0–5° and an additional 60 h at 25° standard workup gave a syrup which was crystallized from MeOH (cooling to −75°) to give 10.7 g (85%) of **10**: mp 57–58°. One recrystallization from MeOH of material from a similar preparation gave pure material: mp 57–58°; $[\alpha]^{23}D$ −9.7° (*c* 1.07, 95% EtOH). Anal. ($C_{17}H_{24}SO_3$) C, H.

(±)-3-Isothujanol *p*-Nitrobenzoate (15). The tosylate from above (10.7 g, 0.035 mol), Ac_2O (1.0 g), anhydrous NaOAc (4.5 g, 0.054 mol), and AcOH (450 ml) were kept for 20 h at 50°. AcOH was evaporated in vacuo, H_2O (30 ml) was added to the residue, and the aqueous solution was extracted with Et_2O (2 × 50 ml). The Et_2O extract was washed with excess 5% $NaHCO_3$ and then brine, dried ($MgSO_4$), and evaporated to give crude **12** (5.9 g) which was dissolved in Et_2O (50 ml) and added dropwise to a solution of $LiAlH_4$ (1.3 g, 0.034 mmol) in Et_2O (200 ml). After 2 h at reflux, the mixture was worked up as described for crude **9** to give the crude (±)-alcohol (4.62 g, 86%) which was treated with *p*-nitrobenzoyl chloride (12.0 g, 0.065 mol) in dry pyridine at 25–30°. After keeping overnight, the mixture was worked up as described[15] and the crude product recrystallized twice from MeOH to give **15** (6.4 g, 61%): mp 72–74°; $[\alpha]^{23}D$ 0.0° (*c* 1.83, $CHCl_3$). Anal. ($C_{17}H_{21}NO_4$) C, H, N.

(±)-3-Isothujanol (13). The (±) ester **15** was hydrolyzed and worked up a described for the hydrolysis of **14** to **9** to give pure **13** (88%): bp 76–78° (5 mm); $[\alpha]^{23}D$ 0.0°. This material was chromatographically (GLC, TLC) and spectroscopically identical (except for optical rotation) with **9** above.

(±)-3-Isothujone (6). Brown[19] oxidation of (±)-3-isothujanol (3.27 g, 0.021 mol) from above followed by chromatography as described for **2** above gave pure **6** (2.7 g, 84%), bp 83–84° (20 mm), $[\alpha]^{23}D$ 0.0° (neat), which was identical (GLC, TLC, spectroscopically), except for optical rotation, with pure **2** described above. The racemic ketone was further characterized as its 2,4-dinitrophenylhydrazone **19** that showed mp 102–103.5° (2-PrOH). Anal. ($C_{16}H_{20}N_4O_4$) C, H, N.

Acknowledgment. We wish to thank Dr. D. M. Cartlidge (MacMillan Bloedel Research Ltd., Vancouver, British Columbia, Canada) for a generous gift of Western Red Cedar leaf oil and Mr. Robert Eiserle (Fritsche, Dodge, and Olcott, Inc., New York, N.Y.) for a generous sample of purified Dalmatian Sage oil. The authors are indebted to Mrs. Louise Atwell for the analgesic testing and to Mr. William Landis and Mr. Noel Whittaker for mass spectral determinations.

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Synthesis and Pharmacology of Novel Anxiolytic Agents Derived from 2-[(Dialkylamino)methyl-4*H*-triazol-4-yl]benzophenones and Related Heterocyclic Benzophenones

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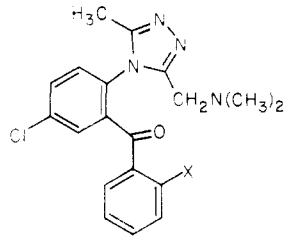
A series of novel [(dialkylamino)methyl-4*H*-1,2,4-triazol-4-yl]benzophenones and related compounds has been prepared via total synthesis from substituted aminodiphenylmethanes or by hydrolysis and subsequent methylation of triazolobenzodiazepines. These new triazole compounds were found to have potent sedative and muscle relaxing activity in mice (i.e., these compounds depressed the traction and dish reflexes). In addition, the title compunds antagonized the clonic convulsions induced in mice by the administration of pentylenetetrazole (Metrazol, 85 mg/kg), with ED_{50}'s varying from 2.0 to 23.0 mg/kg, and the lethality induced by thiosemicarbazide, with ED_{50}'s varying from 0.02 to 9.0 mg/kg. In several biological tests, the potency of seven new benzophenone derivatives approached or exceeded that of diazepam (**35a**) or its glycylaminobenzophenone analogue **36**.

Two recent but unrelated developments in the benzodiazepine antianxiety–hypnotic area have received considerable attention. First, Hester and co-workers[1a] and others in Japan[1b] demonstrated that the fusion of a triazole

ring to the "a" face of a 1,4-benzodiazepine imparted enhanced potency and novel activity to the parent molecule. Secondly, Snyder and co-workers[2a] suggested that clinically effective benzodiazepines exerted their therapeutic effects by mimicking the actions of glycine at its receptor site.[2b] Snyder's results were all the more interesting to us since Sternbach and co-workers[1c] had shown that *o*-glycylaminobenzophenones related to diazepam possessed CNS sedative activity in animals nearly equivalent in potency to the activity displayed by benzodiazepines. In this report we describe the preparation of (dimethylamino)methyltriazolobenzophenone **1** and its derivatives (see Table I) related to 1-methyltriazolobenzodiazepine **2**, and we present evidence that low doses of these new compounds cause CNS depression in laboratory animals. However, since the results of other experiments demonstrated that **1** was, at least in part, metabolized to **2**, we would now speculate that the class of CNS active aminomethyltriazolobenzophenones may actually function in part as prodrug forms[3] of triazolobenzodiazepines.



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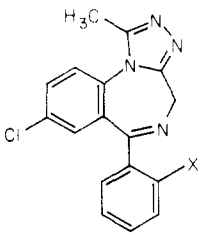


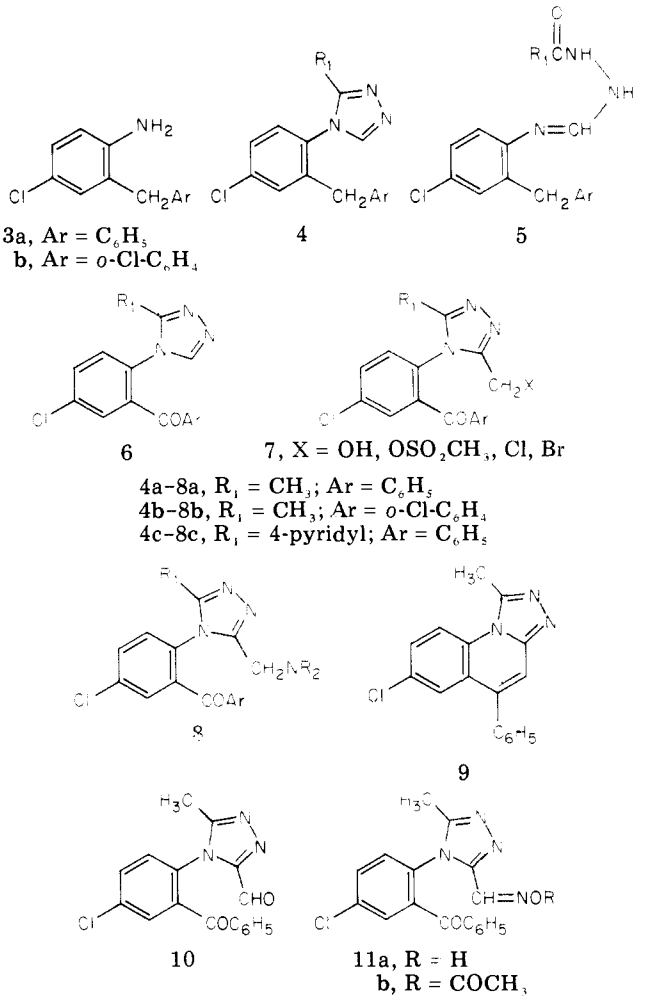
2a, X = H (alprazolam)
b, X = Cl (triazolam)

Chemistry. Aminomethyltriazolobenzophenones. From *o*-Benzylanilines. Our initial goal was to synthesize the intermediates **6** by utilizing the readily available[4-6] *o*-benzylanilines **3**. A mixture of **3** and triethyl orthoformate was heated so that the alcohol generated during the reaction was removed by distillation. The resulting formimino ether was treated with an acyl hydrazide at room temperature to generate **5** which either was isolated and purified or was cyclized directly to give **4**. (The overall yield for the synthesis of **4a** and **4b** without isolating **5a** or **5b** was 63–65%[8].) Triazole **4** was oxidized with Jones reagent in hot acetic acid to the desired benzophenone **6** in 69–74% yield. In an alternative synthesis of triazole **6a**, triazoloquinoline **9**, prepared from 2,6-dichlorophenylquinoline,[9] was oxidized with a variety of reagents to afford mixtures of **6a** and **10** in low to moderate yield.[9b,10]

The desired aminomethyl analogues (i.e., **8**) were obtained from **6** in two ways. In the first method **6** was refluxed in xylene with paraformaldehyde to afford the methyl alcohol derivative **7** (X = OH) whose corresponding chloride (**7**, X = Cl) or bromide (**7**, X = Br) (procedure A) or mesylate (**7**, X = OMs) (procedure A′) was converted to the amine **8**. In the second method (procedure B) **6** was heated with a dialkylamine hydrochloride (R_2NH·HCl) in aqueous glyme solutions of formaldehyde to afford **8** directly. To our knowledge this is the first successful Mannich reaction reported on the 1,2,4-triazole ring system.

From Benzodiazepines. In order to prepare analogues with variations in both R_1 and the heterocyclic ring, a modification of the Eschweiler–Clarke reaction was applied to the readily available triazolo-,[1] oxotriazolo-,[11] and imidazobenzodiazepines.[12] An aqueous solution of 1 equiv of the benzodiazepine and a mixture of 15 molar equiv of formic acid and 9 molar equiv of aqueous formaldehyde was heated to 100° for 1 h to afford dimethylaminomethyl heterocyclic benzophenones. Under these conditions (procedure C), for example, **12**[1e] afforded **26** in 52% crystallized yield (not maximized). Under the same conditions, the 2-methylimidazole **13** afforded the expected Mannich base **14** after 1 h, but on prolonged heating, **14** reacted further with formaldehyde to afford the hydroxymethylated adduct **31** in 60% yield.

Chart I



3a, Ar = C_6H_5
b, Ar = *o*-Cl-C_6H_4

4

5

6

7, X = OH, OSO_2CH_3, Cl, Br

4a–8a, R_1 = CH_3; Ar = C_6H_5
4b–8b, R_1 = CH_3; Ar = *o*-Cl-C_6H_4
4c–8c, R_1 = 4-pyridyl; Ar = C_6H_5

8

9

10

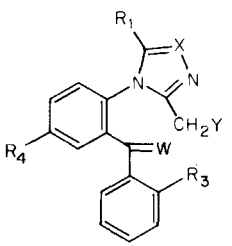
11a, R = H
b, R = $COCH_3$

Diphenylmethanols. The reduction of **18** with sodium borohydride or lithium tri-*tert*-butoxyaluminum hydride (procedure D) afforded two isomeric diphenylmethanols (**20**, R_f = 0.45; **21**, R_f = 0.26, see Table I).[8a] Two *diastereomeric* amino alcohols[13] were formed because the compounds contain two centers of molecular asymmetry: (a) a chiral carbon atom and (b) an unsymmetrically substituted triazole ring held rigidly in one conformation because of an unexpectedly high-energy barrier to ring rotation. (This type of restricted rotation is analogous to that found in ortho-substituted biphenyls.)

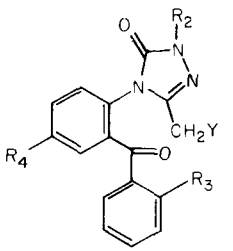
Amino alcohol **29**, isolated as a single diastereomer, was prepared by reducing acetyl oxime **11b** prepared in two steps from aldehyde **10**. (See procedure E in the Experimental Section.)

Miscellaneous. The preparation of the oxotriazolo analogue **33** by a novel methylation and ring opening of the benzodiazepine **33a** with trimethyloxonium tetrafluoroborate is described in detail in procedure F of the Experimental Section.

Table I. Physical Data for Aminomethyltriazolyl-, Oxotriazolyl-, and Imidazolylbenzophenones



type I



type II

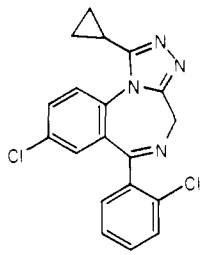
No.	Type	X	R_1	R_2	R_3	R_4	Y	W	Procedure	% yield[a]	Mp, °C	Formula	Analyses[b]
15	I	N	CH_3		Cl	H	NMe_2	O	C	71	147–150[c]	$C_{19}H_{19}ClN_4O$	C, H, N, Cl
16	I	N	CH_3		H	Cl	NMe_2	O	A, C	73, 64	171–172[c]	$C_{19}H_{19}ClN_4O$	C, H, N, Cl
17	I	N	CH_3		Cl	Cl	NMe_2	O	C	59	127.5–130[d]	$C_{19}H_{18}Cl_2N_4O$	C, H, N, Cl
18	I	N	CH_3		H	Cl	c-NC_4H_8	O	A', B	53, 42	174–176[c]	$C_{21}H_{21}ClN_4O$	C, H, N, Cl
19	I	N	CH_3		Cl	Cl	c-NC_4H_8	O	B	46	131–132[c]	$C_{21}H_{20}Cl_2N_4O$	*k*
20	I	N	CH_3		H	Cl	c-NC_4H_8	H, OH	D	*j*	183–185[d]	$C_{21}H_{23}ClN_4O$	C, H, N
21	I	N	CH_3		H	Cl	c-NC_4H_8	OH, H	D	*j*	204–205[d]	$C_{21}H_{23}ClN_4O$	C, H, N, Cl
22	I	N	CH_3		H	Cl	c-NC_4H_8	H, H	B	57	141–144[d]	$C_{21}H_{23}ClN_4$	C, H, N, Cl
23	I	N	CH_3		H	Cl	c-$N(CH_2CH_2)_2O$	O	B	24	128.5–130.5[e]	$C_{21}H_{21}ClN_4O_2$	C, H, N, Cl
24	I	N	CH_3		H	Cl	NHMe	O	A	80	175–176[c]	$C_{18}H_{17}ClN_4O$	C, H, N, Cl
25	I	N	CH_3		H	Cl	NEt_2	O	A, B	85, 53	112–113[f]	$C_{21}H_{23}ClN_4O$	C, H, N, Cl
26	I	N	c-C_3H_5		Cl	Cl	NMe_2	O	C	52	109–115[d]	$C_{21}H_{20}Cl_2N_4O$	C, H, N, Cl
27	I	N			H	Cl	NMe_2	O	C	59	156–159[c]	$C_{22}H_{19}ClN_4O_2$	C, H, N, Cl
28	I	N	4-C_5H_4N		Cl	Cl	NMe_2	O	C	69	171–173.5[g]	$C_{23}H_{19}Cl_2N_5O$	C, H, N, Cl
29	I	N	CH_3		H	Cl	NH_2	OH, H	E	*j*	218–219[h]	$C_{17}H_{17}ClN_4O$	C, H, N, Cl
30	I	CH	H		Cl	Cl	NMe_2	O	C	35	105–108[d]	$C_{19}H_{17}Cl_2N_3O$	C, H, N, Cl
31	I	CCH_3	CH_2OH		Cl	Cl	NMe_2	O	C	60	163–165[c]	$C_{21}H_{21}Cl_2N_3O_2$	*l*
32	II			CH_2OH	Cl	Cl	NMe_2	O	C	50	154–162[c]	$C_{19}H_{18}Cl_2N_4O_3$	C, H, N, Cl
33	II			CH_3	H	Cl	$NHMe_2$	O	F	61	175–177[i]	$C_{18}H_{17}ClN_4O_2 \cdot HCl$	
34	II			$(CH_2)_2$ | NMe_2	H	Cl	NMe_2	O	C	47	85–88[d]	$C_{22}H_{26}ClN_5O_2$	C, H, N, Cl

[a] All values are of isolated, crystallized yields. No effort has been made to maximize these yields. [b] Satisfactory analyses have been obtained for the elements indicated. [c] From ethyl acetate. [d] From ethyl acetate–hexane. [e] From ether. [f] From ethyl acetate–Skellysolve B. [g] From chloroform–hexane. [h] From methanol–ethyl acetate. [i] The hydrochloride salt was crystallized from methanol–ethyl acetate. [j] See the Experimental Section. [k] Calcd for $C_{21}H_{20}Cl_2N_4O$: C, 60.73; H, 4.86; N, 13.49; Cl, 17.07. Found: C, 60.55; H, 4.94; N, 13.41; Cl, 16.66. Recalculated for 2.58% EtOAc found by melt solvent analysis: C, 60.57; H, 4.97; N, 13.14; Cl, 16.63. [l] Calcd for $C_{21}H_{21}Cl_2N_3O_2$: C, 60.29; H, 5.06; N, 10.05; Cl, 16.95. Found: C, 59.93; H, 5.40; N, 9.20; Cl, 15.14. Recalculated for 0.5 mol (10.76% found by melt solvent analysis) of ethyl acetate: C, 59.74; H, 5.50; N, 8.96; Cl, 15.37.

Table II. Pharmacological Data[a] for Aminomethyltriazolyl-, Oxotriazolyl-, and Imidazolylbenzophenones

			Antagonism						
			Nicotine		Thiosemi-			Pentylene-	Potentiation,
No.	Tr	D	TE	D	carbazide	Strychnine	Electroshock	tetrazole	EtOH
15	>100	22	5	5	3.6	>50	>100	7.0	>100
16	5	2.2	0.50	0.50	0.3	5	45	1.1	1.1
17	3.2	0.25	0.14	0.14	0.02	11	50	0.28	0.63
18	4.0	1.3	0.4	0.4	2.0	4	89	2.0	1.8
19	18	1.0	1.3	1.8	1.1	1.0	>100	4.0	6.0
20	>25	16	8	8					
21	>200	5	32	32				14	
22	>100	40	36	36				>100	
23	5.0	1.8	0.45	0.50	0.8	6.3	>50	1.8	4.4
24	2.5	0.8	0.1	0.1	0.3	3.2	63	1.1	2.0
25	2.5	1.0	0.2	0.2	0.6	45	45	0.5	0.6
26	7.1	1.1	0.6	0.6	0.4	5.0	79	1.0	2.2
27	71	28	16	16	8.0	45	>100	23	25
28	>100	20	11	11	4.4	>50	>100		
29	9.0	2.8	1.6	1.6	1.2	28	71	4.0	3.1
30	11	2.2	1.0	1.2	1.1	>50		1.8	2.5
31	18	3.5	1.0	1.0	2.0	>25	100	1.8	18
32	6.3	1.0	0.13	0.13	0.23	12.5	>100	0.32	2.0
33	12.5	4.0	0.45	0.56				5.6	
34	100	28	6.3	6.3	9	>100	>100	18	80
35[a]	5.0	0.31	0.11	0.11	0.20	3.6	20	0.8	1.0
36	32	5.6	0.25	0.25	1.6	22	29		2.5
37	>200	100	23	28				140	
2a	0.6	0.056	0.02	0.02	0.16	0.3	25.50	0.2	0.16
2b	0.6	0.028	0.013	0.014	0.028	0.23	32-50	0.03	0.63

[a] See the Experimental Section for an explanation of the symbols and test procedures. Values in the table are ED_{50}'s expressed in mg/kg. All drugs were administered ip to mice.



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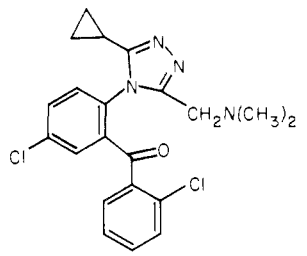

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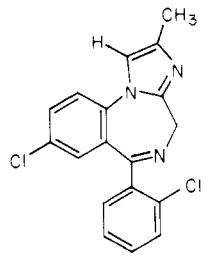

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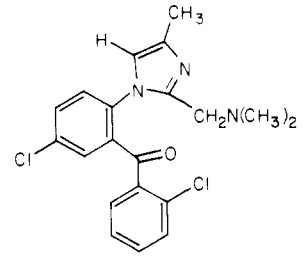

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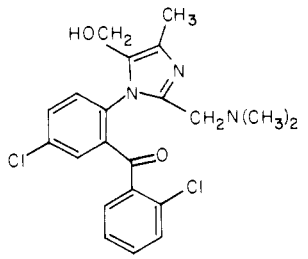

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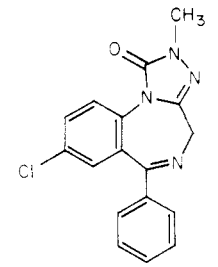
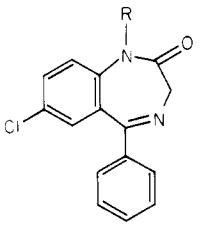


33a

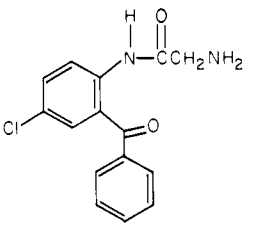
Results

The data presented in Table II are the ED_{50} values obtained for the new compounds in several pharmacological tests which characterize sedative–hypnotic drugs in mice.[8] The results indicate that the class of aminomethyl heterocyclic benzophenones posesses significant CNS sedative (or minor tranquilizer like) activity. Compound **17** was the most active of the new series in the dish, thiosemicarbazide, and pentylenetetrazole assays and was very potent in protecting mice against nicotine lethality. In two or more tests the potency of seven benzophenone analogues (i.e., **16–18**, **23–25**, and **32**) approached or exceeded that of diazepam (**35a**) and its ring-opened analogue **36**.[1c] Furthermore, the heterocyclic benzophenones were far more active than the *o*-glycylaminobenzophenone **37**.[14] However, even the most active benzophenones were less potent than the corresponding triazolobenzodiazepines (cf. **16** with **2a** and **17** with **2b**).

Several features about the structure–activity relationships (SAR) of this series deserve comment. First, compounds **16**, **18**, and **23–25**, which differed structurally only in the nature of the alkyl group on the nitrogen, all had almost identical ED_{50} values in the traction test. The ED_{50} values for these compounds were also similar in the dish, nicotine, and pentylenetetrazole tests. Second, the triazole and oxotriazole (i.e., **32** and **33**) derivatives were generally more potent than the imidazole analogues (i.e., **30** and **31**), a pattern of activity *in mice* also reflected by the corresponding heterocyclic benzodiazepines.[15] Third, although the benzophenones **16**, **17**, and **25** had ED_{50} values comparable to alprazolam (**2a**) and triazolam (**2b**) in protecting mice from the effects of electroshock convulsions, neither series was very potent in this test. Finally



35a, R = CH_3 (diazepam)
b, R = H



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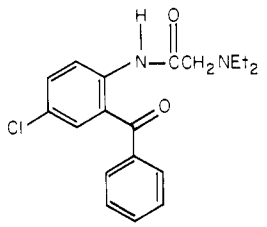

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the reduced pyrrolidino analogues **20**, **21**, and **23** were much less potent than the corresponding ketone **18**.

Discussion

One of the major purposes for preparing the title compounds was to determine whether or not a structure, derived from an *o*-glycylaminobenzophenone which could *not* chemically close to a benzodiazepine, would possess significant CNS sedative activity. The reasons for our interest in this type of benzophenone structure are detailed briefly below.

Snyder and co-workers recently demonstrated that benzodiazepines can displace [^{3}H]strychnine from the glycine receptor[16] in the mammalian central nervous system. This result, coupled with the close correlation between the relative potencies of various benzodiazepines used clinically as antianxiety agents in man and their potencies as anticonvulsants in animals, led Snyder to suggest that the benzodiazepines exerted their activity by mimicking the action of the putative CNS neurotransmitter glycine at its receptor site. The fact that benzodiazepines contain a masked glycine residue in the seven-membered ring seemed to provide further evidence in support of this theory.[17]

We were intrigued with the idea that the benzodiazepine structure provided a means to protect a glycine-type residue and transport it into the CNS. Furthermore, we speculated that, once in the CNS, one possible active form of the drug at a glycine receptor site might be the hydrolyzed or ring-opened *o*-glycylaminobenzophenone (cf. **36** and **37** in Table II). Many years ago Sternbach and co-workers[1c] had shown that these benzophenones were very potent CNS sedatives. However, they also noted that the *primary* aminobenzophenones (i.e., **35b**) readily cyclized to benzodiazepines.[18] Coupled with the fact that dialkylamino derivatives such as **37**[14] (which could not close chemically to benzodiazepines) were very much less potent than **35b**, these observations implied that the benzodiazepine structure (in contrast to a glycylaminobenzophenone structure) was required for CNS activity.

Despite these early indications that *o*-glycylaminobenzophenones were devoid of intrinsic CNS sedative activity, we synthesized and investigated the pharmacology of the title compounds. We were surprised to find that administering low doses of alkylaminomethyltriazol-4-ylbenzophenones to mice sedated the animals and protected them from the convulsant effects of thiosemicarbazide, strychnine, and pentylenetetrazole (see Results). These preliminary screening results were consistent with the hypothesis that an *o*-glycylaminobenzophenone structure represented a biologically active form of benzodiazepine drugs. Such a hypothesis, however, was far from proven, since the observed biological activity of the new class of compounds reported in this paper might just as well have been due to the effects of metabolites of the administered drugs. In fact, other studies carried out in these laboratories[19] have demonstrated that **16** and **23** were at least partially dealkylated metabolically in mice, rats, and monkeys and subsequently cyclized to the known CNS active triazolobenzodiazepine **2a**. It is likely that a rapid in vivo transformation of this type accounts for the fact that amino analogues **16** and **23–25** had ED_{50} values which were practically identical with each other and with the pyrrolidino derivative **18**, in the traction, dish, and other tests (see Results and Table II). Moreover, it probably offers an explanation why the reduced pyrrolidino analogues **20**, **21**, and **23** (which require a further metabolic oxidation step before they are converted to **2a**) were considerably less potent than the ketone **18**.

In conclusion, our results indicate that the class of 2-[(alkylaminomethyl)-4*H*-1,2,4-triazol-4-yl]benzophenones are potentially useful CNS agents which may function, in part, as prodrugs[3] of triazolobenzodiazepines. The question of whether or not the benzodiazepines themselves may serve as precursors to biologically active *o*-glycylaminobenzophenones remains unanswered.

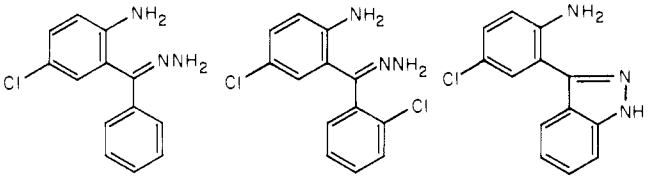
Experimental Section

Chemistry. Melting points, taken with a Thomas-Hoover capillary melting point apparatus, are corrected. The structures of all compounds were supported by ir, uv, NMR, and mass spectral data. Ir spectra were determined in Nujol with a Perkin-Elmer Model 421 recording spectrophotometer. Uv spectra were determined in 95% EtOH with a Cary Model 14 spectrophotometer. NMR spectra were recorded on a Varian Model A-60A; chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were obtained with a Varian MAT CH7 or LKB. Skellysolve B (Sk B) is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo.

Preparation of *o*-Benzylanilines. 3a. A mixture of 27.2 g (0.117 mol) of 2-amino-5-chlorobenzophenone and 23 ml (0.46 mol) of 99% $H_2NNH_2 \cdot H_2O$ in 170 ml of diethylene glycol was refluxed for 7 h. The resulting solution was cooled to room temperature, mixed with 400 ml of H_2O, and extracted with benzene. The benzene layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was crystallized from ether–hexane mixtures to afford hydrazone i in 68% yield: mp 132–134° (lit.[5] 134–135°). Potassium hydroxide pellets (85%, 16.1 g, ~0.245 mol) were ground in a mortar and pestle and dissolved in a separate flask in 85 ml of refluxing diethylene glycol. Volatile materials were distilled until the temperature of the liquid reached 200°. The solution was cooled to room temperature and 13.5 g (0.055 mol) of the hydrazone was added while the syrupy liquid was slowly reheated to 120–150° for 45 min, when gas evolution ceased. After a total period of 1 h the solution was cooled, poured into an ice-cold 5% aqueous sodium hydroxide solution, and extracted with benzene. The benzene layer was separated, dried over magnesium sulfate, and concentrated in vacuo to an orange oil. The product was distilled to afford 9.9 g (89.2%) of yellow oil, bp 125–140° (0.1 mmHg), which was a single component on VPC (a 6-ft column containing 10% UCW 98 suspended on Chromosorb P was used for this analysis). A pure sample was collected via preparative VPC. Anal. ($C_{13}H_{12}ClN$) C, H, N, Cl. It was preparatively more convenient to obtain the aniline without isolating the hydrazone i. The crude yield was 97%; the distilled yield was 89%.

3b. A mixture of 187.5 g (0.702 mol) of 2-amino-2′,5-dichlorobenzophenone and 138 ml (2.76 mol) of 99% hydrazine hydrate in 1020 ml of diethylene glycol was refluxed for 41 h (an unnecessarily long reaction period) to form the hydrazone ii. The reaction mixture was cooled to 60°, treated with 241.5 g (4.30 mol) of ground potassium hydroxide pellets (85%), and heated to

between 140 and 150° until gas evolution ceased. The total heating period was 6 h. The product was worked up from an aqueous sodium hydroxide solution as described for **3a**. The benzene solution of the product, on standing for 3 days, deposited 6.12 g (3.58%) of indazole iii which crystallized from chloroform as needles: mp 187–188.5° (lit.[7a] 182–184°). The benzene layers, which contained **3b**, were dried over magnesium sulfate, filtered, and concentrated in vacuo to a red oil which was distilled at 140–148° (0.15 mm Hg) to afford 140.0 g (71%) of yellow aniline **3b**. The oil could be induced to crystallize from ether–Skelly B mixtures to afford a solid: mp 64.3–65°. Anal. ($C_{13}H_{11}Cl_2N$) C, H, N, Cl.



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Preparation of 2-(4*H*-1,2,4-Triazol-4-yl)benzophenones 6. The general procedure is illustrated by the preparation of 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone (**6a**).

Step 1. 5a. A mixture of 34.51 g (0.158 mol) of 2-benzyl-4-chloroaniline (**3a**), 56 g (0.378 mol) of triethyl orthoformate, and a catalytic amount of the starting amine hydrochloride was heated for 5 h so that the resulting ethanol was distilled. The orange solution was cooled to room temperature, dissolved in 450 ml of absolute ethanol, heated with 23.7 g (0.320 mol) of acetyl hydrazide, and stirred for 5 h (a white solid precipitated after 0.5 h). At this point one could isolate **5a** by dissolving the solid reaction mixture in 1 l. of hot ethyl acetate and treating it with 400 ml of hexane. In this way 36.4 g (76.7%) of 1-acetyl-2-[*N*-(4-chloro-α-phenyl-*o*-tolyl)formimidoyl]hydrazone (**5a**) was obtained as a mixture of isomers of mp 166–169°. The analytical sample had mp 174–175°. Anal. ($C_{16}H_{16}ClN_3O$) C, H, N, Cl.

5b. In the same way 1-acetyl-2-[*N*-[4-chloro-α-(*o*-chlorophenyl)-*o*-tolyl]formimidoyl]hydrazone was isolated in 93% yield: mp 213–214°. Anal. ($C_{16}H_{15}Cl_2N_3O$) C, H, N, Cl.

5c. 1-Isonicotinyl-2-[*N*-(4-chloro-α-phenyl-*o*-tolyl)formimidoyl]hydrazone was isolated from tetrahydrofuran–hexane mixtures in 53% yield, mp 173–178 °C. The analytical sample, recrystallized from dimethylformamide–water mixtures had mp 193–194°. A satisfactory analysis was not obtained for this compound.

Step 2. 4a. A 1-l. flask charged with 28.4 g (0.094 mol) of **5a** in 400 ml of diglyme was heated to 120°. After the starting material dissolved, 20 ml of pyridine was added and the solution was refluxed for 20 h. After 200 ml of pyridine, water, and diglyme mixtures were distilled (140 °C) under partially reduced pressure, 2500 ml of reagent hexane was added to afford, on trituration in an ice bath, 20.8 g (78%) of a solid, mp 135–139°. The analytical sample of 4-(2-benzyl-4-chlorophenyl)-3-methyl-4*H*-1,2,4-triazole (**4a**) had mp 142°. Anal. ($C_{16}H_{14}ClN_3$) C, H, N, Cl.

If the excess triethyl orthoformate was distilled from step 1, then steps 1 and 2 could be combined in one pot to afford the desired triazole in 65% yield.[8b]

4b. 4-[4-Chloro-α-(*o*-chlorophenyl)-*o*-tolyl]-3-methyl-4*H*-1,2,4-triazole was isolated in 66.5% from **5b**: mp 159.5–161°. Anal. ($C_{16}H_{13}Cl_2N_3$) C, H, N, Cl.

4c. 4-[4-Chloro-α-(phenyl-*o*-tolyl)]-3-(4-pyridyl)-4*H*-1,2,4-triazole was obtained in 67% yield (from **5c**): mp 138–142°. In this case it was not necessary to add pyridine to the reaction mixture. The analytical sample, recrystallized from ethyl acetate–hexane mixtures, had mp 145.5–146.5°. Anal. ($C_{20}H_{15}ClN_4$) C, H, N, Cl.

Step 3. 6a.[10] Jones reagent[20] was added to solution of 28.4 g (0.1 mol) of **4a** dissolved in 100 ml of glacial acetic acid. The solution was stirred and heated on a steam bath for 3.5 h, quenched in 4 l. of a cold (0–10°) 5% aqueous sodium hydroxide solution, and extracted with methylene chloride. The extracts were washed with a brine solution, dried over magnesium sulfate, then filtered, and concentrated in vacuo to 27.0 g of a brown solid which crystallized from 300 ml of hot ethyl acetate–hexane mixtures to yield 21.9 g (74%) of 5-chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone (**6a**): mp 168.5–169.5° (lit.[10] mp 168–170°). Anal. ($C_{16}H_{12}ClN_3O$) C, H, N, Cl.

6b. In this (and other) Jones oxidations it was convenient to add isopropyl alcohol to the reaction mixture to destroy excess reagent prior to the aqueous quench. With 33.94 g of starting triazole (0.106 mol), 100 ml of 2-propanol was added just prior to workup and 25.5 g (72%) of 2′,5-dichloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone was obtained: mp 155.5–157.5°. Anal. ($C_{16}H_{11}ClN_3O$) C, H, N, Cl.

6c. 5-Chloro-2-[3-(4-pyridyl)-4*H*-1,2,4-triazol-4-yl]benzophenone was obtained in 69% yield. The analytical sample, deposited as fine needles from chloroform–hexane mixtures, had mp 250–251°. Anal. ($C_{20}H_{12}ClN_4O$) C, H, N, Cl.

5-Chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (7a, X = OH). A stirred mixture of 5-chloro-2-(3-methyl-4*H*-1,2,4-triazolo-4-yl)benzophenone (2.98 g, 10.0 mmol), paraformaldehyde (3 g), and xylene (100 ml) was warmed under nitrogen, in a bath maintained at 125° for 7 h. The mixture was concentrated in vacuo and chromatographed on silica gel (150 g) by eluting with 3% methanol–97% chloroform mixtures. Fractions (50 ml) were collected. The product, eluted in fractions 20–44, was crystallized from ethanol–ethyl acetate mixtures to give 2.39 g (72.8% yield) of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone: mp 138.5–141°. The analytical sample had mp 138–139°. Anal. ($C_{17}H_{14}ClN_3O_2$) C, H, N, Cl.

In the same way 2′,5-dichloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (**7b**, X = OH), mp 191–193°, was obtained as fine needles. Anal. ($C_{17}H_{13}Cl_2N_3O_2$) C, H, N, Cl.

5-Chloro-2-[3-(bromomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (7a, X = Br). A solution of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (328 mg, 1.00 mmol) in dry, hydrocarbon-stabilized chloroform (5 ml) was cooled in an ice bath and treated with phosphorus tribromide (0.1 ml). The colorless solution was kept in the ice bath for 55 min and at ambient temperature (22–24°) for 5 h. The resulting yellow solution was poured onto a mixture of ice and dilute sodium bicarbonate, extracted with chloroform, then washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was crystallized from methylene chloride–ethyl acetate mixtures to give 0.315 g of 5-chloro-2-[3-(bromomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone: mp 200–240°. The analytical sample decomposed between 200 and 240°. Anal. ($C_{17}H_{13}BrClN_3O$) C, H, N, Br, Cl.

5-Chloro-2-[3-(chloromethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (7a, X = Cl).[10] A solution of 5-chloro-2-[3-(hydroxymethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (328 mg, 1.00 mmol) in thionyl chloride (2 ml) was warmed during 40 min to a bath temperature of 78° and kept at 78–83° for 1.25 h. It was then cooled, poured into ice water, neutralized with sodium bicarbonate, and extracted with chloroform. The extract was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was crystallized from ethyl acetate–Skellysolve B hexanes to give 0.265 g of 5-chloro-2-[3-(chloromethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]-benzophenone: mp 144.5–147° (lit.[10] mp 143–144°). Anal. ($C_{17}H_{13}Cl_2N_3O$) C, H, N, Cl.

Procedure A. A stirred suspension of 5-chloro-2-[3-(bromomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone (1.0 g, 2.56 mmol) in tetrahydrofuran (40 ml) was cooled in an ice bath and treated with 32 ml of a saturated solution of dimethylamine in methanol. The mixture was removed from the ice bath, stirred at ambient temperature for 30 min, and concentrated in vacuo. The residue was mixed with water and extracted with methylene chloride. The extract was dried over anhydrous potassium carbonate and concentrated. Crystallization of the residue from ethyl acetate gave 0.66 g of 5-chloro-2-[3-(dimethylaminomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzophenone, mp 168–172° (see Table I, entry 1). Compounds **24** and **25** in Table I were prepared in a similar manner.

Procedure A′. A solution of 0.328 g (1.00 mmol) of 5-chloro-2-[3-methyl-5-(hydroxymethyl)-4*H*-1,2,4-triazol-4-yl]-benzophenone, dissolved in 5.0 ml of methylene chloride, was cooled to 0° in an ice bath. Triethylamine (0.150 g, 1.5 mmol)

was added and the solution was stirred for 5 min at 0°. Cautiously, 0.106 ml (1.3 mmol) of methanesulfonyl chloride was added dropwise over 4 min and the solution was stirred for 20 min. The reaction was quenched on ice and extracted with a saturated aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting mesylate **7a** (X = OSO_2CH_3) [R_f 0.54; the R_f of 5-chloro-2-[3-methyl-5-(chloromethyl)-4*H*-1,2,4-triazol-4-yl]benzophenone was 0.45 in the same TLC analytical system (silica gel, 10% methanol–90% chloroform)], dissolved in 4.0 ml of freshly distilled tetrahydrofuran, was treated at 0° with 0.332 g (2.0 mmol) of potassium iodide followed by 1.0 ml of pyrrolidine. The mixture was stirred at 0° for 10 min, then warmed to room temperature, and stirred overnight. The mixture was quenched in an aqueous 5% sodium hydroxide solution and the product was extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate and concentrated in vacuo to yield a yellow oil which crystallized from ethyl acetate to afford 200 mg of 5-chloro-[3-methyl-5-(pyrrolidinomethyl)-4*H*-1,2,4-triazol-4-yl]benzophenone in the form of fine white needles: mp 174–176° (see Table I, entry 18).

Procedure B. Mannich Reaction. 5-Chloro-2-(3-methyl-4*H*-1,2,4-triazol-4-yl)benzophenone (**6a**, 1.49 g, 5.0 mmol) was added to 3.0 ml of a 37% aqueous formalin solution (~1.1 g, 37 mmol) in 10 ml of diglyme containing 1.07 g (15 mmol) of freshly distilled pyrrolidine and 7.5 ml of 2 N HCl and the resulting mixture was stirred and refluxed for 17 h under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, it was quenched in approximately 40 ml of a 5% aqueous sodium hydroxide solution and the products were extracted with four 30-ml portions of benzene. After drying the benzene extracts over magnesium sulfate, the solvent was removed in vacuo to afford an oil which was warmed, diluted with hexane, and finally cooled to afford 1.04 g of powder. The powder was recrystallized from ethyl acetate–hexane mixtures to afford 0.82 g of white needles of 5-chloro-2-[3-methyl-5-(pyrrolidinomethyl)-4*H*-1,2,4-triazol-4-yl]benzophenone: mp 169.5–171.5 °C (see Table I, entry 18). Compounds **19**, **22**, **23**, and **25** in Table I were prepared analogously.

Procedure C. Eschweiler–Clarke Reaction. A solution of 1 equiv of the appropriate benzodiazepine dissolved in 25 equiv of an aqueous 88% formic acid solution (1.31 g) was treated with 8.3 molar equiv of an aqueous 37% formalin solution (0.675 ml), heated to 100° for from 1 to 24 h and then cooled to room temperature. The resulting solution was quenched in a cold (0–10°) aqueous 5% sodium hydroxide solution and the products were extracted with chloroform, dried over magnesium sulfate, and filtered through Celite to remove polyformaldehyde. In this way compounds **16**, **17**, **26**, **27**, **28**, **30**, **31**, **32**, and **34** were prepared in the yields shown in Table I.

Procedure D. A mixture of 0.3805 g (1.00 mmol) of 5-chloro-2-[5-methyl-3-(pyrrolidinomethyl)-4*H*-1,2,4-triazol-4-yl]benzophenone in 1.0 ml of absolute ethanol was cooled to 0° in an ice bath and treated in one portion with 0.0375 g (1.00 mmol) of sodium borohydride. After stirring the mixture for 5 min at room temperature, the ice bath was removed and the stirring was continued. Within an additional 10 min a clear homogeneous solution formed which was stirred overnight. The reaction mixture was worked up by first cautiously adding hydrochloric acid until gas evolution ceased and then neutralizing with a 5% aqueous sodium hydroxide solution (the pH was made >9). The products were extracted with chloroform, dried over sodium sulfate, and concentrated in vacuo to a diglyme solution. The hot diglyme solution was treated with ether and hexane and cooled to afford 150 mg of a white solid which, after two recrystallizations, afforded 50 mg of white needles of 5-chloro-[5-methyl-3-(pyrrolidinomethyl)-4*H*-1,2,4-triazol-4-yl]benzhydrol (**21**): mp 204–205°. [TLC (silica gel, 10% methanol–chloroform) revealed that this solid corresponded to the slower moving epimer of R_f 0.26.]

The mother liquors from the crystallization were recombined and dissolved in 3 ml of diglyme. To be certain that all boron salts had been decomposed, the solution of mother liquors was refluxed for 3 h with 3.0 ml of methanol and 0.5 ml of propionic acid. It was quenched in an aqueous 5% sodium hydroxide solution and worked up as described above. The material was chromatographed over 20 g of silica gel by eluting with 60 ml of chloroform (fractions A–C), 120 ml of 1% methanol–99% chloroform (fractions D–H), and 200 ml of 5% methanol–95% chloroform. Fractions K and L contained the fast moving epimer of R_f 0.45. Fraction M contained a small amount of a mixture of the two epimers, whereas fractions N–R contained only the epimer of R_f 0.26. These last fractions were combined and crystallized from ethyl acetate–hexane to give 30 mg of white needles, mp 204–205°. The oil from fractions K and L was triturated with ether to yield a white solid which was recrystallized from ethyl acetate–hexane mixture to afford 70 mg of prisms (**20**): mp 183–185° (R_f 0.45).

Procedure E. A stirred mixture of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldehyde (**10**, 3.26 g, 10.0 mmol), hydroxylamine hydrochloride (0.765 g, 11.0 mmol), sodium acetate (0.903 g, 11.0 mmol), ethanol (50 ml), and water (12.5 ml) was refluxed, under nitrogen, for 4.5 h. (The product precipitated from the initially clear solution during the reflux period.) The cooled mixture was poured into cold water, and the solid was filtered, washed with water, and dried to give 2.7 g of crude 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldoxime. This material was crystallized from methylene chloride–methanol mixtures to give 2.50 g of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldoxime (**11a**): mp 276–281° dec. The analytical sample had mp 283.5–284° dec. Anal. ($C_{17}H_{13}ClN_4O_2$) C, H, N, Cl.

A mixture of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,-4-triazole-3-carboxaldoxime (2.10 g) added to an ice-cold solution of acetic anhydride (6 ml) in pyridine (30 ml) was stirred at ambient temperature, under nitrogen, for 18 h and then poured into ice water. The solid was filtered, washed with water, dried, and crystallized from chloroform–ethanol mixtures to give 2.05 g of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldehyde *O*-acetyloxime (11b): mp 171–173°. The analytical sample had mp 170–171°. Anal. ($C_{19}H_{16}ClN_4O_3$) C, H, N, Cl.

A 1 M solution of borane in tetrahydrofuran (68 ml) was added to a stirred, ice-cold solution of 4-(2-benzoyl-4-chlorophenyl)-5-methyl-4*H*-1,2,4-triazole-3-carboxaldehyde *O*-acetyloxime (4.34 g, 11.3 mmol) in 170 ml of THF and the resulting solution was stirred under nitrogen, in an ice bath, for 2 h and at ambient temperature for 18 h. This solution was cooled in an ice bath, treated with 6 N HCl (10.2 ml), and extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and extracted with chloroform. The extract was washed with brine, dried over anhydrous potassium carbonate, and concentrated. The residue was crystallized from methanol–ethyl acetate to give 1.49 g of 5-chloro-2-[3-(aminomethyl)-5-methyl-4*H*-1,2,4-triazol-4-yl]benzhydrol (**29**): mp 209–226°. The analytical sample had mp 218–219°.

Procedure F. A stirred suspension of 1.05 g (2.92 mmol) of 8-chloro-2,4-dihydro-2-methyl-6-phenyl-1*H*-*s*-triazolo[4,3-*a*][1,-4]benzodiazepin-1-one[11] hydrochloride in methylene chloride and H_2O was made alkaline with 15% NaOH. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried (K_2CO_3) and concentrated. The residue was dissolved in benzene and the solution was concentrated in vacuo. A solution of this residue in dry CH_2Cl_2 (20 ml) was treated with trimethyloxonium tetrafluoroborate (0.526 g, 3.6 mmol). After 5 min a thick precipitate formed. An additional 10 ml of methylene chloride was added and the mixture was stirred under nitrogen at ambient temperature for 18 h. The solid was filtered, washed with methylene chloride, and suspended in a mixture of methylene chloride and aqueous potassium carbonate. After 10 min of vigorous stirring, a clear organic layer was obtained. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over potassium carbonate, and concentrated. A solution of the residue in ethyl acetate was acidified with methanolic HCl and the salt was crystallized to give 0.64 g of **33**: mp 177–180° dec. The analytical sample had mp 175–177°.

Pharmacology. Methods. Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all studies reported here. Unless otherwise indicated, the test compounds were dissolved or suspended in 0.25% aqueous methylcellulose solution and administered ip to groups of six mice per dose, at multiple dose levels distributed at 0.3 log intervals. Procedures for measuring

the effect of test compounds on traction (Tr), dish (D), nicotine-induced tonic extensor convulsions (TE) and death (D), thiosemicarbazide- and strychnine-induced lethality, and electroshock convulsions have been described previously.[21] The antagonism of pentylenetetrazole-induced clonic convulsions was also described previously.[1a] ED_{50} values were calculated by the method of Spearman and Karber.[22]

Acknowledgment. The authors are indebted to Mr. A. Koning and Mr. W. Friis for laboratory assistance, to Dr. L. Baczynskyj, Ms. B. Zimmer, Mr. Paul Meulman, and Mr. R. C. Anderson for physical and analytical data, and to Mrs. Helen Branch for preparing this manuscript.

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Conversion of *N*-Alkylaminobenzophenones to Benzodiazepines in Vivo

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The results of this study suggest that 5-chloro-2-[3-methyl-5-(dimethylamino)methyltriazol-4-yl]benzophenone can undergo N-dealkylation and ring closure in vivo to form the corresponding benzodiazepine. The in vivo conversion was found to occur in mice, rats, and monkeys. A variety of substituted aminobenzophenone compounds were also able to undergo these conversions. The conversions to benzodiazepines were confirmed by a comparison of retention times on a gas chromatograph as well as through the use of a GC–mass spectrometer. The results obtained did not prove that the *N*-alkylaminobenzophenones were devoid of activity, but they do suggest that their observed pharmacological activity may be due to the formation of the corresponding benzodiazepines.

A new series of benzodiazepines, the triazolobenzodiazepines,[1-3] has been prepared which has many interesting pharmacological properties.[3] During the course of preparing this new series of compounds, a number of aminobenzophenone analogues were prepared which may be considered open ring analogues of these benzodiazepines[4] and were found to possess antimetrazole activity (Table I), a possible indicator of anxiolytic activity.[3] These "open-ring benzodiazepines" were so designated because the imine bond was absent and the molecule contained a carbonyl group and an alkyl-substituted nitrogen (see the last four structures in Table I).

The biological activity of these *N*-alkylaminobenzophenones was of great interest since the possibilities existed that they may be active in their own right, or they may be active by being converted to benzodiazepines of known