The Action of Organo-lithium Compounds on Quinoxaline. Molecular Compound Formation Involving the Quinoxaline Ring System.

By E. S. Lane and C. Williams.

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Organo-lithium compounds react with a molar proportion of quinoxaline giving a molecular complex between quinoxaline and the 2 : 3-disubstituted 1 : 2 : 3 : 4-tetrahydroquinoxaline. Doubling the quantity of organo-lithium compound used produces the second component only, in high yield. Some additional examples of the tendency of quinoxaline compounds to form molecular complexes are provided and discussed.

In an attempt to devise a new route to 2-substituted quinoxalines we treated phenyl-lithium in ether with a molecular proportion of quinoxaline. By working up in the usual way the only compound isolated was an orange solid (A) melting at 100° which analysed according to the formula $C_{14}H_{12}N_2$ and was reasonably stable to oxidation. It was thought unlikely that this could be 3 : 4-dihydro-2-phenylquinoxaline ($C_{14}H_{12}N_2$) since by analogy with the behaviour of 3-alkyl-3 : 4-dihydro-2-hydroxyquinoxalines (Motylewski, *Ber.*, 1908, **41**, 800) it should be very easily oxidised to 2-phenylquinoxaline. When the quantity of phenyl-lithium used was increased to two molecular proportions the resulting product was the expected 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline in high yield. When the compound (A) was distilled in a vacuum in an attempt to purify it by a method other than by crystallisation, it decomposed to a volatile low-melting basic compound and a residue of relatively non-volatile material. Identification of the volatile base as quinoxaline and of the residue as 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline suggested that (A) was a molecular compound of these two components, and this was confirmed synthetically and spectrophotometrically; an equimolecular mixture of the two components in alcohol gave an ultra-violet absorption spectrum identical with that of (A) and also with that of the compound prepared by mixing equimolecular solutions of the two compounds in a minimum of warm ethanol, separating the crystals which were precipitated on cooling, and recrystallising them from alcohol.

Similar experiments with methyl-lithium in ether gave, from one mol., the molecular compound of quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethylquinoxaline (separated into its components by vacuum-distillation) and, from 2 mols., 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethylquinoxaline. The molecular complex between quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-di-*o*-methoxyphenylquinoxaline was also prepared.

Table 1 records molecular complexes between a variety of quinoxaline derivatives and other organic compounds. Further molecular compounds involving quinoxaline derivatives are known, *e.g.*, 1 : 1 molecular complexes between 2 : 3-dimethylquinoxaline and dimethylglyoxime (Henderson, *J.*, 1929, 466), and 2 : 6 : 7-trimethylquinoxaline and

methylglyoxime, and 2-phenylquinoxaline and phenylglyoxal dioxime (Landquist and Stacey, *J.*, 1953, 2822). On finding a molecular complex of 2-amino-3 : 4-dihydroquinoxaline with 2-aminoquinoxaline, Pfister, Sullivan, Weyland, and Tischler (*J. Amer. Chem. Soc.*, 1951, **73**, 4955) drew attention to its similarity to that of quinhydrone, but the above results indicate that this restriction is not valid. In a preliminary communication (*Chem. and Ind.*, 1953, 1230) we pointed out the possible significance of this tendency to molecular-compound formation in synthetic work in this field. It is not however a general phenomenon and we could not obtain a molecular compound between 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline and 2 : 3-dimethylquinoxaline, although there is evidence of slight interaction (see below). Henderson (*loc. cit.*) has also reported the failure of dimethylglyoxime to form a molecular complex with quinoxaline.

Some of the molecular complexes described above may be regarded as analogous to those obtained by Birtwell in the pyrimidine system (*J.*, 1953, 1725) where it is postulated that the linkage is probably due to hydrogen-bonding. In Table 2 we have reported an

TABLE 1. *Molecular compounds of quinoxaline derivatives.*

Quinoxaline component	Second component	Form and m. p.	Formula	Found (%) C	H	N	Required (%) C	H	N
(Quinoxaline)	Urea	White needles 147—148°	$C_9H_{10}ON_4$	56·9	5·2	29·4	56·8	5·3	29·5
5 : 8-Diethoxy-	Glyoxime	Yellow needles 198—199°	$C_{14}H_{18}O_4N_4$	54·9	5·7	17·5	54·9	5·9	18·3
5 : 8-Diethoxy-2 : 3-dimethyl-	Dimethylglyoxime	Yellow needles 137—138·5°	$C_{32}H_{44}O_6N_6$ *	63·7	7·2	13·9	63·1	7·2	13·8
1 : 2 : 3 : 4-Tetrahydro-2 : 3-diphenyl-	Quinoxaline	Orange 100—100·5°	$C_{28}H_{24}N_4$	80·6	5·6	13·4	80·8	5·8	13·5
,, ,,	Piaselenol	Red prisms 91·5—92°	$C_{26}H_{22}N_4Se$	67·0	4·7	11·7	66·6	4·7	11·9
,, ,,	Piazthiole	Orange rhombs 65—66°	$C_{26}H_{22}N_4S$ †	73·3	5·25	12·9	73·9	5·2	13·3
1 : 2 : 3 : 4-Tetrahydro-2 : 3-dimethyl-	Quinoxaline	Orange prisms 85—86°	$C_{18}H_{20}N_4$	74·2	6·95	18·6	74·0	6·85	19·2

* 2 mols. of quinoxaline deriv. and 1 mol. of dimethylglyoxime; the others are 1 : 1 compounds.
† Found : S, 7·7. Reqd. : S, 7·6%.

intermediate type of molecular interaction between quinoxaline derivatives. This was characterised by colour changes on mixing of the component solutions in absolute ethanol but no complexes could be obtained on concentration, the components crystallising separately. These solutions also exhibited thermochromism, their colour becoming much paler on heating but returning on cooling. This is presumably indicative of a weak type of molecular interaction possibly related to that occurring in the phenazine system where

TABLE 2. *Colour change on admixture in equimolar proportions in absolute ethanol.*

Added comonent	1 : 2 : 3 : 4-Tetrahydro-2 : 3-dimethylquinoxaline	1 : 2 : 3 : 4-Tetrahydro-2 : 3-diphenylquinoxaline
Benzofurazan	Colourless to orange-red	Colourless to orange-red
Piazthiole	Colourless to deep red	Mol. compound formed *
Piaselenole	,, ,,	,, ,,
Phenazine	Yellow to brown	Yellow to deep red
2 : 3-Di-R-quinoxaline.		
R = H	Mol. compound formed *	Mol. compound formed *
R = Me	Colourless to yellow	Colourless to pale yellow
R = Ph	Colourless to orange	Colourless to orange
R = Cl	,, ,,	,, ,,
R = 2-Pyridyl	Colourless to orange-yellow	,, ,,
6-Nitroquinoxaline ...	Orange to brown	Orange to red

* See Table 1.

coloured compounds are obtained between certain phenazine derivatives and their respective dihydrides (Toromanoff, *Compt. rend.*, 1953, **236**, 300; 1952, **235**, 759; Clemo and McIlwain, *J.*, 1934, 1991).

A number of unsuccessful attempts were made to introduce only one substituent into the quinoxaline ring by variation of proportions and reaction conditions used, since it had

been reported that Klein and Spoerri (*J. Amer. Chem. Soc.*, 1951, **73**, 2949) were able to monoalkylate pyrazine, albeit in small yield, by reaction with an alkyl-lithium compound at low temperatures. The formation of the disubstituted tetrahydro-derivative parallels the behaviour of Grignard reagents towards quinoxaline (Bergstrom and Ogg, *ibid.*, 1931, **53**, 245) and it is noteworthy that the yields we obtained from lithium derivatives were much higher than those from the corresponding Grignard reagent.

Experimental

Reaction of Organo-lithium Compounds with Quinoxaline.—(*a*) Lithium foil (1·4 g., 0·2 mole), prepared by repeated hammering and folding of lithium metal moistened with naphtha between steel blocks, was suspended in anhydrous ether (200 ml.) at −10° under nitrogen. Bromobenzene (15·7 g., 0·1 mole) was slowly added during 30 min. at such a rate as to cause slow refluxing. Refluxing was continued for 40 min. by external heat. The mixture was cooled to room temperature, quinoxaline (11 g., 0·085 mole) in ether (30 ml.) was added dropwise during 30 min., and the mixture stirred for 24 hr. Water (300 ml.) was then added, the ethereal layer separated, and the solvent removed by evaporation, leaving a residue of orange-yellow solid (20 g.). The molecular *compound* of quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline formed rhombs from ethyl alcohol (see Table 1).

(*b*) The above experiment was repeated with lithium (2·8 g., 0·4 mole), bromobenzene (31·4 g., 0·2 mole), and quinoxaline (11 g., 0·085 mole). The residue (23·5 g., 98%) of 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline recrystallised from ethyl alcohol as a colourless powder, m. p. 105° (Found : C, 83·7; H, 6·05; N, 9·65. Calc. for $C_{20}H_{18}N_2$: C, 83·7; H, 6·3; N, 9·65%). Bennett and Gibson (*J.*, 1923, 1570) obtained m. p. 106°.

(*c*) By the same procedures lithium (1·4 g., 0·2 mole), methyl iodide and quinoxaline gave quantitative yields (on quinoxaline) of the molecular *compound* (from alcohol) between quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethylquinoxaline (see Table 1), and 1 : 2 : 3 : 4-tetrahydro-2 : 3-dimethylquinoxaline, yellow prisms, m. p. 99—100° (from ethanol) (Found : C, 74·4; H, 8·9; N, 16·7. Calc. for $C_{10}H_{14}N_2$: C, 74·1; H, 8·6; N, 17·3%). Gibson (*J.*, 1927, 342) obtained m. p. 101—102°.

(*d*) Use of *o*-bromoanisole gave a viscous oil (24·5 g.) which solidified after several months at 0°. The molecular *compound* of quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-di-*o*-methoxyphenylquinoxaline formed yellow rosettes, m. p. 106·5—107·5° (from ethanol), with a yellow-green fluorescence in ultra-violet light (not shown by the other compounds) (Found : C, 75·7; H, 5·8; N, 11·0. $C_{30}H_{28}O_2N_4$ requires C, 75·6; H, 5·9; N, 11·8%).

Preparation of Molecular Complexes.—The molecular complexes in Table 1 were prepared by mixing solutions of the two components in molecular proportions in the minimum of warm alcohol. The material crystallising on cooling was filtered off and recrystallised from the same solvent.

A similar procedure was adopted for the compounds listed in Table 2. Here, however, the components were recovered unchanged on concentration.

Action of Heat on the Molecular Complexes.—(*a*) The molecular compound of quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline was heated in a vacuum. Quinoxaline distilled, leaving a residue of the 1 : 2 : 3 : 4-tetrahydro-2 : 3-diphenylquinoxaline, m. p. 105° (from ethanol) (Found : C, 83·7; H, 6·45; N, 9·6%). The quinoxaline was identified as its *perchlorate*, m. p. 193° (needles from acetic acid) (Found : N, 12·1. $C_8H_7O_4N_2Cl$ requires N, 12·15%).

(*b*) Quinoxaline volatilised when the molecular compound of urea and quinoxaline was dried *in vacuo* at 100°.

(*c*) When the molecular compound of quinoxaline and 1 : 2 : 3 : 4-tetrahydro-2 : 3-di-*o*-methoxyphenylquinoxaline was vacuum-distilled, quinoxaline was again obtained as a first fraction followed by a yellow oil. The latter solidified and gave 1 : 2 : 3 : 4-*tetrahydro*-2 : 3-*di*-o-*methoxyphenylquinoxaline* as colourless plates, m. p. 114°, from ethanol (Found : C, 76·55; H, 5·5; N, 7·8. $C_{22}H_{22}O_2N_2$ requires C, 76·3; H, 6·4; N, 8·1%).

(*d*) The molecular compounds of glyoxime with 5 : 8-diethoxyquinoxaline and of dimethylglyoxime with 2 mols. of 5 : 8-diethoxy-2 : 3-dimethylquinoxaline were sufficiently thermally stable to withstand purification by vacuum-sublimation.

Atomic Energy Research Establishment,
Harwell, near Didcot, Berks.

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