o-Nitroaniline Derivatives. Part 8.[1] Synthesis of Some Unsymmetrical Dimethylquinoxalines: A Long-Standing Problem Resolved

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Reduction of *N*-acetonyl-4-methyl-2-nitro-*N*-*p*-tolylsulphonylaniline, using tin(II) chloride in hydrochloric acid, gives 2,7-dimethylquinoxaline (42%) together with di-*p*-tolyl disulphide and toluene-*p*-thiol. 2,6- and 2,5-Dimethylquinoxalines are similarly obtained from the appropriately substituted nitroanilines; the 2,8-dimethyl isomer, however, is obtained impure and in very low yield.

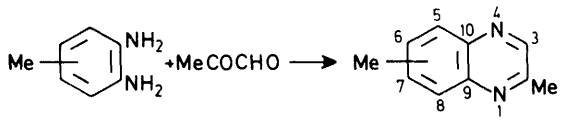
Of the simple quinoxaline derivatives, those unsymmetrically substituted in both rings are among the most difficult to prepare in a pure state. The dimethyl derivatives (1) are no exception: mixtures of 2,6- and 2,7-, and of 2,5- and 2,8-dimethylquinoxalines are easily obtained by condensation of the appropriate diaminotoluene with pyruvaldehyde (Scheme 1),[2] but the isolation of the individual isomers presents considerable difficulty on a preparative scale.

Of the literature methods which claim to give a single isomer, some are definitely incorrect, and none is above suspicion. For example, the so-called '2,5-dimethylquinoxaline' reported by Moriconi, Brady, and Misner[3] is, in fact, the 5,8-dimethyl compound, and the so-called '2,6-dimethylquinoxaline' of Skinner *et al.*[4] is undoubtedly a mixture of the 2,6- and 2,7-dimethyl isomers.

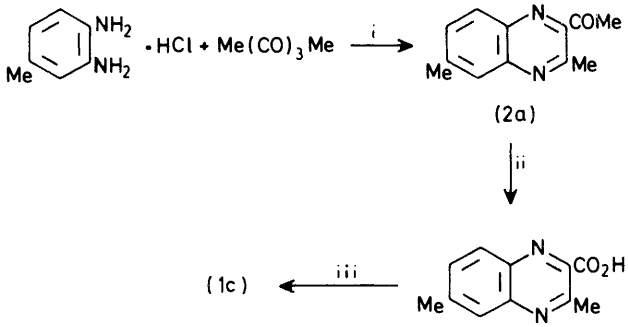
Titov and Kozhokina[5] claim to have prepared 2,7-dimethylquinoxaline by the route outlined in Scheme 2. To us it seems rather unlikely that the first step in this synthesis should give the single product (2a), especially since one of our colleagues has shown[6] that the reaction of 3,4-diaminotoluene with pentanetrione in the presence of hydrochloric acid gives a mixture of (2a) and its isomer (2b) in a ratio of *ca.* 2:1. This mixture has a reasonably sharp melting point (68—70°) and cannot be separated by recrystallisation or sublimation. If the Soviet workers have indeed obtained pure (2a), and thence (1c), it may mean that the isomer ratio [(2a):(2b)] is particularly sensitive to the precise reaction conditions, or it may simply be the result of a fortuitous fractional crystallisation.

Almost a century ago, however, Lellmann and Donner showed[7] that the reduction of 4-methyl-2-nitro-*N*-phenacylaniline (3), using tin(II) chloride in hydrochloric acid, gives 7-methyl-2-phenylquinoxaline (5) (Scheme 3a). The corresponding *N*-acetonyl compounds, *e.g.* (4), which should be, in principle, reducible to dimethylquinoxalines, are unknown. However, we now report that reduction of the *N*-*p*-tolylsulphonyl derivative of (3), *i.e.* (6c), also gives the quinoxaline (5) in 54% yield, and in this series the corresponding *N*-acetonyl compounds (7) are easily prepared.[1] Reduction of these compounds (7) gives the required dimethylquinoxalines (1a—d) (Scheme 3b).

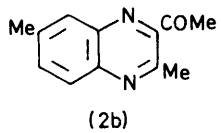
The synthesis of quinoxalines by catalytic hydrogenation of *o*-nitroaniline derivatives[8] suffers from the disadvantage that further hydrogenation to the 1,2,3,4-tetrahydroquinoxaline is relatively easy, and the reaction is thus not easily stopped at the quinoxaline stage. Our reduction method has similar problems, partly because of over-reduction and partly because the tosyl moiety is itself reduced to di-*p*-tolyl disulphide and toluene-*p*-thiol. For the reduction of the *N*-phenacyl compound (3), we have used 9—10 mol equiv. of tin(II) chloride, but in the case of the *N*-acetonyl compounds, 3—4 equiv. give better yields. 2,6- and 2,7-Dimethylquinoxalines are obtained in this way in yields of 43 and 42% respectively; the yield of the 2,5-isomer is considerably smaller (15%). The yield of 2,8-dimethylquinoxaline is very low (<5%); this may be due to the considerable steric hindrance around the nitro group in the precursor (7d).



Scheme 1.



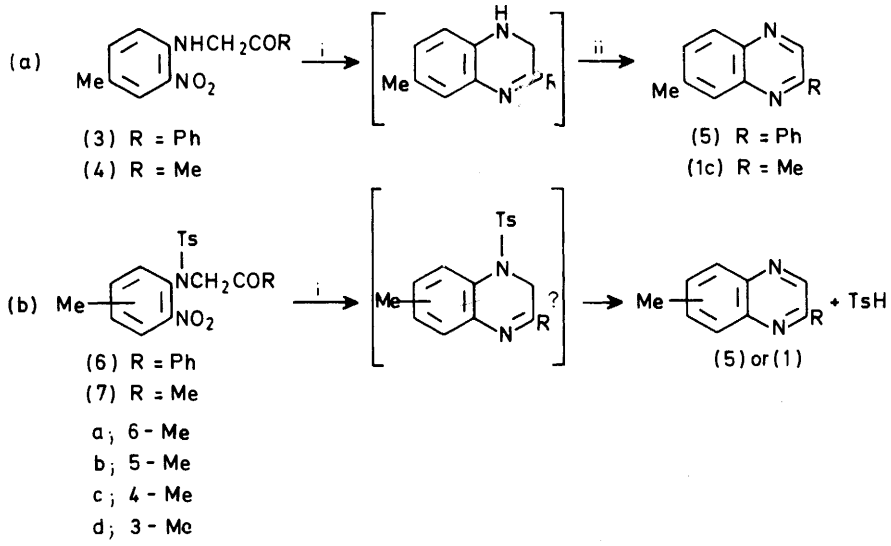
Scheme 2. *Reagents:* i, EtOH, H_2O; ii, Br_2, NaOH; iii, heat, Cu



(2b)

2,6- and 2,7-Dimethylquinoxalines are extraordinarily similar in their physical characteristics, and cannot be distinguished by their ^1H and proton-decoupled ^{13}C n.m.r. spectra. The proton-coupled ^{13}C spectra, however, show characteristic differences in the multiplicity of the ring-junction quaternary carbon resonances.[2]

Prior to the isolation of the individual dimethylquinoxaline isomers (1a—c), ambiguities have existed in the assignment of some of the ^{13}C resonances of methylated quinoxalines



Scheme 3. *Reagents:* i, $SnCl_2$, HCl; ii, O_2

Table. Comparison of observed and calculated ^{13}C n.m.r. chemical shifts for dimethylquinoxalines

		δ/p.p.m.									
Compound		C(2)	C(3)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	Average error (p.p.m.)	Me
(1a)	Obs.[b,c]	153.14	144.53	137.37	128.86	129.57	126.53	142.25	140.21		2-Me 22.28 5-Me 17.03
	Calc.[d]	152.61	143.98	136.74	128.15[e]	129.01	126.01	141.63	139.54	0.60 ± 0.11	
(1b)	Obs.[a,c]	152.48	145.60	127.83	138.96	131.94	127.93	140.28	140.81		2-Me 22.17 6-Me 21.42
	Calc.[d]	152.12	145.19	127.31	138.71	131.54	127.57	139.94	140.43	0.38 ± 0.14	
(1c)	Obs.[a,c]	153.36	144.81	128.40	130.89	140.21	127.33	141.88	139.19		2-Me 22.25 7-Me 21.55
	Calc.[d]	152.90	144.41	128.02	130.48	139.77	126.86	141.51	138.86	0.41 ± 0.08	

[a] Recorded at 20 MHz for solutions in $CDCl_3$. [b] Recorded at 50 MHz for solutions in $CDCl_3$. [c] All signals except C(9) and C(10) of (1b) were assigned unambiguously from the ^1H-coupled spectra. [d] Benzenoid ring shifts were calculated using data for 5- or 6-methylquinoxaline modified by 2-methylquinoxaline substituent effects (Figure): heterocyclic ring shifts were calculated using data for 2-methylquinoxaline,[2] modified by 5- or 6-methylquinoxaline substituent effects (Figure). [e] δ[C(6)] of 5-methylquinoxaline is 129.46 p.p.m. and not as reported in ref. 2.

(*cf.* Table 1 and Figure 1 of ref. 2). These ambiguities include the relative assignments of C(2) and C(3) of the 5- and 6-substituted quinoxalines, and of C(5) and C(8), and C(6) and C(7), of the 2-substituted compounds. With the availability of (1a—c), however, substituent additivity effects can be used to resolve these remaining ambiguities. The substituent effects given here (see Figure) accurately predict the relative order of all these signals for compounds (1a—c), the spectra of which can be assigned independently (Table): the error is consistent, and generally much less than 0.8 p.p.m. Reversal of the substituent effects would give much larger errors (up to 1.5 p.p.m.) with some incorrect assignment predictions. Based on the Figure, a re-examination of the ' ambiguous ' data for mono- and tri-methylquinoxalines given in ref. 2 shows that all the assignments given there are, fortuitously, correct.

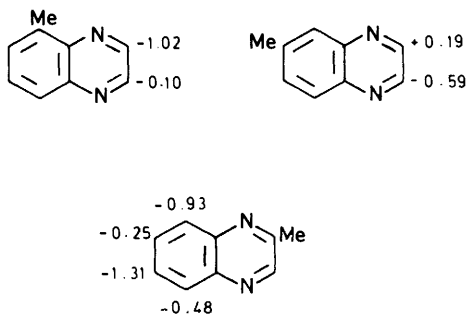


Figure. Substituent effects for 5-, 6-, and 2-methylquinoxalines (following Figure 1, ref. 2)

Experimental

The ^1H n.m.r. spectra were recorded in $CDCl_3$ at 80 MHz, and the shifts are relative to internal tetramethylsilane.

4-Methyl-2-nitro-*N*-phenacyl-*N*-*p*-tolylsulphonylaniline (6c), *N*-acetonyl-6-methyl-2-nitro-*N*-*p*-tolylsulphonylaniline (7a), and *N*-acetonyl-4-methyl-2-nitro-*N*-*p*-tolylsulphonylaniline (7c), were obtained as described in Part 7.[1] *N*-*Acetonyl-5-methyl-2-nitro*-N-p-*tolylsulphonylaniline* (7b) (52%), m.p. 143—144 °C (from ethanol), was similarly obtained from the sodium salt of 5-methyl-2-nitro-*N*-*p*-tolylsulphonylaniline [1] and chloroacetone in dimethylformamide (Found: C, 56.4; H, 5.0; N, 7.5. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7%).

N-*Acetonyl*-3-*methyl*-2-*nitro*-N-p-*tolylsulphonylaniline* (7d).—3-Methyl-2-nitrobenzoic acid [9] was converted, *via* its acid chloride, into the amide (m.p. 189—190 °C, from propan-2-ol), which was converted by the Hofmann rearrangement, with bromine and potassium hydroxide,[10] into 3-methyl-2-nitroaniline, m.p. 102—104 °C (from propan-2-ol; lit.,[10] 107—108 °C). The N-p-*tolylsulphonyl derivative* of this amine, m.p. 102—103 °C (from propan-2-ol–water), was obtained by the standard procedure [1] in 45% yield and, unusually, was colourless (Found: C, 55.1; H, 4.75; N, 9.1. $C_{14}H_{14}N_2O_4S$ requires C, 54.9; H, 4.6; N, 9.1%). It was converted by the usual method [1] into N-*acetonyl*-3-*methyl*-2-*nitro*-N-p-*tolylsulphonylaniline* (7d) (56%), m.p. 135—137 °C (from propan-2-ol; phase change at *ca.* 130 °C) (Found: C, 56.3; H, 5.2; N, 7.5. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7%).

7-*Methyl*-2-*phenylquinoxaline* (5).—The phenacylsulphonamide (6c) (1 g), dissolved in acetic acid (20 ml), was added slowly to a stirred solution of hydrated tin(II) chloride (5 g) in concentrated hydrochloric acid (15 ml) at 60 °C. After 1.5 h at 60 °C, the mixture was heated on a boiling water-bath for 1.5 h, cooled, and poured into sodium hydroxide (22 g) dissolved in water containing crushed ice (total 250—300 ml). The product was filtered off, dried, and chromatographed on silica; the fraction eluted with chloroform was recrystallised from methanol–water to give the quinoxaline (5) (0.28 g, 54%), m.p. 75—76 °C (lit.,[7] 79 °C); δ 2.56 (3 H, s), 7.3—8.3 (8 H, m), and 9.14 (1 H, s, 3-H).

2,x-*Dimethylquinoxalines* (1).—The following procedure is typical. A solution of the acetonylsulphonamide (7c) (5 g) in acetic acid (13 ml) was added in portions to a stirred solution of hydrated tin(II) chloride (10 g) in concentrated hydrochloric acid (10 ml) at 65 °C. After the initial exothermic reaction had subsided, the mixture was stirred at 65 °C for 1 h and at 100 °C for a further 1.5 h. It was then cooled (it smelled strongly of toluene-*p*-thiol), and poured into sodium hydroxide (20 g) dissolved in water containing crushed ice (total 250—300 ml). The product was extracted with diethyl ether, and the aqueous layer saturated with sodium chloride and re-extracted; the extracts were combined, washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica; elution with benzene gave a sequence of three compounds, *viz.* di-*p*-tolyl disulphide, m.p. 44—46 °C (lit.,[11] 47—48 °C; correct ^1H n.m.r. and mass spectrum), 4-methyl-2-nitroaniline, and unchanged sulphonamide (7c). Elution with diethyl ether then gave 2,7-dimethylquinoxaline (0.92 g, 42%), which was purified by sublimation *in vacuo* and had m.p. 79—80 °C (lit.,[5b] 74—75 °C) (Found: C, 76.0; H, 6.4; N, 18.0. Calc. for $C_{10}H_{10}N_2$: C, 75.9; H, 6.4; N, 17.7%); δ 2.56 (3 H, s, 7-Me), 2.72 (3 H, s, 2-Me), 7.49 (1 H, dd, 6-H), 7.76 (1 H, br, 8-H), 7.92 (1 H, d, 5-H), and 8.64 (1 H, s, 3-H); $J_{5,6}$ 8.5 Hz, $J_{6,8}$ 2.0 Hz; *m/z* 158 ($M^{+\cdot}$, 100%), 131 (75), 91 (25), 90 (56), 89 (82), *etc.*

2,6-*Dimethylquinoxaline* (1b) (43%), m.p. 74—75 °C, was similarly obtained from the acetonylsulphonamide (7b) (Found: C, 75.6; H, 6.8; N, 17.8. $C_{10}H_{10}N_2$ requires C, 75.9; H, 6.4; N, 17.7%); δ 2.53 (3 H, s, 6-Me), 2.70 (3 H, s, 2-Me), 7.53 (1 H, dd, 7-H), 7.81 (1 H, br, 5-H), 7.86 (1 H, d, 8-H), and 8.65 (1 H, s, 3-H); $J_{7,8}$ 8.8 Hz, $J_{5,7}$ 2.0 Hz; *m/z* 158 ($M^{+\cdot}$, 100%), 131 (63), 91 (11), 90 (31), 89 (39), *etc.*

2,5-*Dimethylquinoxaline* (1a) (15%) was obtained as a solid which melted around room temperature (22–23 °C) and which darkened rapidly on storage (Found: C, 75.4; H, 6.3; N, 17.55. $C_{10}H_{10}N_2$ requires C, 75.9; H, 6.4; N, 17.7%); δ 2.76, 2.78 (6 H, 2s, 2- and 5-Me), 7.5—7.9 (3 H, m, 6-, 7-, 8-H), and 8.73 (1 H, s, 3-H); *m/z* 158 ($M^{+\cdot}$, 100%), 131 (29), 91 (13), 90 (34), 89 (30), *etc.*

Attempts to prepare 2,8-dimethylquinoxaline (1d) by reduction of (7d) gave a small quantity of a red viscous oil, which on distillation gave a yellow liquid (b.p. 100—110 °C/0.8 mmHg). This had the correct mass spectrum for (1d) [*m/z* 158 ($M^{+\cdot}$, 100%), 131 (53), 116 (32), 91 (29), 90 (46), 89 (51), *etc.*], but the ^1H n.m.r. spectrum showed the presence of substantial impurities and could not be analysed.

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