578. *Organic Complex-forming Agents for Metals. Part II.* Preparation of 5-Hydroxy- and 5 : 8-Dihydroxy-quinoxalines and Related Compounds.*

By E. S. Lane and C. Williams.

5-Hydroxy- and 5 : 8-dihydroxy-quinoxalines containing a variety of 2- and 3-substituents have been prepared by dealkylation of the corresponding 5-methoxy- and 5 : 8-diethoxy-quinoxalines, and characterised as the acetyl derivatives.

This paper reports the preparation of further new complex-forming agents containing the substituents recorded in Part I [1] but based on the less basic quinoxaline ring system. Some compounds of this series have been previously described (for references see Albert and Hampton,[2] and Adachi [3]). King, Clark, and Davis [4] noted that 5 : 8-dihydroxy-quinoxalines possessed indefinite melting points and gave inconsistent analyses. We confirmed this observation and ascribe it partly to the pronounced tendency of quinoxaline derivatives to form molecular complexes, to which we have drawn attention previously, and to the ease with which they are oxidised to *p*-quinonoid derivatives. To obtain the analyses reported below, repeated purification of the compounds was necessary by protracted recrystallisation from selected solvents or, preferably, by vacuum-sublimation. King [4] *et al.* used an isomeric mixture of diamines as starting material, but like Adachi we preferred to use pure *o*-diamines as the primary intermediates and this undoubtedly facilitated the purification of these compounds.

Well-established methods were used for the preparation of the 2 : 3-disubstituted 5-methoxy- and 5 : 8-diethoxy-quinoxalines from the appropriate *o*-diamines and α-diketones (an improved preparation of di-α-pyridyl diketone is described). Similar compounds singly substituted in the 2-position were prepared from the corresponding glyoxal derivative. 2 : 3-Dihydroxyquinoxalines were prepared from the parent diamine and oxalic acid, and were smoothly converted into the 2 : 3-dichloro-compounds by phosphorus oxychloride or phosphorus oxychloride–dimethylaniline.[5] For dealkylation either aluminium chloride in benzene (method A) or boiling aqueous hydrobromic acid (method B) was used, the latter being usually reserved for aryl-substituted quinoxalines.

The hydroxyquinoxalines were characterised as their *O*-acetyl derivatives prepared by use of acetic anhydride, optionally in the presence of pyridine. The base was omitted when acetylating 2 : 3-dichloro-hydroxyquinoxalines owing to side reactions with the reactive chlorine atoms. Similarly, it was not possible to use hydrobromic acid for the dealkylation of 2 : 3-dichloroquinoxalines because of replacement of the chlorine atoms by hydroxyl groups.

The 5-hydroxy- and 5 : 8-dihydroxy-quinoxalines exhibit chelating properties to a varied extent. Preliminary accounts have been given by Irving and Rossotti [6] and by Kawa, Kimura, and Furahata.[7] Their main disadvantages are their low solubility in water and alcohol and their ready oxidisability.

Since hemipyocyanine (1-hydroxyphenazine) is a fungicide a representative selection of our analogous quinoxalines was kindly tested by Mr. W. H. Read of the Glasshouse Crops Research Institute, who reported, however, that they displayed only low fungicidal activity.

Experimental

Determination of the Equivalent Weight of Quinoxalines.—The methods used in Part I were applicable to the compounds described herein.

* Part I, *J.*, 1956, 569.

[1] Lane and Williams, *J.*, 1956, 569.
[2] Albert and Hampton, *J.*, 1952, 4985.
[3] Adachi, *J. Chem. Soc. Japan*, 1955, **76**, 311.
[4] King, Clark, and Davis, *J.*, 1949, 3012.
[5] Landquist, *J.*, 1953, 2816.
[6] Irving and Rossotti, *Analyst*, 1955, **80**, 245.
[7] Kawa, Kimura, and Furuhata, *Proc. Japan Acad.*, 1953, **29**, 344.

TABLE 1. 5-*Methoxyquinoxalines.*

2-Subst.	3-Subst.	M. p.	Equiv. wt. Found	Equiv. wt. Reqd.	Appearance *	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
H	H [a]	100°	—	—	—	—	—	—	—	—	—	—
Me	Me [b]	121	192	188	Plates	$C_{11}H_{12}ON_2$	—	—	14·8	—	—	14·8
OH	OH	272—274	98	96	Powder	See Text	—	—	—	—	—	—
Cl	Cl [c]	144·5—145	—	—	Yellow needles	$C_9H_6ON_2Cl_2$	47·6	2·8	12·0	47·2	2·6	12·2
2-Py	2-Py [d, e]	175·5	—	—	Powder	$C_{19}H_{14}ON_4$	72·3	4·4	17·5	72·6	4·5	17·8
Ph	Ph	190 [f]	—	—	Plates	—	—	—	—	—	—	—
2 : 3-Trimethylene		99·5—102	—	—	—	$C_{12}H_{12}ON_2$	71·9	6·0	14·2	72·0	6·0	14·0
2 : 3-Tetramethylene		95	—	—	Pink prisms	$C_{13}H_{14}ON_2$	72·5	6·9	13·0	72·9	6·5	13·1
2 : 3-Pentamethylene		110·5—114	—	—	Yellow needles	$C_{14}H_{16}ON_2$	73·3	7·4	12·3	73·6	7·1	12·3

TABLE 2. 5-*Hydroxyquinoxalines.*

2-Subst.	3-Subst.	M. p.	Equiv. wt. Found	Equiv. wt. Reqd.	Appearance *	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
H	H [g]	101	—	—	—	—	—	—	—	—	—	—
Me	Me	146	—	—	Yellow cubes	$C_{10}H_{10}ON_2$	68·8	5·3	15·75	69·0	5·7	16·1
Cl	Cl [h]	144	—	—	Yellow needles	$C_8H_4ON_2Cl_2$	45·2	1·8	12·9	44·65	1·9	13·0
2-Py	2-Py [d]	176—177	300	300	Fawn needles	$C_{18}H_{12}ON_4$	71·1	3·8	18·7	72·0	4·0	18·7
Ph	Ph	133—134	302	298	Needles	$C_{20}H_{14}ON_2$	80·6	—	9·2	80·5	4·7	9·4
2 : 3-Trimethylene		139—140	187	186	Fawn powder	$C_{11}H_{10}ON_2$	70·8	5·6	15·1	71·0	5·4	15·1
2 : 3-Tetramethylene		118·5	—	—	Yellow powder	$C_{12}H_{12}ON_2$	72·0	6·1	13·8	72·0	6·0	14·0
2 : 3-Pentamethylene		139—140	212	214	Fawn powder	$C_{13}H_{14}ON_2$	73·0	6·4	13·2	73·0	6·55	13·1

TABLE 3. 5-*Acetoxyquinoxalines.*

2-Subst.	3-Subst.	M. p.	Equiv. wt. Found	Equiv. wt. Reqd.	Appearance *	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
H	H [i]	101	—	—	Solid	—	—	—	—	—	—	—
Me	Me	103	—	—	Cubes	$C_{12}H_{12}O_2N_2$	66·6	5·65	12·6	66·7	5·55	13·0
Cl	Cl	90—94	—	—	Yellow needles	$C_{10}H_6O_2N_2Cl_2$ [j]	47·1	2·25	11·0	46·7	2·3	11·0
2-Py	2-Py [d]	158—159	—	—	Cream powder	$C_{20}H_{14}O_2N_4$	—	4·1	16·3	—	4·1	16·4
Ph	Ph	142	—	—	Powder	$C_{22}H_{16}O_2N_2$	77·8	4·7	8·1	77·6	4·7	8·2
2 : 3-Trimethylene		82—83	—	—	Cream powder	$C_{13}H_{12}O_2N_2$	68·2	5·6	12·1	68·3	5·3	12·3
2 : 3-Tetramethylene		94—95	—	—	Yellow powder	$C_{14}H_{14}O_2N_2$	69·0	5·7	11·7	69·4	5·8	11·6
2 : 3-Pentamethylene		63	—	—	Needles	$C_{15}H_{16}O_2N_2$	69·8	6·3	11·1	70·3	6·25	10·9

* Colourless unless otherwise stated.

[a] King, Clark, and Davis[4] reported m. p. 100—101°. [b] Landquist and Stacey (*J.*, 1953, 2822) obtained m. p. 118°. [c] Found: Cl, 30·9. Reqd., 31·0%. [d] Py = pyridyl. [e] *Perchlorate*, yellow, m. p. 254° (decomp.) (Found: N, 9·8; Cl, 12·4. $C_{11}H_{13}O_5N_2Cl$ requires N, 9·7; Cl, 12·3%). [f] Meldola and Eyre (*J.*, 1902, **81**, 992) give m. p. 191°. [g] King *et al.*[4] reported m. p. 100—101°; Sorkin and Roth (*Helv. Chim. Acta*, 1951, **34**, 427) reported m. p. 102—103°. [h] Did not titrate quantitatively in ethylenediamine owing to interaction of Cl with solvent. [i] King *et al.*[4] reported m. p. 103—104°; Sorkin and Roth (*loc. cit.*) reported m. p. 106·5—108°. [j] Found: Cl, 27·9. Reqd., 27·6%. [k, l] Nietzki and Rechberg[8] give m. p. 127° and 163° respectively. [m] King *et al.*[4] obtained m. p. 230°; Adachi[3] obtained m. p. 236—237°. [n] King *et al.*[4] obtained m. p. 209°; Adachi[3] obtained m. p. 212·5—213·5°. [o] *Perchlorate*, m. p. 225° (decomp.) (Found: N, 7·1; Cl. 8·8. $C_{15}H_{17}O_8N_2Cl$ requires N, 7·2; Cl, 9·1%).

2-Subst.	3-Subst.	M. p.	Equiv. wt. Found	Equiv. wt. Reqd.	Appearance *	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
					TABLE 4. 5 : 8-*Diethoxyquinoxalines.*							
H	H	101·5—101°	—	—	Yellow plates	$C_{12}H_{14}O_2N_2$	—	—	12·6	—	—	12·8
Me	Me [k]	127·5	—	—	—	$C_{14}H_{18}O_2N_2$	68·2	7·3	11·3	68·3	7·3	11·4
OH	OH	271	—	—	Needles	$C_{12}H_{14}O_4N_2$	58·1	5·9	10·8	57·6	5·6	11·2
Cl	Cl	199—199·5	—	—	Orange plates	$C_{12}H_{12}O_2N_2Cl_2$	49·9	4·3	10·1	50·2	4·2	9·8
2-Py	2-Py [d]	175	—	—	Yellow needles	$C_{22}H_{20}O_2N_4$	70·8	5·4	15·0	71·0	5·4	15·1
Ph	H	114—116	—	—	,, ,,	$C_{18}H_{18}O_2N_2$	73·4	6·2	9·25	73·5	6·1	9·5
Pr[i]	H	47—49	—	—	Cream powder	$C_{15}H_{20}O_2N_2$	69·1	7·7	10·65	69·2	7·7	10·8
Me	H	70—73	—	—	,, ,,	$C_{13}H_{16}O_2N_2$	66·8	7·2	11·9	67·2	6·9	12·1
2 : 3-Trimethylene		122—122·5	—	—	Yellow needles	$C_{15}H_{18}O_2N_2$	69·7	6·75	10·9	69·8	7·0	10·85
2 : 3-Tetramethylene		117	—	—	Fawn powder	$C_{16}H_{20}O_2N_2,H_2O$	66·1	7·65	9·55	66·2	7·65	9·65
2 : 3-Pentamethylene		157	—	—	Yellow needles	$C_{17}H_{22}O_2N_2$	69·5	7·95	9·7	70·0	7·7	9·8
Ph	Ph [l]	165	—	—	Yellow prisms							
					TABLE 5. 5 : 8-*Dihydroxyquinoxalines.*							
Me	Me [m]	230—233	—	—	Yellow plates	$C_{10}H_{10}O_2N_2$	63·35	5·3	14·9	63·2	5·3	14·7
Cl	Cl [h]	151—152	—	—	Orange plates	$C_8H_4O_2N_2Cl_2$	41·9	1·9	11·7	41·6	1·7	12·1
2-Py	2-Py [d]	249—250	—	—	Orange powder	$C_{18}H_{12}O_2N_4$	—	—	17·7	—	—	17·7
Ph	H	176	118	119	Orange powder	$C_{14}H_{10}O_2N_2$	70·6	4·2	11·7	70·6	4·2	11·8
Pr[i]	H	120	104	102	Orange needles	$C_{11}H_{12}O_2N_2$	64·3	6·1	13·8	64·7	5·9	13·7
Me	H	182	86	88	Crimson rhombs	$C_9H_8O_2N_2$	61·3	4·6	16·0	61·4	4·5	15·9
2 : 3-Trimethylene		219	—	—	Orange needles	$C_{11}H_{10}O_2N_2$	64·9	4·9	14·3	65·3	4·95	13·7
2 : 3-Tetramethylene		198—199	107·5	108	Orange plates	$C_{12}H_{12}O_2N_2$	66·9	5·6	13·3	66·7	5·6	13·0
2 : 3-Pentamethylene		177—178	—	—	Yellow needles	$C_{13}H_{14}O_2N_2$	68·4	6·45	11·6	67·9	6·1	12·2
Ph	Ph	171	—	—	Orange plates	$C_{20}H_{14}O_2N_2$	76·6	4·4	8·85	76·4	4·5	8·9
					TABLE 6. 5 : 8-*Diacetoxyquinoxalines.*							
H	H [n]	200—202	—	—	Cream plates	$C_{12}H_{10}O_4N_2$	59·2	4·5	11·2	58·5	4·1	11·4
Me	Me	163·5—164	—	—	,, ,,	$C_{14}H_{14}O_4N_2$	61·2	5·3	10·2	61·3	5·1	10·2
Cl	Cl	218	—	—	,, ,,	$C_{12}H_8O_4N_2Cl_2$	45·7	2·5	8·95	45·7	2·5	8·9
2-Py	2-Py [d]	285—287·5	—	—	Needles	$C_{22}H_{16}O_4N_4$	65·5	4·4	14·0	66·0	4·0	14·0
Ph	H	157—158	—	—	Needles	$C_{18}H_{14}O_4N_2$	67·1	4·5	8·75	67·1	4·3	8·7
Pr[i]	H [o]	40—45	—	—	Orange prisms	$C_{15}H_{16}O_4N_2$	—	—	9·7	—	—	9·7
2 : 3-Trimethylene		190—192	—	—	Yellow needles	$C_{15}H_{14}O_4N_2$	62·6	4·9	9·7	62·9	4·9	9·8
2 : 3-Tetramethylene		277—278	—	—	Yellow needles	$C_{16}H_{16}O_4N_2$	64·3	5·1	9·45	64·0	5·3	9·3
2 : 3-Pentamethylene		135—138	—	—	Needles	$C_{17}H_{18}O_4N_2$	64·9	6·1	8·7	64·8	5·7	8·9
Ph	Ph	228	—	—	Needles	$C_{24}H_{1}O_4N_2$	71·7	4·5	7·3	72·4	4·5	7·0

Di-2-pyridyl Diketone (α-*Pyridil*).—The recorded method of oxidising α-pyridoin with fuming nitric acid, followed by heating on a water-bath, gave only a small yield of the required product. By maintaining the reaction mixture at −30° during the oxidation and eliminating the heating, the yield was increased to over 90%.

Preparation of 2 : 3-*Disubstituted* 5-*Methoxy- and* 5 : 8-*Diethoxy-quinoxalines*.—Equimolecular quantities of the appropriate diketones and *o*-diamines (see Part I) were refluxed together in ethanol for 1 hr. The mixture was poured into water, and the insoluble quinoxaline filtered off, distilled *in vacuo* when possible, and recrystallised.

The *compounds* are listed in Tables 1 and 4.

2-*Substituted* 5 : 8-*Diethoxyquinoxalines*.—These were prepared as above, from the appropriate glyoxal in place of the α-diketone (see Table 4).

2 : 3-*Dihydroxy-5-methoxyquinoxaline*.—Equimolecular quantities of 2 : 3-diaminoanisole and oxalic acid were refluxed together for 12 hr. in 4N-hydrochloric acid. The mixture was neutralised with ammonia, and the precipitated *base* filtered off. It formed colourless crystals (from ethylene glycol), m. p. 272—274°. The equivalent weight of this compound was determined in ethylenediamine and gave a satisfactory value but microanalyses were unsatisfactory (Found: C, 50·35; H, 5·6; N, 12·8%; equiv., 98. $C_9H_8O_3N_2$ requires C, 56·25; H, 4·2; N, 14·6%; equiv, 96). Satisfactory microanalyses were obtained from its derivatives (see below).

5 : 8-*Diethoxy*-2 : 3-*dihydroxyquinoxaline* was similarly prepared from oxalic acid and 2 : 3-diaminoquinol diethyl ether (see Table 4).

2 : 3-*Dichloro-5-methoxyquinoxaline*.—2 : 3-Dihydroxy-5-methoxyquinoxaline (4 g.) was refluxed for 1 hr. with dimethylaniline (5 ml.) and phosphorus oxychloride (20 ml.). Excess of phosphorus oxychloride was removed in a vacuum and the residue poured on crushed ice (200 g.). The *base* was filtered off and dried. It formed pale yellow needles, m. p. 144·5—145° (from benzene) (see Table 1).

2 : 3-*Dichloro*-5 : 8-*diethoxyquinoxaline*.—This was similarly prepared from 5 : 8-diethoxy-2 : 3-dihydroxyquinoxaline (16 g.) and phosphorus oxychloride (400 ml.) (see Table 4).

2 : 3-*Disubstituted* 5 : 8-*Dihydroxyquinoxalines*.—(A) The 5 : 8-diethoxy-compound was refluxed for 3 hr. with anhydrous aluminium chloride (2·4 equivs.), in benzene. Water was then added and the mixture extracted with hot benzene. The benzene extract was evaporated to small bulk and the material which separated was recrystallised.

(B) The 5 : 8-diethoxy-compound was refluxed for 6 hr. in hydrobromic acid (48%). After cooling, the mixture was filtered and the solid material hydrolysed with warm water, washed with sodium hydrogen carbonate solution and with water, and recrystallised.

2 : 3-*Disubstituted* 5-*Hydroxyquinoxalines*.—Analogous procedures to the above, but using 1·2 equivs. of anhydrous aluminium chloride, were used.

2 : 3-*Disubstituted* 5-*Acetoxy- and* 5 : 8-*Diacetoxy-quinoxalines*.—The hydroxy-compounds were refluxed in acetic anhydride, excess of reagent was removed under reduced pressure, and the residue recrystallised from ethanol (see Tables 3 and 6).

10 : 13-*Dihydroxydibenzo*[a,c]*phenazine*.—10 : 13-Diethoxydibenzo[*a*,*c*]phenazine [8] (2 g.) was refluxed with 48% hydrobromic acid (60 ml.) for 6 hr. On cooling, the deposited solid was hydrolysed by boiling water to an orange powder (1·6 g.). Recrystallisation from benzyl alcohol gave the *phenolic base* as an orange-red powder, m. p. 280—283° (Found: C, 76·6; H, 3·9; N, 8·8. $C_{20}H_{12}O_2N_2$ requires C, 76·9; H, 3·8; N, 9·0%). A prior preparation attributed to Kawai and Kosaka [9] is mentioned by Kawal, Kimura, and Furahata [7] but without details. The *diacetate* was obtained as yellow-green needles, m. p. 273—273·5° (Found: C, 72·5; H, 4·2; N, 6·85. $C_{24}H_{16}O_4N_2$ requires C, 72·7; H, 4·0; N, 7·1%).

United Kingdom Atomic Energy Authority,
Harwell, Didcot, Berks.

[*Received, March* 13*th*, 1956.]

[8] Nietzki and Rechberg, *Ber.*, 1890, **23**, 1212.
[9] Kawai and Kasaka, *J. Soc. Org. Synth. Chem.*, Japan, 1944, **2**, 73.
[10] Meldola and Eyre, *J.*, 1902, **81**, 992.
[11] Landquist and Stacey, *J.*, 1953, 2822.
[12] Sorkin and Roth, *Helv. Chim. Acta*, 1951, **34**, 427.