Lane and Williams: The Action of

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

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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 phenyllithium 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-dimethylquinoxaline.

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

4107

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 dimethyl-glyoxime 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	Second	Form and	Formula	Fo C	und (' H	%) N	Req C	uired H	(%) N	
(Quinoxaline)	Urea	White needles	C ₉ H ₁₀ ON ₄	56.9	5.2	29·4	56 ·8	5.3	29.5	
$5:8 ext{-Diethoxy-}$	Glyoxime	Yellow needles	$C_{14}H_{18}O_4N_4$	5 4 ·9	5.7	17.5	54 ·9	5.9	18.3	
5:8-Diethoxy-2:3-di-	Dimethyl-	Yellow needles	$C_{32}H_{44}O_6N_6*$	63 ·7	$7 \cdot 2$	13.9	63·1	$7 \cdot 2$	1 3 ·8	
1:2:3:4-Tetrahydro-	Quinox-	Orange	$\mathrm{C_{28}H_{24}N_4}$	80 ·6	5.6	13.4	80.8	5.8	13.5	
2.3-dipitenyi-	Piaselenol	Red prisms	$\mathrm{C_{26}H_{22}N_4Se}$	67·0	4 ·7	11.7	66 ·6	4 ·7	11.9	
,, ,,	Piazthiole	Orange rhombs	$C_{26}H_{22}N_4S^{\dagger}$	73·3	5.25	12.9	73 ·9	$5 \cdot 2$	13.3	
1 : 2 : 3 : 4-Tetrahydro- 2 : 3-dimethyl-	Quinox- aline	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.

	1 1				
1:2:3:4-Tetrahydro-2:3-dimethyl- quinoxaline	1:2:3:4-Tetrahydro-2:3-diphenyl- quinoxaline				
Colourless to orange-red Colourless to deep red	Colourless to orange-red Mol. compound formed *				
Yellow to brown	Yellow to deep red				
ine.					
Mol. compound formed * Colourless to yellow Colourless to orange	Mol. compound formed * Colourless to pale yellow Colourless to orange				
Colourless to orange-yellow Orange to brown * See Table 1.	Orange to red				
	1:2:3:4-Tetrahydro-2:3-dimethyl- quinoxaline Colourless to orange-red Colourless to deep red Yellow to brown ine. Mol. compound formed * Colourless to yellow Colourless to orange Colourless to orange Colourless to orange Yellow to brown Yellow to brown 				

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

4108 The Action of Organo-lithium Compounds on Quinoxaline.

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 C₂₀H₁₈N₂: 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-methoxy-phenylquinoxaline 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. C₈H₇O₄N₂Cl 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-omethoxyphenylquinoxaline 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-2:3di-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.

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