Nucleophilic Character of Alkyl Radicals. Part 15.[1] Selective Homolytic Alkylation of Quinoxaline by *N*-Chloro-amines; Influence of Medium Acidity

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Selective homolytic alkylation of protonated quinoxaline has been achieved by using an alkyl derivative with *N*-chlorodialkylamine as radical source. The method shows great synthetic potential and can also be used for other heteroaromatic bases. A free-radical chain process involving amine radical cations is suggested to explain the clean reaction. Positional selectivity is strongly affected by the medium acidity, and a correlation between the π-electron density of mono- and di-protonated quinoxaline and the substitution orientation is found, in agreement with the nucleophilic character of the alkyl radicals.

PROTONATION of heteroaromatic bases, increasing their nucleophilic reactivity, makes possible a large variety of new types of homolytic substitution involving nucleophilic carbon-centred free-radicals; such reactions have great synthetic interest, owing to their high positional and substrate selectivity.[1] Diprotonation of a diazine further increases its electron-deficiency and should also increase its reactivity towards nucleophilic radicals. We describe here a new, general, and selective method of homolytic alkylation of protonated quinoxalines, and the effect of the acidity of the medium on positional selectivity.

Dialkylamine radical cations are particularly selective hydrogen abstracting species because, in addition to a high sensitivity to steric effects and to C–H bond energies, they show an exceptional sensitivity to polar effects [1,2] [see reaction (i), where X is a substituent with an

$$R_2NH^{+\cdot} + CH_3\text{–}CH_2\text{–}[CH_2]_n\text{–}X \longrightarrow R_2\overset{+}{N}H_2 + CH_3\text{–}\dot{C}H\text{–}[CH_2]_n\text{–}X \quad \text{(i)}$$
(1)

inductive electron-withdrawing effect (F, Cl, Br, I, OH, OR, O_2CR, COR, CO_2R, CN, $CONR_2$, $\overset{+}{N}R_3$, SO_2R, SO_3H, *etc.*) and $n = 1$—8]. When the amine radical cation is generated from a chloro-amine, a chain reaction obtains, with reaction (ii) as the second chain-propagating step.

Absolute rate constants for the addition of alkyl radicals to monoprotonated quinoxaline are very high (10^6—10^7 l mol^{-1} s^{-1}),[3] and even higher values would be

$$CH_3\text{–}\dot{C}H\text{–}[CH_2]_n\text{–}X + R_2N^+HCl \longrightarrow CH_3\text{–}CHCl\text{–}[CH_2]_n\text{–}X + R_2NH^{+\cdot} \quad \text{(ii)}$$

expected for diprotonated quinoxaline. This induced us to utilize radicals of type (1), obtained according to reaction (i), for the homolytic alkylation of quinoxaline.

RESULTS AND DISCUSSION

Our previous attempts to achieve homolytic alkylation of diprotonated quinoxaline have given poor results, essentially for two reasons. (*a*) Quinoxaline is a weak base and diprotonation occurs only in a strongly acidic medium (pK_a estimated [4] to be −5.52); there is incompatibility in using a strongly acidic medium and several conventional sources of alkyl radicals (acyl peroxides, hydroperoxides, 1-oxyhydroperoxides, oxidative decarboxylation of carboxylic acids, *etc.*). (*b*) The success, from a synthetic point of view, of the homolytic aromatic alkylation is determined, in addition to the availability of the radical source and to the positional and substrate selectivity, by the rearomatization of the σ-complex (2) [reaction (iii)]. In the case of diprotonated quinoxaline

$$R^{\cdot} + Ar\text{–}H \longrightarrow [R\text{–}ArH]^{\cdot} \quad \text{(iii)}$$
(2)

the presence of two positive charges makes the oxidation of (2) difficult and leads to considerable amounts of side products.

[1] F. Minisci, *Synthesis*, 1973, 1; *Topics Current Chem.*, 1976, **62**, 1; F. Minisci and O. Porta, *Adv. Heterocyclic Chem.*, 1974, **16**, 123.

[2] F. Minisci, R. Galli, and R. Bernardi, *Tetrahedron Letters*, 1967, 2207; *Chimica e Industria*, 1967, **49**, 594; *Chem. Comm.*, 1967, 903; *J. Chem. Soc.* (*B*), 1968, 324; F. Minisci, G. P. Gardini, and F. Bertini, *Canad. J. Chem.*, 1970, **48**, 544.

[3] T. Caronna, A. Citterio, T. Crolla, and F. Minisci, unpublished results.

[4] P. J. Brignell, C. D. Johnson, A. R. Katritzky, A. N. Shakir, H. O. Tarman, and G. Walker, *J. Chem. Soc.* (*B*), 1967, 248.

The alkylation of quinoxaline in strongly acidic medium by using radicals of type (1) arising from reaction (i) is, on the contrary, a clean reaction. The yields of alkylquinoxaline, based on quinoxaline converted, are almost quantitative. The results in Table 1 show the general character of the reaction. The yields of alkylquinoxalines in which the alkyl group is of type (1) range from 90 to 98%, depending on the structure of the *N*-chlorodialkylamine. *N*-Chlorodimethyl- and di-isobutylamines were used successfully. Dialkylamines with bulky alkyl groups have two main advantages in comparison with dimethylamine. (*a*) They are more selective in ω − 1 hydrogen abstraction. Thus, by using *N*-chlorodimethylamine, in addition to the main substitution products due to the radical (1), small amounts (5—15%) of products arising from the isomeric radicals $^{\bullet}CH_2$-$[CH_2]_{n+1}$-X and CH_3-CH_2-$\dot{C}H$-$[CH_2]_{n-1}$-X were also obtained. With the more selective *N*-chloro-di-isopropyl- and di-isobutyl-amines the amounts of these isomers can be less than 5%. With sources of alkyl radicals such as cycloalkanes, for which there is no problem of selectivity, the yields are in any case quantitative. (*b*) The heavier amines can be more easily recovered, making the following synthetic cycle (iv)—(v) effective. The cycle corresponds to the overall

$$R_2NH + Cl_2 \longrightarrow R_2NCl + HCl \quad \text{(iv)}$$

$$R_2NH^+Cl + R'H + ArH_2^+ \longrightarrow R_2N^+H_2 + R'\text{-}ArH^+ + HCl \quad \text{(v)}$$

reaction (vi), where ArH_2^+ is the protonated heteroaromatic base; thus chlorine is consumed in the alkylation reaction. The conversions indicated in Table 1 can

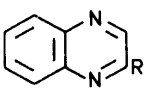
$$R'H + Cl_2 + ArH_2^+ \longrightarrow R'\text{-}ArH^+ + 2HCl \quad \text{(vi)}$$

be further increased by increasing the *N*-chloro-amine : quinoxaline ratio, but the formation of disubstituted products then becomes significant.

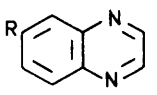
Under the best conditions the reaction is carried out at room temperature by slowly dropping a solution of the *N*-chloroamine in concentrated sulphuric acid into a mixture of sulphuric acid, alkylating agent (R'H), quinoxaline, and a catalytic amount of iron(II) sulphate. (When the alkylating agent is too insoluble in the reaction mixture, the addition of 10—20% of acetic acid can be useful.) Under these conditions the concentration of the *N*-chloroamine is kept low and competition by reaction (ii) is not favoured.

TABLE 1

Alkylation of quinoxaline by *N*-chloro-amines and alkyl derivatives



(I)



(II)

a; R = CHMe·$[CH_2]_4$·OMe
b; R = CHMe·$[CH_2]_3$·COMe
c; R = CHMe·$[CH_2]_3$·CO_2H
d; R = CHMe·$[CH_2]_3$·NH_2
e; R = CHMe·$[CH_2]_4Cl$
f; R = cyclohexyl

Products	Conversion (%)	Yield [a] (%)	B.p. (°C) [M.p. (°C) (solvent)]	Found (%) C	H	N	Formula	Required (%) C	H	N
(Ia)	50	95	171 (1 mmHg)	73.6	8.25	11.4	$C_{15}H_{20}N_2O$	73.75	8.25	11.45
(IIa)			174 (1 mmHg)	73.5	8.4	11.3				
(Ib)	65 [b]	92	180 (1 mmHg)	69.6	7.1	11.0	$C_{15}H_{18}N_2O_2$	69.75	7.0	10.85
(IIb)			185 (1 mmHg)	69.55	6.9	10.7				
(Ic)	42 [c]	96	120 (0.1 mmHg)	68.65	6.45	11.6	$C_{14}H_{16}N_2O_2$	68.85	6.6	11.45
(IIc)			120 (0.1 mmHg)	68.7	6.7	11.4				
(Id)	50	90	150 (0.5 mmHg)	77.7	8.1	19.3	$C_{13}H_{17}N_3$	77.5	7.95	19.5
(IId)			160 (0.5 mmHg)	77.6	8.05	19.45				
(Ie) [d]	40	90		67.7	7.0	11.4	$C_{14}H_{17}ClN_2$	67.6	6.9	11.25
(IIe) [d]				67.6	7.1	11.2				
(If)	40	98	[49 (hexane)]	73.6	7.2	12.1	$C_{14}H_{16}N_2O$	73.65	7.05	12.25
(IIf)			[37 (hexane)]	73.8	7.1	12.4				

[a] Based on converted base and isomer distribution as determined by g.l.c. [b] Determined after methylation of partially hydrolysed acid. [c] Determined as methyl esters. [d] The products decompose on heating.

The clean nature of the reaction is explained, in our opinion, by the free-radical chain mechanism shown in the Scheme. The electrophilic amine cation radicals do

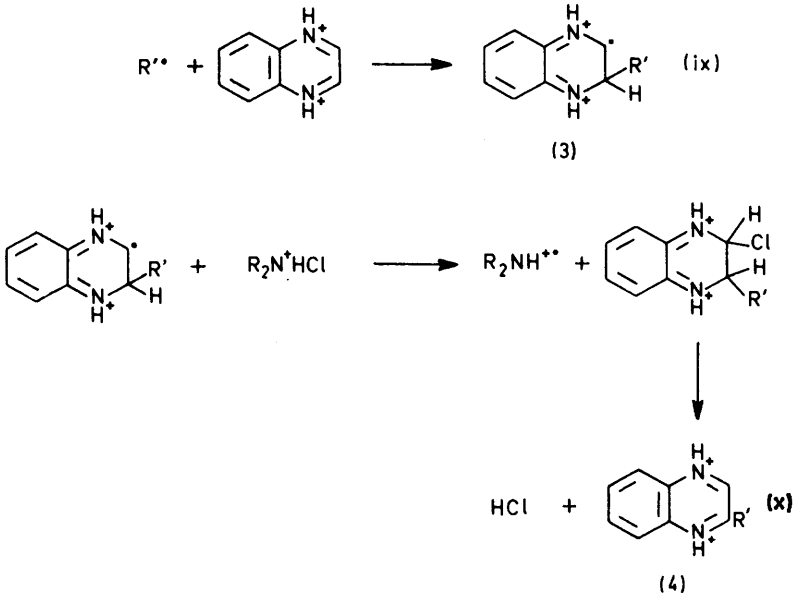
$$R_2N^+HCl + Fe^{2+} \longrightarrow R_2NH^{+\bullet} + FeCl^{2+} \quad \text{(vii)}$$

$$R_2NH^{+\bullet} + R'H \longrightarrow R_2N^+H_2 + R'^{\bullet} \quad \text{(viii)}$$

not attack the electron-deficient base, which, on the contrary, is attacked with high velocity by the nucleophilic alkyl radicals. The high effectiveness of reaction (x), analogous to reaction (ii), must be considered the main cause of the clean rearomatization of the σ-complex (3), which is one of the main difficulties when the homolytic alkylation is carried out in a strongly acidic medium with conventional sources of alkyl radicals. We consider the rearomatization of the σ-complex (3) by oxidation by Fe^{III} unlikely for reasons of both structure and solubility: the presence of two positive charges in (3) makes an electron-transfer process difficult; moreover the solubility of the iron(III) salt is very low in concentrated sulphuric acid. The reaction in fact also takes place in the absence of iron salts, by thermal or photochemical initiation; in these cases the conversions are lower presumably because the kinetic chain of the Scheme is short and thermal and photochemical initiation are much less effective than redox initiation.

The great synthetic potential of this new process is

apparent when one considers the hundreds of radicals of type (1) which can be easily obtained from available cheap materials; it is obviously particularly suited to radicals, such as cycloalkyl, for which there is no selectivity problem. The experimental conditions are simple carried out in aqueous sulphuric acid at concentrations <50%; only position 2 of quinoxaline is effectively attacked. At higher concentrations of sulphuric acid position 6 is also attacked, and in concentrated sulphuric acid the extents of attack at positions 6 and 2 are



SCHEME

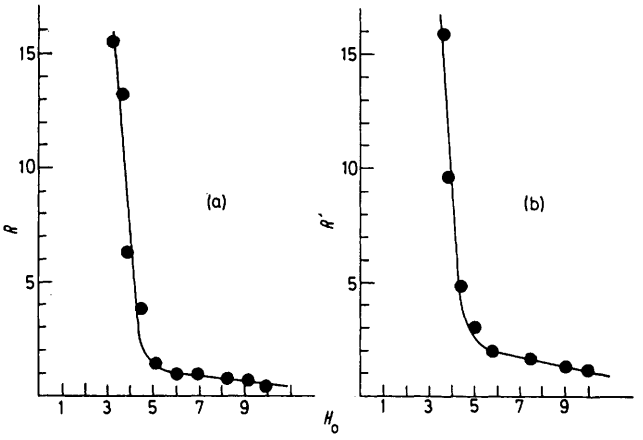
and yields are always high; the lack of any alternative simple route to products of structure (4), where R′ is an alkyl group of type (1), emphasizes the synthetic interest. Moreover, preliminary results [5] indicate that a large variety of heteroaromatic bases can be used (substituted pyridines, quinolines, isoquinolines, pyrazines, pyridazines, pyrimidines, cinnolines, quinazolines, naphthyridines, purines, pteridines, *etc.*).

TABLE 2

Ratios of 2- and 6-cyclohexylquinoxalines at various acidities

% w/w H_2SO_4 in AcOH	2-Isomer (%)	6-Isomer (%)	Ratio (2 : 6)
96	37	63	0.59 : 1
80	45	55	0.82 : 1
70	48	52	0.92 : 1
60	51	49	1.02 : 1
50	49.5	50.5	0.98 : 1
40	60	40	1.51 : 1
30	76	24	3.90 : 1
25	86	14	6.25 : 1
20	93	7	13.29 : 1
15	92	6	15.33 : 1

The behaviour of quinoxaline is of particular interest with regard to positional selectivity. In fact the substitution of protonated heteroaromatic bases by nucleophilic carbon-centred free radicals is characterized by very high selectivity; attack takes place only at positions α and γ to the protonated heterocyclic nitrogen.[1] This behaviour is still observed when the reaction is similar.[6] This is the first time that a benzene ring has been found to be as reactive as a protonated heterocyclic ring in homolytic alkylation of a polycyclic heteroaromatic base. The effect of the acidity of the medium on the



Plots of (a) the ratio (*R*) of 2- and 6-cyclohexylquinoxalines *vs.* H_0 for the system AcOH–H_2SO_4 and (b) the ratio (*R′*) of 2- and 6-(4-butylamino)quinoxalines *vs.* H_0 for the system H_2O–H_2SO_4 in δ-aminoalkylation of quinoxaline by *N*-chlorodi-n-butylamine [6]

ratios of 2- and 6-substituted isomers in cyclohexylation of quinoxaline by cyclohexane and *N*-chlorodimethylamine is shown in Table 2. Figure (a) shows a plot of the ratio 2- and 6-substituted isomers against Hammett acidity

[5] T. Caronna, A. Citterio, T. Crolla, and F. Minisci, *Tetrahedron Letters*, 1976, 1731.

[6] A. Citterio, M. Ghirardini, and F. Minisci, *Tetrahedron Letters*, 1976, 203.

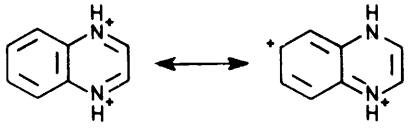
H_0 in acetic–sulphuric acid.[7] At a value of *ca.* −4.5 for H_0, small changes in acidity cause very large changes in isomer ratio, whereas at higher H_0 values the effect of the acidity is small. The same behaviour was observed in water–sulphuric acid mixtures [Figure (b)] for the homolytic δ-aminoalkylation of quinoxaline according to the procedure recently described by us.[6] The fact that the two Figures are almost coincident in two different media is significant with regard to the effect of acidity on reaction rates. It indicates that diprotonation of quinoxaline plays an important role in determining positional selectivity.

TABLE 3

π-Electron density of mono- and di-protonated quinoxalines by n.m.r. analysis and INDO calculation

	Position	*q*(n.m.r.)	*q*(INDO)
Monoprotonated	2	*0.874*	*0.853*
	3	0.918	1.022
	5	0.940	0.965
	6	0.922	0.968
	7	0.914	0.907
	8	0.958	1.036
Diprotonated	2, 3	*0.873*	*0.897*
	5, 8	0.932	1.003
	6, 7	*0.883*	*0.870*

We have previously [8] observed a good correlation between the rates of homolytic alkylation at position 2 in protonated 4-substituted pyridines and the chemical shifts of the protons at position 2. It was concluded that the major factor controlling both the chemical reactivity and the shielding of the hydrogen nuclei *meta* to the substituent is the electron density at position 2, in agreement with the nucleophilic character of the alkyl radicals. Table 3 gives experimental (from chemical shifts) and the calculated (INDO) values of electron densities at the various carbon atoms of mono- and di-protonated quinoxaline.[9] In monoprotonated quinoxaline C-2 shows a significantly higher electron deficiency than all other carbon atoms; this agrees with the selectivity of substitution at position 2 of monoprotonated quinoxaline in this reaction and in all the other substitutions by nucleophilic radicals. In diprotonated quinoxaline the electron densities of the equivalent C-2 and -3 do not substantially differ from those of the equivalent C-6 and -7, whereas the electron densities of C-5 and -8 are significantly higher. A large contribution of the resonance form (5), characterized by the highest charge separation, explains such behaviour. These data also agree with the change in positional selectivity in homolytic alkylation of quinoxaline in concentrated sulphuric acid; the similarity in extents of attack at positions 2 and 6 is in good agreement with the electron densities.



(5)

TABLE 4

N.m.r. and mass spectral data for compounds (I) and (II)

	N.m.r. (δ values)									
	Aromatic				>CH–					
Compd.	H-1, -3 (2 H, s)	H-5 (1 H, d)	H-7 (1 H, d)	H-8 (1 H, d)	(1 H, sext)	CH_3 (3 H, d)	CH_2X (2 H, t)	$-CH_2-$	X	*m/e* [a]
(IIa)	8.82	7.88	7.63	8.04	2.96	1.44	3.30	1.3—1.9 (6 H, m)	3.25 (3 H, s, OCH_3)	244 (*M*), 229, 197, 185, 183, 171, 158, *152*, 146, 143, 131, 45
(IIb)	8.81	7.94	7.70	8.11	2.95	1.38	2.41	1.4—2.3 (4 H, m)	3.67 (3 H, s, OCH_3)	258 (*M*), 227, 185, *171*, 157, 143, 60
(IIc)	8.80	7.93	7.68	8.10	2.95	1.38	2.43	1.3—2.4 (4 H, m)	11.10 (1 H, s, OH)	244 (*M*), 185, 171, 157, 143, *129*, 102, 60
(IId)	8.82	7.90	7.65	8.10	2.97	1.40	3.43	1.2—2.2 (6 H, m)		248 (*M*), 213, 185, 171, *158*, 157, 144, 136
(IIe)	8.78	7.89	7.65	8.04	2.95	1.42	2.68	1.4—2.0 (4 H, m)	3.43br (2 H)	215 (*M*), 198, 197, 172, 171, *157*, 144, 131, 30
(IIf)	8.80	7.91	7.67	8.05	2.80			1.1—2.3 (10 H, m)		*212* (*M*), 183, 169, 157, 156, 155, 144, 143, 131, 115, 102, 77, 76, 41, 39
	H-3		H-5—8							
(Ia)	8.75		7.64—8.16		3.16	1.42	3.33	1.4—2.2 (6 H, m)	3.28 (3 H, s, OCH_3)	244 (*M*), 229, 185, 172, 171, *158*, 157, 144
(Ib)	8.75		7.6—8.2		3.16	1.40	2.41	1.4—2.3 (4 H, m)	3.67 (3 H, s, OCH_3)	258 (*M*), 227, 185, 171, *158*, 157, 144, 73, 60
(Ic)	8.76		7.6—8.3		3.16	1.41	2.45	1.4—2.2 (4 H, m)	11.15 (1 H, s, OH)	244 (*M*), 185, 172, 171, *158*, 144, 60
(Id)	8.76		7.7—8.2		3.17	1.42	3.42	1.3—2.2 (6 H, m)		248 (*M*), 213, 212, 172, 171, *158*, 144, 131
(Ie)	8.74		7.6—8.1		3.16	1.34	2.68	1.4—2.0 (4 H, m)	3.43 (2 H, m)	215 (*M*), 198, 172, 159, *158*, 157, 144, 129, 30
(If)	8.76		7.5—8.3		2.94			1.2—2.2 (10 H, m)		212 (*M*), 183, 171, 169, 157, 144, 129, 104, 103, 77, 55

[a] Base peak in italics.

[7] N. F. Hall and W. F. Spengeman, *J. Amer. Chem. Soc.*, 1940, **62**, 2487.

[8] F. Minisci, R. Mondelli, G. Gardini, and O. Porta, *Tetrahedron*, 1972, **28**, 2403.

[9] R. Pastor, J. Musso, and A. Cambon, *Bull. Soc. chim. France*, 1973, 3009.

Thus what seemed to be anomalous behaviour in the homolytic substitution once again supports the pre-eminent importance of polar effects [1,8] in determining reaction rates and the consequent selectivity.

Further corroboration of this behaviour is given by the results of homolytic alkylation of phenazine,[10] which has no free position in the heterocyclic ring. In monoprotonated phenazine substitution takes place to similar extents at positions 1 and 2. In diprotonated p enazine position 2 is about ten times more reactive than position 1, in agreement with the results obtained with quinoxaline.

Owing to the high acidic character of diprotonated quinoxaline (pK_2 −5.52), the expected high nucleophilic reactivity cannot be checked by studying reactions of classical ionic nucleophilic species, which cause deprotonation of the base. This problem does not exist with nucleophilic free radicals, which are, in our opinion, powerful means for investigating the nucleophilic reactivity of highly electron-deficient protonated heteroaromatic bases.

EXPERIMENTAL

N.m.r. spectra were recorded with a Varian HA-100 (or A60) spectrometer (Me_4Si as internal standard; solvent $CDCl_3$). Mass spectra were obtained with a Hitachi-Perkin-Elmer RMU 6D spectrometer at 70 eV by use of an all-glass inlet system. For analytical and quantitative g.l.c. a Hewlett–Packard 5750 G instrument, with flame ionization detector (6 ft × ⅛ in steel column packed with 10% UCC-W-982 on Chromosorb W a.w. DMCS, 80—100 mesh) was used. Column chromatography and preparative t.l.c. were carried out on Kieselgel PF 254 (Merck).

All reagents were commercial products, distilled before use (purity ⩾98%). *N*-Chloro-dimethyl- and -di-isobutyl-amine were prepared by chlorination of the corresponding amines with sodium hypochlorite.[11]

General Procedure for the Alkylation of Quinoxaline.—A solution of *N*-chlorodi-isobutylamine (0.05—0.1 mol) in concentrated sulphuric acid was added dropwise (2—3 h) at room temperature to a mixture of quinoxaline (0.05 mol), finely powdered iron(II) sulphate heptahydrate (0.005 mol), and the alkyl derivative (0.15 mol) [acetic acid (10 ml) was added for insoluble materials], in concentrated sulphuric acid (60 ml) with vigorous stirring. Iron(II) sulphate heptahydrate (0.01 mol) was added in portions during the reaction, and the solution was stirred for an additional 1—2 h to ensure completion. The solution was poured on ice (500 g) and extracted with chloroform (2 × 150 ml). After basification with 12N-sodium hydroxide the solution was again extracted with chloroform (2 × 150 ml). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated. The residue was analysed by g.l.c. (with an internal standard). The results are given in Table 1.

The product was isolated by column chromatography on silica gel [ethyl acetate–hexane (9 : 1) as eluant for the compounds a, b, e, and f, and ethyl acetate–methanol (7 : 3) for compounds c and d] Analyses and spectral data (n.m.r. and mass) are listed in Tables 1 and 4. The ratio of (II) to (I) for concentrated sulphuric acid is 3 : 1 for all cases except R = cyclohexyl (see Table 2).

Thermal Reactions of Quinoxaline with Cyclohexane and N-Chlorodimethylamine.—A solution of quinoxaline (0.01 mol), cyclohexane (0.03 mol), and *N*-chlorodimethylamine (0.01 mol) in sulphuric acid–acetic acid (4 : 1; 25 ml) was heated at 70 °C for 1 h. Analysis of samples of the reaction mixture showed a conversion of 15%, and a ratio of 2- to 6-cyclohexylquinoxaline of 0.8 : 1.

Reactions at Various Acidities of Quinoxaline with Cyclohexane and N-Chlorodimethylamine.—The reactions were carried out under nitrogen at 25 °C; finely powdered iron(II) sulphate (0.005 mol) was added to 10 ml of a mixture of quinoxaline (0.01 mol), the *N*-chloro-amine (0.01 mol), and cyclohexane (0.05 mol) in acetic–sulphuric acid (20 ml). G.l.c. analysis of the products is reported in Table 2.

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[10] T. Caronna, A. Citterio, and T. Crolla, *Org. Prep. Proc. Int.*, in the press.

[11] G. H. Coleman, *J. Amer. Chem. Soc.*, 1933, **55**, 3001.