{12}H_{14}N_4O_2$: 246.1115. Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 47.57; H, 3.38; N, 17.07. Found:

C, 58.30; H, 5.65; N, 22.70. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.35 (bs, 1H), 8.00 (bs, 1H), 7.0 (m, 2H), 6.50 (d, J = 3 Hz; 1H), 5.50 (bs, 1H), 4.10 (s, 2H), 2.75 (s, 3H), 2.20 (s, 3H).

3,4-Dihydro-7-t-butyl-4-methyl-quinoxaline-2-carboxyureide (7) 7-tBu.

This compound was obtained as a red solid (0.04 g, 15 %), mp 250 °C (decomp) Eims : m/z 288.1577. Calcd for $C_{15}H_{20}N_4O_2$: 288.1586. Anal. Calcd for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.75; H, 6.90; N,19.50. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.35 (bs, 1H), 7.95 (bs, 1H), 7.2 (m, 2H), 6.55 (d, J = 3 Hz; 1H), 5.65 (br s, 1H), 4.10 (s, 2H), 2.80 (s, 3H), 1.25 (s, 9H).

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