vent was evaporated. The residue was recrystallized from toluene to give 6.6 g (55%) of 98, mp 221–223°.

1-Ethyl-4,6-dihydro-3-methyl-8-(α,α,α-trifluoro-o-tolyl)pyrazolo[4,3-e][1,4]diazepin-5(1 *H*)-one (111). Method L. Compound 83 (11 g, 0.029 mol) was dissolved in 110 ml of glacial HOAc and hydrogenated in the presence of 1 g of 5% Pd/C for 2.5 hr. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, washed twice with a saturated $NaHCO_3$ solution, and dried ($MgSO_4$), and the solvent was evaporated. The ir spectra suggested the presence of the uncyclized 4-(2-aminoacetamido) derivative, so the oil was refluxed 2.5 hr in toluene containing 1 ml of HOAc. Evaporation of the solvent and crystallization of the residue from toluene gave 5 g (49%) of 111, mp 195–197°.

4-(2-Azidoacetamido)-1-ethyl-3-methylpyrazol-5-yl α,α,α-Trifluoro-o-tolyl Ketone (83). A mixture of 14 g (0.033 mol) of 82 and 3.2 g (0.05 mol) of NaN_3 in 25 ml of DMF was stirred at 40° for 3 hr and poured into 400 ml of ice water. The precipitate was collected, washed with H_2O, and air-dried to give 11.8 g (92%) of 83, mp 104–105° (EtOAc–petroleum ether).

4-(2-Bromoacetamido)-1-ethyl-3-methylpyrazol-5-yl α,α,α-Trifluoro-o-tolyl Ketone (82). A solution of 14 g (0.047 mol) of 67 in 200 ml of $ClCH_2CH_2Cl$ was mixed with 50 ml of H_2O and 10 g of $CaCO_3$ was added. Bromoacetyl bromide (13 g, 0.065 mol) was added dropwise as the temperature rose to 40°. The mixture was stirred another 2 hr and filtered. The organic layer was separated and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized from ether to give 14 g (71%) of 82, mp 122–124°.

4,6-Dihydro-2,3,4-trimethyl-8-phenyl-5*H*-pyrazolo[4,3-e]diazepin-5-one (87). Method M. A solution of 7.5 g (0.03 mol) of 86 in 40 ml of DMF was treated portionwise with 1.5 g (0.03 mol) of NaH (50% dispersion in mineral oil). After stirring for 0.5 hr, 3 ml of methyl iodide was added and stirring was continued for 4 hr. The mixture was diluted with 250 ml of H_2O and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was crystallized from $CHCl_3$–petroleum ether to give 4 g (50%) of 99, mp 170–173°.

8-(*m*-Bromophenyl)-1-ethyl-4,6-dihydro-3-methylpyrazolo[4,3-e][1,4]diazepin-5(1*H*)-one (109). Method N. Compound 98 (20 g, 0.075 mol) was dissolved at room temperature in a mixture of 90 ml of concentrated H_2SO_4 and 10 ml of H_2O; then 12 g of bromine and 14 g of silver sulfate[16] were added in portions with vigorous stirring as the temperature rose to 36°. The mixture was stirred for 6 hr, allowed to stand overnight, and filtered. The filtrate was poured into 600 ml of ice water and made basic with concentrated NaOH, and the mixture was extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated. The residue was crystallized from EtOAc to give 18.5 g (71%) of 109, mp 227–228°.

1-Ethyl-4,6-dihydro-3-methyl-8-(*m*-nitrophenyl)pyrazolo[4,3-e][1,4]diazepin-5(1*H*)-one (110). Method N. Compound 98 (15 g, 0.055 mol) was dissolved in 40 ml of concentrated H_2SO_4 and was added dropwise with stirring at 10° to a mixture of 40 g of fuming H_2SO_4 (20% SO_3) and 13 ml of 90% HNO_3 acid. The mixture was stirred at 10° for 1 hr, then an additional 2 hr at 25°, and then added slowly to a mixture of 350 g of ice and 350 ml of concentrated NH_4OH. The yellow precipitate was collected, washed with H_2O, and dried at 50° *in vacuo* to give 15.3 g (88%) of 110, mp 155–157° dec. Hydrolysis gave a single amino ketone 66 in 73% yield whose HCl salt melted at 192–194°.

Acknowledgments. The authors are indebted to Dr. B. P. H. Poschel, Dr. G. Chen, and Dr. D. McCarthy and staff for the neuro- and psychopharmacology of these compounds. We thank Mr. C. Myhrum, Mr. J. Sanchez, Mrs. Joan Nogas, and Mrs. L. Zwiesler for the preparation of many of the compounds described; to Mr. W. Pearlman for conducting the hydrogenation reactions employed; and to Mr. H. Troutman, Mr. N. Jenesel, and Mr. D. Johnson for development work in the large-scale synthesis of Cl-683. We are indebted to Mr. C. Childs and coworkers for the microanalyses and gc and to Dr. J. Vandenbelt and staff for the determination of the spectral data.

References

(1) R. Littell and D. Allen, Jr., *J. Med. Chem.*, 8, 722 (1965).
(2) H. DeWald, U. S. Patent 3,557,095 (1971); Y. L'Italien and I. Nordin, U. S. Patent 3,553,209 (1971).
(3) H. DeWald and D. Butler, U. S. Patent 3,558,605 (1971).
(4) M. Nakanishi, T. Tahara, K. Araki, M. Shiroki, T. Tsumagari, and Y. Takigawa, *J. Med. Chem.*, 16, 214 (1973).
(5) F. Tinney, Belgium Patent 745,560 (1970); U. S. Patent 3,558,606 (1971); and Invag. A. G. Netherlands Patent 6,918,485 (1970).
(6) K. v. Auwers and H. Hollman, *Chem. Ber.*, 59, 601 (1926).
(7) K. v. Auwers and T. Breyhan, *J. Prakt. Chem.*, 143, 259 (1935).
(8) C. Musante, *Gazz. Chim. Ital.*, 75, 121 (1945); *Chem. Abstr.*, 41, 4144i (1947).
(9) G. Archer and L. Sternbach, *Chem. Rev.*, 68, 747 (1968); J. Peterson and K. Lakowitz, *Acta Chem. Scand.*, 23, 971 (1969); F. McMillan and I. Pattison, French Patent 1,394,287 (1965).
(10) R. Fryer, B. Brust, and L. Sternbach, *J. Chem. Soc.*, 4977 (1963).
(11) G. Chen, C. Ensor, and I. Clarke, *AMA Arch. Neurol. Psychiat.*, 66, 329 (1951); 68, 498 (1952); G. Chen, R. Porterman, C. Ensor, and A. Bratton, Jr., *J. Pharmacol. Exp. Ther.*, 103, 54 (1951).
(12) B. P. H. Poschel, *Psychopharmacologia*, 19, 193 (1971).
(13) M. Olds, *J. Comp. Physiol. Psychol.*, 62, 136 (1966); B. P. H. Poschel and F. Ninteman, *Life Sci.*, 7, 317 (1968).
(14) R. Santos, C. Bowling, L. Mudgil, and J. Nodine, *Pharmacologist*, 13, 205 (1971).
(15) L. Knorr, *Justus Liebigs Ann. Chem.*, 279, 188 (1894).
(16) D. Derbyshire and W. Walters, *J. Chem. Soc.*, 573 (1950).

1-Polyfluoroalkylbenzodiazepines.[1] 1

Martin Steinman,* John G. Topliss, Robert Alekel, Yee-Shing Wong, and Eunice E. York

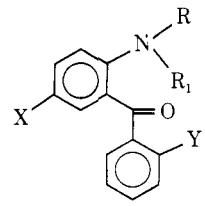
Department of Medicinal Chemistry, Schering Corporation, Bloomfield, New Jersey 07003. *Received June 18, 1973*

A series of 1-polyfluoroalkylbenzodiazepin-2-ones, -2-thiones, and 1-polyfluoroalkyl-2,3-dihydrobenzodiazepine derivatives was prepared and found to have potent antipentylenetetrazole activity combined with low toxicity. The structure–activity relationships are discussed as well as syntheses and structural determinations.

The medical importance of the benzodiazepines (*e.g.*, diazepam, Ia) as compounds possessing antianxiety, muscle relaxant, and sedative activity[2] encouraged the present studies which were aimed at preparing potent agents with therapeutic advantages over known compounds. Since metabolic studies have shown that with diazepam, for example, the principal phase I reaction is dealkylation and then further oxidation to yield a mixture of compounds each with a mix of activities,[3,4] the idea of preparing compounds more resistant to dealkylation[5] arose and 1,1-dihydroperfluoroalkyl groups, such as trifluoroethyl and pentafluoropropyl, were incorporated into the structure (Ib,c).† It was subsequently found that the main urinary metabolite of halazepam in man (after deconjugation) is

† There is considerable evidence that biological oxidations may involve an oxenoid mechanism (analogous to carbene) according to Hamilton.[5] Thus, the lowered electron density of the methylene in the 1,1-dihydroperfluoroalkyl group would not be expected to facilitate oxygen insertion.

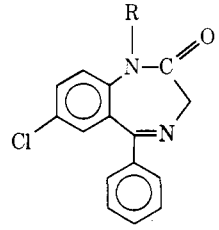
Table I.[a] *o*-Aminobenzophenones and Derivatives



No.	X	Y	R	R_1	Mp, °C	Yield, %	Purification solvent	Formula	Analyses
1	Cl	H	CH_2CF_3	H	100–101	75	EtOH	$C_{15}H_{11}ClF_3NO$	C, H, Cl, F, N
2	Cl	Cl	CH_2CF_3	H	119–120	72	Hex[b]	$C_{15}H_{10}Cl_2F_3NO$	C, H, N
3	Cl	F	CH_2CF_3	H	54–57	20	Pentane[b]	$C_{15}H_{10}ClF_4NO$	C, H, Cl, F, N
4	H	H	CH_2CF_3	H	87–89	71	$CHCl_3$	$C_{15}H_{12}F_3NO$	C, H, F, N
5	NO_2	H	CH_2CF_3	H	97–98	27	$CHCl_3$–Hex[b]	$C_{15}H_{11}F_3N_2O_3$	C, H, N
6	Cl	H	$CH_2CF_2CF_3$	H	91–92	45	Hex[b]	$C_{16}H_{11}ClF_5NO$	C, H, N
7	Cl	H	CH_2CF_3	$COCH_2Br$	115–116.5	85	PhH–Hex	$C_{17}H_{12}BrClF_3NO_2$	C, H, N
8	Cl	H	CH_2CF_3	$COCH_2Phth$[c]	201–201.5	33	EtOH	$C_{25}H_{16}ClF_3N_2O_4$	C, H, N
9	Cl	Cl	CH_2CF_3	$COCH_2Br$	95–97	80	CH_2Cl_2–Hex	$C_{17}H_{11}BrCl_2F_3NO_2$	C, H, Cl, N
10	Cl	Cl	CH_2CF_3	$COCH_2NH_2$	161–162	55	CH_2Cl_2–Hex	$C_{17}H_{13}Cl_2F_3N_2O_2$	C, H, N
11	H	H	CH_2CF_3	$COCH_2Br$	134–136	95	PhH	$C_{17}H_{13}BrF_3NO_2$	C, H, N
12	NO_2	H	CH_2CF_3	$COCH_2Br$	122–124	20	CH_2Cl_2–Hex	$C_{17}H_{12}BrF_3N_2O_4$	C, H, N
13	NO_2	H	H	$NHCH_2CONHCH_2CF_3$	224–225	100	CH_2Cl_2–Hex	$C_{17}H_{14}F_3N_3O_4$	C, H, N

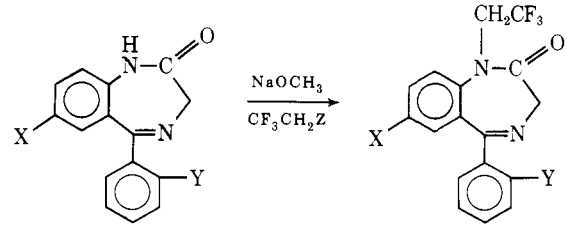
[a]Starting material for **1, 2, 4,** and **6** was available from Aldrich Chemical Co.; for **5,** see K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 1505 (1950). Compound **3** was prepared by method K. [b]First subjected to chromatography on silica gel with PhH–Hex. [c]Phthalimido.

the 3-hydroxylated derivative.‡ Preliminary clinical reports indicate that halazepam has antianxiety activity without adverse effects.[6,7]



Ia, R = CH_3 diazepam
b, R = CH_2CF_3 Sch 12041, halazepam
c, R = $CH_2CF_2CF_3$

Chemistry.§ The 1-trifluoroethylbenzodiazepin-2-one system (III) was prepared in low yield by forming the anion of II and adding trifluoroethyl iodide. This reaction could not be substantially improved by altering the reaction conditions or by the use of trifluoroethyl benzenesulfonate[8] as the alkylating agent.



II III

Z = I, $OSO_2C_6H_5$, OSO_2CCl_3

The possibility of introducing the polyfluoroalkyl group at an earlier stage in the synthesis was then investigated. Dickey[9] has prepared some trifluoroethylanilines by treatment of the aniline with 2-chloro-1,1,1-trifluoroethane, and other variations, all of which are autoclave reactions. These methods, however, would not be useful for alkylating the aminobenzophenones due to their tendency to dimerize.[10] Hanson[11] has described trifluoromethanesulfonate esters (triflates, IV) as active alkylating agents (Scheme I). In the present work the corresponding trichloromethanesulfonates (triclates, V) were prepared and used as a perhaps more convenient alternative to obtain the N-alkylated anilines and aminobenzophenones, VIa,b. Compound Va is a more active alkylating agent than the corresponding benzenesulfonate[8] or tosylate,[12] both of which were also investigated in attempts to prepare these compounds (VI). Yields of VI ranged up to 95%; in most cases no attempt was made to optimize yields. The triclates V were not found to substantially improve the direct alkylation of the benzodiazepinone system (II → III).

Scheme I

$$CF_3SO_2OCH_2R_F \quad (IV)$$

$$CCl_3SO_2Cl + R_FCH_2OH \longrightarrow CCl_3SO_2OCH_2R_F \quad (Va,b)$$

$$2ArNH_2 + V \longrightarrow ArNHCH_2R_F + ArNH_2 \cdot CCl_3SO_3H \quad (VIa,b)$$

a, $R_F = CF_3$
b, $R_F = CF_3CF_2$

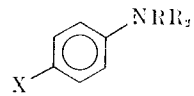
Scheme II illustrates two varieties of a generally applicable pathway to the benzodiazepine system *via* a dehydration to form the imine bond.[13,14] The intermediates and products are listed in Tables I–III. All structures of type X spontaneously cyclized with method B except for one case, 10 (X = Y = Cl). The corresponding 2-one system **37** was prepared by oxidation of **39**.

The 2,3-dihydrobenzodiazepine system XV was prepared by cyclizing the appropriate benzoyl derivative of an ethylenediamine (Scheme III).[15] The ethylenediamines were prepared by treatment of an aniline with ethylenimine or alternatively by reduction of the aminoacetylaniline **23** with diborane to give **24**.

‡ Unpublished data, Dr. B. Katchen, Department of Biochemistry, Schering Corp.

§ Roman numerals are used to indicate generic formulas.

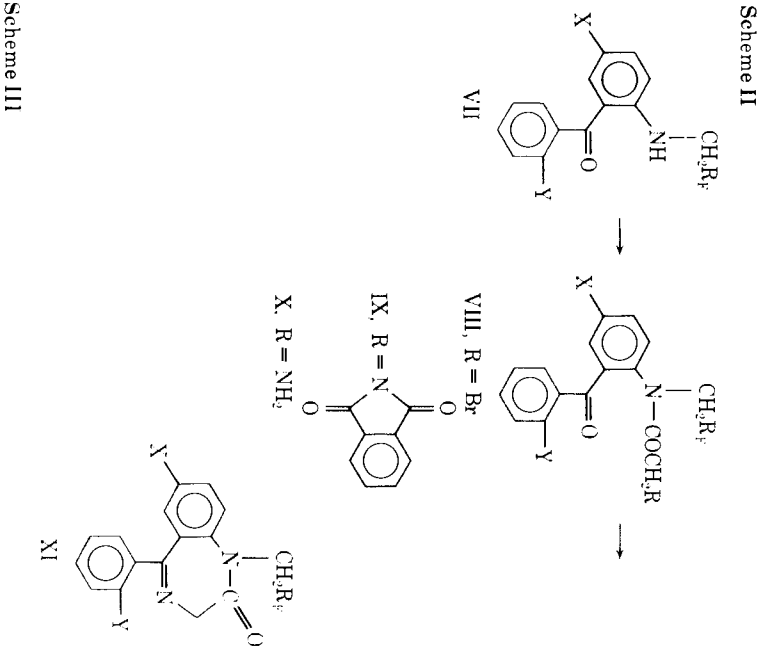
Table II. Anilines and Derivatives



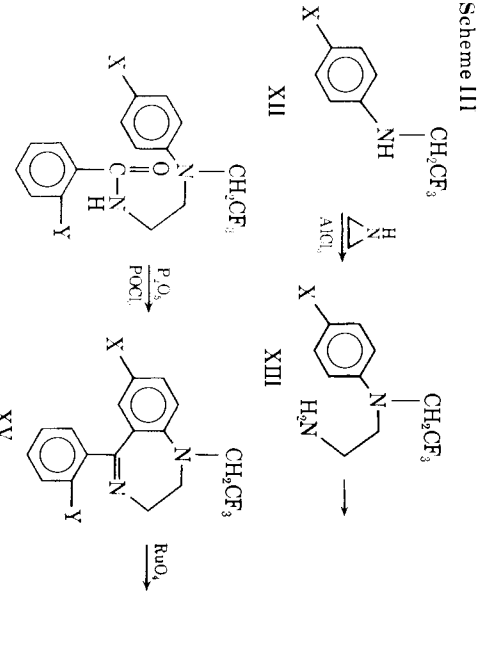
No.	X	R	R_2	Mp or bp (mm), °C	Yield, %	Purification solvent	Formula	Analyses
14	Cl	CH_2CF_3	H	116–119 (16 mm)	95		$C_8H_7ClF_3N$	C, H, F, N
15[a]	Cl	CH_2CF_3	$CH_2CH_2NH_2$	139–142	53	PhH	$C_{10}H_{12}ClF_3N_2 \cdot HCl$	C, H, F, N
16	NO_2	CH_2CF_3	H	111–112	52	PhH–Hex	$C_8H_7F_3N_2O_2$	C, H, F, N
17	NO_2	CH_2CF_3	$COCH_2Br$	114–115	85	CH_2Cl_2–Hex	$C_{10}H_8BrF_3N_2O_3$	C, H, Br, F, N
18[b]	NO_2	H	$CH_2CH_2NHCH_2CF_3$	72–73.5	57	$CHCl_3$–Hex	$C_{10}H_{12}F_3N_3O_2$	C, H, F, N
19	NO_2	H	$CH_2CONHCH_2CF_3$	156–157	34	CH_2Cl_2–Hex	$C_{10}H_{10}F_3N_3O_3$	C, H, N
20	H	CH_2CF_3	H	130–131 (11 mm)[c]	72		$C_8H_8F_3N$	C, H, F, N
21	Br	CH_2CF_3	H	150 (34 mm)	80		$C_8H_7BrF_3N$	C, H, Br, F, N
22	Br	CH_2CF_3	$COCH_2Br$	60–63	84	CH_2Cl_2–Hex	C_9H_9BrNO	C, H, Br, N
23	Br	CH_2CF_3	$COCH_2NH_2$	205–208	89	*i*-PrOH–Et_2O	$C_{10}H_{10}BrF_3N_2O \cdot HCl$	C, H, Br, Cl, N
24[b]	Br	CH_2CF_3	$CH_2CH_2NH_2$	*d*			$C_{10}H_{12}BrF_3N_2$	
25	Cl	CH_2CF_3	$(CH_2)_2NHCOC_6H_5$	131–132	40	Et_2O	$C_{17}H_{16}ClF_3N_2O$	C, H, Cl, F, N
26	Cl	CH_2CF_3	$(CH_2)_2NHCO$-*o*-ClC_6H_4	84–85	56	Et_2O–Hex	$C_{17}H_{15}Cl_2F_3N_2O$	C, H, Cl, F, N
27	Cl	CH_2CF_3	$(CH_2)_2NHCO$-*o*-FC_6H_4	80–82	38	CH_2Cl_2–Hex	$C_{17}H_{15}ClF_4N_2O$	C, H, Cl, F, N
28	NO_2	H	$(CH_2)_2N(CH_2CF_3)CO$-*o*-FC_6H_4	133–134	50	$CHCl_3$–Hex	$C_{17}H_{15}F_4N_3O_3$	C, H, F, N
29	H	CH_2CF_3	$(CH_2)_2NHCO$-*o*-FC_6H_4	76–78	54	Et_2O–Hex	$C_{17}H_{16}F_4N_2O$	C, H, F, N
30	Br	CH_2CF_3	$(CH_2)_2NHCO$-*o*-FC_6H_4	75–77	25[e]	Et_2O–Hex	$C_{17}H_{15}BrF_4N_2O$	C, H, Br, F, N

[a] Made by method F. [b] Made by method E. [c] Reported by Dickey[9] as 84–85° (15 mm) and 135–136° (12 mm). [d] The crude oil was used to prepare **30**. [e] Overall yield from **23**.

Scheme II

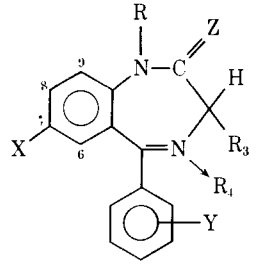


Scheme III



Oxidation with RuO_4[16] provides another general path to the 2-one system XVI and treatment of the latter with P_2S_5 in dioxane gives the 2-thiones XVII. In general, pyridine has been used as the solvent in the preparation of 2-thiones,[2,17] but in this series P_2S_5 in pyridine gave unsatisfactory results, and the use of dioxane as solvent greatly improved the reaction.

Table III. Benzodiazepines

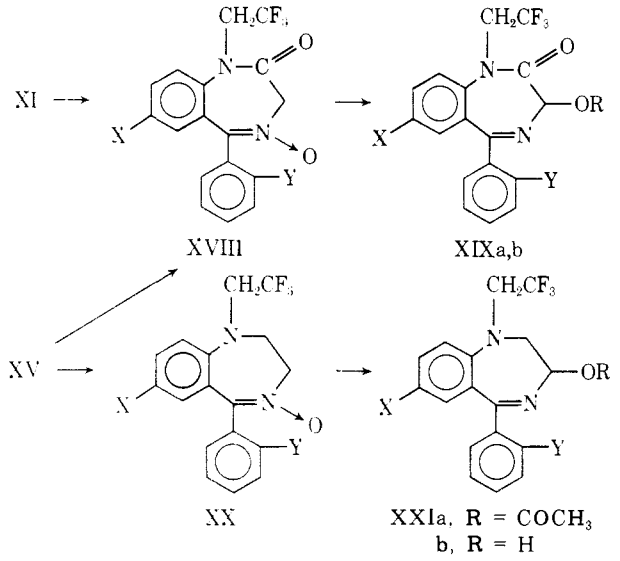


No.	X	Y	Z	R	R_3	R_4	Mp, °C	Yield, %	Purification solvent	Formula	Analyses	Method[a]	ED_{50}, mg/kg po, *vs.* pentylenetetrazole convulsions in mice
31	Cl	H	O	CH_2CF_3	H		164–166	3.6	Me_2CO–Hex	$C_{17}H_{12}ClF_3N_2O$	C, H, N	A	2.5
								50				B	
								48				C	
32	Cl	H	O	CH_2CF_3	H	O	192–194	70	Me_2CO–Et_2O	$C_{17}H_{12}ClF_3N_2O_2$	C, H, N	G	1.7
33	Cl	H	O	CH_2CF_3	OAc		193–194	75	Me_2CO–Hex	$C_{19}H_{14}ClF_3N_2O_3$	C, H, N		10
34	Cl	H	O	CH_2CF_3	OH		186–187	75	EtOH–Hex	$C_{17}H_{12}ClF_3N_2O_2$	C, H, N		1.2
35	Cl	H	S	CH_2CF_3	H		169–170	40	CH_2Cl_2–Hex	$C_{17}H_{12}ClF_3N_2S$	C, H, N, S		5
36	Cl	H	H_2	CH_2CF_3	H		66–67.5	40	Pet. ether	$C_{17}H_{14}ClF_3N_2$	C, H, Cl, F, N		5–10
37	Cl	*o*-Cl	O	CH_2CF_3	H		105–107	57	CH_2Cl_2–Hex	$C_{17}H_{11}Cl_2F_3N_2O$	C, H, N	D	1
38	Cl	*o*-Cl	O	CH_2CF_3	H	O	208–210	19	CH_2Cl_2–Hex	$C_{17}H_{11}Cl_2F_3N_2O_2$	C, H, N	H	17
39	Cl	*o*-Cl	H_2	CH_2CF_3	H		188–198	42	EtOH–Et_2O	$C_{17}H_{13}Cl_2F_3N_2 \cdot HCl$	C, H, N		0.5
40	Cl	*o*-Cl	H_2	CH_2CF_3	H	O	137–138	66	CH_2Cl_2–Hex	$C_{17}H_{13}Cl_2F_3N_2O$	C, H, N	H	>30
41	Cl	*o*-Cl	H_2	CH_2CF_3	OAc		127–131	63	Et_2O–Hex	$C_{19}H_{15}Cl_2F_3N_2O_2$	C, H, N		>30
42	Cl	*o*-F	O	CH_2CF_3	H		124–127	65	CH_2Cl_2–Hex	$C_{17}H_{11}ClF_4N_2O$	C, H, Cl, N	D	0.1
43	Cl	*o*-F	O	CH_2CF_3	H	O	196–199	55	CH_2Cl_2–Hex	$C_{17}H_{11}ClF_4N_2O_2$	C, H, N	G	5 (3–10)
44	Cl	*o*-F	O	CH_2CF_3	OAc		156–158.5	60	CH_2Cl_2–Hex	$C_{17}H_{13}ClF_4N_2O_3$	C, H, N		0.8 (0.3–1)
45	Cl	*o*-F	S	CH_2CF_3	H		138–139	64	CH_2Cl_2–Hex	$C_{17}H_{11}ClF_4N_2S$	C, H, F, N		0.4
46	Cl	*o*-F	H_2	CH_2CF_3	H		83–85	75	CH_2Cl_2–Hex	$C_{17}H_{13}ClF_4N_2$	C, H, Cl, F, N		1
47	Cl	*o*-F	H_2	CH_2CF_3	H	O	163–165	83	CH_2Cl_2–Hex	$C_{17}H_{13}ClF_4N_2O$	C, H, Cl, F, N	J	36
48	H	H	O	CH_2CF_3	H		138–139	65	EtOH	$C_{17}H_{13}F_3N_2O$	C, H, F, N	B	100
49	Cl	*m*-NO_2	O	CH_2CF_3	H		230–231	74	Me_2CO	$C_{17}H_{11}ClF_3N_3O_3$	C, H, Cl, N		60
50	NO_2	H	O	CH_2CF_3	H		161–162	20	Me_2CO–MeOH	$C_{17}H_{12}F_3N_3O_3$	C, H, N		30
51	H	*o*-F	H_2	CH_2CF_3	H		91–93	66	Et_2O–Hex	$C_{17}H_{14}F_4N_2$	C, H, N		>100
52	Cl	H	O	$CH_2CF_2CF_3$	H		196–197	64	$CHCl_3$–Hex	$C_{18}H_{12}ClF_5N_2O$	C, H, F, N	B	30
53	NO_2	*o*-F	H_2	CH_2CF_3	H		123–125	14	CH_2Cl_2–Hex	$C_{17}H_{14}F_4N_3O_2$	C, H, N		2.5
54	7,9-$(NO_2)_2$	*o*-F	H_2	CH_2CF_3	H		188–190	11	CH_2Cl_2–Hex	$C_{17}H_{12}F_4N_4O_4$	C, H, N		>100
55	7-Cl-9-NO_2	*o*-F	H_2	CH_2CF_3	H		138–139	41	PhH–Hex	$C_{17}H_{12}ClF_4N_3O_2$	C, H, N		>100
56	Br	*o*-F	H_2	CH_2CF_3	H		97–98	82	Et_2O–Hex	$C_{17}H_{13}BrF_4N_2$	C, H, Br, N		0.15 (0.1–0.3)

[a]Where applicable.

Since benzodiazepines are generally metabolized to 3-hydroxy derivatives, the latter were prepared for testing by first employing the Polonovskii rearrangement[18] on the nitrones XVIII and XX to obtain XIX and XXI, respectively. The acetates were hydrolyzed to the corresponding 3-hydroxy compounds (Scheme IV). In one case of the oxidation of XV (X = Y = Cl, 39) with *m*-chloroperbenzoic acid, the nitrone of the 2-one system, XVIII, was obtained as well as the expected nitrone XX, after chromatographic separation.

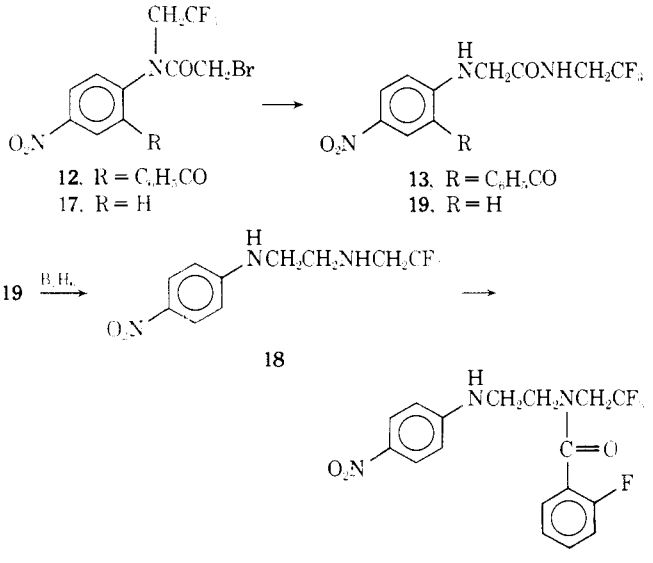
Scheme IV



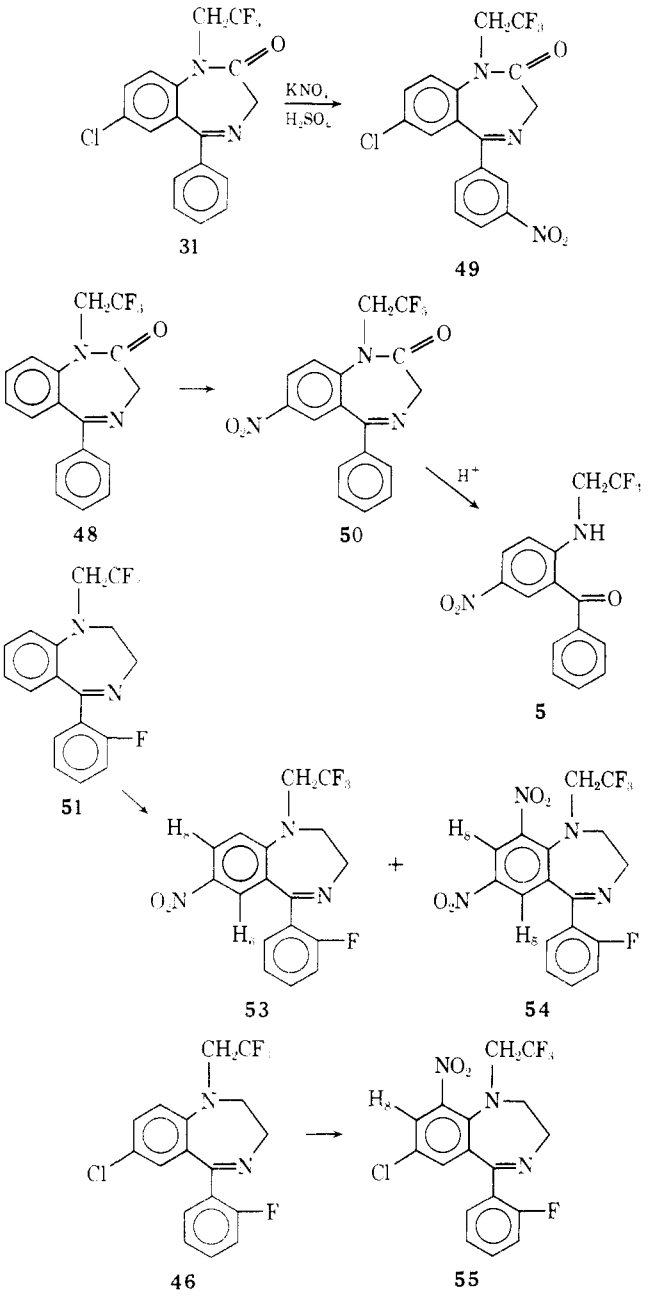
It was found that several 7-nitrobenzodiazepines were not accessible by the methods in Schemes II and III due to the unexpected rearrangement shown in Scheme V. The bromoacetamidobenzophenone **12** and the bromoacetylaniline **17** give **13** and **19**, respectively, upon treatment with ammonia. Similar rearrangements of nitrobenzophenones have been observed by other workers.[19,20] The amide **19** was treated with diborane to obtain the diamine **18**. The mono-*o*-fluorobenzoyl derivative **28** was prepared, but this was not the desired intermediate for benzodiazepine synthesis. All the spectral data supported these structures, in particular the mass spectra.

The desired nitrobenzodiazepines were prepared under mild nitrating conditions, KNO_3-H_2SO_4 in the cold (Scheme VI). All structures are unequivocal on the basis of nmr. In addition, the structures of **49**, **50**, and **53** could be predicted from previous work[21,22] which indicates that nitration occurs first in the 7 position, if it is available, and then in the meta position of the 5-phenyl ring. Compound **50** was hydrolyzed to benzophenone **5** which was independently prepared.

Scheme V



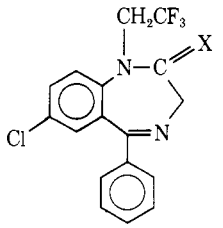
Scheme VI



Structures **54** and **55** were expected because the fluorine in the 5-phenyl deactivates the ring to further substitution and then once the 7 position is substituted, further substitution occurs in the 9 position. The nmr for **53** (100 MHz) shows as the most downfield shift H-8 at δ 8.57 as four lines (J_o = 9, J_m = 3 Hz) and H-6 at δ 7.86 as a doublet (J_m = 3 Hz). Compound **54** (100 MHz) shows H-8 as the most downfield proton at δ 8.76 (J_m = 3 Hz) and H-6 at δ 8.02, a four-line multiplet (J_m = 3 and J_F = 1 Hz). Compound **55** shows only H-8 separated from the rest of the aromatic multiplets at δ 7.90 (J_m = 2.5 Hz).

Spectral Data. An examination of the nmr spectra of

structures **36**, **31**, and **35** illustrates generalities in this series. Compound **36**, the 2,3-dihydro system, has a two-proton quartet for the $-CH_2CF_3$ group at δ 3.75 (J = 8.5 Hz); the other four aliphatic protons on C-2 and C-3 coincidently appear as a singlet at the same chemical shift, δ 3.75. (In DMSO the quartet and singlet are separated.) The 2-one system **31** shows the $-CH_2CF_3$ group as an ABX_3 system with 13 of the 16 lines (for four quartets) visible, three lines being coincident with other lines. The shifts are δ_A 5.19 (J_{AX} = 9 Hz), δ_B 4.05 (J_{BX} = 8 and J_{AB} = 15 Hz). The C-3 protons appear as two doublets, δ_D 4.84 and δ_E 3.79 (J_{DE} = 11 Hz). The spectrum of the 2-thione system, **35**, is virtually identical but shifted downfield.



36, X = H, H
31, X = O
35, X = S

Pharmacology and Structure-Activity Relationships. The test used as a measure of tranquilizing activity was antagonism of pentylenetetrazole-induced convulsions in mice.[23] The compounds were administered to groups of five male CF No. 1S mice and pentylenetetrazole, 125 mg/kg ip, was administered 1 hr after the test compound. Antagonism was measured by the per cent of mice protected against tonic extension. ED_{50} values were calculated by the method of Litchfield and Wilcoxon (Table III).[24]

The test used as a measure of neurological impairment or side effect potential was impairment of wire maneuver performance, also called the traction test.[25,26] The percentage of mice unable to climb onto a wire and balance themselves within 15 sec after being suspended by the forepaws was determined 60 min after administration of each test compound. The oral dose (mg/kg) to produce impairment in 50% of the mice (ID_{50}) was determined according to Litchfield and Wilcoxon.[24]

A comparison of **31**, the 1-trifluoroethylbenzodiazepinone, and **52**, the corresponding 1-pentafluoropropyl, shows that the trifluoroethyl group confers greater activity. In light of previous findings[2] it is surprising that **50**, a 7-nitrobenzodiazepinone, is not more active, since electron-withdrawing groups at C-7, including nitro, are said to give active compounds. An ortho halogen in the 5-phenyl ring consistently increases activity in this series. A comparison of the activities of compounds which differ structurally only at the 2-carbon atom indicates C=O > C=S > CH_2 for activity (**42**, **45**, and **46**, respectively).

A comparison of diazepam, Ia, and halazepam, Ib, in the present test system shows that diazepam is more potent (ED_{50} of 1 and 2.5 mg/kg, respectively). However, the 1-trifluoroethylbenzodiazepines in general produce less neurotoxicity in mice than diazepam. The relative specificity of the tranquilizing effect of a drug is indicated by the therapeutic index (ID_{50}/ED_{50}), a larger number indicating greater specificity and less neurotoxicity. The therapeutic indices of some representative compounds are: diazepam, 2.0; halazepam, 8.0; **36**, 5.3; and **35**, 13.6. Furthermore, the oral LD_{50} in mice for diazepam is reported to be 620 mg/kg while in experiments with halazepam, there was no lethality at 4000 mg/kg.[6,7]

Experimental Section[=]

Benzodiazepin-2-one Syntheses. 7-Chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (31). Method A. A solution of 0.51 g (0.022 g-atom) of Na in 50 ml of MeOH was added to 5.0 g (0.019 mol) of 7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one[13] in 150 ml of MeOH. The solution was evaporated to dryness *in vacuo* and the Na salt dissolved in 30 ml of DMF. This solution was slowly treated with 5.85 g (0.028 mol) of 2,2,2-trifluoroethyl iodide. After stirring overnight at 60-70° the solution was cooled and evaporated to a residue which was treated with H_2O and extracted with Et_2O. The organic layer was dried and evaporated and the residue was dissolved in PhH and chromatographed on alumina (100 g) using PhH to elute. The appropriate fractions were recrystallized from acetone-hexane to give **31**.

Ammonia Treatment of Bromoacetyl Derivatives. Method B. A solution of 0.1 mol of the 2-bromoacetamidobenzophenone or bromoacetylaniline in alcohol-free $CHCl_3$ was treated with NH_3 gas for 18 hr at room temperature. After washing with H_2O and drying (Na_2SO_4), the solvent was evaporated and the residue recrystallized from the solvent indicated to yield either **XI**, **10**, **13**, **19**, or **23**. (In the preparation of benzodiazepinone **31**, the first crop was a higher melting side product which will be described elsewhere.)

7-Chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (31). Method C. A solution of 0.5 g (0.001 mol) of **8** in 25 ml of EtOH containing 0.15 g (0.003 mol) of $H_2NNH_2 \cdot H_2O$ was heated under reflux for 2 hr, concentrated to about half-volume, and cooled. The precipitate was removed by filtration and the filtrate was acidified with 5% HCl, heated to 80°, and cooled to room temperature. The solution was made alkaline with 5% NaOH and extracted with CH_2Cl_2. The organic layer was dried and evaporated at a residue which was crystallized with acetone-hexane; recrystallization yielded **31**.

1,3-Dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-ones (XI). Method D. A solution of 2.8 mmol of XV in 30 ml of CH_2Cl_2 at 0° was treated with 10 mmol of RuO_4 (prepared from RuO_2[27]) in 225 ml of CCl_4 over 30 min. After another 30 min at 0°, 7 ml of i-PrOH in 200 ml of H_2O was added. The mixture was filtered through Celite, dried (Na_2SO_4), and evaporated *in vacuo*. Hexane was added to the residue and crystals were obtained.

Ethylenediamines. Method E. To a solution of 17 ml of 1 *M* borane in THF under N_2 at 0° was added 2.8 g (0.01 mol) of **19** in 20 ml of THF.[28] After a further 10 min at 0°, the solution was heated to reflux for 15 min and then cooled to room temperature. HCl (10 ml, 6 *N*) was added slowly. The THF was removed as H_2 was evolved. NaOH solution (50%) was added to pH 11, and the solution was extracted with CH_2Cl_2 three times. The combined organic extracts were dried (Na_2SO_4), treated with Darco, and evaporated to a residue which was crystallized to yield **18**.

In the same manner, treatment of **23** gave **24** as an oil which was not distilled but used to make **30**.

Method F. The method of Kaegi was used.[15] It was found that the commercial ethylenimine did not require distillation before use.

Benzodiazepine Oxidations (Scheme IV). Benzodiazepin-2-one 4-Oxides (XVIII). Method G. CH_3CO_3H (40%) in CH_3CO_2H was used according to Bell, *et al.*[29]

Oxidation of 7-Chloro-5-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-1,4-benzodiazepine (39). Method H. A solution of 7.5 g (0.02 mol) of **39** and 4.14 g (0.024 mol) of *m*-chloroperbenzoic acid (MCPB) in 30 ml of $ClCH_2CH_2Cl$ was refluxed for 4 hr, cooled, diluted with 100 ml of CH_2Cl_2, and washed with 5% HCl, 10% NaOH, and then H_2O. After removal of solvent *in vacuo* the residue was chromatographed on 400 g of silica gel using CH_2Cl_2-EtOAc (1:1), collecting 250-ml fractions. Fractions 4-6 yielded, after crystallization, **40**. Fractions 10 and 11 yielded, after crystallization, **38**.

7-Chloro-1-(2,2,2-trifluoroethyl)-5-(2-fluorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine 4-Oxide. Method J. A solution of 0.1

[=] Nmr spectra were determined on a Varian A-60A spectrometer (60 MHz) or when indicated on the HA-100 spectrometer (100 MHz), in $CDCl_3$ (Me_4Si) unless other solvent is specified, and mass spectra on a Varian-Mat CH5 spectrometer using an electron impact source at 70 eV and 250°. All melting points were determined on a Kofler apparatus and are corrected. The ir spectra (Nujol) were determined with a Perkin-Elmer 221 spectrophotometer and uv spectra (MeOH) with a Cary 15 spectrophotometer. Where analyses are indicated only by the symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

g (0.28 mmol) of 46 and 0.054 g (0.31 mmol) of MCPB in 10 ml of $ClCH_2CH_2Cl$ was stirred at 45° overnight and then refluxed for 3 hr. After cooling, the solution was adsorbed on a column of 35 g of silica gel and ether was used to wash off the front-running yellow material. The material remaining was then obtained by treating the removed adsorbent with EtOAc. Crystallization yielded 47.

Hydrolysis of Benzodiazepin-2-ones to Aminobenzophenones 3 and 5. Method K. The hydrolyses were carried out according to Sternbach, *et al.*[22]

Polyfluoroalkyl Trichloromethanesulfonates (V). A mixture of 5.0 g (0.05 mol) of 2,2,2-trifluoroethanol and 11.3 g (0.052 mol) of trichloromethanesulfonyl chloride in 15 ml of H_2O was stirred at 50° and 2.2 g (0.055 mol) of NaOH in 9 ml of H_2O was added. After 2 hr at this temperature it was allowed to cool overnight. Petroleum ether was used to extract the sulfonate ester and this solution was then washed several times with concentrated aqueous NH_3 and then H_2O. After filtering and evaporating the solvent, the remaining oil was distilled: 101–102° (38 mm); 7.9 g (87%); $n^{24.5}{}_D$ 1.4240. *Anal.* ($C_3H_2Cl_3F_3O_3S$) Cl, F, S.

The pentafluoropropyl ester was prepared in the same manner in 75% yield: bp 77–79° (10 mm); $n^{24.5}{}_D$ 1.4085. *Anal.* ($C_4H_2Cl_3F_5O_3S$) Cl, F, S.

2-Polyfluoroalkylaminobenzophenones (VII) and *N*-(2,2,2-Trifluoroethyl)anilines (XII). A solution of 2 mol of the aminobenzophenone or aniline and 1 mol of polyfluoroalkyl trichloromethanesulfonate in 600 ml of xylene was stirred under reflux for 10 hr and then cooled and filtered. The filter cake was washed with Et_2O and the washings were combined with the filtrate. (The starting aminobenzophenone or aniline was recovered from the precipitate by treatment with Na_2CO_3 solution.) The organic solution was concentrated *in vacuo* and the residue was either distilled, crystallized, or chromatographed and then recrystallized.

2-Bromoacetamidobenzophenones (VIII) and Bromoacetylanilines. A solution of 0.1 mol of the base and 0.12 mol of bromoacetyl bromide in 500 ml of benzene was refluxed for 4 hr. The solution was then cooled, washed with water, dried, and concentrated *in vacuo*. The crystalline residue was recrystallized.

2-[*N*-(2,2,2-Trifluoroethyl)phthalimidoacetamido]-5-chlorobenzophenone (8). 2-[*N*-(2,2,2-Trifluoroethyl)amino]-5-chlorobenzophenone (4.60 g, 0.015 mol) in 150 ml of PhH was added to 3.26 g (0.015 mol) of phthalimidoacetyl chloride[30] in 150 ml of PhH and the mixture was refluxed for 3 hr and cooled. After washing with saturated aqueous $NaHCO_3$ and H_2O, the PhH solution was dried and evaporated to a residue which was crystallized from EtOH to yield 8.

1,3-Dihydro-5-aryl-2*H*-1,4-benzodiazepine-2-thiones (XVII). A solution of 25 g (0.071 mol) of the benzodiazepin-2-one 31 and 17.3 g (0.078 mol) of P_2S_5 in 250 ml of dry *p*-dioxane was heated under reflux for 5 hr. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and filtered through activated alumina. Chromatography on silica gel using PhH as eluent gave 35.

The thione 45 was prepared in analogous fashion from 42 except that the residue in CH_2Cl_2 was filtered through silica gel and then subjected to crystallization to give 45.

Nitrations of Benzodiazepines and Benzodiazepin-2-ones. A solution of 0.1 mol of KNO_3 in 20 ml of cold concentrated H_2SO_4 was added dropwise with stirring to 0.1 mol of the benzodiazepine or benzodiazepin-2-one in 100 ml of concentrated H_2SO_4 at 0–5°. After stirring at this temperature for about 4 hr the mixture was poured onto ice and neutralized with NH_4OH at 0°. The precipitate was collected, washed with H_2O, and either crystallized or chromatographed first.

3-Acetoxybenzodiazepines (XIXa and XXIa). The acetic anhydride method of Bell was used.[18]

3-Hydroxybenzodiazepin-2-ones (XIXb). The 3-acetoxy derivative (3.0 g) in 30 ml of EtOH and 30 ml of NH_4OH was allowed to stand overnight. The solvent was decanted from the crystals which were then recrystallized.

***N*-Aroylethylenediamines (XIV and 28).** A solution of 1 mol of the ethylenediamine and 1 mol of triethylamine in 1 l. of dry PhH was treated with 1 mol of the aroyl chloride at 0°. After stirring overnight at room temperature the solid was filtered off and the filtrate was washed with 10% aqueous Na_2CO_3 and then H_2O. After drying the solvent was removed *in vacuo* and the residue was crystallized (or first chromatographed).

2,3-Dihydro-5-aryl-1*H*-1,4-benzodiazepines (XV). The cyclization was accomplished with P_2O_5 and $POCl_3$ according to Kaegi[15] and the benzodiazepines were isolated either as the free base or, in one case, as the HCl salt.

Acknowledgments. The authors are indebted to Dr. Allen Barnett for the biological data reported herein and to the Physical and Analytical Chemical Research Department for the spectra and microanalyses.

References

(1) Presented in part at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, FLUO 21.
(2) L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, 10, 34 (1971), and references cited therein.
(3) M. A. Schwartz, B. A. Koechlin, E. Postma, S. Palmer, and G. Krol, *J. Pharmacol. Exp. Ther.*, 149, 423 (1965).
(4) J. A. F. DeSilva, B. A. Koechlin, and G. Bader, *J. Pharm. Sci.*, 55, 692 (1966).
(5) G. A. Hamilton, "Progress in Bioorganic Chemistry," Vol. 1, E. T. Kaiser and F. J. Kezdy, Ed., Interscience, New York, N. Y., 1971, p 83.
(6) D. M. Gallant and M. P. Bishop, *Curr. Ther. Res.*, 13, 107 (1971); (b) K. Y. Ota, A. A. Kurland, and I. Turek, *ibid.*, 13, 463 (1971).
(7) T. Itil, P. Gannon, R. Cora, N. Polvan, S. Akpinar, F. Elveris, and E. Eskazan, *Behav. Neuropsychiat.*, 4, 15 (1972).
(8) E. T. McBee, D. H. Campbell, and C. W. Roberts, *J. Amer. Chem. Soc.*, 77, 3149 (1955).
(9) J. B. Dickey, E. B. Towne, M. S. Bloom, G. J. Taylor, H. M. Hill, R. A. Corbitt, M. A. McCall, and W. H. Moore, *Ind. Eng. Chem.*, 46, 2213 (1954), and references cited therein.
(10) W. Metlesics, T. Resnick, G. Silverman, R. Tavares, and L. H. Sternbach, *J. Med. Chem.*, 9, 633 (1966).
(11) R. L. Hansen, *J. Org. Chem.*, 30, 4322 (1965).
(12) G. V. D. Tiers, H. A. Brown, and T. S. Reid, *J. Amer. Chem. Soc.*, 75, 5978 (1953).
(13) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, 27, 3788 (1962).
(14) Delmar, Netherlands Patent 6,500,446; *Chem. Abstr.*, 64, 5120 (1966).
(15) H. H. Kaegi, *J. Label. Compounds*, 4, 363 (1968).
(16) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, 5, 731 (1968).
(17) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, 29, 231 (1964).
(18) S. C. Bell and S. J. Childress, *ibid.*, 27, 1691 (1962).
(19) (a) K. Ishizumi, S. Inaba, and H. Yamamoto, *Chem. Pharm. Bull.*, 20, 592 (1972); (b) S. Inaba, K. Ishizumi, K. Mori, and H. Yamamoto, *ibid.*, 19, 722 (1971).
(20) N. W. Gilman and L. H. Sternbach, *J. Heterocycl. Chem.*, 8, 297 (1971).
(21) R. Ian Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 4977 (1963).
(22) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Pharm. Chem.*, 6, 261 (1963).
(23) G. M. Everett and R. K. Richards, *J. Pharmacol. Exp. Ther.*, 81, 402 (1944).
(24) J. T. Litchfield and F. Wilcoxon, *ibid.*, 96, 99 (1949).
(25) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DaVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, 7, 415 (1964).
(26) R. Nakajima, C. Hattori, and Y. Nagawa, *Jap. J. Pharmacol.*, 21, 489 (1971).
(27) H. Nakata, *Tetrahedron*, 19, 1959 (1963).
(28) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 86, 3566 (1964).
(29) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, 27, 562 (1962).
(30) S. Gabriel, *Ber.*, 40, 2649 (1907).