Amino Acid Amide Derivatives of 2-[3-(Aminomethyl)-4*H*-1,2,4-triazol-4-yl]benzophenones, a Novel Class of Annelated Peptidoaminobenzophenones[1]

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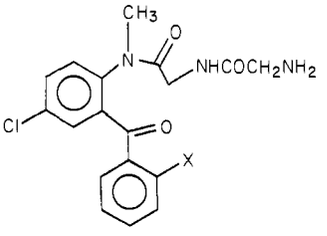
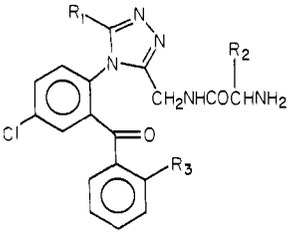
A series of the title compounds was prepared via condensation of the 3-(aminomethyl)triazolylbenzophenone (**5**) with N-protected amino acids, followed by deprotection, amination of the 3-[(chloroacetamido)methyl]triazolylbenzophenone (**6a,b**), or reduction of the relevant azide derivative (**6c**). Some of the title compounds were also derived directly from the quinazolines **3** or **4** by acid-induced rearrangement, followed by deprotection. These new amino acid amide derivatives of the triazolylbenzophenones (**2**) were evaluated for central nervous system (CNS) activity. Members of this class of compounds exhibited a high level of CNS activities. For example, 2',5-dichloro-2-[3-[(glycylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (**2c**) was as active as triazolam, with an ED_{50} of 0.58 mg/kg (mice, po), against antifighting activity in the foot shock-induced fighting test. Other triazolylbenzophenone derivatives (**2a–f**) showed similar pharmacological activities.

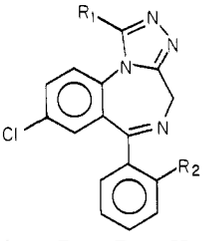
In continuation of our search for better drugs that act on the central nervous system, we reported previously the synthesis of a series of peptidoaminobenzophenones as a novel class of ring-opened analogues of the 1,4-benzodiazepines. We also showed that compounds of this type displaying favorable pharmacological characteristics could serve as interesting prodrugs which might be converted by biotransformation into 1,4-benzodiazepines with concomitant liberation of innocuous amino acids.[2-5] As an extension of this work, we became interested in the synthesis and pharmacological activities of the compounds derived from heterocyclic annelation of peptidoaminobenzophenones, which are formally regarded as ring-opened derivatives of a triazolobenzodiazepine. The fusion of a triazole ring to the amide moiety of a 1,4-benzodiazepine is known to be useful for imparting enhanced potency and novel activity to the parent benzodiazepine.[6] For example, derivatives of the 6-aryl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine, such as estazolam, alprazolam, and triazolam, have potent anxiolytic, hypnotic, and antidepressant activities and have been shown to be clinically useful.[6-10] This paper deals with the synthesis and pharmacological activities of some amino acid derivatives of 2-[3-(aminomethyl)-4*H*-1,2,4-triazol-4-yl]benzophenone (**2a–f**)[11] as a novel class of annelated peptidoaminobenzophenones.



1a, X = Cl
b, X = H



2a, $R_1 = R_2 = R_3 = H$
b, $R_1 = CH_3$; $R_2 = R_3 = H$
c, $R_1 = CH_3$; $R_2 = H$; $R_3 = Cl$
d, $R_1 = CH_3$; $R_2 = H$; $R_3 = F$
e, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$; $R_3 = Cl$
f, R_1 = c-Pr; $R_2 = H$; $R_3 = Cl$



estazolam, $R_1 = R_2 = H$
alprazolam, $R_1 = CH_3$, $R_2 = H$
triazolam, $R_1 = CH_3$, $R_2 = Cl$

Chemistry. A variety of the amino acid amide derivatives of the 3-(aminomethyl)triazolylbenzophenones (**2a-f**) were prepared via several routes (A–D) as shown in Scheme I. The main features of these routes consisted of conversion of the quinazoline **3** or **4** into 5-chloro(and/or 2',5-dihalogeno)-2-[3-(aminomethyl)-5-substituted-4*H*-1,2,4-triazol-4-yl]benzophenone dihydrobromide (**5**) and subsequent conversion of **5** with an appropriate two-carbon unit to yield 5-chloro(and/or 2,5-dihalogeno)-2-[3-[[(α-aminoacyl)amido]methyl]-5-substituted-4*H*-1,2,4-triazol-4-yl]benzophenone (**6**), which was finally transformed into

(1) This paper is part 6 of a series of "Benzophenone Related Compounds". Part 5: Hirai, K.; Ishiba, T.; Sugimoto, H.; Fujishita, T. *J. Org. Chem.* **1981**, *46*, 4489.
(2) Hirai, H.; Ishiba, T.; Sugimoto, H.; Sasakura, K.; Fujishita, T.; Toyoda, T.; Tsukinoki, Y.; Joyama, H.; Hatakeyama, H.; Hirose, K. *J. Med. Chem.* **1980**, *23*, 764.
(3) Hirai, K.; Ishiba, T.; Sugimoto, H.; Fujishita, T.; Tsukinoki, Y.; Hirose, K. *J. Med. Chem.* **1981**, *24*, 20.
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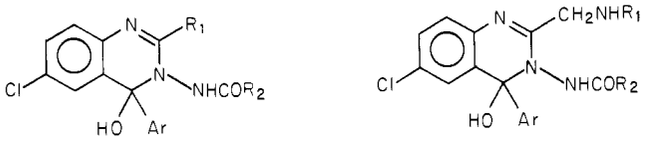
(5) Fujimoto, M.; Tsukinoki, Y.; Hirose, K.; Hirai, K.; Okabayashi, T. *Chem. Pharm. Bull.* **1980**, *28*, 1374. Fujimoto, M.; Tsukinoki, Y.; Hirose, K.; Kuruma, K.; Konaka, R.; Okabayashi, T. *Ibid.* **1980**, *28*, 1378.
(6) Hester, J. B., Jr.; Rudzik, A. D.; Kambar, B. V. *J. Med. Chem.* **1971**, *14*, 1078.
(7) Meguro, K.; Tawada, H.; Miyano, H.; Sato, Y.; Kuwada, Y. *Chem. Pharm. Bull.* **1973**, *21*, 2383.
(8) Hester, J. B., Jr.; Rudzik, A. D.; Von Voigtlander, P. F. *J. Med. Chem.* **1980**, *23*, 42. *Ibid.* **1980**, *23*, 643.
(9) Nakajima, R.; Hattori, C.; Nagawa, Y. *Jpn. J. Pharmacol.* **1971**, *21*, 489.
(10) Nakajima, R.; Take, Y.; Moriya, R.; Saji, Y.; Yui, T.; Nagawa, Y. *Jpn. J. Pharmacol.* **1971**, *21*, 497.
(11) During the course of our work, a report describing the independent synthesis of some of our target compounds (**2a,c,e**) appeared in the patent literature; Hassel et al. prepared similar 2-[3-[[(α-aminoacyl)amino]methyl]-4*H*-1,2,4-triazol-4-yl]-benzophenones by ring cleavage of the diazepine ring, followed by amino acid coupling with the *N*-hydroxysuccimide esters: Hassel, C. H.; Johnson, W. A. Ger. Offen. 2537069, 1976; *Chem. Abstr.* **1976**, *85*, 78365x.

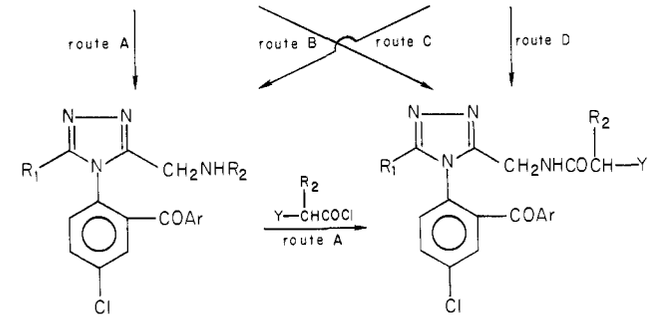
0022-2623/82/1825-1466$01.25/0

Scheme I



3a, $R_1 = CH_3$; $R_2 = CH_2NHZ$; Ar = C_6H_5
b, $R_1 = CH_3$; $R_2 = CH_2NHZ$; Ar = C_6H_4Cl-*o*
c, $R_1 = H$; $R_2 = CH_2NHCOCH_2NHZ$; Ar = C_6H_5
d, $R_1 = CH_3$; $R_2 = CH_2NHZ$; Ar = C_6H_4F-*o*[a]

4a, $R_1 = Z$, $R_2 = CH_3$, Ar = C_6H_4Cl-*o*
b, $R_1 = COCH_2NPht$; $R_2 = CH_3$; Ar = C_6H_4Cl-*o*
c, $R_1 = COCH_2NHZ$; $R_2 = CH_3$; Ar = C_6H_4Cl-*o*
d, $R_1 = COCH_2Cl$; $R_2 = CH_3$; Ar = C_6H_4Cl-*o*
e, $R_1 = Z$; R_2 = c-Pr; Ar = C_6H_4Cl-*o*



5a, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_5
b, $R_1 = CH_3$; $R_2 = Z$; Ar = C_6H_4Cl-*o*
c, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4Cl-*o*
d, $R_1 = CH_3$; $R_2 = Z$; Ar = C_6H_4F-*o*[a]
e, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4F-*o*
f, R_1 = c-Pr; $R_2 = Z$; Ar = C_6H_4Cl-*o*

6a, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_5, Y = Cl
b, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4Cl-*o*; Y = Cl
c, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4Cl-*o*; Y = N_3
d, $R_1 = R_2 = H$; Ar = C_6H_5; Y = NHZ
e, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4Cl-*o*; Y = NHZ
f, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_5; Y = NPht
g, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4Cl-*o*; Y = NPht
h, $R_1 = CH_3$; $R_2 = CH_2Ph$; Ar = C_6H_4Cl-*o*; Y = NPht
i, $R_1 = CH_3$; $R_2 = H$; Ar = C_6H_4F-*o*; Y = NPht
j, R_1 = c-Pr; $R_2 = H$; Ar = C_6H_4Cl-*o*; Y = NPht

2a–f ← omination, reduction or deprotection

[a] Reference 13.

2a–f. Compounds **6** could also be derived directly from quinazolines **3** or **4**.

Route A consisted of treating the quinazoline **3a**, **3b**, or **3d** with AcOH, followed by its deprotection, to obtain the 3-(aminomethyl)triazolylbenzophenone **5a**, **5b**, or **5e**, which was then condensed with Pht-Gly-Cl[12] in DMF–benzene. The resultant phthaloyl derivatives **6f,g,i** were finally deprotected with hydrazine hydrate to obtain the desired compounds. By this method, **2b–d** were prepared from the corresponding quinazoline **3**. Alternatively, the key intermediate (**5c**) was treated with chloroacetyl chloride to afford the 3-[(chloroacetamido)methyl]triazolylbenzophenone (**6b**), which was then converted into **2c** by treatment with NaN_3 in an inert solvent, followed by reduction of the resultant azido compound (**6c**) with $SnCl_2 \cdot 2H_2O$ in aqueous sodium hydroxide.

Route B, which was used to prepared **2a** or the ring-opened derivative of estazolam, consisted of treatment of the quinazoline **3c** with AcOH to yield 3-[[[*N*-(benzyloxycarbonyl)glycyl]amino]methyl]triazol-4-yl-benzophenone (**6d**), which was subsequently deprotected to obtain **2a**. The starting quinazolines **3a–c** were prepared from the aminobenzophenone (**7**) via Scheme II, while **3d** was prepared according to the method of Kuwada et al.[13]

The aminobenzophenone **7a** was treated with ethyl orthoacetate to obtain the imino ether **9a**,[14] which was then condensed with Z-Gly-$NHNH_2$ in EtOH in the presence of AcOH to afford the desired quinazoline **3a** in good yield. However, treatment of the imino ether **9b** with Z-Gly-$NHNH_2$ in the same manner resulted in a poor yield of **3b**. A relatively higher yield was obtained when the thio amide **11** was treated with Z-Gly-$NHNH_2$ to obtain **3b**. The intermediate thio amide **11** was prepared from **7b** via the amidine derivative **10**.[14] Condensation of the quinazoline **8**[14] with Z-Gly-Gly-OH in HMPA in $SOCl_2$ gave the peptidoaminoquinazoline **3c** easily.

Route C, which was used to prepare **2c** and **2f**, consisted of treatment of the quinazoline **4a** or **4e** with AcOH to obtain the above-mentioned intermediate **5b** or **5f** and subsequent transformation of **5b** into **2c** via **6g** and of **5f** into **2f** via **6j**, as described for route A.

Route D, which was an alternative route to **2c**, consisted of treatment of the quinazolines **4b–d** with AcOH to obtain the 3-[[(N^{α}-protected-glycyl)amino]methyl]triazol-4-yl-benzophenone **6g,e** and the 3-[(chloroacetamido)-methyl]triazol-4-ylbenzophenone (**6b**), respectively. The desired compound **2c** was obtained by deprotection of **6e** and **6g** or by treatment of **6b** with liquid NH_3. Starting quinazolines of the **4** type were prepared from 2-amino-2′,5-dichloroaminobenzophenone (**7b**) as shown in Scheme III. Treatment of **7b** with *N*-(benzyloxycarbonyl)glycine orthoester (**13a**),[15] derived from aminoacetonitrile, gave the imino ether (**14a**), which was then converted into the quinazoline (**4a**) upon treatment with $CH_3CONHNH_2$ in ethanol or stepwise treatment of **14a** with $NH_2NH_2 \cdot H_2O$ and CH_3COCl via **15**. Acylation of **15** with cyclopropanecarboxylic acid with $SOCl_2$–HMPA as a condensing agent gave **4e** in good yield. Use of *N*-chloroacetylglycine orthoester **13b** instead of **13a** gave the imino ether **14b** in the same manner, which was then converted into **4d** upon treatment with $CH_3CONHNH_2$. Deprotection of **4a** with HBr–AcOH and subsequent condensation of the resultant quinazoline dihydrobromide (**16**) with N-protected glycyl chloride gave **4b** and **4c** in good yield. Alternatively, **4c** was obtained by treatment of **14c** with $AcNHNH_2$ and **4d** by chloroacetylation of the quinazoline **16**.

Results and Discussion

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

Antianxiety activity was measured by the antagonism of foot shock induced fighting (taming), anticonvulsant activity was measured by the degree of protection against convulsions induced by pentylenetetrazole, muscle relaxation was measured with the rotatory drum (rotorod), and sedative activity was measured by potentiation of the loss

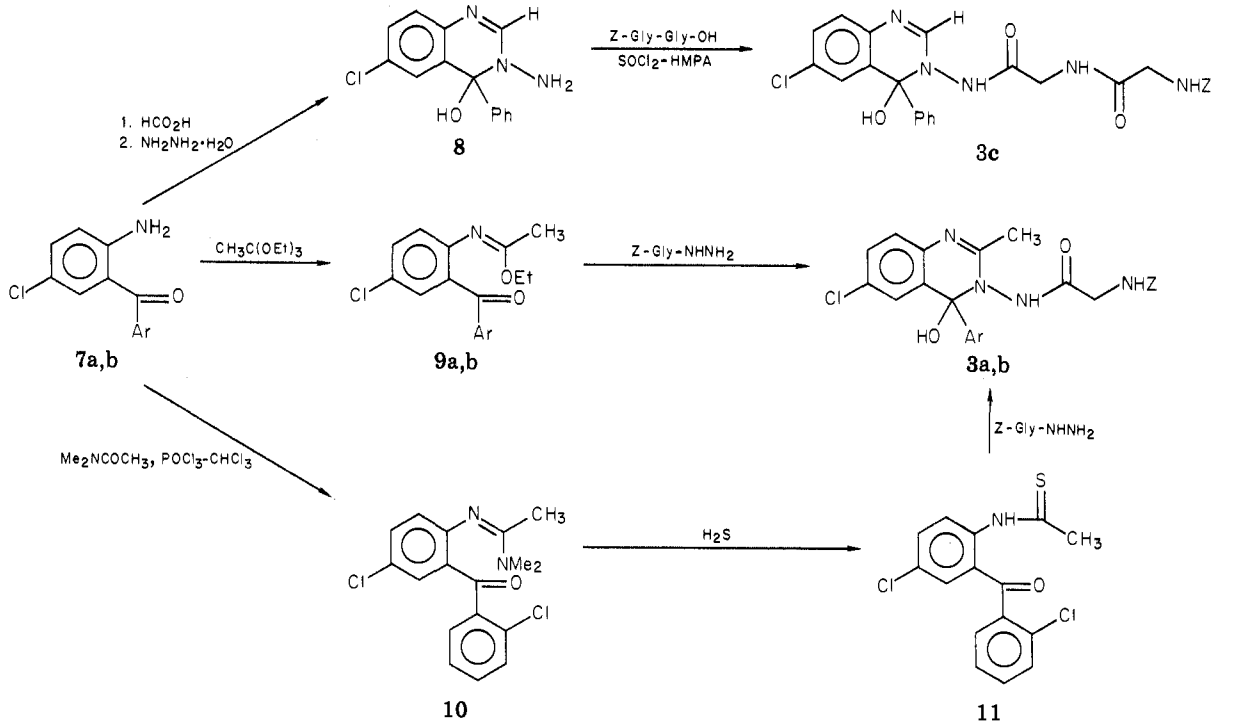
(12) Abbreviations used are those recommended by the IUPAC–IUB commission of Biochemical Nomenclature Symbols for Amino Acid Derivatives and Peptides [*J. Biol. Chem.* **1972**, *247*, 977]. Additional abbreviations used are: Z, benzyloxycarbonyl; Pht, phtaloyl.

(13) Kuwada, Y.; Meguro, K.; Tawada, H. Japan Kokai, 85095, 1974; *Chem. Abstr.* **1974**, *82*, 31364*u*.

(14) Meguro, K.; Tawada, H.; Kuwada, Y. *Chem. Pharm. Bull.* **1973**, *21*, 1619.

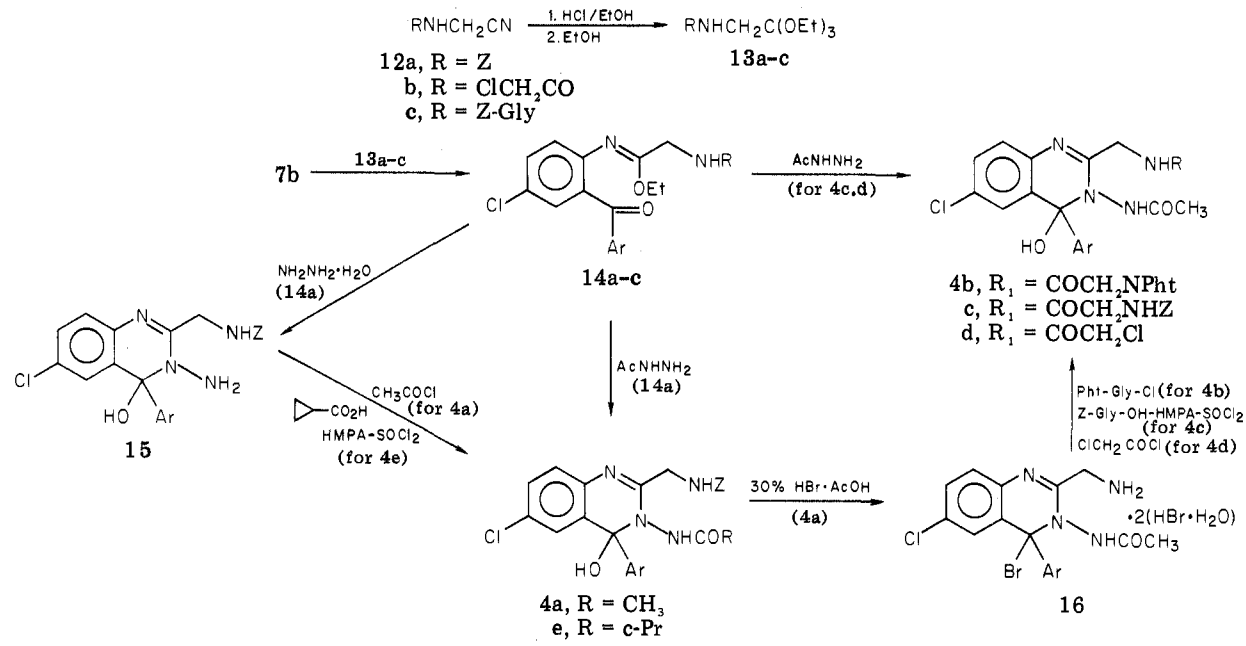
(15) Zemliyka, J.; Chlaclek, S. *Collect. Czech. Chem. Commun.* **1966**, *31*, 3775.

Scheme II[a]



[a] a, Ar = C_6H_5; b, Ar = C_6H_4Cl-*o*.

Scheme III[a]



[a] Ar = C_6H_4Cl-*o*.

of the righting reflex induced by thiophental sodium and chloroprothixene and inhibition of spontaneous motor activity.[2]

The results are shown in Table III with data for alprazolam, triazolam, estazolam, and **1a,b** included for comparison. The data showed that this class of compounds had a very high level of CNS activity.

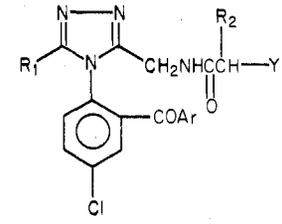
Compound **2c** was highly effective for antgonizing the effects of pentylenetetrazole and potentiation of thiopental sodium, being equipotent with alprazolam in this regard and more active in the antifighting (taming) test. Moreover, **2c** was more active than estazolam in the battery of tests. In the taming test, the potency of **2c** approached that of triazolam but did not exceed it in most tests.

Compound **2d**, which has a fluorine atom instead of a chlorine at the 2′ position of **2c**, showed greater potency than that of **2c** in most tests.

Generally speaking, introduction of a methyl substituent into the triazole ring or a chlorine or fluorine atom at the ortho position in the benzoyl benzene ring gives compounds with enhanced activities as has been seen with the triazolobenzodiazepines.[6]

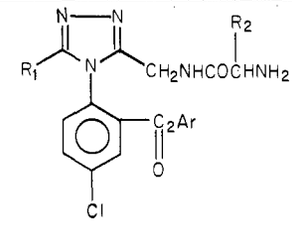
As was the case in the annelated 1,4-benzodiazepine series,[6] the fusion of a triazole ring to the anilide moiety of peptidoaminobenzophenone **1** resulted in enhancement of activities over those of the parent compounds (compare

Table I. Physical and Analytical Data for 2-[3-[(Substituted-amino)methyl]-5-substituted-4*H*-1,2,4-triazol-4-yl]benzophenone (6)



no.	R_1	R_2	Ar	Y	synth route	mp, °C	formula	anal.
6a	CH_3	H	C_6H_5	Cl	A	140–142	$C_{19}H_{16}N_4O_2Cl_2$	C, H, N, Cl
6b	CH_3	H	C_6H_4Cl-*o*	Cl	A	151–153	$C_{19}H_{15}N_4O_2Cl_3$	C, H, N, Cl
6c	CH_3	H	C_6H_4Cl-*o*	N_3	A	powder	$C_{19}N_{15}N_7O_2Cl_2$	
6d	H	H	C_6H_5	NHZ	B	oil	$C_{26}H_{22}N_5O_4Cl$	
6e	CH_3	H	C_6H_4Cl-*o*	NHZ	D	160–162	$C_{27}H_{23}N_5O_4Cl_2$	C, H, N, Cl
6f	CH_3	H	C_6H_5	NPht	A	251–253	$C_{27}H_{20}N_5O_4Cl$	C, H, N, Cl
6g	CH_3	H	C_6H_4Cl-*o*	NPht	A, C, D	223–231	$C_{27}H_{19}N_5O_4Cl_2$	C, H, N, Cl
6h	CH_3	CH_2Ph	C_6H_4Cl-*o*	NPht	A	238–240	$C_{34}H_{25}N_5O_4Cl_2$	C, H, N, Cl
6i	CH_3	H	C_6H_4F-*o*	NPht	A	229–230	$C_{27}H_{19}N_5O_4ClF$	C, H, N, Cl, F
6j	c-Pr	H	C_6H_4Cl-*o*	NPht	C	228–230	$C_{29}H_{21}N_5O_4Cl_2$	C, H, N, Cl

Table II. Physical and Analytical Data for 2-[3-[[(α-Aminoacyl)amido]methyl]-4*H*-1,2,4-triazol-4-yl]benzophenone (2)



no.	R_1	R_2	Ar	mp,[a] °C	yield, %	formula	anal.[b]
2a	H	H	C_6H_5	140 (aq CH_3CN)	13[c]	$C_{18}H_{16}N_5O_2Cl\cdot 1.5[(CO_2H)_2\cdot H_2O]$	C, H, N, Cl
2b	CH_3	H	C_6H_5	110–113 (AcOEt)	38[d]	$C_{19}H_{18}N_5O_2Cl\cdot H_2O$	C, H, N, Cl
				112–114 (aq CH_3CN)		$C_{19}H_{18}N_5O_2Cl\cdot(CO_2H)_2\cdot 2H_2O$	C, H, N, Cl
2c	CH_3	H	C_6H_4Cl-*o*	163–165 (CH_2Cl_2–AcOEt)	86.4[e]	$C_{19}H_{17}N_5O_2Cl_2$	C, H, N, Cl
				>167 (95% EtOH)	91[f]	$C_{19}H_{17}N_5O_2Cl_2\cdot HCl\cdot H_2O$	C, H, N, Cl
				178.5–181.5 (EtOH–AcOEt)	51.1[g]	$C_{19}H_{17}N_5O_2Cl_2\cdot 2HCl\cdot H_2O$	C, H, N, Cl
				97 (bubbling) (EtOH)		$C_{19}H_{17}N_5O_2Cl_2\cdot C_4H_4O_4\cdot 0.5H_2O$[h]	H, N, Cl; C[m]
				227–230 (95% EtOH)		$C_{19}H_{17}N_5O_2Cl_2\cdot H_3PO_4$	C, H, N, Cl, P
2d	CH_3	H	C_6H_4F-*o*	135–137 (AcOEt)	85.2[i]	$C_{19}H_{17}N_5O_2ClF$	C, H, N, Cl, F
2e[k]	CH_3	CH_2Ph	C_6H_4Cl-*o*	68 (aq CH_3CN)	84[j]	$C_{26}H_{23}N_5O_2Cl_2\cdot(CO_2H)_2\cdot H_2O$	C, H, N, Cl
2f	c-Pr	H	C_6H_4Cl-*o*	148–151 (AcOEt)	63[l]	$C_{21}H_{19}N_5O_2Cl_2$	C, H, N, Cl

[a] Solvents used for recrystallization are indicated in parentheses. [b] Analyses of the elements indicated were within ±0.3% of theory. [c] Treatment of 6d with 30% HBr in AcOH. [d] Hydrazinolysis of 6f. [e] Hydrazinolysis of 6g. [f] Hydrogenation of 6c with $SnCl_2\cdot 2H_2O$. [g] Amination of 6b. [h] Maleate. [i] Hydrazinolysis of 6i. [j] Hydrazinolysis of 6h. [k] $[\alpha]^{24}_D$ + 29 ± 0.7° (*c* 1.009, EtOH). [l] Hydrazinolysis of 6j. [m] C: calcd, 50.84; found, 51.31.

2c with **1a**, and **2a** with **1b**). Pharmacological profiles of ring-opened compounds were not identical with those of the corresponding cyclized 1,4-benzodiazepines, which were generally less active in this series. However, it is noteworthy that the sleep-inducing effect of the open-ring compound **2a** evaluated by chlorprothixene hypnosis[16] is better than that of the corresponding cyclized compound, estazolam. Compound **2e**, which has a terminal L-phenylalanyl group instead of a glycyl group, also showed very high activities. This series of compounds may release the terminal amino acids by enzymatic action and then cyclize chemically forming triazolobenzodiazepines in the body as has been discussed for the peptidoaminobenzophenone derivatives.[2-5] As in the the case of the peptidoaminobenzophenone series, the 4*H*-*s*-triazole-annelated peptidoaminobenzophenones synthesized here gave water-soluble salts despite the fact that the triazolobenzodiazepines are almost insoluble in water (e.g., **2c**·$HCl\cdot H_2O$; 109 mg/mL aqueous solution at 25 °C; triazolam: 0.015 mg/mL aqueous solution at 25 °C).

(16) According to Zbinden, chloroprothixene hypnosis in mice correlates considerably with the hypnotic properties in humans: Zbinden, G.; Randall, L. O. *Adv. Pharmacol.* **1967**, *5*.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were determined with a JASCO DS-403G spectrometer, UV spectra with a Hitachi RMU6E spectrophotometer, and NMR spectra with Varian A-60 and T-60 instruments with tetramethylsilane as an internal standard. When a compound was prepared by separate routes, its identity was established by comparison of TLC, IR, and NMR spectra of the different samples. All experiments requiring anhydrous conditions were carried out under a stream of N_2 with dried solvents; hexamethylphosphoric triamide (HMPA), dimethylformamide (DMF), acetonitrile (CH_3CN), and ether were dried over preconditioned 4A molecular sieves. All the extracts were dried over anhydrous Na_2SO_4.

3-[[(Benzyloxycarbonyl)glycyl]amino]-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxy-2-methylquinazoline (3b). A suspension of 0.18 g (2.5 mmol) of 2-thioacetamido-

Table III. Pharmacoligical Activity in Mice[a]

compd	ED_{50},[b] mg/kg, po					
	anti-pentylene-tetrazole	rotorod performance	spont mot act.[c]	taming	thiopental sodium narcosis	chlorprothixene hypnosis
2a	1.37 (1.02-1.85)[d]	11.76 (9.55-14.49)	31.7 (20.4-79.6)	5.71 (4.10-8.97)	1.97 (1.70-2.34)	1.66 (1.16-2.40)
2b	0.38 (0.31-0.46)	3.94 (3.06-5.07)	4.25 (3.21-5.32)	3.02 (2.17-4.09)	0.72 (0.66-0.80)	0.94 (0.62-1.62)
2c	0.26 (0.22-0.31)	2.09 (1.66-2.63)	0.31 (0.24-0.36)	0.58 (0.43-0.75)	0.27 (0.18-0.52)	0.62 (0.42-0.89)
2d	0.09 (0.03-0.15)	1.84 (1.52-2.24)	1.52 (1.24-1.89)	0.28 (0.20-0.48)	0.25 (0.19-0.40)	0.16 (0.09-0.24)
2f	0.88 (0.55-1.39)	18.74 (11.35-31.09)	1.50 (0.69-2.32)	2.34 (2.05-2.72)	4.94 (3.81-7.28)	0.49 (0.32-0.78)
2e	0.31 (0.20-0.42)	1.83 (1.31-2.55)	0.38 (0.15-0.57)	0.55 (0.40-0.78)	1.52 (1.21-2.12)	0.23 (0.16-0.32)
alprazolam	0.22 (0.16-0.27)	2.22 (1.64-3.00)	0.94 (0.71-1.21)	1.09 (0.68-2.45)	0.36 (0.32-0.42)	0.25 (0.17-0.38)
triazolam	0.039 (0.02-0.06)	0.83 (0.68-1.01)	0.054 (0.047-0.064)	0.4 (0.3-0.6)	0.18 (0.09-0.96)	0.27 (0.17-0.44)
estazolam	0.52 (0.34-0.74)	5.44 (3.97-7.46)	3.09 (2.25-5.03)	2.62 (2.31-2.99)	2.32 (1.91-2.98)	6.22 (4.22-8.93)
1a[e]	0.56 (0.37-0.68)	35.4 (23.3-53.7)	1.4 (1.17-1.76)	3.2 (1.8-5.4)	0.80 (0.58-1.17)	2.59 (1.73-4.72)
1b[e]	2.16 (1.50-2.91)	29.3 (19.1-42.0)	15.2 (11.7-22.0)	10.86 (7.61-15.57)	5.2 (3.7-11.4)	

[a] All samples were administered orally and estimated at 60 min after dosing. [b] ED_{50} values were determined on the free base. [c] ED_{30} values. [d] 95% confidence limits are given in parentheses. [e] Reference 2.

2',5-dichlorobenzophenone (11), prepared by the method described below, 0.64 g (2.9 mmol) of Z-Gly-$NHNH_2$, and 0.15 g of AcOH in 20 mL of EtOH was stirred at room temperature for 14 h. The resultant suspension was evaporated in vacuo, and the residue was chromatographed on a column of silica gel with AcOEt as an eluent, giving 0.27 g (33%) of **3b**, mp 142–147 °C (acetone). Anal. ($C_{25}H_{22}N_4O_4Cl_2$) C, H, N, Cl.

2-Thioacetamido-2',5-dichlorobenzophenone (11). H_2S gas was passed through a suspension of 0.91 g (2.7 mmol) of 2-(*N*,*N*-dimethylacetamidino)-2',5-dichlorobenzophenone (10)[14] in 20 mL of EtOH for 10 min. The resultant solution was stirred for 3 h at room temperature and evaporated, leaving an oily residue, which was partitioned between $CHCl_3$ and water. The organic layer was dried and evaporated in vacuo. Chromatography of the residue on a silica gel column with $CHCl_3$ as eluent gave 0.57 g (64.8%) of 11, mp 98–100 °C (*n*-hexane). Anal. ($C_{15}H_{11}NOSCl_2$) C, H, N, Cl.

Alternate Route to 3b from 9b. A mixture of 0.84 g (2.5 mmol) of **9b**,[14] 0.67 g (3 mmol) of Z-Gly-$NHNH_2$, and 1.5 g of AcOH in 20 mL of EtOH was stirred at room temperature for 6 h. The resultant solution was concentrated in vacuo, and the residue was partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was dried, concentrated, and recrystallized from AcOEt–ether, giving 0.23 g (17%) of **3b**.

By the same procedure, **3-[[(benzyloxycarbonyl)glycyl]amino]-6-chloro-3,4-dihydro-4-hydroxy-2-methyl-4-phenylquinazoline** (**3a**) was obtained in 60% yield from **9a**,[14] mp 125–128 °C (lit.[13] mp 125–127 °C).

3-[[[(Benzyloxycarbonyl)glycyl]glycyl]amino]-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline (3c). To a solution of 13.6 g (51 mmol) of Z-Gly-Gly-OH in 68 mL of HMPA and 34 mL of CH_3CN was added dropwise 4.9 g (41.7 mmol) of $SOCl_2$ at −18 °C, after which the reaction mixture was cooled to −25 °C. To this solution was added 8.8 g (32 mmol) of the quinazoline **8**[14] and the resultant mixture was stirred for 2 h at −20 °C. The reaction mixture was neutralized with aqueous $NaHCO_3$. The pale-yellow precipitate was collected by filtration, washed with water and ether three times, dried, and recrystallized from acetone, yielding 6.5 g of **3c**: mp 162–164 °C; IR (Nujol) 3320, 3240, 1730, 1685, 1660, 1615 cm^{-1}. Anal. ($C_{26}H_{24}N_5O_5Cl$) H, N, Cl; C: calcd, 59.82; found, 59.35.

3-[[(Benzyloxycarbonyl)glycyl]amino]-6-chloro-3,4-dihydro-4-(2-fluorophenyl)-4-hydroxy-2-methylquinazoline (**3d**). This compound was prepared according to patent literature.[13]

3-(Acetylamino)-2-[[(benzyloxycarbonyl)amino]methyl]-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxyquinazoline (**4a**). A solution of 33.5 g (0.123 mol) of *N*-(benzyloxycarbonyl) glycine iminoethyl ester hydrochloride[17] in 84.7 g of EtOH was stirred at room temperature for 14 h. The precipitated NH_4Cl was removed by filtration, and the filtrate was evaporated in vacuo. The oily residue thus obtained was dissolved in 200 mL of benzene and treated with 16.3 g (61 mmol) of the aminobenzophenone **7b** and 2 mL of AcOH, followed by heating at reflux temperature for 4 h. The reaction mixture was evaporated, and the residue was treated with 13.6 g (0.18 mmol) of $CH_3CONHNH_2$ and 2 mL of AcOH under stirring at room temperature. The precipitated solid, collected by filtration and washed with ether, gave 17.2 g (54.7%) of **4a**, mp 132–134 °C dec (AcOEt). Anal. ($C_{25}H_{22}N_4O_4Cl_2$) C, H, Cl.

Alternate Route to 4a via 15. To a solution of 2.36 g (5 mmol) of **15** in 15 mL of DMF was added 0.79 g (10 mmol) of CH_3COCl, and the resultant mixture was stirred at room temperature for 5 h and allowed to stand overnight. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated, yielding 2.1 g (81.7%) of **4a**, mp 132–134 °C dec (AcOEt).

3-Amino-2-[[(benzyloxycarbonyl)amino]methyl]-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxyquinazoline (**15**). A suspension of 55.5 g (0.2 mol) of *N*-(benzyloxycarbonyl)glycine iminoethyl ester hydrochloride[17] in 138.2 g of dry EtOH was stirred at room temperature for 22 h. The precipitated NH_4Cl was removed with suction, and the filtrate was concentrated in vacuo. The residue was dissolved in 400 mL of dry benzene and treated with 26.6 g (0.1 mol) of **7b** and 4 mL of AcOH, followed by heating at reflux temperature for 3 h. The resultant solution was evaporated in vacuo to give the crude imino ether (**14a**) as an oil, which was then dissolved in 200 mL of EtOH and treated with 20 mL of $NH_2NH_2 \cdot H_2O$ and 4 mL of AcOH. This mixture was heated at reflux for 2 h and set aside overnight; then the precipitated crystals were collected by filtration and washed with EtOH and ether to give 36.5 g (77%) of **15**: mp 155–173 °C dec; UV (EtOH) λ_{max} 215 nm (log ϵ 4.51 sh), 200 (4.17 sh), 290 (4.09), 320 (3.52 sh). Anal. ($C_{23}H_{20}H_4Cl_2O_3$) C, H, N, Cl.

3-(Acetylamino)-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxy-2-[[(phthaloylglycyl)amino]methyl]-qulnazoline (**4b**). To a solution of 1.65 g (7.4 mmol) of Pht-

(17) Mengelberg, M. *Chem. Ber.* **1956**, *89*, 1185.

Gly-Cl in 20 mL of HMPA was added 2.3 g (4.46 mmol) of **16**, which was prepared from **4a** as described below, and the resultant mixture was stirred at room temperature for 3 h. The reaction mixture was partitioned between ether and aqueous $NaHCO_3$. The resulting precipitate was collected by filtration, dissolved in $CHCl_3$, dried, and evaporated to give 1.15 g (50%) of **4b**: mp 165–168 °C (AcOEt); UV (EtOH) λ_{max} 219 nm (log ϵ 4.85), 286 (4.14). Anal. ($C_{27}H_{21}N_5O_5Cl_2$) C, H, N, Cl.

Preparation of 16 from 4a. A mixture of 2.7 g (5.2 mmol) of **4a** and 6 mL of 30% HBr–AcOH was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ether, and the precipitated solid was collected by filtration: yield 2.85 (89.6%) of **16**; mp 169–175 °C dec. Anal. ($C_{17}H_{15}N_4OCl_2Br\cdot 2(HBr\cdot H_2O)$ C, H, N, Cl, Br.

3-(Acetylamino)-2-[[[(benzyloxycarbonyl)glycyl]amino]methyl]-4-(2-chlorophenyl)-6-chloro-3,4-dihydro-4-hydroxyquinazoline (4c). A solution of 0.94 g (4.5 mmol) of Z-Gly-OH in 15 mL of HMPA and 1 mL of CH_3CH was treated with 0.26 g (3.6 mmol) of $SOCl_2$ at −5 to −3 °C. To the resultant solution was added 1.38 g (2.2 mmol) of **16**, and the reaction mixture was brought to room temperature overnight with stirring. The resulting mixture was partitioned between ether and aqueous $NaHCO_3$. Collection of the precipitated solid by filtration gave 1.2 g (97.3%) of **4c**, mp 161–166 °C dec (AcOEt). Anal. ($C_{27}H_{25}N_5O_5Cl_2$) C, H, N, Cl.

Alternate Route to 4c from 13c via 14c. A suspension of 3.3 g (10 mmol) of *N*-(benzyloxycarbonyl)glycylglycine iminoethyl ester hydrochloride (**13c**) in 14 g of dry EtOH was stirred at room temperature for 8 days. The precipitated NH_4Cl was removed with suction, and the filtrate was concentrated in vacuo. The residue was dissolved in 20 mL of dry benzene and treated with 1.33 g (5 mmol) of the aminobenzophenone **7b** and 0.2 mL of AcOH, followed by heating at reflux temperature for 1.5 h. The resultant solution, when evaporated in vacuo, gave the crude imino ether **14c** as a viscous oil, which was then dissolved in 20 mL of EtOH and treated with 1.5 g (20 mmol) of $CH_3CONHNH_2$ and 0.2 mL of AcOH. After being stirred at room temperature overnight, the reaction mixture was partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was dried and evaporated. Trituration of the residue with a small amount of AcOEt gave 0.16 g (28%) of **4c**, mp 161–166 °C dec.

[[(Benzyloxycarbonyl)glycyl]amino]acetonitrile (12c). To a stirred solution of 6.3 g (30 mmol) of Z-Gly-OH in 40 mL of HMPA was added 2.88 g (36 mmol) of $SOCl_2$ at −5 to −2 °C. To the resulting solution was added a suspension of 3.08 g (20 mmol) of $NH_2CH_2CN\cdot H_2SO_4$ in 20 mL of HMPA at −10 to 0 °C with stirring. The resulting mixture was stirred at 0 °C for 1 h and then allowed to come to room temperature overnight. The resultant solution was partitioned between AcOEt and aqueous $NaHCO_3$, and the organic layer was dried and evaporated to give an oily residue, which was crystallized upon trituration with ether to give 4.0 g (81%) of **12c**, mp 144–146 °C (AcOEt). Anal. ($C_{12}H_{13}N_3O_3$) C, H.

***N*-[(Benzyloxycarbonyl)glycyl]glycine Iminoethyl Ester Hydrochloride (13c).** HCl gas was passed through a suspension of 3.46 g of Z-Gly-NHCH$_2$CN (**12c**) in 12 mL of dry EtOH and 8.7 mL of dry ether for 15 min at 0 °C. After being stirred at 0 °C overnight, the resultant suspension was diluted with a large amount of dry ether, and the precipitate was collected by filtration, yielding 3.75 g of **13c**, which was used without further purification for the preparation of **4c** via **14c**.

3-(Acetylamino)-2-[(α-chloroacetamido)methyl]-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxyquinazoline (4d). A mixture of 1.4 g (5.5 mmol) of *N*-(chloroacetyl)glycine ethyl orthoester (**13b**), which was prepared from [(chloroacetyl)amino]acetonitrile as described below, 1.0 g (3.8 mmol) of **7b**, and 15 g of 4A molecular sieves in 10 mL of dry benzene was left standing for 4 days with occasional swirling. The molecular sieves were removed by filtration and washed with dry benzene, and the filtrate was evaporated in vacuo. The residue was dissolved in 3 mL of dry EtOH and treated with 0.42 g (5.7 mmol) of $CH_3CONHNH_2$ at room temperature for 14 h with stirring. The precipitated solid, collected by filtration and washed thoroughly with ether, gave 1.2 g (68.5%) of **4d**, mp 160 °C dec.

Alternate Route to 4d from 16. To a mixture of 0.45 g (4 mmol) of $ClCH_2COCl$ and 12 mL of HMPA was added 1.27 g (2.2 mmol) of **16**, and the resultant mixture was stirred at room temperature for 5 h. The reaction mixture was mixed with ether and washed with aqueous $NaHCO_3$ and brine. The precipitate, collected by filtration and dried, gave 0.63 g (61.5%) of **4d**.

***N*-(Chloroacetyl)glycine Ethyl Ortho Ester (13b).** HCl gas was passed through a solution of 13.4 g (0.1 mol) of [(chloroacetyl)amino]acetonitrile (**12b**)[18] in 100 mL of dry EtOH at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was diluted with 200 mL of dry ether. Collection of the resultant precipitate by filtration gave 17.9 (78%) of the iminoethyl ester hydrochloride: mp 125 °C dec; IR (Nujol) 3300, 3200, 1700, 1670, 1640, 1525 cm^{-1}. A suspension of 17.5 g (87.9 mmol) of this hydrochloride in 300 mL of dry EtOH and ether (1:1 v/v) was stirred at room temperature for 2 days. The precipitate was filtered off with suction, and the filtrate was concentrated in vacuo to leave an oil, which upon recrystallization from dry ether gave 15.9 g (77%) of **13b**, mp 98–99 °C. Anal. ($C_{10}H_{20}NO_4Cl$) C, H, N.

2-[[(Benzyloxycarbonyl)amino]methyl]-3-[(cyclopropylcarbonyl)amido]-6-chloro-4-(2-chlorophenyl)-3,4-dihydro-4-hydroxyquinazoline (4e). To a stirred solution of 2.0 g (23 mmol) of cyclopropanecarboxylic acid in 28 mL of HMPA and 2 mL of CH_3CN was added dropwise 1.56 g (13 mmol) of $SOCl_2$ at −10 to −5 °C. After 15 min, 5.6 g (12 mmol) of quinazoline **15** was added, and the mixture was stirred at 0 °C for 4 h, diluted with a large amount of ether, and neutralized with aqueous $NaHCO_3$. The resulting precipitate was collected by filtration, washed with H_2O and ether, and dried over P_2O_5 to give 4.7 g (73%) of **4e**: IR (Nujol) 3320, 3240, 1705, 1680, 1620, 1595 cm^{-1}.

2′,5-Dichloro-2-[3-[[(benzyloxycarbonyl)amino]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (5b) (Route C). A mixture of 0.411 g of **4a** and 4 mL of AcOH was heated at reflux temperature for 2.5 h. The reaction mixture was evaporated in vacuo, and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated to give 0.31 g (78%) of **5b**, mp 139–140 °C. Anal. ($C_{25}H_{20}N_4O_3Cl_2$) C, H, N, Cl.

Alternate Route to 5b from 3b (Route A). Compound **5b** was also prepared from **3b** according to the procedure of Kuwada et al.[13]

2′,5-Dichloro-2-[3-(aminomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (5c). A suspension of 150 g (0.3 mol) of **5b** in 320 mL of 30% HBr–AcOH was stirred at room temperature for 1.5 h. The resultant clear solution was diluted with 2 L of dry ether, and the supernatant ether was removed by decantation. The crude product was dissolved in 2 L of dry CH_3CN, heated at reflux for 1 h, and chilled. The crystalline precipitate was collected by filtration and washed with 1 L of CH_3CN–Et_2O (1:1 v/v) to give 157.4 g (99%) of **5c**, mp 211–213 °C (CH_3CN). Anal. ($C_{17}H_{14}N_4OCl_2\cdot 2HBr$) C, H, N, Cl, Br.

By the same procedure, **5a** was prepared from the corresponding *N*-carbobenzyloxy derivative,[13] mp 241–245 °C (CH_3CN) (hygroscopic). Anal. ($C_{17}H_{15}N_4OCl\cdot 2HBr$) H, N, Cl, Br; C: calcd, 41.79; found, 41.35.

2′,5-Dichloro-2-[3-[[(benzyloxycarbonyl)amino]methyl]-5-cyclopropyl-4*H*-1,2,4-triazol-4-yl]benzophenone (5f) (Route C). A mixture of 4.5 g of **4e** in 50 mL of AcOH was heated at reflux for 5 h and concentrated in vacuo. The residue was partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was separated, dried, and concentrated in vacuo to give a viscous oil, which was purified by silica gel chromatography with AcOEt–MeOH (10:1, v/v) as an eluent and afforded 1.0 g (25%) of **5f**: mp 115–116 °C (AcOEt–*n*-hexane); IR ($CHCl_3$) 3420, 1720, 1680, 1590 cm^{-1}; NMR ($CDCl_3$) δ 0.7–0.6 (m, 5 H), 4.13–4.43 (m, 2 H), 4.97 (s, 2 H), 6.17 (br m, 1 H). Anal. ($C_{27}H_{22}N_4O_3Cl_2$) C, H, N, Cl.

5-Chloro-2-[3-[(α-chloroacetamido)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6a) (Route A). To a stirred solution of 0.5 g (1 mmol) of **5a** in 3 mL of DMF was added dropwise 0.2 g (1.7 mmol) of $ClCH_2COCl$ under ice-bath cooling. The reaction mixture was allowed to come to room temperature overnight, diluted with 3 mL of water, neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was

(18) Suzue, S.; Irikura, T. *Chem. Pharm. Bull.* 1968, *16*, 1417.

washed with brine, dried, and evaporated in vacuo. Crystallization of the residue from AcOEt–*n*-hexane gave 0.35 g (84.8%) of **6a**, mp 140–142 °C. Anal. ($C_{19}H_{16}N_4O_2Cl_2$) C, H, N, Cl.

2′,5-Dichloro-2-[3-[(α-chloroacetamido)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6b) (Route A). With **5c** as a starting material, the reaction was carried out as described for the preparation of **6a** and gave **6b** as crystals, which melted at 151–153 °C (AcOEt–*n*-hexane), in 82% yield. Anal. ($C_{19}H_{15}N_4O_2Cl_3$) C, H, N, Cl.

Alternate Route to 6b from 4d (Route D). A solution of 0.5 g (1 mmol) of **4d** and 0.1 g of AcONa in 80% aqueous AcOH was heated at reflux for 1.5 h. The reaction mixture was evaporated in vacuo, and the residue was partitioned between 1 N NaOH and AcOEt. The organic layer was washed with brine, dried, and evaporated to give 0.65 g of crude product, which when purified by silica gel chromatography with AcOEt/MeOH (4:1, v/v) as eluent gave 0.22 g (48.5%) of **6b**, mp 152–153 °C.

2′,5-Dichloro-2-[3-[(α-azidoacetamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6c). To a solution of 1.5 g (3.5 mmol) of **6b** in 15 mL of DMF was added dropwise 0.23 g (3.5 mmol) of NaN_3, and the resultant mixture was stirred at room temperature for 2.3 h and left standing overnight. The whole mixture was evaporated in vacuo, and the residue was partitioned between $CHCl_3$ and water. The organic layer was dried and evaporated to give 1.45 g (93.2%) of **6c**: IR (Nujol) 2100 cm^{-1} (N_3); NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.9 (s, 2 H), 4.20 (d like, 2 H), 8.37 (m, 1 H).

5-Chloro-2-[3-[[[(benzyloxycarbonyl)glycyl]amino]-methyl]-4*H*-1,2,4-triazol-4-yl]benzophenone (6d) (Route B). A solution of 1.5 g (3.1 mmol) of **3c** in 20 mL of AcOH was heated at reflux for 2 h. The reaction mixture was evaporated in vacuo, and the residue was partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated to afford an oil, which was chromatographed on a silica gel column with AcOEt–MeOH (4:1, v/v) as eluent to give 0.52 g of **6d** as an oil: IR ($CHCl_3$) 3400, 3280, 1720, 1680 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (br d, 2 H), 5.1 (s, 2 H).

2′,5-Dichloro-2-[3-[[α-[(benzyloxycarbonyl)amino]acetamido]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6e) (Route D). A solution of 1.71 g (3 mmol) of **4c** in 17 mL of AcOH was heated at reflux for 3 h. The reaction mixture was evaporated in vacuo, and the residue was partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was washed, dried, and evaporated. The residue was chromatographed on a column of silica gel with MeOH as eluent to give 0.93 g (56.2%) of **6e**, mp 160–162 °C (AcOEt). Anal. ($C_{27}H_{23}N_5O_4Cl_2$) C, H, N, Cl.

5-Chloro-2-[3-[[(phthaloylglycyl)amino]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6f) (Route A). To a stirred solution of 1.5 g (8.5 mmol) of Pht-Gly-Cl in 20 mL of benzene and 10 mL of DMF was added 2.3 g (7 mmol) of **5a** under ice cooling. The resultant solution was allowed to gradually come to room temperature overnight. After neutralization with aqueous $NaHCO_3$, the reaction mixture was shaken with AcOEt. The precipitated crystals, collected by filtration and washed with MeOH, gave 1.68 g of **6f**: mp 251–253 °C; IR ($CHCl_3$) 1780, 1720, 1690 cm^{-1}. Anal. ($C_{27}H_{20}N_5O_4Cl$) C, H, N, Cl.

Alternate Route to 6f from 6a. A stirred suspension of 1.35 g (3.3 mmol) of **6a** and 0.7 g (3.8 mmol) of potassium phthalimide in 10 mL of DMF was warmed at 50–60 °C for 3 h. The resultant mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to leave a colorless solid, which when recrystallized from AcOEt–ether gave **6f**, mp 251–253 °C.

2′,5-Dichloro-2-[3-[[(phthaloylglycyl)amino]methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6g) (Route D). A solution of 1.15 g (2 mmol) of **4b** in 11 mL of AcOH was heated at reflux for 2.5 h. The reaction mixture was evaporated in vacuo, and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated to leave an oily residue, which upon trituration with AcOEt gave 0.4 g (36%) of **6g**, mp 223-231 °C. Anal. ($C_{27}H_{19}N_5O_4Cl_2$) C, H, N, Cl.

Alternate Route to 6g from 5c (Route A). With **5c** as a starting material, the reaction was done as described for the preparation of **6f** and gave **6g** in 69% yield.

Alternate Route to 6g from 6b. Compound **6b** was treated with potassium phthalimide as described for the preparation of **6f** and gave **6g** as crystals, which melted at 223–231 °C in almost quantitative yield.

2′,5-Dichloro-2-[3-[[(phthaloyl-L-phenylalanyl)amino]-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6h) (Route A). To a solution of 2.7 g (8.6 mmol) of L-Pht-Phe-Cl in 26 mL of benzene and 13 mL of DMF was added 3.0 g (5.7 mmol) of **5c** with stirring at 0 °C. The stirred mixture was allowed to come to room temperature overnight. The resultant mixture was diluted with aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried, and evaporated in vacuo to give 2.5 g (68.3%) of **6h**: mp 238–240 °C (EtOH); IR (Nujol) 3190, 1780, 1715, 1680, 1590 cm^{-1}. Anal. ($C_{34}H_{25}N_5O_4Cl_2$) C, H, N, Cl.

5-Chloro-2′-fluoro-2-[3-[[(phthaloylglycyl)amino]-methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6i) (Route A). A mixture of 2.4 g (5 mmol) of **5d**[13] and 7 mL of 25% HBr–AcOH was stirred at room temperature for 1.5 h. The resultant solution was diluted with 50 mL of ether, and the precipitate was collected by filtration, washed with ether (2 × 50 mL), and suspended in 30 mL of benzene. The resulting suspension was treated with a solution of 2.2 g (10 mmol) of Pht-Gly-Cl in 15 mL of DMF at room temperature overnight under stirring. The reaction mixture was basified by addition of aqueous $NaHCO_3$, and the precipitate was collected by filtration to give 2.3 g (86.5%) of **6i**, mp 229–230 °C (EtOH). Anal. ($C_{27}H_{19}N_5O_4ClF$) C, H, N, Cl, F.

2′,5-Dichloro-2-[3-[[(phthaloylglycyl)amino]methyl]-5-cyclopropyl-4*H*-1,2,4-triazol-4-yl]benzophenone (6j) (Route A). A mixture of 1.1 g (2.1 mmol) of **5f** in 30% HBr–AcOH was stirred at room temperature for 1 h and diluted with a large amount of dry ether. The precipitate was collected by decantation and dissolved in 20 mL of benzene and 10 mL of DMF. To the resultant solution was added 3.0 g (13.4 mmol) of Pht-Gly-Cl, and the reaction mixture was stirred at room temperature for 3 h. The resulting solution was poured into water, and the organic layer was separated, dried, and evaporated to give a viscous oil, which upon trituration with AcOEt–Et_2O afforded 0.9 g (74%) of **6j**: mp 228–230 °C (EtOH); IR (Nujol) 3220, 1770, 1710 (br) cm^{-1}. Anal. ($C_{29}H_{21}N_5O_4Cl_2$) C, H, N, Cl.

5-Chloro-2-[3-[(glycylamino)methyl]-4*H*-1,2,4-triazol-4-yl]benzophenone (2a). To a solution of 2.1 g (4.36 mmol) of **6d** in 4 mL of anisole was added 3 mL of 30% HBr–AcOH. The resultant mixture was stirred for 1 h and diluted with dry ether to obtain a hygroscopic precipitate, which was washed several times with dry ether and dissolved in 20 mL of CH_2Cl_2. The methylene chloride solution was washed with aqueous $NaHCO_3$ and brine, dried, and evaporated to leave an oily residue, which was purified by silica gel chromatography with MeOH as eluent to give 0.39 g (13%) of **2a** as colorless oil: IR ($CHCl_3$) 3300, 1670, 1595 cm^{-1}; NMR ($CDCl_3$) δ 1.70 (br m, 2 H), 3.27 (br m, 2 H), 4.47 (AB q, 2 H), 8.07 (s, 1 H); **2a sesquioxalate sesquihydrate**, mp 140 °C (bubbling) (aq CH_3CN). Anal. ($C_{18}H_{16}N_5O_2Cl·1.5[(C-O_2H)_2·H_2O]$) C, H, N, Cl.

5-Chloro-2-[3-[(glycylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2b). To a solution of 2.3 g (4.5 mmol) of **6f** in 20 mL of EtOH was added 0.92 g (18 mmol) of $NH_2NH_2·H_2O$, and the resultant solution was heated at reflux for 1 h. The precipitated phthalhydrazide was removed with suction, and the filtrate was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated to give **2b** in 38% yield, mp 110–113 °C (AcOEt). Anal. ($C_{19}H_{18}N_5O_2Cl·H_2O$) C, H, N, Cl. **2b oxalate dihydrate**: mp 112-114 °C (aq CH_3CN). Anal. ($C_{19}H_{18}N_5O_2Cl·(CO_2H)_2·2H_2O$) C, H, N, Cl.

2′,5-Dichloro-2-[3-[(glycylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2c). To a stirred suspension of 0.38 g (0.9 mmol) of **6c** in 10 mL of 95% EtOH was added dropwise a solution of 0.29 g (1.4 mmol) of $SnCl_2·2H_2O$ in 4.1 mL of 2 N NaOH at 0 to 4 °C. The reaction mixture was shaken with $CHCl_3$, and the organic layer was evaporated in vacuo to give 0.33 g (91%) of **2c**, mp 163-165 °C. Anal. ($C_{19}H_{17}N_5O_2Cl_2$) C, H, N, Cl.

2c dihydrochloride hydrate: mp 178.5–181.5 °C (EtOH–AcOEt). Anal. ($C_{19}H_{17}N_5O_2Cl_2·2HCl·H_2O$) C, H, N, Cl.

2c hydrochloride hydrate: mp > 167 °C (95% EtOH). Anal. ($C_{19}H_{17}N_5O_2Cl_2 \cdot HCl \cdot H_2O$) C, H, N, Cl.

2c maleate hemihydrate: mp 97 °C (bubbling) (EtOH). Anal. ($C_{19}H_{17}N_5O_2Cl_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N, C.

2c phosphate: mp 227–230 °C (95% EtOH). Anal. ($C_{19}H_{17}N_5O_2Cl_2 \cdot H_3PO_4$) C, H, N, Cl, P.

Alternate Route to 2c from 6b. A mixture of (2 mmol) of **6b** and 15 mL of 15% NH_3–MeOH was left standing at room temperature for 3 days. The reaction mixture was evaporated in vacuo. The residue was chromatographed on a column of silica gel with MeOH as eluent, affording 0.42 g (51%) of **2c**.

Alternate Route to 2c from 6e. With **6e** as starting material, the reaction was carried out as described for the preparation of **2a** and gave **2c** in 60% yield.

Alternate Route to 2c from 6g. With **6g** as starting material, the reaction was carried out as described for the preparation of **2b** and gave **2c** in 86.4% yield.

5-Chloro-2′-fluoro-2-[3-[(glycylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2d). A mixture of 2.0 g (3.8 mmol) of **6i** and 0.49 g (9.9 mmol) of $NH_2NH_2 \cdot H_2O$ in 15 mL of EtOH was heated at reflux for 30 min. The precipitated phthalhydrazide was removed with suction, and the filtrate was evaporated in vacuo. The residue was then partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was washed with brine, dried, and evaporated to give 1.3 g (85.2%) of **2d**, mp 135-137 °C (AcOEt). Anal. ($C_{19}H_{17}N_5O_2ClF$) C, H, N, F, Cl.

2′,5-Dichloro-2-[3-[(L-phenylalanylamino)methyl]-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2e). A suspension of 2.4 g (3.8 mmol) of **6h** and 0.2 g of $NH_2NH_2 \cdot H_2O$ in 20 mL of EtOH was refluxed for 1 h. The precipitate was removed with suction and the filtrate was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried and evaporated to give a viscous oil, which upon treatment with 0.4 g (4.4 mmol) of $(CO_2H)_2$ in AcOEt yielded 1.9 g of the oxalate of **2e**: mp > 68 °C (aq CH_3CN). $[\alpha]^{24}_D$ +29.0 ± 0.7° (*c* 1.099, EtOH). Anal. ($C_{26}H_{23}N_5O_2Cl_2 \cdot (CO_2H)_2 \cdot H_2O$) C, H, N, Cl.

2′,5-Dichloro-2-[3-[(glycylamino)methyl]-5-cyclopropyl-4*H*-1,2,4-triazol-4-yl]benzophenone (2f). To a suspension of 0.8 g (1.4 mmol) of **6j** in 30 mL of EtOH was added 0.2 g (3.4 mmol) of $NH_2NH_2 \cdot H_2O$, and the mixture was heated at reflux for 2 h. The precipitated phthalhydrazide was removed with suction, and the filtrate was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The organic layer was dried and evaporated to give an oily residue, which was chromatographed on a SiO_2 column with MeOH as an eluent, affording 0.4 g (63%) of **2f**: mp 148–151 °C (AcOEt); IR (Nujol) 3300, 1660 (br), 1590 cm^{-1}; NMR ($CDCl_3$) δ 0.67–1.73 (m, 5 H), 1.80 (br m, 2 H), 3.30 (br m, 2 H), 4.0–4.67 (m, 2 H), 8.43 (br m, 1 H), 7.23–7.97 (m, 7 H). Anal. ($C_{21}H_{19}N_5O_2Cl_2$) C, H, N, Cl.

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.

Rotorod Performance Test.[19] Groups of five mice were used. Sixty minutes after a mouse had received a dose of a drug, it was put on a wood rod, 3 cm in diameter, turning at 5 rpm, and the number of animals falling off with 2 min was counted. ED_{50} values were estimated by the up and down method.[20]

Antipentylenetetrazole Activity.[21] The test was performed with a group of ten mice. The animals were challenged with a subcutaneous injection of 125 mg/kg of pentylenetetrazole at 60 min after dosing. The dose required to prevent convulsion and death in 50% of the animals during 2 h of observation was defined, and ED_{50} values were estimated by the probit method.

Spontaneous Motor Activity.[22] Spontaneous motor activities of mice were quantitated with an "Animex" activity meter (Type S, AB Farad, Sweden). Five groups per dose (each group consisting of three mice) were measured for 10 min, beginning at 60 min after dosing. ED_{30} values were defined as the dose of drug required for a 30% reduction of control responses and were estimated by regression analysis.

Taming. A modification of the method of Tedeshi et al.[23] was used. A pair of mice was confined under an inverted circular glass enclosure and given foot shocks (5 Hz, 2 ms, DC 50 V). Five pairs of mice were used for each dose. Pairs showing 15–20 fighting episodes during 3 min were selected, and the number of responses before and at 60 min after dosing was counted. ED_{50} values were defined as those doses causing a 50% inhibition of the response and were calculated by regression analysis.

Thiopental Narcosis. Groups of ten mice pretreated with test drugs were challenged with an intravenous injection of 35 mg/kg of thiopental sodium. ED_{50} values were defined as those doses needed for a 50% increase in the duration of anesthesia and were estimated by regression analysis.

Chlorprothixene Hypnosis.[16] Groups of ten mice were treated with a combination of test drugs and chlorprothixene (2 mg/kg, ip). Sixty minutes later, each animal was placed on its back, and the duration of the loss of the righting reflux was measured. The number of animals remaining in the supine position for more than 30 s was counted, and the ED_{50} values were estimated by probit analysis.

Acknowledgment. The authors thank Dr. H. Otsuka, the former director of this laboratory, for this encouragement. Thanks are also due to Drs. W. Nagata, T. Sugasawa, and K. Yamamoto of this laboratory for their helpful advice throughout this work.

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Synthesis and Pharmacological Activity of 6-Aryl-2-azabicyclo[4.2.1]nonanes

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A series of 6-phenyl-, 6-(*m*-methoxyphenyl)-, and 6-(*m*-hydroxyphenyl)-2-azabicyclo[4.2.1]nonanes was synthesized by a sequence involving alkylation of an appropriate 2-arylcyclopentanone with an aminoalkyl substituent. Subsequent ring closure at the other α position on the cyclopentanone ring and Wolff–Kishner reduction afforded the title compound. Several derivatives of these materials showed activity in an antinociceptive assay comparable to codeine. Most analogues were either inactive or toxic.

For some time we have been interested in developing structure–activity relationships for a series of benzo-fused azabicyclic systems, which are generally thought of as "simplified morphines". The prototype of these systems is benzomorphan (1), but many others are now known, including the benzazocines **2**[1] and **3**[2] and the benazepines

0022-2623/82/1825-1473$01.25/0