[Chem. Pharm. Bull. 28(7)2024—2028(1980)]

Cyclic Guanidines. XI.[1] Hydroxy and Aminoimidazo[2,1-*b*]-quinazolines and Related Compounds

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(Received January 5, 1980)

The Phenyl-substituted 1-methyl tricyclic guanidine (**1**) having an imidazo- or pyrimido-[2,1-*b*]quinazoline ring was easily oxidized at the methine group adjacent to the aromatic rings to give the 5-hydroxy- or 6-hydroxy derivative (**2**), respectively. Reaction of 2-aminobenzophenone with 2-chloro-2-imidazoline gave the 1-unsubstituted 5-hydroxyimidazo[2,1-*b*]quinazoline derivative (**5**). The structures of compounds **2** and **5** are discussed. 1-Hydroxy- (**13**) and 1-amino tricyclic guanidines (**16**) were prepared by the reaction of 2-chloro-3-(2-chloroethyl)-4-phenyl-3,4-dihydroquinazoline with hydroxylamine and hydrazine, respectively.

Compounds **2**, **5** and **13** showed hypoglycemic and platelet aggregation inhibitory activity.

Keywords——oxidation with benzoyl peroxide; 1- or 5-hydroxyimidazo[2,1-*b*]-quinazoline derivatives; 1-aminoimidazo[2,1-*b*]quinazoline derivative; tautomeric forms; hypoglycemic activity

Recently, a new preparation method for cyclic tri- and tetrasubstituted N-hydroxyguanidines by means of a ring formation procedure was reported.[3] The reaction of 2-phenyliminoimidazolidine with peracid also gave the corresponding N-hydroxy derivative.[4] These results prompted us to study oxidation reactions of the previously reported hypoglycemic tricyclic guanidines[5] (**1** and **4**) and to prepare their N-hydroxy and N-amino derivatives.

In an attempt to prepare N-oxides of 1-methyl-5-phenylimidazoquinazoline[5] (**1a**) and 1-methyl-6-phenylpyrimidoquinazoline[5] (**1b**), we found that treatment of **1a**, **b** with hydrogen peroxide or 3-chloroperbenzoic acid in various solvents did not give any oxidized products; the starting materials were recovered. Reaction of **1a**, **b** with benzoyl peroxide in chloroform afforded the 5- and 6-hydroxy derivatives[6] (**2a**, **b**), respectively, which showed that the oxidation took place at the methine group adjacent to the phenyl ring. Similar results were recorded in the oxidations of 1-methyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline[7] and tricyclic isoindoline.[8]

The oxidation of 1-unsubstituted tricyclic guanidine[5] (**4**) with benzoyl peroxide was attempted, but the expected 5-hydroxy imidazoquinazoline (**5**) was not formed. This compound (**5**) was prepared, however, by the reaction of 2-aminobenzophenone (**9**) with 2-chloro-2-imidazoline.[9] The hydroxyl groups of the above compounds (**5**, **2a**, **b**) were convertible into ethoxy groups (**7**, **8a**, **b**) by heating in ethanol.

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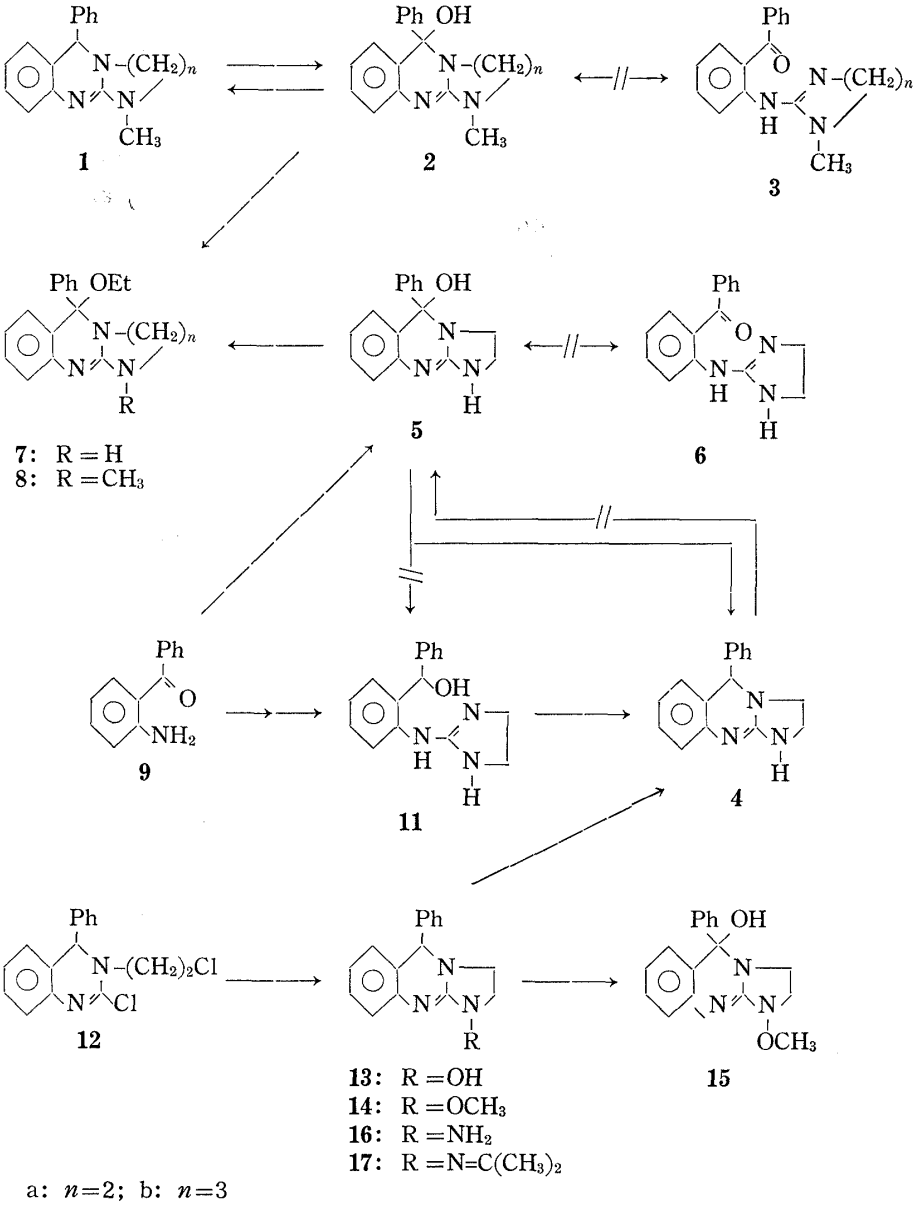

Chart 1

Metresics *et al.*[8] reported that the oxidized condensation product of 2-benzoylbenzaldehyde and ethylenediamine takes two tautomeric forms, 2-(2-imidazolin-2-yl)benzophenone and 5-phenyl-2,3-dihydro-5H-imidazo[2,1-*b*]isoindol-5-ol, in solution. On the other hand, Barcza *et al.*[10] reported that the compound obtained from 4-chlorobenzoylbenzaldehyde and ethylenediamine exists only in the ring-closed carbinolamine form both in solution and in the solid state. Therefore, it is of interest to determine the tautomeric forms of **5** and **2** in solution and in the solid state.

Catalytic hydrogenation of **5** with palladium-charcoal (Pd–C) in an acidic medium gave compound **4**[5] which was also obtained by chlorination of **11** followed by treatmnet with sodium hydroxide. If **5** has the benzophenone structure, the reduction product must be **11**, which was prepared by the reaction of 2-aminobenzhydrol (**10**) with 2-chloro-2-imidazoline. Similar results were obtained in the reduction of **2**. Hence, **2** and **5** have the ring-closed structures.

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These structures of **2** and **5** are consistent with their spectral data. The main absorption bands in the IR spectra of **2** and **5** were similar to those of **8** and **7**, respectively. The UV absorption curves of **2** and **5** were also similar to those of **8** and **7**, respectively. In the NMR spectra of **2a** and **5**, the methylene protons at C-2 and C-3 were observed at δ 2.9—3.7 as multiplet signals, differing from the singlet signal (δ 3.40) of the imidazoline ring of **11**. In the MS of 5, the main fragment ions were *m/e* 245 (100%, [M–H_2O–H_2]) and 172 (60%, [M–OH–C_6H_5]), but the molecular ion was not observed. On the other hand, the main peaks of **2a** were *m/e* 279 (65%, [M]), 262 (100%, [M–OH]), and 186 (85%, [M–OH–C_6H_5]). These frgments represent loss of the substitutents at C-5 in **5** and **2a**, respectively, and are compatible with the carbonylamine formula. As decribed above, the structures of **2** and **5** are ring-closed forms, not the ring-opened ones (**3** and **6**), both in solution and in the solid state.

Since the oxidation of tricyclic guanidine derivatives with peracid cannot occur on the nitrogen atoms, an alternative method for the preparation of the N-hydroxide was sought. Reaction of 2-chloro-3-(2-chloroethyl)-4-phenyl-3,4-dihydroquinazoline[5] (**12**) with hydroxylamine gave the 1-hydroxy derivative (**13**), which was alkylated with methyl iodide to give the 1-methoxy derivative (**14**). Catalytic hydrogenation of **13** yielded the 1-unsubstituted derivative (**4**). Compound **4** was also obtained by reaction of **14** with zinc in acetic acid. Treatment of **14** with benzoyl peroxide gave the 5-hydroxy derivative (**15**). Reaction of **12** with hydrazine in ethanol afforded the 1-aminotricyclic guanidine (**16**), from which, on treatment with acetone, the 1-isopropylideneamino derivative (**17**) was obtained.

Compounds **2a**, **b**, **5** and **13** showed hypoglycemic activity in normal fasted rats. Compound **5** also inhibited platelet aggregation induced by collagen in rats *in vitro*.

Experimental

All melting points are uncorrected. IR spectra were recorded with a Hitachi 285 spectrometer. UV spectra were taken with a Hitachi 323 spectrometer. MS were determined on a JEOL OISG-2 mass spectrometer. NMR spectra were taken with Hitachi Perkin-Elmer R-20B (60 MHz) and Varian EM-360 (60 MHz) spectrometers with tetramethylsilane as an internal standard (δ value). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. For column chromatography, silica gel (Merck, 0.05—0.2 mm) was used.

5-Hydroxy-1-methyl-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**2a**)——Benzoyl peroxide (2.60 g, 11 mmol) was added to a solution of 2.60 g (10 mmol) of **1a** in 20 ml of $CHCl_3$ in an ice bath. The mixture was allowed to stand at room temperature for 6—8 hr. The red reaction mixture was washed with saturated $NaHCO_3$ solution and water, dried, and concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$–Me_2CO to give 1.80 g (56%) of **2a**, mp 198—199°. IR ν_{max}^{KBr} cm^{-1}: 1620, 1590, 1565, 1490, 1470, 1440, 1280, 1015. UV λ_{max}^{EtOH} nm (ε): 273 (15800), $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 250 (34800), $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 272 (15700). NMR (CF_3CO_2H) δ: 7.8—8.7 (9H, m, aromatic protons), 5.0, 4.5 (2H×2, m, CH_2), 3.74 (3H, s, CH_3). MS *m/e* (int.): 279 (55, M), 263 (26), 262 (100), 261 (29), 260 (31), 201 (58), 186 (85), 184 (36), 77 (35). *Anal.* Calcd for $C_{17}H_{17}N_3O$–$0.5H_2O$: C, 70.81; H, 6.25; N, 14.57. Found: C, 70.96; H, 6.06; N, 14.40.

6-Hydroxy-1-methyl-6-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[2,1-*b*]quinazoline (**2b**)——Following the procedure for the preparation of **2a**, treatment of 0.55 g (2 mmol) of **1b** in 5 ml of $CHCl_3$ with 0.53 g (2.2 mmol) of benzoyl peroxide gave 0.36 g (63%) of **2b**, mp 193—195° ($CHCl_3$–Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 1540, 1500, 1475, 1440, 1400, 1005. UV λ_{max}^{EtOH} nm (ε): 284 (15900), $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 251 (28500), $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 280 (19000). NMR (CF_3CO_2H) δ: 7.6—8.6 (9H, m, aromatic protons), 4.5, 4.0 (2H×2, m, N–CH_2), 2.5 (2H, m, CH_2). MS *m/e* (int.): 293 (64, M), 277 (71), 276 (84), 248 (45), 216 (64), 200 (100), 172 (37), 77 (42). *Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.50; H, 6.24; N, 14.43.

Reduction of 5-Hydroxy-1-methyl-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**2a**)——Compound **2a** (0.29 g, 1 mmol) in a mixture of 1 ml of conc. HCl, 5 ml of H_2O and 10 ml of EtOH was hydrogenated over 0.1 g of 10% Pd-C at room temperature under atmospheric pressure. When hydrogen absorption had ceased the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was treated with 10% NaOH solution and the solid separated was filtered, washed with H_2O and MeOH to give 0.23 g (88%) of **1a**.[5] MS *m/e* (int.): 264 (15), 263 (62, M), 220 (19), 187 (21), 186 (100), 77 (6).

Reduction of 6-Hydroxy-1-methyl-6-phenyl-1,2,3,4-tetrahydro-6H-pyrimido[2,1-*b*]quinazoline (**2b**)——Following the procedure for the reduction of **2a**, compound **2b** (0.29 g, 1 mmol) in a mixture of HCl–aq. EtOH was hydrogenated over 10% Pd-C to give 0.24 g (88%) of **1b**.[5] MS *m/e* (int.): 278 (30), 277 (97, M), 201 (32), 200 (100), 172 (61), 77 (14).

5-Phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (4)——A solution of 10 g (33 mmol) of **11** in 50 ml of conc. HCl was heated at 85° for 3 hr with stirring, then poured into ice-cold 10% NaOH solution. The mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give 5.80 g (70%) of **4**,[5] mp 277—278° (dec.) (EtOH), which was identical with a sample reported previously.[5]

5-Hydroxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (5)——2-Chloro-2-imidazoline sulfate[10] (7.20 g, 36 mmol) was added to a solution of 4.3 g (0.108 mol) of NaOH in 80 ml of H_2O. The mixture was extracted with $CHCl_3$ and the extract was dried over Na_2SO_4. After removal of the Na_2SO_4 by filtration, 4.70 g (24 mmol) of **9** was added to the filtrate. The mixture was allowed to stand at room temperature overnight. After removing the precipitate, the filtrate was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with Et_2O to remove unreacted **9**. The water layer was neutralized with 10% NaOH solution and the precipitate was collected and recrystallized from iso-PrOH to give 2.80 g (44%) of **5**, mp 203—204°. IR ν_{max}^{KBr} cm^{-1}: 1640, 1590, 1570, 1490, 1470, 1440, 1280, 1015. UV λ_{max}^{EtOH} nm (ε): 273 (15400), $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 244 (26900), $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 268 (15600). NMR (DMSO-d_6) δ: 6.65—7.6 (9H, m, aromatic protons), 2.9—3.7 (4H, m, CH_2). MS *m/e* (int.): 249 (28), 248 (15), 247 (36), 246 (54), 245 (100), 244 (59), 172 (60), 170 (14), 77 (12). *Anal.* Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.20; H, 5.71; N, 15.62.

Reduction of 5-Hydroxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (5)——Following the procedure for the reduction of **2a**, compound **5** (0.53 g, 2 mmol) in a mixture of HCl–aq. EtOH was hydrogenated over 10% Pd-C to give 0.47 g (83%) of the hydrochloride of **4**. MS *m/e* (int.): 250 (10), 249 (51, M), 248 (15), 172 (100).

5-Ethoxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (7)——A solution of 0.30 g (1.13 mmol) of the free base of **5** in 20 ml of EtOH was heated under reflux for 2 hr and concentrated *in vacuo* to give 0.29 g (88%) of **7**, mp 183—184° (EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1640, 1590, 1565, 1490, 1470, 1450, 1440, 1280, 1045. UV λ_{max}^{EtOH} nm (ε): 272 (16200), $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 244 (25400), $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 268 (16000). NMR ($CDCl_3$) δ: 6.6—7.7 (9H, m, aromatic protons), 2.9—3.6 (6H, m, CH_2), 1.13 (3H, t, CH_3). MS *m/e* (int.): 293 (6, M), 249 (22), 248 (100), 247 (40), 246 (69). *Anal.* Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.33. Found: C, 73.49; H, 6.55; N, 14.15.

Compounds **8a, b** were prepared similarly from **2a, b**, respectively. The physical data for **8a, b** are as follows.

(**8a**)——Yield 72%, mp 94—95° (EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1630, 1590, 1565, 1470, 1440, 1280, 1045. UV λ_{max}^{EtOH} nm (ε): 274 (16200), $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 250 (32800), $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 272 (16000). NMR ($CDCl_3$) δ: 6.75—7.7 (9H, m, aromatic protons), 2.9—3.5 (6H, m, CH_2), 3.04 (3H, s, CH_3), 1.16 (3H, t, CH_3). MS *m/e* (int.): 307 (13, M), 263 (25), 262 (100). *Anal.* Calcd for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.44; H, 6.71; N, 13.66.

(**8b**)——Yield 76%, mp 139—141° (EtOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1540, 1500, 1470, 1410, 1060. UV λ_{max}^{EtOH} nm (ε): 284 (16000), $\lambda_{max}^{0.1N\ HCl}$ nm (ε): 251 (26000), $\lambda_{max}^{0.1N\ NaOH}$ nm (ε): 280 (18800). NMR ($CDCl_3$) δ: 6.65—7.7 (9H, m, aromatic protons), 2.85—3.4 (6H, m, CH_2), 3.22 (3H, s, CH_3), 1.55—2.05 (2H, m, CH_2), 1.17 (3H, t, CH_3). MS *m/e* (int.): 321 (22, M), 277 (25), 276 (100), 248 (26). *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.73;H, 7.21; N, 13.07. Found: C, 74.43; H, 7.07; N, 12.79.

2-[2-(α-Hydroxybenzyl)phenylamino]imidazoline Hydrochloride (11)——Compound **10** (9.00 g,45 mmol) was added to a solution of 2-chloro-2-imidazoline prepared from 9.0 g (45 mmol) of the sulfate. The mixture was stirred for 8 hr. The resulting precipitate was collected and recrystallized from EtOH–H_2O to give 9.3 g (70%) of **11**, mp 215—218°. IR ν_{max}^{KBr} cm^{-1}: 3250, 1655, 1600. NMR (DMSO-d_6) δ: 7.1—7.8 (4H, m, aromatic protons), 7.30 (5H, s, C_6H_5), 6.03 (1H, s, CH), 3.40 (4H, s, CH_2). *Anal.* Calcd for $C_{16}H_{18}ClN_3O$: C, 63.26; H, 5.97; N, 13.99. Found: C, 63.19; H, 5.88; N, 13.99.

1-Hydroxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (13)——Sodium methoxide (5.4 g, 0.1 mol) was added to a solution of 6.95 g (0.1 mol) of H_2NOH–HCl in 100 ml of MeOH and the resulting precipitate was filtered off. Compound **12** (3.05 g, 10 mmol) was added to the filtrate and the mixture was heated under reflux for 10—15 min. After cooling, the mixture was made alkaline with 10% NaOH solution and concentrated *in vacuo*. The residue was mixed with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give 1.70 g (64%) of **13**, mp 211—212° (MeOH). IR ν_{max}^{KBr} cm^{-1}: 3100—2400, 1630, 1590, 1475. NMR (DMSO-d_6–CF_3CO_2H) δ: 7.38 (5H, s, C_6H_5), 6.8—7.4 (4H, m, aromatic protons), 3.0—3.8 (4H, m, CH_2). MS *m/e* (int.): 266 (21), 265 (91, M), 249 (48), 247 (42), 246 (25), 245 (38), 244 (38), 188 (97), 172 (100), 171 (55), 170 (76). *Anal.* Calcd for $C_{16}H_{15}N_3O$–$0.5H_2O$: C, 70.05; H, 5.88; N, 15.32. Found: C, 70.29; H, 5.59; N, 15.06.

Reduction of 1-Hydroxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (13)——Compound **13** (0.53 g, 2 mmol) in a solution of 1 ml of conc. HCl, 5 ml of H_2O and 20 ml of EtOH was hydrogenated over 0.1 g of 10% Pd-C under atmospheric pressure. The reaction mixture was worked up as usual to give 0.24 g (48%) of **4**.

1-Methoxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (14)——NaH (50% oil suspension) (0.20 g, 4 mmol) was added to a solution of 0.53 g (2 mmol) of **13** in 10 ml of DMF and the mixture was stirred at room temperature for 30 min. MeI (0.56 g, 4 mmol) was added to the mixture, and the whole was

stirred at room temperature for 1 hr. The mixture was poured into ice-water and extracted with benzene. The extract was washed with H_2O, dried, and concentrated *in vacuo* to give 0.43 g (77%) of **14**, mp 174—175° (Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 1635, 1590, 1475. NMR ($CDCl_3$) δ: 7.35 (5H, s, C_6H_5), 6.6—7.3 (4H, m, aromatic protons), 3.98 (3H, s, CH_3), 3.5, 3.0 (2H×2, m, CH_2). *Anal.* Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 73.21; H, 6.21; N, 15.11.

Reduction of 1-Methoxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (14)——A mixture of 0.28 g (1 mmol) of **14** and 0.58 g of Zn powder in AcOH was stirred at room temperature for 1 hr then concentrated *in vacuo*. The residue was mixed with H_2O and insoluble material was filtered off. The filtrate was made alkaline with 10% NaOH solution and the resulting precipitate was collected to give 0.15 g (60%) of **4**.

5-Hydroxy-1-methoxy-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (15)——Following the procedure for the synthesis of **2a**, 0.28 g (1 mmol) of **14** in 5 ml of $CHCl_3$ was treated with 0.33 g (1.25 mmol) of benzoyl peroxide to give 0.17 g (58%) of **15**, mp 191—192° (dec.) ($CHCl_3$–Me_2CO). IR ν_{max}^{KBr} cm^{-1}: 1640, 1635, 1475. NMR ($CDCl_3$) δ: 6.7—7.5 (9H, m, aromatic protons), 3.87 (3H, s, CH_3), 3.2—3.7 (4H, m, CH_2). *Anal.* Calcd for $C_{17}H_{17}N_3O_2$–$0.5H_2O$: C, 67.09; H, 5.96; N, 13.81. Found: C, 67.35; H, 5.76; N, 13.98.

1-Amino-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (16)——A mixture of 3.05 g (10 mmol) of **12** and 2.0 g (40 mmol) of hydrazine hydrate in 40 ml of EtOH was heated under reflux for 4 hr. After cooling, the reaction mixture was made alkaline with 10% NaOH solution and concentrated *in vacuo*. The residue was mixed with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo* to give 2.00 g (76%) of **16**, mp 143—145° (MeOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3340, 1630, 1590. NMR ($CDCl_3$) δ: 6.7—7.3 (4H, m, aromatic protons), 7.30 (5H, s, C_6H_5), 5.43 (1H, s, CH), 3.0—3.4 (4H, m, CH_2), 4.25 (2H, br s, NH_2). *Anal.* Calcd for $C_{16}H_{16}N_4$: C, 72.21; H, 6.10; N, 21.20. Found: C, 72.46; H, 6.14; N, 20.92.

1-Isopropyrideneamino-5-phenyl-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (17)——A solution of 0.50 g (1.9 mmol) of **16** in 10 ml of Me_2CO was heated under reflux for 2 hr, then concentrated *in vacuo*. The residue was chromatographed on silica gel (15 g). The eluate with $CHCl_3$ was collected to give 0.42 g (73%) of **17** as an oil. IR ν_{max}^{Neat} cm^{-1}: 1620, 1580, 1560, 1470. NMR ($CDCl_3$) δ: 6.6—7.2 (4H, m, aromatic protons), 7.73 (5H, s, C_6H_5), 5.44 (1H, s, CH), 3.4, 3.1 (2H×2, m, CH_2), 2.18 (3H, s, CH_3), 2.11 (3H, s, CH_3). *Anal.* Calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 74.72; H, 6.89; N, 18.27.

Acknowledgement The authors are grateful to Drs. Y. Abiko and S. Ashida, Messrs. K. Kameda and S. Ono, and Miss K. Sakuma for carrying out biological assays. Thanks are also due to the staff of this Institute for elemental analysis.