

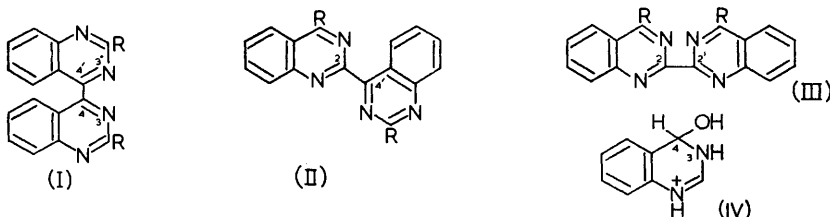
220. Quinazolines. Part VI.<sup>1</sup> 2,2'- and 4,4'-Biquinazolinyls.

By W. L. F. ARMAREGO and R. E. WILLETTE.

Quinazoline and 2-methylquinazoline react with aqueous sodium cyanide to give 4,4'-biquinazolinyl and its 2,2'-dimethyl derivative but 4-methylquinazoline does not dimerise in this way. In aqueous solution the cation of 4,4'-biquinazolinyl is predominantly hydrated across the 3,4- and 3',4'-double bonds. The cation of the 2,2'-isomer is anhydrous and this is explained by coplanarity of the molecule.

ADDITION of nucleophilic reagents such as sodium bisulphite and hydrogen cyanide<sup>2,3</sup> to quinazoline gives 3,4-dihydroquinazolinium-4-sulphonate and 4-cyano-3,4-dihydroquinazoline. We find that quinazoline reacts differently with aqueous sodium cyanide followed by gentle oxidation, to give a nitrile-free product m. p. 245—246°.\* The molecular weight, chemical analysis, and infrared spectra suggested that it was a biquinazolinyl, and we shall show that it is the 4,4'-isomer.

The ultraviolet spectrum of the neutral species in water closely resembles that of quinazoline. This spectrum is only slightly shifted at pH 0, but when the species is kept in acid the spectrum altered considerably: the peak at 321 m $\mu$  moved to 271 m $\mu$ . The spectral changes are reversed on neutralisation. Similar changes in spectrum occur with quinazoline<sup>2,4</sup> although in acid solution they take place much more rapidly. In quinazoline these were shown to be due to covalent addition of water across the 3,4-double bond in the cation.<sup>2,5</sup> The neutral species of the biquinazolinyl in water is anhydrous, for the ultraviolet spectra in water and cyclohexane are similar. Covalent addition of water in the cation was confirmed by the following experiments: (a) The spectrum in anhydrous dichloroacetic acid had a peak at 321 m $\mu$  similar to that found in the anhydrous neutral molecule but absent in the hydrated cation (cf.<sup>6</sup>). (b) Measurement of the ultraviolet spectra in solutions of increasing acid strength (decreasing water activity), after equilibration, showed that at high  $H_0$  values the spectrum of the anhydrous cation was obtained. This spectrum was stable for four hours and was very similar to that of the cation formed immediately on acidifying a solution of the neutral species (cf.<sup>1</sup>). (c) When a neutral solution was acidified, the rate of change of optical density observed at a suitable wavelength (320 m $\mu$ ) showed that hydration of the cation followed first order kinetics ( $t_{\frac{1}{2}}$  2.7 min. at 20° and pH 0.39) and was acid catalysed (cf.<sup>4</sup>). Attempts to measure the ionisation constant of the biquinazolinyl gave  $pK_a$  values of  $\sim 1$  for the anhydrous species and  $\sim 4$  for the hydrated species but the spreads were very large caused by overlapping of the  $pK_a$  values.



The biquinazolinyl has formula (I; R = H) because the other two possibilities (II; R = H) and (III; R = H) were excluded by chemical and spectroscopic evidence. Oxidation of the biquinazolinyl gave a 50% yield of 4-hydroxyquinazoline, whereas oxidation

\* T. Higashino informed us that he had prepared this compound in 1956 but did not establish its structure.

<sup>1</sup> Part V, Armarego, *J.*, 1962, 5030.

<sup>2</sup> Albert, Armarego, and Spinner, *J.*, 1961, 2689.

<sup>3</sup> Higashino, *J. Pharm. Soc. Japan.*, 1960, **80**, 245.

<sup>4</sup> Armarego, *J.*, 1962, 561.

<sup>5</sup> Albert, Armarego, and Spinner, *J.*, 1961, 5267.

<sup>6</sup> Armarego, *J.*, 1963, 4304.

of (III; R = H) would have produced 2- and/or 2,4-dihydroxyquinazoline whose properties are well known. Thus (III; R = H) was excluded by comparison with an independently synthesised specimen. As with quinazoline, 2-methylquinazoline and sodium cyanide gave a high-melting compound which behaved similarly to the product from quinazoline. 4-Methylquinazoline, however, was unchanged after 1 week of the same treatment. This observation supports formulæ (I; R = H) and (I; R = Me) for the products from quinazoline and 2-methylquinazoline, respectively, and was confirmed by nuclear magnetic resonance spectra (see below). No reaction was observed when quinazoline was kept at pH 12 (the pH equal to that of the original cyanide solution) for 4 days, proving that it was not the hydroxyl ions that brought about the condensation. The reaction may well be of the benzoin type followed by ready oxidation to the fully aromatic system. All attempts to prepare 4,4'-biquinazolinyll by reaction of 4-chloroquinazoline with copper bronze, reduction with chromous chloride, or by synthesis from *oo'*-dinitrobenzil were unsuccessful.

TABLE I.

Ultraviolet spectra of biquinazolinylls (in H <sub>2</sub> O at 20°).					
Compound	Species <sup>a</sup>	$\lambda_{\max}$ . (m $\mu$ )	log $\epsilon$	pH or $H_0$	
4,4'-Biquinazolinyll	N	223 + 245; 284; 319	4.56 + 4.17; 3.61; 3.88	— <sup>b</sup>	
	N	218 + 230; 253; 321	4.70 + 4.59; 3.95; 3.83	8	
	AC	321	3.89	-0.9 <sup>a</sup>	
	HC <sup>c</sup>	271 + 292	3.94 + 3.78	0	
2,2'-Dimethyl-4,4'-biquinazolinyll	N	215.5 + 227; 250; 322	4.81 + 4.67; 4.05; 3.88	— <sup>b</sup>	
	N	221 + 259; 280; 327	4.74 + 3.84; 3.67; 3.85	8	
	AC <sup>c</sup>	225; 317	4.51; 3.85	0	
	HC <sup>c</sup>	270.5 + 286	3.98 + 3.83	0	
2,2'-Biquinazolinyll	N	227 + 256; 300.5	4.20 + 4.78; 4.11	— <sup>f</sup>	
	N	236 + 259; 309	4.31 + 4.81; 4.09	8	
	AC	252.5; 317	4.54; 4.11	0	
4,4'-Dimethyl-2,2'-biquinazolinyll	N	250; 294	4.73; 4.18	— <sup>f</sup>	
	N	224 + 257; 308	4.23 + 4.70; 4.02	8	
	AC	238 + 267; 320	4.26 + 4.62; 4.10	0	
2,2'-Biquinolinyll	N	226.5 + 252 + 285; 302 + 312 + 324 + 339	4.23 + 4.72 + 4.88; 4.22 + 4.28 + 4.34 + 4.26	— <sup>b</sup>	
	N	256; 329	4.77; 4.27	8.3 <sup>g</sup>	
	AC	263.5 + 290 + 300; 354	4.60 + 3.84 + 3.78; 4.39	0	

<sup>a</sup> N = neutral species, HC = hydrated di-cation, AC = anhydrous di-cation. Although the  $pK_a$  values are not known, a study of the spectra at various pH values indicated that the above are almost pure species. <sup>b</sup> Cyclohexane. <sup>c</sup> After equilibrating for 1 hr. <sup>d</sup> In dichloroacetic acid. <sup>e</sup> Measured after 3 min. of mixing. <sup>f</sup> 2% Ethanol free chloroform in cyclohexane. <sup>g</sup> In 25% aqueous ethanol. Inflexions are in italics.

The large hypsochromic shifts of the ultraviolet spectra on protonation in 4,4'-biquinazolinyll (50 m $\mu$ , compare 45 m $\mu$  for quinazoline<sup>2</sup>) and 2,2'-dimethyl-4,4'-biquinazolinyll (57 m $\mu$ , compare 52 m $\mu$  for 2-methylquinazoline<sup>2</sup>) strongly indicate that the cations are predominantly hydrated (>90%) across the 3,4- and 3',4'-double bonds. A 4-methyl group in quinazoline decreases considerably the extent of hydration in the quinazoline cation;<sup>1,2</sup> an effect which was proved to be mainly steric. Hydration in the cations of (I; R = H) and (I; R = Me) is thus explained by the size of the 4-substituent whose rotational motion is restricted by the 5,5'-hydrogen atoms and the lone electron pair on N-3 and N-3', an obstruction which is greatly relieved by hydration (*i.e.*, by the carbon atoms at positions 4 and 4' becoming tetrahedral). This steric effect, which favours hydration in the cations (a nucleophilic attack at position 4) is reinforced by the strong electron attracting property of the 4-substituent.

For comparison, 2,2'-biquinazolinyll (III; R = H), and 4,4'-dimethyl-2,2'-biquinazolinyll (III; R = Me) were synthesised from the corresponding *NN'*-(di-*o*-acylphenyl)-oxanilides with alcoholic ammonia at 135–140° in high yields. In these examples also an examination of the ultraviolet spectra at various pH values indicated that the spectra of the neutral species were formed above pH 8 and the protonated species below pH 0.5, but accurate  $pK_a$  values could not be obtained because of overlap. The spectra of the neutral

species of the 2,2'-biquinazolinyls showed a band at  $\sim 260$   $m\mu$  and one at  $\sim 310$   $m\mu$  (see Table I) and protonation only caused systematic shifts of both bands, none of which was typical of quinazoline. This difference from quinazoline was not due to hydration in both the neutral species and cations because the spectrum of (III; R = H) in cyclohexane was similar to that obtained in aqueous solution. Rapid reaction techniques<sup>4</sup> confirmed that the cations were anhydrous.

The ultraviolet spectra of the 4,4'-biquinazolinyls resemble those of 1,1'-binaphthyl and 4,4'-biquinolinyl in that they are similar (except for larger  $\epsilon$  values in each case) to quinazoline, naphthalene,<sup>7</sup> and quinoline,<sup>8</sup> respectively. In binaphthyls and biquinolinyls this similarity has been attributed to restricted rotation about the 1,1'- and the 4,4'-bonds; the two halves of the molecules are not coplanar, and the two chromophores are not highly conjugated with one another and hence give a spectrum similar to each chromophore. In the latter case this was conclusively proved by resolution giving the optically active forms.<sup>8,9</sup> The neutral species of the 2,2'-biquinazolinyls also resemble those of 2,2'-binaphthyl<sup>7</sup> and 2,2'-biquinolinyl (see Table I) because they are all coplanar and in this respect are different from the above isomers. They all show an intense band in the 250—260  $m\mu$  region (and a less intense band in the 305—315  $m\mu$  region) which has been called the "conjugation band"<sup>10</sup> and in 2,2'-binaphthyl was attributed to conjugation between the two halves of each molecule through the joining bond.<sup>7</sup> It is not surprising therefore to find that 4,4'-biquinazolinyl cation is hydrated because it lacks complete conjugation, but that 2,2'-biquinazolinyl gives an anhydrous cation. Hydration across the 3,4- and 3'4'-double bonds in the latter would involve the disruption of a highly conjugated system. In contrast with the colourless 4,4'-biquinazolinyls, the 2,2'-isomers are yellow.

TABLE 2.  
Nuclear magnetic resonance spectra in  $CDCl_3$  at  $40^\circ$ .

Compound	$\delta$ -Values (p.p.m.) <sup>a</sup> for protons		
	Heterocyclic ring	Me	Aromatic
Quinazoline .....	(1) 9.51; (1) 9.37	—	(4) 8.3—7.5
Quinazoline cation <sup>b</sup> .....	(1) 8.35; (1) 6.42	—	(4) 7.7—7.2
2-Methylquinazoline .....	(1) 9.55	(3) 3.02	(4) 8.3—7.5
4-Methylquinazoline .....	(1) 9.34	(3) 2.87	(4) 8.3—7.5
2,4-Dimethylquinazoline.....	—	(3) 2.86; (3) 2.81	(4) 7.8—7.3
4,4'-Biquinazolinyl .....	(2) 9.57	—	(8) 8.3—7.5
2,2'-Dimethyl-4,4'-biquinazolinyl .....	—	(6) 3.03	(8) 8.3—7.5
2,2'-Biquinazolinyl .....	(2) 9.73	—	(8) 8.5—7.5
4,4'-Dimethyl-2,2'-biquinazolinyl .....	—	(6) 3.18	(8) 8.3—7.5

<sup>a</sup> Tetramethylsilane as internal standard. Figures in brackets indicate the integration for the number of hydrogen atoms. <sup>b</sup> In 10% trifluoroacetic acid with sodium trimethylsilylpropane sulphonate as internal standard.

*Nuclear Magnetic Resonance Spectra.*—The spectra of four quinazolines and four biquinazolinyls were measured and are recorded in Table 2. The 2- and 4-hydrogen atoms in quinazoline absorb at low field and the peaks are split ( $J = 8.4$  c/sec.). The spectrum of quinazoline in 10% trifluoroacetic acid is altered and is in agreement with the formation of the hydrated (covalent) cation (IV). One of the two peaks at low field moves upfield to  $\delta = 6.42$  p.p.m., and is undoubtedly caused by the 4-hydrogen atom whose environment has altered compared with that found in a saturated system. This provides the first direct proof of the structure of the hydrated quinazoline cation. A 4- or 2-methyl group has little effect on the chemical shift of the 2- or 4-hydrogen atom, respectively.

<sup>7</sup> Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199; Gillam and Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold, London, 1957, p. 280.

<sup>8</sup> Crawford and Smyth, *J.*, 1952, 4133.

<sup>9</sup> Bell, Morgan, and Smyth, *Chem. and Ind.*, 1951, 634.

<sup>10</sup> Bevan in "Steric Effects in Conjugated Systems," ed. Gray, Butterworths, London, 1958, p. 24.

The signal at low field ( $\delta = 9.57$  p.p.m.) in (I; R = H) is not split and integrates for 2 protons, *viz.* the 2- and 2'-hydrogen atoms, and confirms that the molecule is symmetrical. There are no other signals except for the eight "aromatic" protons of the benzene rings. In (I; R = Me) the signal at low field found in (I; R = H) is replaced by a signal at  $\delta = 3.03$  p.p.m. which integrates for six protons and is due to the 2- and 2'-methyl groups, and proves that this molecule too is symmetrical. Likewise, the 2,2'-biquinazolinyls were shown to be symmetrical. The positions of the signals could not be correlated with the electronic structure of the substituents because the positions of the signals appear to alter with changes in concentration. The insoluble nature of the biquinazolinyls in trifluoroacetic acid made spectral measurement of the cations difficult. None of the hydrogens in the compounds studied could be exchanged by deuterium after shaking the deuteriochloroform solutions with deuterium oxide for 15–30 min., although in some cases the positions of the peaks were altered slightly.

#### EXPERIMENTAL

Microanalyses were by Dr. J. E. Fildes and her staff. The purity of materials was examined as before.<sup>4</sup>

**4,4'-Biquinazolinyll.**—Sodium cyanide (11.3 g., 10 mol.) in water (45 ml.) and quinazoline (3 g., 1 mol.) in water (9 ml.) were kept at 20°. After 24 hr. the crystalline solid (3 g.) was collected, washed with water, and dried. The crude product had m. p. 198–200° (effervescence with liberation of some hydrogen cyanide). This product (2.3 g.) in boiling benzene (600 ml.) was treated with manganese dioxide<sup>11</sup> (15 g.) and kept at 20° for 24 hr. with occasional shaking. The mixture was heated to boiling again, filtered, and concentrated to 150 ml. *in vacuo* at 30°, and the needles of 4,4'-biquinazolinyll (1.3 g., 56%), m. p. 246–247°, were recrystallised from benzene [Found: C, 74.4; H, 3.9; N, 21.6%; *M* (ebullioscopic in benzene), 253. C<sub>16</sub>H<sub>10</sub>N<sub>4</sub> requires C, 74.4; H, 3.9; N, 21.7%; *M* 258]. The above crude material (120 mg.) and alumina (2 g.; B.D.H. for chromatography) in benzene (20 ml.) when treated as above gave a 33% yield of 4,4'-biquinazolinyll. The more intense infrared bands had  $\nu$  1630, 1575, 1550, 1510, 1380, 1360, 1150, 1090, 960, 775, and 760 cm.<sup>-1</sup>, and the above purification did not make significant changes in the spectrum.

**2,2'-Dimethyl-4,4'-biquinazolinyll.**—A reaction as described above but using 2-methylquinazoline gave a 48% yield of 2,2'-dimethyl-4,4'-biquinazolinyll, m. p. 219–220°, which was recrystallised from benzene–light petroleum (b. p. 40–60°) [Found: C, 75.55; H, 5.0; N, 19.6%; *M* (Rast) 291. C<sub>18</sub>H<sub>14</sub>N<sub>4</sub> requires C, 75.5; H, 4.9; N, 19.6%; *M* 286].

**Oxidation of 4,4'-Biquinazolinyll.**—The biquinazolinyll (50 mg.) in glacial acetic acid (3 ml.) and hydrogen peroxide (0.5 ml., 30 vol.) was kept at 20° for 3 days and evaporated to dryness at 30°/0.5 mm. The residue in water (3 ml.) was adjusted to pH 4 and then evaporated to dryness; the residue extracted with boiling ethanol (30 ml.), and the extract treated with charcoal, filtered, and evaporated again. The residue was extracted with benzene and filtered and the filtrate concentrated to 10 ml., diluted with light petroleum (b. p. 40–60°), and, on cooling, gave 4-hydroxyquinazoline (28 mg., 50%) which had ultraviolet and infrared spectra and m. p. and mixed m. p. identical with those of an authentic sample.

**NN'-(Di-*o*-formylphenyl)oxanilide.**—*o*-Aminobenzaldehyde<sup>12</sup> (2.42 g., 4 mol.) in dry benzene (50 ml.) was cooled and treated with oxalyl chloride (0.42 ml., 1 mol.) and kept at 20° for 3 hr. The solid was filtered off, suspended in saturated sodium hydrogen carbonate (400 ml.), stirred well, collected, washed with water, and dried at 100°. Crystallisation of the product from a large volume of acetic acid gave NN'-(*di-*o*-formylphenyl*)oxanilide (2.53 g., 86%), m. p. 314–315° (Found: C, 65.2; H, 3.9; N, 9.5. C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> requires C, 64.9; H, 4.1; N, 9.5%).

**2,2'-Biquinazolinyll.**—The above anilide (0.50 g.) and saturated ethanolic ammonia (25 ml.) were heated in a sealed tube at 135–140° for 28 hr. The yellow needles were collected and recrystallised from butan-1-ol to give 2,2'-biquinazolinyll (0.36 g., 83%), m. p. 285–286° (Found: C, 74.75; H, 3.9; N, 21.75. C<sub>16</sub>H<sub>10</sub>N<sub>4</sub> requires C, 74.4; H, 3.9; N, 21.7%); the more intense infrared bands had  $\nu$  1610, 1578, 1542, 1480, 1395, 1380, 1320, 1145, 1075, 793, 755, and 745 cm.<sup>-1</sup>

<sup>11</sup> Attenburrow, *J.*, 1952, 1094.

<sup>12</sup> Smith and Opie, *Org. Synth.*, 1955, Col. Vol. III, 56.

Similarly, 4,4'-dimethyl-2,2'-biquinazolinyll, m. p. 245—246° (compare lit.,<sup>13</sup> m. p. 249—250°), was prepared in quantitative yield from *NN'*-(di-*o*-acetylphenyl)oxanilide<sup>13</sup> (Found: C, 75.9; H, 5.3; N, 19.4. Calc. for C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>: C, 75.5; H, 4.9; N, 19.6%).

*Physical Measurements.*—Ultraviolet spectra were scanned on a Perkin-Elmer Spectracord model 4000A, and the maxima checked with an Optica manual instrument. Infrared spectra (KBr discs) were measured with a Unicam S.P. 200 spectrometer and nuclear magnetic resonance measurements were made with a Varian A 60 instrument.

We thank Professor A. Albert for most helpful discussions.

DEPARTMENT OF MEDICAL CHEMISTRY, INSTITUTE OF ADVANCED STUDIES,  
AUSTRALIAN NATIONAL UNIVERSITY, CANBERRA, AUSTRALIA. [Received, April 20th, 1964.]

<sup>13</sup> Schofield, J., 1954, 4034.

---