Interaction of Alkali Metals with Unsaturated Heterocyclic Compounds. 3. Quinazoline and Its 2- and 4-Phenyl Derivatives

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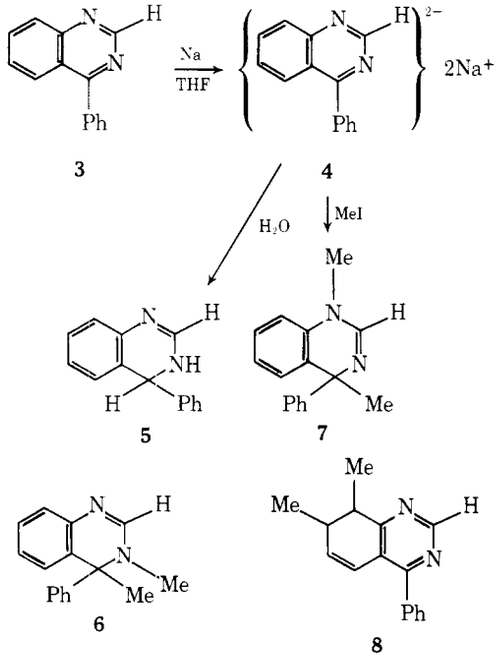
Prompted by an HMO calculation on the quinazoline radical anion which showed a high spin density in the 4 position, a study of the effect of a phenyl substituent at the 2 and 4 positions of the quinazoline nucleus upon reductive metalations of the compound was undertaken. Thus quinazoline, 2-phenyl- and 4-phenylquinazoline were reduced with sodium in tetrahydrofuran, the anionic derivatives characterized by chemical reactions, and the results compared with our earlier study of 2,4-diphenylquinazoline. 4-Phenylquinazoline formed a monomeric dianion which was characterized by protonation and alkylation (MeI). The latter reaction produced three dimethyldihydroquinazolines including one in which the alkylation had occurred in the benzo ring. Both quinazoline and 2-phenylquinazoline formed dimeric dianions which were characterized by protonation and oxidation. The dianion of 2-phenylquinazoline was examined further by alkylation (MeI) and acylation ($ClCO_2Et$). Regioselectivity was observed in these reactions and, in the case of the alkylation reactions, this was attributed to the steric effect of the 2-phenyl substituent.

Recently, the reductive metalation of 2,4-diphenylquinazoline by sodium to form a monomeric dianion has been described[1] as well as some aspects of the chemical behavior of this dianion. Since HMO calculations[2] applied to the quinazoline radical anion itself indicated that the charge density was high at the two heteroatoms while the spin density was especially high at the 4 position, the relative importance of the two phenyl substituents became of interest. It was expected that the 4-phenyl substituent would prove important in stabilizing the radical anion generated as an intermediate in the reduction while the 2-phenyl substituent would be relatively unimportant. The present report describes the results obtained in the reduction of quinazoline (**1**) and 2-phenyl- and 4-phenylquinazoline (**2** and **3**, respectively), which support these expectations.

Results

4-Phenylquinazoline (**3**) (Scheme I) in tetrahydrofuran (THF) was converted to a monomeric dianion **4** by reduction with sodium. This was established both by the amount of alkali metal which reacted and by the formation of 3,4-dihydro-4-phenylquinazoline (**5**) on protonation.

Scheme I. Reactions of the 4-Phenylquinazoline Dianion



In order to compare the chemical behavior of **4** with that of the related dianion[1] of 2,4-diphenylquinazoline, alkylation of **4** with methyl iodide was examined. As expected, both 3,4- and 1,4-dihydrodimethylquinazolines (**6** and **7**) were formed and identified by spectral correlations[3] with known analogues. However, unlike the earlier alkylation of the 2,4-diphenylquinazoline dianion, the 3,4-dihydro product **6** predominated.

A third methylation product, **8**, was isolated as well and its structure assigned on the basis of spectral data. The infrared spectrum showed absorption bands characteristic of the pyrimidine ring and the NMR spectrum showed resonances characteristic of vinyl protons while the methyl resonances appeared as doublets. Decoupling of the NMR spectrum suggested the substitution shown which is similar to that of a related product isolated elsewhere.[1]

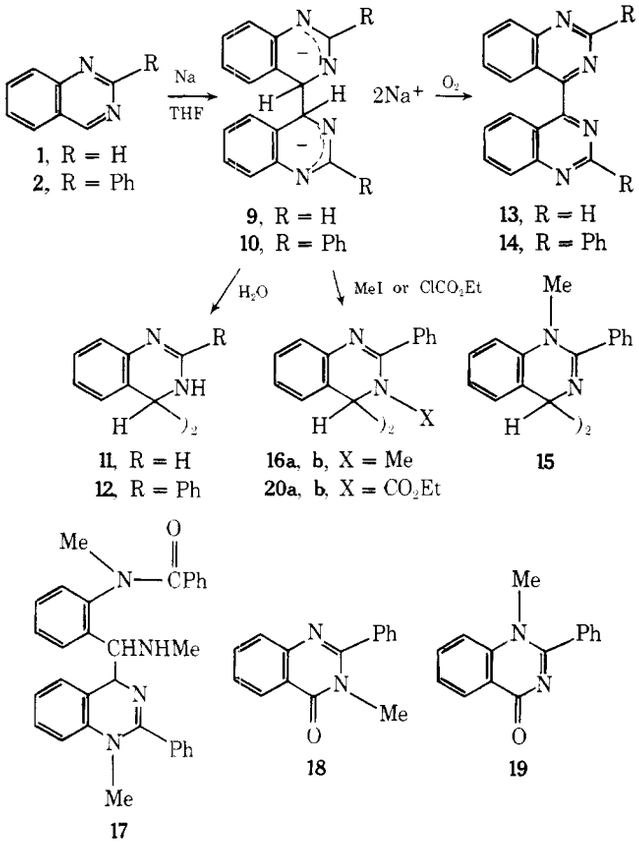
Quinazoline (**1**) and 2-phenylquinazoline (**2**) both formed dimeric dianions **9** and **10** (Scheme II) on similar reductions with sodium. Again this was indicated by the amount of alkali metal reacting and by the products formed on protonation. This last reaction produced the 4,4′-bis(3,4-dihydroquinazolinyl) derivates **11** and **12**, the former having been prepared[4] earlier by the electrochemical reduction of quinazoline.

The presence of some 3,4-dihydro-2-phenylquinazoline among the reaction products of the reductive metalation of **2** suggested that the formation of dianion **10** was not quantitative but either the radical anion or monomeric dianion of **2** was present. A similar situation has been reported for the reductive dimerization of Schiff bases[5] and, indeed, would account for the observation that predominantly one diastereomer[5,6] was formed in the dimerization of **1** and **2**.

Oxidation of the dimeric dianions **9** and **10** produced both the original quinazolines and the 4,4′-bisquinazolines **13** and **14**. Regeneration of the starting quinazoline again suggests that electron transfer from an equilibrium concentration of the monomer radical anion occurred rapidly resulting in a reversal of the dimerization. The rather favorable yield of **13** was unexpected in view of the reported failure[4] of the aromatization of **11** to **13** with alkaline ferricyanide which produced only **1**.

The chemical behavior of dianion **12** was examined further to see if any regioselective factors were operating to limit the potential formation of six isomeric–diasteromeric products. Indeed, alkylation of **12** with methyl iodide produced a complex mixture but this was, in part, due to the partial oxidation

Scheme II. Reactions of the Dimeric Dianions of Quinazoline and 2-Phenylquinazoline



of the products producing the oxoquinazoline **18** and, in one extreme case, **19**. In addition, a ring-opened alkylation product **17** was isolated. The assigned structure of **17** is compatible with the chemical shifts of the methyl groups in which the most upfield methyl was coupled to an amino hydrogen and the other two methyls have chemical shifts in agreement with model compounds.[3] The ultraviolet and infrared spectra support the assignment[3] of the 3,4-dihydroquinazoline structure.

Insofar as alkylation products were concerned, the major product was one of the diasteromeric bis(1,4-dihydroquinazolinyl) derivatives **15**; relatively small yields of the two diastereomeric bis(3,4-dihydroquinazolinyl) compounds **16a** and **16b** were isolated. Again the correlation[3] between structure and spectral properties was used in assigning structures **15** and **16**.

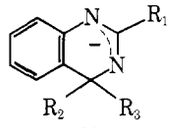
Acylation of **10** with ethyl chloroformate produced chiefly one diastereomer of the bis(3,4-dihydroquinazolyl) compound **20a**. A small yield of the second diastereomer **20b** was also obtained. Both these compounds are considered to be bis(3,4-dihydroquinazolinyl) derivatives because of the pattern of the absorption bands[3] in the 1550–1650-cm^{-1} region of the ir spectrum. In addition, a small yield of a third dimeric product, **21**, was isolated which, because of an AB quartet for the benzylic protons in the NMR spectrum, was considered to possess both a 1,4-dihydro- and 3,4-dihydroquinazolyl ring system. This assignment was supported by the ir spectrum, where bands characteristic of both ring systems were present.

Discussion

The experimental observations just described establish that a 4-phenyl substituent on a quinazoline nucleus has a profound effect on a reductive metalation while a 2-phenyl substituent does not. There are two possible explanations for this effect—either the 4-phenyl substituent prevents dimerization of the initially formed radical anion or the radical anion is sufficiently stabilized by the delocalizing effect on the 4-phenyl substituent that it can be reduced further to the monomeric dianion.

A consideration of the uv spectra of quinazoline and its phenylated derivatives is instructive. With the reservation that the compound with the greater number of phenyl substituents has the larger extinction coefficients, the spectra of 4-phenylquinazoline and quinazoline resemble one another, while that of 2-phenyl- and 2,4-diphenylquinazoline are also similar. This indicates that, while the 2-phenyl substituent is conjugated with the quinazoline ring, the 4-phenyl substituent is not, probaby owing to the interaction of the ortho protons with the proton at the 5 position. While this spectral data was obtained on the parent compounds, it is suggestive that in the case of the radical anions, it is steric rather than electronic effects which control the reductive metalation. This has been suggested earlier by Eisch[7] in cases involving the phenanthridine ring system.

Isomeric mixtures of 1,4-and 3,4-dihydroquinazolines arise by reaction of anionic species such as **21**[8] at either of the two



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heteroatoms N-1 or N-3. Kinetically, reaction should be favored at N-3 since this portion of the ambident anion resembles an aliphatic amine anion and would be expected to be more nucleophilic than the aromatic amine anionic site N-1. Thermodynamically, preference for reaction at N-3 can be anticipated as well, since in the product the double bond is conjugated with the benzo ring.

Approximately a 3:1 preference for reaction at N-3 is observed in the methylation of the 4-phenylquinazoline dianion, **4**. However, a 2-phenyl substituent reverses this regioselectivity so that a 2:1 preference for N-1 alkylation is seen both in the case of the dimeric dianion **10** and the monomeric dianion of 2,4-diphenylquinazoline.[1] This can be attributed to the steric effect of the 2-phenyl substituent which in combination with the R_2 and R_3 groups markedly slows reaction at N-3.

The regioselectivity observed in the acylation reactions cannot be considered until the possibility of rearrangement[9] of the ethoxycarbonyl group is excluded or established. Indeed, the completely opposite results obtained in the acylation of the dimeric dianion **10** and the monomeric dianion of 2,4-diphenylquinazoline[1] suggest strongly that factors additional to those mentioned in the alkylation reaction are operating.

The isolation of the benzo-alkylated product **8** is interesting in view of the earlier suggestion[1] that such products may arise by a single electron transfer (SET) mechanism with subsequent coupling of the radical anion-radical pair. Such a mechanism would be less likely for the primary halide used here than for the tertiary halide used in the earlier study. However, in the present case, two factors probably favored the SET mechanism. Firstly, the alkylation was effected at ambient temperatures which might permit electron transfer to compete with nucleophilic substitution. It is noteworthy that benzo-alkylation products were reduced markedly when the reaction temperature was reduced. Secondly an alkyl iodide was used in the present study, and these, as indicated by their half-wave reduction potentials, are particularly prone to reduction by single electron transfer.

Experimental Section

Melting points were measured with a Mel-Temp apparatus usually in open capillaries and are uncorrected. A few melting points were

determined in nitrogen-filled sealed capillaries and these are designated (St). Infrared spectra were recorded on a Beckman IR-10 spectrometer using chloroform solutions unless otherwise specified. NMR spectra were determined on a Varian T-60 spectrometer using deuteriochloroform solutions with chemical shifts reported in δ units downfield from internal tetramethylsilane. Uv spectra were recorded on a Unicam SP800 spectrophotometer and mass spectra were determined with an AEI MS-30 double beam double focusing mass spectrometer at 70 eV with perfluorokerosene in the reference beam. Analyses were performed by MHW Laboratories, Garden City, Mich.

Quinazoline[10] (mp 48–49 °C), 2-phenylquinazoline[11] (mp 99–101 °C), and 4-phenylquinazoline[12] (mp 99–100 °C) were prepared by literature procedures.

The reductive metalation of the quinazolines was effected in Schlenk tubes by procedures described earlier[13] with 100% excess of sodium and 200 ± 25 ml of tetrahydrofuran (THF) per gram of substrate and a reaction time of 24 h. The anionic derivative was drained from excess sodium into a nitrogen-filled flask for further treatment. Unless otherwise specified, reaction products were isolated by diluting the reaction mixture with water, extracting with ether, drying the extract with magnesium sulfate, and concentrating on a rotary evaporator. Column chromatography of the crude products was effected on 0.05–0.20 mm silica gel (E. Merck) or neutral alumina (E. Merck).

Preliminary experiments in which aliquot samples of the anionic reduction products were quenched in water and the inorganic base titrated showed that the reductive metalations were complete in 24 h, and that the product contained the equivalent of 2.2 g-atoms of sodium per mole of 4-phenylquinazoline (deep blue solution) and 1.2 g-atoms of sodium per mole of quinazoline (violet solution, mauve precipitate) or 2-phenylquinazoline (greenish precipitate, yellow solution).

Monomeric Dianion, 4, of 4-Phenylquinazoline (3). A. Protonation. The deep blue solution of dianion **4** prepared from 0.41 g (2 mmol) of **3** was treated at −78 °C with water. The crude product was chromatographed on alumina using chloroform to give 37 mg (9%) of **3**. Chloroform-5% methanol removed a second fraction, 0.35 g (85%) of 3,4-dihydro-4-phenylquinazoline (**5**), mp 159–164 °C. Recrystallization from acetone raised the melting point to 165–166 °C, undepressed on mixing with authentic material.[11]

B. Methylation. The dianion, **4**, prepared from 0.51 g (2.5 mmol) of 4-phenylquinazoline, was treated at 20 °C with 0.85 g (6 mmol) of methyl iodide. After 4 h, water was added and the crude product isolated and chromatographed on 15 g of silica gel.[20] Benzene–ether (1:1, 200 ml) eluted 0.24 g of a mixture whose further separation is described below. A further 100 ml of solvent removed 92 mg (16%) of 1,4-dihydro-1,4-dimethyl-4-phenylquinazoline (**7**) as an oil: NMR δ 1.87 (s, 3, CMe), 3.20 (s, 3, NMe), 6.6–7.6 (m, 10, aromatic H and H-2); ir 1650, 1480, 1445, 1050, 700 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 283 (3.81), 220 nm (4.21); mass spectrum *m/e* (rel intensity) 236 (3, M$^+$) 222 (27), 221 (100), 159 (69), 110 (14). The hydrochloride was prepared and purified by repeated precipitation from ethanol by ether, mp 252–253 °C.

Anal. Calcd for $C_{16}H_{16}N_2$·HCl: C, 70.45; H, 6.28; N, 10.27; Cl, 13.00. Found: C, 70.50; H, 6.38; N, 10.11; Cl, 13.01.

Continued elution of the column with ether–benzene (1:1, 100 ml) and finally with methanol–chloroform (1:4) gave 0.24 g (42%) of 3,4-dihydro-3,4-dimethyl-4-phenylquinazoline (**6**) as an oil: NMR δ 1.98 (s, 3, CMe), 2.72 (s, 3, NMe), 6.4–7.7 (m, 10, aromatic H and H-2); ir 1620, 1600, 1570, 1485, 1370, 695 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 228 (4.17), 233 (4.18), 297 (3.84), 312 (3.75), 328 nm (3.45); mass spectrum *m/e* (rel intensity) 236 (9, M$^+$), 222 (17), 221 (100), 159 (56). The hydrochloride was prepared and purified as in the case of **7**, mp 265–266 °C. The analytical data suggested that the salt contained solvent of crystallization.[14]

Anal. Calcd for $(C_{16}H_{16}N_2$·HCl)·$\frac{3}{4}C_2H_5OH$: C 68.39; H, 7.05; N, 9.12; Cl, 11.54. Found: C, 67.94; H, 6.91; N, 9.13; Cl, 11.88.

The first fraction isolated by column chromatography was separated by preparative thin layer chromatography on silica gel using two developments with petroleum ether–ether (2:1). The second and third bands from the origin contained the largest portion of material. The material from the second band (87 mg) was rechromatographed to give 51 mg (10%) of 4-phenylquinazoline. The material from the third band (50 mg) was purified by rechromatography on a silica gel plate to give the analytical sample of **8**: NMR[15] δ 1.15 (d, 3, J = 8 Hz, 7-Me), 1.33 (d, 3, J = 8 Hz, 8-Me), 2.0–3.3 (m, 2, H-7 and H-8), 6.0–6.23 (q, 1, H-6, $J_{5,6}$ = 11, $J_{6,7}$ = 5 Hz), 6.5–6.7 (d, 1, H-5, $J_{5,6}$ = 11 Hz), 7.3–8.0 (m, 5, aromatic H), 8.99 (s, 1, H-2); ir 2970, 1545, 1450, 1440, 1410, 940, 695 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 242 (4.28), 269 (4.24), 305 nm (sh, 3.90); mass spectrum *m/e* (rel intensity) 237 (17), 236 (69, M$^+$), 235 (57), 221 (74), 118 (100).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.85. Found: C, 81.34; H, 6.95; N, 11.70.

Performing this alkylation at −78 °C gave a product mixture containing much less of **8** as indicated by the weak aliphatic methyl resonances in the 1.1–1.3 ppm region of the NMR spectrum of the crude reaction product.

Dimeric Dianion, 9, of Quinazoline (1). A. Protonation. The dianion **9** prepared from 0.62 (4.8 mmol) of quinazoline was treated under nitrogen at −78 ° with 2 ml of water. Saturated ammonium chloride solution (10 ml) was added and the mixture was poured into 400 ml of water. The mixture was washed by decantation with four 50-ml portions of ether. Evaporation of the ether gave 54 mg of 4,4′-bisquinazoline (**13**) (9%) identified by comparison of the ir and NMR spectra with those of an authentic sample.[17]

The precipitated hydrochloride salt of **11** was isolated by filtration of the aqueous layer and dried, 0.505 g (63%), mp 295–296 °C after recrystallization from ethanol. The free base was regenerated from 223 mg of the salt by treatment with ethanolic sodium hydroxide to give 140 mg (representing 51% yield) of **11**, mp 276–277 °C (reported[4] 274 °C) having an ir spectrum identical with that of an authentic sample.[16]

B. Oxidation. The dimeric dianion **9** prepared from 0.57 g (4.4 mmol) of quinazoline was cooled to −78 °C and dry oxygen passed through the solution for 10 min. The decolorized solution was warmed to 20 °C and treated with water and the crude product (0.48 g) isolated. Recrystallization from benzene gave 0.25 g (44%) of 4,4′-bisquinazoline (**13**): mp 246–248 °C (reported[17] 246–247 °C); ir 1618, 1560, 1540, 1490, 1370, 1325 cm^{-1}; NMR agreed with that reported[17]; mass spectrum *m/e* (rel intensity) 258 (50, M$^+$), 257 (100), 129 (10), 102 (17). The filtrate from **13** was evaporated and the residue sublimed (80 °C, 0.25 Torr) to give 0.10 g (17%) of quinazoline, mp 45–47 °C, as sublimate.

Dimeric Dianion 10 of 2-Phenylquinazoline (2). A. Protonation. The dianion **10** was prepared from 0.76 g (3.7 mmol) of 2-phenylquinazoline and protonated with water. The crude product was triturated with 5 ml of ether and filtered to give 0.56 g of **12** (74%) mp 182–190 °C (St). The crude **12** was purified by preparing the hydrochloride salt (benzene, gaseous HCl) and recrystallizing this from 1:1 ethanol–ether giving 0.42 g, mp 290–295 °C. The free amine was regenerated with aqueous potassium hydroxide and recrystallized from benzene–hexane (1:3) giving 0.26 g of **12**: mp 197–198 °C (St); NMR δ 5.03 (s, 2, H-4 and H-4′), 6.3–7.0 (broad s, 2, NH), 7.1–7.4 (m, 20, H-2, H-2′, and aromatics); ir 3440 (NH), 1620 w, 1595 m, 1565 s (3,4-dihydroquinazoline pattern[3]), 1515, 1490, 1475, 1445, 690 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 325 (4.00), 305 (4.06), 235 nm (4.55).

Anal. Calcd for $C_{28}H_{22}N_4$: C, 81.14; H, 5.35; N, 1352. Found: C, 81.10; H, 5.36; N, 13.52.

The ether-soluble material from the initial treatment of the crude reaction product was separated by preparative TLC (silica gel) with benzene–pentane as developing solvent to give 42 mg of **12**, 36 mg (5%) of 3,4-dihydro-2-phenylquinazoline, and 21 mg of 2-phenylquinazoline, identified via their spectral properties.

B. Oxidation. The dianion **10** prepared from 0.51 g (2.5 mmol) of 2-phenylquinazoline was treated at −78 °C with oxygen for 25 min and then allowed to warm to 20 °C while agitated by a continuous stream of oxygen. Water was added and the crude product isolated and triturated with 20 ml of diethyl ether. The insoluble material, 78 mg (15%), mp 287–288 °C dec, was 4,4′-bis(2-phenylquinazoline) (**14**). An analytical sample was obtained by passing a benzene solution through a short column of alumina (35 g): mp 288–289 °C dec; ir (KBr) 1610, 1560, 1530, 1480, 1450, 1440, 1375, 1330, 755, 695, 675 cm^{-1}; uv (dioxane) λ_{max} (log ϵ) 267 (4.85), 336 nm (3.92); mass spectrum *m/e* (rel intensity) 410 (M$^+$, 100), 409 (100), 258 (25), 257 (47), 205 (60), 103 (32), 102 (60).

Anal. Calcd for $C_{28}H_{18}N_4$: C, 81.93; H, 4.42; N, 13.65. Found: C, 81.80; H, 4.56; N, 13.48.

The ether-soluble fraction was chromatographed on alumina (activity III) using benzene as eluent to give 0.34 g (66%) of 2-phenylquinazoline and 64 mg (12%) (eluted with chloroform–methanol) of **12**, both identified by comparison of their spectra with those of authentic samples.

C. Methylation. The dimeric dianion **10** prepared from 1.06 g (52 mmol) of 2-phenylquinazoline was treated at −78 °C with 0.74 g (52 mmol) of methyl iodide. After 1 h reaction, the solution was allowed to warm to 20 °C and stand for 24 h and the crude reaction product (1.22 g) isolated. Trituration with 10 ml of ether gave 0.59 g of insoluble material which was dissolved in 5 ml of hot benzene and precipitated with 20 ml of 80–100 °C petroleum ether. The precipitated

material (0.30 g) was chromatographed on 50 g of alumina (activity III) using benzene–chloroform (3:1) graded to chloroform to give, in order of elution, 36 mg (3%) of **16a** and 0.26 g of **15.**

The isolated **16a** was purified by precipitation from hot chloroform with petroleum ether to give an analytical sample: mp 262–265°C dec (St); NMR δ 2.8 (s, 6, NCH_3), 4.5 (s, 2, benzylic H), 6.9–7.8 (m, 18, aromatic H); ir 2940 (broad), 1590, 1550, 1530, 1480, 1400, 1170, 1060 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 240 (4.38), 312 (4.05), 323 nm (4.045); mass spectrum *m/e* (rel intensity) 442 (0.2, M^+), 441 (0.3), 222 (28), 221 (100), 206 (28), 179 (13).

Anal. Calcd for $C_{30}H_{23}N_4$: C, 81.41; H, 5.93; N, 12.66. Found: C, 81.14; H, 6.01; N, 12.42.

The isolated **15** was recrystallized from benzene–petroleum ether (1:2) to give the analytical sample: mp 221–223 °C dec (St); NMR δ 2.45 (s, 6, NCH_3), 5.15 (s, 2, benzylic H), 6.5–7.8 (m, 18, aromatic H); ir 2940 (broad), 1630, 1480, 1380, 1350, 1060 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 236 (4.39), 301 nm (3.80); mass spectrum *m/e* (rel intensity) 442 (0.3, M^+), 441 (0.5), 222 (22), 221 (76), 207 (21), 206 (100), 205 (30), 179 (55), 103 (21).

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.41; H, 5.93; N, 12.66. Found: C, 81.31; H, 5.96; N, 12.64.

The combined solvent-soluble portion of the reaction product (0.92 g) was chromatographed on 100 g of alumina (activity III) using benzene graded to benzene–chloroform (1:1) to give in order of elution 66 mg of **18** (5%), 153 mg (13%) of **17**, 148 mg (13%) of **16b**, 293 mg of an unresolved mixture, and finally 186 mg of additional **15** (total yield 39%).

The **18** was purified by recrystallization from 3:1 petroleum ether–benzene: mp 136–137 °C (reported[18,19] 136–138 and 133 °C); the NMR, ir, and uv spectra agreed with those reported[19] and the analytical data confirmed the structure; mass spectrum *m/e* (rel intensity) 236 (60, M^+), 235 (100), 118 (13).

The **17** was recrystallized from petroleum ether–25% benzene to give an analytical sample: mp 194–195 °C; NMR δ 2.70 (s in presence of D_2O, 3, $CHNHCH_3$), 3.04 (s, 3) and 3.24 (s, 3) (aryl NCH_3), 5.4 (broad s, 1, $NHCH_3$), 5.65 and 6.07 (AB q, 2, J = 10.5 Hz, benzylic H), 6.4–7.8 (m, 18, aromatic H); ir 3460 (NH), 1620 (C=O), 1480, 1370, 1060 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 238 (4.30), 292 (3.82), 312 nm (sh, 3.68); mass spectrum *m/e* (rel intensity) 474 (0.2, M^+), 473 (0.3), 253 (3), 222 (18), 221 (100), 206 (7), 118 (9), 105 (16).

Anal. Calcd for $C_{31}H_{30}N_4O$: C, 78.44; H, 6.38; N, 11.81. Found: C, 78.46; H, 6.39; N, 11.80.

The **16b** was purified by precipitation from hot chloroform with petroleum ether: mp 268–271 °C dec (St); NMR δ 2.50 (s, 6, CH_3), 4.81 (s, 2, benzylic H), 7.0–7.8 (m, 18, aromatic H); ir 2940 (broad), 1550, 1480, 1400, 1340, 1160, 1060, cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 245 (4.35), 310 (4.06), 330 nm (4.01); mass spectrum *m/e* (rel intensity) 442 (0.1, M^+), 441 (0.2), 222 (25), 221 (100), 206 (21), 179 (9), 119 (9).

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.41; H, 5.93; N, 12.66. Found: C, 81.64; H, 5.97; N, 12.61.

During the course of one methylation reaction, the reaction product was isolated with diethyl ether containing an appreciable amount of peroxide and extensive oxidation occurred. The crude product was separated into an acid soluble and an acid-insoluble fraction by extraction of a chloroform solution with aqueous sodium bisulfate. The chloroform soluble material (0.51 g) had spectral properties (NMR, ir) identical with those of **18** isolated previously.

The material recovered from the aqueous bisulfate solution by adding base and extracting with ether (0.52 g) was boiled with 10 ml of 1:1 benzene–petroleum ether. The soluble material (0.20 g had a complex NMR spectrum and was not further investigated. The insoluble material (0.215 g) was chromatographed on alumina (activity III) with benzene graded to chloroform to give 151 mg of **19.** Three recrystallizations from benzene gave a sample of mp 166–168 °C (reported[19] 165–166 °C) with ir, NMR, and uv spectra agreeing with those reported[19] and with satisfactory elemental analysis.

D. With Ethyl Chloroformate. The crude reaction product (1.38 g) from the dimeric dianion generated from 1.04 g (5 mmol) of 2-phenylquinazoline and 0.85 g (7.8 mmol) of ethyl chloroformate was heated with 30 ml of diethyl ether. After cooling, the insoluble solid, **20a,** was filtered and dried, 0.76 g (54%), mp 243–244 °C. Recrystallization from ethanol gave an analytical sample: mp 244–245 °C; NMR δ 0.73 (t, 6, J = 7 Hz, CH_2CH_3), 3.4–4.2 (m, 4, CH_2CH_3), 5.34 (s, 2, benzylic H), 6.0–8.4 (m, 18, aromatic H); ir 1730 (C=O), 1600, 1570, 1380, 1340, 1250 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 225 (4.35), 231 (4.35), 240 (4.33), 266 (4.28), 310 nm (4.28); mass spectrum *m/e* (rel intensity) 558 (0.1 M^+), 280 (20), 279 (100, $M^+/2$), 235 (67), 207 (71), 206 (31).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03. Found: C, 73.36; H, 5.48; N, 10.06.

The ether was evaporated from the ether-soluble products and the residue (0.58 g) treated with 3 ml of ether. The insoluble material, 0.12 g, mp 182–190 °C, consisted of 14% **20a** and 86% **20b** (by NMR) (7% yield of **20b**). Two recrystallizations from ethanol gave an analytical sample: mp 198–199 °C; NMR δ 0.73 (t, 6, J = 6 Hz, CH_2CH_3), 3.90 (q, 4, J = 6 Hz, CH_2CH_3), 5.46 (s, 2, benzylic H), 6.7–8.0 (m, 18, aromatic H); ir (CCl_4) 1730 (C=O), 1600, 1560, 1380, 1330, 1260, 690 cm^{-1}; uv (EtOH) λ_{max} (log ϵ) 231 (4.37), 242 (4.36), 266 (4.23), 317 nm (4.22); mass spectrum *m/e* (rel intensity) 558 (0.1, M^+), 280 (23, 279 (100, $M^+/2$), 208 (14), 207 (91), 206 (25).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10, H, 5.41; N, 10.03. Found: C, 72.97; H, 5.16; N, 10.28.

The ether filtrate from the impure **20b** was evaporated and the residue (0.37 g) was chromatographed on 50 g of silica gel using 30–60 °C petroleum ether–20% diethyl ether as eluting solvent and collecting the eluent in 20-ml fractions. Fractions 34–41 (128 mg) were crystallized from 2 ml of hot ethanol to give 16 mg of **20b,** mp 195–198 °C, undepressed on mixing with an authentic sample. The filtrate was evaporated and the residue (93 mg) recrystallized from 30–60 °C petroleum ether to give 73 mg (5% yield) of "unsymmetrically acylated dimer", **21**: mp 117–121 °C; NMR δ 0.87 and 0.95 (two t, J = 7 Hz, 6, CH_2CH_3), 3.4–4.4 (m, 4, CH_2CH_3), 5.02 and 5.44 (AB q, J = 10 Hz, 2, CHCH), 6.1–8.4 (m, 18, aromatic H); ir 1730 (C=O), 1640, 1590, 1570 (1,4- and 3,4-dihydroquinazolinyl bands), 1370, 1250 cm^{-1}; uv (MeOH) λ_{max} (log ϵ) 241 (4.45), 314 nm (4.05); mass spectrum *m/e* (rel intensity) 280 (31), 279 (63), 236 (21), 235 (69), 208 (21), 207 (100), 206 (25), 205 (15), 179 (18), 129 (20).

Anal. Calcd for $C_{34}H_{30}N_4O_4$: C, 73.10; H, 5.41; N, 10.03. Found: C, 73.27; H, 5.43; N, 10.06.

Fractions 42–50 from the chromatography (112 mg) contained additional **21** but its isolation could not be effected.

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Registry No.—**1,** 253-82-7; **2,** 25855-20-3; **3,** 17629-01-5; **4,** 60621-22-9; **5,** 1904-72-9; **6,** 60538-79-6; **6** HCl, 60538-80-9; **7,** 60538-81-0; **7** HCl, 60538-82-1; **8,** 60538-83-2; **9,** 60538-84-3; **10,** 60538-85-4; **11,** 60662-04-6; **11** HCl, 60538-86-5; **12,** 60662-05-7; **12** HCl, 60538-87-6; **13,** 963-80-4; **14,** 60538-88-7; **15,** 60538-89-8; **16a,** 60538-90-1; **16b,** 60538-91-2; **17,** 60538-92-3; **20a,** 60538-93-4; **20b,** 60538-94-5; **21,** 60538-95-6; methyl iodide, 74-88-4; ethyl chloroformate, 541-41-3.

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