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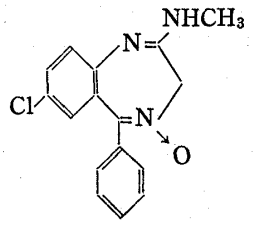
Peptido-aminobenzophenones—Novel Open-ring Derivatives of 1,4-Benzodiazepines[1]

A number of peptido-aminobenzophenones were prepared as ring-opened derivatives of 1,4-benzodiazepines. These compounds were prepared from 2-aminobenzophenones, 2-aminobenzhydrols, or indoles and appropriate protedcted dipeptides or protected amino acids by coupling, oxidation (if necessary), and deprotection. Some title compounds had very high activities in antipentylenetetrazole and fighting tests in mice when orally administered. Very weak toxicity was also found in these compounds. Water solubility of peptido-aminobenzophenone salts and pH of their aqueous solution were also tested.

Keywords——minor tranquilizer activities; water-solubility; diazepam; amido coupling reactions; intramolecular hydrogen bonding

Since the initial discovery of chlordiazepoxide (**1**), a considerable number of molecular modifications of the basic 1,4-benzodiazepine nucleus have been performed. Thus, a number of 1,4-benzodiazepines are currently widely used as tranquilizers, hypnotics, muscle relaxants, anticonvulsants, *etc.*[2–4] One representative of this class of compounds is diazepam (**8**). Much research effort in this area has been directed mainly to compounds containing the 1,4-benzodiazepine ring.



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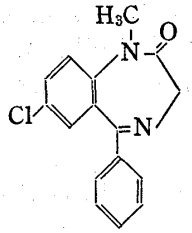

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Recently, we became interested in the open-ring derivatives of 1,4-benzodiazepines and now wish to report our synthesis of a novel series of peptido-aminobenzophenones.[5,6]

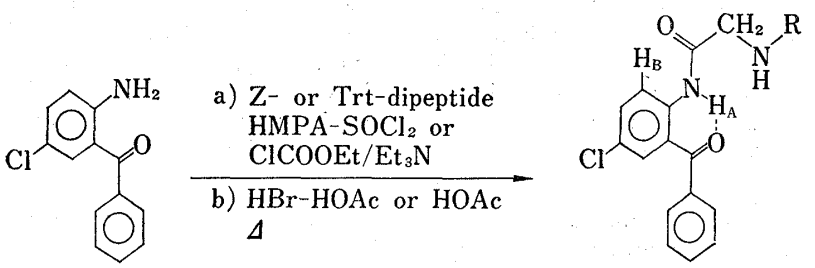
After 2-aminobenzophenone (**2**) was coupled with the appropriate Z- or Trt-dipeptide by HMPA-$SOCl_2$ or ClCOOEt–Et_3N, the coupling products were treated with HBr–HOAc or HOAc to remove the Z- or Trt-groups. Dipeptido-aminobenzophenones (**3a**—**e**) were obtained as crystals.[7]

Chart 1 showd the conformations of these compounds based on their nuclear magnetic resonance (NMR) and infrared (IR) data. Characteristic spectra were obtained as exemplified by the case of **3a**, mp 135—136°, IR (KBr) 1630 cm^{-1} (C=O....HN); NMR ($CDCl_3$) δ: 1.85 (2H, broad s, NH_2), 3.52 (2H, s, $C\underline{H}_2NH_2$), 4.13 (2H, d, J=4.5 Hz, $-COC\underline{H}_2NH-$), 7.3—7.8

1) This paper is part 1 of a series on "Benzophenone related Compounds."
2) L.H. Sternbach, *Angew. Chem. Int. Ed. Engl.*, **10**, 34 (1971).
3) L.O. Randall, W. Schallek, L.H. Sternbach, and R.Y. Ning in "Psychopharmacological Agents," Vol. III, ed. by M. Gordon, Academic Press, New York, N.Y., 1974, p. 175.
4) G. Garattini, E. Mussini, and L.O. Randal (ed.), "The Benzodiazepines," Raven Press, New York, N.Y., 1973.
5) Recently, the dipeptide derivatives of 2-aminobenzophenones were reported as 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)).
6) Earlier reports in this field have already been made from our laboratory (K. Hirai, T. Ishiba, K. Sasakura, and H. Sugimoto, Beglgium Patent, 832 190 (1975)).
7) All products gave the expected analytical and spectroscopic data.

(7H, m, aromatic H), 8.07 (1H, broad, $CH_2N\underline{H}$), 8.63 (1H, d, J=9.5 Hz, aromatic H_B), 11.10 (1H, broad s, C=O....H_AN–).

These spectra indicated that the existence of intramolecular hydrogen bonding of aniline H_A proton to the carbonyl oxygen of benzophenone and ortho H_B proton in aniline was deshielded by the adjacent amido carbonyl group.[8,9]



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3a : R=Gly-
3b : R=DL-Ala-
3c : R=DL-Val-
3d : R=DL-Gly(α-Ph)-
3e : R=L-Leu-

Chart 1

Surprisingly, dipeptido-aminobenzophenones (**3**) exhibited significant central nervous system (CNS) activities similar to chlordiazepoxide in mice on oral administration, despite earlier observations that the specific effect of the 1,4-benzodiazepines is a function of the diazepine ring.[10]

If the molecular rigidity due to the intramolecular hydrogen bonding in **3** were to be released, a geometry close to that of 1,4-benzodiazepine would be expected. Thus, peptido-N-alkylaminobenzophenones were synthesized to obtain pharmacologically more active compounds. Synthesis was achieved by Methods A—C (Chart 2).

1-Alkyl-2-aminomethyl-3-aryl-5-chloroindole (**4**) was acylated with activated Z- or Trt-amino acids. Coupling products were oxidized with chromic anhydride in AcOH to give the benzophenone derivatives. The Z group was removed by HBr-HOAc to give **7a—g,j** (Method A). Amido coupling of 2-alkylaminobenzhydrol (**5**) with activated Z- or Pht-dipeptide followed by Jones oxidation gave 2-(N-alkyl-N-Z- or Pht-dipeptidyl)aminobenzophenones. The phthalyl group was readily removed by hydrazinolysis without affecting the benzoyl carbonyl group. In this Method B, **7b,d,e,g,h,i** were obtained. The coupling reaction between 2-alkylaminobenzophenone (**6**) and Trt-dipeptide was also conducted by using HMPA-$SOCl_2$ at low temperature. Reaction of **6** with Pht-dipeptidyl chloride in warm benzene also gave the coupling products in excellent yields. Trityl or phthalyl groups were readily removed to give **7a,b** (Method C). These peptido-N-alkylaminobenzophenones (**7**) were characterized as appropriate acid salts. For example, 2-*o*-chlorobenzoyl-4-chloro-N-methyl-N$^{\alpha}$-glycylglycinanilide hydrate (**7b**), mp *ca.* 95—100°, was converted into hydrochloride, oxalate mesylate, hydrobromide, nitrate, tartrate, hemisulfate, hemicitrate, maleate, and succinate.

As expected, very high activities for antipentylenetetrazole and fighting tests, possible indicators of the antianxiety potency in humans,[3,4] were observed when **7** were orally administered to mice[11] (Table I).

8) V. Šunjić, F. Kajfež, I. Štromar, N. Blažević, and D. Kolbach, *J. Het. Chem.*, **10**, 591 (1973).
9) A. Walser, A. Szente, and J. Hellerbach, *J. Org. Chem.*, **38**, 449 (1973).
10) H. Oelschläger, W.Z. Behrendt, and H. Hoffmann, *Arzneim. Forsch.*, **23**, 802 (1973).
11) The details of SAR will be presented in near future.

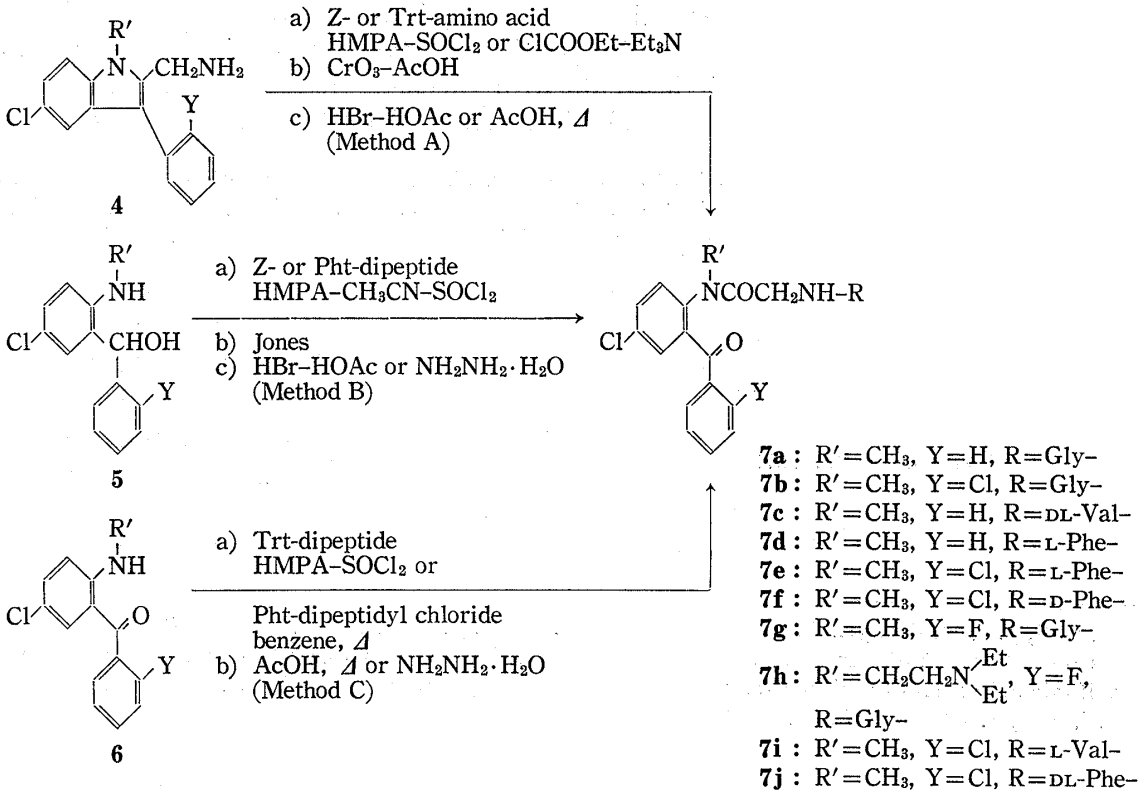

Chart 2

TABLE I. Pharmacological Data[a)]

Compd	ED_{50}, mg/kg			LD_{50}, mg/kg
	Anti-pentylene-tetrazole	Footshock anti-fighting	Rotarod performance test	Acute toxicity
7a	1.0	10.5	36.6	1309
7b·H_2O	0.58	3.0	27.7	1255
7g·HCl	0.33	1.6	17.0	>1000
Chlordiazepoxide (**1**)	3.7	24.0	50.0	1090
Diazepam (**8**)	1.19	6.0	9.03	1459

a) The compounds were tested orally in mice for the pharmacological effects according to previously described procedures.[3,4,12)]

TABLE II. Solubility and pH of the Aqueous Solution of **7b** Salts

Salt	mg/ml/aq 25°	pH of aq sol. at 5 mg/ml
HCl	133	3.7
CH_3SO_3H	142	4.3

12) M. Ogata, H. Matsumoto, and K. Hirose, *J. Med. Chem.*, **20**, 776 (1977).

Recently, open-ring triazolobenzodiazepine derivatives were reported to exhibit significants CNS activity.[13] Our results indicated that a novel series of peptido-aminobenzophenones are potentially useful CNS agents with excellent pharmacological characteristics and are interesting as novel water-soluble derivatives of 1,4-benzodiazepines[14] (Table II).

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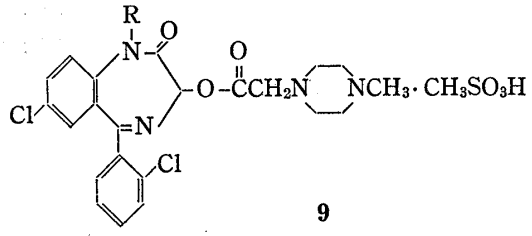
13) M. Gall, J.B. Hester, Jr., A.D. Rudzik, and R.A. Lahti, *J. Med. Chem.*, **19**, 1057 (1976).
14) As one of recent efforts to get water-soluble-derivatives of 3-hydroxy-1,4-benzodiazepines, methanesulfonic acid salts of amino ester derivatives (**9**) have been prepared (A.Nudelman, R.J. McCaully, and S.C. Bell, *J. Pharm. Sci.*, 63, 1880 (1974).



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Synthesis and Mutagenicity of 10-Azabenzo[*a*]pyrene-4,5-oxide and Other Pentacyclic Aza-arene Oxides

Aza-arene oxides, dibenz[*a,j*]acridine-5,6-oxide, dibenz[*a,h*]acridine-12,13-oxide, dibenz[*c,h*]acridine-5,6-oxide, and 10-azabenzo[*a*]pyrene-4,5-oxide were synthesized and their mutagenic activity to *Salmonella typhimurium* strains TA 98 and TA 100 was tested.

Keywords——arene oxide; aza-arene oxide; 10-azabenzo[*a*]pyrene; 10-azabenzo-[*a*]pyrene-4,5-oxide; dibenzacridine oxide; mutagenicity.

Chemical and biological interests on arene oxides have been focussed, and the rapid progress on the study of polycyclic arene oxides is remarkable.[1] However only a little attention has been paid on the chemistry and biochemistry of aza-arene oxides which are possible metabolic intermediates and activated form of carcinogenic aza-arenes.[2] Many aza-arenes have been known to be carcinogenic, and some of them have quite high activity.[3] They were also

1) D.M. Jerina and J.W. Daly, *Science*, **185**, 573 (1974).
2) Y. Kitahara, K. Shudo and T. Okamoto, *Heterocycles*, **8**, 363 (1977).
3) A. Dipple, "Polynuclear Aromatic Carcinogens, in Chemical Carcinogens (ACS Monograph 173)", ed. by C.E. Searle, American Chemical Society, 1976, p. 245—314.