for 1 h, worked up, and analyzed by GLC (Table I).

**Reaction of Acetone with Sulfuryl Chloride in Methylene Chloride in the Presence of Methanol.** To a solution of acetone (5.8 g, 100 mmol) and methanol (9.6 g, 300 mmol) in methylene chloride (50 mL) was added sulfuryl chloride (14.8 g, 110 mmole) dropwise over 10 min. After the evolution of gases stopped (HCl, $SO_2$, $CH_3Cl$), GLC analysis indicated that only unreacted acetone and monochloroacetone were present. After the solution was washed with the saturated solution of sodium bicarbonate and dried over the magnesium sulfate, distillation gave 85% yield of monochloroacetone and unreacted acetone.

When the reaction was carried out in the absence of methanol, a 2:1 mixture of monochloroacetone/1,1-dichloroacetone and unreacted acetone was obtained.

**Reaction of Phenol with Sulfuryl Chloride in the Presence of Ether and Other Organic "Bases".** Phenol (9.4 g, 100 mmol) and sulfuryl chloride (13.5 g, 100 mmol) were dissolved in methylene chloride (50 mL). Dropwise addition of ether (7.4 g) led to an instantaneous and exothermic reaction with evolution of hydrogen chloride and sulfur dioxide (when an alcohol was used instead of the diethyl ether, the corresponding alkyl chlorides were also formed). GLC analysis indicated that only monochlorophenols were produced. Usual workup followed by the evaporation of the solvent afforded the products. A similar reaction procedure was followed when other organic "bases" different than ether (alcohols, thioethers, sulfoxides, and crown ethers) were used. The results are summarized in Table II. In the absence of the "base" there was no reaction between phenol and sulfuryl chloride in methylene chloride solution even under reflux.

**Reaction of Bisphenol A with Sulfuryl Chloride in Ether.** To a solution of bisphenol A (17.2 g, 75 mmol) in ether (100 mL) was added slowly sulfuryl chloride (22.3 g, 165 mmol) at room temperature with stirring. The reaction is exothermic, and initially the temperature rose to 30 °C. However, the evolution of gaseous byproducts maintained the temperature below 30 °C. When evolution of gases stopped, the solution was refluxed for 1 h. After the solution was washed with the saturated solution of sodium bicarbonate and dried over sodium sulfate, evaporation of the solvent gave 75% yield of 3,3'-dichloro-4,4'-isopropylidenediphenol.

**Reaction of 4-*tert*-Butylphenol with Sulfuryl Chloride in Methyene Chloride in the Presence of Methanol.** To a solution of 4-*tert*-butylphenol (15 g, 100 mmol) in methylene chloride (50 mL) was added methanol (3.2 g, 100 mmol) dropwise at room temperature. After the usual workup, 2-chloro-4-*tert*-butylphenol was obtained in 95% yield.

**Acknowledgment.** We thank Mr. Edward H. Manahan for his valuable assistance in all phases of this work.

**Registry No.** Sulfuryl chloride, 7791-25-5; cyclohexanone, 108-94-1; bisphenol A, 80-05-7; 4-*tert*-butylphenol, 98-54-4; acetone, 67-64-1; phenol, 108-95-2.

# N-Substituted (Sarcosylamino)benzophenones. Their Synthesis and Conversion into Heterocycles[1,2]

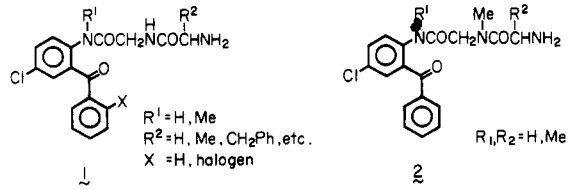
Kentaro Hirai,* Teruyuki Ishiba, Hirohiko Sugimoto, and Toshio Fujishita

*Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan*

*Received May 5, 1981*

A synthetic study of N-substituted (sarcosylamino)benzophenones **2** is described. The target molecules **2** were found to be reactive under neutral conditions, affording intramolecularly cyclized products. Compounds **6a** and **13a** were converted into pyrazino[2,1-*b*]quinazoline **9a** and pyrazino[2,3-*b*]quinoline **18a**, respectively. The new heterocycles were characterized, and possible mechanisms are proposed for their formation.

Recently we have reported the synthesis of a novel series of (peptidoamino)benzophenones **1**[1,3] as ring-opened de-




**1** **2**

rivatives of 1,4-benzodiazepine. These compounds possess significant central nervous system (CNS) activities. We thought that appropriate modification of this system would produce compounds with qualitatively different pharmacological profiles.

A marked difference in the CNS activities between aniline N-Me and N-H derivatives in **1** has been observed. Furthermore, release of terminal amino acid from **1** followed by cyclization leads to 1,4-benzodiazepine. Introduction of a methyl group to the nitrogen atom in dipeptide bond part of **1** would change its activities by affecting the dipeptide bond (N(Me)-CO) cleavage in vivo as well as inhibiting the formation of 1,4-benzodiazepine. Thus, preparation of **2** is of interest from the synthetic and pharmacological points of view. We found that the target molecules **2** were particulary reactive in solution, undergoing cyclization to afford pyrazino[2,1-*b*]quinazoline or pyrazino[2,3-*b*]quinoline derivatives and/or cleavage of anilide bond to give aminobenzophenones depending on the substituent ($R^1$, $R^2$). A noteworthy feature of this cyclization is that it takes place essentially under neutral condition, whereas the cyclization of [[(iodoacetyl)-glycyl]amino]benzophenone and [[(cyanoacetyl)glycyl]-amino]benzophenone to form oxazolo[3,2-*d*][1,4]benzo-

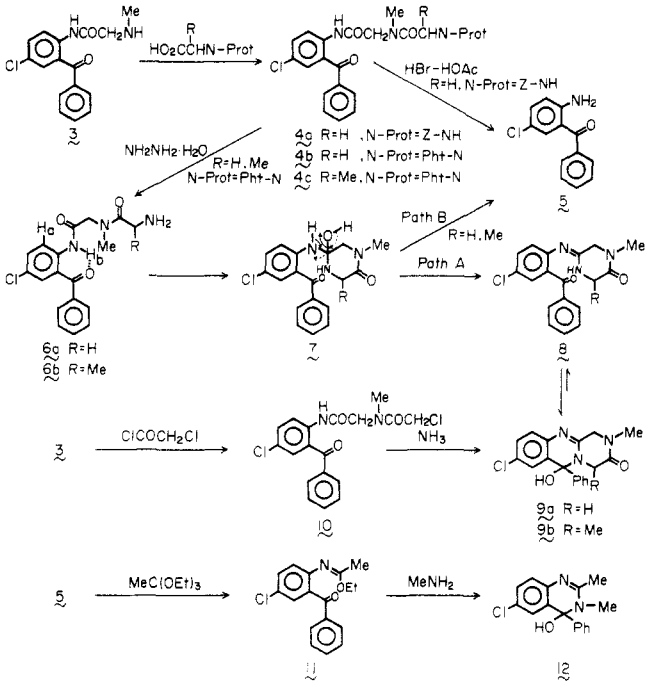
(1) This paper is part 5 of a series on "Benzophenone Related Compounds". Part 4: Hirai, K.; Ishiba, T.; Sugimoto, H.; Fujishita, T.; Tsukinoki, Y.; Hirose, K. *J. Med. Chem.* **1981**, *24*, 20.

(2) A part of this paper was presented at the 12th Congress of Heterocyclic Chemistry, Tokyo, Japan, 1979. For an abstract, see: *Heterocycles* **1980**, *14*, 121.

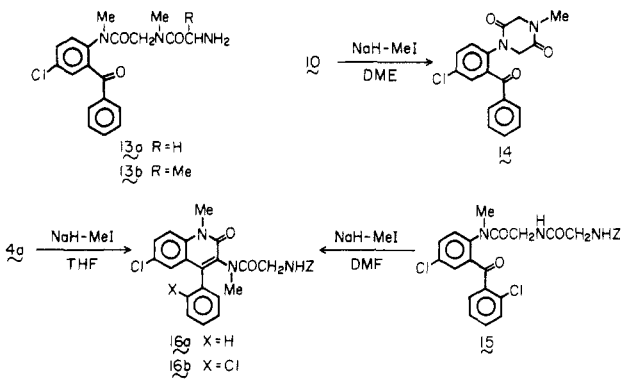
(3) (a) Hirai, K.; Ishiba, T.; Sugimoto, H.; Sasakura, K.; Fujishita, T.; Tsukinoki, Y.; Hirose, K. *Chem. Pharm. Bull.* **1978**, *26*, 1947. (b) Hirai, K.; Ishiba, T.; Sugimoto, H.; Sasakura, K.; Fujishita, T.; Toyoda, T.; Tsukinoki, Y.; Jōyama, H.; Hatakeyama, H.; Hirose, K. *J. Med. Chem.* **1980**, *23*, 764.

0022-3263/81/1946-4489$01.25/0 

Scheme I



Scheme II



diazepine and Smiles rearranged quinolone derivatives, respectively, requires the presence of strong base such as NaH.[4]

## Results and Discussion

**Synthesis of [(Glycylsarcosyl)amino]benzophenone and Its Conversion into Pyrazino[2,1-*b*]quinazoline.** The chosen synthetic approach to **6** employed (sarcosylamino)benzophenone **3**[5] as starting material (Scheme I). Compound **3** was coupled with *N*-(benzyloxycarbonyl)glycine (Z-Gly-OH) activated by $SOCl_2$ in hexamethylphosphoric triamide[6] (HMPA) to afford [[[*N*-(benzyloxycarbonyl)glycyl]sarcosyl]amino]benzophenone **4a** in 85% yield. However, deprotection[7] of **4a** with HBr in HOAc did not lead to the desired [(glycylsarcosyl)amino]benzophenone **6a** and produced only aminobenzophenone **5** by cleavage of the anilide bond. This result suggested that the anilide bond of **4a** and/or **6a** is readily cleaved in acidic media, and the Z group in **4a** is not appropriate as the protecting group. Thus, we prepared [[(*N*-phthaloylglycyl)sarcosyl]amino]benzophenone **4b** as the precursor of **6a**. *N*-Phthaloylglycine (Pht-Gly-OH) was activated by $SOCl_2$ in HMPA and coupled with **3** to give **4b** in 94% yield. Treatment of **4b** with hydrazine hydrate in refluxing EtOH gave complex mixtures, and the main product was **5**. Mild reaction conditions were required to obtain **6a**. Therefore, hydrazinolysis was carried out in chloroform–EtOH at 0 °C to room temperature. After the usual workup, isolation by short-column chromatography afforded the expected **6a** as an oily product in low yield.[8]

The structure of **6a** was confirmed by its spectral data. The IR ($CHCl_3$) spectrum of **6a** clearly showed the presence of amide carbonyl and benzoyl carbonyl groups at 1680 and 1640 $cm^{-1}$, respectively. In the NMR ($CDCl_3$) spectrum, a broad singlet at $\delta$ 1.77 was attributed to amino protons and a singlet at $\delta$ 3.13 to the *N*-methyl group. The singlet signals at $\delta$ 3.68 and 4.23 were assigned to two methylene protons. Also, a doublet ($J$ = 10 Hz) due to an aromatic $H_a$ proton, which was deshielded by the adjacent amide carbonyl group, appeared at $\delta$ 8.60, and a broad singlet at $\delta$ 10.8 was assigned to an anilide $H_b$ proton which was intramolecularly hydrogen bonded to the carbonyl oxygen of the benzophenone.

Isolated **6a** itself was very reactive and immediately changed into the insoluble[9] compound **9a**, which was identified as the monodehydrated product of **6a** by its elemental analysis and mass spectrum ($M^+$, $m/e$ 341). In the UV (EtOH) spectrum of **9a**, strong absorptions at 225 and 289 nm were characteristic of 3,4-dihydroquinazoline derivatives.[10] The IR (Nujol) spectrum showed absorption at 1670 $cm^{-1}$ due to the amide (lactam) band.

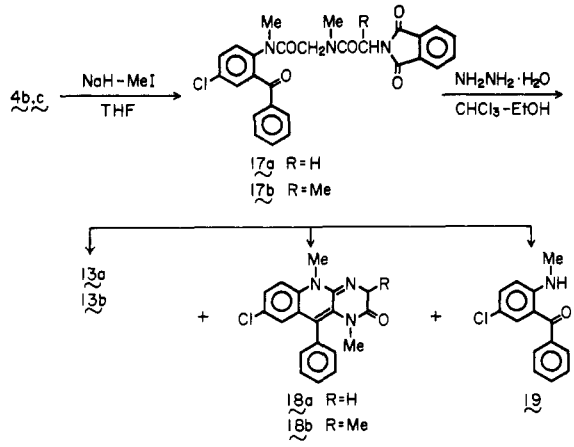
In order to confirm the structure of **9a**, we tried a model experiment. Treatment of imino ether **11**[10a] with methylamine in EtOH gave 6-chloro-2,3-dimethyl-3,4-dihydro-4-phenylquinazoline (**12**), which displayed a UV spectrum very similar to that of **9a**. Thus, the structure of **9a** was assigned as 8-chloro-1,2-dihydro-6-hydroxy-2-methyl-6-phenylpyrazino[2,1-*b*]quinazolin-3(4*H*)-one. Compound **9a** was also prepared in 66% yield by ammonolysis of **10**, which was readily available from **3** by chloroacetylation.

A possible mechanism to account for the formation of **9a** from **6a** is presented in Scheme I. Initial intramolecular attack of the terminal amino group in **6a** at the anilide carbonyl carbon gives the intermediate **7**. Subsequent dehydration (path A) produces the amidine **8**, which is the tautomer of **9a**. Compound **9a** is supposed to be more thermodynamically stable than **8**. On the other hand, compound **5**, being a good leaving group, may be formed through an addition and elimination process (path B). Indeed, conversion of **6a** into **9a** is accompanied by concomitant formation of a trace amount of **5**. This result directed our attention toward the reactivity of [(alanylsarcosyl)amino]benzophenone **6b**. Coupling of **3** with *N*-phthaloyl-DL-alanine gave the corresponding **4c**, followed by deprotection with hydrazine hydrate in EtOH at room temperature to afford **6b**. However, compound **6b** was more stable than **6a** and did not form pyrazino[2,1-*b*]quinazoline **9b**, gradually producing only **5**. The difference of reactivities between **6a** and **6b** is not clear.

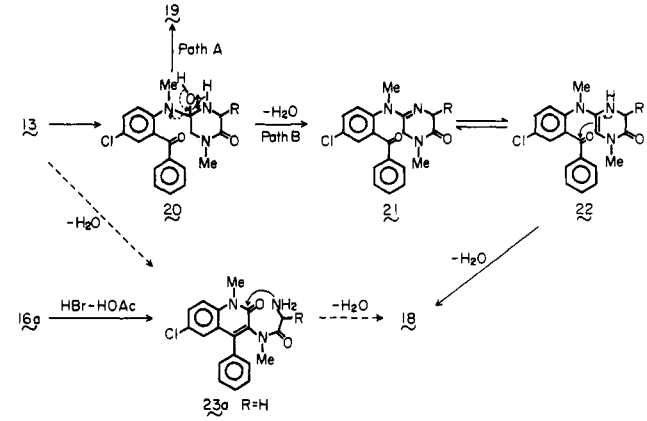
**Synthesis of [(*N*-Glycylsarcosyl)methylamino]benzophenone and Its Conversion into Pyrazino[2,3-*b*]quinoline.** We next investigated the synthesis of [(glycylsarcosyl)methylamino]benzophenone **13a** and its

(4) Hirai, K.; Ishiba, T.; Fujishita, T.; Sugimoto, H. *Heterocycles* **1980**, *14*, 635.
(5) Fryer, R. I.; Brust, B.; Sternbach, L. H. *J. Chem. Soc.* **1964**, 3097.
(6) Normant, J. F.; Deshayes, H. *Bull. Soc. Chim. Fr.* **1972**, 2854.
(7) Catalytic hydrogenation of **4a** was incomplete.
(8) Probably **6a** was converted into **9a** during isolation and was not eluted well.
(9) Compound **9a** did not dissolve in most of organic solvents, and the NMR spectrum was not determined.
(10) (a) Meguro, K.; Tawada, H.; Kuwada, Y. *Chem. Pharm. Bull.* **1973**, *21*, 1619. (b) Derig, M. E.; Fryer, R. I.; Hillery, S. S.; Metlesis, W.; Silverman, G. *J. Org. Chem.* **1971**, *36*, 782.

Scheme III



Scheme IV



reactivity. Attempts to synthesize **13a** by initial alkylation of **10**, **4a** and **15** were unsuccessful (Scheme II). Treatment of **10** with NaH–MeI in 1,2-dimethoxyethane (DME) afforded exclusively piperazine-2,5-dione **14** via intramolecular N-alkylation. Furthermore, N-methylation of **4a** and **15**[3] with NaH–MeI in THF or DMF gave quinolone derivatives[5] **16a** and **16b**, respectively. Finally, target molecule **13a** was synthesized as shown in Scheme III. Compound **4b**, a precursor of **6a**, was successfully converted into N-methylated **17a** in 66% yield by treatment with NaH in THF at −5 °C for 30 min, followed by addition of MeI at room temperature for 2 h. Cyclized quinolone was not detected from the reaction mixture, although a trace of starting material **4b** was recovered. Thus, **17a** was treated with hydrazine hydrate in chloroform–EtOH at room temperature overnight. The crude product mixture, which showed several spots on TLC, was subjected to column chromatography. Three products were identified as (methylamino)benzophenone **19**, pyrazino[2,3-*b*]quinoline **18a**, and the desired **13a**, isolated in 1%, 2%, and 73% yields, respectively.

The NMR ($CDCl_3$) spectrum of **13a** was complicated by the presence of its rotational isomer along the amide bond. The structure of **13a** was confirmed by its formation of a salt with oxalic acid. The mass spectrum of the oxalate showed the peak at $m/e$ 373 due to free amine **13a**. Furthermore, **13a** was characterized by elemental analysis of its oxalate. The structure of **18a** was based on the spectral data. In the IR (Nujol) spectrum of **18a**, strong absorption at 1670 $cm^{-1}$ indicated the presence of amide carbonyl. While in the NMR ($CDCl_3$) spectrum, two singlets at $\delta$ 2.60 and 3.68 were assigned to the 1-methyl and the 5-methyl groups, respectively. Furthermore, a singlet due to methylene protons appeared at $\delta$ 4.47. The mass spectrum of **18a** showed the molecular ion peak at $m/e$ 337. Finally, X-ray analysis[11] determined the structure of **18a** definitely.

We next studied the reactivity of **13a**. Monitoring the reaction of **13a** in chloroform solution by TLC showed the gradual appearance of **18a** and **19**. It should be noted that the cyclized product **18a** was derived from the isolated **13a**, although the conversion into **18a** was slow and not accelerated under acidic (*p*-toluenesulfonic acid) or basic ($Al_2O_3$) conditions. The methanolic solution of **13a**, which had been left to stand for 6 days, afforded **18a** in 49% yield from **17a**. Similarly, **13b** was obtained by deprotection of **17b** with hydrazine hydrate. Allowing the crude **13b** to stand in MeOH gave **18b** in 32% yield from **17b**. An explanation of the conversion of **13** into **18** and **19** under neutral condition is shown in Scheme IV.

Intramolecular addition of the terminal amino group in **13** at the anilide carbonyl carbon leads to intermediate **20**. Addition and elimination (path A) occur to form **19** as a leaving group. Alternatively, subsequent dehydration (path B) in **20** produces an equilibrium mixture of amidine **21** and enamine **22**. Thus, the intramolecular condensation of enamine **22** with the ketone carbonyl affords **18**. An alternative reaction mechanism might be considered which involves the initial formation of quinolone **23** from **13**, followed by cyclization to yield **18**. However, **23a**, which was derived by deprotection of **16a** with HBr in HOAc, did not afford **18a** under neutral conditions.

This result suggested that the formation of **18** proceeds via path B. The double bond of 1,4-pyrazine in **22** was activated by the presence of electron-donating groups. Thus, the intramolecular attack toward the benzoyl carbonyl carbon might be facilitated even under neutral condition to afford **18**.

## Experimental Section

Melting points were obtained on a Yamato apparatus in open capillary tubes and are uncorrected. IR spectra were determined on either a JASCO DS-403G or a Hitachi 215 spectrophotometer and are reported in reciprocal centimeters. NMR spectra were determined on a Varian T-60 instrument and chemical shifts are reported in parts per million ($\delta$) down field from internal tetramethylsilane. UV spectra were measured with a Hitachi EPS-2 spectrophotometer. Mass spectra were recorded with a Hitachi RMU-6E spectrometer. All experiments requiring anhydrous conditions were carried out under a stream of nitrogen, and tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from lithium aluminum hydride.

Hexamethylphosphoric triamide (HMPA), dimethylformamide (DMF), and acetonitrile (MeCN) were dried over 4-Å molecular sieves.

**2′-Benzoyl-4′-chloro-*N*-[*N*-(benzyloxycarbonyl)glycyl]-sarcosinanilide (4a).** To a solution of 1.05 g (5.02 mmol) of Z-Gly-OH in 5 mL of HMPA was added 600 mg (5.04 mmol) of $SOCl_2$ dropwise at −8 to −5 °C. After the mixture was stirred for 15 min, a solution of 1.52 g (5.02 mmol) of 2′-benzoyl-4′-chlorosarcosinanilide (**3**) in 10 mL of EtOAc was added dropwise, and the mixture was stirred for 5 h at −5 °C to room temperature. The reaction mixture was poured onto ice–water and neutralized with aqueous $NaHCO_3$. The organic phase was separated, washed three times with water, and dried over $Na_2SO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography on $SiO_2$ with $CH_2Cl_2$–EtOAc (1:1, v/v) as eluant, affording 2.12 g (85%) of **4a**: mp 108–110 °C (from EtOAc–*n*-hexane); NMR ($CDCl_3$) $\delta$ 3.13 (s, 3 H, $NCH_3$), 4.07–4.37 (m, 4 H, $2CH_2$), 5.13 (s, 2 H, $CH_2Ph$), 5.83 (br m, 1 H, NHZ), 7.23–7.93 (m, 12 H, aromatic), 8.57 (d, $J$ = 9 Hz, 1 H, aromatic), 11.0 (br s, 1 H, NH); IR ($CHCl_3$) 3380, 1730, 1665 $cm^{-1}$. Anal. Calcd for $C_{26}H_{24}N_3O_5Cl$: C, 63.22; H, 4.90; N, 8.51; Cl, 7.18. Found: C,

(11) The confirmatory X-ray structural study will be presented in *Cryst. Struct. Commun.*

63.17; H, 4.74; N, 8.47; Cl, 7.42.

**Deprotection of 4a.** A solution of 500 mg (1.01 mmol) of **4a** in 2 mL of 30% HBr in HOAc was stirred for 45 min at room temperature. Excess ether was added, and the supernatant ether was removed by decantation. The crude product was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The organic phase was separated and dried over $Na_2SO_4$. The solvent was removed in vacuo, and 210 mg (90%) of 2-amino-5-chlorobenzophenone (**5**) was obtained. NMR and IR spectra of **5** were identical with those of an authentic sample.

**2′-Benzoyl-4′-chloro-*N*-(*N*-phthaloylglycyl)sarcosinanilide (4b).** To a solution of 2.7 g (13.2 mmol) of Pht-Gly-OH in 20 mL of HMPA and 5 mL of MeCN was added 1.56 g (13.1 mmol) of $SOCl_2$ dropwise at −10 °C. The mixture was stirred for 15 min, and a solution of 3.0 g (9.9 mmol) of **3** in 20 mL of ether was added dropwise at −5 °C. The reaction mixture was gradually warmed to 0 °C and stirred for 2 h. Excess ether was added, and the mixture was neutralized with aqueous $NaHCO_3$. The resulting precipitate was collected by filtration and washed several times with water. Recrystallization from EtOH–$CH_2Cl_2$ gave 4.6 g (94%) of **4b**: mp 163–164 °C; NMR ($CDCl_3$) δ 3.30 (s, 3 H, $NCH_3$), 4.23 (s, 2 H, $CH_2$), 4.77 (s, 2 H, $CH_2$), 7.33–7.97 (m, 11 H, aromatic), 8.62 (d, $J$ = 10 Hz, 1 H, aromatic), 11.2 (s, 1 H, NH); IR (Nujol) 3340, 1775, 1715, 1675, 1660 $cm^{-1}$. Anal. Calcd for $C_{26}H_{20}N_3O_5Cl$: C, 63.74; H, 4.11; N, 8.58; Cl, 7.24. Found: C, 64.04; H, 4.07; N, 8.66; Cl, 7.32.

**Deprotection of 4b.** To a solution of 600 mg (1.22 mmol) of **4b** in 10 mL of $CHCl_3$ and 9 mL of EtOH was added 300 mg (5.99 mmol) of hydrazine hydrate at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C to room temperature, and the separated phthalhydrazide was removed by filtration. The filtrate was concentrated in vacuo, and the residue was partitioned between $CH_2Cl_2$ and diluted $NH_4OH$. The organic phase was separated, followed by acidification with 3 N HCl. The aqueous phase was made basic with diluted $NH_4OH$, extracted with $CH_2Cl_2$, and dried over $Na_2SO_4$. The solvent was concentrated in vacuo to half of its volume and gave 250 mg (60%) of 8-chloro-1,2-dihydro-6-hydroxy-2-methyl-6-phenylpyrazino[2,1-*b*]quinazolin-3(4*H*)-one (**9a**). Compound **9a** was characterized without further purification: mp 200 °C dec; IR (Nujol) 1670, 1605 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 225 nm (log ε 4.22), 289 (4.10); mass spectrum, $m/e$ (relative intensity) 341 (73, $M^+$), 324 (53), 264 (100), 77 (95). Anal. Calcd for $C_{18}H_{16}N_3O_2Cl$: C, 63.25; H, 4.71; N, 12.29; Cl, 10.37. Found: C, 63.24; H, 4.68; N, 12.49; Cl, 10.34.

**Isolation of 2′-Benzoyl-4′-chloro-*N*-glycylsarcosinanilide (6a).** Compound **6a** was isolated to confirm its structure and converted into **9a**. Hydrazinolysis of **4b** was done as stated above. After the resulting phthalhydrazide had been removed by filtration, the filtrate was concentrated in vacuo at 0 °C, and the residue was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo at 0 °C. The residual oil was immediately purified by short-column chromatography on $SiO_2$ with MeOH as eluant and afforded a small amount (<10%) of **6a** as a viscous oil: $R_f$ 0.15; NMR ($CDCl_3$) δ 1.77 (br s, 2 H, $NH_2$), 3.13 (s, 3 H, $NCH_3$), 3.68 (s, 2 H, $CH_2$), 4.23 (s, 2 H, $CH_2$), 7.33–7.87 (m, 7 H, aromatic), 8.60 (d, $J$ = 10 Hz, 1 H, aromatic), 10.8 (br s, 1 H, NH); IR ($CHCl_3$) 3250, 1680, 1640 (br) $cm^{-1}$. A solution of isolated **6a** in $CHCl_3$ was allowed to stand for a short time, **9a** was precipitated, and a trace of **5** was obtained from the mother liquor.

**Chloroacetylation of 3.** A mixture of 910 mg (3.00 mmol) of **3** and 510 mg (4.52 mmol) of chloroacetyl chloride in 15 mL of benzene was refluxed for 1 h. The reaction mixture was evaporated to dryness. The residue was chromatographed on $SiO_2$ with $CH_2Cl_2$–EtOAc (10:1, v/v) as eluant and afforded 1.0 g (87%) of 2′-benzoyl-4′-chloro-*N*-(chloroacetyl)sarcosinanilide (**10**) as a viscous oil: NMR ($CDCl_3$) δ 3.27 (s, 3 H, $NCH_3$), 4.20 (s, 2 H, $CH_2$), 4.30 (s, 2 H, $CH_2$), 7.37–7.87 (m, 7 H, aromatic), 8.67 (d, $J$ = 10 Hz, 1 H, aromatic), 11.0 (s, 1 H, NH); IR ($CHCl_3$) 3285, 1690, 1665, 1640 $cm^{-1}$.

**Ammonolysis of 10; Alternative Preparation of 9a.** To a solution of 500 mg (1.32 mmol) of **10** in 10 mL of dioxane was added 5 mL of 10% $NH_3$ in EtOH, and the solution was allowed to stand for 1 day. The resulting precipitate was collected by filtration and thoroughly washed with EtOH, affording 300 mg (66%) of **9a**.

**2′-Benzoyl-4′-chloro-*N*-(phthaloyl-DL-alanyl)sarcosinanilide (4c).** Compound **4c** was prepared by the same method as for **4b** in 89% yield: mp 163–164 °C (from EtOAc–*n*-hexane); NMR ($CDCl_3$) δ 1.70 (d, $J$ = 7 Hz, 3 H, $CH_3$), 3.12 (s, 3 H, $NCH_3$), 3.93 and 4.57 (AB q, $J$ = 17 Hz, 2 H, $CH_2$), 5.35 (br q, 1 H, CH), 7.30–8.00 (m, 11 H, aromatic), 8.47 (br m, 1 H, aromatic), 10.8 (s, 1 H, NH); IR (Nujol) 3250, 1770, 1700, 1660 $cm^{-1}$. Anal. Calcd for $C_{27}H_{22}N_3O_5Cl$: C, 64.35; H, 4.40; N, 8.34; Cl, 7.04. Found: C, 64.55; H, 4.52; N, 8.19; Cl, 7.14.

**Deprotection of 4c.** A solution of 1.00 g (1.98 mmol) of **4c** and 300 mg (5.99 mmol) of hydrazine hydrate in 5 mL of EtOH and 5 mL of $CHCl_3$ was stirred at room temperature for 15 h. The resulting precipitates were filtered off, and the filtrate was concentrated in vacuo. The residue was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$, and the organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was separated by chromatography on $SiO_2$ with EtOAc as eluant, affording 135 mg (29%) of **5**. Further elution with MeOH gave 260 mg (36%) of 2′-benzoyl-4′-chloro-*N*-(DL-alanyl)sarcosinanilide (**6b**) as a viscous oil: NMR ($CDCl_3$) δ 1.33 (d, $J$ = 7 Hz, 3 H, $CH_3$), 1.72 (br m, 2 H, $NH_2$), 3.20 (s, 3 H, $NCH_3$), 3.90 and 4.53 (AB q, $J$ = 16 Hz, 2 H, $CH_2$), 4.00 (br q, 1 H, CH), 7.17–7.83 (m, 7 H, aromatic), 8.65 (d, $J$ = 10 Hz, 1 H, aromatic), 11.0 (br s, 1 H, NH); IR ($CHCl_3$) 3275, 1680, 1640 (br), 1590 $cm^{-1}$. A solution of **6b** in $CHCl_3$ kept at room temperature for a long time produced **5** exclusively and **9b** was not detected.

**6-Chloro-2,3-dimethyl-3,4-dihydro-4-hydroxy-4-phenylquinazoline (12).** A mixture of 500 mg (1.66 mmol) of 5-chloro-2-[(1-ethoxyethylidene)amino]benzophenone (**11**) and 5 mL of 30% methylamine in EtOH was allowed to stand for 2 days. The separated crystals were collected by filtration and thoroughly washed with EtOH and ether, affording 280 mg (59%) of **12**, which was characterized without further purification: mp 214–217 °C dec; IR (Nujol) 1600, 1580 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 225 nm (log ε 4.22), 290 (4.10); mass spectrum, $m/e$ (relative intensity) 286 (54, $M^+$), 269 (50), 209 (100), 77 (49). Anal. Calcd for $C_{16}H_{15}N_2OCl$: C, 67.02; H, 5.27; N, 9.77; Cl, 12.36. Found: C, 67.13; H, 5.29; N, 9.81; Cl, 12.25.

**1-(2-Benzoyl-4-chlorophenyl)-4-methylpiperazine-2,5-dione (14).** To a slurry of 70 mg (2.9 mmol) of *n*-hexane-washed NaH in 5 mL of DME was slowly added a solution of 1.1 g (2.9 mmol) of **10** at 0 °C. After 15 min, 0.50 g (3.5 mmol) of MeI was added, and the mixture was gradually warmed to room temperature. After being stirred for 2 h, the reaction mixture was poured onto ice–water and extracted with EtOAc. The EtOAc extract was washed with water and dried over $Na_2SO_4$. The solvent was removed in vacuo, and the residue was recrystallized from EtOAc, affording 0.95 g (95%) of **14**: mp 148–149 °C; NMR ($CDCl_3$) δ 2.92 (s, 3 H, $NCH_3$), 3.83 (s, 2 H, $CH_2$), 4.37 (s, 2 H, $CH_2$), 7.17–7.90 (m, 8 H, aromatic); IR (Nujol) 1685, 1675, 1655, 1590 $cm^{-1}$. Anal. Calcd for $C_{18}H_{15}N_2O_3Cl$: C, 63.07; H, 4.41; N, 8.17; Cl, 10.34. Found: C, 62.98; H, 4.46; N, 8.37; Cl, 10.26.

**6-Chloro-1-methyl-3-[methyl[*N*-(benzyloxycarbonyl)glycyl]amino]-4-phenyl-2(1*H*)-quinolone (16a).** To a slurry of 100 mg (4.17 mmol) of *n*-hexane-washed NaH in 10 mL of THF was added dropwise a solution of 1.98 g (4.01 mmol) of **4a** in 60 mL of THF at −5 to 0 °C. After the mixture was stirred for 15 min, 800 mg (5.64 mmol) of MeI was added, and the mixture was gradually warmed to room temperature and stirred for 1 h. The reaction mixture was poured onto ice–water and extracted with EtOAc. The extract was washed with water and dried over $Na_2SO_4$. Removal of the solvent in vacuo and purification of the residual oil by chromatography on $SiO_2$ with EtOAc as eluant gave 950 mg (48%) of **16a**: mp 209–210 °C (from EtOH); NMR ($CDCl_3$) δ 2.87 and 2.92 (2 s, 3 H, $NCH_3$), 3.78 (s, 3 H, $NCH_3$), 3.67–4.17 (m, 2 H, $CH_2$), 5.05 (s, 2 H, $CH_2Ph$), 5.62 (br s, 1 H, NH), 7.02–7.67 (m, 13 H, aromatic); IR (Nujol) 3320, 1720, 1675, 1630, 1580 $cm^{-1}$. Anal. Calcd for $C_{27}H_{24}N_3O_4Cl$: C, 66.19; H, 4.94; N, 8.58; Cl, 7.24. Found: C, 66.40; H, 4.93; N, 8.58; Cl, 7.48.

**6-Chloro-4-(2-chlorophenyl)-1-methyl-3-[methyl[*N*-(benzyloxycarbonyl)glycyl]amino]-2(1*H*)-quinolone (16b).** To a solution of 1.32 g (2.50 mmol) of *N*-[*N*-(benzyloxycarbonyl)glycyl]-*N*′-methyl-4′-chloro-2′-(2-chlorobenzoyl)glycinanilide (**15**) in 10 mL of DMF was added 0.12 g (2.5 mmol) of NaH (50% dispersion in mineral oil) portionwise at room temperature. After 15 min, 0.43 g (3.0 mmol) of MeI was added, and the reaction

mixture was stirred at room temperature for 1.5 h. The DMF was removed in vacuo, and the residue was partitioned between EtOAc and water. The organic phase was washed with water, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was triturated with ether and recrystallized from EtOAc, affording 0.60 g (46%) of **16b**: mp 208–209 °C; NMR ($CDCl_3$) δ 2.90 and 2.98 (2 s, 3 H, $NCH_3$), 3.82 (s, 3 H, $NCH_3$), 3.93 (m, 2 H, $CH_2$), 5.07 (s, 2 H, $CH_2Ph$), 5.58 (br s, 1 H, NH), 6.88–7.73 (m, 12 H, aromatic); IR (Nujol) 3300, 1730, 1680, 1630 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 212 nm (log ε 4.68), 240 (4.59), 283 (3.83), 350 (3.84), 368 (sh, 3.68). Anal. Calcd for $C_{27}H_{23}N_3O_4Cl_2$: C, 61.84; H, 4.42; N, 8.01; Cl, 13.52. Found: C, 61.84; H, 4.52; N, 7.94; Cl, 13.57.

**N-Methylation of 4b.** To a slurry of 360 mg (15.0 mmol) of *n*-hexane-washed NaH in 20 mL of THF was added dropwise a solution of 7.35 g (15.0 mmol) of **4b** in 80 mL of THF at −5 °C over 30 min. After the mixture was stirred at the same temperature for 30 min, 4.50 g (31.7 mmol) of MeI was added, and the mixture was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was poured onto ice–water and extracted twice with EtOAc. The extracts were washed with water and dried over $Na_2SO_4$. The solvent was removed in vacuo, and the residue was separated by chromatography on $SiO_2$ with $CH_2Cl_2$–EtOAc (4:1 v/v) as eluant, affording 5.0 g (66%) of *N'*-methyl-2'-benzoyl-4'-chloro-*N*-(*N*-phthaloylglycyl)sarcosinanilide (**17a**) as a viscous oil: NMR ($CDCl_3$) 2.93, 2.97, 3.03, and 3.18 (4 s, 6 H, $2NCH_3$), 3.77–4.83 (m, 4 H, $2CH_2$), 7.37–7.97 (m, 12 H, aromatic); IR ($CHCl_3$) 1775, 1720, 1665 (br) $cm^{-1}$.

**Deprotection of 17a.** A mixture of 2.00 g (3.97 mmol) of **17a** and 480 mg (9.59 mmol) of hydrazine hydrate in 10 mL of $CHCl_3$ and 10 mL of EtOH was stirred at room temperature for 12 h, and the separated phthalhydrazide was removed by filtration. The filtrate was concentrated in vacuo, and the residue was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The organic phase was separated, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was separated by chromatography on $SiO_2$. Elution with $CH_2Cl_2$ gave 10 mg (1%) of 5-chloro-2-(methylamino)benzophenone (**19**) which was identical with an authentic sample (IR and NMR spectra). Elution with EtOAc gave 35 mg (2%) of 8-chloro-1,5-dimethyl-10-phenyl-1*H*-pyrazino[2,3-*b*]quinolin-2-(3*H*)-one (**18a**): mp 205 °C dec (from EtOAc–$CH_2Cl_2$); NMR ($CDCl_3$) δ 2.60 (s, 3 H, $NCH_3$), 3.68 (s, 3 H, $NCH_3$), 4.47 (s, 2 H, $CH_2$), 6.97–7.70 (m, 8 H, aromatic); IR (Nujol) 1670, 1625, 1595 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 243 nm (log ε 4.28), 258 (sh, 4.25), 262 (4.24), 299 (3.54), 311 (3.51), 374 (3.91); mass spectrum, *m/e* (relative intensity) 337 (100, $M^+$), 308 (86), 260 (35). Anal. Calcd for $C_{19}H_{16}N_3OCl$: C, 67.55; H, 4.73; N, 12.44; Cl, 10.49. Found: C, 67.74; H, 4.67; N, 12.58; Cl, 10.68. Further elution with MeOH gave 1.1 g (73%) of *N'*-methyl-2'-benzoyl-4'-chloro-*N*-glycylsarcosinanilide (**13a**) as a viscous oil. Compound **13a** was treated with excess of oxalic acid in MeOH and afforded the corresponding oxalate, which was recrystallized from aqueous MeCN: mp 113–115 °C; mass spectrum, *m/e* (relative intensity) 373 (3), 355 (7), 337 (100), 308 (88), 105 (38). Anal. Calcd for $C_{19}H_{20}N_3O_3Cl{\cdot}2CO_2H{\cdot}0.75H_2O$: C, 52.83; H, 4.96; N, 8.80; Cl, 7.43. Found: C, 52.80; H, 4.81; N, 8.83; Cl, 7.27.

**Formation of 18a from 13a in MeOH.** Hydrazinolysis of **17a** (2.6 g, 5.2 mmol) was carried out by the same procedure to afford 1.9 g of the crude **13a**. Compound **13a** was dissolved in 20 mL of MeOH and allowed to stand at room temperature in the dark for 6 days. The separated yellow crystals were collected by filtration and washed with MeOH, affording 820 mg (47%) of **18a**. The mother liquor was concentrated in vacuo, and the residue was separated by chromatography on $SiO_2$. Elution with $CH_2Cl_2$ gave 35 mg (2.8%) of **19**. Continued elution with EtOAc gave 40 mg (2.3%) of **18a**.

***N*-[*N*-Phthaloyl-DL-alanyl]-*N'*-methyl-2'-benzoyl-4'-chlorosarcosinanilide (17b).** To a slurry of 96 mg (4.0 mmol) of *n*-hexane-washed NaH in 20 mL of THF was added portionwise 2.02 g (4.0 mmol) of **4c** at −8 to 0 °C. After the mixture was stirred for 30 min, 750 mg (5.28 mmol) of MeI was added, and the mixture was gradually warmed to room temperature and then stirred for 1.5 h. The reaction mixture was poured onto ice–water and extracted twice with EtOAc. The combined extracts were washed with water and dried over $Na_2SO_4$. The solvent was removed, and the residue was chromatographed on $SiO_2$ with $CH_2Cl_2$–EtOAc (4:1, v/v), affording 1.3 g (63%) of **17b** as a viscous oil: NMR ($CDCl_3$) δ 1.70 (br d, *J* = 7 Hz, 3 H, $CH_3$), 3.00 (br s, 6 H, $2NCH_3$), 3.72 and 4.60 (AB q, *J* = 16 Hz, 2 H, $CH_2$), 5.22 (br q, *J* = 7 Hz, 1 H, CH), 7.17–7.97 (m, 12 H, aromatic); IR ($CHCl_3$) 1775, 1720, 1660 (br) $cm^{-1}$.

**Deprotection of 17b and Formation of 8-Chloro-10-phenyl-1,3,5-trimethyl-1*H*-pyrazino[2,3-*b*]quinolin-2-(3*H*)-one (18b).** To a solution of 2.0 g (3.9 mmol) of **17b** in 10 mL of $CHCl_3$ and 10 mL of EtOH was added 0.46 g (9.6 mmol) of hydrazine hydrate, and the mixture was stirred at room temperature overnight. The resulting precipitate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The organic phase was separated and dried over $Na_2SO_4$. Removal of the solvent in vacuo afforded 1.4 g of the crude product, which was dissolved in 13 mL of MeOH and allowed to stand at room temperature in the dark for 10 days. The solution was concentrated, and the residue was purified by chromatography on $SiO_2$. Elution with $CH_2Cl_2$ afforded 20 mg (2.1%) of **19**. Further elution with EtOAc gave 0.44 g (32%) of **18b**: mp 179–180 °C (from EtOAc–*n*-hexane); NMR ($CDCl_3$) δ 1.47 (d, *J* = 7 Hz, 3 H, $CH_3$), 2.57 (s, 3 H, $NCH_3$), 3.67 (s, 3 H, $NCH_3$), 4.42 (q, *J* = 7 Hz, 1 H, CH), 7.07–7.67 (m, 8 H, aromatic); IR (Nujol) 1670, 1620, 1595 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 243 nm (log ε 4.58), 262 (4.59), 300 (3.88), 311 (3.87), 376 (3.94); mass spectrum, *m/e* (relative intensity) 351 (55, $M^+$), 336 (100), 323 (45), 322 (39), 308 (90). Anal. Calcd for $C_{20}H_{18}N_3OCl$: C, 68.28; H, 5.16; N, 11.94; Cl, 10.08. Found: C, 68.53; H, 5.19; N, 11.94; Cl, 10.18. Elution with MeOH gave 0.50 g (33%) of **13b** as a viscous oil. The NMR ($CDCl_3$) spectrum of free amine **13b** showed a complicated pattern due to the presence of a rotational isomer. An attempt to make the corresponding salt (oxalate) was unsuccesful.

**6-Chloro-1-methyl-3-(methylglycylamino)-4-phenyl-2-(1*H*)-quinolone (23a).** To a suspension of 40 mg (0.82 mmol) of **16a** in 0.5 mL of HOAc was added a solution of 0.5 mL of 25% HBr in HOAc, and the mixture was stirred for 15 min at room temperature. Excess ether was added, and the supernatant ether was removed by decantation. The crude product was partitioned between $CH_2Cl_2$ and aqueous $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and concentrated in vacuo to afford 25 mg (86%) of **23a** as an oily product: NMR ($CDCl_3$) δ 1.63 (br m, 2 H, $NH_2$), 2.85 and 2.92 (2 s, 3 H, $NCH_3$), 3.20 (br m, 2 H, $CH_2$), 3.80 (s, 3 H, $NCH_3$), 6.97–7.67 (m, 8 H, aromatic). Compound **23a** was dissolved in MeOH and allowed to stand for 1 week. Formation of cyclized product **18a** was not observed.

**Registry No.** **3**, 57180-64-0; **4a**, 78823-08-2; **4b**, 74280-26-5; **4c**, 78823-09-3; **5**, 719-59-5; **6a**, 74280-34-5; **6b**, 78823-10-6; **9a**, 74280-28-7; **10**, 74280-33-4; **11**, 49691-59-0; **12**, 74280-29-8; **13a**, 74280-35-6; **13a** oxalate, 78823-11-7; **13b**, 78823-12-8; **14**, 74280-23-2; **15**, 59179-98-5; **16a**, 78823-13-9; **16b**, 74280-30-1; **17a**, 74280-31-2; **17b**, 78823-14-0; **18a**, 74280-32-3; **18b**, 78823-15-1; **19**, 1022-13-5; **23a**, 78823-16-2; Z-Gly-OH, 1138-80-3; Pht-Gly-OH, 4702-13-0; Pht-DL-alanine, 21860-84-4.