may open *in vivo* so that inactivity cannot be assigned to the aziridine *per se*, although the present compounds were unchanged by a 5-hr incubation at 37° in aqueous solution buffered at pH 7.3. The pK_a of Ia (7.2) is little different from that of aziridine itself (8.0) but is somewhat less than that of the more basic amphetamine (9.90[12]). It is possible that this leads to inefficient binding of the title compounds to a receptor because of the reduced availability of the nitrogen lone pair, a condition previously proposed for the reduced activity of the even less basic 2-amino-3-phenyl-1,1,1-trifluoropropanes[4] and 1-cyanophenethylamines.[5]

Experimental Section†

Phenylalaninyl Hydrogen Sulfates. A. To a cold suspension of 4-chlorophenylalaninol (18.3 g, 0.1 mole) in H_2O (30 ml) was added cold concd H_2SO_4 (10 g, 0.1 mole). The light yellow solution was heated at 120° to remove H_2O, the final traces being removed on the rotary evaporator. Recrystallization of the brown residue from 40% aqueous EtOH, with concentration of the mother liquors, gave 19 g (67%) of yellow needles, mp 277–279°. *Anal.* ($C_9H_{12}ClNO_4S \cdot H_2O$) C, H, N.

Phenylalaninyl hydrogen sulfate, obtained in 70% yield by the same procedure, had mp 253–255° (lit.[6] 265–270°). *Anal.* ($C_9H_{13}NO_4S \cdot H_2O$) C, H, N.

B. Dicyclohexylcarbodiimide (24.7 g, 0.12 mole) in DMF (50 ml) was added at 0° to a solution of 4-methoxyphenylalaninol (6.2 g, 0.033 mole) in DMF (60 ml). Concd H_2SO_4 (6 g, 0.0333 mole) in DMF (25 ml) was then added dropwise over 30 min at 0°. The mixture was stirred for 90 min at room temperature, the solid dicyclohexylurea was filtered off, and the filtrate was evaporated to dryness. The residue was washed well with cold water and recrystallized from aqueous EtOH, mp 255–256°, yield 4.4 g (55%). *Anal.* ($C_{10}H_{15}NO_5S$) C, H, N.

2-Benzylaziridine Hydrogen Maleates. A. 2-Benzylaziridine (Ia), bp 68–70° (0.5 mm), was prepared by continuous distillation from a mixture of aqueous NaOH and phenylalaninyl hydrogen sulfate.[6] **2-Benzylaziridine hydrogen maleate** had mp 93–94° (EtOH–Et_2O), yield 56%. *Anal.* ($C_9H_{11}N \cdot C_4H_4O_4$) C, H, N.

B. Typically, 6.5 g of 4-chlorophenylalaninyl hydrogen sulfate and 50 ml of 35% aqueous NaOH were refluxed together for 2 hr. The mixture was cooled, extracted with Et_2O, dried ($MgSO_4$), and distilled as a pale yellow oil, bp 97–98° (0.5 mm). Addition of a saturated ethereal solution of maleic acid gave the **hydrogen maleate** (Ib), which was recrystallized from EtOH–Et_2O as colorless plates, mp 94–95°, yield 3.0 g (42%). *Anal.* ($C_9H_{10}ClN \cdot C_4H_4O_4 \cdot H_2O$) C, H, N. **2-(4-Methoxybenzyl)aziridine hydrogen maleate** (Ic) had mp 96–97° (EtOH–Et_2O), yield 36%. *Anal.* ($C_{10}H_{13}N \cdot C_4H_4O_4$) C, H, N.

Acknowledgments. We thank Messrs. D. A. Buxton, D. M. Green, and A. Muir for the pharmacological data and Mr. D. B. Coult for pK_a determinations.

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†Melting points are uncorrected and were measured in an Electrothermal capillary apparatus. Satisfactory analyses (within ±0.4% of the theoretical values) were obtained for all compounds, which were identified by ir and nmr spectroscopy. pK_a values were determined potentiometrically with a Radiometer Titrograph SBR 2c.

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Central Nervous System Depressants. 10. 1-Carbamoylbenzodiazepines†,[1]

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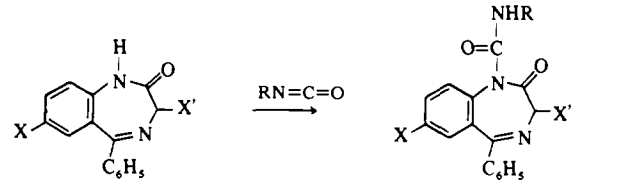
A considerable number of diazepam analogs have been reported in which other groups were substituted for the 1-methyl. In general, any such substituent containing more than 3 carbon atoms has been less active in tests thought to correlate with antianxiety activity.[2] In this work a series of 1-carbamoyl derivatives (1) is reported. These compounds



1

1, X = Cl; X' = H; R = $CH_2CH{=}CH_2$

were prepared by treatment of 1-unsubstituted benzodiazepin-2-one with the appropriate isocyanate. This procedure is exemplified in the Experimental Section by the preparation of **1**, and the compounds are listed in Table I.

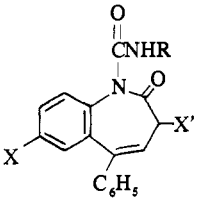
After the start of this work it came to our attention that Usui, *et al.*,[3] had prepared a similar series of benzodiazepine derivatives. However, our series overlapped theirs in only one compound, the methylcarbamoyl analog (**10**). Even though this was one of their more active compounds, our compound **1** proved to be more active in mice on all the parameters used (Table II).

Pharmacology. The pharmacologic results obtained with this series of 1-carbamoylbenzodiazepines are presented in Table II, and the results are compared to those obtained with diazepam in the same test systems. Compound 1, the allylcarbamoyl analog, was the most active compound in this series. It was equipotent or more active than diazepam on all end points except the antagonism of pentylenetetrazol-induced clonic convulsions and the potentiation of ethanol narcosis. The activity of the allyl derivative (**1**) in the traction and strychnine tests may indicate potent muscle relaxant activity.

Substitution of a cyano group for a chloro group in position 7 (**2**) markedly decreased the pharmacologic activity. Compound **2** was inactive in antagonizing strychnine lethality and pentylenetetrazol-induced clonic convulsions and on all other end points it was weakly active. Substitution of a cyano group (RO5-4528) for the chloro group in the diazepam series produced a compound more potent on almost all test systems except the simple reflex tests (chimney, dish, and pedestal) and antagonism of pentylenetetrazol-induced seizures. It appears therefore that the structure-activity relationships for the 1-carbamoylbenzodiazepines may be different from those established for the 1-methyl derivatives.

†Presented in part at the Sixth Great Lakes Regional Meeting of the American Chemical Society, Houghton, Mich., June 22, 1972.

Table I. 1-Carbamoylbenzodiazepines



No.	X	X'	R	Cryst solvent	Yield,[a] %	Mp,[b] °C	Empirical formula and analyses[c]
1	Cl	H	$CH_2CH=CH_2$	*i*-PrOH	88.6	103–105	$C_{19}H_{16}ClN_3O_2$
2	C≡N	H	$CH_2CH=CH_2$	*i*-PrOH	75	137.5–139	$C_{20}H_{16}N_4O_2$
3	Cl	H	$CH_2CH=CHCH_3$[d]	C_6H_{12}	23	114–116	$C_{20}H_{18}ClN_3O_2$
4	Cl	H	$CHCH_2CH_2$[e]	CH_2Cl_2–C_6H_{12}	32	213.5–214.5[e]	$C_{19}H_{16}ClN_3O_2$
5	Cl	H	$CH(CH_2)_4CH_2$	*i*-PrOH	46	134.5–136	$C_{22}H_{22}ClN_3O_2$
6	Cl	H	CH_2CH_2Cl	*i*-PrOH	80	110–113	$C_{18}H_{15}Cl_2N_3O_2$
7	Cl	H	CH_2COOEt	*i*-PrOH	79	125–127.5	$C_{20}H_{18}ClN_3O_4$
8	Cl	$OCOCH_3$	CH_3	EtCOMe	81.5	170–171	$C_{19}H_{16}ClN_3O_4$
9	Cl	$OCONHCH_3$	CH_3	*i*-PrOH	70	174–175	$C_{19}H_{17}ClN_4O_4$
10	Cl	H	CH_3[f]	Et_2O	90	147.5–148.5[f]	$C_{17}H_{14}ClN_3O_2$

[a] Yields are calculated on material melting not less than 2° below the highest mp obtained. [b] See footnote ‡. [c] All these benzodiazepines were analyzed for C, H, N, and Cl (except 2). See footnote ‡. [d] The crude product was purified by column chromatograph on SiO_2 and eluted with 5% MeOH in PhH. The appropriate fractions were combined, evaporated, and repeatedly fractionally crystallized from cyclohexane. [e] The crude product was purified by column chromatography on SiO_2 and eluted with 1% MeOH in $CHCl_3$. The appropriate fractions were combined, evaporated, and crystallized first from cyclohexane, then from *i*-PrOH, and finally from a mixture of CH_2Cl_2 and cyclohexane. The product exhibited a double mp, first melting at 144–145°, resolidifying at 146–148° and then melting at 213.5–214.5°. [f] Usui, *et al.*,[3] report mp 150°.

Table II. Pharmacology[a]

No.	Tr_{50}[b]	Ch_{50}[b]	D_{50}[b]	P_{50}[b]	Nicotine (TE) antag[b]	Thiosemicarbazide antag[c]	Strychnine antag[c]	Electroshock antag[d]	Pentylenetetrazol antag[d]	EtOH potentiation[e]
1	2.8	0.8	0.8	0.8	0.2	1.1	9.0	23	1.6	2.0
2	50	16	6.3	9.0	4.5	4.0	>50		>25	12
3	10	3.1	2.0	4.0	1.6	2.0	13	>100	3.2	
4	20	7.0	2.8	7.0	2.8	3.1	40	200	18	20
5	>100	71	56	89	45	>25	>50		>25	>100
6	16	>6.3	3.5	4.0	0.3	2.5	11	>50	2.8	2.3
7	45	6.0	9.0	10	3.0	2.8	>50	>50	10	7.0
8	112	36	13	15	4.0	25	>50	>50	28	>100
9	>200	45	45	71	126					
10[f]	11	4.5	3.1	>6.3	1.1	2.0	32	>50	2.2	2.8
Diazepam[g]	7	2.0	0.7	1.3	0.28	0.7	8.0	50	0.8	0.9
RO5-4528[g,h]	3.6	2.0	0.8	1.1	0.06	0.15	5.6	28	1.6	0.4

[a] Carworth Farms male, albino mice (CF-1), weighing 18–22 g, were used for all studies reported here. The test compounds were dissolved or suspended in 0.25% aqueous methylcellulose soln and administered ip. Values are ED_{50}'s expressed in mg/kg. [b] Procedures for measuring the effects of the compound on overt behavior, traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), pedestal (P_{50}), and antagonism of nicotine-induced tonic extensor convulsions (TE) have been described previously.[6] [c] Procedures for the antagonism of thiosemicarbazide (TSC), electroshock convulsions, and strychnine lethality have been described.[7] [d] Procedures for measuring antagonism of pentylenetetrazole-induced convulsions have been described.[8] [e] Procedures for measuring potentiation of ethanol narcosis have been described.[9] [f] See ref 3. [g] The authors thank Hoffman-LaRoche Inc. for a sample. [h] 2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-7-carbonitrile.

Extending the length of the side chain from allyl (**1**) to crotyl (**3**) decreased the activity of the compound in all test systems. Substitution of cyclopropyl (**4**) or cyclohexyl (**5**) in place of the allyl group also markedly decreased the activity.

Two other compunds in this series had potent central nervous system depressant activity. These were the compounds where R was either CH_2CH_2Cl (**6**) or CH_3 (**10**). However, both of these compounds were less active than the allyl derivatives (**1**). Compound **6**, although much weaker than the allyl derivative (**1**) on simple reflexes and strychnine end points, approached the allyl derivative in potency on anticonvulsant end points (nicotine, thiosemicarbazide, and pentylenetetrazol antagonism) and also in its ability to potentiate ethanol narcosis. Thus, compound **6** may be an active anticonvulsant with weak effects as a muscle relaxant or CNS depressant. Compound **10** was also much more active on anticonvulsant end points than on those measuring CNS depression.

It appears from this small series of compounds that 1-carbamoylbenzodiazepines possess potent CNS depressant and anticonvulsant activity. They may have a different structure–activity relationship pattern than do 1-methyl-substituted benzodiazepines. The substantiation of this hypothesis requires the testing of more 7-substituted derivatives and also the effect of substitution on the 5-phenyl ring of the molecule.

Experimental Section‡

N-Allyl-7-chloro-2,3-dihydro-2-oxo-5-phenyl-1*H*-1,4-benzodiazepine-1-carboxamide (**1**). A mixture of 16.26 g (0.06 mole) of

‡ Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir (Nujol mull), usually nmr (in DMSO-d_6 or $CDCl_3$), and often mass spectra were obtained on pure compounds and were in accordance with the proposed structure. Where analyses were indicated only by symbols of the elements of functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical.

7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one, 125 ml of THF, and 45 ml of allyl isocyanate (added 25 ml at start and 10 ml after 1 and after 3 days) was stirred under N_2 and under reflux for 5 days. The reaction was followed by tlc (on SiO_2, with 5% MeOH in $CHCl_3$). The mixture was filtered and evaporated *in vacuo*. $PhCH_3$ was added and evaporated to remove excess isocyanate, and the resulting gum was crystallized from 250 ml of *i*-PrOH. Thus 18.8 g (88.6%) of white fluffy needles was obtained, mp 103–105°.

Crotyl Isocyanate. To a suspension of 41.54 g (0.256 mole) of 1,1'-carbonyldiimidazole in 100 ml of CH_2Cl_2 was slowly added, with stirring during 0.5 hr at 25°, 18.0 g (0.256 mole) of crotylamine. After standing overnight, the solution was slowly distilled through an 18-cm, glass-helices-packed, column. After removing the CH_2Cl_2, a fraction boiling at 45–46° (56 mm) was collected. This was redistilled at atmospheric pressure yielding 9.7 g (39.9%) of colorless liquid, bp 113°. Ir and nmr support the structure, and gc indicates it was greater than 94.7% pure. Christophersen and Holm[4] report bp 116°.

Cyclopropyl Isocyanate. A suspension of 35.8 g (0.55 mole) of NaN_3 in 200 ml of triethylene glycol dimethyl ether in a 1-l. flask fitted with a stirrer, thermometer, dropping funnel, and a Vigreux column to which was attached a Dry Ice cooled, two-necked flask was cooled to 5°, and 52.25 g (0.5 mole) of cyclopropylcarbonyl chloride was slowly added under N_2 during 10 min. After stirring at 0–25° for 1 hr, the mixture was slowly heated in a water bath. At about 55° N_2 started to come off and it was evolved rapidly at 70–103°. The flask was then heated in an oil bath up to 171°, and the product was distilled at 56 mm. Solvent refluxed in the bottom of the column. The distillate was redistilled through an 18-cm, glass-helices-packed column giving 25.67 g (62%) of colorless liquid, bp 87° (atm), $n^{26}D$ 1.4210; d_4^{25} 1.00. Jones and Scott[5] apparently prepared this but did not isolate or characterize it.

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Derivatives of Indole-1-acetic Acid as Antiinflammatory Agents

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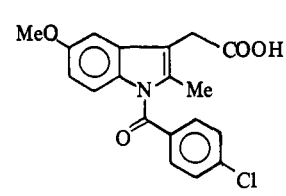
In view of the activity of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (1, Indomethacin) as an antiinflammatory agent, a study of molecular models showed **2** to be spatially similar to Indomethacin (1). The related isomer **3** was sufficiently similar to merit investigation also.



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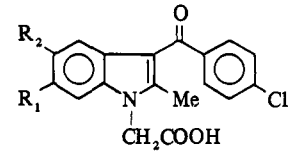
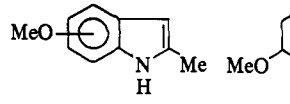


2, R_1 = MeO; R_2 = H
3, R_1 = H; R_2 = MeO

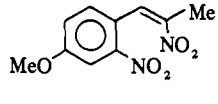
The publication of **2**[1] prompts us to report our findings in this area.

Results and Discussion

Preparation of **2** and **3** proceeded by similar routes, but for **2** the indole **4a** was required. This was prepared by catalytic hydrogenation of **5**.

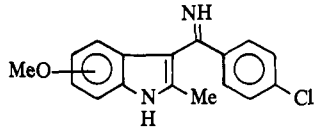


4a, 6-MeO
4b, 5-MeO

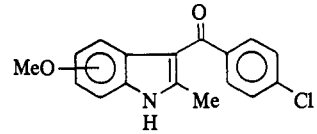


5

The general synthetic pathway involved the condensation of *p*-chlorobenzonitrile with **4a** or **4b** to yield the imines **6a** and **6b**, respectively. It was anticipated that the imines would readily hydrolyze to the corresponding ketones **7a** and **7b**, but this was not the case.



6a, 6-MeO
6b, 5-MeO

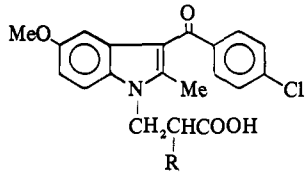


7a, 6-MeO
7b, 5-MeO

Alkylation of **6a** or **6b** with ethyl bromoacetate in acetone in the presence of anhydrous K_2CO_3 proceeded smoothly, and alkaline hydrolysis (3 *N* NaOH) of the intermediate esters gave the desired products **2** and **3**.

A comparison of the pK_{mcs} and distribution coefficients indicated that **2** and **3** are significantly more acidic than Indomethacin (**1**), as can be seen from Table I.

In order to obtain molecules with acidity similar to indomethacin (**1**), the corresponding 1-propionic and 1-isobutyric acid derivatives **8** and **9** were prepared by the con-



8, R = H
9, R = Me

densation of **6b** with methyl acrylate and methyl methacrylate, respectively, followed by alkaline hydrolysis of the intermediate esters. As can be seen from Table I, the acidity of these compounds now approximates that of **1**.

Table I

Compound	pK_{mcs}	*P* ($CHCl_3$–aqueous buffer, pH 6.9)
1	6.45	37.2
2	4.97	0.13
3	5.00	0.13
8	6.08	11.9
9	6.26	60.0