# A Palladium-Catalyzed Carbonyl Insertion Route to Pyrido[2,1-*b*]quinazoline Derivatives

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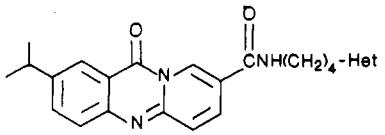
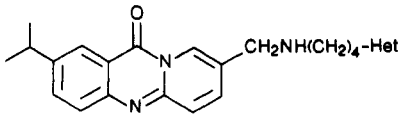
A synthesis of 8-substituted pyrido[2,1-*b*]quinazoline derivatives is described involving as the key step the palladium-catalyzed carbonyl insertion reaction of 5-substituted 2-(2-bromoanilino)pyridines. This methodology provides a new and flexible route to the pyrido[2,1-*b*]quinazoline and related ring systems.

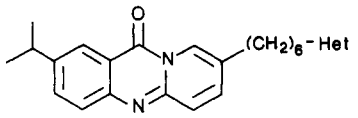
We have recently described the preparation and antiallergy activity of a series of *N*-[(heteroaromatic)alkyl]-pyrido[2,1-*b*]quinazoline-8-carboxamides.[1] Structure–activity studies indicated that the pyridine- and imidazole-substituted derivatives **1a** and **1b** were the most interesting of these agents, and **1a** was selected for in-depth evaluation. The necessity of producing large amounts of **1a** while simultaneously carrying out the synthesis of a wide range of analogues prompted a search for a more general and efficient route to this class of compounds. Of particular interest in this regard were the analogues **2** and **3**, which were not readily available by the previously reported route.[1] In the work detailed below, we describe a carbonyl insertion process that provides a new and convenient access to pyrido[2,1-*b*]quinazoline derivatives and illustrate its utility with the preparation of **1a**, **2**, and **3**.




**1a,b**




**2a,b**



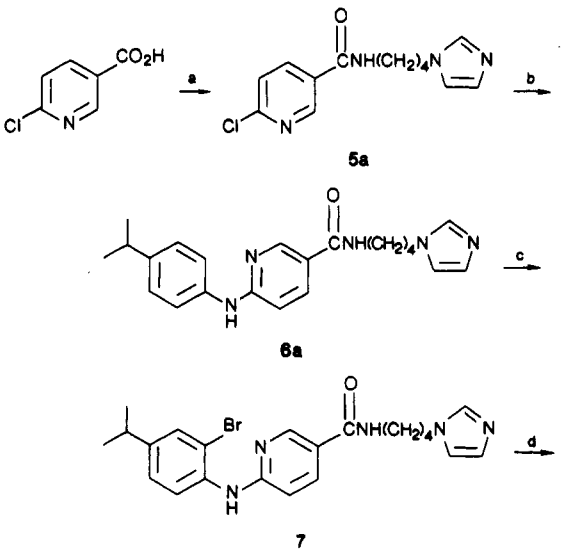

**3a,b**

a series, Het = 

b series, Het = 

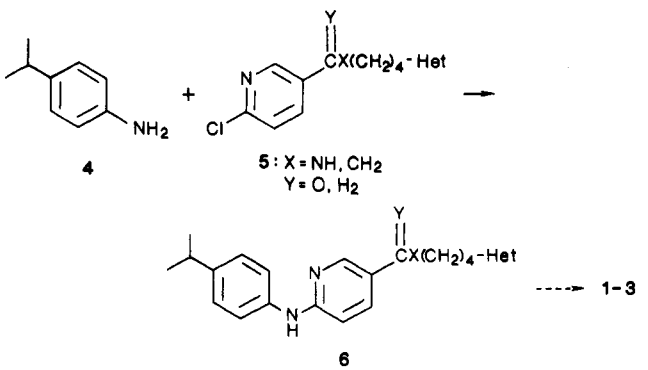
Previous routes to pyrido[2,1-*b*]quinazolines have involved reaction between an anthranilic acid derivative and a 2-halopyridine and generally proceed in satisfactory yields only when the pyridines are activated by additional electron-withdrawing groups.[2-5] The shortcomings of this process reflect the fact that anthranilic acids are poor nucleophiles. We therefore considered an approach based on the condensation of 4-isopropylaniline (**4**) with various 2-chloropyridinyl derivatives **5** in which the required side chains were already elaborated. The synthetic plan then called for insertion of a carbonyl group into the product **6** and ring closure.

Scheme I[a]




[a] (a) $SOCl_2$, then (1*H*-imidazol-1-yl)butanamine; (b) **4**, heat; (c) $Br_2$, HOAc; (d) CO, DMF, water, $Ph_3P$, $(Ph_3P)_2PdCl_2$, $Bu_3N$.

While these condensations proved eminently feasible with Y = O leading ultimately to **1a**, the reactions with Y = H that would lead to **2** and **3** were not clean and the products (**6**, Y = H) were oils, which proved dificult to purify. Thus, for the latter target compounds, we adopted an alternative approach that would allow introduction of the basic side chain later in the synthesis.




Accordingly, we developed the synthesis of **1a** illustrated in Scheme I and adapted it to the preparation of **2** as

(1) Tilley, J. W.; Levitan, P.; Lind, J.; Welton, A. F.; Crowley, H. J.; Tobias, L.; O'Donnell, M. *J. Med. Chem.* **1987**, *30*, 185.
(2) Reissert, A. *Chem. Ber.* **1895**, *28*, 119.
(3) Spaeth, E.; Kuffner, F. *Chem. Ber.* **1938**, *71*, 1657.
(4) Schwender, C. F.; Sunday, B.; Herzig, D. J.; Kusner, E. K.; Schumann, P. R.; Gawlak, D. L. *J. Med. Chem.* **1979**, *22*, 748.
(5) Tilley, J. W.; LeMahieu, R. A.; Carson, M.; Kierstead, R. W.; Baruth, H. W.; Yaremko, B. *J. Med. Chem.* **1980**, *23*, 92.

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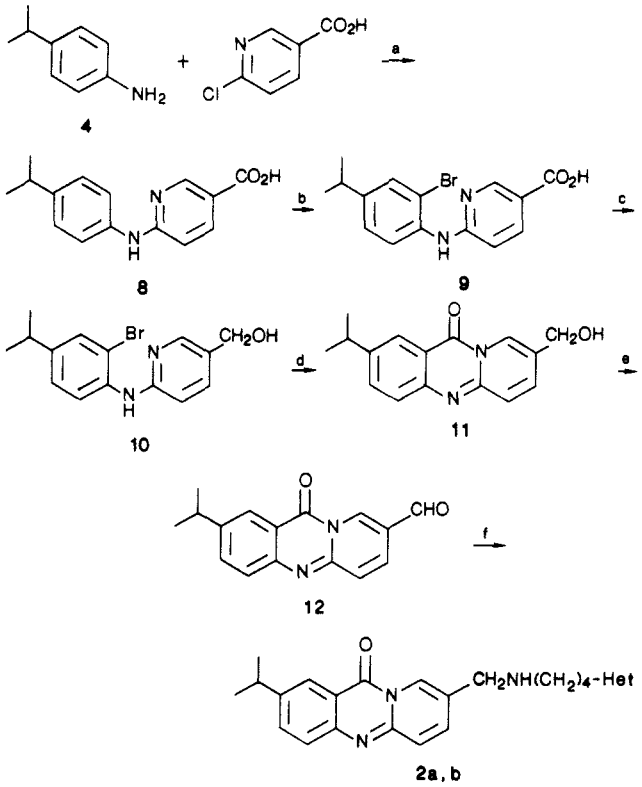
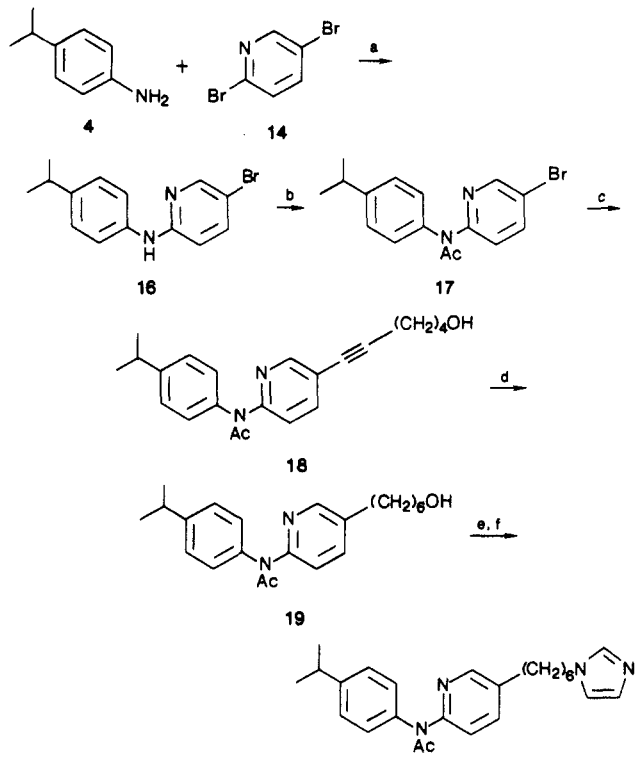
Scheme II[a]



[a] (a) Heat; (b) $Br_2$, HOAc; (c) $BH_3$, THF; (d) CO, *tert*-butyl alcohol, water, $Ph_3P$, $(Ph_3P)_2PdCl_2$, $Bu_3N$; (e) pyridinium chlorochromate, $CH_2Cl_2$; (f) heteroaromatic butanamine, $NaCNBH_3$, HOAc.

Scheme III[a]



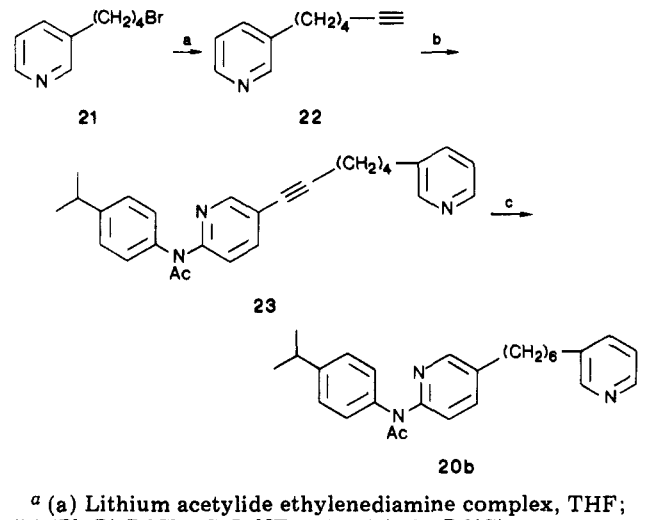
[a] (a) Heat; (b) $Ac_2O$; (c) 5-hexynol, $(Ph_3P)_2PdCl_2$, CuI, $NEt_3$; (d) $H_2$, Pd(C); (e) methanesulfonyl chloride, $NEt_3$; (f) NaH, imidazole, DMF.

shown in Scheme II. The 6-chloronicotinamide **5a**, readily prepared from 6-chloronicotinoyl chloride and (1*H*-imidazol-1-yl)butanamine,[1] was condensed with 4-isopropylaniline to afford the anilinopyridine **6a**. The crude product from this condensation was brominated with bromine in acetic acid to give the bromide **7**, which was readily purified by crystallization. When this material was treated with carbon monoxide in the presence of bis(triphenylphosphine)palladium dichloride, tributylamine, and aqueous dimethylformamide, under conditions previously shown to be useful for the carbonylation of 2-bromoacetanilides,[6] the pyrido[2,1-*b*]quinazoline **1a** was obtained directly in 50% yield for the four steps.

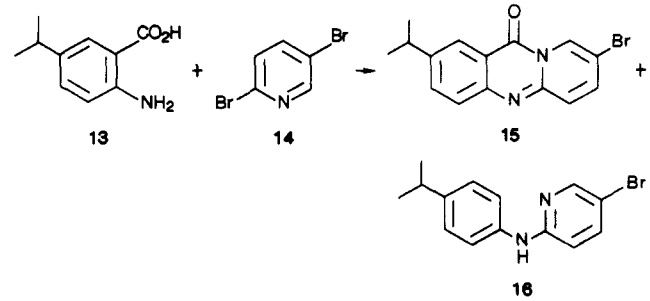
The bromo acid **9** (Scheme II) was similarly prepared and reduced to the key bromo alcohol **10** with borane methyl sulfide. Carbonylation as above using aqueous *tert*-butyl alcohol as the solvent to facilitate product isolation gave the pyrido[2,1-*b*]quinazoline alcohol **11** in 70% yield after acidification. Pyridinium chlorochromate oxidation to give the aldehyde **12** and subsequent sodium cyanoborohydride mediated reductive amination with (1*H*-imidazol-1-yl)butanamine and 3-pyridinebutanamine then afforded the target amines **2a** and **2b**, respectively.

Our initial target for the preparation of **3a** and **3b** was the 8-bromopyrido[2,1-*b*]quinazoline **15** to which we anticipated coupling the side chains by means of appropriately functionalized alkynes. However, when 2,5-dibromopyridine (**14**) was condensed with 5-isopropylanthranilic acid (**13**), decarboxylation leading to the anilinopyridine derivative **16** proved to be a major side reaction and only minor amounts of the desired **15** were obtained. To circumvent this difficulty, a stepwise approach was pursued as shown in Schemes III–V.

Scheme IV[a]

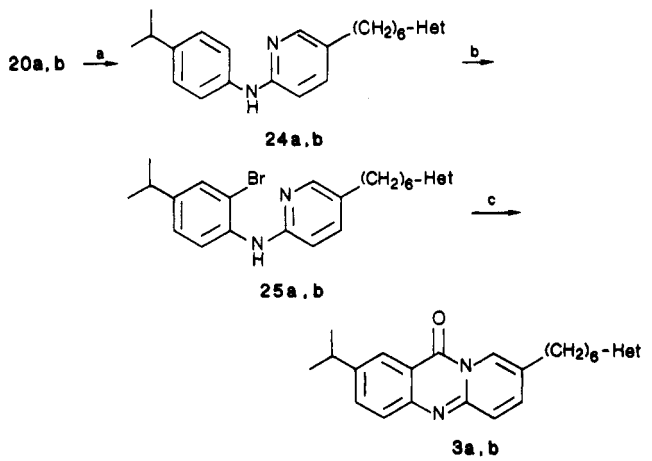


[a] (a) Lithium acetylide ethylenediamine complex, THF; (b) $(Ph_3P)_2PdCl_2$, CuI, $NEt_3$, **17**; (c) $H_2$, Pd(C).



(6) Valentine, D.; Tilley, J. W.; LeMahieu, R. *J. Org. Chem.* 1981, *46*, 4614.

Scheme V[a]



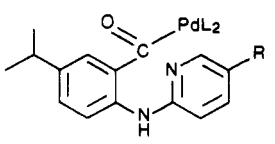

[a] (a) 6 N HCl; (b) $Br_2$, HOAc; (c) CO, *tert*-butyl alcohol, water, $(Ph_3P)_2PdCl_2$, $Bu_3N$.

Synthesis of the imidazole-containing intermediate **20a** is shown in Scheme III. When a neat mixture of 4-isopropylaniline (**4**) and 2,5-dibromopyridine (**14**) was heated, the diphenylamine derivative **16** was obtained, this time in 81% yield, but failed to undergo a palladium-catalyzed addition to 5-hexynol under standard conditions.[1] Reasoning that the 2-aminopyridinyl moiety of **16** might be complexing the catalyst, the corresponding acetamide **17** was prepared and was found to be an excellent substrate for the coupling reaction. Treatment of **17** with 5-hexynol in the presence of bis(triphenylphosphine)palladium chloride, cuprous iodide, and triethylamine afforded the acetylene **18** in 92% yield. Hydrogenation of the triple bond, conversion of the primary alcohol to the mesylate, and reaction with the sodium salt of imidazole then gave **20a**.

For the preparation of the corresponding pyridine, **20b**, the 3-pyridinylhexyne **22** was formed in 79% yield by reaction of lithium acetylide ethylenediamine complex with 3-(4-bromobutyl)pyridine (**21**). This material was coupled to the bromide **17** in the presence of palladium(0) and hydrogenated as shown in Scheme IV to afford **20b** in 67% yield for the two steps. The remaining steps leading to **3a** and **3b** were carried out in a similar manner for both the imidazole and pyridine series (Scheme V).

The acetamides **20** were hydrolyzed with dilute hydrochloric acid, and the resulting anilinopyridines **24** were brominated with bromine in acetic acid as above to give the bromides **25**, each of which contained traces of dibrominated material even after chromatography. These compounds were used as is in the palladium-catalyzed carbonylation reaction to give moderate yields of **3a** and **3b** (35% and 65%, respectively).

In the above work, we have shown four examples of a pyrido[2,1-*b*]quinazoline synthesis that proceeds by carbonyl insertion into a 5-substituted 2-(2-bromoanilino)-pyridine. Although we cannot rule out a stepwise mechanism, we presume that this process proceeds through an acyl palladium species such as **26**, which undergoes nucleophilic attack by the pyridine nitrogen, leading to ring closure with loss of palladium(0) and a proton. It has been shown to be compatible with a variety of functional groups including amides, primary alcohols, aromatic amines, and heteroaromatic rings and allows for a greater flexibility in selection of substituents on the ultimate pyrido[2,1-*b*]-quinazoline ring than was practical with previous syntheses.




**26**

## Experimental Section

Melting points were taken on a Büchi 510 melting point apparatus and are uncorrected. Proton magnetic resonance spectra were taken on a Varian XL-100 or XL-200 spectrometer, and shifts are reported in ppm downfield from tetramethylsilane used as an internal reference. Infrared spectra were obtained on a Beckman IR-9 or IR-12 spectrometer, and characteristic peaks are reported in $cm^{-1}$. Mass spectra were taken on a CEC 21-110 mass spectrometer at 70 eV. NMR, IR, and MS spectral data were recorded for each compound reported and were consistent with the assigned structures. Preparative high-pressure liquid chromatography (HPLC) was performed on silica gel Prep-Pak 500 cartridges using a Water Associates Prep LC 500A. Dry dichloromethane was distilled from $P_2O_5$, DMF was dried over Linde 3A sieves, and triethylamine was distilled from calcium hydride. Evaporation refers to concentration under aspirator pressure using a Büchi rotary evaporator. Except where noted otherwise, drying refers to the drying of combined extracts over potassium carbonate.

**6-Chloro-*N*-[4-(1*H*-imidazol-1-yl)butyl]-3-pyridinecarboxamide Hydrochloride (5a).** A 2-L three-necked flask was charged with 157.6 g (1.00 mol) of 6-chloronicotinic acid and 500 mL of thionyl chloride. The mixture was heated to reflux until a clear solution formed (3.5 h). Excess thionyl chloride was removed by distillation at 60 °C (35 mm). The residue of acid chloride crystallized to a light tan solid.

This material was taken up in 200 mL of dry acetonitrile and placed in an addition funnel. A second addition funnel was charged with 140 g (1.00 mol) of 1-(4-aminobutyl)-1*H*-imidazole[1] in 400 mL of dry acetonitrile. The contents of both funnels were added dropwise with stirring to a 3-L flask over a 1-h period, during which the temperature rose to 60 °C. The resulting mixture was stirred for 1 h, during which product began to separate. A 2-L portion of ether was added, and stirring was continued for an additional hour. The product was collected by filtration, washed with ether, and air-dried to give 304.9 g (96.8%) of bone white solid suitable for use in the next step. This material was essentially pure by silica gel TLC (16:4:1 ethyl acetate–ethanol–aqueous ammonia). An analytical sample was recrystallized from ethyl acetate–hexane: mp 69–71 °C. IR ($cm^{-1}$) ($CHCl_3$) 3455, 1670 (s); MS, *m/e* (relative intensity) 291 (1), 289 (1), 140 (40), 106 (100); NMR ($CDCl_3$) $\delta$ 1.68 (m, 4 H), 2.08 (m, 2 H), 3.48 (m, 2 H), 6.84 (br, 1 H), 7.19–7.49 (m, 3 H), 8.08 (d of d, 1 H, $J$ = 8 Hz, $J$ = 2.5 Hz), 8.39 (s, 2 H), 8.72 (d, 1 H, $J$ = 2.5 Hz). Anal. Calcd for $C_{15}H_{16}ClN_3O$: C, 62.18; H, 5.57; N, 14.50; Cl, 12.23. Found: C, 61.93; H, 5.71; N, 14.71; Cl, 12.41.

***N*-[4-(1*H*-Imidazol-1-yl)butyl]-6-[(4-isopropylphenyl)-amino]-3-pyridinecarboxamide (6a).** A 2-L flask was charged with 304.3 g (0.965 mol) of **5a**, 143.0 g (1.06 mol) of 4-isopropylaniline, and 600 mL of 2-methoxyethanol. This mixture was stirred at reflux for 10 h. It was then cooled and poured into a mixture of 1.5 L of water, 1.5 L of saturated sodium carbonate solution, 2 L of ether, and 1.5 L of ethanol. The layers were separated, the aqueous layer was extracted two times with dichloromethane, and the combined organic layers were dried and concentrated. The oily residue was stirred with 1 L of ether, and seed crystals were added to induce crystallization. After stirring in an ice bath for 2 h, the solid was collected and washed with ether, water, and again with ether. The crude product, obtained as an off-white solid, was dried under vacuum overnight to give 327.3 g (89.9%) of material, mp 130–136 °C, giving one major spot on TLC analysis. An analytical sample was obtained by recrystallization from ethyl acetate–ether, mp 150–152 °C. Anal. Calcd for $C_{22}H_{27}N_5O$: C, 70.00; H, 7.21; N, 18.55. Found: C, 70.06; H, 7.13; N, 18.41.

***N*-[4-(1*H*-Imidazol-1-yl)butyl]-6-[[2-bromo-4-(1-methylethyl)phenyl]amino]-3-pyridinecarboxamide (7).** A 2-L

three-necked flask equipped with an addition funnel, thermometer, and a stirrer was placed in an ice bath and charged with 163.7 g (0.465 mol) of the crude **6a** obtained above in 600 mL of glacial acetic acid. The addition funnel was charged with 24 mL (0.465 mol) of bromine in 50 mL of acetic acid. The bromine solution was added dropwise with stirring and at such a rate so as to keep the temperature below 15 °C. The addition was complete in 1 h. The acetic acid was removed under reduced pressure, and the residue was taken up in 500 mL of water. This solution was washed with 2 × 500 mL of ethyl acetate. The combined organic layers were extracted with 200 mL of water and discarded. The combined aqueous layers were made basic by addition of excess sodium carbonate solution and were extracted with 2 × 1 L of ethyl acetate. The combined extracts were dried and concentrated. The residue crystallized on standing to give 175.6 g (88.6%) of **7** as a light yellow solid. This material was recrystallized from a 10:1 toluene–ethyl acetate mixture to give 144.8 g (73%) of colorless crystals, mp 91–94 °C. Anal. Calcd for $C_{22}H_{26}BrN_5O$: C, 57.90; H, 5.74; N, 15.35; Br, 17.51. Found: C, 57.93; H, 5.71; N, 15.00; Br, 17.57.

***N*-[4-(1*H*-Imidazol-1-yl)butyl]-2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxamide (1a).** A 1-L glass autoclave liner was charged with 136.0 g (0.30 mol) of **7**, 2.5 g (3.56 mmol) of bis(triphenylphosphine)palladium dichloride, 2.5 g (9.6 mmol) of triphenylphosphine, 77 mL of tributylamine, and 390 mL of 1:10 aqueous DMF. The mixture was degassed with nitrogen, placed in the autoclave, swept three times with carbon monoxide, and then heated for 12 h at 100 °C, under 200 psi of carbon monoxide. The cooled mixture was filtered, and 200 mL of glacial acetic acid was used to rinse the liner and filter pad. The filtrate was concentrated, using a 70 °C water bath. The residue was taken up in 500 mL of water, washed with 3 × 300 mL of ethyl acetate, and then made alkaline by adding saturated aqueous sodium carbonate solution. The resulting precipitate was filtered, thoroughly washed with water, and dried in vacuum to give 119.8 g (99.8%) of crude product as a yellow powder. The purity of material thus obtained, typically >90%, was raised to >99% by serial recrystallization from acetonitrile, DMF–aqueous ammonia–water, and 2-butanone with a 70–75% recovery. The **1a** thus prepared was shown by spectral and TLC comparisons to be identical with material obtained by the route described in ref 1.

**2-[[4-(1-Methylethyl)phenyl]amino]pyridine-5-carboxylic Acid (8).** A mixture of 34.2 g (0.254 mol) of 4-isopropylaniline (**4**) and 20.0 g (0.27 mol) of 6-chloronicotinic acid was heated to a bath temperature of 150 °C for 3 h. The resulting solid mass was partitioned between 10% aqueous sodium hydroxide solution and toluene. The aqueous layer was acidified to pH 7 with hydrochloric acid, and the resulting precipitate was recrystallized from DMF–water to give 20.13 g (62%) of **8**: mp 260–264 °C; IR ($cm^{-1}$) (KBr) 2460 (br), 1620 (s); NMR ($Me_2SO$) $\delta$ 1.19 (d, 2 H, $J$ = 7 Hz), 2.84 (m, 1 H, $J$ = 7 Hz), 6.68 (d, 1 H, $J$ = 9 Hz), 7.13 (d, 2 H, $J$ = 8 Hz), 7.44 (d, 2 H, $J$ = 8 Hz), 7.91 (d of d, 1 H, $J$ = 9 Hz, $J$ = 2 Hz), 8.65 (d, 1 H, $J$ = 2 Hz), 9.35 (br, 1). Anal. Calcd for $C_{15}H_{16}N$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.27; H, 6.33; N, 11.08.

**2-[[2-Bromo-4-(1-methylethyl)phenyl]amino]pyridine-5-carboxylic Acid (9).** To a solution of 19.85 g (0.0775 mol) of **8** and 7.62 g (0.093 mol) of sodium acetate in 425 mL of acetic acid was added 4.8 mL (0.09 mol) of bromine with ice-bath cooling so as to maintain the internal temperature between 22 and 25 °C. The reaction mixture was stirred for 25 min and was concentrated. The residue was triturated with water to give a granular solid, which was recrystallized from 400 mL of ethanol and 75 mL of water to afford 22.7 g of **9**, mp 204–211 °C. Recrystallization from ethyl acetate–hexane gave 17.13 g (66%): mp 225–227 °C; IR ($cm^{-1}$) ($CHCl_3$) 1687 (s); MS, $m/e$ (relative intensity) 336 (20), 334 (20), 255 (100); NMR ($Me_2SO$) $\delta$ 1.19 (d, 6 H, $J$ = 7 Hz), 2.85 (m, 1 H, $J$ = 7 Hz), 6.81 (d, 1 H, $J$ = 8 Hz), 7.17 (d, 1 H, $J$ = 8 Hz), 7.58 (d, 1 H, $J$ = 8 Hz), 7.95 (d, of d, 1 H, $J$ = 2 Hz, $J$ = 8 Hz), 8.67 (d, 1 H, $J$ = 2 Hz). Anal. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; Br, 23.84; N, 8.36. Found: C, 53.66; H, 4.51; Br, 23.97; N, 8.34.

**2-[[2-Bromo-4-(1-methylethyl)phenyl]amino]pyridine-5-methanol (10).** A solution of 17.13 g (0.0511 mol) of **9** in 150 mL of dry THF was treated with 11 mL (0.11 mol) of borane–methyl sulfide complex over the course of 10 min. The reaction mixture was heated to reflux for 4 h, was allowed to cool, and was quenched by the careful addition of 80 mL of 10% sodium hydroxide solution. The mixture was heated to reflux for 5 h and partially concentrated, and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with saturated potassium carbonate solution, dried, and concentrated. The residue was purified by preparative HPLC eluting with ethyl acetate to give 14.64 g (89%) of **10** as an oil: IR ($cm^{-1}$) ($CHCl_3$) 3605 (m), 3405 (m); MS, $m/e$ (relative intensity) 322 (8), 320 (10), 241 (100); NMR ($CDCl_3$) $\delta$ 1.23 (d, 6 H, $J$ = 7 Hz), 2.85 (m, 1 H, $J$ = 7 Hz), 4.56 (s, 2 H), 6.76 (d, 1 H, $J$ = 8.5 Hz) 7.12–7.72 (m, 4 H), 8.12 (br s, 1 H). Anal. Calcd for $C_{15}H_{17}BrN_2O{\cdot}0.1C_4H_8O_2$: C, 56.04; H, 5.44; N, 8.49; Br, 24.22. Found: C, 56.35; H, 5.73; N, 8.19; Br, 24.23.

**2-(1-Methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-methanol (11).** An 80-mL glass liner was charged with 13.32 g (41.5 mmol) of **10**, 1.12 g (4.2 mmol) of triphenylphosphine, 11.0 mL (46 mmol) of tri-*n*-butylamine, 26 mL of *tert*-butyl alcohol, and 1.3 mL of water and was degassed with argon, and 1.00 g (1.42 mmol) of bis(triphenylphosphine)palladium dichloride was added. The liner was placed in a stainless steel bomb, was pressurized to 200 psi with carbon monoxide, and was heated to 100 °C. After 6 h, the mixture was cooled and diluted to 300 mL with dichloromethane and a little acetic acid. The organic solution was washed with 3 × 100 mL of water, dried over magnesium sulfate, and concentrated to give 22.91 g of a yellow solid. Recrystallization from acetonitrile gave 5.07 g (46%) of **11**, mp 151–153 °C. The filtrate was concentrated and purified by preparative HPLC eluting with ethyl acetate to afford 2.70 g (24%): mp 153–154 °C; IR ($cm^{-1}$) ($CHCl_3$) 3605 (s), 1690 (s), 1658 (s); MS, $m/e$ (relative intensity) 268 (60), 253 (100); NMR ($CDCl_3$) $\delta$ 1.36 (d, 6 H, $J$ = 7 Hz), 3.08 (m, 1 H, $J$ = 7 Hz), 4.70 (s, 2 H), 7.45–7.70 (m, 4 H), 8.24 (br s, 1 H), 8.76 (br s, 1 H). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.46; H, 5.74; N, 10.54.

**2-(1-Methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxaldehyde (12).** A solution of 7.77 g (29 mmol) of **11** in 60 mL of dry dichloromethane was treated with 9.36 g (43 mmol) of pyridinium chlorochromate. After 3 h, the mixture was diluted with ethyl acetate, filtered, and concentrated. The residue was chromatographed over 200 g of silica gel eluting with ethyl acetate to give 4.68 g (61%) of **12**: mp 186–188 °C; IR ($cm^{-1}$) ($CHCl_3$) 1698 (s); MS, $m/e$ (relative intensity) 266 (40), 251 (100); NMR ($CDCl_3$) $\delta$ 1.37 (d, 6 H, $J$ = 7 Hz), 3.15 (m, 1 H, $J$ = 7 Hz), 7.46 (d, 1 H, $J$ = 9 Hz), 7.80 (m, 3 H), 7.85 (d, 1 H, $J$ = 9 Hz), 8.31 (br s, 1 H), 9.35 (d, 1 H, $J$ = 2 Hz). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 71.85; H, 5.16; N, 10.80.

**8-[[[4-(1*H*-Imidazol-1-yl)butyl]amino]methyl]-2-(1-methylethyl)-11*H*-pyrido[2,1-*b*]quinazolin-11-one Trihydrochloride Hemihydrate (2a).** A mixture of 2.00 g (7.51 mmol) of **12**, 1.10 g (7.9 mmol) of (1*H*-imidazol-1-yl)butanamine,[1] 1.33 mL (22.5 mmol) of acetic acid, and 0.314 g (5.0 mmol) of sodium cyanoborohydride in 20 mL of methanol was stirred for 2 h and was concentrated. The residue was diluted with water and dilute hydrochloric acid and was washed with dichloromethane. The aqueous layer was made basic and was extracted with dichloromethane. The combined organic layers were washed with water, dried, and concentrated to a dark oil, which was chromatographed over 100 g of silica gel, eluting with 89:10:1 ethyl acetate–methanol–triethylamine to give a yellow oil, which was acidified with hydrochloric acid and crystallized from ethanol–ether to afford 1.98 g (57%) of **2a**: mp 242–247 °C; IR ($cm^{-1}$) (KBr) 2780–2405, 1718 (s); MS, $m/e$ (relative intensity) 389 (100); NMR ($Me_2SO$) $\delta$ 1.31 (d, 6 H, $J$ = 7 Hz), 1.5–2.1 (m, 4 H), 2.9–3.2 (m, 3 H), 7.71–8.20 (m, 7 H), 8.59 (m, 1 H), 9.31 (br, 1 H). Anal. Calcd for $C_{23}H_{27}N_5O{\cdot}3HCl{\cdot}0.5_2O$: C, 54.39; H, 6.15; N, 13.78; Cl, 20.94; $H_2O$, 1.80. Found: C, 54.61; H, 6.31; N, 13.98; Cl, 21.19; $H_2O$, 1.78.

**2-(1-Methylethyl)-8-[[[4-(3-pyridinyl)butyl]amino]-methyl]-11*H*-pyrido[2,1-*b*]quinazolin-11-one Trihydrochloride Hemihydrate (2b).** A mixture of 2.68 g (10.1 mmol)

of **12**, 1.65 g (11 mmol) of 3-pyridinebutanamine, 0.44 g (7 mmol) of sodium cyanoborohydride, and 1.78 mL (30 mmol) of acetic acid in 30 mL of methanol was stirred for 2 h over 3A molecular sieves. The mixture was concentrated, and the residue was dissolved in 200 mL of dichloromethane, washed with 50-mL portions of dilute potassium carbonate solution and water, dried, and concentrated. The residue was purified by preparative HPLC, eluting with 94:5:1 dichloromethane–methanol–triethylamine. The product-containing fractions were combined, dissolved in dichloromethane, washed with water, dried, evaporated, acidified with hydrochloric acid, and recrystallized from ethanol–ether to give 2.44 g (47%) of **2b**: mp 244–249 °C; IR ($cm^{-1}$) (KBr) 3465 (br), 3420 (br), 2760–2340 (br), 1722 (s); MS, *m/e* (relative intensity) 400 (55); NMR ($Me_2SO$) δ 1.31 (d, 6 H, *J* = 7 Hz), 1.76 (br, 4 H), 2.80–3.30 (m, 5 H), 4.39 (br, 2 H), 7.90–8.92 (m, 9 H), 9.30 (br, 1 H). Anal. Calcd for $C_{25}H_{28}N_4O{\cdot}3HCl{\cdot}0.5H_2O$: C, 57.86; H, 5.83; N, 10.79; Cl, 20.49; $H_2O$, 1.73. Found: C, 57.64; H, 5.88; N, 10.82; Cl, 19.97; $H_2O$, 1.93.

**5-Bromo-2-[[4-(1-methylethyl)phenyl]amino]pyridine (16).** A mixture of 24.00 g (0.176 mol) of 4-(1-methylethyl)aniline (**4**) and 20.96 g (0.088 mol) of 2,5-dibromopyridine (**14**) was heated to a bath temperature of 160–180 °C for 2 h. While still warm, the reaction mixture was diluted with 100 mL of ethyl acetate and washed with 100 mL of saturated potassium carbonate. The aqueous layer was extracted with 75 mL of ethyl acetate, and the combined organic layers were dried. The solid obtained after evaporation was crystallized from hexane to give 20.89 g (81%) of **16**, mp 98–100 °C. The analytical sample was obtained from ethyl acetate–hexane: mp 99–101 °C; IR ($cm^{-1}$) ($CHCl_3$) 3455, 3415; MS, *m/e* (relative intensity) 292 (45), 290 (45), 275 (100); NMR ($CDCl_3$) δ 1.24 (d, 6 H, *J* = 7 Hz), 2.89 (m, 1 H, *J* = 7 Hz), 6.70 (d, 1 H, *J* = 9 Hz), 7.19 (s, 4 H), 7.50 (d of d, 1 H, *J* = 9 Hz, *J* = 2.25 Hz), 8.80 (d, 1 H, *J* = 2.5 Hz). Anal. Calcd for $C_{14}H_{15}BrN_2$: C, 57.75; H, 5.19; Br, 27.44; N, 9.62. Found: C, 57.82; H, 5.21; Br, 27.21; N, 9.63.

***N*-(5-Bromo-2-pyridinyl)-*N*-[4-(1-methylethyl)phenyl]acetamide (17).** A solution of 38.93 g (0.134 mol) of **16** in 40 mL of acetic anhydride and 400 mL of acetic acid was heated to reflux for 3 h. The solvent was evaporated, and the red residue was distilled to give 44.45 g (quantitative) of **17**: bp 150–160 °C (0.05 mm); IR ($cm^{-1}$) ($CHCl_3$) 1674 (s); MS, *m/e* (relative intensity) 334 (15), 332 (15); NMR ($CDCl_3$) δ 1.26 (d, 6 H, *J* = 7 Hz), 2.08 (s, 3 H), 2.96 (m, 1 H, *J* = 7 Hz), 7.22–7.90 (m, 6 H), 8.43 (d, 1 H, *J* = 3 Hz). Anal. Calcd for $C_{16}H_{17}BrN_2O$: C, 57.67; H, 5.14; Br, 24.00; N, 8.41. Found: C, 57.46; H, 5.00; Br, 24.29; N, 8.34.

***N*-[5-(6-Hydroxyhex-1-ynyl)-2-pyridinyl]-*N*-[4-(1-methylethyl)phenyl]acetamide (18).** A solution of 10.15 g (30.0 mmol) of **17** and 4.0 g (40.8 mmol) of 5-hexyn-1-ol in 40 mL of dichloromethane and 12.5 mL of triethylamine was degassed with argon, and 0.70 g (1.0 mmol) of bis(triphenylphosphine)palladium chloride and 100 mg of cuprous iodide was added. The resulting mixture was heated to reflux for 5 h, diluted with 120 mL of dichloromethane, washed with 3 × 50 mL of water, and dried. The crude material obtained from concentration was filtered through a plug of silica gel and purified by preparative HPLC eluting with 7:3 ethyl acetate–hexane to give 9.83 g (92%) of **18** as an oil containing a trace of ethyl acetate: IR ($cm^{-1}$) ($CHCl_3$) 2235 (w), 1672 (s); MS, *m/e* (relative intensity) 350 (25), 308 (100); NMR ($CDCl_3$) δ 1.26 (d, 6 H, *J* = 7 Hz), 1.7 (m, 4 H), 2.10 (s, 3 H), 2.47 (m, 2 H) 2.95 (m, 1 H, *J* = 7 Hz), 3.72 (m, 2 H), 7.15–7.75 (m, 6 H), 8.42 (d, 1 H, *J* = 3 Hz). Anal. Calcd for $C_{22}H_{26}N_2O_2{\cdot}0.2C_4H_8O_2$ C, 74.40; H, 7.56; N, 7.61. Found: C, 74.25; H, 7.65; N, 7.60.

***N*-[5-(6-Hydroxyhexyl)-2-pyridinyl]-*N*-[4-(1-methylethyl)phenyl]acetamide (19).** A solution of 9.83 g (0.028 mol) of **18** in 220 mL of ethanol was hydrogenated over 0.50 g of platinum oxide, and the crude product was purified by preparative HPLC eluting with ethyl acetate to give 8.58 g (86%) of **19** as an oil: IR ($cm^{-1}$) ($CHCl_3$) 1668 (s); MS, *m/e* (relative intensity) 354 (20), 312 (100); NMR ($CDCl_3$) δ 1.24 (d, 6 H, *J* = 7 Hz), 1.3–1.8 (m, 8 H), 2.08 (s, 3 H), 2.58 (t, 2 H, *J* = 7 Hz), 2.91 (m, 1 H, *J* = 7 Hz), 3.62 (t, 2 H, *J* = 6 Hz), 7.33–7.52 (m, 6 H), 8.25 (d, 1 H, *J* = 2 Hz). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.54; H, 8.53; N, 7.90. Found: C, 73.88; H, 8.49; N, 7.90.

***N*-[5-[6-(1*H*-Imidazol-1-yl)hexyl]-2-pyridinyl]-*N*-[4-(1-methylethyl)phenyl]acetamide (20a).** A solution of 14.83 g (0.0418 mol) of **19** and 6.4 mL (0.046 mol) of triethylamine in 75 mL of dichloromethane was cooled in an ice bath as 3.6 mL (0.046 mol) of methanesulfonyl chloride was added over 15 min. The resulting mixture was stirred for 1 h at 0 °C, diluted to 250 mL with ether, washed with water and brine, and dried. The residue from evaporation was dissolved in 50 mL of DMF and added to a room temperature solution of the sodium salt of imidazole formed by reaction of 5.7 g (0.082 mol) of imidazole with 3.5 g (0.082 mol) of sodium hydride in 50 mL of DMF at 60 °C for 15 min. The mixture was heated to 60 °C for 2 h, cooled, and diluted with water and 6 N HCl. The aqueous solution was washed with ether and ethyl acetate, was made basic with sodium hydroxide, and was extracted with ethyl acetate. The combined extracts were dried and evaporated to give 16.30 g (96%) of a yellow oil, which was suitable for use in the next step. A portion was purified for analysis by silica gel chromatography eluting with 2:10:88 triethylamine–methanol–ethyl acetate: IR ($cm^{-1}$) ($CHCl_3$) 1668 (s); MS, *m/e* (relative intensity) 404 (15), 362 (100); NMR ($CDCl_3$) δ 1.25 (d, 6 H, *J* = 7 Hz), 1.28–1.84 (m, 8 H), 2.08 (s, 3 H), 2.57 (t, 2 H, *J* = 7 Hz), 2.92 (m, 1 H, *J* = 7 Hz), 3.92 (t, 1 H, *J* = 6 Hz), 6.89–7.51 (m, 9 H), 8.24 (br, 1 H). Anal. Calcd for $C_{25}H_{32}N_4O$: C, 74.22; H, 7.97; N, 13.88. Found: C, 74.00; H, 8.04; N, 13.81.

**6-(3-Pyridyl)-1-hexyne (22).** A suspension of 19.0 g (0.20 mol) of lithium acetylide ethylenediamine complex in 100 mL of $Me_2SO$ was maintained at 20–23 °C as 19.3 g (0.0654 mol) of 3-(4-bromobutyl)pyridine hydrobromide (**21**) was added portionwise. The resulting mixture was stirred for 2 h and quenched by the addition of 500 mL of ice and water. The aqueous solution was extracted with ether, and the combined extracts were washed with water and brine and dried. The residue from evaporation was purified by preparative HPLC eluting with 6:4 hexane–ethyl acetate, and the product was distilled to give 8.17 g (79%) of **22**: bp 105–120 °C (0.05 mm); IR ($cm^{-1}$) ($CHCl_3$) 3305 (w), 2215 (w); MS, *m/e* (relative intensity) 159 (30), 131 (100); NMR ($CDCl_3$) δ 1.40–2.75 (m, 9 H), 7.21–7.52 (m, 2 H), 8.42 (br, 2 H). Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.03; H, 8.54; N, 9.04.

***N*-[4-(1-Methylethyl)phenyl]-*N*-[5-[6-(3-pyridinyl)hexyl]-2-pyridinyl]acetamide (20b).** A solution of 12.2 g (0.0382 mol) of **17** and 8.1 g (0.0511 mol) of **22** in 50 mL of dichloromethane and 15.6 mL of triethylamine was degassed with argon, and 877 mg (1.24 mmol) of bis(triphenylphosphine)palladium dichloride and 125 mg (0.64 mmol) of cuprous iodide were added. The reaction mixture was heated to reflux for 5 h and diluted with ethyl acetate. The resulting mixture was filtered. The filtrate was made acidic with 1 N hydrochloric acid, the layers were separated, and the aqueous layer was washed with ethyl acetate and made basic with sodium hydroxide. The aqueous phase was extracted with dichloromethane, and the combined extracts were dried and evaporated to give an oil, which was purified by HPLC eluting with 2.5% methanol–dichloromethane to afford 11.4 g of an oil. This oil was dissolved in 130 mL of ethanol and hydrogenated over 0.7 g of platinum oxide. The catalyst was filtered and the solvent evaporated to give 10.5 g (67%) of **20b**. A portion was purified on a silica gel column eluting with 4.5% methanol–dichloromethane to give the analytical sample: IR ($cm^{-1}$) ($CHCl_3$) 1668 (s); MS, *m/e* (relative intensity) 415 (27), 373 (100); NMR ($CDCl_3$) δ 1.24 (d, 6 H, *J* = 7 Hz), 1.3–1.75 (m, 8 H), 2.09 (s, 3 H), 2.58 (m, 4 H), 2.92 (m, 1 H, *J* = 7 Hz), 7.20–7.51 (m, 8 H), 8.26 (m, 1 H), 8.44 (m, 2 H). Anal. Calcd for $C_{27}H_{33}N_3O$: C, 78.03; H, 8.00; N, 10.11. Found: C, 77.95; H, 8.08; N, 10.03.

**5-[6-(1*H*-Imidazol-1-yl)hexyl]-2-[[4-(1-methylethyl)phenyl]amino]pyridine (24a).** A solution of 16.30 g (0.0402 mol) of **20a** in 130 mL of 6 N HCl was heated to reflux for 24 h and was evaporated to dryness. The residue was dissolved in water, made basic with sodium hydroxide, and extracted with ethyl acetate. The combined organic layers were washed with water and brine and were dried. The residue from evaporation was purified by preparative HPLC eluting with 3:1:96 methanol–triethylamine–dichloromethane to give 12.77 g (87%) of **24a** as an oil: IR ($cm^{-1}$) ($CHCl_3$) 3415; MS, *m/e* (relative intensity) 362 (45); high-resolution MS (molecular ion) calcd 362.2437, observed 362.2454; NMR ($CDCl_3$) δ 1.25 (d, 6 H, *J* = 7 Hz), 1.3–1.85 (m, 8 H), 2.48 (m, 2 H), 2.87 (m, 1 H, *J* = 7 Hz), 3.91 (m, 2 H),

6.61-7.44 (m, 10 H), 7.98 (br, 1 H).

**2-[[4-(1-Methylethyl)phenyl]amino]-5-[6-(3-pyridinyl)-hexyl]pyridine (24b)** was prepared similarly to **24a** above. From 10.3 g (0.025 mol) of **20b** there was obtained 8.5 g (92%) of **24b** suitable for use in the next step: IR ($cm^{-1}$) ($CHCl_3$) 3420 (w); MS, *m/e* (relative intensity) 373 (10), 277 (100); NMR ($CDCl_3$) $\delta$ 1.25 (d, 6 H, $J$ = 7 Hz), 1.3-1.75 (m, 8 H), 2.4-3.0 (m, 5 H), 6.38 (br, 1 H), 6.78-7.47 (m, 8 H), 7.99 (br, 1 H), 8.43 (br, 2 H).

**2-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-[6-(1*H*-imidazol-1-yl)hexyl]pyridine (25a).** A solution of 11.6 g (0.032 mol) of **24a** and 2.62 g (0.032 mol) of sodium acetate in 170 mL of acetic acid was held at room temperature with a water bath as 1.64 mL (0.032 mole of bromine was added over 10 min. After 1 h, the reaction mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and dilute potassium carbonate. The organic layer was dried and evaporated, and the residue was purified by preparative HPLC eluting with 4:1:95 methanol-triethylamine-dichloromethane. The product-containing fractions were taken up in ethyl acetate, washed with water, dried, and evaporated to give 11.8 g (84%) of **25a** contaminated with a trace of dibrominated compound: MS, *m/e* (relative intensity) 442 (20), 440 (20); NMR ($CDCl_3$) $\delta$ 1.20-1.95 (m, 14 H), 2.50 (m, 2 H), 2.86 (m, 1 H, $J$ = 7 Hz), 3.91 (m, 2 H), 6.88 (br, 1 H), 7.06 (br, 1 H), 7.17-7.60 (m, 5 H), 7.97 (m, 1 H), 8.38 (m, 1 H).

**2-[[2-Bromo-4-(1-methylethyl)phenyl]amino]-5-[6-(3-pyridinyl)hexyl]pyridine (25b)** was obtained as above. With 7.6 g (0.020 mol) of **24b**, 1.6 g (0.020 mol) of sodium acetate, and 1.0 mL (0.020 mol) of bromine in 50 mL of acetic acid as starting material, there was obtained 4.3 g (48%): MS, *m/e* (relative intensity) 453 (11), 451 (11); high-resolution MS (molecular ion) calcd 451.1623, observed 451.1634; NMR ($CDCl_3$) $\delta$ 1.21 (d, 6 H, $J$ = 7 Hz), 1.3-1.75 (m, 8 H), 2.40-2.96 (m, 5 H), 6.64 (br, 1 H), 6.75 (d, 1 H, $J$ = 9 Hz), 7.04-7.52 (m, 5 H), 7.82 (d, 1 H, $J$ = 9 Hz), 8.04 (br, 1 H), 8.42 (br, 2 H).

**2-(1-Methylethyl)-8-[6-(1*H*-imidazol-1-yl)hexyl]-11*H*-pyrido[2,1-*b*]quinazolin-11-one (3a)** was prepared by carbonylation of **25a** as described above for **11**. From 11.8 g (0.0267 mol) of **25a**, 1.12 g (0.042 mole of triphenylphosphine, and 7.2 mL (0.03 mol) of tributylamine in 20 mL of *tert*-butyl alcohol and 1.1 mL of water, there was obtained, after preparative chromatography eluting with 2:1:97 methanol-triethylamine-dichloromethane and recrystallization from ethyl acetate-hexane, 3.66 g (35%) of **3a**: mp 77-82 °C; IR ($cm^{-1}$) ($CHCl_3$) 1682 (s), 1651 (s); MS, *m/e* (relative intensity) 388 (100); NMR ($CDCl_3$) $\delta$ 1.30-1.95 (m, 14 H), 2.63 (m, 2 H), 3.11 (m, 1 H, $J$ = 7 Hz), 3.83 (m, 2 H), 6.90 (br, 1 H), 7.05 (br, 1 H), 7.37-7.45 (m, 3 H), 7.75 (m, 2 H), 8.28 (br, 1 H), 8.64 (br, 1 H). Anal. Calcd for $C_{24}H_{28}N_4O$: C, 74.20; H, 7.26; N, 14.42. Found: C, 74.12; H, 7.30; N, 14.52. Treatment with excess ethanolic hydrochloric acid, evaporation, and recrystallization from ethanol-ether afforded 4.17 g of the dihydrochloride salt, mp 251-256 °C. Anal. Calcd for $C_{24}H_{28}N_4O \cdot 2H_2O$: C, 62.47; H, 6.55; N, 12.14; Cl, 15.37. Found: C, 62.49; H, 6.35; N, 12.13; Cl, 15.09.

**2-(1-Methylethyl)-8-[6-(3-pyridinyl)hexyl]-11*H*-pyrido[2,1-*b*]quinazolin-11-one (3b)** was prepared from 4.0 g (8.84 mmol) of **25b**, 0.26 g (1.0 mmol) of triphenylphosphine, 0.35 g (0.5 mmol) of bis(triphenylphosphine) palladium dichloride, and 0.35 mL of water in 7 mL of *tert*-butyl alcohol as described above for **11**. The crude product was chromatographed over silica gel eluting with ethyl acetate and recrystallized from ethyl acetate-hexane to afford 2.27 g (65%): mp 62-64 °C; IR ($cm^{-1}$) ($CHCl_3$) 1683 (s), 1652 (s); MS, *m/e* (relative intensity) 399 (100); NMR ($CDCl_3$) $\delta$ 1.20-1.80 (m, 14 H), 2.62 (m, 4 H), 3.10 (m, 1 H, $J$ = 7 Hz), 7.08-7.73 (m, 6 H), 8.25 (br, 1 H), 8.40 (br, 2 H), 8.53 (br, 1 H). Anal. Calcd for $C_{26}H_{29}N_3O$: C, 78.16; H, 7.32; N, 10.52. Found: C, 77.82; H, 7.34; N, 10.18.

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# Enones with Strained Double Bonds. 10. Use of Flash Vacuum Pyrolysis To Obtain Bicyclo[3.3.1]non-1-en-3-one[1]

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Pyrolysis of the furan adducts **3** in the gas phase at low pressure ($10^{-4}$ mm) formed a mixture of furan and the bicyclic enone **2a** with a bridgehead double bond that could be collected in a cold trap. NMR, IR, and UV spectra of this mixture were obtained. Although the enone **2a** reacted rapidly with methanol and more slowly with furan, efforts to find products from the reaction of the enone **2a** with either ground-state oxygen or one of several unsaturated compounds **9**, **11**, **12**, or **13** were unsuccessful. Instead, at temperatures above -40 °C the enone **2a** reacted with itself to form a mixture of the three dimers **4a**, **4b**, and **4c**.

In earlier studies[3-5] bicyclo[3.3.1]non-1-en-3-one (**2a**, Scheme I), prepared either by dehydrobromination of the bromo ketone **1b** or by pyrolysis of the furan adduct **3** (a mixture of diastereoisomers), was found to undergo reaction with a variety of other materials such as nucleophiles or dienes. In the absence of other reagents, the enone **2a** reacted rapidly with itself even at room temperature in the

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