Spectral and Structural Correlations of 1,4- and 3,4-Dihydroquinazolines

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Alkylation of the nucleophilic addition product of 2,4-diphenylquinazoline and organometallic derivatives produced a mixture of 1,4- and 3,4-dihydroquinazoline dreivatives. The structures were established through pmr correlations of chemical shifts of the N-CH_3 groups produced when the alkylating agent was methyl iodide.

Spectra (uv, pmr) of known open-chain amidines were used to confirm the structures of the isomeric dimethyl 2,4-diphenyldihydroquinazolines. The uv spectra of 2-phenyl-3,4-dihydroquinazolines possessed an absorption maximum at 320 nm while the 1,4-dihydroanalogues had a maximum at 290 nm. Characteristic absorptions in the 1550-1650 cm^{-1} region of the infrared spectra also differentiated these two groups of compounds. Removal of the 2-phenyl substituent renders these correlations less reliable.

During a study (1) of the chemical behaviour of anionic species derived from 2,4-diphenylquinazoline (**1**), it became necessary to prepare reference samples of dihydroquinazoline derivatives with known structure. The well-known (2) propensity of quinazolines to undergo nucleophilic addition at the 3,4-double bond provided a useful starting point. Thus organometallic compounds have been shown (3) to generate 4-substituted-3,4-dihydroquinazolines. However, alkylation of the initially formed nucleophilic addition product provided two disubstituted dihydroquinazolines and the problem arose of establishing which of these was the 1,4- and which the 3,4-dihydro derivative. This report describes the spectral correlations which proved useful in resolving this question.

As an example, treatment of **1** with methyllithium provided the addition product **2** and, on subsequent protonation, the 3,4-dihydro derivative **3**. However alkylation of

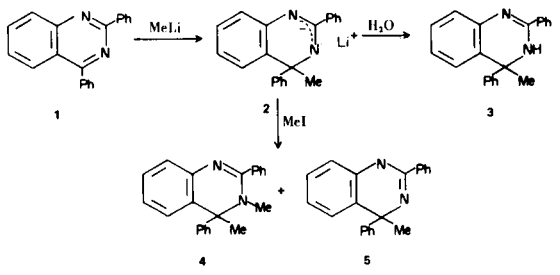
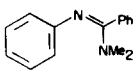
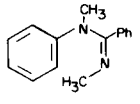
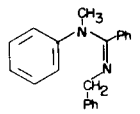


TABLE I

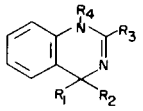
Amidines: Open-chain Analogues of Dihydroquinazolines

Compound	Spectral data (solvent) UV (Ethanol) λ max nm (log ε)	IR (Carbon Tetrachloride) cm^{-1} (assignment)	NMR (Deuteriochloroform) δ ppm (assignment)
6 	285 (sh, 3.6) 235 (4.10)	1610 (C = N) 1590 (C = C) 1390 (C - N)	2.98 (s, NMe_2) 6.4-7.4 (m, aromatics)
7 	265 (s., 3.82) 247 (sh., 3.95) 223 (4.04)	1625 (C = N) 1590, 1490 (C = C) 1345 (C - N)	3.00 (s, = NMe) 3.40 (s, NMe) 7.03, 7.20 (two s, aromatics)
8 	269 (sh., 3.87) 250 (s., 3.92) 222 (4.12)	1620 (C = N) 1500, 1600 (C = C) 1340 (C - N)	3.40 (s, NMe) 4.45 (s, CH_2) 7.03, 7.18, 7.32 (three s, aromatics)

(a) Structures are drawn to emphasize their relationships to dihydroquinazolines and do not imply stereochemical relationships.

TABLE II

Spectral Data of 1,4-Dihydroquinazolines

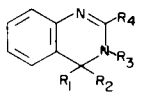


		UV (Ethanol)	Spectral data (solvent) IR (Carbon Tatrachloride)	NMR (Deuteriochloroform)
5	$R_1 = R_3 =$ Ph $R_2 = R_4 =$ Me	290 (3.70) 245 (sh., 4.0) 222 (4.24)	1630 (C = N) (a) 1600, 1580 1360 (C - N)	2.00 (s, C-Me) 3.03 (s, N-Me) 6.8-7.7 (m, aromatics)
6	$R_1 = R_2 =$ H R_3 = Ph; R_4 = Me	292 (3.56) 242 (sh., 3.98) 229 (4.02)	1635 (C = N) (a) 1600, 1590, 1580 1370 (C - N)	3.17 (s, N-Me) 4.70 (s, CH_2) 6.8-7.5 (m, aromatics)
10	$R_1 = R_3 =$ Ph R_2 = Me; $R_4 = CO_2Et$	245 (sh., 4.12) 233 (4.22)	1635 (C = N) (a) 1610, 1580 1340 (C - N) 1740 (C = O) 1220 (C - O)	2.03 (s, C-Me) 0.68 (t, CH_3CH_2) 3.77 (q, CH_3CH_2) 7-8 (m, aromatics)
14	$R_1 = R_2 =$ H $R_3 = R_4 =$ Me	278 (3.67) 219 (3.99)	1640 (C = N) (a) 1600, 1590 1365 or 1350 (C - N)	2.18 (s, C-Me) 3.27 (s, N-Me) 4.47 (s, CH_2) 6.7-7.4 (m, aromatics)
17	$R_1 = R_3 =$ Ph $R_2 = R_3 = CO_2Et$	250 (sh., 4.15) 233 (4.25)	1635 (C = N) (a) 1605, 1580 1340 (C - N) 1740 (C = O) 1230 (C - O)	0.77 (t, CH_3CH_2) 3.87 (q, CH_3CH_2) 1.20 (t, CH_3CH_2) 4.27 (q, CH_3CH_2) 7-8 (m, aromatics)

(a) Most intense absorption in the 1550-1650 cm^{-1} region.

TABLE III

Spectral Data of 3,4-Dihydroquinazoline



		UV (Ethanol)	Spectral data (solvent) IR (Chloroform)	NMR (Deuteriochloroform)
3	$R_1 = R_4 =$ Ph R_2 = Me; R_3 = H	320 (3.91) 234 (4.42)	1570 (C = C) (a) 1600, 1620 1380 (C - N)	1.97 (s, C-Me) 5.5 (broad s, NH) 6.6-8.0 (m, aromatics)
4	$R_1 = R_4 =$ Ph $R_2 = R_3 =$ Me	310-315 (3.85) 232 (4.26)	1560 (C = C) (a,b) 1590, 1610, 1615 1375 (C - N)	2.03 (s, C-Me) 2.52 (s, NH) 6.5-7.8 (m, aromatics)
11	$R_1 = R_4 =$ Ph $R_2 = R_3 =$ H	318 (3.81) 236 (4.37)	1570 (C = C) (a,b) 1600, 1630 1380 (C - N)	5.87 (s, PhC*H*) 5.0 (broad s, NH) 6.9-8.0 (m, aromatics)
12	$R_1 = R_2 = R_3 =$ H $R_4 =$ Ph	319 (3.78) 234 (4.30)	1562 (C = C) (a) 1595, 1620, 1650 1380 (C - N)	4.69 (s, CH_2) 5.62 (s, NH) 6.9-8 (m, aromatics)
13	$R_1 = R_4 =$ Ph $R_2 = R_3 = -(CH_2)_3-$	323 (3.87) 305 (sh., 3.79) 238 (4.22)	1540 (C = C) (a) 1580, 1600 1390 (C - N)	1.6-2.0 (t, CH_2) 2.5-3.0 (t, CH_2) 3.3-4.0 (m, CH_2) 7-8 (m, aromatics)
15	$R_1 =$ Ph $R_2 = R_3 = R_4 =$ H	290 (3.78) 227 (5.23)	1620 (C = N) (a) 1580, 1600 1380 (C - N)	5.87 (s, PhC*H*) 4.70 (s, NH) 7-7.6 (m, aromatics)
16	$R_1 = R_2 = R_3 =$ H $R_4 =$ Me	288 (3.73) 223 (3.98)	1600 (C = C) (a) 1585, 1625, 1670 1340 (C - N)	2.00 (s, Me) 4.62 (s, CH_2) 5.73 (s, NH) 6.8-7.4 (m, aromatics)

(a) Most intense absorption in the 1550-1650 cm^{-1} region. (b) In carbon tetrachloride.

2 with methyl iodide produced two dimethyl-2,4-diphenyldihydroquinazolines **4** and **5**. The nmr spectrum of the product mixture showed three singlets due to the methyl substituents, the largest being assigned (3) to the 4-methyl substituent of both **4** and **5**.

Prompted by the considerable difference in chemical shifts of the two N-Me groups, open-chain analogues **6** (5), **7** (6), **8** (7) (Table I) were prepared. Their nmr spectra indicated that the 1-Me (cf. **7** and **8**) of **5** should appear at a position further downfield than the 3-Me (cf. **6**) of **4**. A similar relationship has been noted in the isomeric 1-(or 3)-methyl-4-phenyl-1,2,3,4-tetrahydroquinazolines (4).

In support of the structural assignments of **4** and **5**, the uv spectra of **3** and **4** were similar in having a maximum at 315-320 nm reflecting the conjugation of two aromatic rings with the azomethine group (8). In contrast, **5** showed an absorption maximum at about 290 nm since only one aromatic ring is conjugated to the azomethine group. This relationship was examined further by means of the dihydroquinazolines **9** (9) and **10** (10) (Table II) and **11**, **12** (11) and **13** (1) (Table III). In general, 2-phenyl-3,4-dihydroquinazoline derivatives possessed a λ max at approximately 320 nm while the 2-phenyl-1,4-dihydroquinazolines showed a λ max at 290 nm.

Interestingly, the same correlation held for the open-chain analogues (Table I) although the λ max were shifted to shorter wave lengths. This shift may reflect a decrease in the coplanarity of the phenyl substituents due to the steric interference of the additional substituent on the azomethine group.

This correlation is most obvious with a 2-phenyl substituent. Removal of the aryl group as in **14** (12) (Table II), **15** (3), **16** (12) (Table III) provided compounds with absorption maxima at lower wave lengths and closer together. However, the same trend is observed, with the 3,4-dihydroquinazoline having the greater λ max.

The infrared spectra of these compounds were of particular interest. All the compounds showed a minimum of three absorption bands in the region 1620-1635, 1590-1600 and 1540-1580 cm^{-1} and occationally a fourth band was observed between the last two. All 2-phenyl-3,4-dihydroquinazolines examined showed the most intense band of this group in the 1540-1570 cm^{-1} region (C=C). In contrast, the 2-phenyl-1,4-dihydroquinazolines had the intense band at 1630-1635 cm^{-1} (C=N). The weaker bands thus appeared as side-bands on this intense absorption, their location being on opposite sides depending on whether the compound was a 1,4- or 3,4-dihydro derivative.

It is not clear whether or not this relationship depends on the 2-phenyl substituent. Thus **14** (Table II) with a 2-methyl substituent still shows a strong absorption at 1640 cm^{-1}. However, **16** with no 2-substituent, although it has a strong band at 1585 shows an even stronger one at 1600 cm^{-1}. Unfortunately, infrared data on other compounds similarly substituted is too limited to resolve this question.

Compound **17** (1) (Table II) illustrates the application of these correlations. The uv spectral correlation failed since the carbethoxy groups perturbed the absorption maxima (*e.g.*, **10**, Table II). However, the infrared spectrum showed a strong band at 1635 cm^{-1} with side bands at 1605 and 1580 clearly suggesting the 1,4-dihydroquinazoline structure shown.

EXPERIMENTAL

Melting points were determined with a Mel-temp apparatus and are uncorrected. Analyses are by MHW Laboratories, Garden City, Michigan. The spectra were recorded on Beckmann IR-10 (ir), Unicam SP-800 (uv) and Varian T-60 (nmr) instruments. The nmr spectra were determined in deuteriochloroform and are reported in ppm downfield from TMS as the internal standard (δ scale).

2,4-Diphenylquinazoline (14) was purified by distillation (b.p. 227° at 2 mm) followed by recrystallization from ethanol, white needles, m.p. 121-122°.

2-Phenylquinazoline was prepared by a published procedure (9), m.p. 100-101°.

Preparation of 2,4-Diphenyl-4-methyl-3,4-dihydroquinazoline (**3**).

A solution of 2.82 g. (0.01 mole) of **1** in 100 ml. of DEE was treated with 5.5 ml. of 2.2 *M* solution of methyllithium (Alfa Inorganics). The yellow mixture was stirred for 3 hours, then treated with 8 ml. of water and poured into cold aqueous ammonium chloride. The ether layer was separated, washed with water, dried and evaporated giving 2.88 g. of crude product. Recrystallization from benzene/petroleum ether gave 1.65 g. (55%) of **3**, m.p. 173-174°.

The analytical sample, m.p. 174-175° was obtained by recrystallization from benzene.

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.34; H, 6.02; N, 9.22.

Preparation of 3,4- and 1,4-Dimethyl-2,4-diphenyldihydroquinazoline (**4** and **5**).

The preceding reaction was repeated with 1.45 g. (0.005 mole) of **1**, 4 ml. (0.0088 mole) of a 2.2 *M* methyllithium solution. After stirring the yellow mixture for 4.5 hours, 2.0 g. (0.014 mole) of methyl iodide was added and stirring continued for another 12 hours. Water was added and the crude product (1.7 g.) isolated as described previously. The nmr showed singlets at 2.0, 2.52 and 3.03 δ in the ratio of 2.7:1:1.7.

The crude product (1.0 g.) was separated by chromatography on 60 g. of silica gel using benzene containing 0.40% diethyl ether. There was isolated 0.10 g. (10%) of **1**, 0.57 g. (60%) of **5** and 0.30 g. (30%) of **4** (% yields are corrected for the aliquot portion of crude product used).

The crude **5** was recrystallized from cyclohexane/pentane, m.p. 94.5-95.5°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.64; H, 6.33; N, 8.84.

The crude **4** was recrystallized from cyclohexane/pentane, m.p. 114-115°.

Anal. Found: C, 84.59; H, 6.24; N, 8.74.

Preparation of 2,4-Diphenyl-3,4-dihydroquinazoline (**11**).

The published procedure (3) for similar compounds was followed. Phenylmagnesium bromide (0.02 mole) in 50 ml. of DEE was treated at 0° with 2.5 g. (0.0122 mole) of 2-phenylquinazoline in 50 ml. of DEE. After stirring overnight, the reaction mixture was hydrolyzed with aqueous ammonium chloride. The ether layer was separated, washed with water, dried and evaporated. Recrystallization of the residue from 1:1 benzene:petroleum ether gave 2.1 g. (60%) of **11**, m.p. 152-154°. An analytical sample was obtained by chromatography on alumina (activity III) had m.p. 156-157°.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.22; H, 5.82; N, 9.66.

Preparation of 1-Carbethoxy-4-methyl-2,4-diphenyl-1,4-dihydroquinazoline (**10**).

A solution of 0.3 g. (0.001 mole) of **3** in 200 ml. of DEE was treated with 1.5 g. (0.014 mole) of ethyl chloroformate and the mixture stirred at room temperature for 2 days. The solution was then shaken with 10% aqueous potassium hydroxide, water and dried. Removal of the solvent gave material showing only one carbethoxy group and tlc showed only one product, **10**, in addition to **3**. Separation was effected by chromatography on silica gel using pentane-15% ether as eluent. The product, **10**, (0.10 g. 27%) was obtained as a gum which slowly crystallized from cold cyclohexane-pentane, m.p. 76-78°. Two additional crystallizations gave an analytical sample.

Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.78; H, 6.11; N, 7.42.

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