Peptidoaminobenzophenones, a Novel Class of Ring-Opened Derivatives of 1,4-Benzodiazepines[1]

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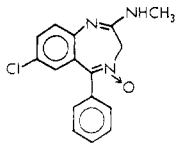
A series of novel peptidoaminobenzophenones has been prepared via several routes and was evaluated for CNS activity. The structure–activity relationships in the series are discussed. In general, dipeptido-*N*-methylaminobenzophenones showed higher activities than the corresponding NH derivatives. Some compounds had very high activities in antipentylenetetrazole and antifighting tests in mice when orally administered. Very weak toxicity was also found in these compounds. Water solubility of the peptidoaminobenzophenones and their salts were tested. Possible in vivo conversion of peptidoaminobenzophenone by enzymatic cleavage of the terminal amino acid, followed by chemical cyclization to 1,4-benzodiazepine, is also discussed. Such novel open-ring derivatives of 1,4-benzodiazepine may serve as useful CNS agents.

A considerable number of molecular modifications of the 1,4-benzodiazepine nucleus have been performed since the initial discovery of chlordiazepoxide (1) by Sternbach. Now, the 1,4-benzodiazepines are known as a remarkable class of compounds with potent minor tranquilizer, muscle-relaxant, anticonvulsant, and sedative-hypnotic activities.[2] The best known representative of this class of compounds is diazepam (2).



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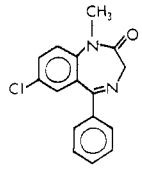

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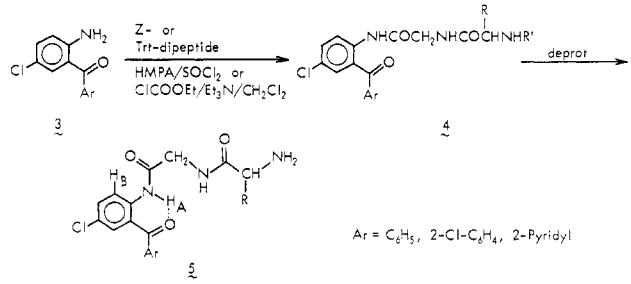
Metabolic precursors of 1,4-benzodiazepines or compounds which have configurations resembling theirs may possess similar biological activities. Based on these ideas, we became interested in the biological activities of a novel class of acylic compounds. This paper describes the synthesis, CNS activities, and physicochemical properties of a series of peptidoaminobenzophenones.[3,4]

Chemistry. 2-Aminobenzophenone (3) was coupled with the appropriate activated Z or Trt dipeptides.[5] The

Scheme I



coupling products (4) were treated with HBr/AcOH or AcOH to remove the Z or Trt group to give dipeptidoaminobenzophenones **5a–h** (Scheme I, Tables III and IV). Characteristic spectra were obtained, as exemplified by the case of **5g** showing the following infrared (IR) and nuclear magnetic resonance (NMR) spectra: IR (KBr) 1637 cm^{-1} (C=O···HN); NMR ($CDCl_3$) δ 1.87 (2 H, br s, NH_2), 3.57 (2 H, s, CH_2NH_2), 4.22 (2 H, d, J = 6 Hz, $-COCH_2NH-$), 7.17–7.68 (6 H, m, aromatic H), 8.15 (1 H, br, CH_2NH), 8.80 (1 H, d, J = 9 Hz, aromatic H_b), 11.8 (1 H, br s, C=O···H_aN). These spectra indicated that the aniline H_a proton was intramolecularly hydrogen bonded to the carbonyl oxygen of the benzophenone and that the ortho H_b proton in aniline was deshielded by the adjacent amido carbonyl group.[6,7]

In order to release the molecular rigidity due to the intramolecular hydrogen bonding in **5**, peptido-*N*-alkylaminobenzophenones were prepared. The synthetic route used to prepare these compounds is shown in Scheme II (methods A–D).

Method A consisted of the coupling reaction of 1-alkyl-2-(aminomethyl)-3-aryl-5-chloroindole (6) with activated Z or Trt amino acids and oxidation of the coupling products (7) with chromium trioxide in AcOH giving the benzophenone derivatives (8). The Z group was removed by HBr/AcOH to yield peptido-*N*-alkylaminobenzophenones (9). For the coupling of protected amino acids with aminomethylindoles (6), hexamethylphosphoramide (HMPA)/$SOCl_2$[8] was found to be a useful reagent.

However, when this procedure (HMPA/$SOCl_2$) was applied to *N*-alkylaminobenzophenones (10), which have a less reactive NH group due to hydrogen bonding and

(1) This paper is part 2 of a series on "Benzophenone Related Compounds". Part 1: K. Hirai, T. Ishiba, H. Sugimoto, K. Sasakura, T. Fujishita, Y. Tsukinoki, and K. Hirose, *Chem. Pharm. Bull.*, **26**, 1947 (1978).

(2) For reviews, see (a) L. H. Sternbach, *J. Med. Chem.*, **22**, 1 (1979); (b) *Fortschr. Arzneimittelforsch.*, **22**, 229 (1978); (c) S. Garattini, E. Mussini, and L. O. Randall, Eds., "The Benzodiazepines", Raven Press, New York, 1973; (d) D. J. Greenblatt and R. I. Shader, Eds., "Benzodiazepines in Clinical Practice", Raven Press, New York, 1974; (e) L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning, *Med. Chem. (Academic)*, **3**, 175 (1974); (f) L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).

(3) Recently, the dipeptide derivatives of 2-aminobenzophenones were reported to be latentiated 1,4-benzodiazepines: C. H. Hassall, S. W. Holmes, W. H. Johnson, A. Kröhn, C. E. Smithen, and W. A. Thomas, *Experientia*, **33**, 1492 (1977); C. H. Hassall, W. H. Johnson, A. Kroehn, C. E. Smithen, and W. A. Thomas, *Ger. Offen.*, 2537069 (1976); *Chem. Abstr.*, **85**, 78365*x* (1976).

(4) Earlier reports in this field have already been made from this laboratory: K. Hirai, T. Ishiba, K. Sasakura, and H. Sugimoto, *Ger. Offen.*, 2535171 (1976); *Chem. Abstr.*, **84**, 180642*b* (1976).

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

(6) V. Šunjć, F. Kajfež, I. Stromar, N. Blazvič, and D. Kolbach, *J. Heterocycl. Chem.*, **10**, 591 (1973).

(7) A. Walser, A. Szente, and J. Helberbach, *J. Org. Chem.*, **38**, 449 (1973).

(8) J. F. Normant and H. Deshayes, *Bull. Soc. Chim. Fr.*, 2854 (1972).

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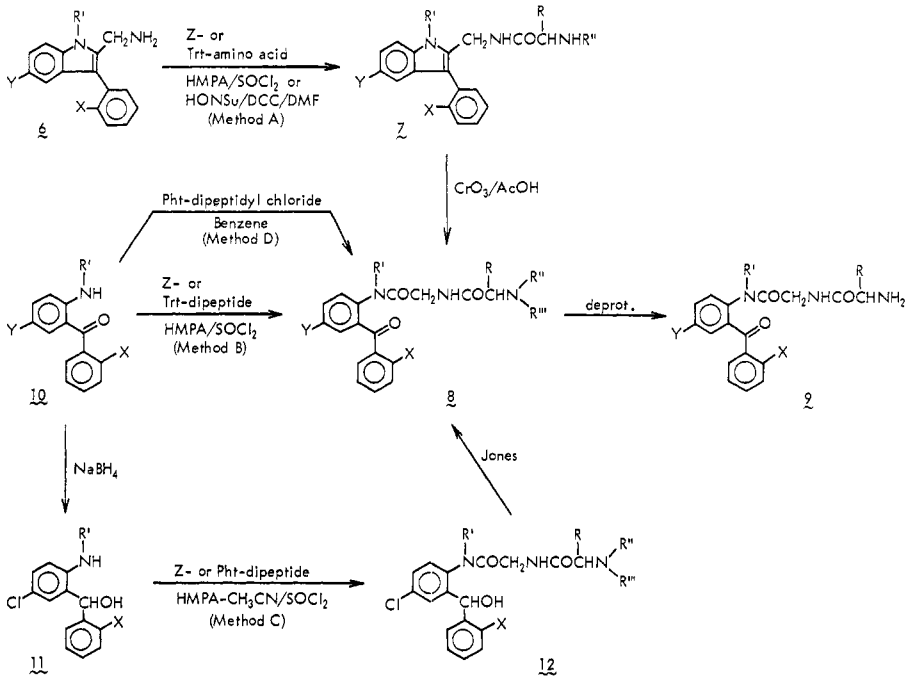
Scheme II



conjugation with the benzoyl carbonyl group, coupling with the protected dipeptide gave a low yield of the desired products (method B). Moreover, the use of elevated temperatures was precluded by the instability of the protected dipeptides to the reagent.

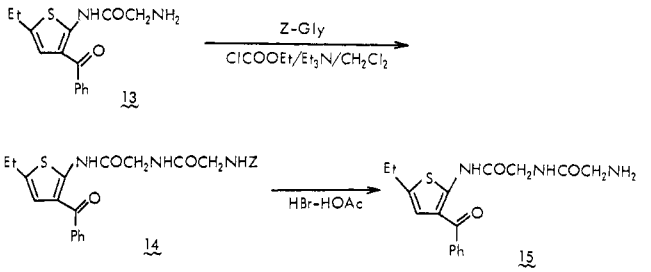
By contrast, aminobenzhydrol (**11**), which was readily prepared from aminobenzophenones (**10**) by $NaBH_4$ reduction or from secondary anilines and benzaldehyde,[9] coupled with Z or Trt dipeptides smoothly, even at low temperatures (−15 to −20 °C), afforded coupling products (**12**). Jones oxidation of **12** readily gave **8** (method C).

Finally, we later found that the direct acylation of **10** could be achieved with phthalyldipeptidyl chloride, giving the coupling products (**8**) in excellent yield (method D). The Pht group was readily removed by hydrazinolysis without affecting the benzoyl carbonyl group to give **9** (Tables V–VIII).

These dipeptido-*N*-alkylaminobenzophenones (**9**) were characterized as appropriate acid salts. For example, 4-chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-N^{α}-glycylglycinanilide (**9f**)[10] was converted into its hydrochloride, hydrobromide, hemisulfate, nitrate, phosphate, mesylate, oxalate, hemicitrate, maleate, and succinate (Table IX).

Analogues of peptidoaminobenzophenone in which the benzene ring in the benzoyl group is replaced by a pyridine ring (i.e., **5h**) were prepared by the method shown in Scheme I. The thiophene analogue **15** was prepared from 2-(glycylamino)-3-benzoylthiophene (**13**)[11] by coupling with Z-Gly followed by deprotection (Scheme III).

Scheme III



Results and Discussion

The dipeptidoaminobenzophenones (**5**, **9**, and **15**) were submitted to pharmacological tests in mice by oral administration. Antifighting activity was measured by the antagonism against foot-shock induced fighting, anticonvulsant activity by the degree of protection against convulsion induced by pentylenetetrazole (this test is a very sensitive measure of the CNS-depressant effect[12] and correlates to the human antianxiety potency[13,14]), sedative activity by the potentiation of thiopental sodium induced loss of the righting reflex and the inhibition of the spontaneous motor activity, and muscle relaxation by rotarod performance test. Table I shows these results and the acute toxicity (in mg/kg) for all tested compounds along with comparative data for diazepam and chlordiazepoxide.

The first active compound to be synthesized was 2-benzoyl-4-chloro-N^{α}-glycylglycinanilide (**5a**), which showed significant CNS activity. The introduction of the chlorine atom to the ortho position of the benzoyl group as in **5g** produced a decrease in the activities despite the fact that the addition of an *o*-chloro atom to the 5-phenyl group has been shown to increase the activity of the 1,4-benzodiazepines.[12] Replacing the terminal glycine residue in **5a** with a leucine residue yielded a compound (**5d**) which exhibited the same degree of activity in the antipentylenetetrazole test but had no effect in the rotarod performance test at a 100 mg/kg dose. Replacement with DL-valine or DL-α-phenylglycine residues (**5c**,**e**) produced lower activities in the antipentylenetetrazole test. When

(9) T. Sugasawa, T. Yoyoda, M. Adachi, and K. Sasakura, *J. Am. Chem. Soc.*, **100**, 4842 (1978).
(10) The structure of the free base of the compound **9f** was determined by X-ray analysis: S. Shiro, H. Nakai, S. Matsutani, and K. Hirai, unpublished results.
(11) M. Nakanishi, T. Tahara, K. Araki, M. Shiroki, T. Tsumaguri, and Y. Takigawa, *J. Med. Chem.*, **16**, 214 (1973).
(12) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, "Drugs Affecting the Central Nervous System", A. Burger, Ed., Marcel Dekker, New York, 1968, p 237.
(13) G. Zbinden and L. O. Randall, *Adv. Pharmacol.*, **5**, 213 (1967).
(14) Reference 2c, p 27.

Table I. Pharmacological Activity in Mice[a]

compd	ED_{50},[b] mg/kg: spontaneous motor act.	rotarod performance	antipentylenetetrazole	antifighting	MED,[c] mg/kg: potentiation of thiopental sodium	LD_{50}, mg/kg
5a		52.4	14.1	14.6	25.0	>1000
5b						>1000
5c		>100	27.4			>1000
5d		>100	15.9		25.0	>1000
5e		>100	27.4			>1000
5f		>100	>100			>1000
5g		>100	22.0		10.0	>1000
5h		59.5	2.8			
15		>100	>100			
9a	15.1	29.4	1.0	10.5	2.5	750
9b	>50	73.5	3.4	21.5	10.0	>1000
9c	23.4	70.7	3.9	15.1	5.0	>1000
9d		>100	15.8			>1000
9e		>100	5.7		5.0	>1000
9f	1.4	35.4	0.56	3.2	0.5	>1000
9g	5.5	37.5	1.6	17.1	5.0	>1000
9h	>50	52.2	1.0	10.2	1.0	>1000
9i	>50	77.1	4.8	20.4	10.0	>1000
9j	>25	>100	1.6			750
9k	3.1	16.7	0.3	1.6	0.1	>1000
9l	25	50.8	1.98	9.4		>1000
diazepam	8.45 (6.27-15.83)[d]	17.7 (13.4-23.4)	1.19 (0.92-1.49)	6.1 (3.4-27.7)	0.5	1385.9 (1087.8-1781.7)
chlordiazepoxide	56.09 (42.85-78.04)	82.3 (60.1-115.7)	2.71 (1.71-3.90)	27.1 (21.4-36.1)	2.5	1079.0 (974.4-1186.8)

[a] All samples were administered orally and estimated at 60 min after dosing. [b] ED_{50} values were obtained by graphical interpolation. [c] Minimum effective dose (Student's t test). [d] 95% confidence limits are given in parentheses.

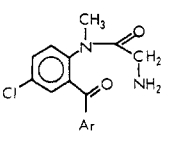
the terminal amino group was protected by the Z or Pht group, the compounds did not show CNS activities. The terminal β-alanyl derivative (**5f**) was also found to be almost inactive. Although the pyridine analogue (**5h**) showed a high level of activity in the antipentylenetetrazole test, the thiophene analogue **15** was almost inactive.

A marked increase was found in antipentylenetetrazole activity in the *N*-methylaniline derivative **9a** over that of the corresponding NH derivative **5a**. This fact suggested that release of the intramolecular hydrogen bonding between the aniline NH and the benzoyl carbonyl group in **5a** played an important role in determining the level of CNS activity. This conclusion was also supported by the observation that activities of other *N*-methylaniline derivatives (**9**) were higher than those of the corresponding NH derivatives (**5**). However, introduction of an isopropyl group at the nitrogen of aniline (**9d**) produced less activity than the NH derivative.

The introduction of chlorine or fluorine atoms in the ortho position of the benzoyl group enhanced antipentylenetetrazole activity as has been seen with 1,4-benzodiazepine.[12]

According to Snyder's proposal[15] that benzodiazepines exert their activities by mimicking the action of the putative CNS neurotransmitter glycine at its receptor site, Gall et al. speculated, but were unable to prove, that one possible active form of benzodiazepines at a glycine receptor site might be the hydrolyzed or ring-opened *o*-glycylaminobenzophenone.[16a]

Since dipeptidoaminobenzophenones release the terminal amino acids in vivo by enzymatic action, dipeptidoaminobenzophenones are direct precursors of *o*-glycylaminobenzophenone.[16b] However, in order to account for the increased CNS activity in *N*-methylaniline derivatives compared with the corresponding NH derivatives, the cyclization step to 1,4-benzodiazepines at physiological pH also should be taken into consideration.[17] *o*-Glycyl-*N*-methylaminobenzophenones (**16**) cyclized to 1,4-benzodiazepines much more readily than the corresponding NH dervatives (**17**).[18]



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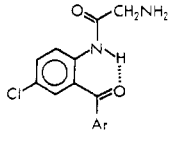

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Recently, a high-affinity, stereospecific, saturable binding site for 1,4-benzodiazepines has been reported in mammalian CNS.[19-23] The potency of various 1,4-benzodiazepines in preventing [^{3}H]diazepam binding

(15) S. H. Snyder, *Br. J. Pharmacol.*, **53**, 473 (1975).
(16) (a) M. Gall, J. B. Hester, Jr., A. D. Rudzik, and R. A. Lathi, *J. Med. Chem.*, **19**, 1057 (1976); (b) R. A. Lathi and M. Gall, *ibid.*, **19**, 1064 (1976).
(17) Our preliminary kinetic studies on the cyclization of *o*-glycylaminobenzophenone and *o*-glycyl-*N*-methylaminobenzophenone suggested that the *N*-methyl derivative followed first-order rate kinetics (τ 12.6 min at 37 °C in pH 7.52 buffer), but the NH derivative showed consecutive reaction and a detectable intermediate: K. Hirai and H. Sugimoto, unpublished results. For a recent discussion on the cyclization rates of *o*-glycylaminobenzophenones, see ref 3 and V. Šunjić, J. Kuftinec, and F. Kajfež, *Arzneim.-Forsch.*, **25**, 340 (1975).
(18) *o*-Glycylaminobenzophenone was obtained in crystalline form, whereas the N-methylated derivative could not be isolated; it cyclized spontaneously to the benzodiazepine: A. Walser, A. Szente, and J. Hellerbach, *J. Org. Chem.*, **38**, 449 (1973).
(19) R. F. Squires and C. Braestrup, *Nature (London)*, **266**, 732 (1977).
(20) C. Braestrup and R. F. Squires, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 3805 (1977).
(21) H. Möhler and T. Okada, *Life Sci.*, **20**, 2101 (1977).
(22) H. B. Bosmann, K. R. Case, and P. Distefano, *FEBS Lett.*, **82**, 368 (1977).
(23) C. Braestrup, R. Albrechtsen, and R. F. Squires, *Nature (London)*, **269**, 702 (1977).

Table II. Solubility of 9f, Its Salts, and Diazepam, and pH of the Aqueous Solution of 9f Salts

compd	mg/mL, 25 °C	pH of aq soln at 5 mg/mL
9f	18.6 7.25 3.90 2.01 0.63 (aq) (pH[a] 2.0) (4.0) (5.0) (6.0)	
9f·HCl	133 (aq)	3.7
9f·CH_3SO_3H	142 (aq)	4.3
diazepam	0.0433 (aq)	

[a] Briton-Robinson buffer solution.

correlates well with their potency in pharmacological tests in animals and with their clinical efficacy in man,[23,24] suggesting this site may be a pharmacological diazepam receptor in the brain.

Our recent experiments[25,26] on the inhibition of specific [^{3}H]diazepam binding to the rat brain membrane by peptido-*N*-methylaminobenzophenones indicated that they have a low affinity for 1,4-benzodiazepine receptors but were converted into compounds having a high affinity by incubation with crude synaptosomes from rat brain or rat liver homogenates. Thus, the observed pharmacological effects of peptidoaminobenzophenone could be wholly or partially due to the formation of an active metabolite by cleavage of the terminal amino acid followed by cyclization. However, the pharmacological profiles of peptidoaminobenzophenones were not identical with those of the corresponding cyclized 1,4-benzodiazepines, suggesting that they exert their pharmacological activities as total effects of those of various metabolites.[27] Also, terminal D-amino acid derivatives[28] have been found to have significant antipentylenetetrazole activity in mice on po administration, although the activity was much weaker than the corresponding terminal L-amino acid derivative. Therefore, some in vivo biotransformation could have taken place in the terminal D-amino acid derivative upon oral administration to mice.[29]

Conclusions

Peptidoaminobenzophenones are especially interesting as characteristic prodrugs[30] which are hydrolyzed enzymatically and then cyclized chemically to give biologically active 1,4-benzodiazepines, with the components liberated into the body being innocent amino acids.[31] Furthermore, in contrast with the fact that 1,4-benzodiazepines are practically insoluble in water,[32] peptidoaminobenzophenones have enhanced solubility in aqueous media and give water-soluble salts as shown in Table II.

These observations indicate that peptidoaminobenzophenones[33] are a new series of psychotropically active compounds which possess characteristic physical properties and pharmacological profiles.[34] Further work is in progress to evaluate these compounds as useful CNS agents, and the results will be presented elsewhere.[35]

Experimental Section

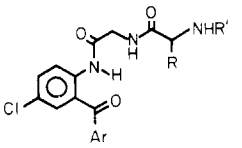
Chemistry. Melting points were determined in a Yamoto capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian HA-100, Varian A-60, or Varian T-60 spectrometer, and chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (Me_4Si) as an internal standard. Ultraviolet spectra were obtained with a Hitachi EPS-2 spectrophotometer. Infrared spectra were obtained with a JASCO DS-403G spectrometer. Mass spectra were run on a Hitachi RMU-6E spectrometer. Solvents used for recrystallization are indicated in parentheses next to the melting point.

Preparation of N-Unsubstituted Anilides. 2-Benzoyl-4-chloro-N^{α}-(tritylglycyl)glycinanilide (4b). To a solution of tritylglycylglycine (5.00 g, 13.4 mmol) in HMPA (24 mL) was added dropwise at −8 to −2 °C $SOCl_2$ (1.60 g, 13.4 mmol), and the resultant mixture was stirred at −5 °C for 20 min. Next, it was mixed with 2-amino-5-chlorobenzophenone (**3**, Ar = C_6H_5; 3.08 g, 13.3 mmol) and allowed to stand at room temperature overnight. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was triturated with Et_2O, giving **4b**: yield 1.70 g (22%); mp 187–188 °C (AcOEt); UV λ_{max} (EtOH) 237.5 nm, 274 (sh), 343 (log ϵ 4.51, 4.03, 3.53); NMR ($CDCl_3$) δ 3.10 (br s, 2 H, Trt-NHCH_2), 4.17 (br s, 2 H, J = 7 Hz, CH_2), 6.92–7.67 (m, 22 H, aromatic), 7.93 (br s, 1 H, NH), 8.68–8.83 (m, 1 H, aromatic), 11.3 (br s, 1 H, ArNH). Anal. ($C_{36}H_{30}N_3O_3Cl$) C, H, N, Cl. Compounds **4a,c,g–i** (Table III) were prepared in a similar manner.

2-Benzoyl-4-chloro-N^{α}-[(benzyloxycarbonyl)leucyl]-glycinanilide (4e). To a solution of Z-leucylglycine (4.05 g, 12.5 mmol) in dry CH_2Cl_2 (50 mL) were added Et_3N (1.75 mL, 12.6 mmol) and $ClCOOC_2H_5$ (1.20 mL, 12.5 mmol) at −10 °C, and the mixture was stirred at the same temperature for 20 min. To this mixture a solution of **3** (Ar = C_6H_5; 2.91 g, 12.6 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise at 0 °C. The solution was

(24) H. Mohler and T. Okada, *Science*, **198**, 849 (1977).
(25) M. Fujimoto, Y. Tsukinoki, K. Hirose, K. Hirai, and T. Okabayashi, *Chem. Pharm. Bull.*, submitted.
(26) M. Fujimoto, Y. Tsukinoki, K. Hirose, K. Kuruma, R. Konaka, and T. Okabayashi, *Chem. Pharm. Bull.*, in press.
(27) Lorazepam, *N*-methyllorazepam, chlordesmethyldiazepam, and chlordiazepam were determined as metabolites when **9f** was administered to dogs, unpublished results.
(28) The optical purity of peptidoaminobenzophenones having terminal L- and D-amino acids was determined by high-performance LC measurement of the coupling products with trifluoroacetyl-L-proline, ensuring a purity of more than 98.5%: Y. Mori and M. Konishi, unpublished results.
(29) Hassal et al. reported that compounds with terminal D-amino acids were not cleaved and had no 1,4-benzodiazepine-like pharmacological activity in mice on iv administration (ref 3). Investigations on the details of the course of po administration of terminal L- and D-amino acids derivatives are in progress. Y. Mori and M. Konishi, unpublished results.
(30) For reviews of prodrugs, see (a) N. J. Harper, *Prog. Drug Res.*, **4**, 222 (1962); (b) A. A. Sinkula and S. H. Yalkowsky, *J. Pharm. Sci.*, **64**, 181 (1975); (c) V. Stella, *ACS Symp. Ser.*, **no. 14**, 1 (1975).
(31) Some compounds coupled with amino acids or peptides were recently prepared in order to obtain favorable properties compared to parent compounds: (a) A. M. Felix, D. D. Winter, S.-S. Wang, I. D. Kulesha, W. R. Povl, D. L. Hane, and H. Sheppard, *J. Med. Chem.*, **17**, 422 (1974); (b) K. Shimada, Y. Fuji, and T. Nambara, *Chem. Pharm. Bull.*, **21**, 1031 (1973); (c) H. Dittner, H. Stormann, and R. Enzenhofer, *Arzneim.-Forsh.*, **26**, 2145 (1976); (d) N. Bodor, K. B. Sloan, T. Higuchi, and K. Sasahara, *J. Med. Chem.*, **20**, 1435 (1977).
(32) The acid addition salts of amino ester derivatives of 3-oxy-substituted 1,4-benzodiazepines were previously prepared to obtain water-soluble derivatives suitable for parenteral administration, which might diminish the incidence of pain subsequent venous inflammation often encountered with injectable formulation of 1,4-benzodiazepine: A. Nudelman, R. J. McCaully, and S. C. Bell, *J. Pharm. Sci.*, **63**, 1880 (1974).
(33) The synthesis and pharmacological results of other various types of peptide derivatives will be presented elsewhere.
(34) Hassal et al. pointed out that peptidoaminobenzophenones could serve as probenzodiazepines which could have favorable characteristics, such as a rate of metabolism or water solubility at physiological pH, that could provide an improved presentation of the benzodiazepine in vivo (ref 3).
(35) K. Hirose, A. Matsushita, M. Eigyo, H. Joyama, A. Fujita, Y. Tsukinoki, T. Shiomi, and K. Matsubara, *Arzneim.-Forsch.*, in press.

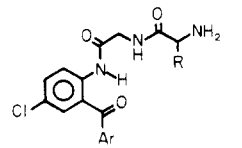
Table III. Protected Dipeptidoaminobenzophenones (4)



no.	Ar	R R'-NHCHCO-	mp, °C (solvent)[a]	yield, %	formula	anal.[b]
4a	C_6H_5	Z-Gly-	163-164 (EA)	23[c]	$C_{25}H_{22}N_3O_5Cl$	C, H, N, Cl
4b	C_6H_5	Trt-Gly-	187-188 (EA)	23[c]	$C_{36}H_{30}N_3O_3Cl$	C, H, N, Cl
4c	C_6H_5	Z-DL-Ala-	148-149 (MC)	22.2[c]	$C_{26}H_{24}N_3O_5Cl$	C, H, N, Cl
4d	C_6H_5	Z-DL-Val-	158-168 (M-ET)	27.7[d]	$C_{28}H_{28}N_3O_5Cl$	H, N, Cl; C[e]
4e	C_6H_5	Z-Leu-	98-100 (ET)	46.5[d]	$C_{29}H_{30}N_3O_5Cl$	C, H, N, Cl
4f	C_6H_5	Z-DL-Gly(α-Ph)-	93-95 (M-ET)	14.9[d]	$C_{31}H_{26}N_3O_5Cl$	C, H, N, Cl
4g	C_6H_5	Z-β-Ala-	150-155 (MC-M)	21.8[c]	$C_{26}H_{24}N_3O_5Cl$	C, H, N, Cl
4h	C_6H_4-2-Cl	Z-Gly-	166-167 (EA)	15.4[c]	$C_{25}H_{21}N_3O_5Cl_2$	C, H, N, Cl
4i	C_6H_4-2-Cl	Trt-Gly-	217-218 (EA)	15.6[c]	$C_{36}H_{29}N_3O_5Cl_2$	C, H, N, Cl
4j	2-pyridyl	Z-Gly-	154-155 (MC-M)	42.2[c]	$C_{24}H_{21}N_4O_5Cl$	C, H, N, Cl

[a] Solvents used for recrystallization are indicated next to the melting point. Solvents are abbreviated as follows: ET, ether; EA, ethyl acetate; MC, methylene chloride; E, ethanol; M, methanol; PE, petroleum ether; H, *n*-hexane; W, water; AN, acetonitrile; AA, acetic acid. [b] Analyses of the elements indicated were within ±0.4% of theory except where indicated. [c] Coupling was carried out using HMPA/$SOCl_2$. [d] Coupling was carried out using ClCOOEt/Et_3N. [e] C: calcd, 66.96; found, 66.39.

Table IV. Dipeptidoaminobenzophenones (5)



no.	Ar	R H_2NCHCO-	mp, °C (solvent)[a]	yield, %	formula	anal.[b]
5a	C_6H_5	Gly-	135-136 (EA)	80[c]	$C_{17}H_{16}N_3O_3Cl$	C, H, N, Cl
5b	C_6H_5	DL-Ala-	131-132 (MC-H)	55[d]	$C_{18}H_{18}N_3O_3Cl\cdot 0.5H_2O$	C, H; N[e]
5c	C_6H_5	DL-Val-	119-121 (ET)	76.2[d]	$C_{20}H_{22}N_3O_3Cl$	C, H, N, Cl
5d	C_6H_5	Leu-	145-147 (ET)	70.3[d]	$C_{21}H_{24}N_3O_3Cl$	C, H, N, Cl
5e	C_6H_5	DL-Gly(α-Phe)-	amorphous	31.8[d]	$C_{23}H_{20}N_3O_3Cl$	C, H, N, Cl
5f	C_6H_5	β-Ala-	178-182 (MC-M)[f]	86.4[d]	$C_{18}H_{18}N_3O_3Cl\cdot 0.5(COOH)_2\cdot 2H_2O$	C, H, N
5g	C_6H_4-2-Cl	Gly-	145-147 (EA)	78[d]	$C_{17}H_{15}N_3O_3Cl_2$	C, H, N, Cl
5h	2-pyridyl	Gly-	192-194 (M-EA)[g]	100[d]	$C_{16}H_{15}N_4O_3Cl\cdot 2HBr\cdot 0.5CH_3CO_2C_2H_5$	H, N, Cl, Br; C[h]

[a,b] See corresponding footnotes in Table III. [c] Trt group was removed by heating with AcOH. [d] Z group was removed by treatment with HBr-HOAc. [e] N: calcd, 11.39; found, 10.73. [f] Hemioxalate. [g] Dihydrobromide. [h] C: calcd, 39.12; found, 38.35.

stirred under ice cooling for 1.25 h, at room temperature for 1.5 h, and then refluxed overnight. The reaction mixture was poured onto a mixture of aqueous K_2CO_3 and ice and then extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a column of silica gel containing H_2O (3 wt %), which was eluted with benzene to remove the starting **3** (Ar = C_6H_5) and then with benzene/AcOEt (9:1, v/v), giving **4e**: yield 3.13 g (46.5%); mp 98–100 °C (Et_2O); IR ($CHCl_3$) 3425, 3315, 1700, 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.78–1.00 (br m, 6 H, 2 × Me), 1. 37–2.00 (br m, 3 H, $-CH_2CH-$), 3.93–4.17 (m, 2 H, $COCH_2$), 4.17–4.63 (m, 1 H, C*H*NH), 5.08 (s, 2 H, CH_2Ph), 5.52 (d, *J* = 8 Hz, 1 H, N*H*CH), 7.12 (br t, *J* = 6 Hz, 2 H, NHCH_2), 7.28 (s, 5 H, Ph), 7.33–7.83 (m, 7 H, aromatic), 8.47–8.07 (m, 1 H, aromatic), 10.9 (br s, 1 H, ArNH). Anal. ($C_{29}H_{30}N_3O_5Cl$) C, H, N, Cl. Compounds **4d** and **4f** (Table III) were prepared in a similar manner.

2-Benzoyl-4-chloro-*N*$^{\alpha}$-glycylglycinanilide (5a). A solution of **4b** (1.7 g, 2.9 mmol) in 50 vol % AcOH (20 mL) was heated on a steam bath for 20 min. After the solution cooled, the precipitated solids were filtered off, and the filtrate was neutralized with aqueous $NaHCO_3$ and then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated, giving **5a**: yield 0.80 g (80%); mp 135–136 °C (AcOEt); UV λ_{max} (EtOH) 241 nm, 275 (sh), 340 (log ε 4.44, 4.03, 3.55); NMR ($CDCl_3$) δ 1.85 (br s, 2 H, NH_2), 3.52 (br s, 2 H, C$H_2$$NH_2$), 4.14 (br d, *J* = 5 Hz, 2 H, CH_2), 7.28–7.82 (m, 7 H, aromatic), 8.07 (br s, 1 H, CH_2NH), 8.53–8.72 (m, 1 H, aromatic), 11.1 (br s, 1 H, ArNH). Anal. ($C_{17}H_{16}N_3O_3Cl$) C, H, N, Cl.

2-Benzoyl-4-chloro-*N*$^{\alpha}$-leucylglycinanilide (5d). Compound **4e** (3.10 g, 5.78 mmol) was dissolved in 24% HBr–AcOH (15 mL) under ice cooling, and the solution was stirred at room temperature for 1.5 h. Ether was added to the mixture, which was then allowed to stand for 30 min. The precipitate was filtered off, dissolved in cold H_2O, and washed with CH_2Cl_2/Et_2O (1:2, v/v). The aqueous layer was separated, made alkaline with aqueous K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated, giving **5d**: yield 1.63 g (70.3%); mp 145–147 °C (Et_2O); IR ($CHCl_3$) 3325, 1685, 1639 cm^{-1}; $[\alpha]^{24.5}_D$ +50.7 ± 0.9° (*c* 1.001, EtOH); MS *m/e* 401 (M^+); NMR ($CDCl_3$) δ 0.75–1.15 (br d, 6 H, 2 × Me), 1.23–2.17 (br m, 5 H, CH_2CH and NH_2), 3.37–3.78 (br m, 1 H, COCH<), 4.12 (br d, *J* = 6 Hz, 2 H, $COCH_2$), 7.33–7.83 (m, 7 H, aromatic), 8.17 (br m, 1 H, N*H*CH_2), 8.55–8.77 (m, 1 H, aromatic), 11.1 (br s, 1 H, ArNH). Anal. ($C_{21}H_{24}N_3O_3Cl$) C, H, N, Cl. Compounds **5b,c,e–g** (Table IV) were prepared in a similar manner.

4-Chloro-2-(2-pyridylcarbonyl)-*N*$^{\alpha}$-[(benzyloxycarbonyl)glycyl]glycinanilide (4j). To a solution of Z-glycylglycine (1.72 g, 6.46 mmol) in HMPA (7 mL) and CH_3CN (3.5 mL) was added dropwise at −18 to −12 °C over 5 min $SOCl_2$ (0.679 g, 5.70 mmol). After the mixture was stirred for 10 min,

a solution of 2-(2-amino-5-chlorobenzoyl)pyridine[36] (3, Ar = 2-pyridyl; 1.00 g, 4.30 mmol) in HMPA (3 mL) and CH_3CN (1.5 mL) was added, and the mixture was allowed to stand at −20 °C overnight. Next, it was poured into a mixture of ice and aqueous K_2CO_3 and then extracted with Et_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue, chromatographed on a column of silica gel containing H_2O (3 wt %) with AcOEt as an eluant, gave **4j**: yield 0.870 g (42.2%); mp 154–155 °C (CH_2Cl_2–MeOH); IR ($CHCl_3$) 3438, 3316, 1698, 1648 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (br d, J = 6 Hz, 2 H, $COCH_2$), 4.08 (br d, J = 6 Hz, 2 H, $COCH_2$), 5.10 (s, 2 H, CH_2Ph), 5.88 (br m, 1 H, NH), 7.00–8.00 (m, 11 H, NH and 10 aromatic), 8.47–8.78 (m, 2 H, 2 aromatic), 11.2 (br s, 1 H, ArNH). Anal. ($C_{24}H_{21}N_4O_5Cl$) C, H, N, Cl.

4-Chloro-2-(2-pyridylcarbonyl)-N^{α}-glycylglycinanilide (5h). Compound **4j** (0.75 g, 1.6 mmol) was dissolved in 24% HBr–AcOH under ice cooling, and the solution was stirred at room temperature for 1.25 h. Ether was added to the reaction mixture, and the precipitated solids were collected by filtration and then dried to give **5h**: yield 0.80 g (100%); mp 192–194 °C dec (MeOH–AcOEt); IR (Nujol) 1731, 1687 cm^{-1}.

Preparation of Indole Starting Materials 6. Ethyl 5-Chloro-3-(o-chlorophenyl)-1-methylindole-2-carboxylate (18b). To a suspension of NaH (50% oil dispersion; 3.60 g, 75.0 mmol) in DMF (30 mL), a solution of ethyl 5-chloro-3-(o-chlorophenyl)indole-2-carboxylate (**19b**)[37] (25.1 g, 75.1 mmol) in DMF (120 mL) was added dropwise at 21–27 °C over 30 min. The solution was stirred at room temperature for 1.5 h and then CH_3I (11.7 g) was added, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice–water (600 mL) and the precipitated solid was collected by filtration and dried, giving **18b**: yield 23.8 g (94.5%); mp 78–81 °C, UV λ_{max} (EtOH) 219 nm, 231, 240, 303, 335 (sh) (log ε 4.48, 4.49, 4.51, 4.21, 3.80); IR (Nujol) 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.08 (s, 3 H, N-CH_3), 4.12 (q, J = 7 Hz, 2 H, CH_2CH_3), 7.00–7.70 (m, 7 H, aromatic). Anal. ($C_{18}H_{15}NO_2Cl_2$) C, H, N, Cl.

5-Chloro-3-(o-chlorophenyl)-1-methylindole-2-carboxylic Acid (20b). Compound **18b** (22.6 g, 64.9 mmol) was added to a solution of 86% KOH (8.45 g, 130 mmol) in EtOH (260 mL), and the mixture was refluxed for 2 h and then poured into ice–water (230 mL), followed by the addition of concentrated HCl (12 mL). The precipitated solids were collected by filtration, washed with H_2O, and then dried, giving **20b**: yield 20.5 g (98.5%); mp 229–231 °C (benzene); UV λ_{max} (EtOH) 220 nm, 238, 301, 325 (sh) (log ε 4.43, 4.47, 4.13, 3.81). Anal. ($C_{16}H_{11}NO_2Cl_2$) C, H, N, Cl.

5-Chloro-3-(o-chlorophenyl)-1-methylindole-2-carboxamide (21b). A suspension of **20b** (19.8 g, 61.8 mmol) in $SOCl_2$ (22.1 g, 186 mmol) was refluxed for 3 h. After removing excess $SOCl_2$ in vacuo, the residue, dissolved in THF (220 mL), was treated with dry gaseous NH_3 for 1 h under ice cooling, and the resulting mixture was stirred at room temperature for 3 h. The solution was evaporated and the residue was washed with H_2O, giving **21b**: yield 19.5 g (98%); mp 177–178 °C (benzene); UV λ_{max} (EtOH) 222 nm, 242 (sh), 300 (log ε 4.49, 4.37, 4.07); IR (Nujol) 1670 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (s, 3 H, NCH_3), 5.75 (br s, 2 H, NH_2), 7.13–7.68 (m, 7 H, aromatic). Anal. ($C_{16}H_{12}N_2OCl_2$) C, H, N, Cl.

2-(Aminomethyl)-5-chloro-3-(o-chlorophenyl)-1-methylindole Hydrochloride (6b). A suspension of $LiAlH_4$ (6.50 g, 170 mmol) in anhydrous Et_2O (400 mL) was treated portionwise over 15 min with compound **21b** (18.2 g, 57.0 mmol). The mixture was stirred at room temperature for 0.5 h and then at reflux for 4 h. After cooling and cautious addition of AcOEt (10 mL) and H_2O (41 mL), the organic layer was separated, dried (Na_2SO_4), and evaporated. The residue, dissolved in EtOH, was treated with 20 mL of 20% HCl–EtOH. The precipitated solids were collected by filtration and dried, giving **6b**: yield 15.2 g (78%); mp 263–265 °C dec (EtOH); UV λ_{max} (EtOH) 230 nm, 282, 298, 310 (sh) (log ε 4.57, 3.95, 3.88, 3.78); NMR (Me_2SO-d_6) δ 3.97 (s, 3 H, NCH_3), 4.15 (br s, 2 H, CH_2), 7.17–7.80 (m, 7 H, aromatic). Anal. ($C_{16}H_{15}N_2Cl_3$) C, H, N, Cl.

Ethyl 5-Chloro-3-(o-fluorophenyl)-1-methylindole-2-carboxylate (18c). N-Methylation of ethyl 5-chloro-3-(o-fluorophenyl)indole-2-carboxylate (**19c**)[37] was carried out in 88% yield by the procedure described for the preparation of **18b** from **19b**: mp 77–78 °C; NMR ($CDCl_3$) δ 1.03 (t, J = 7 Hz, 3 H, CH_2CH_3), 4.07 (s, 3 H, NCH_3), 4.17 (q, J = 7 Hz, 2 H, CH_2CH_3), 7.00–7.57 (m, 7 H, aromatic). Anal. ($C_{18}H_{15}NO_2ClF$) C, H, N, Cl, F.

5-Chloro-3-(o-fluorophenyl)-1-methylindole-2-carboxylic Acid (20c). Hydrolysis of **18c** was carried out in 98% yield by the procedure described for the preparation of **20b** from **18b**: mp 232–234 °C; IR (Nujol) 1665 cm^{-1}; NMR (Me_2SO-d_6) δ 4.05 (s, 3 H, NCH_3), 7.03–7.90 (m, 7 H, aromatic). Anal. ($C_{16}H_{11}NO_2ClF$) C, H, N, Cl, F.

5-Chloro-3-(o-fluorophenyl)-1-methylindolecarboxamide (21c). Amidation of **20c** was carried out in 100% yield by the procedure described for the preparation of **21b** from **20b**: mp 160–162 °C (n-hexane–CH_2Cl_2); NMR ($CDCl_3$) δ 3.98 (s, 3 H, NCH_3), 5.90 (br s, 2 H, NH_2), 7.06–7.53 (m, 7 H, aromatic). Anal. ($C_{16}H_{12}N_2OClF$) C, H, N, Cl, F.

2-(Aminomethyl)-5-chloro-3-(o-fluorophenyl)-1-methylindole Hydrochloride (6c). Reduction of **21c** was carried out in 20.4% yield by the procedure described for the preparation of **6b** from **21b**: mp ~259 °C dec (EtOH); NMR ($CDCl_3$) (free base) δ 1.55 (br s, 2 H, NH_2), 3.82 (s, 3 H, NCH_3), 3.90 (s, 2 H, CH_2), 7.07–7.60 (m, 7 H, aromatic). Anal. ($C_{16}H_{15}N_2Cl_2F$) C, H, N, Cl, F.

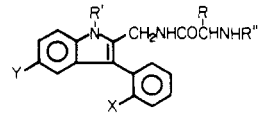
Method A. 5-Chloro-3-(o-chlorophenyl)-1-methyl-2-[[N^{α}-(tritylglycyl)amino]methyl]indole (7f). To a solution of tritylglycine (3.11 g, 10.0 mmol) in HMPA (16 mL) was added dropwise at −7 to −2 °C over 5 min $SOCl_2$ (1.20 g, 10.1 mmol), and the mixture was stirred at −5 °C for 10 min. To it was added a solution of **6b** generated from its hydrochloride salt (3.42 g, 10.0 mmol) and Et_3N (1.50 mL, 10.8 mmol) in Et_2O (15 mL), and this mixture was allowed to stand at room temperature overnight, then neutralized with aqueous $NaHCO_3$, and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue, chromatographed on a column of silica gel with AcOEt, gave **7f**: yield 2.15 g (35.6%); mp 198–200 °C (EtOH); UV λ_{max} (EtOH) 230 nm, 284 (log ε 4.69, 4.01); IR (Nujol) 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (br s, 1 H, Trt-NH), 2.95 (br s, 2 H, $COCH_2$), 3.73 (s, 3 H, N-CH_3), 4.30–4.83 (m, 2 H, indole-CH_2), 5.83 (br s, 1 H, NHCO), 6.93–7.60 (m, 22 H, aromatic). Anal. ($C_{37}H_{31}N_3OCl_2$) C, H, N, Cl. Compounds **7a–e,g,h,k** (Table V) were prepared in a similar manner.

5-Chloro-3-(o-chlorophenyl)-1-methyl-2-[[N^{α}-[(benzyloxycarbonyl)phenylalanyl]amino]methyl]indole (7i). DCC (2.36 g, 11.4 mmol) was added to a solution of **6b** (3.50 g, 11.5 mmol), Z-phenylalanine (3.43 g, 11.5 mmol), and N-hydroxysuccinimide (1.32 g, 11.5 mmol) in dry DMF (69 mL), and the mixture was stirred at −20 °C for 2 h and then at room temperature for 2 h. After being allowed to stand in a refrigerator for 2 days, the reaction mixture was filtered, and the filtrate was mixed with H_2O (300 mL) and neutralized with aqueous $NaHCO_3$. The resulting precipitate obtained by filtration was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and then concentrated. The residue was washed with Et_2O, giving **7i**: yield 6.10 g (90.7%); mp 150–155 °C (AcOEt); NMR ($CDCl_3$) δ 2.92 (d, J = 8 Hz, 2 H, CH_2Ph), 3.48 and 3.52 (2 s, 3 H, NCH_3), 3.98–4.58 (m, 3 H, NH and indole-CH_2), 4.92 and 4.93 (2 s, 2 H, Z-CH_2), 5.35 (d, J = 8 Hz, 1 H, CH), 6.25 (br s, 1 H, NH), 6.92–7.63 (m, 17 H, aromatic). Anal. ($C_{33}H_{29}N_3O_3Cl_2$) C, H, N, Cl. Compound **7j** (Table V) was prepared in a similar manner.

4-Chloro-2-(o-chlorobenzoyl)-N-methyl-N^{α}-[(benzyloxycarbonyl)glycyl]glycinanilide (8g). To a solution of **7g** (9.10 g, 17.1 mmol) in AcOH (55 mL) was added dropwise at below 20 °C a solution of CrO_3 (5.50 g, 55.0 mmol) in H_2O (5.1 mL), and the resulting mixture was allowed to stand at room temperature overnight. The reaction mixture was mixed with ice–water and extracted with AcOEt, and then the organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on a column of silica gel and eluted with AcOEt, giving **8g**: yield 3.60 g (37.2%). Compounds **8a,c–f,i–k,m** (Table VII) were prepared in a similar manner.

(36) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).
(37) S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.*, **19**, 263 (1971).

Table V. Indoles (7)



no.	X	Y	R'	R''-NHCHCO-	mp, °C (solvent)[a]	yield, %	formula	anal.[b]
7a	H	Cl	CH_3	Z-Gly-	150-153 (ET-PE)[c]	53.8[d]	$C_{26}H_{24}N_3O_3Cl$	C, H, N, Cl
7b	H	Cl	CH_3	Z-DL-Val-	242-247 (MC-M)	32.6[d]	$C_{29}H_{30}N_3O_3Cl$	C, H, N, Cl
7c	H	Cl	CH_3	Z-Phe-	255-257 (MC-M)	38.5[d]	$C_{33}H_{30}N_3O_3Cl$	C, H, N, Cl
7d	H	Cl	*i*-Pr	Z-Gly-	173-175 (MC-M)	23.2[d]	$C_{28}H_{28}N_3O_3Cl$	C, H, N, Cl
7e	H	Cl	$CH_2CH_2NEt_2$	Z-Gly-	181-184 (E-PE)	23.6[d]	$C_{31}H_{35}N_4O_3Cl$	C, H, N, Cl
7f	Cl	Cl	CH_3	Trt-Gly-	198-200 (E)	35.6[d]	$C_{37}H_{31}N_3OCl_2$	C, H, N, Cl
7g	Cl	Cl	CH_3	Z-Gly-	96-98 (ET)	85[d]	$C_{26}H_{23}N_3O_3Cl_2$ $0.5(C_2H_5)_2O$	C, H, N, Cl
7h	Cl	Cl	CH_3	Z-DL-Phe-	174-176 (EA)	54[d]	$C_{33}H_{29}N_3O_3Cl_2$	C, H, N, Cl
7i	Cl	Cl	CH_3	Z-Phe-	150-155 (EA)	90.7[e]	$C_{33}H_{29}N_3O_3Cl_2$	C, H, N, Cl
7j	Cl	Cl	CH_3	Z-D-Phe-	171-173 (EA)	75[e]	$C_{33}H_{29}N_3O_3Cl_2$	C, H, N, Cl
7k	F	Cl	CH_3	Z-Gly-	166-167 (H-MC)	90[d]	$C_{26}H_{23}N_3O_3ClF$	C, H, N, Cl, F

[a,b] See corresponding footnotes in Table III. [c] Isomorphous crystals showed mp 183-185 °C (IR spectrum in $CHCl_3$ was identical with that of the crystals of mp 150-153 °C). [d] Coupling was carried out using HMPA/$SOCl_2$. [e] Coupling was carried out using HONSu/DCC/DMF.

Method B. 2-Benzoyl-4-chloro-*N*-methyl-*N*$^{\alpha}$-(trityl-glycyl)glycinanilide (8b). Coupling of **10** (R' = Me; X = H; Y = Cl) with tritylglycylglycine was carried out by the procedure described for the preparation of **4b** from **3** (Ar = Ph) in a 12.6% yield.

Method C. 2',5-Dichloro-2-(methylamino)benzhydrol (11b, R' = CH_3; X = Cl). To a solution of $NaBH_4$ (1.20 g, 31.7 mmol) in THF (10 mL) was added dropwise a solution of **10b** (R' = CH_3; X = Y = Cl) (3.12 g, 11.1 mmol) in THF (20 mL). The resulting mixture was mixed with H_2O (5 mL) and stirred at room temperature overnight; then H_2O was added again and the mixture was evaporated in vacuo. The residue was brought to pH 8-9 with dilute HCl and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated, giving **11b**:[9] yield 3.05 g (97.1%); mp 105.5-106.5 °C (Et_2O-*n*-hexane). Anal. ($C_{14}H_{13}NOCl_2$) C, H, N, Cl.

4-Chloro-2-(*o*-chloro-α-hydroxybenzyl)-*N*-methyl-*N*$^{\alpha}$-[(benzyloxycarbonyl)glycyl]glycinanilide (12c, R' = CH_3; R = R'' = H; R''' = $C_6H_5CH_2OCO$; X = Cl). To a solution of Z-glycylglycine (4.00 g, 15.0 mmol) in HMPA (20 mL) and CH_3CN (10 mL) was added dropwise at -18 °C $SOCl_2$ (1.77 g, 14.9 mmol), and the solution was stirred at -18 °C for 30 min. To this, a solution of **11b** (2.20 g, 7.80 mmol) in HMPA (10 mL) and CH_3CN (5 mL) was added dropwise at -18 °C, and the mixture was stirred at the same temperature for 8 h then allowed to stand at -20 °C overnight. Next, it was mixed with H_2O, made alkaline with aqueous $NaHCO_3$, and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on a column of silica gel and eluted with AcOEt, giving **12c**: yield 3.31 g (79.8%); mp 57-60 °C; NMR ($CDCl_3$) δ 3.07 and 3.12 (2 s, 3 H, N-CH_3), 3.57-3.90 (m, 4 H, 2 × CH_2), 5.00 (s, 2 H, Z-CH_2), 6.03 (br s, 2 H, CH and NH), 6.90-8.03 (m, 12 H, aromatic). Anal. ($C_{26}H_{25}N_3O_5Cl_2$) C, H, N, Cl. Compounds **12a,d,g** (Table VI) were prepared in a similar manner.

4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-*N*$^{\alpha}$-[(benzyloxycarbonyl)glycyl]glycinanilide (8g). To a solution of **12c** (21.8 g, 41.0 mmol) in Me_2CO (300 mL) was added Jones reagent[38] dropwise until the reaction mixture remained red. The resulting mixture was filtered to remove the precipitate. The red filtrate was mixed with *i*-PrOH until the red filtrate became green, then the mixture was filtered, and the filtrate was neutralized with aqueous $NaHCO_3$ and evaporated. The residue was mixed with H_2O and extracted with $CHCl_3$. The organic layer was decolorized with active carbon and filtered, and then the filtrate was dried (Na_2SO_4) and evaporated, giving **8g**: yield 21.3 g (98.5%); syrup; IR ($CHCl_3$) 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ 3.07 and 3.10 (2 s, 3 H, NCH_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). Anal. ($C_{26}H_{23}N_3O_5Cl_2$) C, H, N, Cl. Compounds **8a,c,d,h,j,l,n,o** (Table VII) were prepared in a similar manner.

4-Chloro-2-(*o*-chloro-α-hydroxybenzyl)-*N*-methyl-*N*$^{\alpha}$-(phthalylglycyl)glycinanilide (12e). To a solution of phthalylglycylglycine (138 g, 526 mmol) in HMPA (340 mL) and CH_3CN (170 mL) was added dropwise at -22 to -20 °C $SOCl_2$ (35.0 mL, 487 mmol), and the solution was cooled to -33 °C. To this a solution of **11b** (95.0 g, 337 mmol) in HMPA (240 mL) and CH_3CN (95 mL) was added dropwise, and the mixture was stirred at -35 to -30 °C for 5 h, and then Et_2O (200 mL) and H_2O (200 mL) were added. After neutralization with aqueous $NaHCO_3$, H_2O (1 L) was added followed by extraction with Et_2O. The organic layer was allowed to stand to precipitate **12e**. The separated gum from the aqueous layer was extracted with $CHCl_3$, the organic layer was dried (Na_2SO_4) and evaporated, and the residue was washed with EtOH and Et_2O, giving **12e**: total yield 142 g (80.5%); mp 213-214 °C (EtOH); IR (Nujol) 3260, 1775, 1730, 1660, 1640, 1560, 1540 cm^{-1}; NMR (Me_2SO-d_6) δ 2.83 and 3.12 (2 s, 3 H, N-CH_3), 3.50-3.73 (m, 2 H, CH_2NH), 4.30 (s, 2 H, Pht-NCH_2), 6.03 (br s, 1 H, CH), 7.17-7.58 (m, 7 H, aromatic), 7.83 (br s, 4 H, aromatic). Anal. ($C_{26}H_{21}N_3O_5Cl_2$) C, H, N, Cl. Compounds **12b** and **12f** (Table VI) were prepared in a similar manner.

4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-*N*$^{\alpha}$-(phthalyl-glycyl)glycinanilide (8g). Jones oxidation of **12e** was carried out by the procedure described for the preparation of **8g** from **12c** in a 90% yield.

4-Chloro-2-(*o*-fluoro-α-hydroxybenzyl)-*N*-[2-(diethyl-amino)ethyl]-*N*$^{\alpha}$-(phthalylglycyl)glycinanilide (12h). To a solution of 4'-chloro-*N*-[2-(diethylamino)ethyl]-2'-(*o*-fluoro-α-hydroxybenzyl)-2-aminoacetanilide[39] (6.20 g, 15.2 mmol) in THF (100 mL) was added phthalylglycyl chloride (4.40 g, 19.7 mmol). The mixture was stirred for 3 h and then evaporated, and the residue was extracted with $CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$ and then with H_2O and evaporated, giving **12h**: yield 6.40 g (70.8%); mp 166-168 °C (AcOEt); NMR ($CDCl_3$) δ 0.98 (t, *J* = 6 Hz, 3 H, CH_2CH_3), 2.28-2.85 (m, 2 H, COCH_2NH), 4.38 and 4.47 (2 s, 2 H, Pht-N-CH_2), 6.00 and 6.15 (2 s, 1 H, CH), 6.85-8.05 (m, 11 H, aromatic). Anal. ($C_{31}H_{32}N_4O_5ClF$) C, H, N, Cl, F.

Method D. 4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-*N*$^{\alpha}$-(phthalylglycyl)glycinanilide (8h). To a solution of **10b** (R' = CH_3; X = Y = Cl) (3.20 g, 11.4 mmol) in benzene, phthalylglycylglycyl chloride (4.00 g, 14.3 mmol) was added portionwise, and the resulting mixture was stirred at 70-80 °C for 1 h. The

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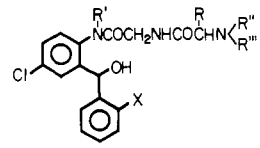
(39) R. I. Fryer and L. H. Sternbach (Hoffmann-La Roche), Japanese Patent 49-10676 (1974).

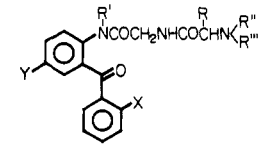
Table VI. Benzhydrols (12)



no.	X	R'	R'''	mp, °C (solvent)[a]	yield, %	formula	anal.[b]
12a	H	CH_3	Z-Gly-	75–78	59	$C_{26}H_{26}N_3O_5Cl\cdot0.5H_2O$	C, H, N, Cl
12b	H	CH_3	Pht-Gly-	126–127 (EA)	78	$C_{26}H_{22}N_3O_5Cl\cdot0.5H_2O$	C, H, N, Cl
12c	Cl	CH_3	Z-Gly-	57–60	79.8	$C_{26}H_{25}N_3O_5Cl_2$	C, H, N, Cl
12d	Cl	CH_3	Z-DL-Val-	172–173 (E)	70.7	$C_{29}H_{31}N_3O_5Cl_2$	C, H, N, Cl
12e	Cl	CH_3	Pht-Gly-	213–214 (E)	80.5	$C_{26}H_{21}N_3O_5Cl_2$	C, H, N, Cl
12f	F	CH_3	Pht-Gly-	193–194 (M)	59.4	$C_{26}H_{21}N_3O_5ClF$	C, H, N, Cl, F
12g	Cl	CH_3	Z-Pht-	amorphous		$C_{33}H_{31}N_3O_5Cl_2$	C, H, N, Cl
12h	F	$CH_2CH_2NEt_2$	Pht-Gly-	166–168 dec (EA)	70.8[c]	$C_{31}H_{22}N_4O_5ClF$	C, H, N, Cl, F

[a,b] See corresponding footnotes in Table III. [c] Obtained from 4'-chloro-*N*-[2-(diethylamino)ethyl]-2'-(2-fluoro-α-hydroxybenzyl)-2-aminoacetanilide as described under Experimental Section.

Table VII. Protected Dipeptido-*N*-alkylaminobenzophenones (8)



no.	X	Y	R'	R'''	mp, °C (solvent)[a]	yield, %	formula	anal.[b]
8a	H	Cl	CH_3	Z-Gly-	45–50	90.3[c]	$C_{26}H_{24}N_3O_5Cl\cdot0.25CHCl_3$	C, H, N, Cl
8b	H	Cl	CH_3	Trt-Gly-	amorphous	12.6[d]	$C_{37}H_{32}N_3O_3Cl\cdot0.5H_2O$	C, H, N, Cl
8c	H	Cl	CH_3	Z-DL-Val-	syrup	*c, e*		
8d	H	Cl	CH_3	Z-Phe-	syrup	*c, e*		
8e	H	Cl	*i*-Pr	Z-Gly-	amorphous	62.6[f]		
8f	H	Cl	$CH_2CH_2NEt_2$	Z-Gly-	syrup	37.5[f,e]		
8g	Cl	Cl	CH_3	Z-Gly-	syrup	98.5[c]	$C_{26}H_{23}N_3O_5Cl_2$	C, H, N, Cl
8h	Cl	Cl	CH_3	Pht-Gly-	217 (E)	93.7[g]	$C_{26}H_{19}N_3O_5Cl_2$	C, H, N, Cl
8i	Cl	Cl	CH_3	Z-DL-Phe-	syrup	58[f]	$C_{33}H_{29}N_3O_5Cl_2$	C, H, N; Cl[h]
8j	Cl	Cl	CH_3	Z-Phe-	amorphous	57[f]		
8k	Cl	Cl	CH_3	Z-D-Phe	syrup	51[f]		
8l	Cl	Cl	CH_3	Z-DL-Val	syrup	*c, d*		
8m	F	Cl	CH_3	Z-Gly-	syrup	39[f,e]		
8n	F	Cl	CH_3	Pht-Gly-	213–213 (C-M)	96[c]	$C_{26}H_{19}N_3O_5ClF\cdot H_2O$	C, H, N, F; Cl[i]
8o	F	Cl	$CH_2CH_2NEt_2$	Pht-Gly-	186–187 (M)	75.9	$C_{31}H_{30}N_4O_5ClF$	C, H, N, Cl, F

[a,b] See corresponding footnotes in Table III. [c] Method C. [d] Method B. [e] Crude product was used for the next reaction without further purification. [f] Method A. [g] Method D. [h] Cl: calcd, 11.46; found, 10.96. [i] Cl: calcd, 6.74; found, 7.44.

precipitated solids were collected by filtration, washed with benzene and EtOH, and then dried, giving **8h**: 5.60 g (93.7%); mp 217 °C (EtOH); IR (Nujol) 3220, 1770, 1720, 1715, 1680, 1660, 1650 cm^{-1}; NMR (Me_2SO-d_6) δ 3.03 and 3.07 (2 s, 3 H, NCH_3), 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). Anal. ($C_{26}H_{19}N_3O_5Cl_2$) C, H, N, Cl.

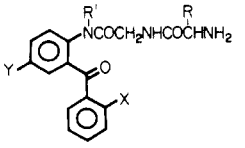
4-Chloro-2-(*o*-chlorobenzoyl)-*N*-methyl-*N*$^{\alpha}$-glycylglycinanilide (9f). (A) A suspension of **8h** (81.0 g, 154 mmol) in EtOH (50 mL) was refluxed, mixed with $NH_2NH_2\cdot H_2O$ (20 mL, 400 mmol), and refluxed again for 0.5 h. After the solution cooled, the separated phthalylhydrazide was removed by filtration, the filtrate was evaporated, and the residue was triturated with diluted EtOH, followed by washing with Et_2O, giving **9f**: yield 57.3 g (90%); mp 95–100 °C (EtOH–H_2O); IR (Nujol) 3480, 3360, 3300, 3240, 3190, 1660, 1590 cm^{-1}; NMR ($CDCl_3$) δ 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). Anal. ($C_{18}H_{17}N_3O_3Cl_2\cdot H_2O$) C, H, N, Cl. Compounds **9k** and **9l** were prepared in a similar manner.

(B) A solution of **8g** (3.60 g, 6.81 mmol) in HBr–AcOH (21.8%) (11.5 mL) was stirred at room temperature for 1.5 h. The solution was mixed with Et_2O to precipitate the solids. The solids were collected by filtration, dissolved in H_2O, and neutralized with aqueous $NaHCO_3$. The precipitate, collected by filtration, gave **9f**: yield 1.80 g (68%). Compounds **9a–e,g–k** (Table VIII) were prepared in a similar manner.

2-Benzoyl-4-chloro-*N*-methyl-*N*$^{\alpha}$-glycylglycinanilide (9a). Deprotection of **8b** was carried out by the procedure described for the preparation of **5a** from **4b** with a 78% yield: NMR ($CDCl_3$) δ 1.58 (br s, 2 H, NH_2), 3.07 and 3.27 (2 s, 3 H, NCH_3), 3.30 (br s, 2 H, CH_2NH_2), 3.65–4.03 (m, 2 H, CH_2NH), 7.00–8.00 (m, 9 H, NH and aromatic).

3-Benzoyl-2-[[(benzyloxycarbonyl)glycyl]glycinamido]-5-ethylthiophene (14). To a solution of Z-glycine (0.727 g, 3.46 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.352 g, 3.48 mmol) and $ClCOOC_2H_5$ (0.378 g, 3.48 mmol) at −20 to −30 °C, and the resulting mixture was stirred at below −10 °C for 40 min. To this mixture, a solution of **13**[11] (1.00 g, 3.48 mmol) in CH_2Cl_2

Table VIII. Dipeptido-*N*-alkylaminobenzophenones (9)



no.	X	Y	R'	R H$_2$NCHCO-	conjugated acid	mp, °C (solvent)[a]	yield, %	formula	anal.[b]
9a	H	Cl	CH_3	Gly-		amorphous[m]	82.7[c]	$C_{18}H_{18}N_3O_3Cl\cdot0.5H_2O$	C, H, Cl; N[d]
9b	H	Cl	CH_3	DL-Val-	$(COOH)_2$	amorphous	72.5[c,e]	$C_{21}H_{24}N_3O_3Cl\cdot0.5(COOH)_2\cdot0.5H_2O$	C, H; N[f]
9c	H	Cl	CH_3	Phe-	HCl	amorphous	65.4[c,e]	$C_{25}H_{24}N_3O_3Cl\cdot HCl$	C, H, N
9d	H	Cl	*i*-Pr	Gly-	HBr	150-153	71.6[c]	$C_{22}H_{22}N_3O_3Cl\cdot HBr\cdot H_2O$	C, H, N, Cl
9e	H	Cl	$CH_2CH_2NEt_2$	Gly-	HCl	amorphous	80.1[c]	$C_{23}H_{29}N_4O_3Cl\cdot2HCl$	H, Cl; C,[g] N[h]
9f	Cl	Cl	CH_3	Gly-		95-100 (N-W)	90[i]	$C_{18}H_{17}N_3O_3Cl_2\cdot H_2O$	C, H, N, Cl
9g	Cl	Cl	CH_3	DL-Phe-	HBr	206-209 dec	84[c]	$C_{25}H_{23}N_3O_3Cl_2\cdot HBr\cdot H_2O$	C, H, N, Cl, Br
9h	Cl	Cl	CH_3	Phe-[j]	$(COOH)_2$	amorphous	71[c]	$C_{25}H_{23}N_3O_3Cl_2\cdot(COOH)_2$	C, H, N, Cl
9i	Cl	Cl	CH_3	D-Phe-[k]	HBr	amorphous	84[c]	$C_{25}H_{23}N_3O_3Cl_2\cdot HBr$	C, H, N, Cl
9j	Cl	Cl	CH_3	DL-Val	HCl	100-103 dec (E-ET)	51.8[c,e]	$C_{21}H_{23}N_3O_3Cl_2\cdot0.5HCl\cdot H_2O$	C, H, N, Cl
9k	F	Cl	CH_3	Gly-	HCl	amorphous	52[c]	$C_{18}H_{17}N_3O_3ClF\cdot HCl$	C, H, N, F; Cl[l]
9l	F	Cl	$CH_2CH_2NEt_2$	Gly-	$(COOH)_2$	amorphous	62.1[i]	$C_{23}H_{28}N_4O_3ClF\cdot2(COOH)_2\cdot0.5H_2O$	C, H, N, Cl, F

[a,b] See corresponding footnotes in Table III. [c] From Z derivative. [d] N: calcd, 11.39; found, 10.74. [e] Yield from corresponding 7. [f] N: calcd, 9.22; found, 8.31. [g] C: calcd, 53.34; found, 53.78. [h] N: calcd, 10.82; found, 10.24. [i] From Pht derivative. [j] $[\alpha]^{25}_D$ +27.9 ± 0.7° (*c* 1.011, MeOH). [k] $[\alpha]^{26}_D$ −31.7 ± 0.7° (*c* 1.026, MeOH). [l] Cl: calcd, 17.11; found, 16.59. [m] Phosphate: mp 197-204 °C dec (E-W), $C_{18}H_{18}N_3O_3Cl\cdot H_3PO_4$, C, H, N, P, Cl. Tartarate: mp 197-202 °C dec (E-W), $C_{18}H_{18}N_3O_3Cl\cdot C_4H_6O_6$, C, H, N, Cl. Methanesulfonate: mp 192-194 °C dec (E), $C_{18}H_{18}N_3O_3Cl\cdot CH_3SO_3H$, C, H, N, S, Cl.

Table IX. Conjugated Acid Salts of 2-(*o*-Chlorobenzoyl)-4-chloro-*N*-methyl-N^{α}-glycylglycinanilide (9f)

conjugated acid	formula	mp, °C (solvent)	anal.[b]
HCl	$C_{18}H_{17}N_3O_3Cl_2\cdot HCl$	207-208 (E)	C, H, N, Cl
CH_3SO_3H	$C_{18}H_{17}N_3O_3Cl_2\cdot CH_3SO_3H$	217-218 (E-AN)	C, H, N, Cl, S
HBr	$C_{18}H_{17}N_3O_3Cl_2\cdot HBr$	187-189 dec (AN)	C, H, N, Cl, Br
H_3PO_4	$C_{18}H_{17}N_3O_3Cl_2\cdot H_3PO_4$	185-188 dec (W-E)	C, H, N, Cl, P
HNO_3	$C_{18}H_{17}N_3O_3Cl_2\cdot HNO_3\cdot H_2O$	122-130 (W-AN)	C, H, N; Cl[c]
tartaric acid	$C_{18}H_{17}N_3O_3Cl_2\cdot C_4H_6O_6\cdot2H_2O$	123-132 (W-E)	C, H, N, Cl
H_2SO_4	$C_{18}H_{17}N_3O_3Cl_2\cdot H_2SO_4\cdot H_2O$	193-196 dec (W-E)	C, H, N, Cl, S
citric acid	$C_{18}H_{17}N_3O_3Cl_2\cdot C_6H_8O_7\cdot H_2O$	123-126 (W-E)	C, H, N, Cl
maleic acid	$C_{18}H_{17}N_3O_3Cl_2\cdot C_4H_4O_4$	132-134 (W-E)	C, H, N, Cl
succinic acid	$(C_{18}H_{17}N_3O_3Cl_2)_2\cdot C_4H_6O_4$	167-169 (W-E)	H, N, Cl; C[d]
oxalic acid	$C_{18}H_{17}N_3O_3Cl_2\cdot C_2H_2O_4$	145-155 dec (W-E)	C, H, N, Cl

[a,b] See corresponding footnotes in Table III. [c] Cl: calcd, 14.12; found, 14.76. [d] C: calcd, 52.99; found, 52.58.

(10 mL) was added dropwise under ice cooling with stirring and then stirred at room temperature for 40 min. After refluxing for 17 h, the reaction mixture was poured into ice–water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and concentrated. The residue, chromatographed on silica gel and eluted with $CHCl_3$, gave **14**: yield 1.25 g (75.2%); syrup; IR ($CHCl_3$) 3440–3200, 1720–1680 cm^{-1}; NMR ($CDCl_3$) δ 4.05 (d, J = 6 Hz, 2 H, $COCH_2$), 4.17 (d, J = 6 Hz, 2 H, $COCH_2$), 6.05 (t, J = 6 Hz, 1 H, Z-N*H*), 6.72 (t, J = 1 Hz, thiophene-H), 12.3 (br s, 1 H, thiophene-NH).

3-Benzoyl-2-(glycylglycinamido)-5-ethylthiophene (15). A solution of **14** (1.25 g, 2.61 mmol) in 24% HBr–AcOH (7 mL) was stirred at room temperature for 2 h. The precipitate obtained upon adding ether (40 mL) was decanted, washed with Et_2O, dissolved in an aqueous Na_2CO_3 solution, and extracted with $CHCl_3$. The organic layer was washed with a saturated aqueous NaCl solution, dried ($MgSO_4$), and evaporated, giving **15**: yield 0.745 g (82.7%); paste; IR ($CHCl_3$) 3356, 3206, 1680, 1611 cm^{-1}; NMR ($CDCl_3$) δ 1.82 (br s, 2 H, NH_2), 3.53 (s, 2 H, $COCH_2$), 4.23 (d, J = 5 Hz, 2 H, $COCH_2$), 6.73 (t, J = 1 Hz, 1 H, thiophene-H), 8.17 (br s, 1 H, CH_2NH), 12.4 (br s, 1 H, thiophene-NH).

To a solution of **15** in $CHCl_3$ was passed through dry HCl and was then evaporated, giving **15**·HCl: mp 190–192 °C dec (MeOH–Et_2O); IR (KBr) 3535, 3465, 3200, 1700, 1690 cm^{-1}. Anal. ($C_{17}H_{20}N_3O_3SCl$) H, N, Cl; C: calcd, 53.46; found, 52.50

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. The ED_{50} and LD_{50} for diazepam and chlordiazepoxide were calculated with their 95% confidence limits according to the probit method.[40]

Spontaneous Motor Activity.[41] Spontaneous motor activity of mice was quantitated using an "Animex" activity meter.[41] Five groups per dose (each group consisting of three mice) were measured for 10 min, beginning at 60 min after dosing. A dose for 50% reduction of the control response (ED_{50}) was obtained by graphical interpolation.

Rotarod Performance Test.[42] Groups of five mice were used. A mouse was put on a wooden rod, 3 cm in diameter, turning at

(40) C. I. Bliss, *Q. J. Yearb. Pharmacol.*, **11**, 192 (1938).
(41) T. H. Svensson and G. Thieme, *Psychopharmacologia*, **14**, 157 (1969).
(42) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.*, **46**, 208 (1957).

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 obtained by graphical interpolation.

Antipentylenetetrazol Activity.[43] The test was performed with a group of five mice. The animals were challenged with a subcutaneous injection of 125 mg/kg pentylenetetrazol 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 obtained by graphical interpolation.

Antifighting Activity.[44] A pair of mice was confined during foot shock (5 Hz, 2 ms, DC 50 V) by being placed under an inverted circular glass enclosure (1-L beaker). Pairs showing 15–20 fighting episodes in 3 min were selected. Five pairs of mice were used for each dose, and the number of responses before and at 60 min after dosing was counted. The dose causing 50% inhibition of the response (ED_{50}) was obtained by graphical interpolation.

Potentiation of Thiopental Sodium. Five mice per group were used. Sixty minutes after administration of the test compound, the animals were challenged with an intravenous injection of 35 mg/kg thiopental sodium. The minimum effective doses of the compounds for potentiation of thiopental sodium induced anesthesia were compared.

Acute Toxicity. The acute toxicity of each compound was determined with groups of one to three mice on the 7th day after oral administration. The LD_{50} was obtained by graphical interpolation.

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Inhibitors of Indoleethylamine *N*-Methyltransferase. Derivatives of 3-Methyl-2-thiazolidinimine. In Vitro, in Vivo, and Metabolic Studies

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A variety of substituent groups has been attached to the exocyclic imine function of 2-imino-3-methylthiazolidine (1) in a search for metabolic precursors of this potent inhibitor of the enzyme indoleethylamine *N*-methyltransferase (INMT) which would exhibit superior pharmacodynamic properties in animals. It has been determined that chemically stable derivatives of 1 based on succinic, nicotinic, and N-acylated amino acids, although they lack in vitro efficacy, are potent inhibitors of INMT when administered orally or intravenously to rabbits. Metabolic studies carried out with ^{14}C-labeled *N,N'*-bis(3-methyl-2-thiazolidinylidene)succinamide (3) have established that conversion of this compound to 1 occurs both in the whole rabbit and in the isolated rabbit liver. 1 itself has been shown to be metabolically inert in rabbits, being excreted primarily in the urine.

The possibility that methylated indoleethylamine derivatives, such as *N,N*-dimethyltryptamine (DMT), may play a role in schizophrenia continues to attract attention.[1,2] The enzyme indoleethylamine *N*-methyltransferase (INMT), which catalyzes the methylation of indoleethylamines,[3] has been reported to be present in a number of species and tissues.[4] Although DMT has been shown to produce psychotomimetic effects in man,[5-7] there is as yet no convincing evidence for elevated DMT levels in schizophrenics, perhaps because of its rapid metabolism in vivo.[8,9] Inhibitors of INMT, which would effectively block the biosynthesis of dimethylindoleethylamines in man, may permit one to obtain more conclusive evidence concerning the possible contribution of indoleethylamine derivatives to schizophrenia.

We have reported recently on a series of monocyclic amidine derivatives which were shown to be potent inhibitors of INMT.[10] With these amidines (in which one of the nitrogens existed as an exocyclic imine function) the only permissible substituents, if high in vitro potencies were to be realized, were methyl or ethyl groups on the annular nitrogen. Substituents on the exocyclic nitrogen, or on other ring atoms, consistently caused a decrease in potency. Because it was anticipated that these small basic molecules might be of short duration of action in vivo, due to rapid elimination, it became of interest to explore the effect on in vivo activity of the introduction of substituents at the exocyclic nitrogen, which would be expected to show metabolic lability. Substituents of this type might modify

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