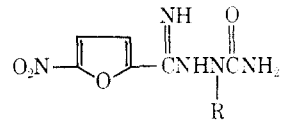
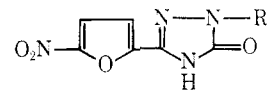
TABLE I



No.	R	Mp, °C	Yield, %	Recrystn solvent	Formula[a]
2	H	274–275	51	DMF–MeCN	$C_6H_7N_5O_4$
3	CH_3	195–196	64	MeOH or DMF	$C_7H_9N_5O_4$
4	CH_2CH_3	173–174	60	H_2O	$C_8H_{11}N_5O_4$
5	CH_2CH_2OH	181–182	40	MeOH	$C_8H_{11}N_5O_5$



6	H	277–279	78	H_2O	$C_6H_4N_4O_4$
7	CH_3	275–276	73	H_2O	$C_7H_6N_4O_4$
8	CH_2CH_3	243–244	56	AcOH	$C_8H_8N_4O_4$
9	CH_2CH_2OH	263–264	38	AcOH	$C_8H_8N_4O_5$

[a] All compounds analyzed for C, H, and N within ±0.40% of the theoretical values.

TABLE II

ANTIBACTERIAL TESTING OF 3-(5-NITRO-2-FURYL)-Δ^2-1,2,4-TRIAZOLIN-5-ONES

	Minimal inhibitory concentration, μg ml[a]								
No.	Mi-6[b]	Es-2	Ps-10	Pr-12	SaD-13	StA-1	StB-12	Er-4	Ae-6
6	200	10	>200	>200	100	12.5	100	12.5	>200
7	25	3.1	>200	>200	6.25	25	>200	3.1	200
8	25	12.5	>100	>100	12.5	100	>100	6.25	>100
9	6.25	0.38	>50	>50	3.1	50	>50	3.1	>50
Nitrofurazone[c]	12.5	3	>100	100	3	6	12.5	12.5	100

[a] Minimal inhibitory concentration is the lowest concentration of compound that prevents visible growth after 24 hr of incubation. [b] The Norwich Pharmacal Co. strain number: Mi-6 = *Staphylococcus aureus*, Es-2 = *Escherichia coli*, Ps-10 = *Pseudomonas aeruginosa*, Pr-12 = *Proteus vulgaris*, SaD-13 = *Salmonella typhosa*, StA-1 = *Streptococcus pyogenes*, StB-12 = *Streptococcus agalactiae*, Er-4 = *Erysipelothrix insidiosa*, Ae-6 = *Aerobacter aerogenes*. [c] Furacin(R), for comparison.

The mixture was cooled to room temperature and filtered. The orange solid was washed successively with H_2O, *i*-PrOH, and Et_2O and then air dried. A warm solution of the crude salt in DMF was diluted with MeCN and kept at room temperature until crystallization was complete. Conversion of the salt into the free base **2** was effected with aqueous Na_2CO_3 solution.

Compounds **3–5** were prepared similarly from **1** and the appropriately 2-substituted semicarbazides except that the crude salts were obtained by dilution of the reaction mixtures with Et_2O.

3-(5-Nitro-2-furyl)-Δ^2-1,2,4-triazolin-5-one (6).—A solution of 60 g (0.28 mol) of **2**·HCl in 450 ml of $PhNO_2$ was refluxed for 15 min, cooled, and diluted with 400 ml of Et_2O. The dark solid was filtered off, washed with Et_2O, and dried.

Compounds **7–9** were prepared similarly from the appropriate intermediates **3–5**.

Acknowledgments.—The authors are grateful to Mr. G. Gustin and Mr. M. Tefft for the elemental analyses and to Mrs. P. Curtis for the nmr spectra.

Synthesis of 1-Phenyl-2-styryl-3,5-dioxopyrazolidines as Antiinflammatory Agents

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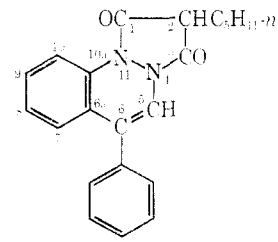
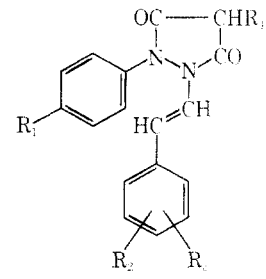
A series of 1-phenyl-2-styryl-3,5-dioxopyrazolidine derivatives was synthesized for antiinflammatory testing, and it was found that some of these compounds were more potent inhibitors than phenylbutazone or oxyphenbutazone in the carrageenin-induced foot edema test in rats.

In a previous paper,[1] it was reported that 1,2-pentylmalonyl-1,2-dihydro-4-phenylcinnoline (I) showed potent antiinflammatory activity. This prompted us to prepare 1-phenyl-2-styryl-3,5-dioxopyrazolidines (II), because the intrinsic antiinflammatory activity of I might be due to the presence of a 3,5-dioxopyrazolidine ring and the activity might be kept when the C_6–C_{6a} bond of I is cleaved. Based on this hypothesis, various derivatives of II have been prepared for antiinflammatory tests.[2]



I



II

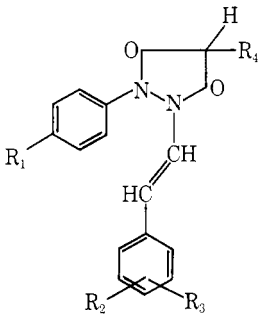
Compounds (II) based on the same concept were recently suggested to have antiinflammatory activity, though their synthesis has not been described.[3]

(1) U. Jahn and Th. Wagner-Jauregg, *Arzneim. Forsch.*, **18**, 120(1948).

(2) H. Yamamoto and S. Kaneko, Japan Patent Application No. 68-5501 and 68-5815 (Aug 1968).

(3) F. Schatz und Th. Wagner-Jauregg, *Helv. Chim. Acta*, **51**, 1919 (1968).

TABLE I



Compd	Substituent R1	R2	R3	R4	Mp, °C (RS[a])	Prepn	Yield	Formula	Analyses[c]
1	H	H	H	n-C_4H_9	166 (A)	A, B	30,[d] 40[e]	$C_{21}H_{22}N_2O_2$	C, H, N
2	CH_3	H	H	n-C_4H_9	138–139 (B)	A, B	20,[d] 32[e]	$C_{22}H_{24}N_2O_2$	C, H, N
3	Cl	H	H	n-C_4H_9	147–148 (B)	A, B	30,[d] 35[e]	$C_{21}H_{21}N_2O_2Cl$	C, H, N, Cl
4	H	4-CH_3	H	n-C_4H_9	180–181 (B)	B	30[e]	$C_{22}H_{24}N_2O_2$	C, H, N
5	CH_3	4-CH_3	H	n-C_4H_9	162–163 (B)	B	8[e]	$C_{23}H_{26}N_2O_2$	C, H, N
6	Cl	4-CH_3	H	n-C_4H_9	155–156 (B)	B	13[e]	$C_{22}H_{23}N_2O_2Cl$	C, H, N, Cl
7	H	4-$CH(CH_3)_2$	H	n-C_4H_9	148–149 (B)	B	15[e]	$C_{24}H_{28}N_2O_2$	C, H, N
8	CH_3	4-$CH(CH_3)_2$	H	n-C_4H_9	147–148 (B)	B	7[e]	$C_{25}H_{30}N_2O_2$	C, H, N
9	Cl	4-$CH(CH_3)_2$	H	n-C_4H_9	137–138 (B)	B	10[e]	$C_{24}H_{27}N_2O_2Cl$	C, H, N, Cl
10	H	4-OCH_3	H	n-C_4H_9	150–151 (C)	B	25[e]	$C_{22}H_{24}N_2O_3$	C, H, N
11	CH_3	4-OCH_3	H	n-C_4H_9	133–134 (C)	B	10[e]	$C_{23}H_{26}N_2O_3$	C, H, N
12	Cl	4-OCH_3	H	n-C_4H_9	127–128 (B)	B	15[e]	$C_{22}H_{23}N_2O_3Cl$	C, H, N, Cl
13	H	2-OCH_3	H	n-C_4H_9	110–111 (C)	B	20[e]	$C_{22}H_{24}N_2O_3$	C, H, N
14	CH_3	2-OCH_3	H	n-C_4H_9	123–124 (C)	B	8[e]	$C_{23}H_{26}N_2O_3$	C, H, N
15	Cl	2-OCH_3	H	n-C_4H_9	128–129 (C)	B	12[e]	$C_{22}H_{23}N_2O_3Cl$	C, H, N, Cl
16	H	3-OCH_3	4-OCH_3	n-C_4H_9	108–109 (B)	A, B	15,[d] 20[e]	$C_{23}H_{26}N_2O_4$	C, H, N
17	CH_3	3-OCH_3	4-OCH_3	n-C_4H_9	120–121 (B)	A, B	7,[d] 12[e]	$C_{24}H_{28}N_2O_4$	C, H, N
18	Cl	3-OCH_3	4-OCH_3	n-C_4H_9	123–124 (B)	A, B	10,[d] 15[e]	$C_{23}H_{25}N_2O_4Cl$	C, H, N, Cl
19	H	3-OCH_2O-4		n-C_4H_9	145–146 (B)	A, B	15,[d] 20[e]	$C_{.2}H_{24}N_2O_4$	C, H, N
20	CH_3	3-OCH_2O-4		n-C_4H_9	133–134 (B)	A, B	5,[d] 10[e]	$C_{23}H_{26}N_2O_4$	C, H, N
21	Cl	3-OCH_2O-4		n-C_4H_9	155–156 (B)	A, B	20,[d] 30[e]	$C_{22}H_{23}N_2O_4Cl$	C, H, N, Cl
22	H	2-OCH_3	5-CH_3	n-C_4H_9	98–99 (B)	B	11[e]	$C_{23}H_{26}N_2O_3$	C, H, N
23	CH_3	2-OCH_3	5-CH_3	n-C_4H_9	114–115 (B)	B	8[e]	$C_{24}H_{28}N_2O_3$	C, H, N
24	Cl	2-OCH_3	5-CH_3	n-C_4H_9	113–114 (B)	B	12[e]	$C_{23}H_{25}N_2O_3Cl$	C, H, N, Cl
25	H	2-OCH_3	3-CH_3	n-C_4H_9	89–90 (C)	B	10[e]	$C_{23}H_{26}N_2O_3$	C, H, N
26	CH_3	2-OCH_3	3-CH_3	n-C_4H_9	107–108 (C)	B	6[e]	$C_{24}H_{28}N_2O_3$	C, H, N
27	Cl	2-OCH_3	3-CH_3	n-C_4H_9	102–103 (B)	B	10[e]	$C_{23}H_{25}N_2O_3Cl$	C, H, N, Cl
28	H	4-Cl	H	n-C_4H_9	190–191 (B)	A, B	30,[d] 35[e]	$C_{21}H_{21}O_2N_2Cl$	C, H, N, Cl
29	CH_3	4-Cl	H	n-C_4H_9	178–179 (B)	A, B	10,[d] 15[e]	$C_{22}H_{23}N_2O_2Cl$	C, H, N, Cl
30	Cl	4-Cl	H	n-C_4H_9	172–173 (B)	A, B	15,[d] 20[e]	$C_{21}H_{20}N_2O_2Cl_2$	C, H, N, Cl
31	H	H	H	n-C_5H_{11}	142–143 (B)	1, 2	40,[e] 30[d]	$C_{22}H_{24}N_2O_2$	C, H, N

[a] Recrystallization solvent: A, EtOAc; B, C_6H_6–EtOH; C, EtOH. [b] Preparation method: A, general method A; B, general method B; 1, Method 1; 2, method 2. [c] Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [d] Method A. [e] Method B.

Chemistry.—1-Phenyl-2-styryl-3,5-dioxopyrazolidines (II) were prepared from phenylacetaldehydes phenylhydrazones (VII), which were obtained by treating phenylacetaldehydes (VI) with phenylhydrazines. Compound VI was prepared by the following three routes (Scheme I): (A) oxidation of 3-phenylglycols (III) with $Pb(OAc)_4$ in C_6H_6,[4] (B) decarboxylation of sodium β-phenylglycidates (IV),[5] and (C) catalytic hydrogenation of acid chloride V in the presence of Rosemund's catalyst.[6]

Reaction of VI with phenylhydrazines readily gave VII in good yield. When VII was acylated with diethyl alkylmalonate in the presence of NaOEt, migration of the $C{=}N^2$ double bond accompanies the acylation, and the formation of a pyrazolidine ring is achieved. During this reaction, N^1-acylphenylhydrazones (VIII) seem to be formed as intermediates, though this is not certain.

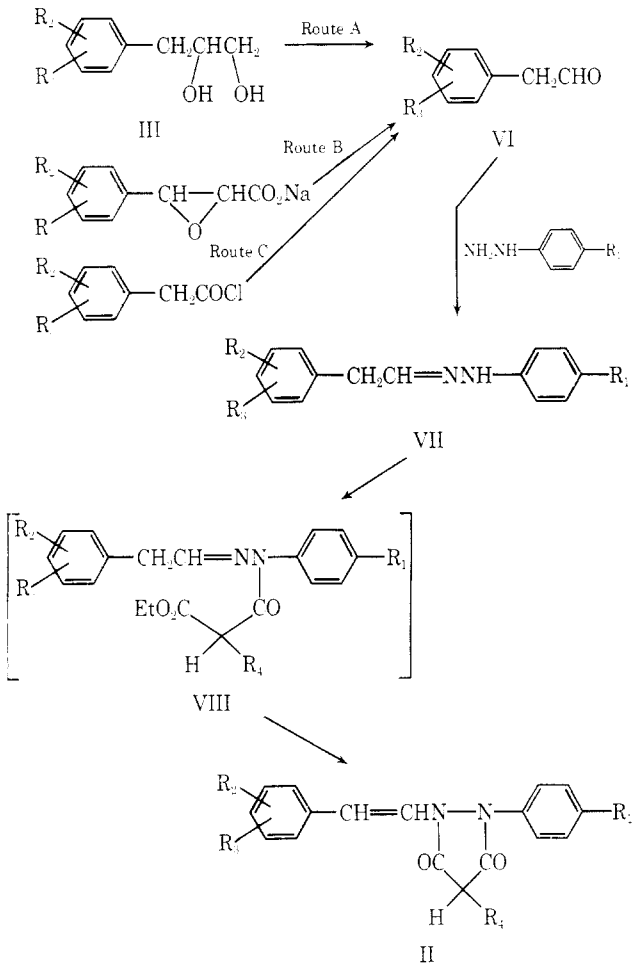
The structure of the resulting products (II) was determined by the elementary analysis and ir, uv, and nmr spectra. For example, the structure of 1-phenyl-2-styryl-4-n-butyl-3,5-dioxopyrazolidine is confirmed by the elementary analysis and the ir bands at 1760, 1710, and 1650 cm^{-1}, the nmr olefinic proton signals at δ 6.0 (J = 15 Hz) due to the *trans* configuration, and the uv maxima at 270 mμ (ε 16,300) and 305 (15,000).

Pharmcological Results.—Compounds **1**, **2**, **10**, **11**, **12**, **19**, **20**, and **30** showed remarkable inhibitory activity on rat paw edema induced by injection of carrageenin. Especially, **2** and **12** exhibited more potent activity than phenylbutazone and oxyphenbutazone.

In these compounds, the p-methyl substituent of the phenyl ring increases the intrinsic activity in general (**2**, **11**, **20**), while the p-chloro substituent decreases the activity except in **12**. The p-methoxy or 3,4-methyl-

(4) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 4252 (1956).
(5) Y. Ban and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **6**, 574 (1958).
(6) K. W. Rosemund and F. Zetzche, *Ber.*, **54**, 425 (1921).

SCHEME I



enedioxy substituent of the styryl group tends to enhance toxicity as well as inhibitory activity (**10**, **11**, **12**, **19**, **20**). Conversely, *p*-alkyl substituents, *e.g.*, Me or *i*-Pr, in the styryl group seems to decrease the activity.

Experimental Section[7]

1-Phenyl-2-styryl-4-*n*-butyl-3,5-dioxopyrazolidines (II). Method A.—A mixture of 0.1 mol of a suitable phenylacetaldehyde phenylhydrazone derivative and 20 g of diethyl *n*-butylmalonate in 150 ml of xylene was added to a solution of NaOEt (2 g of Na) in 100 ml of EtOH. The mixture was heated at 100° with stirring to slowly evaporate EtOH from the mixture during 2 hr, and the residual mixture was heated at 140° for 7 hr. After cooling, the reaction mixture was poured into H_2O, acidified with dilute HCl, and extracted with EtOAc. The extract was washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting oily residue crystallized on treatment with EtOH and was recrystallized from C_6H_6–MeOH to give the corresponding II derivative. See Table I for melting points and yields.

Method B.—A mixture of 0.07 mol of a suitable *p*-chlorophenylacetaldehyde derivative and 0.07 mol of a suitable phenylhydrazine derivative in 100 ml of C_6H_6 was warmed at 50–60° for 1 hr. This reaction mixture was decanted to remove the resulting H_2O and was dried (Na_2SO_4). A solution of the resulting phenylacetaldehyde phenylhydrazone derivative and 0.07 mol of diethyl *n*-butylmalonate in C_6H_6 was added to a solution of NaOEt (2 g of Na) in 100 ml EtOH. The resulting mixture was heated with stirring at 80–90° to remove EtOH and C_6H_6. After excess solvent was distilled off, 100 ml of xylene was added to the

(7) Melting points are uncorrected, and determined in open capillary tubes. Ir spectra were recorded on a Simadzu IR-27G spectrophotometer and nmr spectra were taken on a Varian A-60 spectrophotometer.

TABLE II: ANTIINFLAMMATORY ACTIVITY[a]

No.	Dose[b] (mg/kg)	Inhibition[c] of edema, %	Toxicity[d]
1	200	32.3	−
2	400	42.0	++
2	50	26.9	−
	100	53.8	−
	400	68.9	++
3	200	25.6	−
4	200	10.2	−
5	200	0	−
6	200	7.0	−
7	200	16.0	−
8	200	10.7	−
9	200	8.8	−
	400	21.5	−
10	50	16.1	−
	200	62.3	+
	400	63.6	++
11	50	34.5	−
	200	62.3	+
	400	71.4	++
12	20	18.7	−
	50	45.0	−
	200	78.1	++
13	200	0	−
	400	37.0	−
14	200	0	−
15	200	9.7	−
	400	29.3	−
16	200	33.3	−
	400	45.7	−
17	200	32.1	−
	400	43.2	+
18	200	25.9	−
19	50	36.6	−
	200	37.4	+
	400	65.3	++
20	50	36.6	−
	200	57.2	+
	400	61.1	++
21	200	28.6	++
22	200	17.4	−
	400	40.7	−
23	200	20.4	−
24	200	5.1	−
	400	30.7	−
25	200	28.7	−
	400	38.3	+
26	200	10.2	−
	400	25.0	−
27	200	21.6	−
	400	31.8	−
28	200	37.5	−
	400	43.2	−
29	200	25.0	−
	400	31.8	−
30	50	30.5	−
	200	52.2	+
	400	62.5	++
31	50	21.6	−
	100	37.8	−
	200	41.2	+
Phenylbutazone	50	31.0	−
	200	52.1	−
	400	53.5	+
Oxyphenbutazone	200	47.3	−
	400	51.0	+

[a] Evaluation of antiinflammatory activity. [b] Administration of the test compounds and [c] measurement of foot volume were carried out by the procedure described previously in ref 8. [d] (−) no blood in feces, body weight gain normal; (+) no blood in feces, body weight decreased; (++) blood in feces, body weight decreased.

reaction mixture and it was heated at 140° for 10 hr. After cooling, the reaction mixture was poured into H_2O and acidified with dilute HCl. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. The oily residue crystallized on treatment with EtOH and was recrystallized from EtOH to give the corresponding 1-phenyl-2-styryl-4-*n*-butyl-3,5-dioxopyrazolidine derivative.

1-Phenyl-2-styryl-4-*n*-pentyl-3,5-dioxopyrazolidine (31). Method 1.—A solution of 5 g of phenylacetaldehyde phenylhydrazone and 17 g of diethyl *n*-pentylmalonate in 150 ml of xylene was added to a solution of NaOEt (3 g of Na) in 100 ml of EtOH. The mixture was stirred at 100° until the EtOH was removed from the mixture; stirring was continued at 140° for an additional 14 hr. The reaction mixture was poured into H_2O and acidified with dilute HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc. The extract was combined with the organic layer, washed with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue crystallized on treatment with EtOH. Recrystallization from EtOH–C_6H_6 gave 10 g of **31**.

Method 2.—A mixture of 6 g of phenylacetaldehyde and 5.5 g of phenylhydrazine in 150 ml of C_6H_6 was heated at 50–60° for 0.5 hr. The reaction mixture was decanted to remove H_2O and dried (Na_2SO_4). The solution of phenylacetaldehyde phenylhydrazone in C_6H_6 was added to a solution of NaOEt (2 g of Na) and 12 g of diethyl *n*-pentylmalonate in 100 ml of EtOH. After excess of the solvent was distilled off, 100 ml of xylene was added to the residual mixture and the mixture was heated at 140° for 10 hr. By subsequent treatment similar to that of method 1 1.5 g of **31** was obtained.

Pharmacological Tests.—The antiinflammatory activity of these compounds was tested in the carrageenin-induced foot edema in rats.[8] The results are shown in Table II.

Acknowledgment.—The authors wish to express their appreciation to Dr. H. Nakatani, Mr. C. Saito, and Mr. H. Awata for the pharmacological screening data and Mr. Iwai and coworkers for the analytical data.

(8) H. Yamamoto and M. Nakao, *J. Med. Chem.* **12**, 176–178 (1969).

2-Trifluoromethoxydibenz[*b*,*e*][1,4]diazepine and 2-Trifluoromethoxydibenz[*b*,*f*][1,4]-oxazepine Derivatives

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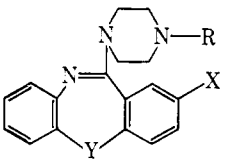
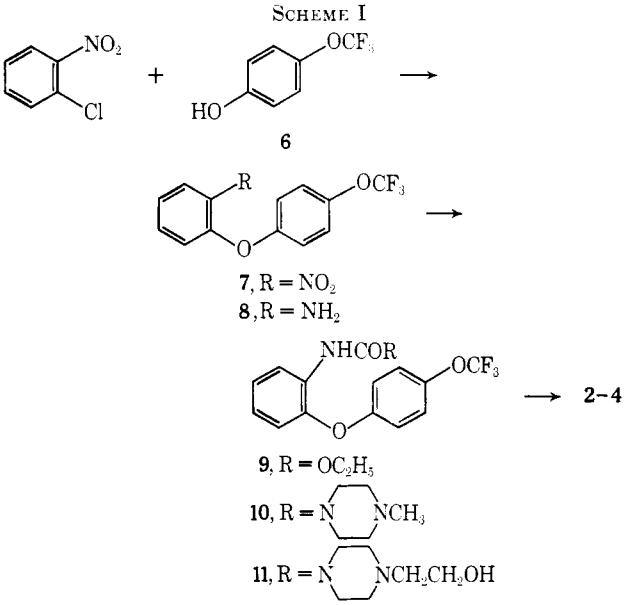
In view of the interest of these laboratories in the action on the central nervous system elicited by 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine (**1**)[1b,2] and the demonstrated ability of the trifluoromethoxy group to function as a pseudohalogen,[3] we have prepared the 2-trifluoromethoxy analogs, *e.g.*, **2–5**, of **1** and certain congeners in order to assess their effects on the CNS.

The preparation of the dibenz[*b*,*f*][1,4]oxazepines **2–4** from *p*-trifluoromethoxyphenol (**6**) proceeded as noted



1, R = CH_3; X = Cl; Y = O
2, R = CH_3; X = CF_3O; Y = O
3, R = CH_2CH_2OH; X = CF_3O; Y = O
4, R = CH_2CH_2Cl; X = CF_3O; Y = O
5, R = CH_3; X = CF_3O; Y = NCH_3

SCHEME I



6

7, R = NO_2
8, R = NH_2

9, R = OC_2H_5
10, R = N NCH$_3$
11, R = N NCH_2CH_2OH

in Scheme I. Ring closure of the piperazinecarboxanilide II ($POCl_3$, P_2O_5) gave the hydroxyethyl derivative **3** in one instance, but repetition with newly opened $POCl_3$ gave the cholorethyl derivative **4**.

With one exception the preparation of the related dibenz[*b*,*e*][1,4]diazepine **5** was accomplished by procedures previously found useful for the synthesis of members of this series.[4] Attempts to prepare the requisite diphenylamine **14** by Cu-catalyzed condensation of *p*-trifluoromethoxyaniline and 2-nitrochlorobenzene proved unsatisfactory. However, Chapman rearrangement[5] of imino ether **12** proved to be an excellent alternative. The conversion of **14** into the desired **4** is outlined in Scheme II.

Pharmacology.—Compounds **2–5** were tested for their ability to induce ataxia, to decrease locomotor activity, and to afford protection against electroshock-induced and strychnine-induced convulsions in mice. The activities of the more interesting trifluoromethoxy compounds are given in Table I. Comparable data for the corresponding chloro derivatives are included. These limited tests suggest that the replacement of 2-Cl by OCF_3 in the 11-(4-substituted 1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine series results in compounds having similar profiles of CNS effects.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Where analyses are

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