at room temperature for 19 hr. and was then treated with 1 ml. of water, 3.48 g. of amylamine, and 500 ml. of ether. The gummy crystalline precipitate was washed with ether (decantation) and then recrystallized from ethanol; yield 2.5 g. (65%), m.p. 184–185°. The crystalline product gave a negative ferric chloride test for the free phenolic group.

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.92; H, 4.87; N, 5.25. Found: C, 53.65; H, 4.90; N, 5.47.

N-Phthalyl(3-carboxy-4-methoxyphenyl)alanine.—A mixture of 12.0 g. (0.046 mole) of 3-carboxy-4-methoxyphenylalanine, 7.5 g. (0.051 mole) of phthalic anhydride, and 75 ml. of dry pyridine was refluxed for 1.5 hr. with the exclusion of moisture and concentrated *in vacuo*, and the residue was dissolved in 30 ml. of acetic anhydride. The resulting solution was refluxed for 10 min., cooled, poured onto 300 g. of ice, and stored overnight in a refrigerator. The precipitate was filtered off and recrystallized from 75 ml. of ethyl acetate; yield 13.8 g. (69%). The purified product melted first at 170–171°, solidified, and remelted at 218–219°.

Anal. Calcd. for $C_{19}H_{15}NO_7$: C, 61.77; H, 4.09; N, 3.79. Found: C, 61.87; H, 4.41; N, 4.01.

L-N-Phthalyl-3-carboxy-4-methoxyphenylalanine Brucine Salt.—A solution of N-phthalyl-3-carboxy-4-methoxyphenylalanine brucine salt obtained by dissolving 50.2 g. (0.136 mole) of N-phthalyl-3-carboxy-4-methoxyphenylalanine and 53.8 g. (0.136 mole) of brucine in 735 ml. of near-boiling 60% ethanol was allowed to cool slowly to room temperature overnight. The precipitate of colorless needles was filtered off [yield 45 g. (87%), m.p. 167–172°, $[\alpha]^{25}D$ −86.3° (0.200 g. in 10 ml. of 60% ethanol)] and recrystallized from 250 ml. of 60% ethanol; yield 39 g. (74.4%), m.p. 167–172°, $[\alpha]^{25}D$ −114.3° (0.194 g. in 10.00 ml. of 60% ethanol).

Anal. Calcd. for $C_{42}H_{21}N_3O_{11}\cdot 2H_2O$: C, 63.04; H, 5.56; N, 5.25. Found: C, 63.05; H, 5.69; N, 5.47.

L-N-Phthalyl-3-carboxy-4-methoxyphenylalanine.—A suspension of 63.5 g. (0.0795 mole) of L-N-phthalyl-3-carboxy-4-methoxyphenylalanine brucine salt was made basic with 160 ml. of 1 *N* NaOH, stirred for 0.5 hr. at room temperature, and filtered. The filtrate was extracted 7 times with 150-ml. portions of chloroform until it gave a negative test for brucine and then acidified with 170 ml. of 1 *N* HCl. The precipitate (29.1 g., 94%) which formed in the mixture on standing overnight in the refrigerator melted at 133–134° and had $[\alpha]^{25}D$ −206° (0.0601 g. in 3.00 ml. of ethanol). It was recrystallized several times from a mixture of ethyl acetate and cyclohexane with no change in optical rotation.

Anal. Calcd. for $C_{19}H_{15}NO_7$: C, 61.77; H, 4.09; N, 3.79. Found: C, 62.77; H, 4.00; N, 4.50.

L-3-Carboxy-4-methoxyphenylalanine.—A suspension of 24 g. (0.065 mole) of L-N-phthalyl-3-carboxy-4-methoxyphenylalanine in 1.68 l. of approximately 1 *N* HCl was refluxed for 24 hr. and then concentrated *in vacuo* to a small volume. *o*-Phthalic acid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was dissolved in water and the solution again was concentrated to dryness *in vacuo*. This was repeated several times to ensure complete removal of excess HCl. The residue was dissolved in water and treated with 9 g. of Ag_2CO_3. The precipitate of AgCl was filtered off, the filtrate was treated with H_2S, filtered, and concentrated *in vacuo*. Benzene was added to the residue and the remaining water was removed by azeotropic distillation. The solid residue was leached several times with hot purified dioxane and dried; yield 12.06 g. (78%), m.p. 91° (partially melted), 236–238° dec., $[\alpha]^{25}D$ −17.9° (0.00983 g. in 1.00 ml. of water). After recrystallization from acetonitrile–water, the preparation had $[\alpha]^{25}D$ −19.1° (2.62 mg. in 1.00 ml. of water), $[\alpha]^{25}D$ −1.81° (2.21 mg. in 1 ml. of 1 *N* HCl), and the same melting point as the crude material. The more positive rotation of the product in 1 *N* HCl suggests an L-configuration in accordance with the rule of Lutz and Jirgensons.[17]

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48; N, 5.86. Found: C, 54.98; H, 5.59; N, 5.76.

Acknowledgment.—We wish to express our appreciation to Drs. F. Häfliger, M. Weiner, and P. Greengard, each of whom arranged some of the biological studies reported in this paper.

(17) O. Lutz and B. Jirgensons, *Ber.*, **63**, 448 (1930); **64**, 1221 (1931).

Quinazolines and 1,4-Benzodiazepines. XXV.[1] Structure–Activity Relationships of Aminoalkyl-Substituted 1,4-Benzodiazepin-2-ones

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The syntheses of a number of 1,3-dihydro- and 1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-ones, having basic (aminoalkyl) side chains in positions 1 or 4, are described. The acute toxicities of these compounds were determined and the compounds were screened for sedative, muscle relaxant, taming, and anticonvulsant effects in mice, and for sedative and muscle relaxant activity in cats. Many of these benzodiazepinones showed central nervous system activity qualitatively similar to that of chlordiazepoxide. Optimal activity was observed in compounds having a 2-fluorophenyl substituent in position 5. The tetrahydrobenzodiazepinones showed significantly less CNS activity than the corresponding dihydro compounds.

In continuation of our studies of psychopharmacologically active 1,4-benzodiazepines, we have prepared the compounds listed in Tables I and II by four methods.

Alkylation of 1,3-dihydro-2H-1,4-benzodiazepin-2-ones with sodium methoxide and various aminoalkyl halides (method A) gave the 1-substituted benzodiazepin-2-ones listed in Table I. An alternative route (method B) was found useful in cases where the necessary aminoalkyl halide was not available. Alkylation of 1,4-benzodiazepin-2-ones with 1-bromo-3-chloropropane gave compounds of type II, which readily underwent nucleophilic replacement of chlorine by amines.[2]

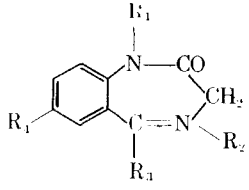
The tetrahydrobenzodiazepinones (Table II) were made either by alkylation of 1,3,4,5-tetrahydrobenzo-

(1) Paper XXIV: W. Metlesics, R. Tavares, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1311 (1965).

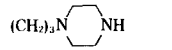
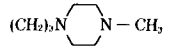
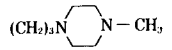
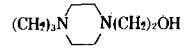
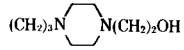
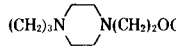
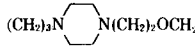
(2) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, **82**, 2039 (1960).

TABLE I

1-AMINOALKYL-1,3-DIHYDRO-2H-1,4-BENZODIAZEPIN-2-ONES



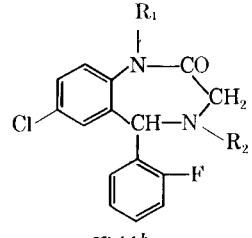
Compd.	R_1	R_2	R_3	R_7	Method	Recrystn. solvent[a]	M.p., °C	Yield,[b] %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	$(CH_2)_2N(CH_3)_2$		C_6H_5	Cl	A	Et–H	96–98	25	$C_{19}H_{20}ClN_3O$	66.76	5.90	12.29	66.39	5.69	12.11
2	$(CH_2)_2N(CH_3)_2$		C_6H_5	NO_2	A	Et–Pet	121–122	44	$C_{19}H_{20}N_4O_3$	64.76	5.72		65.08	5.82	
3	$(CH_2)_2N(CH_3)_2$		C_6H_5	NO_2	A	M–Et	232–233 dec.	40	$C_{19}H_{20}N_4O_3 \cdot 2HCl$	53.65	5.21		53.96	5.08	
4	$(CH_2)_2N(CH_3)_2$		C_6H_5	CF_3	A	M–Et	217–221	52	$C_{20}H_{20}F_3N_3O \cdot 2HCl$	53.58	4.94		53.71	5.17	
5	$(CH_2)_2N(CH_3)_2$	O	C_6H_5	Cl	A	Ac–Pet	146–147	64	$C_{19}H_{20}ClN_3O_2$	63.77	5.63		64.03	5.23	
6	$(CH_2)_2N(CH_3)_2$[c]	O	C_6H_5	Cl	A	Al–Et	217–218	58	$C_{19}H_{20}ClN_3O_2 \cdot HCl$	57.87	5.37		58.33	5.22	
7	$CH(CH_3)CH_2N(CH_3)_2$		C_6H_5	Cl	A	H	134–135	55	$C_{20}H_{22}ClN_3O$	67.50	6.23	11.81	67.44	5.98	11.73
8	$CH(CH_3)CH_2N(CH_3)_2$		C_6H_5	Cl	A	I–Et	165–168 dec.	50	$C_{20}H_{22}ClN_3O \cdot 2HCl$	56.02	5.64		56.42	6.12	
9	$(CH_2)_2N(C_2H_5)_2$		C_6H_5	Cl	A	P	79–81	46	$C_{21}H_{24}ClN_3O$	68.18	6.54	11.37	68.26	6.77	11.22
10	$(CH_2)_2N(C_2H_5)_2$	O	C_6H_5	Cl	A	Et	121–122	32	$C_{21}H_{24}ClN_3O_2$	65.36	6.27		65.32	5.98	
11	$(CH_2)_2N(C_2H_5)_2$		o-ClC_6H_4	Cl	A	H	68–70	35	$C_{21}H_{23}Cl_2N_3O$	62.38	5.73	10.39	62.54	5.94	10.23
12	$(CH_2)_2N(C_2H_5)_2$		o-FC_6H_4	Cl	A	M–Et	190–220	43	$C_{23}H_{23}ClFN_3O \cdot 2HCl$	54.73	5.47		54.79	5.61	
13	$(CH_2)_2N(C_2H_5)_2$		2-Pyridyl	Br	A	M–Et	176–180 dec.	50	$C_{20}H_{23}BrN_4O \cdot HCl$	53.16	5.35		53.18	5.14	
14	$(CH_2)_2$–N⟨ ⟩		C_6H_5	Cl	A	H	106–107	88	$C_{21}H_{22}ClN_3O$	68.56	6.03	11.42	68.75	5.90	11.31
15	$(CH_2)_2$–N⟨ ⟩		C_6H_5	Cl	A	Ac	157–159	79	$C_{21}H_{22}ClN_3O \cdot C_4H_4O_4$	62.04	5.41	8.68	62.43	5.37	8.81
16	$(CH_2)_2$–N⟨ ⟩		C_6H_5	Cl	A	H	90–92	90	$C_{22}H_{21}ClN_3O$	69.19	6.33	11.00	69.19	5.95	10.92
17	$(CH_2)_2$–N⟨ ⟩		C_6H_5	Cl	A	Ac	172–173	81	$C_{22}H_{21}ClN_3O \cdot C_4H_4O_4$	62.70	5.67	8.44	62.87	5.85	8.40
18	$(CH_2)_2$–N⟨ ⟩NH		C_6H_5	Cl	A	Ac	172–178 dec.	69	$C_{21}H_{23}ClN_4O \cdot 2C_4H_4O_4$	56.62	5.08	9.11	56.68	5.19	8.95
19	$(CH_2)_2$–N⟨ ⟩O		C_6H_5	Cl	A	Ac–H	144–146	83	$C_{21}H_{22}ClN_3O_2$	65.70	5.78	10.94	65.65	5.78	11.17
20	$(CH_2)_2$–N⟨ ⟩O		C_6H_5	Cl	A	Ac	156–157	79	$C_{21}H_{22}ClN_3O_2 \cdot C_4H_4O_4$	60.05	5.24	8.40	60.60	5.32	8.30
21	$(CH_2)_2$–N⟨ ⟩N–CH_3		C_6H_5	Cl	A	Ac–H	159–160	66	$C_{22}H_{25}ClN_4O$	66.56	6.35		66.58	6.33	
22	$(CH_2)_2$–N⟨ ⟩N–CH_3		C_6H_5	Cl	A	M–H	158–160	59	$C_{22}H_{25}ClN_4O \cdot 2C_4H_4O_4$	57.27	5.29	8.91	57.38	5.38	8.87
23	$(CH_2)_2$–N⟨ ⟩N–CH_3		o-FC_6H_4	Cl	A	M–Et	225–234	37	$C_{22}H_{21}ClFN_3O \cdot 3HCl$	50.40	5.19		50.19	5.16	
24	$(CH_2)_3NHCH_3$		o-FC_6H_4	Cl	B	M–Et	193–196 dec.	86	$C_{19}H_{19}ClFN_3O \cdot 2HCl$	52.73	4.89		53.54	5.36	
25	$(CH_2)_3N(CH_3)_2$		C_6H_5	Cl	A	H	90–92	64	$C_{20}H_{22}ClN_3O$	67.50	6.23	11.81	67.80	6.22	11.78
26	$(CH_2)_3N(CH_3)_2$		C_6H_5	NO_2	A	Al	192–193 dec.	60	$C_{20}H_{22}N_4O_3 \cdot HCl$	59.62	5.75		59.58	5.99	

27	$(CH_2)_3N(CH_3)_2$	*o*-FC_6H_4	Cl	A	M–Et	180–200 dec.	61	$C_{20}H_{21}ClFN_3O\cdot 2HCl$	53.77	5.19		53.56	4.80		
28	$(CH_2)_3N(CH_3)_2$	2-Pyridyl	Br	A	M–Et	181–183 dec.	48	$C_{19}H_{21}BrN_4O\cdot 2HCl$	48.12	4.89		48.12	5.54		
29	$(CH_2)_3N(C_2H_5)_2$	C_6H_5	Cl	A + B	H	89–91	61	$C_{22}H_{26}ClN_3O$	68.83	6.83		69.01	7.03		
30	$(CH_2)_3N(C_2H_5)_2$	C_6H_5	Cl	A + B	Al–Ac–Et	208–210	85	$C_{22}H_{26}ClN_3O\cdot 2HCl$	57.84	6.18		58.09	6.14		
31	$(CH_2)_3N(C_2H_5)_2$	*o*-FC_6H_4	Cl	A	Al–Et	182–192 dec.	86	$C_{22}H_{25}ClFN_3O\cdot 2HCl$	56.99	5.79	8.85	56.89	5.57	8.72	
32		*o*-FC_6H_4	Cl	B	M–Et	235–255	78	$C_{22}H_{21}ClFN_4O\cdot HCl$	58.44	5.58		58.67	5.62		
33		C_6H_5	Cl	B	M	180–182	80	$C_{23}H_{27}ClN_4O\cdot 2C_4H_4O_4$	57.90	5.49	8.71	58.21	5.74	8.77	
34		*o*-FC_6H_4	Cl	B	M	185–187	78	$C_{23}H_{26}ClFN_4O\cdot 2C_4H_4O_4$	56.32	5.18		56.17	5.24		
35		C_6H_5	Cl	B	Ac	121–123	79	$C_{21}H_{29}ClN_4O_2\cdot 2C_4H_4O_4$	57.10	5.54	8.32	57.14	5.76	8.01	
36		*o*-FC_6H_4	Cl	B	Ac	120–123	51	$C_{27}H_{28}ClFN_4O_2\cdot 2C_4H_4O_4$	55.61	5.25		55.63	5.51		
37		*o*-FC_6H_4	Cl	B	Ac	115–122	15	$C_{26}H_{30}ClFN_4O_2\cdot 2C_4H_4O_4$	56.94	5.30		57.37	5.58		
38		*o*-FC_6H_4	Cl	B	Ac	125–133	24	$C_{26}H_{32}ClFN_4O_2\cdot 3C_4H_4O_4$	57.54	5.59		57.80	5.51		

[a] Ac = acetone, Al = ethyl alcohol, Et = ether, H = hexane, I = isopropyl alcohol, M = methanol, P = pentane, Pet = petroleum ether (b.p. 30–60°). [b] Values obtained are from a single experiment; no attempts have been made to obtain optimal yields. [c] During the course of our work, a publication by Bell, *et al.*,[14] reported the synthesis of this compound (lit.[14] m.p. 211–212°), in 10% yield, by an analogous method.

TABLE II

SUBSTITUTED 7-CHLORO-5-(2-FLUOROPHENYL)-1,3,4,5-TETRAHYDRO-2H-1,4-BENZODIAZEPIN-2-ONES

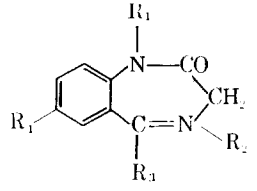


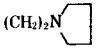
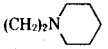
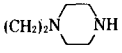
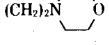
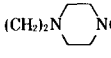
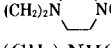
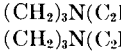
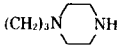
Compd.	R_1	R_2	Method	Recrystn. solvent[a]	M.p., °C.	Yield,[b] %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
39	CH_3	$(CH_2)_2N(C_2H_5)_2$	C	Ac–Et	186–193	30	$C_{22}H_{27}ClFN_3O\cdot HCl$	60.00	6.41		59.88	6.32	
40	$(CH_2)_2N(C_2H_5)_2$	H	D	Et–P	98–99	72	$C_{21}H_{25}ClFN_3O$	64.69	6.46		64.75	6.53	
41	$(CH_2)_2N(C_2H_5)_2$	H	D	M–Et	175–190	72	$C_{21}H_{25}ClFN_3O\cdot 2HCl$	54.50	5.88		53.74	6.52	
42	$(CH_2)_2N(C_2H_5)_2$	CH_3	A	P	83–85	78	$C_{22}H_{27}ClFN_3O$	65.42	6.74		65.63	7.02	
43	$(CH_2)_3NHCH_3$	H	D	M–Et	230–235 dec.	73	$C_{19}H_{21}ClFN_3O\cdot 2HCl\cdot H_2O$	50.40	5.56	9.28	50.46	6.02	9.72
44	$(CH_2)_3N(CH_3)_2$	H	D	M–Et	186–200	85	$C_{20}H_{23}ClFN_3O\cdot 2HCl$	53.52	5.61		53.40	6.03	
45	$(CH_2)_3N(C_2H_5)_2$	H	D	M–Et	237–242 dec.	70	$C_{22}H_{27}ClFN_3O\cdot 2HCl$	55.40	6.13	8.81	55.44	6.07	8.66

[a] Ac = acetone, Et = ether, P = pentane, M = methanol. [b] Values obtained are from single experiments; no attempts have been made to obtain optimal yields.

TABLE III

PHARMACOLOGICAL ACTIVITY OF 1-AMINOALKYL-1,3-DIHYDRO-2H-1,4-BENZODIAZEPIN-2-ONES



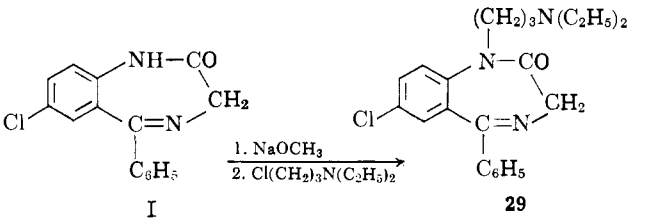
Compd.	R_1	R_2	R_3	Muscle relaxant and taming activity (mice) —ED_{50}, mg./kg. *p.o.*— Inclined screen	Fighting	Behavior (cat) MED, mg./kg. *p.o.*	Anticonvulsant activity (mice) ED_{50}, mg./kg. *p.o.* — Antipentylene-tetrazole	Antimax. shock	Antimin. shock	Acute toxicity (mice) LD_{50}, mg./kg. i.p.
1	$(CH_2)_2N(CH_3)_2$	C_6H_5	Cl	250	100	5	6.3	35	264	>400
3	$(CH_2)_2N(CH_3)_2$	C_6H_5	NO_2	150	20	0.5	7.1	200	88.1	>400
4	$(CH_2)_2N(CH_3)_2$	C_6H_5	CF_3	50	20	20	6.5	22	75	280
5[a]	$(CH_2)_2N(CH_3)_2$	C_6H_5	Cl	400	>100	10	17	265	>800	>400
8	$CH(CH_3)CH_2N(CH_3)_2$	C_6H_5	Cl	500	>100	>20	5	48	100	310
9	$(CH_2)_2N(C_2H_5)_2$	C_6H_5	Cl	300	100	5	3.2	50	350	>400
11	$(CH_2)_2N(C_2H_5)_2$	o-ClC_6H_4	Cl	475	100	10	22	150	440	
12	$(CH_2)_2N(C_2H_5)_2$	o-FC_6H_4	Cl	200	20	2	1.6	83	75	290
13	$(CH_2)_2N(C_2H_5)_2$	2-Pyridyl	Br	90	20	2	3	300	>400	296
15		C_6H_5	Cl	250	>100	>20	>400	133	>400	177
17		C_6H_5	Cl	250	>100	>20	15	150	800	191
18		C_6H_5	Cl	300	100	>20	21	334	>800	145
20		C_6H_5	Cl	300	>100	10	8.9	86	527	358
22		C_6H_5	Cl	350	>100	10	8.4	150	400	>400
23		o-FC_6H_4	Cl	200	40	2	9.7	200	>400	210
24	$(CH_2)_3NHCH_3$	o-FC_6H_4	Cl	300	100	1.0	7.5	300	>400	270
25	$(CH_2)_3N(CH_3)_2$	C_6H_5	Cl	350	>100	>50	150	>800	>800	230
26	$(CH_2)_3N(CH_3)_2$	C_6H_5	NO_2	165	40	10	18.8	400	334	362
27	$(CH_2)_3N(CH_3)_2$	o-FC_6H_4	Cl	300	80	2.5	6.5	334	>800	265
28	$(CH_2)_3N(CH_3)_2$	2-Pyridyl	Br	400	>100	20	73	400	>800	345
30	$(CH_2)_3N(C_2H_5)_2$	C_6H_5	Cl	400	100	>10	300	>400		205
31	$(CH_2)_3N(C_2H_5)_2$	o-FC_6H_4	Cl	200	100	2	35	333	400	179
32		o-FC_6H_4	Cl	225	>100	20	75	>100	>100	100
33		C_6H_5	Cl	400	>100	>10	78	266	>400	315

Compd.	R_1	R_3	R_4	Muscle relaxant and taming activity (mice) ED_{50}, mg./kg. p.o. Inclined screen	Fighting	Behavior (cat) MED, mg./kg. p.o.	Anticonvulsant activity (mice) ED_{50}, mg./kg. p.o. Antipentylenetetrazole	Antimax. shock	Antimin. scork	Acute toxicity (mice) LD_{50}, mg./kg. i.p.
34	$(CH_2)_3N(CH_3)_2$	*o*-FC_6H_4	Cl	125	80	>10	16	175	>200	126
35	$(CH_2)_3N(CH_2)_2OH$	C_6H_5	Cl	450	>100	>10	52	300	>800	>400
36	$(CH_2)_3N(CH_2)_2OH$	*o*-FC_6H_4	Cl	100	>100	>20	14	200	352	165
37	$(CH_2)_3N(CH_2)_2OCH{=}CH_2$	*o*-FC_6H_4	Cl	200	60	5	16	400	400	284
38	$(CH_2)_3N(CH_2)_2OCH_2CH_3$	*o*-FC_6H_4	Cl	200	40	2.5	3.4	309	>400	187
Chlordiazepoxide (Librium®)				100	40	10	18	92	150	268
Diazepam (Valium®)				25	10	1	2	12	27	220

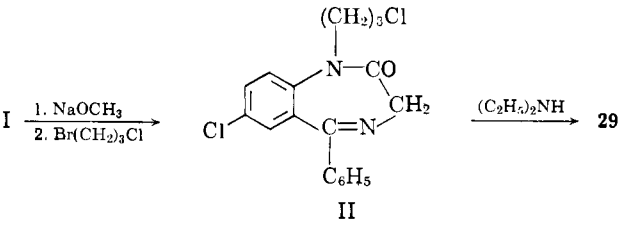
[a] R_2 = O.

diazepinones (method C) or by catalytic reduction of the corresponding dihydro compounds (method D).

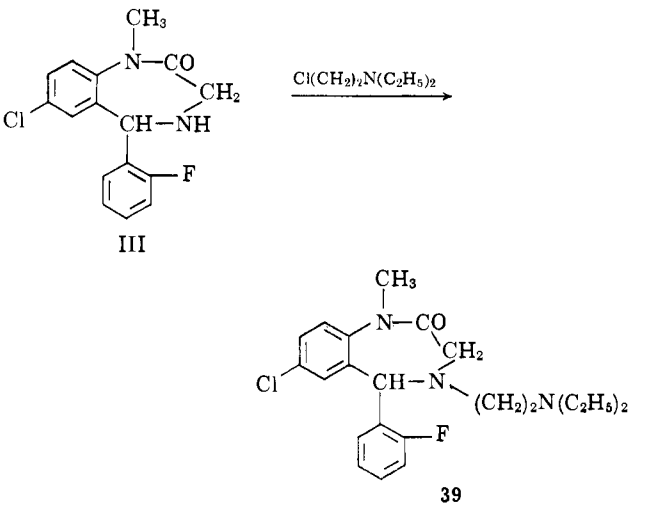
method A



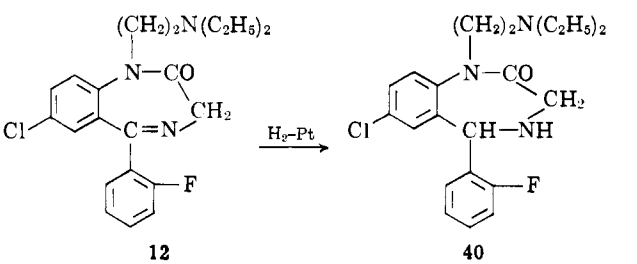
method B



method C



method D



Pharmacology.—The central nervous system effects of the compounds contained in this paper are given in Tables III and IV. The compounds were screened for sedative, muscle relaxant, taming, anticonvulsant, and lethal effects in mice and for sedative and muscle relaxant effects in cats.

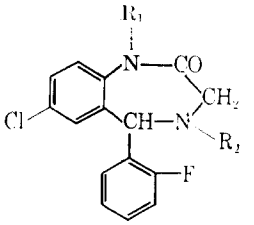
Structure–Activity Relationships.—In the screening tests which were used for measurement of central nervous system effects, chlordiazepoxide and diazepam had the activities recorded in Table III.[3]

Many of the aminoalkyl-substituted benzodiazepinones described in the present report had many of the

(3) (a) L. O. Randall, W. Schallek, G. A. Heise, E. F. Keith, and R. E. Bagdon, *J. Pharmacol. Exptl. Therap.*, **129**, 163 (1960); (b) L. O. Randall, G. A. Heise, W. Schallek, R. E. Bagdon, R. Banziger, A. Boris, R. A. Moe, and W. B. Abrams, *Current Therap. Res.*, **3**, 405 (1961).

TABLE IV

PHARMACOLOGICAL ACTIVITY OF SUBSTITUTED 7-CHLORO-5-(2-FLUOROPHENYL)-1,3,4,5-TETRAHYDRO-2H-1,4-BENZODIAZEPIN-2-ONES



Compd.	R_1	R_2	Muscle relaxant and taming activity (mice) ED_{50}, mg./kg. *p.o.* Inclined screen	Fighting	Behavior (cat) MED, mg./kg. *p.o.*	Anticonvulsant activity (mice) ED_{50}, mg./kg. *p.o.* Antipentylene-tetrazole	Antimax. shock	Antimin. shock	Acute toxicity (mice) LD_{50}, mg./kg. i.p.
39	CH_3	$(CH_2)_2N(C_2H_5)_2$	>50	>50	>10	100	200	>200	>400
40	$(CH_2)_2N(C_2H_5)_2$	H	250	>100	40	14	133	353	
41	$(CH_2)_2N(C_2H_5)_2$	H	250	>100	>20	36	166	300	305
42	$(CH_2)_2N(C_2H_5)_2$	CH_3	500	>100	>20	800	353	800	>400
43	$(CH_2)_3NHCH_3$	H	450	>100	20	400	533	>800	300
44	$(CH_2)_3N(CH_3)_2$	H	250	>100	20	>400	300	>800	325
45	$(CH_2)_3N(C_2H_5)_2$	H	300	>100	>20	>400	300	>400	280

qualitative effects of chlordiazepoxide in causing taming, muscle relaxation, and sedation in mice and cats and had similar anticonvulsant effects in mice. Most of the compounds caused respiratory failure at lethal doses, but some induced sedation similar to chlordiazepoxide while others caused excitation, tremors, and convulsions at lethal doses.

Compounds having a substituted aminoethyl side chain in position 1 (Table III) generally had greater anticonvulsant activity than the corresponding aminopropyl homologs. It was also observed that a terminal dialkylamino group on the side chain resulted in more potent anticonvulsant activity than in compounds having a terminal heterocyclic substituent. Compounds having a 2-fluorophenyl substituent in position 5 (Table III) were generally more potent than those having a phenyl or 2-chlorophenyl group in the same position. Variation of substituents in the 7-position (Table III) did not have a consistent effect on potency, since similar effects were found for 7-chloro-, 7-bromo-, 7-trifluoromethyl-, or 7-nitro-substituted compounds. The tetrahydrobenzodiazepinones (Table IV) usually showed less activity than the corresponding dihydro compounds (Table III).

Methods

Muscle Relaxant, Taming, and Lethal Effects in Mice.—The sedative and muscle relaxant effects and acute toxicity were determined in mice. Six mice at three dose levels were used for each determination. The sedative or muscle relaxant dose (PD_{50}) was calculated as the dose which caused half the mice to slide off a 30° inclined screen. The lethal dose (LD_{50}) was calculated as the dose which killed half of a group of treated mice. The blocking dose for taming pairs of fighting mice was determined on mice which were stimulated by an electric current applied through a grid to the feet according to the method of Tedeschi, *et al.*[4] The 100% blocking dose in 3 pairs of mice was determined.

Anticonvulsant Activity in Mice.—The minimal electroshock convulsant threshold was measured on groups of 8 mice at a minimum of three dose levels by the method of Swinyard, *et al.*[5] The dose level at which half the mice were protected against a minimal seizure was recorded as the ED_{50}.

Maximal seizures were also induced by the technique of Swinyard, *et al.*[5] Tests were carried out on groups of 8 mice at a minimum of three dose levels. The dose which prevented toxic hind limb extension in half the mice was calculated as the ED_{50}.

The antipentylenetetrazole test was carried out on groups of 8 mice at a minimum of three dose levels according to the method of Everett and Richards.[6] The ED_{50} was calculated as the dose which prevented convulsions in half the mice after administration of 125 mg./kg. s.c. of pentylenetetrazole. ED_{50} and LD_{50} values were calculated by the method of Miller and Tainter.[7]

Behavior in Cats.—Gross behavioral observations were made in cats after oral administration. The minimum effective dose for sedation or muscle relaxation was estimated.

Experimental Section

All melting points were determined on a Kofler hot stage microscope and are corrected. The starting 1,4-benzodiazepin-2-ones are all known compounds,[8-14] and the aminoalkyl halides used were commercially available or were made from the corresponding hydrochlorides by treatment with excess 50% NaOH solution at 0° and extraction with toluene.

Only one representative example of each procedure is described. The remainder of the products were made in an analogous way, as indicated in Tables I and II.

Hydrochlorides were made by dissolving the base in a slight excess of methanolic 2 *N* HCl, followed by addition of ether to precipitate the crystalline salt.

Maleates were made from the base and maleic acid in methanol, ethanol, or acetone.

7-Chloro-1-(3-diethylaminopropyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (29). Method A.—To a solution of 27.1 g. (0.10 mole) of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (I) in 250 ml. of anhydrous N,N-dimethylformamide was added 5.94 g. (0.11 mole) of sodium methoxide. The mixture was stirred and heated on a steam bath for 15 min., with protection from atmospheric moisture,

(4) R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exptl. Therap.*, **125**, 28 (1959).

(5) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *ibid.*, **106**, 319 (1952).

(6) G. M. Everett and R. K. Richards, *ibid.*, **81**, 402 (1944).

(7) L. C. Miller and M. C. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 261 (1944).

(8) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(9) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(10) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(11) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

(12) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

(13) R. I. Fryer, G. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(14) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

and then a solution of 3-chloro-N,N-diethylpropylamine (made from 20.5 g., 0.11 mole, of the corresponding hydrochloride) in 200 ml. of anhydrous toluene was added over 30 min. Stirring and heating were continued for 1.5 hr. longer, and then the mixture was concentrated *in vacuo* and poured into a large volume of ice water. The product was isolated by extraction with methylene chloride and recrystallization from hexane (Table I).

Method B. [*Via* **7-Chloro-1-(3-chloropropyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (II)**].—To a solution of 6.75 g. (0.025 mole) of I in 40 ml. of anhydrous N,N-dimethylformamide was added 1.4 g. (0.026 mole) of sodium methoxide, and the mixture was stirred and heated on the steam bath for 30 min. After being cooled to 30°, it was treated with 2.66 ml. (0.0275 mole) of 1-bromo-3-chloropropane and stirred at 20° for 66 hr. The solvent was evaporated *in vacuo*, and the residue was extracted with methylene chloride. The crude product was purified by filtration of an ether solution through Woelm neutral alumina activity I. Crystallization from hexane–ether gave II as colorless rods, m.p. 87–90° (86%).

Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O$: C, 62.26; H, 4.64. Found: C, 62.13; H, 4.74.

A mixture of 10 g. (0.0288 mole) of II, 4.37 g. (0.0288 mole) of NaI, 5.9 ml. (0.0574 mole) of diethylamine, and 50 ml. of 2-butanone was stirred and refluxed for 18 hr. After evaporation *in vacuo*, the residue was partitioned between methylene chloride and water, and the organic layer was extracted with dilute HCl. The aqueous acid layer was made basic with NaOH solution, and the product was isolated by extraction with methylene chloride. Recrystallization from hexane gave **29**, identical with material prepared by method A.

7-Chloro-1-(3-chloropropyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one. Method B.—Alkylation of 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one with 1-bromo-3-chloropropane, as described for the synthesis of II, and isolation of the product in the same manner gave colorless prisms, m.p. 86–89° (48%).

Anal. Calcd. for $C_{18}H_{15}Cl_2FN_2O$: C, 59.19; H, 4.14. Found: C, 59.27; H, 4.31.

7-Chloro-4-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1-methyl-2H-1,4-benzodiazepin-2-one Hydrochloride (41). Method C.—A solution of 2 g. (6.5 mmoles) of 7-chloro-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-1-methyl-2H-1,4-benzodiazepin-2-one (IV) in 10 ml. of N,N-dimethylformamide was treated with a solution of 5.3 g. (34.8 mmoles) of 2-chloro-N,N-diethylethylamine in 10 ml. of anhydrous toluene and 1 g. (66 mmoles) of NaI. The mixture was stirred for 16 hr. at 50°, and then it was evaporated *in vacuo*. The residue was dissolved in 75 ml. of methylene chloride, washed with water, dried ($MgSO_4$), and filtered over 10 g. of Woelm activity I neutral alumina. Evaporation of the eluates and conversion of the residue to the hydrochloride gave colorless prisms (Table II).

7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (40). Method D.—A solution of 26.4 g. (68.4 mmoles) of 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**12**) in 150 ml. of glacial acetic acid was hydrogenated, at atmospheric pressure and temperature, over a prereduced platinum catalyst (prepared from 1.5 g. of PtO_2). When absorption of hydrogen had ceased (1 equiv.), the catalyst was removed by filtration, and the product was isolated in the usual manner. Recrystallization from ether–petroleum ether gave **40** (Table II).

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses, to Dr. J. Pritchard, Dr. V. Toome, and Mr. S. Traiman for the infrared and ultraviolet spectra, to Mrs. Barbara Weiss for compilation of the tables, and to Mrs. B. Kappell, Miss D. Hane, and Mrs. D. Kelly for the pharmacological data.

Further Syntheses in the Study of Structure–Activity Relationships of Neuropharmacologically Active Amino Acids

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N-Methylation of cysteine and homocysteine sulfinic acids did not increase the excitatory action of these substances on neurones within the cat central nervous system. This result was similar to that previously obtained with the sulfonic acid analogs and was again in marked contrast to the unique potency-increasing effect of N-methylation of D-aspartic acid. N-Phenyl-DL-aspartic acid and the methyl esters of ethanolamine, choline, and serine phosphates displayed little or no neuropharmacological action under the test conditions employed.

γ-Aminobutyric acid and glutamic acid have strong actions on a variety of nervous and muscular tissues.[1a] The former substance depresses neuronal and muscular activity while the latter substance is an excitant, causing repetitive firing of neurones in vertebrate and invertebrate animals, and muscular contraction in invertebrates. Structure–activity relationships have been extensively investigated, leading to the conclusion that depressant activity is a consequence of one anionic and one cationic group separated by a distance corresponding to two or three carbon atoms, whereas excitant action is due to these same structural features together with the presence of a second anionic group, which is optimally attached α with respect to the carbon atom bearing the positively charged group.[2–6] The most active depressant found in these studies was 3-aminopropane-1-sulfonic acid,[3–4] while the strongest excitants were N-methyl-D-aspartic acid and D-homocysteic acid.[3–5] Details of the syntheses of a variety of related amino acids have been reported.[6]

The present extension of these studies was undertaken for a dual purpose. First, it was desired to compare the effects of N-methylation of cysteinesulfinic acid and of homocysteinesulfinic acid with those observed on N-methylation of aspartic, cysteic, glutamic, and homocysteic acids. Second, it was desired to

(1) (a) D. R. Curtis and J. C. Watkins, in preparation; (b) D. R. Curtis in "Physical Techniques in Biological Research," Vol. 5, W. L. Nastuk, Ed., Academic Press Inc., New York, N. Y., 1964, p. 144.

(2) D. R. Curtis and J. C. Watkins, *J. Neurochem.*, **6**, 117 (1960).

(3) D. R. Curtis, J. W. Phillis, and J. C. Watkins, *Brit. J. Pharmacol.*, **16**, 262 (1961).

(4) D. R. Curtis and J. C. Watkins, *Nature*, **191**, 1010 (1961).

(5) D. R. Curtis and J. C. Watkins, *J. Physiol.*, **166**, 1 (1963).

(6) J. C. Watkins, *J. Med. Pharm. Chem.*, **5**, 1187 (1962).