**3-(Methoxycarbonyl)-3-acetamido-6-phthalimido-1-hexene (12).** A solution of $HN_3$ in $CHCl_3$ (51 mL of a 2.04 M solution, 105 mmol) was added to the ketone (34.4 g, 105 mmol) in $CHCl_3$. This solution was then added to a mixture of concentrated $H_2SO_4$ (50 mL) and $CHCl_3$ (200 mL) under $N_2$ at room temperature. On completion of the addition the mixture was stirred at room temperature for 15 min and then poured on ice. The mixture was extracted with $CHCl_3$, washed with $NaHCO_3$, dried, and evaporated. The residue was then chromatographed on silica gel (300 g), and the product (25.3 g, 70%) eluted with 7% methanol/$CHCl_3$ as an oil.

A sample was distilled (Kugelrohr, 250 °C, 0.02 mm) for analysis and was found to solidify on standing. Anal. ($C_{18}H_{20}N_2O_5$) C, H, N.

**α-Vinylornithine Hydrochloride (2).** A solution of the amide 12 (26.3 g, 0.076 mol) and hydrazine hydrate (4.2 g, 0.084 mol) in ethanol (500 mL) was heated under reflux overnight. When the solution cooled, a white precipitate was filtered off and the filtrate was evaporated. The residue was then heated under reflux with 6 N HCl (150 mL) for 2 h and then filtered, washed with $CH_2Cl_2$, and evaporated to yield an oil (15.6 g). This dihydrochloride was dissolved in ethanol (250 mL) and treated with $Et_3N$ (6.8 g, 0.67 mmol, 9.4 mL). The resulting precipitate was filtered off and recrystallized from EtOH/water (9:1) to afford a colorless solid (8.2 g, 55%), mp 242 °C. Anal. ($C_7H_{15}ClN_2O_2$) C, H, N.

**Enzyme Preparation.** Rat liver ODC was prepared from the livers of rats which had been injected with thioacetamide (150 mg/kg of body weight) 18 h before sacrifice and was purified about tenfold by acid treatment at pH 4.6 as described by Ono et al.[22] The specific activity of this preparation was 0.2 nmol of $CO_2$ $min^{-1}$ (mg of protein)$^{-1}$.

**Assay of Time-Dependent Inhibition of Ornithine Decarboxylase (in Vitro).** Assay and measurement of the kinetic constants of the inhibition were performed essentially as described previously.[3]

**Measurement of Ornithine Decarboxylase Activity (ex Vivo).** Male rats of the Sprague–Dawley strain (200–220 g of body weight), purchased from Charles-River, France, were given food and water ad libitum under a constant 12 h light–12 h dark lighting schedule. Animals were killed by decapitation at about the same time of day to minimize effects due to diurnal fluctuations. α-Ethynylornithine hydrochloride, dissolved in 0.9% saline, was injected intraperitoneally. Rats given saline served as controls. Immediately after sacrifice the ventral prostate, testis, and thymus were excised and homogenized, and the corresponding ODC activities were measured according to a published procedure.[4]

**Data Processing.** Kinetic constants were calculated by the method of Kitz and Wilson[13] using a least-squares fit of the data points with a Hewlett-Packard 9820 calculator (accuracy better than 20%). Ex vivo values of ODC activity were the mean ± SEM of five animals. The significance of the differences between control and treated animals was calculated by Student's *t* test with the above-described calculator.

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(22) M. Ono, H. Inoue, F. Suzuki, and Y. Takeda, *Biochim. Biophys. Acta*, 284, 285 (1972).

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# Novel Peptidoaminobenzophenones, Terminal N-Substituted Peptidoaminobenzophenones, and *N*-(Acylglycyl)aminobenzophenones as Open-Ring Derivatives of Benzodiazepines[1,2]

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Peptidoaminobenzophenones (1), terminal N-substituted peptidoaminobenzophenones (14), and acylglycylaminobenzophenones (16) were prepared as a novel series of ring-opened derivatives of 1,4-benzodiazepine. Z-Gly- and Z-Ala-*N*-methylaminobenzophenones (4) were treated with HBr–HOAc to give Gly- and Ala-*N*-methylaminobenzophenone hydrobromides (8). Reaction of 8 with chloroacetyl chloride in dimethylformamide (DMF) or hexamethylphosphoramide (HMPA) gave chloracetamide (13), which was allowed to react with various amines to afford a number of terminal N-substituted derivatives (14). Reaction of 8 with various acyl halides in HMPA or DMF gave a number of acylglycyl-*N*-methylaminobenzophenones (16). Peptidoaminobenzophenones (1) were also prepared by several convenient methods. Many of these compounds exhibited high CNS activity in animals when given orally. In antianxiety activity the potency of some compounds is equal to or higher than that of diazepam.

In the previous paper,[3] we reported a series of peptidoaminobenzophenones (1) as a novel class of ring-opened derivatives of 1,4-benzodiazepine. Hassall et al. have also reported peptidoaminobenzophenones as being novel latentiated 1,4-benzodiazepines.[4] The interesting pharmacological and physicochemical properties of peptidoaminobenzophenones prompted us to investigate various types of these and related compounds. Here we report the synthesis and pharmacological activities of some peptidoaminobenzophenones, terminal nitrogen substituted peptidoaminobenzophenones (14), and acylglycyl-*N*-methylaminobenzophenones (16).

**Chemistry.** According to our method reported in the preceding paper,[1] protected amino acids were coupled with aminobenzophenones (**2a–d**) by $SOCl_2$ in hexamethylphosphoramide (HMPA) to obtain Z-Gly-[5] and Z-Ala-aminobenzophenones (**3a–e**) in high yields (Scheme I). The amides (**3a–e**) were readily N-methylated via sodio derivatives to give the *N*-methyl derivatives (**4a–d**). The coupling reaction of Z-amino acids with *N*-methylaminobenzophenones (**2e**) also gave the *N*-methylamides (**4a**).

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(1) This paper is Part 4 of a series on "Benzophenone Related Compounds". Part 3: Hirai, K.; Ishiba, T.; Fujishita, T.; Sugimoto, H. *Heterocycles* **1980**, *14*, 635.

(2) A part of this paper was presented at the ACS/CSJ Chemical Congress, a joint meeting of the American Chemical Society and the Chemical Society of Japan. See K. Hirai, T. Ishiba, H. Sugimoto, T. Fujishita, Y. Tsukinoki, and K. Hirose, In "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, Apr 1–6, 1979; American Chemical Society: Washington, D.C., 1979; Abstr MEDI 6.

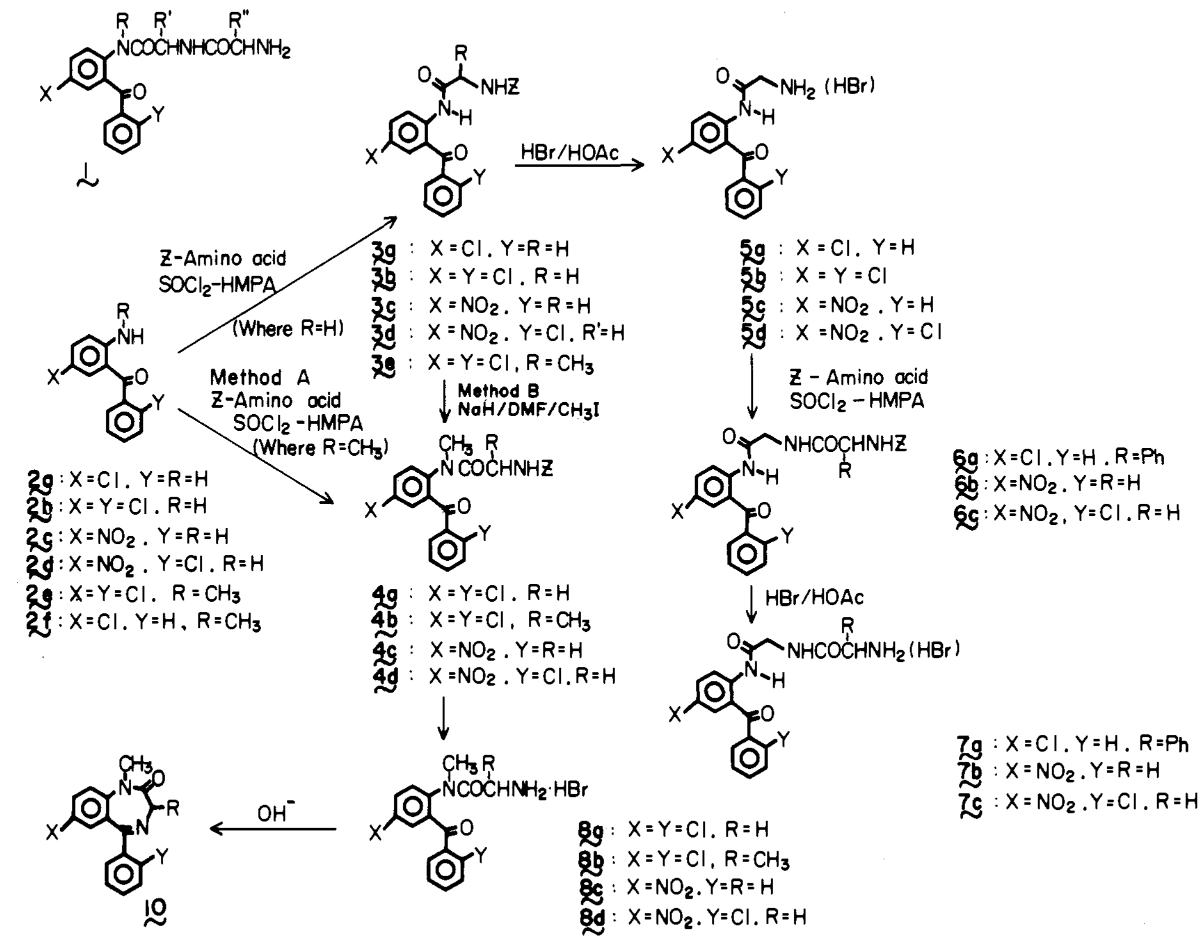
(3) Hirai, K.; Ishiba, T.; Sugimoto, H.; Sasakura, K.; Fujishita, T.; Toyoda, T.; Tsukinoki, Y.; Joyama, H.; Hatakeyama, H.; Hirose, K. *J. Med. Chem.* **1980**, *23*, 764.

(4) Hassall, C. H.; Holmes, S. H.; Johnson, W. H.; Kröhn, A.; Smithen, C. E.; Thomas, W. *Experientia* **1977**, *33*, 1492.

(5) Abbreviations used are those recommended by the IUPAC–IUB Commission of Biochemical Nomenclature Symbols for Amino Acid Derivatives and Peptides [*J. Biol. Chem.* **1972**, *247*, 977]. Additional abbreviations used are: Z, benzyloxycarbonyl; Pht, phthalyl.

0022-2623/81/1824-0020$01.00/0

Scheme I



Treatment of **3a–d** with hydrobromic acid in acetic acid resulted in the cleavage of the Z group and gave the free glycylaminobenzophenones (**5a–d**). Z-Amino acids were then coupled with **5a–d**, and subsequent removal of the Z group gave the dipeptidoaminobenzophenones (**7a–c**).

On the other hand, treatment of the *N*-methylamides (**4a–d**) with hydrobromic acid in acetic acid afforded the hydrobromides (**8a–d**). The coupling reaction of **8a,b** with phthalylglycyl chloride in dimethylformamide (DMF) or HMPA solution was carried out in the absence of base to give the Pht-dipeptido-*N*-methylaminobenzophenone (**9a,b**) in high yields without contamination by cyclized 1,4-benzodiazepines (**10**).[6] Phthalyl derivatives (**9**) could also be obtained by the reaction of **13b** with potassium phthalimide. The phthalyl group in **9a,b** was readily removed by hydrazinolysis using $NH_2NH_2{\cdot}H_2O$ in boiling EtOH to give the dipeptido-*N*-methylaminobenzophenones (**12a,b**) in high yields. The coupling reaction of Z-glycine with **8c,d** was carried out by $SOCl_2$ in HMPA and subsequent removal of the Z group in the coupling products gave **12c,d** (Scheme II).

When the hydrobromide (**8a**) was treated with chloracetyl chloride in DMF or HMPA solution, the chloracetamide (**13a**) was readily obtained. Since the chloracetyl derivatives **13** are important key intermediates for obtaining the compounds having terminal functional groups, the reaction of **13** with various amines, including $NH_3$, was carried out to obtain a variety of amino derivatives (**14a–j**).

In the course of preparing 3-acetamido-2(1*H*)-quinolinone, Fryer et al.[7] obtained acetylglycylaminobenzophenone (**15a**) by acetylation of glycylaminobenzophenone (**5a**) using sodium acetate and acetic anhydride (Scheme III). The *o*-chloro derivative (**15b**) was also obtained from **5b** by this method.

We tried to prepare the *N*-methyl derivative (**16a**) by condensation of the *N*-methylaminobenzophenone (**2e**) with acetylglycine by $SOCl_2$ in HMPA. However, the condensation product (**16a**) was not obtained and the starting material was recovered. On the other hand, *N*-methylaminobenzhydrol (**17**) coupled with acetylglycine by $SOCl_2$ in HMPA to give the condensation product **18**. Jones oxidation of **18** readily gave **16a**.[8]

The most satisfactory result was obtained in the preparation of **16** by direct acylation of the hydrobromide (**8a**). When **8a** was treated with various acyl halides in DMF or HMPA solution in the absence of base, the corresponding acylglycyl-*N*-methylaminobenzophenones (**16a–j**) were obtained in excellent yield. The coupling reaction of benzoylglycine with *N*-methylaminobenzophenone gave the benzoylglycyl-*N*-methylaminobenzophenone (**16k**).

## Results and Discussion

The compounds synthesized here were submitted to pharmacological tests in mice by oral administration.

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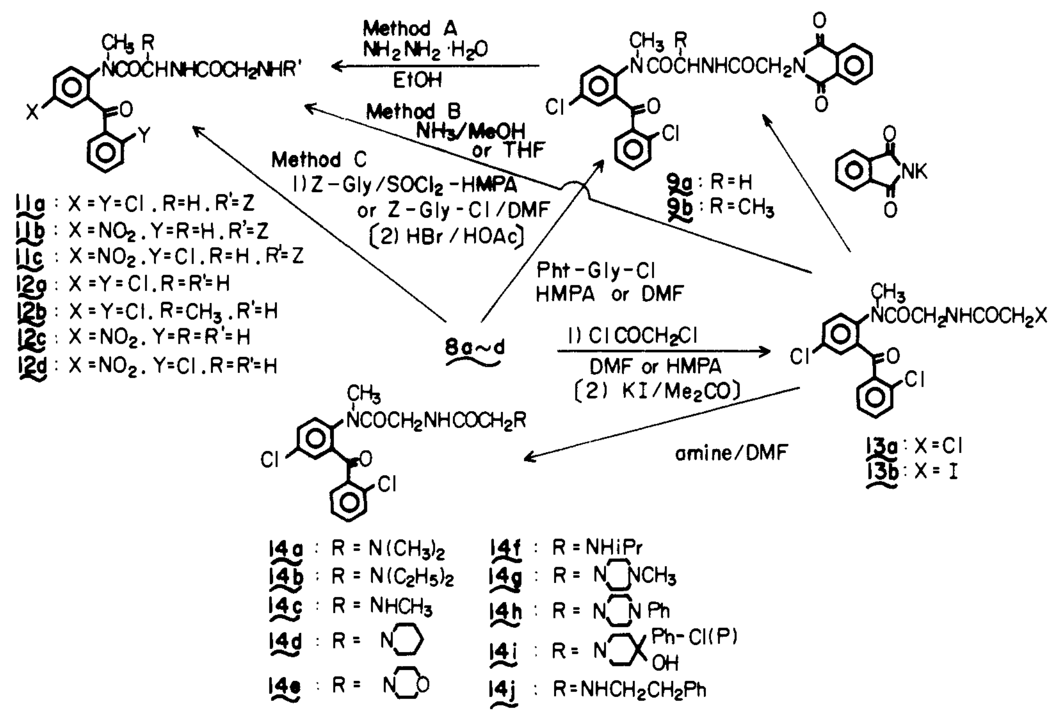
(6) The free bases of the *N*-methyl derivatives (**7**) were never isolated due to the spontaneous cyclization to the 1,4-benzodiazepines (**10**). Walser, A.; Szente, A.; Hellerbach, J. H. *J. Org. Chem.* **1973**, *38*, 449.

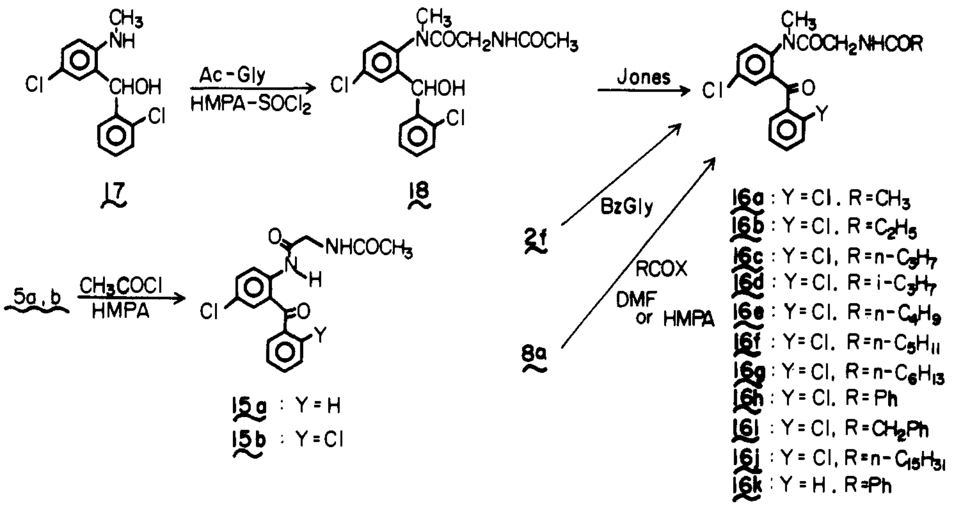
(7) Fryer, R. I.; Brust, B.; Sternbach, L. H. *J. Chem. Soc.* **1964**, 3097.

(8) The formation of acetylglycyl-*N*-methylaminobenzophenone by chromic acid oxidation of 4-acetyl-7-chloro-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one has been described by Ishizumi, K.; Mori, K.; Inaba, S.; Yamamoto, H. *Chem. Pharm. Bull.* **1975**, *23*, 2169.

Scheme II



Scheme III



Antianxiety activity was tested by antagonism of pentylenetetrazole-induced convulsion[9-11] and muscle relaxation by the rotarod performance test. Table I shows these results and the acute toxicity (in mg/kg) for all tested compounds, along with the data for diazepam, nitrazepam, and chlordiazepoxide.

The Gly-Ala-*N*-methylaminobenzophenone (**12b**) was more active than the Gly-Gly derivative (**12a**) for antipentylenetetrazole and rotarod performance tests in mice. The ring-opened derivative of nitrazepam (**7b**) was less active than nitrazepam. However, substitution of the methyl group at the aniline NH group potentiated the activities in these tests, and the compound **12c** was as good or better than nitrazepam. An *o*-chloro substituent on the benzoyl group (viz., **12d**) did not enhance the activities.

The terminal amino substituted compounds (**14**) showed CNS activities, and some of them were more potent than chlordiazepoxide. Compound **14f** was equipotent with diazepam. Although the terminal acyl derivatives having the aniline NH group (**15**) showed very weak or no CNS activities, high activities were observed in the *N*-methyl derivatives (**16**). Introduction of the chlorine atom in Y of **16** enhanced the activities, though the opposite was observed with **15**. The antipentylenetetrazole activity of **16** increased with an increasing number of the carbon atoms of the acyl groups from C-1 to C-3 (**16a–c**), except for the *i*-Pr derivative (**16d**), and then decreased in activity from C-4 (**16e**), leading to no activity with C-15 (**16j**). Maximum activity was observed in the *n*-butyl derivative (**16e**). In general, these compounds (structure **16**) showed weak activity in the rotarod performance test.

It seems reasonable to assume that terminal acyl derivatives (**16**) and terminal N-substituted derivatives (**14**) can be cleaved at these terminal acyl or N-substituted glycyl groups[12] as well as terminal amino acids in pepti-

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(9) Sternbach, L. H.; Randall, L. O.; Banziger, R.; Lehr, H. "Drugs Affecting the Central Nervous System", Burger, A., Ed.; Marcel Dekker: New York, 1968; p 237.

(10) Zbinder, G.; Randall, L. O. *Adv. Pharmacol.* **1967**, *5*, 213.

(11) Garattini, S.; Mussini, E.; Randall, L. O., Ed. "The Benzodiazepines"; Raven Press: New York, 1973.

Table I. Pharmacological Activity in Mice[a]

| | $ED_{50}$, mg/kg | | | | $ED_{50}$, mg/kg | | |
|---|---|---|---|---|---|---|---|
| compd | antipentylenetetrazole | rotarod performance | $LD_{50}$, mg/kg | compd | antipentylenetetrazole | rotarod performance | $LD_{50}$, mg/kg |
| 7a | 28.0 | >100 | >1000 | 15a | 37.0 | >100 | >1000 |
| 7b | 4.82 | 24.8 | >1000 | 15b | >100 | >100 | >1000 |
| 7c | 2.64 | 63.9 | 750 (P)[b] | 16a | 2.3 | 58.0 | >1000 |
| 12a | 0.58 | 27.7 | >1000 | 16b | 1.4 | 36.0 | >1000 |
| 12b | 0.47 | 8.5 | 750 (P) | 16c | 0.98 | 55.2 | >1000 |
| 12c | 0.28 | 2.94 | | 16d | 6.0 | >100 | >1000 |
| 12d | 0.32 | 10.0 | | 16e | 1.3 | 90.0 | >1000 |
| 14a | 2.6 | 26.0 | >1000 | 16f | 1.90 | 90.0 | >1000 |
| 14b | 2.2 | 34.0 | >1000 | 16g | 1.90 | 70.0 | >1000 |
| 14c | 1.55 | | >1000 | 16h | 2.9 | >100 | >1000 |
| 14d | 7.5 | >100 | >1000 | 16i | 35.0 | >100 | >1000 |
| 14e | 14.0 | >100 | >1000 | 16j | >100 | >100 | >1000 |
| 14f | 1.0 | 13.0 | 750 (P) | 16k | 7.6 | >100 | >1000 |
| 14g | 59.0 | >100 | >1000 | diazepam | 1.19 | 17.7 | 1386 |
| 14h | 75.0 | >100 | >1000 | chlordiazepoxide | 2.71 | 82.3 | 1079 |
| 14i | 27.0 | >100 | >1000 | nitrazepam | 0.23 | 4.25 | |
| 14j | 1.6 | 86.0 | >1000 | | | | |

[a] All samples were administered orally and estimated at 60 min after dosing. [b] P = presumed.

doaminobenzophenones (**12**), followed by nonenzymatic ring closures forming benzodiazepines in vivo. In fact, other studies in these laboratories[13,14] have demonstrated that **14** and **16** had low affinity for benzodiazepine receptors but were converted into compounds having high affinity for the receptors by incubation with rat liver homogenates, and benzodiazepines were detected in rat brain after administration of **12**.

Our results indicate that appropriate combination of the terminal groups and substituents in the benzene rings in classes of these compounds provides potentially useful CNS agents with different half-lives and favorable physicochemical and pharmacological characteristics.

## Experimental Section

**Chemistry.** Melting points were determined in a Yamato capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian A-60 or T-60 spectrometer, and chemical shifts are reported as $\delta$ (parts per million) relative to tetramethylsilane ($Me_4Si$) as an internal standard. Ultraviolet spectra were obtained with a Hitachi EPS-2 spectrophotometer. Infrared spectra were obtained with a JASCO DS 403G spectrometer. Solvents used for recrystallization are given in parentheses next to the melting point.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*$^{\alpha}$-(benzyloxycarbonyl)glycinanilide (3b).** To a solution of 12.6 g (60.0 mmol) of Z-glycine in 70 mL of HMPA and 20 mL of MeCN was added 6.55 g (55.0 mmol) of $SOCl_2$ dropwise at -4 to -5 °C, and the resulting mixture was stirred for 10 min at -5 °C. 2-Amino-2′,5-dichlorobenzophenone (**2b**; 13.3 g, 50.0 mmol) was added portionwise, and the mixture was allowed to stand overnight at room temperature. This was neutralized with aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated in vacuo. The residue was triturated with ether to afford 21.9 g (96.0%) of **3b**: mp 146–147 °C (AcOEt) (lit.[15] mp 148–149 °C); UV (EtOH) $\lambda_{max}$ 240 nm (log $\epsilon$ 4.51), 267 (4.08), 273 (4.03), 349 (3.69); NMR ($CDCl_3$) $\delta$ 4.12 (d, 2 H, $J$ = 6 Hz, $COCH_2$), 5.20 (s, 2 H, $CH_2Ph$), 5.63 (br t, 1 H, $J$ = 6 Hz, $CH_2NH$), 7.20–7.67 (m, 11 H, aromatic), 8.75 (d, 1 H, $J$ = 9 Hz, aromatic), 11.82 (br s, 1 H, ArNH).

By the same procedure, **3a,c–e** were prepared, and the results are summarized in Table II.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-*N*$^{\alpha}$-(benzyloxycarbonyl)glycinanilide (4a; Method A).** To a solution of 2.10 g (10.0 mmol) of Z-glycine in 15 mL of HMPA and 2 mL of MeCN was added 1.20 g (10.0 mmol) of $SOCl_2$ dropwise at -8 to -5 °C, and the resulting mixture was stirred for 15 min at -7 °C. Then 2.80 g (10.0 mmol) of 2-(methylamino)-2′,5-dichlorobenzophenone (**2e**)[1] was added portionwise, and the mixture was allowed to stand overnight at room temperature. The mixture was neutralized with aqueous $NaHCO_3$ and then extracted with ether. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated in vacuo. The residue was separated by column chromatography on silica gel with $CHCl_3$ as eluant to yield 3.80 g (81.0%) of **4a**: mp 90–92 °C ($Et_2O$); UV (EtOH) $\lambda_{max}$ 250 nm (log $\epsilon$ 4.00, sh), 290 (3.34); NMR ($CDCl_3$) $\delta$ 3.07 and 3.18 (2 s, 3 H, Me), 3.57–3.93 (br m, 2 H, $COCH_2$), 5.07 (s, 2 H, $CH_2Ph$), 5.63 (br m, 1 H, NH), 7.00–7.73 (m, 12 H, aromatic).

By the same procedure, **4b** was prepared from Z-L-alanine and **2e**, and the results are summarized in Table II.

**Methylation of 3b (Method B).** To a solution of 21.6 g (47.2 mmol) of **3b** in 100 mL of DMF was added 2.50 g (52.0 mmol) of NaH (50% oil dispersion) at 2 to 5 °C, and the mixture was stirred for 15 min at the same temperature. Then 8.80 g (62.0 mmol) of $CH_3I$ was added dropwise at 2 to 5 °C, followed by an additional 2-h stirring at the same temperature. Excess water was added and the mixture was extracted with $CHCl_3$. The organic layer was separated, dried over $Na_2SO_4$, and concentrated. The residue was triturated with ether to give 19.3 g (86.5%) of **4a**, which had IR and NMR spectra identical with those of the sample prepared above.

By the same procedure, **4b–d** were prepared, and the results are summarized in Table II.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-glycinanilide Hydrobromide (5b).** A mixture of 2.29 g (5.00 mmol) of **3b** in 4 mL of 30% HBr in AcOH was stirred for 1.5 h at room temperature. Excess ether was added, and the precipitate was collected by filtration. The residue was washed with ether and dried in vacuo to give 2.00 g (94.8%) of **5b**, mp 120–122 °C.

By the same procedure, **5a,c,d** were prepared, and the results are summarized in Table II.

**2-Benzoyl-4-chloro-*N*$^{\alpha}$-(benzyloxycarbonyl)-DL-($\alpha$-phenylglycyl)glycinanilide (6a).** To a cooled solution (-5 to -3 °C) of 2.14 g (7.50 mmol) of Z-DL-$\alpha$-phenylglycine in 12 mL of HMPA was added 0.890 g (7.50 mmol) of $SOCl_2$ dropwise, and

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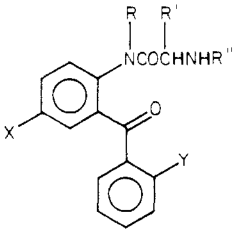
(12) Conversion of *N*-alkylaminobenzophenones to benzodiazepines in vivo has been reported. Lathi, R. A.; Gall, M. *J. Med. Chem.* **1976**, *19*, 1064.

(13) Fujimoto, M.; Tsukinoki, Y.; Hirose, K.; Hirai, K.; Okabayashi, T. *Chem. Pharm. Bull.* **1980**, *28*, 1374.

(14) Fujimoto, M.; Tsukinoki, Y.; Hirose, K.; Kuruma, K.; Konaka, R.; Okabayashi, T. *Chem. Pharm. Bull.* **1980**, *28*, 1378.

(15) Stempel, A.; Landgraf, F. W. *J. Org. Chem.* **1962**, *27*, 4675.

Table II. Physical and Analytical Data for the Amino Acid Substituted Aminobenzophenones



| no. | X | Y | R | R' | R'' | yield, % | salt | mp, °C | recrystn solvent | formula | anal. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 3a | Cl | H | H | H | Z | 89.0 | | 112–114[a] | AcOEt | $C_{23}H_{19}ClN_2O_4$ | C, H, N, Cl |
| 3b | Cl | Cl | H | H | Z | 96.0 | | 146–147[b] | AcOEt | $C_{23}H_{18}Cl_2N_2O_4$ | C, H, N, Cl |
| 3c | $NO_2$ | H | H | H | Z | 97.0 | | 164–166 | AcOEt | $C_{23}H_{19}N_3O_6$ | C, H, N |
| 3d | $NO_2$ | Cl | H | H | Z | 69.3 | | 153–154 | AcOEt | $C_{23}H_{18}ClN_3O_6$ | C, H, N, Cl |
| 3e | Cl | Cl | H | $CH_3$[c] | Z | 80.5 | | 149–151 | AcOEt | $C_{24}H_{20}Cl_2N_2O_4$ | C, H, N, Cl |
| 4a | Cl | Cl | $CH_3$ | H | Z | 81.0 | | 90–92 | $Et_2O$ | $C_{24}H_{20}Cl_2N_2O_4$ | C, H, N, Cl |
| 4b | Cl | Cl | $CH_3$ | $CH_3$[c] | Z | 86.5,[d] 66.3[e] | | oil | | $C_{25}H_{22}Cl_2N_2O_4$ | |
| 4c | $NO_2$ | H | $CH_3$ | H | Z | 88.2 | | amorphous | | $C_{24}H_{21}N_3O_6$ | |
| 4d | $NO_2$ | Cl | $CH_3$ | H | Z | 52.6 | | 129–132 | AcOEt | $C_{24}H_{20}ClN_3O_6$ | C, H, N, Cl |
| 5a | Cl | H | H | H | H | | | *f, g* | | $C_{15}H_{13}ClN_2O_2$ | |
| 5b | Cl | Cl | H | H | H | 94.8 | HBr | 120–122 | *h* | $C_{15}H_{12}Cl_2N_2O_2 \cdot HBr \cdot H_2O$ | C, H, N, Br, Cl |
| 5c | $NO_2$ | H | H | H | H | 95 | HBr | 222–224 | *i* | $C_{15}H_{12}N_3O_4 \cdot HBr \cdot 0.5H_2O$ | C, H, N, Cl |
| 5d | $NO_2$ | Cl | H | H | H | | HBr | *g* | | $C_{15}H_{12}ClN_3O_4 \cdot HBr$ | |
| 8a | Cl | Cl | $CH_3$ | H | H | 97 | HBr | 156–159 | $CH_3CN$ | $C_{16}H_{14}Cl_2N_2O_2 \cdot HBr$ | C, H, N, Br, Cl |
| 8b | Cl | Cl | $CH_3$ | $CH_3$ | H | oil | HBr | *g* | | $C_{17}H_{16}Cl_2N_2O_2 \cdot HBr$ | |
| 8c | $NO_2$ | H | $CH_3$ | H | H | *j* | HBr | *g* | | $C_{16}H_{15}N_3O_4 \cdot HBr$ | |
| 8d | $NO_2$ | Cl | $CH_3$ | H | H | 100 | HBr | *g* | | $C_{16}H_{14}ClN_3O_4 \cdot HBr$ | |

[a] Literature mp 116–117 °C (ref 14). [b] Literature mp 148–149 °C (ref 14). [c] L form. [d] Method B (Experimental Section). [e] Method A (Experimental Section). [f] Literature mp of free base 101–103 °C (ref 14). [g] The crude product was used for further reaction without purification. [h] Washed with $Et_2O$–$Me_2CO$. [i] Washed with $CH_3CN$. [j] Hygroscopic amorphous.

stirring was continued for an additional 10 min at −5 °C. Then 2.17 g (7.50 mmol) of **5a** was added in small portions and the mixture was stirred overnight at room temperature. The mixture was neutralized with aqueous $NaHCO_3$ and then extracted with AcOEt. The organic phase was washed with $H_2O$, dried over $Na_2SO_4$, and concentrated. The residue was separated by column chromatography on silica gel with AcOEt as eluant to afford 1.97 g (47.2%) of **6a**: mp 109–113 °C (AcOEt); UV (EtOH) $\lambda_{max}$ 240 nm (log $\epsilon$ 4.42), 270 (4.03, sh), 337 (3.39); NMR ($CDCl_3$) $\delta$ 3.98 and 4.08 (dd, 2 H, $J$ = 6 Hz, $COCH_2$, 5.05 (s, 2 H, $CH_2Ph$), 5.44 (d, 1 H, $J$ = 7 Hz, CHPh), 6.33 (br d, 1 H, $J$ = 7 Hz, $CH_2NH$), 6.79 (br t, 1 H, $J$ = 6 Hz, $CH_2NH$), 7.08–7.82 (m, 17 H, aromatic), 8.37–8.65 (m, 1 H, aromatic), 10.88 (br s, 1 H, NHAr).

By the same procedure, **6b** and **6c** were prepared, and the results are summarized in Table III.

**2-Benzoyl-4-chloro-$N^{\alpha}$-DL-($\alpha$-phenylglycyl)glycinanilide (7a).** A solution of 1.5 g (2.7 mmol) of **6a** in 5 mL of 21.8% HBr in AcOH was stirred for 1 h at room temperature. Excess ether was added and the precipitate was separated by filtration. The residue was partitioned between aqueous $NaHCO_3$ and AcOEt. The organic layer was chromatographed on silica gel. Elution with AcOEt yielded 0.80 g (90%) of **7a**: mp 116–118 °C (AcOEt); UV (EtOH) $\lambda_{max}$ 240 nm (log $\epsilon$ 4.44), 275 (sh, 3.99), 340 (3.45); NMR ($CDCl_3$) $\delta$ 2.08 (br s, 2 H, $NH_2$), 4.03 and 4.13 (dd, 2 H, $J$ = 4 Hz, $COCH_2$), 4.70 (br s, 1 H, CHPh), 7.15–7.78 (m, 12 H, aromatic), 7.78–8.20 (m, 1 H, $CH_2NH$), 8.52–8.75 (m, 1 H, aromatic), 11.08 (br s, 1 H, ArNH).

By the same procedure **7b** and **7c** were prepared, and the results are summarized in Table III.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-glycinanilide Hydrobromide (8a).** A solution of 2.1 g (4.5 mmol) of **4a** in 6 mL of 20% HBr in AcOH was stirred for 1 h at room temperature. Excess ether was added and the precipitate was separated by filtration, followed by washing with ether and acetone to afford 1.8 g (97%) of **8a**: mp 156–159 °C (MeCN); UV (EtOH) $\lambda_{max}$ 218 nm (log $\epsilon$ 4.44, sh), 258 (3.95 sh), 290 (3.32).

By the same procedure **8b–d** were prepared and used for further reaction without purification.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-(phthalylglycyl)glycinanilide (9a).** A mixture of 0.628 g (1.50 mmol) of **8a** and 0.437 g (2.00 mmol) of phthalylglycyl chloride in 7 mL of DMF was stirred for 3 h at room temperature. The solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$ and washed with $H_2O$. The organic layer was dried over $Na_2SO_4$ and concentrated, followed by trituration with ether to yield 0.710 g (93.5%) of **9a**: mp 217 °C (EtOH); IR (Nujol) 3220, 1770, 1720, 1715, 1680, 1660, 1650 cm$^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 3.03 and 3.07 (2 s, 3 H, NMe), 3.40–3.77 (m, 2 H, $CH_2NH$), 4.23 (br s, 2 H, $CH_2$), 7.16–7.80 (m, 11 H, aromatic).

By the same procedure **9b** was prepared and used for further reaction without purification.

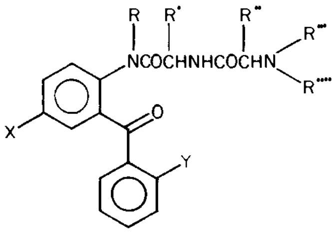
**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-(chloroacetyl)glycinanilide (13a).** To a solution of 1.8 g (3.8 mmol) of **8a** in 10 mL of HMPA (DMF could also be used) was added 0.73 g (6.5 mmol) of $ClCOCH_2Cl$ under ice cooling, and the mixture was stirred for 2 h at the same temperature and then for 3 h at room temperature. The solution was neutralized with aqueous $NH_4OH$ and extracted with ether. The organic phase was washed with $H_2O$, dried over $Na_2SO_4$, and concentrated to afford 1.6 g (89%) of **13a**: mp 136.5–137.5 °C (AcOEt); NMR ($CDCl_3$) $\delta$ 3.12 and 3.22 (2 s, 3 H, Me), 3.78 (d, 2 H, $NHCH_2$) 4.02 (s, 2 H, $CH_2Cl$), 7.20–7.70 (m, 8 H, aromatic and NH).

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-(iodoacetyl)glycinanilide (13b).** A mixture of 6.20 g (15.0 mmol) of **13a** and 2.74 g (15.5 mmol) of KI in 60 mL of acetone was refluxed for 1 h. The mixture was concentrated in vacuo and the residue was dissolved in $CHCl_3$ and $H_2O$. The organic layer was separated, dried over $Na_2SO_4$, and concentrated in vacuo. Trituration of the residue with ether yielded 6.90 g (91.5%) of **13b**: mp 172–174 °C (AcOEt); NMR ($CDCl_3$) $\delta$ 3.15 and 3.22 (2 s, 3 H, Me), 3.67–4.00 (m, 2 H, $CH_2NH$), 3.73 (s, 2 H, $CH_2I$), 6.90–7.77 (m, 8 H, aromatic and NH).

**Alternate Route to 9a from 13b.** A mixture of 1.01 g (2.00 mmol) of **13b** and 0.340 g (2.00 mmol) of potassium phthalimide in 10 mL of DMF was stirred for 3 h at room temperature and then allowed to stand overnight at room temperature. The reaction mixture was poured into 100 mL of $H_2O$ and the precipitate was collected by filtration, followed by drying in vacuo to give 1.00 g (98%) of **9a**.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-glycylglycinanilide (12a; Method A).** A suspension of 81.0 g (154 mmol) of **9a** in 50 mL of EtOH was refluxed, hydrazine hydrate (20 mL,

Table III. Physical and Analytical Data for the Dipeptidoaminobenzophenones



| no. | X | Y | R | R' | R'' | R''' | R'''' | salt | yield, % | mp, °C | recrystn solvent | formula | anal. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6a | Cl | H | H | H | Ph[a] | H | Z | | 47.2 | 109–113 | AcOEt | $C_{31}H_{26}ClN_3O_5$ | C, H, N, Cl |
| 6b | $NO_2$ | H | H | H | H | H | Z | | 85.5 | 140–142 | AcOEt | $C_{25}H_{22}N_4O_7$ | C, H, N |
| 6c | $NO_2$ | Cl | H | H | H | H | Z | | 92.0[b] | 158–160 | AcOEt | $C_{25}H_{21}ClN_4O_7$ | C, H, N, Cl |
| 7a | Cl | H | H | H | Ph[a] | H | H | | 70.0 | 116–118 | AcOEt | $C_{23}H_{20}ClN_3O_3$ | C, H, N, Cl |
| 7b | $NO_2$ | H | H | H | H | H | H | HBr | 94.0 | 206–208 dec | *c* | $C_{17}H_{16}N_5O_5\cdot HBr\cdot 0.5H_2O$ | H, Cl; C,[d] N[e] |
| 7c | $NO_2$ | Cl | H | H | H | H | H | HBr | 89.0 | 203–205 dec | *c* | $C_{17}H_{15}ClN_4O_5\cdot HBr$ | C, H, N, Cl |
| 9a | Cl | Cl | $CH_3$ | H | H | *o*-$C_6H_4(CO)_2$ | | | 93.5 | 217 | EtOH | $C_{26}H_{19}Cl_2N_3O_5$ | C, H, N, Cl |
| 9b | Cl | Cl | $CH_3$ | $CH_3$[f] | H | *o*-$C_6H_4(CO)_2$ | | | 54.2[g] | *h* | | $C_{27}H_{21}Cl_2N_3O_5$ | |
| 11a | Cl | Cl | $CH_3$ | H | H | H | Z | | 53.0 | oil | | $C_{26}H_{23}Cl_2N_3O_5$ | C, H, N, Cl |
| 11b | $NO_2$ | Cl | $CH_3$ | H | H | H | Z | | 47.8[n] | 95–98 | AcOEt | $C_{26}H_{24}N_4O_7\cdot 0.5AcOEt$ | C, H, N |
| 11c | $NO_2$ | Cl | $CH_3$ | H | H | H | Z | | 74.0 | oil | | | |
| 12a | Cl | Cl | $CH_3$ | H | H | H | H | | 90.0,[i] 29.0,[j] 68.0[k] | 95–100 | EtOH–$H_2O$ | $C_{18}H_{17}Cl_2N_3O_3\cdot H_2O$ | C, H, N, Cl |
| 12b | Cl | Cl | $CH_3$ | $CH_3$[f] | H | H | H | HCl | 40.5[i] | 130[l] | *c* | $C_{19}H_{19}N_3O_3Cl_2\cdot HCl\cdot 0.5H_2O$ | H, N, Cl; C[m] |
| 12c | $NO_2$ | H | $CH_3$ | H | H | H | H | | 80.8[k] | 113–116 | AcOEt | $C_{18}H_{18}N_4O_5$ | C, H, N |
| 12d | $NO_2$ | Cl | $CH_3$ | H | H | H | H | | 38.3[k] | 109–112 | AcOEt | $C_{18}H_{17}ClN_4O_5\cdot 0.5C_4H_8O_2$ | C, H, N |
| 14a | Cl | Cl | $CH_3$ | H | H | $CH_3$ | $CH_3$ | | 82.9 | 135–137 | AcOEt | $C_{20}H_{21}Cl_2N_3O_3$ | C, H, N, Cl |
| 14b | Cl | Cl | $CH_3$ | H | H | $C_2H_5$ | $C_2H_5$ | | 88.9 | 113–115 | AcOEt | $C_{22}H_{25}Cl_2N_3O_3$ | C, H, N, Cl |
| 14c | Cl | Cl | $CH_3$ | H | H | H | $CH_3$ | | 42.9 | 102–103 | AcOEt | $C_{19}H_{19}Cl_2N_3O_3$ | C, H, N, Cl |
| 14d | Cl | Cl | $CH_3$ | H | H | $-(CH_2)_5-$ | | | 100 | 83–86 | AcOEt | $C_{19}H_{19}Cl_2N_3O_3\cdot 0.5C_4H_8O_2$ | C, H, N, Cl |
| 14e | Cl | Cl | $CH_3$ | H | H | $-(CH_2)_2O(CH_2)_2-$ | | HCl | 86.2 | 122–124 | AcOEt | $C_{22}H_{23}Cl_2N_3O_4$ | C, H, N, Cl |
| 14f | Cl | Cl | $CH_3$ | H | H | H | *i*-$C_3H_7$ | HCl | 98.0 | 207–209 | EtOH | $C_{21}H_{23}Cl_2N_3O_3\cdot HCl$ | C, H, N, Cl |
| 14g | Cl | Cl | $CH_3$ | H | H | $-(CH_2)_2NCH_3(CH_2)_2-$ | | HCl | 89.3 | 236–238 | EtOH–$H_2O$ | $C_{23}H_{26}Cl_2N_4O_3\cdot 2HCl\cdot 0.5H_2O$ | C, H, N, Cl |
| 14h | Cl | Cl | $CH_3$ | H | H | $-(CH_2)_2NPh(CH_2)_2-$ | | HCl | 97.6 | 155–164 dec | EtOH | $C_{28}H_{28}Cl_2N_4O_3\cdot 2HCl\cdot H_2O$ | C, H, N, Cl |
| 14i | Cl | Cl | $CH_3$ | H | H | $-(CH_2)_2C(OH)C_6H_4Cl$-*p*-$(CH_2)_2-$ | | | 84.7 | 148–150 | AcOEt | $C_{29}H_{28}Cl_3N_3O_4$ | C, H, N, Cl |
| 14j | Cl | Cl | $CH_3$ | H | H | H | $CH_2CH_2Ph$ | $(COOH)_2$ | 100 | 185–187 | MeOH | $C_{26}H_{25}Cl_2N_3O_4\cdot C_2H_2O_4$ | C, H, N, Cl |

[a] DL form. [b] Yield from 3d. [c] Washed with $Et_2O$. [d] C: calcd, 45.76; found, 45.21. [e] N: calcd, 12.55; found, 11.86. [f] L form. [g] Yield from 4b. [h] The crude product was used for further reaction without purification. [i] Method A (Experimental Section). [j] Method B (Experimental Section). [k] Method C (Experimental Section). [l] $[\alpha]^{25.5}_D$ −11.2 ± 0.5° (*c* 1.02, MeOH). [m] C: calcd, 49.31; found, 49.90. [n] Yield from 4c.

400 mmol) was added in small portions, and refluxing was continued for 30 min. After the mixture was cool, the precipitated phthalhydrazide was removed by filtration. The filtrate was concentrated and the residue was triturated with diluted EtOH, followed by washing with ether to yield 57.3 g (90.0%) of **12a**: mp 95–100 °C ($EtOH-H_2O$); UV (EtOH) $\lambda_{max}$ 255 nm (log $\epsilon$ 3.98, sh), 290 (3.39); NMR ($CDCl_3$) $\delta$ 1.65 (br s, 2 H, $NH_2$), 3.08 and 3.20 (2 s, 3 H, $NCH_3$), 3.32 (br s, 2 H, $CH_2NH_2$), 3.67–4.03 (m, 2 H, $CH_2NH$), 7.10–7.67 (m, 7 H, aromatic), 7.83 (br s, 1 H, NH).

Compound **12b** was prepared in a similar manner (Table III).

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-[(benzyloxycarbonyl)glycyl]glycinanilide (11a; Method C).** A mixture of 4.2 g (10 mmol) of **8a** and Z-glycyl chloride, which was prepared from 3.15 g of Z-glycine and 3.45 g of $PCl_5$ in 16 mL of ether at 0 °C, in 40 mL of DMF was stirred for 2.5 h at room temperature and allowed to stand overnight at room temperature. The solution was neutralized with aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and concentrated. The residue was chromatographed on silica gel with AcOEt as eluant to give 3.1 g (53.0%) of **11a** as an oil: IR ($CHCl_3$) 1720, 1660 cm$^{-1}$; NMR ($CDCl_3$) $\delta$ 3.07 and 3.10 (2 s, $CH_3$), 3.78 (br s, 4 H, 2 $CH_2$), 5.02 (s, 2 H, Z-$CH_2$), 5.78 (br s, 1 H, NH), 6.88–7.58 (m, 12 H, aromatic).

**Alternate Route to 12a from 11a (Method C).** A solution of 3.60 g (6.81 mmol) of **11a** in 11.5 mL of 21.8% HBr in AcOH was stirred for 1.5 h at room temperature. Excess ether was added, and the precipitate was collected by filtration and dissolved in $H_2O$. Neutralization with aqueous $NaHCO_3$ afforded a precipitate, which was collected by filtration to yield 1.80 g (68.0%) of **12a**.

**2-(*o*-Chlorobenzoyl)-4-nitro-*N*-methyl-$N^{\alpha}$-[(benzyloxycarbonyl)glycyl]glycinanilide (11c).** To a solution of 1.73 g (8.20 mmol) of Z-glycine in 30 mL of HMPA and 5 mL of MeCN was added 0.850 g (7.10 mmol) of $SOCl_2$ dropwise at −8 to −6 °C, and stirring was continued for 20 min at −8 °C. Then, 2.36 g (5.50 mmol) of **8d** was added and the mixture was stirred for 5 h at room temperature. The usual workup (neutralization with aqueous $NaHCO_3$, extraction with AcOEt, drying, and concentration) yielded 2.20 g (74.0%) of **11c** as an oil: NMR ($CDCl_3$) $\delta$ 3.20 (br s, 3 H, Me), 3.83 (br s, 4 H, 2 $CH_2$), 5.12 (br s, 2 H, $CH_2Ph$), 5.73 (br s, 1 H, Z-NH), 6.67–8.63 (m, 13 H, aromatic and NH).

Compound **11b** was prepared in a similar manner in 47.8% yield as an oil: NMR ($CDCl_3$) $\delta$ 3.20 (br s, 3 H, NMe), 3.73–4.10 (m, 4 H, 2 $CH_2$), 5.30 (s, 2 H, $CH_2Ph$), 5.57–5.97 (m, 1 H, Z-NH), 6.77–7.20 (br s, 1 H, CONH), 7.42 (s, 5 H, aromatic), 7.43–8.57 (m, 8 H, aromatic).

**2-(*o*-Chlorobenzoyl)-4-nitro-*N*-methyl-$N^{\alpha}$-glycylglycinanilide (12d).** A solution of 2.2 g (4.1 mmol) of **11c** in 9 mL of 30% HBr in AcOH was stirred for 2 h at room temperature. Excess ether was added and the precipitate was collected by filtration. The residue was partitioned between aqueous $NaHCO_3$ and $CH_2Cl_2$. The organic layer was separated, dried over $Na_2SO_4$, and concentrated in vacuo, followed by column chromatography on silica gel with MeOH as eluant, to give 0.70 g (34%) of **12d**: mp 109–112 °C (AcOEt); NMR ($CDCl_3$) $\delta$ 1.62 (br s, 2 H, $NH_2$), 3.03–3.60 (m, 5 H, Me and $CH_2NH_2$), 3.60–4.07 (br s, 2 H, $CH_2NH$), 7.17–8.50 (m, 7 H, aromatic).

Compound **12c** was prepared by the same procedure, and the results are summarized in Table III.

**Alternate Route to 12a from 13b (Method B).** To a suspension of 1.10 g (2.18 mmol) of **13b** in 20 mL of THF was introduced gaseous ammonia for 30 min at room temperature, and the mixture was stirred for 5 h at room temperature. The solvent was removed in vacuo. The residue was taken up in $CHCl_3$ and $H_2O$. The organic layer was separated, dried over $Na_2SO_4$, and concentrated. The product was chromatographed on silica gel with MeOH as eluant to give 0.24 g (29%) of **12a**.

**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-(dimethylglycyl)glycinanilide (14a).** A mixture of 1.01 g (2.00 mmol) of **13b** and 0.800 g (7.10 mmol) of 40% dimethylamine–ethanol in 20 mL of $CHCl_3$ and 10 mL of MeOH was stirred for 3 h at room temperature. The solvent was removed in vacuo and the residue was partitioned between AcOEt and $H_2O$. The organic layer was separated, dried over $Na_2SO_4$, and concentrated. The crude product was chromatographed on a silica gel with acetone as eluant to give 0.700 g (82.9%) of **14a**: mp 135–137 °C (AcOEt); UV (EtOH) $\lambda_{max}$ 220 nm (log $\epsilon$ 4.41, sh), 250 (4.01, sh), 290 (3.35); NMR ($CDCl_3$) $\delta$ 2.32 (s, 6 H, $NMe_2$), 2.95 (s, 2 H, $CH_2NMe_2$), 3.10 and 3.21 (2 s, 3 H, NMe), 3.67–4.00 (m, 2 H, $CH_2NH$), 7.17–7.93 (m, 8 H, aromatic and NH).

By the same procedure **14b–j** were prepared, and the results are summarized in Table III.

**4-Chloro-2-(*o*-chlorobenzoyl)-$N^{\alpha}$-acetylglycinanilide (15b).** A mixture of 1.62 g (3.80 mmol) of **5b** and 0.463 g (5.90 mmol) of MeCOCl in 10 mL of HMPA was stirred for 3 h at room temperature. The solution was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with $H_2O$, separated, dried over $Na_2SO_4$, and concentrated to give 1.25 g (89.3%) of **15b**: mp 176–178 °C (AcOEt); UV (EtOH) $\lambda_{max}$ 240 nm (log $\epsilon$ 4.52), 262 (4.10), 273 (4.05), 350 (3.72); NMR ($CDCl_3$) $\delta$ 2.15 (s, 3 H, Me), 4.13 (d, 2 H, $J = 6$ Hz, $CH_2$), 6.47 (br t, 1 H, $J = 6$ Hz, $CH_2NH$), 7.20–7.60 (m, 6 H, aromatic).

Compound **15a** was prepared in a similar manner in 64% yield, mp 136–138 °C (lit.[7] mp 137–139 °C).

**4-Chloro-2-(*o*-chloro-2-hydroxybenzyl)-*N*-methyl-$N^{\alpha}$-acetylglycinanilide (18).** To a solution of 0.76 g (6.5 mmol) of acetylglycine in 8 mL of HMPA and 2 mL of MeCN was added 0.66 g (5.5 mmol) of $SOCl_2$ dropwise at −35 to −32 °C, the mixture was stirred at −35 °C for 10 min, and then 1.41 g (5.0 mmol) of **17** was added. The mixture was allowed to stand overnight at room temperature and then neutralized with aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated, followed by trituration with ether, to give 0.60 g (32%) of **18**: mp 192.5–194.5 °C; NMR ($Me_2SO$-$d_6$) $\delta$ 1.78 and 1.85 (2 s, 3 H, COMe), 2.78–3.45 (2 s, 3 H, NMe), 3.57 (d, 2 H, $J = 6$ Hz, $CH_2$), 6.07 (br s, 1 H, CH), 6.23 (br t, 1 H, NH), 7.17–7.67 (m, 7 H, aromatic). Anal. Calcd for $C_{18}H_{18}N_2O_3Cl_2$: C, 56.71; H, 4.76; N, 7.35; Cl, 18.60. Found: C, 56.77; H, 4.95; N, 7.14; Cl, 18.52.

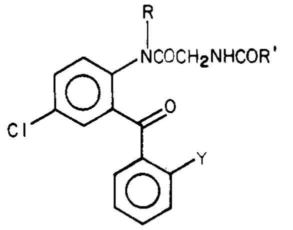
**4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-$N^{\alpha}$-acetylglycinanilide (16a).** To a solution of 0.381 g (1.00 mmol) of **17** in 25 mL of acetone was added Jones reagent at below 0 °C until the reaction mixture remained red. The resulting mixture was filtered. To the filtrate was added *i*-PrOH until the red filtrate became green, and then the mixture was filtered. The filtrate was neutralized with aqueous $NaHCO_3$ and concentrated. The residue was partitioned between $CHCl_3$ and $H_2O$. The organic layer was treated with Norit A, filtered, followed by drying over $Na_2SO_4$, and concentrated to give 0.252 g (66.5%) of **16a**: mp 172–174 °C (AcOEt); UV (EtOH) $\lambda_{max}$ 215 nm (log $\epsilon$ 4.46, sh), 250 (4.01, sh), 290 (3.35); NMR ($CDCl_3$) $\delta$ 1.94 and 1.99 (2 s, 3 H, COMe), 3.13 and 3.22 (2 s, 3 H, NMe), 3.63–4.00 (m, 2 H, $CH_2$), 6.33–6.66 (m, 1 H, NH), 7.17–7.73 (m, 7 H, aromatic). Anal. Calcd for $C_{18}H_{16}N_2O_3Cl_2$: C, 57.01; H, 4.25; N, 7.39; Cl, 18.70. Found: C, 57.04; H, 4.34; N, 7.44; Cl, 18.84.

**Alternate Route to 16a from 8a.** A solution of 0.837 g (2.00 mmol) of **8a** and 0.390 g (5.00 mmol) of MeCOCl in 8.5 mL of DMF was stirred for 3.5 h at room temperature and allowed to stand overnight at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between aqueous $NaHCO_3$ and $CHCl_3$. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and concentrated. The residue was chromatographed on a column of silica gel with acetone as eluant to yield 0.360 g (47.4%) of **16a**.

The results obtained with similarly prepared **16b–j** are listed in Table IV.

**4-Chloro-2-benzoyl-*N*-methyl-$N^{\alpha}$-benzoylglycinanilide (16k).** To a solution of 1.17 g (6.53 mmol) of benzoylglycine in 8.0 mL of HMPA and 2.0 mL of MeCN was added 0.655 g (5.51 mmol) of $SOCl_2$ dropwise at −35 to −30 °C over 3 min, and then the mixture was stirred for an additional 5 min at −35 to −40 °C. To this solution was added 1.23 g (5.00 mmol) of **2f** portionwise, and then the mixture was stirred at ambient temperature and allowed to stand overnight at room temperature. Excess ether and aqueous $NaHCO_3$ were added. The organic layer was washed with $H_2O$, separated, dried, and concentrated to a residue, which was chromatographed on silica gel with ether as eluant to give 0.800 g (39.2%) of **16k**: mp 73–75 °C (AcOEt–ether); UV (EtOH) $\lambda_{max}$ 215 nm (log $\epsilon$ 4.44, sh), 250 (4.26, sh), 290 (3.44, sh); NMR ($CDCl_3$) $\delta$ 3.10 and 3.28 (2 s, 3 H, Me), 3.87–4.13 (m, 2 H, $CH_2$), 6.87–7.90 (m, 14 H, aromatic and NH). Anal. Calcd for $C_{23}H_{19}N_2O_3Cl\cdot0.5H_2O$: C, 66.43; H, 4.85; N, 6.74; Cl, 8.52. Found:

Table IV. Physical and Analytical Data for the Acylglycylaminobenzophenones



| no. | Y | R | R′ | yield, % | mp, °C | recrystn solvent | formula | anal. |
|---|---|---|---|---|---|---|---|---|
| **15a** | H | H | $CH_3$ | 64 | 136–138[a] | AcOEt | $C_{17}H_{15}ClN_2O_2$ | C, H, N, Cl |
| **15b** | Cl | H | $CH_3$ | 89.3 | 176–178 | AcOEt | $C_{17}H_{14}Cl_2N_2O_3$ | C, H, N, Cl |
| **16a** | Cl | $CH_3$ | $CH_3$ | 47.4 | 172–174 | AcOEt | $C_{18}H_{16}Cl_2N_2O_3$ | C, H, N, Cl |
| **16b** | Cl | $CH_3$ | $C_2H_5$ | 88.6 | 113–114 | AcOEt | $C_{19}H_{18}Cl_2N_2O_3$ | C, H, N, Cl |
| **16c** | Cl | $CH_3$ | $n$-$C_3H_7$ | 85.6 | 113.5–115.5 | AcOEt | $C_{20}H_{20}Cl_2N_2O_3$ | C, H, N, Cl |
| **16d** | Cl | $CH_3$ | $i$-$C_3H_7$ | 91.7 | 116.5–117.5 | AcOEt | $C_{20}H_{20}Cl_2N_2O_3$ | C, H, N, Cl |
| **16e** | Cl | $CH_3$ | $n$-$C_4H_9$ | 92.0 | 114–115 | AcOEt | $C_{21}H_{22}Cl_2N_2O_3$ | C, H, N, Cl |
| **16f** | Cl | $CH_3$ | $n$-$C_5H_{11}$ | 89.2 | 86–88 | AcOEt | $C_{22}H_{24}Cl_2N_2O_3$ | C, H, N, Cl |
| **16g** | Cl | $CH_3$ | $n$-$C_6H_{13}$ | 93.2 | 77–79 | AcOEt | $C_{23}H_{26}Cl_2N_2O_3$ | C, H, N, Cl |
| **16h** | Cl | $CH_3$ | $C_6H_5$ | 77.0 | 74–76 | AcOEt | $C_{23}H_{18}Cl_2N_2O_3 \cdot 0.5C_4H_8O_2$ | C, H, N, Cl |
| **16i** | Cl | $CH_3$ | $C_6H_5CH_2$ | 85.3 | 106–108 | AcOEt | $C_{24}H_{20}Cl_2N_2O_3$ | C, H, N, Cl |
| **16j** | Cl | $CH_3$ | $n$-$C_{15}H_{31}$ | 45.5 | 98–99 | AcOEt | $C_{32}H_{44}Cl_2N_2O_3$ | C, H, N, Cl |
| **16k** | H | $CH_3$ | $C_6H_5$ | 39.2[b] | 73–75 | AcOEt | $C_{23}H_{19}ClN_2O_3$ | C, H, N, Cl |

[a] Literature mp 137–139 °C (ref 7). [b] Yield from **8a**.

C, 66.77; H, 5.17; N, 6.32; Cl, 8.37.

**Pharmacology.** The experiments were conducted on albino male mice (DS-strain, Aburahi Farm, Shionogi, 20–24 g). All compounds were suspended in an aqueous solution of arabic gum and administered orally.

**Rotarod Performance Test.**[16] Groups of five mice were used. A mouse was put on a wood rod, 3 cm in diameter, turning at 5 rpm at 60 min after dosing, and the number of animals falling off the rod within 2 min was counted. The $ED_{50}$ was estimated by graphic method.[17]

**Antipentylenetetrazole Activity.**[18] The test was performed with a group of five mice. The animals were challenged with subcutaneous injection of 125 mg/kg pentylenetetrazole at 60 min after dosing. The dose required to prevent convulsion and death in 50% ($ED_{50}$) of the animals during a 2 h observation was estimated by graphical method.[17]

**Acute Toxicity.** The acute toxicity of each compound was estimated with groups of one to three mice on the 7th day after oral administration. $LD_{50}$ values could not be calculated because of the weak toxicities. The $LD_{50}$ values of the three reference benzodiazepines were determined by the probit method.[19]

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