Novel Polycyclic Heterocycles. Derivatives of 5,11-Dihydrodibenz[*b*,*e*][1,4]oxazepine and 5,11-Dihydrodibenzo[*b*,*e*][1,4]thiazepine[1]

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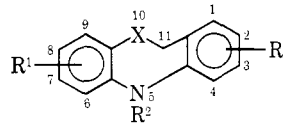
A number of 5-substituted 5,11-dihydrodibenz[*b*,*e*][1,4]oxazepines and 5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepines have been prepared. When the 5-substituent is 3-[1-(2-hydroxyethyl)-4-piperazinyl]propyl and a substituent like Cl or CF_3 is in the 3, or 7 position, the compounds show antianxiety effects at lower doses and CNS depressant activity at higher doses. When the 5 substituent is a simple dialkylaminoalkyl group, then the compounds are not CNS depressants at either dose level, but instead are CNS stimulants, but only at the higher dose range.

In our earlier papers[2] we have described the synthesis of a number of derivatives of 5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine (**1**) and compared several of these for their antihistaminic and anticonvulsant activities. The present paper is concerned largely with a comparison of the CNS effects of a wider variety of derivatives of that heterocycle as well as of derivatives of the related heterocycle, 5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine (**2**).



1, X = O; R^2 = H
2, X = S; R^2 = H
3, R = $(CH_2)_3Cl$
4, R = $CH_2CH{:}CH_2$
R, R^1 = H, Cl, Br, CF_3

The synthetic route to *ar*-substituted **1** described previously,[2a] involved the preparation initially of an *o*-bromobenzyl-*o*-nitrophenyl ether, followed by Fe–HCl reduction to the *o*-(*o*-bromobenzyloxy)aniline·HCl, then formanilide formation and cyclization in DMF. N-Formylation was essential for cyclization since the aniline derivative did not cyclize.

The availability of a large number of aminophenols suggested their use as intermediates; however, reaction of *o*-aminophenol with *o*-bromobenzyl bromide and base gave only *o*-[*N*,*N*-di(*o*-bromobenzyl)amino]-phenol plus large amounts of unresolvable by-products. The *o*-formamidophenols were highly and specifically reactive and gave the (*o*-bromobenzyloxy)formanilides directly in good yield. While the *o*-acetamidophenols were equally reactive toward *o*-bromobenzyl bromide, the (*o*-bromobenzyloxy)acetanilides were less satisfactory in the subsequent cyclization step, requiring much higher reaction temperatures and giving lower yields of **1**. It was noteworthy that the *o*-bromobenzyloxy carbanilides cyclized as readily as did the formanilides.

With *o*-aminobenzenethiols, *o*-bromobenzyl bromides and base reacted almost exclusively with the thiol group to give the *o*-(*o*-bromobenzylthio)anilines. These were isolated most conveniently as their hydrochlorides, converted by means of formic acid–sodium formate into the formanilides, and then cyclized to **2**. *o*-Aminobenzenethiol and formic acid, even under N_2, gave only 2,2′-dithiodiformanilide and not the desired *o*-mercaptoformanilide; thus, this class of compounds was not readily available for reaction with the *o*-bromobenzyl bromides.

The orginal procedure[2a] for cyclization involved the use of DMF, anhydrous K_2CO_3, and Cu bronze at about 155°. Invariably, the reaction gave highly colored crude products from which it was difficult to isolate the N-formylated **1** or **2**. The problem was readily solved with **1** and its *ar*-substituted derivatives by saponifying the crude mixture and then selectively extracting the desired product from the highly colored by-products with a solvent like hexane. This procedure was also effective for **2**(R = R^1 = H), but could not be used to prepare 3- or 7-substituted derivatives of **2**, since in DMF only highly colored tars were isolated. Once **1** and **2** were isolated they could not be reformylated by any of the known procedures although they could be N-acetylated with Ac_2O–*p*-toluenesulfonic acid. Since the *N*-formyl derivatives were required for another pharmacodynamic study, it was decided to investigate other solvents in place of DMF in the hope (a) that these derivatives might be more easily isolated and (b) that another solvent might lead to the *ar*-substituted **2**. This study has now shown that Dowtherm A (a eutectic of biphenyl and diphenyl ether), diethylbenzene, and diphenyl ether were far superior to DMF, giving excellent yields of N-formylated **1** and **2** and *none* of the colored by-products formed in DMF. Several other solvents, *e.g.*, isopropylbenzene, *p*-isopropyltoluene, biphenyl, and nitrobenzene were inferior to the three mentioned above.

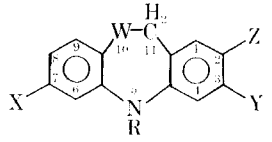
In our earlier paper,[2a] **1** was reacted with an aminoalkyl halide in either THF or DMSO, using NaH to generate the heterocyclic anion. We have now found that the heterocycles **1** and **2** react readily with dialkylaminoalkyl halides in Me_2CO, employing granular NaOH as the base. Since a major part of the present investigation required the preparation of 5-{3-[1-(2-hydroxyethyl)-4-piperazinyl]-propyl} derivatives, these were prepared *via* the 5-(3-chloropropyl) compounds **3** by reaction with 2-piperazineethanol. The procedure developed for **3** was an outgrowth of the Me_2-

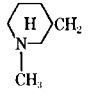
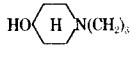
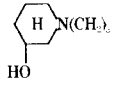
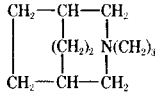
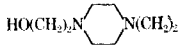
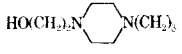
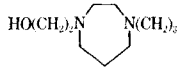
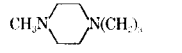
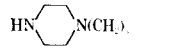
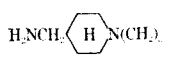
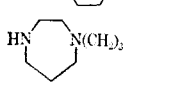
(1) Presented in part before the Division of Medicinal Chemistry, 159th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(2) (a) H. L. Yale and F. Sowinski, *J. Med. Chem.*, **7**, 609 (1964); (b) H. L. Yale and F. Sowinski, *ibid.*, **10**, 1022 (1967); (c) H. L. Yale, *ibid.*, **11**, 396 (1968).

Table I

Basic Derivatives of 5,11-Dihydrodibenz[*b*,*e*][1,4]oxazepine and 5,11-Dihydrodibenzo[*b*,*e*][1,4]thiazepine



						Bases						Salts							
No.	W	X	Y	Z	R	Formula	Mp or bp, °C (mm)	Yield, %[a]	Analyses			Formula	Mp, °C	Recrystn solvent	Yield, %	Analyses			
1	O	CF_3	H	H	$(CH_3)_2N(CH_2)_2$	$C_{18}H_{19}F_3N_2O$		100[c]				$C_{18}H_{19}F_3N_2O \cdot C_4H_4O_4$	166–167	A	60	C	H	N	NE[d]
2	O	CF_3	H	H	$(C_2H_5)_2N(CH_2)_2$	$C_{20}H_{23}F_3N_2O$	152–157 (0.2)	80	C	H	N	$C_{20}H_{23}F_3N_2O \cdot C_4H_4O_4$	150–152	A	87	C	H	N	
3	O	CF_3	H	H	$H_2N(CH_2)_3$	$C_{17}H_{17}F_3N_2O$		86[c]				$C_{17}H_{17}F_3N_2O \cdot HCl$	176–180 dec	B	81			N	NE[d] Cl⁻
4	O	CF_3	H	H	$(CH_3)_2N(CH_2)_3$	$C_{19}H_{21}F_3N_2O$		72[c]				$C_{19}H_{21}F_3N_2O \cdot HCl$	184–187	B	51	C	H	N	Cl⁻
5a	O	CF_3	H	H	$(CH_2)_4N(CH_2)_3$	$C_{21}H_{23}F_3N_2O$	170–180 (0.12)	73	C	H	N	$C_{21}H_{23}F_3N_2O \cdot HCl$	173–176	A	84	C	H	N	
5b												$C_{21}H_{23}F_3N_2O \cdot C_2H_2O_4$	183–185	C	53	C	H	N	
6	O	CF_3	H	H	$(CH_2)_5N(CH_2)_3$	$C_{22}H_{25}F_3N_2O$		73[c]			N	NE[d] $C_{22}H_{25}F_3N_2O \cdot C_2H_2O_4$	167–170	D	93			N	NE[d,e]
7	O	CF_3	H	H		$C_{21}H_{23}F_3N_2O$	200–220 (0.07)	42			N	NE[d] $C_{21}H_{23}F_3N_2O \cdot C_{28}H_{16}O_6$[f]	175–200	g	100	C	H	N	
8	O	CF_3	H	H		$C_{22}H_{25}F_3N_2O_2$	c	100			N	NE[d]			h				
9	O	CF_3	H	H		$C_{22}H_{25}F_3N_2O_2$	c	100			N	NE[d]			h				
10	O	CF_3	H	H		$C_{23}H_{29}F_3N_2O$	i	64			N	NE[d] $C_{23}H_{29}F_3N_2O \cdot HCl$	239–240	D	48			N	NE[d] Cl⁻
11	O	CF_3	H	H		$C_{29}H_{36}F_3N_3O_2$	c	5				$C_{29}H_{36}F_3N_3O_2 \cdot 2C_4H_4O_4 \cdot 0.5H_2O$	178–180	E	5	C	H	N	
12a	O	CF_3	H	H		$C_{25}H_{31}F_3N_3O_2$	i	41			N	NE[d] $C_{25}H_{29}F_3N_2O \cdot 2HCl$[f]	197–200	D	70	C	H	N	NE[d] Cl⁻
12b												$C_{25}H_{29}F_3N_2O \cdot 2C_4H_4O_4$	158–161	E	77	C	H	N	
12c												$C_{25}H_{29}F_3N_2O \cdot C_6H_8O_7 \cdot 2H_2O$	110–114 dec	k	56			N	
12d												$C_{25}H_{29}F_3N_2O \cdot C_{28}H_{16}O_6 \cdot H_2O$[f,g]	146–164	g	100			N	NE[e]
13	O	CF_3	H	H		$C_{24}H_{30}F_3N_3O_2$	c	98				$C_{24}H_{30}F_3N_3O_2 \cdot 2C_4H_4O_4$	117–120	F	85	C	H	N	
14	O	CF_3	H	H		$C_{22}H_{25}F_3N_2O$	c	90				$C_{22}H_{26}F_3N_3O \cdot 2HCl$	256–258 dec	B	81	C	H	N	Cl⁻
15	O	CF_3	H	H		$C_{21}H_{23}F_3N_2O \cdot H_2O$	c	95			N	NE[e]	$C_{21}H_{24}F_3N_3O \cdot 2C_4H_4O_4$	156–159	E	77			N	NE[d]
16	O	CF_3	H	H		$C_{23}H_{25}F_3N_2O$	200–210 (0.05)	81	C	H	N	$C_{23}H_{25}F_3N_2O \cdot 2C_4H_4O_4$	163–167	E	74	C	H	N	
17	O	CF_3	H	H		$C_{22}H_{26}F_3N_3O$	c	65			N	NE[d]	$C_{22}H_{26}F_3N_3O \cdot 2C_4H_4O_4$	118–121	F	61	C	H	N	

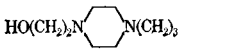
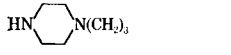
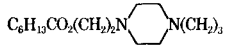
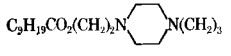
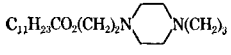
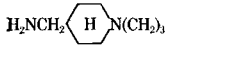
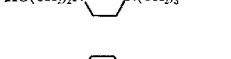
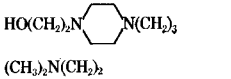
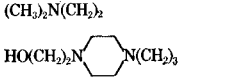
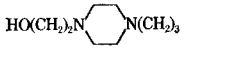
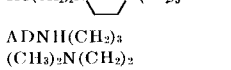
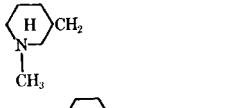
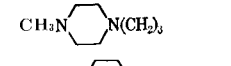
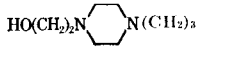
18	O	CF_3	H	H	ADNH$(CH_2)_3$[e]	$C_{27}H_{31}F_3N_2O$	*c*	*m*				$C_{27}H_{31}F_3N_2O \cdot HCl$	244–249	E	32			N	NE[d]	Cl^-
19	O	CF_3	H	H	$H_2NC(:NH)NH(CH_2)_3$	$C_{18}H_{19}F_3N_4O$	*c*	*m*				$C_{18}H_{19}F_3N_4O \cdot 0.5H_2SO_4$	199–206 dec	G	43	C	H	N		*n*
20	O	Cl	H	H		$C_{22}H_{28}ClN_3O_2$	91–93[o]	100	C	H	N	$C_{22}H_{28}ClN_3O_2 \cdot 2HCl$	224–226 dec	D					NE[d]	Cl^-
20a												$C_{22}H_{28}ClN_3O_2 \cdot 2C_4H_4O_4$	171–173 dec	D	67	C	H	N		
21	O	Cl	H	H		$C_{20}H_{24}ClN_3O$	*c*	89				$C_{20}H_{24}ClN_3O \cdot 2C_4H_4O_4$	159–160 dec	D	68	C	H	N		
22	O	Cl	H	H		$C_{29}H_{40}ClN_3O_3$	*c*	98	C	H	N	$C_{29}H_{40}ClN_3O_3 \cdot 2C_4H_4O_4$	171–172	H	78	C	H	N		
23	O	Cl	H	H		$C_{32}H_{46}ClN_3O_3$	*c*	99	C	H	N	$C_{32}H_{46}ClN_3O_3 \cdot 2C_4H_4O_4$	171–172	H	78	C	H	N		
24	O	Cl	H	H		$C_{34}H_{50}ClN_3O_3$	*c*	94				$C_{34}H_{50}ClN_3O_3 \cdot 2C_4H_4O_4$	170–171	D	49	C	H	N		
25	O	Cl	H	H		$C_{22}H_{28}ClN_3O$	160–165 (0.05)	44	C	H	N	$C_{22}H_{28}ClN_3O \cdot 2C_4H_4O_4$	168–170	D	55	C	H	N		
26	O	H	Cl	H	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{19}ClN_2O$	154–159 (0.3) 61–63	82	C	H	N	Cl	$C_{17}H_{19}ClN_2O \cdot HCl$	230–232 dec	A	67	C	H	N		Cl^p
27a	O	H	Cl	H		$C_{22}H_{28}ClN_3O_2$	*c*	80				$C_{22}H_{28}ClN_3O_2 \cdot 2HCl$	227–230	*q*	82	C	H	N	NE[d]	Cl^-
27b												$C_{22}H_{28}ClN_3O_2 \cdot 2C_4H_4O_4$	170–171	E	63	C	H	N		
28	O	Cl	Cl	H		$C_{22}H_{27}Cl_2N_3O_2$		65				$C_{22}H_{27}Cl_2N_3O_2 \cdot 2C_4H_4O_4$	153–156	E	78	C	H	N		Cl^-
29	O	H	Cl	Br	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{18}BrClN_2O$	200–210 (0.05)	100	C	H	N		$C_{17}H_{18}BrClN_2O \cdot H_3PO_4$	224–226	I	49					*i*
30	O	H	Cl	Br		$C_{22}H_{27}BrClN_3O_2$	*c*	38				$C_{22}H_{27}BrClN_3O_2 \cdot 2HCl \cdot 0.5H_2O$	215–217	E	65	C	H	N	NE[d]	
31	O	H	H	H	$H_2N(CH_2)_3$	$C_{16}H_{18}N_2O$	40[j]	*c*	C	H		NE	$C_{16}H_{18}N_2O \cdot HCl$	249–253	H	48	C	H	N	NE[d]	Cl^-
32	O	H	H	H	$(C_2H_5)_2N(CH_2)_3$	$C_{20}H_{26}N_2O$	180–185 (0.05)	100							*h*						
33	O	H	H	H	$H_2NC(:NH)NH(CH_2)_3$	$C_{17}H_{20}N_4O$	*m*					$C_{17}H_{20}N_4O \cdot 0.5H_2SO_4$	206–211	J	21			N		*n*
34	O	H	H	H		$C_{22}H_{29}N_3O_2$	*c*					$C_{22}H_{29}N_3O_2 \cdot 2HCl \cdot H_2O$	193–195	D	12			N		Cl^-
35	S	CF_3	H	H	$(CH_3)_2N(CH_2)_2$	$C_{18}H_{19}F_3N_2S$	180–190 (0.5)	95	C	H	N		$C_{18}H_{19}F_3N_2S \cdot HCl$	238–243	K	53	C	H	N		
36	S	CF_3	H	H		$C_{23}H_{28}F_3N_3OS$	220–230 (0.05)	52[m]	C	H	N		$C_{23}H_{28}F_3N_3OS \cdot 2C_4H_4O_4$	171–174	E	75	C	H	N		
37	S	CF_3	H	H	ADNH$(CH_2)_3$	$C_{21}H_{31}F_3N_2S$	*c*					$C_{21}H_{31}F_3N_2S \cdot HCl$	260–262	E	50	C	H	N		*n*
38a	S	H	H	H	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{20}N_2S$	*c*	82				$C_{17}H_{20}N_2S \cdot C_4H_4O_4$	154–155	D	46			N		
38b												$C_{17}H_{20}N_2S \cdot 1.5H_3PO_4$	199–201	L	55			N		
39	S	H	H	H	$(C_2H_5)_2N(CH_2)_2$	$C_{19}H_{24}N_2S$	175–178 (0.1)	68	C	H	N	*n*	$C_{19}H_{24}N_2S \cdot 2H_3PO_4$	148–151	B	65				NE[d]	*t*
40	S	H	H	H	$(CH_3)_2N(CH_2)_3$	$C_{18}H_{22}N_2S$	178–180 (0.1)	22			N	NE[d]	$C_{18}H_{22}N_2S \cdot 1.5H_3PO_4$	166–168	M	58				NE[d]	*t*
41	S	H	H	H	$(C_2H_5)_2N(CH_2)_3$	$C_{20}H_{26}N_2S$	190–195 (0.06)	80	C	H	N	*u*	$C_{20}H_{26}N_2S \cdot C_2H_2O_4$	144–145	D	54	C	H	N		*n*
42	S	H	H	H	$(CH_3)_2NCH(CH_3)CH_2$[u]	$C_{18}H_{22}N_2S$	178–182 (0.1)		C	H	N	*n*	$C_{18}H_{22}N_2S \cdot H_3PO_4 \cdot H_2O$[s]	225–226	L	49				NE[d]	*n*
43	S	H	H	H	$(CH_3)_2NCH_2CH(CH_3)CH_2$	$C_{19}H_{24}N_2S$	165–168 (0.15)	70	C	H	N	*n*	$C_{19}H_{24}N_2S \cdot 1.5H_3PO_4$	209–211	L	21				NE[d]	*t*
44	S	H	H	H		$C_{20}H_{24}N_2S \cdot H_2O$		*i*				NE[n]	$C_{20}H_{24}N_2S \cdot 1.5H_3PO_4 \cdot 2H_2O$	246–249 dec	M	48					*t*
45	S	H	H	H		$C_{21}H_{27}N_3S$	81–85	69	C	H	N	*n*	$C_{21}H_{27}N_3S \cdot 2C_4H_4O_4$	190–192	E	88	C	H	N		*n*
46	S	H	H	H		$C_{22}H_{29}N_3OS$	*c*	7				$C_{22}H_{29}N_3OS \cdot 2C_4H_4O_4$	157–159	E	63	C	H	N		

TABLE I (*Continued*)

No.	W	X	Y	Z	R	Bases: Formula	Bases: Mp or bp, °C (mm)	Bases: Yield, %[a]	Bases: Analyses	Salts: Formula	Salts: Mp, °C	Salts: Recrystn solvent	Salts: Yield, %	Salts: Analyses
47	S	Cl	H	H	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{19}ClN_2S$	155–157 (0.05)		C H N NE[d]	$C_{17}H_{19}ClN_2S \cdot C_4H_4O_4$	170–172	D	77	C H N NE[d,e]
48	S	Cl	H	H	$(CH_3)_2N(CH_2)_3$	$C_{18}H_{21}ClN_2S$	79–81	72	C H N *n*	$C_{18}H_{21}ClN_2S \cdot C_4H_4O_4$	153–155 dec	D	87	C H N Cl-*n*
49a 49b	S	Cl	H	H	$HO(CH_2)_2N$⟨ ⟩$N(CH_2)_3$	$C_{22}H_{28}ClN_3OS$	245 (0.03)	100	C H N NE[d]	$C_{22}H_{28}ClN_3OS \cdot 2HCl$ $C_{22}H_{28}ClN_3OS \cdot 2C_4H_4O_4$	233–235 dec 155–157 dec	E E	41 56	NE[d] Cl-*n* NE[d,e] Cl-*p*
50	S	Cl	Cl	H	$HO(CH_2)_2N$⟨ ⟩$N(CH_2)_3$	$C_{22}H_{27}Cl_2N_3OS$	*i*	53	NE[f]	$C_{22}H_{27}Cl_2N_3OS \cdot 2HCl$	222–224	D	63	C H N
51	S	Cl	H	H	$ADNH(CH_2)_3$	$C_{26}H_{31}ClN_2S$				$C_{26}H_{31}ClN_2S \cdot HCl$	234–236	N	26	C H N
52	SO	H	H	H	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{20}N_2OS$				$C_{17}H_{20}N_2OS \cdot 1.5H_3PO_4$	58 dec	*h*	72	N NE[d]
53	SO	Cl	H	H	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{19}ClN_2OS$	103–104	24	C H N NE[d]					
54	SO_2	Cl	H	H	$(CH_3)_2N(CH_2)_2$	$C_{17}H_{19}ClN_2O_2S$	168–170	18	C H N NE[d]					

[a] Yields are based on the quantity of material used in the reaction directly involved in the preparation of the compound listed and represent the purified materials except for the *bases* which were not distilled. [b] Recrystallization solvents are: (A) dry Me_2CO–dry Et_2O; (B) abs EtOH–dry Et_2O; (C) *n*-PrOH; (D) *i*-PrOH; (E) MeCN; (F) dry MeCN–dry Et_2O; (G) H_2O; (H) abs EtOH; (I) dry MeCN–abs EtOH; (J) abs MeOH dry Et_2O; (K) *i*-PrOH–Et_2O; (L) 95% EtOH; (M) MeCN–H_2O; (N) EtCN. [c] Bases not distd. [d] Titration in glacial AcOH with $HClO_4$. [e] Titration in aq EtOH with aq NaOH. [f] Pamoate salt. [g] Not recrystallized. [h] No suitable salt could be prepared. [i] Isolated from purified salt by treatment with base; not distilled. [j] Crystallizes as the alcoholate which is stable even after 5 hr at 80° (1 mm). *Anal.* (C, H, N, NE_2[d] total volatiles). The solvate free dihydrochloride is obtained by heating at 140° (1 mm) for 3 hr. [k] Crude salt washed with anhyd Et_2O. [l] AD = Adamantyl. [m] See Experimental Section for details. [n] *Anal.* (S). [o] Recrystallized from cyclohexane. [p] Total Cl. [q] Base was released from recrystallized dimaleate and converted into a very hygroscopic dihydrochloride. The latter was not recrystallized but dried *in vacuo* at 80° prior to analysis. [r] *Anal.* (Br, P). [s] The monohydrate was stable at 110° (<1 mm); at 140° (<1 mm) it lost both HCl and H_2O. [t] *Anal.* (P, S). [u] A careful search failed to uncover the isomeric product; the structure of this side chain is inferred but not proven (*cf.* H. L. Yale, F. Sowinski, and J. Bernstein, *J. Amer. Chem. Soc.*, **79**, 4375 (1957)). [v] *Anal.* (Cl, S).

CO–NaOH method mentioned above, namely reaction of the heterocycle **1** or **2** with $Cl(CH_2)_3Br$ in EtCOMe, using granular NaOH to form the anion. Derivatives of **3** were formed in 50–75% yields along with 15–25% of the 5-allyl derivatives **4**. The separation of **3** and **4** could be effected by tlc on silica gel but this was not essential for the synthesis. When the mixture was treated directly with 2-piperazineethanol,[3] the aq acid-soluble derivative was easily separated from the neutral **4**. At this time, it is not known whether additional **4** was formed during the reaction of **3** with 2-piperazineethanol. While NaH in DMF also gave the heterocyclic anion, the yields of **3** were significantly lower than those obtained with EtCOMe–NaOH.

The 7-substituted derivatives of **1** and **2** were readily available from the 2-nitro- or 2-formamido-*p*-substituted phenol, or the 2-amino-*p*-substituted benzenethiol, respectively. To prepare the 3-chloro derivatives, *p*-chlorotoluene was subjected to Fe-catalyzed bromination. The monobromo fraction consisted largely of **2**-bromo-*p*-chlorotoluene (**5**), along with lesser amounts presumably of 3-bromo-*p*-chlorotoluene (**6**). The residue from **5** and **6** was almost pure 2,5-dibromo-4-chlorotoluene (**7**). Allylic bromination of the mixture of **5** and **6** gave principally two isomeric benzyl bromides (**8**), while **7** similarly treated gave principally 2,5-dibromo-4-chlorobenzyl bromide (**9**). Both **8** and **9** were used directly in the next step without purification. The two benzyl ethers derived from **8** were readily separated during the work-up of the reaction mixture. Compound **9** led eventually to the 2-bromo-3-chloro derivative of **1**.

The 10-oxides of **2** were prepared by treating the *N*-formyl derivatives (**10**) with 1 equiv of *m*-chloroperbenzoic acid in $CHCl_3$ at room temperature and then saponifying to remove the *N*-formyl group. Alternately, the protonated 5-dialkylaminoalkyl derivative of **2** and EtOH–H_2O_2 under reflux also gave the 10-oxides. Performic acid and **10** reacted spontaneously and were subsequently heated at 90–95° to give the 10,10-dioxides,[4] these again could be saponified to remove the *N*-formyl group.

The 5-{3-(2-hydroxyethyl)-4-piperazinyl]propyl} derivatives were esterified with heptanoyl, decanoyl, and dodecanoyl chlorides, but with greater difficulty than that encountered with the same derivatives of 2-(trifluoromethyl)phenothiazine.[4]

The base-catalyzed addition of **1** to acrylonitrile gave the 5-propionitrile (**11**); LAH reduction of **11** at about 5° gave the 5-(3-aminopropyl) derivative **12**.[5] The reaction of **3** with K phthalimide in DMF gave the phthalimidopropyl intermediate **13** and **13** with H_2NNH_2 gave **12**. Finally, **12** and 2-methyl-2-thiopseudourea gave the guanidine derivative.

The 5-propionitrile, **11**, and aq alkaline H_2O_2 regenerated **1**. The amide **14** was formed in excellent

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

(4) H. L. Yale, A. Cohen, and F. Sowinski, *J. Med. Chem.*, **6**, 347 (1963). Such compounds would be expected to have a long duration of activity following parenteral administration. For example, fluphenazine enanthate (Prolixin Enanthate®) has been marketed as a parenterally administered, long-acting antipsychotic agent: a single 25 mg dose will exert its therapeutic effects for 1–2 weeks.

(5) An excess of LAH and higher temperatures are to be avoided; hydrogenolysis of the heterocyclic benzyl ether can be a competing reaction. The use of LAH–$AlCl_3$ results in extensive hydrogenolysis (see Experimental Section for details).

yield, however, by hydration with 97% H_2SO_4 at 25–30°.

The heterocycle **1** reacted with $COCl_2$ to give low yields of the carbamoyl chloride;[2c] **2** was even less reactive than **1** toward $COCl_2$, and gave very low yields of the carbamoyl chloride. The carbamoyl chloride with NH_3 gave the urea in only about 1% yield, overall.

Pharmacology and Ancillary Activities.—The major pharmacological work-up was done with two compounds, **12a**·2HCl and **27a**·2HCl. The two compounds were very similar in the several tests enumerated below both as to CNS activity and potency.

Conflict Behavior.—This procedure measures the tendency of the rat to repeat a response for which it has previously been punished. The extent to which the animal repeats the punished response is considered to be a reflection of its decreased anxiety concerning the punishment. After ip doses of 2.0–3.0 mg/kg of either **12a**·2HCl or **27a**·2HCl, the rats responded more often than did saline treated controls and at about the same rate as did rats similarly doses at 8.0 mg/kg with chlordiazepoxide (**15**) or chlorpromazine (**16**).

Pole Jump Conditioned Avoidance.—In this standard procedure, a decrease in avoidance response is considered a measure of the tranquilizing or depressant properties of a compound. Both **12a**·2HCl and **27a**·2HCl, in ip doses of 0.5–1.0 mg/kg, produced a significant increase in avoidance response without affecting escape latency; at 1.0 mg/kg, **16** produced no effect on avoidance response. At 3.0–5.0 mg/kg, **12a**·2HCl and **27a**·2HCl effectively reduced avoidance response without affecting escape latency. At higher doses, avoidance behavior was further reduced and escape latency increased. In this test, **15** showed no activity until high doses were used and then there occurred only an increase in escape latency.

Avoidance Acquisition.—In this procedure, naive rats are placed in a chamber with a wheel mounted on the wall. After 10 sec, a foot shock is presented; turning the wheel stops the shock and resets the timer for another 10 sec. The animal can postpone all shocks by making responses at intervals of less than 10 sec. At 3.0–5.0 mg/kg, **12a**·2HCl and **27a**·2HCl produced a significant increase in response, and on a mg/kg basis were more potent than either **15** or **16**.

Motor Activity.—In this standardized test in the rat, **12a**·2HCl, **27a**·2HCl, and **16** were equipotent in decreasing motor activity.

Timing Behavior.—This procedure measures the ability of the rat to estimate time and has been shown to be an indication of the stimulant properties of a compound. At ip doses of 1.0–1.5 mg/kg, **12a**·2HCl and **27a**·2HCl led to stimulation (premature responding) as did D-amphetamine sulfate at 1.0–2.0 mg/kg or **15** at 4.0–8.0 mg/kg. At 3.0 mg/kg, **12a**·2HCl and **27a**·2HCl caused a decrease in responding similar to that observed with **16** at 3.0 mg/kg and thioridazine (**17**) at 6.0 mg/kg.

Muricide Activity.—Inhibition of mouse killing activity by rats may be related to the stimulant activity of a compound. In this test, **12a**·2HCl and **27a**·2HCl, ip, exhibited greater activity (ED_{50} = 10.0 mg/kg) than did **15** (ED_{50} = 30.0 mg/kg); imipramine, **16** and **17** were slightly more effective (ED_{50} = 7.5, 5.5, and 7.0 mg/kg, respectively).

Both **12a**·2HCl and **27a**·2HCl were inactive in the rat in tests designed to demonstrate analgesia, antioxotremorine, antireserpine temperature depression, or anticonvulsant activities. Repeated ip dosage to mature female rats at 1.5 mg/kg per day for 10 days did not induce cumulative behavioral effects and did not cause changes in endocrine variables. In addition, no tolerance to behavioral effects was seen.

In the cat, **12a**·2HCl and **27a**·2HCl produced marked inhibition of motor activity at ip doses of 1.0 mg/kg; some ataxia was produced at doses of 30 mg/kg or higher.

Neither compound induced cardiovascular toxicity at cumulative intravenous doses of 51 mg/kg or cumulative oral doses of 64, 96, or 128 mg/kg in the dog.

In vitro, the two compounds at 2.0–8.0 mcg/ml produced little or no inhibition of acetylcholine, oxytocin, angiotensin, bradykinin, histamine, or serotonin.

Structure–Activity Relationships.—Among the dibenzoxazepines, the most potent CNS depressant activities are seen when the side chain at position 5 is 3-[1-(1-(2-hydroxyethyl)-4-piperazinyl]propyl and a substituent like Cl or CF_3 is at positions 3 or 7. When Cl is at position 3, the presence of Br at 2 does not significantly alter potency, but when Cl is present at both positions 3 and 7, there is a decrease in potency. A decrease in potency is also seen when any other side chain is attached at 5 to either the 3- or 7-substituted heterocycle; one particularly unexpected decrease is that observed with the homopiperazinyl derivative related to **12a** or **27a**. A decrease in potency is also seen when S replaces O in the highly active **12a** or **27a**. With side chains like dimethylaminopropyl, the compounds tend to be stimulant rather than depressant at high doses; at low doses, they show only slight CNS activity.

Experimental Section

Method A. 4-{3-[5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepin-5-yl]propyl}-1-piperazineethanol Dihydrochloride (I-12a). A. α,α,α-Trifluoro-6′-hydroxy-*m*-formotoluidide.—Hydrogenation of 66.0 g (0.32 mol of α,α,α-trifluoro-2-nitro-*p*-cresol,[6] 6.0 g of 5% Pd–C, and 150 ml of abs EtOH at 3.5 kg/cm² was complete in 1 hr. To the filtered EtOH solution was added 94 ml of 98–100% HCO_2H and the EtOH distilled under N_2 by means of a steam bath until the still head temperature reached 82°. The residual liquid was heated 1 hr under reflux, cooled somewhat, and poured with stirring onto 270 g of ice to give 55.3 g (85% yield) of air-dried product, mp 172–173°. An analytical sample was recrystallized from toluene, mp 174–176°. *Anal.* ($C_8H_6F_3NO_2$) C, H, N.

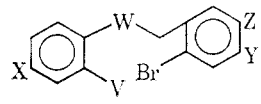
B. 6′-[(*o*-Bromobenzyl)oxy]-α,α,α-trifluoro-*m*-formotoluidide (II-3).—To 265.0 g (1.29 mol) of the above formotoluidide, 324.0 g (1.29 mol) of *o*-bromobenzyl bromide, and 2600 ml of abs EtOH, under N_2 and with stirring, was added in 1 hr 69.8 g (1.29 mol) of NaOMe in 750 ml of abs EtOH. The dark solution was stirred at room temperature for 5 hr when the color changed to a light yellow and a solid sepd. The mixture was poured into 12 l. of H_2O, agitated thoroughly; the solid was filtered and air-dried to give 551.0 g of crude (II-3), mp 141–151° (see Table II for melting point and analytical data for purified II-3 and related structures), suitable for cyclization.

C. 5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepine (III-1).—To 1960 ml of DMF, 164.0 g (1.2 mol of K_2CO_3, and 14.0 g of Cu bronze, under reflux, was added in 2 hr a solution of 233.0 g (0.62 mol) of II-3 in 1960 ml of DMF. During the addition, after 1 hr, an additional 86.0 g of K_2CO_3 was added. Subsequently, stirring and heating under reflux were continued for 1.5 hr, the mixture was filtered hot, and the filtrate coned *in*

(6) R. M. Pettit and J. C. Tatlow, *J. Chem. Soc.*, 3852 (1954).

TABLE II

o-BROMOBENZYL ETHERS AND THIOETHERS



No.	V	W	X	Y	Z	Formula	Mp, °C	Recryst solvent	Yield, %	Analyses
1	O_2N	O	CF_3	H	H	$C_{14}H_9BrF_3NO_3$	107–109	A	84[b]	N[c]
2	$NH_2 \cdot HCl$	O	CF_3	H	H	$C_{14}H_{11}BrF_3NO \cdot HCl$	175–177 dec	B	74	N[d]
3	NHCHO	O	CF_3	H	H	$C_{15}H_{11}BrF_3NO_2$	159–160	C	85	N[c]
4	$NHCOCH_3$	O	CF_3	H	H	$C_{16}H_{13}BrF_3NO_2$	140–142	D	96	N[c]
5	O_2N	O	H	Cl	H	$C_{13}H_9BrClNO_3$	120–122	E	59	C, H, N
6	$NH_2 \cdot HCl$	O	H	Cl	H	$C_{13}H_{11}BrClNO \cdot HCl$	209–211 dec	F	78	C, H, N
7	NHCHO	O	H	Cl	H	$C_{14}H_{11}BrClNO_2$	140–142	G	60	N[c]
8	O_2N	O	Cl	Cl	H	$C_{13}H_8BrCl_2NO_3$	165–167	H	59	C, H, N
9	$NH_2 \cdot HCl$	O	Cl	Cl	H	$C_{13}H_{10}BrCl_2NO \cdot HCl$	204–205	F	59	C, H, N
10	NHCHO	O	Cl	Cl	H	$C_{14}H_{10}BrCl_2NO_2$	155–156	F	61	C, H, N
11	$NHCO_2CH_3$	O	H	H	H	$C_{15}H_{14}BrNO_3$	87–88	I	72	C, H, N[e]
12	NHCHO	O	H	Cl	Br	$C_{14}H_{10}Br_2ClNO_2$	201–203	F	46	C, H, N
13	$NH_2 \cdot HCl$	S	CF_3	H	H	$C_{14}H_{11}BrF_3NS \cdot HCl$	148–150	*f*	50	*g*
14	NHCHO	S	CF_3	H	H	$C_{15}H_{11}BrF_3NOS$	87–89	I	56	C, H, N[h]
15	$NH_2 \cdot HCl$	S	Cl	H	H	$C_{13}H_{11}BrClNS \cdot HCl$	187–189 dec	B	60	C, H, N[h]
16	NH_2	S	Cl	H	H	$C_{13}H_{11}BrClNS$	63–64	J		C, H, N[h]
17	NHCHO	S	Cl	H	H	$C_{14}H_{11}BrClNOS$	86–88	F	68	C, H, N[h]
18	NHCHO	S	H	H	H	$C_{14}H_{13}NOS$[i]	60–61	K	75	N[h]
19	$NH_2 \cdot HCl$	S	H	H	H	$C_{13}H_{12}BrNS \cdot HCl$	189–193 dec	L	80	N[j]
20	NHCHO	S	H	H	H	$C_{14}H_{12}BrNOS$	111–113	M	96	N[c]
21	NH_2	S	Cl	Cl	H	$C_{13}H_{10}BrCl_2NS$	67–68	J	31	C, H, N[h]
22	NHCHO	S	Cl	Cl	H	$C_{14}H_{10}BrCl_2NOS$	92–94	K	67	C, H, N[h]

[a] Recrystallization solvents used are: (A) 95% EtOH; (B) MeCN; (C) C_6H_6–ligroin (3:1); (D) MeOH; (E) Abs EtOH; (F) *i*-PrOH; (G) Skellysolve V; (H) PhMe; (I) hexane; (J) petroleum ether; (K) ligroin; (L) 10% aq HCl; (M) heptane. [b] See Experimental Section for details. [c] *Anal.* (Br). [d] *Anal.* (Br, Cl). [e] *Anal.* (NCHO). [f] Purified by sublimation. [g] *Anal.* (Br, Cl, S). [h] *Anal.* (S). [i] H in place of *o*-Br in general structure. [j] *Anal.* (Cl, S).

vacuo to dryness. This viscous purple residue was dissolved in 1560 ml of 95% EtOH, 312 ml of 25% aqueous NaOH was added; the mixture was heated under reflux for 1 hr, and again coned *in vacuo*. The residual purple solid was washed thoroughly with H_2O, filtered, and air-dried to give 141.0 g (86%) yield of (III-1), mp 112–117° (see Table III for melting point and analytical data for purified III-1 and related structures), suitable for the alkylation step.

D. 4-{3-[5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]-oxazepin-5-yl]propyl}-1-piperazineethanol Dihydrochloride (I-12a).—A suspension of 62.5 g (0.24 mol) of III-1, 625 ml of EtCOMe, 150.0 g (0.98 mol) of $Cl(CH_2)_3Br$, and 76.5 g (1.9 mol) of granular NaOH was heated under reflux for 8.5 hr; an additional 76.5 g of granular NaOH was added and the whole was stirred and heated under reflux for an additional 14 hr. During the heating the color of the reaction mixture changed from deep purple to light yellow. The cooled reaction mixture was diluted with 450 ml of ice–H_2O and stirred in the cold until no more solid remained, the EtCOMe layer sepd, the aq phase extracted with 100 ml of EtCOMe, and the combined organic phases were washed with 3 portions of satd NaCl, dried, and coned to about 350 ml. (See below for the isolation of the 3-chloropropyl derivative III-8.) To this solution was added 34.0 g (0.26 mol) of 2-piperazineethanol and 18.9 g (0.12 mol) of NaI, and the whole stirred and heated under reflux for 19 hr, and coned to dryness *in vacuo*. The residue was distributed between 250 ml each of H_2O and Et_2O, the Et_2O layer sepd, the H_2O layer extracted with two 250-ml portions of Et_2O, the combined Et_2O extracts were washed with 50 ml of satd aq NaCl, and the Et_2O solution was extracted with two 100-ml portions of cold 10% aq H_3PO_4 (see below for the isolation of the 5-(allyl) derivative III-7). The H_3PO_4 extracts were combined, layered with 200 ml of fresh Et_2O, cooled, neutralized with 50% aq KOH, and satd with solid K_2CO_3. The Et_2O layer was sepd, the aq layer extracted with two 250-ml portions of fresh Et_2O, and the combined Et_2O extracts were washed with 50 ml of saturated aq NaCl, dried, and coned to give 44.0 g of crude base I-12a.

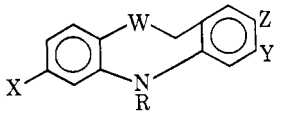
The crude base (44.0 g) was dissolved in 400 ml of MeCN with stirring, and (at the boiling point) a hot solution of 26.1 g (0.225 mol) of maleic acid in 260 ml of MeCN was added to the basic soln. A colorless solid sepd after several minutes. The whole was stirred while cooling, and the solid filtered and air-dried to give 63.2 g (89% yield) of crude dimaleate I-12b, mp 157–159°. To a suspension of 37.3 g of the crude dimaleate in 450 ml of Et_2O and 220 ml of H_2O was added portionwise 59.4 g (0.56 mol) of Na_2CO_3, the solutions were sepd, the aq layer was extracted with two 150-ml portions of Et_2O, and the combined Et_2O extracts were washed with two 50-ml portions of satd aq NaCl, and dried. To the filtered, cooled Et_2O solution with stirring was added slowly 147 ml of 2.6 *N* Et_2O–HCl, the solvent decanted from the gummy ppt, the ppt dissolved in 230 ml of Me_2CO, and the solution diluted with 470 ml of Et_2O to give crystalline dihydrochloride. When filtered and dried *in vacuo* for 3 hr at 100° the product sintered at 145–150° and melted at 192–198°. Analyses of this material indicated that this was the dihydrate. *Anal.* ($C_{23}H_{28}F_3N_2O_2 \cdot 2HCl \cdot 2H_2O$: C, H, N. Recrystallization of dihydrate from 400 ml of *i*-PrOH gave the alcoholate stable *in vacuo* after 5 hr at 80°; the alcoholate sintered at 116° and melted at 195–198°. *Anal.* ($C_{23}H_{28}F_3N_3O_2 \cdot 2HCl \cdot C_3H_8O$): C, H, N; N. E. From the alcoholate, on drying at 140° for 3 hr *in vacuo*, was obtained the unsolvated dihydrochloride (I-12a), 21.5 g (75% yield based on crude dimaleate), mp 197–200°. (See Table I for analytical data on this compound as well as all of the other 5-(aminoalkyl) derivatives.)

4-{3-[5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepin-5-yl]propyl}-1-piperazineethanol Pamoate (I-12d).—To 1.05 g (0.002 mol) of I-12a·2HCl in 2.5 ml of H_2O with stirring was added 0.86 g (0.002 mol) of sodium pamoate. Separation of the yellow salt occurred promptly; this was filtered, washed with H_2O, and dried to give 1.45 g of I-12d. No suitable recrystallization solvent was found for this salt.

4-{3-[5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepin-5-yl]propyl}-1-piperazineethanol Dicitrate (I-12c).—A solution of 0.88 g (0.002 mol) of I-12a base in 30 ml of Et_2O was added to 0.84 g (0.004 mol) of citric acid·$2H_2O$ in 30 ml of abs EtOH. A gummy ppt sepd. The mixture was stirred and refluxed for 0.5 hr, kept 18 hr at room temperature, the solvents were decanted, and the gum was triturated in the cold with 60 ml of anhyd Et_2O to give 0.9 g of crystalline I-12c. No suitable recrystallization solvent was found for this salt.

Table III

Nonbasic Derivatives of 5,11-Dihydrodibenz[b,e][1,4]oxazepines and Thiazepines



No.	W	X	Y	Z	R	Formula	Mp, °C	Recryst solvent[a]	Yield, %	Analyses
1	O	CF_3	H	H	H	$C_{14}H_{10}F_3NO$	125–127	A	81	C, H, N
2	O	CF_3	H	H	CHO	$C_{15}H_{10}F_3NO_2$	132–134	B	60	C, H, N
3	O	CF_3	H	H	$COCH_3$	$C_{16}H_{12}F_3NO_2$	95–97	C	50	C, H, N
4	O	CF_3	H	H	$(CH_2)_2CN$	$C_{17}H_{13}F_3N_2O$	161–163	D	62	C, H, N
5	O	CF_3	H	H	$(CH_2)_2CONH_2$	$C_{17}H_{15}F_3N_2O_2$	149–151	E	62	C, H, N
6	O	CF_3	H	H	$(CH_2)_3$-phthalimide	$C_{25}H_{19}F_3N_2O_3$	112–114	F	20	N[b]
7	O	CF_3	H	H	CH_3CHCH_2	$C_{17}H_{14}F_3NO$	60–65	c		C, H, N
8	O	CF_3	H	H	$(CH_2)_3Cl$	$C_{17}H_{15}ClF_3NO$	73–76	c		N[d]
9	O	Cl	H	H	CHO	$C_{14}H_{10}ClNO_2$	126–128	C	90	C, H, N
10	O	Cl	H	H	$COCH_3$	$C_{15}H_{12}ClNO_2$	123–124	C	70	C, H, N
11	O	H	Cl	H	H	$C_{13}H_{10}ClNO$	113–115	G	70	C, H, N[d]
12	O	H	Cl	H	CHO	$C_{14}H_{10}ClNO_2$	129–131 dec	C	70	C, H, N[d]
13	O	H	Cl	H	$(CH_2)_3Cl$	$C_{16}H_{15}Cl_2NO$	70–73	H	80	C, H, N
14	O	Cl	Cl	H	H	$C_{13}H_9Cl_2NO_2$	168–170	B	60	C, H, N
15	O	Cl	Cl	H	CHO	$C_{14}H_9Cl_2NO_2$	145–149	C	55	C, H, N
16	O	Cl	Cl	H	$COCH_3$	$C_{15}H_{11}Cl_2NO_2$	154–156	I	62	C, H, N
17	O	H	Cl	Br	H	$C_{13}H_9BrClNO$	187–189	I	78	C, H, N
18	O	H	Cl	Br	CHO	$C_{14}H_9BrClNO_2$	120–124	A	77	C, H, N
19	O	H	Cl	Br	$COCH_3$	$C_{15}H_{11}BrClNO$	108–110	I	47	C, H, N
20	O	H	H	H	$COCH_3$	$C_{15}H_{13}NO_2$	113–114	J	50	C, H, N
21	O	H	H	H	CO_2CH_3	$C_{15}H_{13}NO_3$	121–123	B	39	C, H, N
22	O	H	H	H	$(CH_2)_2CN$	$C_{16}H_{14}N_2O$	138–140	K	31	C, H, N
23	O	H	H	H	$(CH_2)_2CONH_2$	$C_{16}H_{16}N_2O_2$	155–157	F	79	C, H, N
24	S	H	H	H	H	$C_{13}H_{11}NS$	118–119[e]	E	80	N[f]
25	S	H	H	H	CHO	$C_{14}H_{11}NOS$	125–127	C	48	C, H, N
26	S	H	H	H	$COCH_3$	$C_{15}H_{13}NOS$	110–112	E	60	C, H, N[f]
27	S	H	H	H	CO_2CH_3	$C_{15}H_{13}NO_2S$	183–185	F	3	N[f]
28	S	H	H	H	$CONH_2$	$C_{14}H_{12}N_2OS$	215–217	M	1.2	N[f]
29	S	CF_3	H	H	H	$C_{14}H_{10}F_3NS$	113–114	B	74	C, H, N
30	S	CF_3	H	H	CHO	$C_{15}H_{10}F_3NOS$	115–117	B	50	C, H, N
31	S	Cl	H	H	$CH_2{=}CHCH_2$	$C_{16}H_{15}ClNS$	76–78	B		N[f]
32	S	Cl	H	H	H	$C_{13}H_{10}ClNS$	115–117	I	76	C, H, N[e]
33	S	Cl	H	H	CHO	$C_{14}H_{10}ClNOS$	163–164	D	78	C, H, N[e]
34	S	Cl	H	H	$COCH_3$	$C_{15}H_{12}ClNOS$	173–175	I	78	C, H, N
35	SO	H	H	H	H	$C_{13}H_{11}NOS$	167–169	L	54	C, H, N
36	SO	Cl	H	H	H	$C_{13}H_{10}ClNOS$	233–235 dec	D	70	C, H, N
37	SO	Cl	H	H	CHO	$C_{14}H_{10}ClNO_2S$	220–221	D	66	C, H, N
38	SO_2	Cl	H	H	H	$C_{13}H_{10}ClNO_2S$	222–233 dec	D	90	C, H, N
39	SO_2	Cl	H	H	CHO	$C_{14}H_{10}ClNO_3S$	235–237 dec	D	66	C, H, N
40	SO_2	Cl	H	H	$COCH_3$	$C_{15}H_{12}ClNO_3S$	228–230	D	57	f
41	S	Cl	Cl	H	H	$C_{13}H_9Cl_2NS$	160–161	I	80	C, H, N
42	S	Cl	Cl	H	CHO	$C_{14}H_9Cl_2NOS$	169–171	D	65	C, H, N

[a] Recrystallization solvents used are: (A) ligroin; (B) hexane; (C) *i*-Pr_2O; (D) MeCN; (E) Skellysolve E; (F) 95% EtOH; (G) C_6H_6–hexane; (H) *i*-PrOH; (I) cyclohexane; (J) heptane; (K) MeOH; (L) PhMe; (M) C_6H_6. [b] *Anal.* (sapon equiv). [c] See Experimental Section for details. [d] *Anal.* (Cl). [e] Soc. des usines chim. Rhone Poulenc, French Patent 1,176,115 reported mp 121–122°. [f] *Anal.* (S).

5,11-Dihydro-7-(trifluoromethyl)dibenz[b,e][1,4]oxazepine-5-carboxaldehyde (III-2). Cyclization in Dowtherm A.—A mixture of 5.6 g (0.115 mol) of II-3, 9.5 g of K_2CO_3, 0.4 g of Cu bronze, and 100 ml of Dowtherm A was stirred and heated for 2 hr at an internal temp of 160–165°, filtered hot, and the filtrate concd to dryness *in vacuo*. The residue solidified when treated with a few milliliters of hexane; filtration gave 5.4 g (quantitative yield) of III-2. This product (2.9 g), 40 ml of 95% ethanol, and 8 ml of 25% aq NaOH were refluxed for 1 hr, concd to dryness *in vacuo;* the residue, stirred with 100 ml of H_2O, filtered, and dried, gave 2.6 g (99% yield) of III-1.

5-(Allyl)-5,11-dihydro-7-(trifluoromethyl)dibenz[b,e][1,4]oxazepine (III-7).—The Et_2O solution remaining from the aq H_3PO_4 extractions was freed of solvent and the residue fractionated to give an oil, bp 135–137° (0.110 mm) which crystallized spontaneously, mp 60–65°. Analyses (see Table III) established this material as III-7, and this structure was confirmed by the ir spectrum (the overtone of the terminal CH_2 912-cm^{-1} band was at 1820 cm^{-1} and the C=C stretch at 1650 cm^{-1}) and by the nmr spectrum [the CH_2 group of the allyl side chain was a 2-proton doublet at τ 5.64 (J = 5) and the vinyl and terminal olefins were represented by a 3-proton complex multiplet at τ 3.9–4.9 (excluding the 2-proton $PhCH_2$ singlet at τ 4.76)].

5-(3-Chloropropyl)-5,11-dihydro-7-(trifluoromethyl)dibenz[b,e][1,4]oxazepine (III-8).—A portion of an EtCOMe solution obtained as above and containing the 3-chloropropyl derivative was freed of solvent and the residue distd; the fraction, bp 135–140° (0.1 mm) crystallized spontaneously to give III-8. This material gave acceptable Cl, H, and N analyses but the C value was 0.77% high.

Method B. 4-[3-(7-Chloro-5,11-dihydrodibenzo[b,e][1,4]thiazepin-5-yl)propyl]-1-piperazineethanol Dihydrochloride (I-49a).

(a) [(*o*-Bromobenzyl)thio]-5-chloroanilide Hydrochloride (II-15).—To a slurry of 37.08 g (0.19 mol) of 2-amino-4-chlorothiophenol·HCl[7] in 150 ml of abs EtOH at 10–15° was added dropwise a solution of 25.0 g (0.46 mol) of NaOMe in 170 ml of abs EtOH the cooling bath was removed, and 40.0 g (0.186 mol) of *o*-bromobenzyl bromide added in one portion. The mixture was stirred for 10 min at room temperature, heated under reflux for 1 hr, cooled, 100 ml of Et_2O added, the solid filtered, the filtrate dild with 100 ml of concd HCl (d 1.18), and the ppt filtered to give 42.0 g of II-15. A small portion of II-15 suspended in water and the whole treated with satd aq $NaHCO_3$ gave the aniline derivative (II-16).

(b) 2′-[(*o*-Bromobenzyl)thio]-5-chloroformanilide (II-17).—A solution of 84.0 g (0.23 mol) of II-15, 37.0 g (0.54 mol) of HCO_2Na, and 550 ml of 98–100% HCO_2H was heated under reflux for 3 hr, cooled to 60°, and poured into 4 l. of ice–H_2O. The solid was filtered and stirred with 100 ml of satd aq $NaHCO_3$, filtered, and dried to give 76.0 of II-17.

(c) 7-Chloro-5,11-dihydrodibenzo[*b,e*][1,4]thiazepine-5-carboxaldehyde (III-33).—A mixture of 30.0 g (0.084 mol) of II-17, 57.0 g (0.42 mol) of K_2CO_3, 2.4 g of Cu bronze, and 200 ml of Dowtherm A was stirred and heated at 160–165° for 1 hr, filtered hot, and the filtrate concd *in vacuo* to dryness. The solid residue was treated with Et_2O to give 18.0 g of III-33. The subsequent steps in the synthesis giving eventually I-49a and I-49b were carried out as described in method A.

Cyclizations of II-17 in Solvents Other Than Dowtherm A. (a) Diphenyl Ether.—A mixture of 5.6 g (0.015 mol) of II-17, 9.5 g of K_2CO_3, 0.4 g Cu bronze, and 100 ml of Ph_2O was stirred and heated at an internal temp of 160–165° for 2 hr and the reaction worked up as above gave 3.24 g (90% yield) of III-32.

(b) Biphenyl.—The previous experiment was repeated except that 100 g of Ph_2 was substituted for the Dowtherm A. The yield of III-32 was 2.56 g (71%).

(c) Isopropylbenzene.—The (a) experiment was repeated, with 100 ml of isopropylbenzene replacing the Dowtherm A and the heating was done under reflux (148–150° internal temp); the yield of III-32 was 1.36 g (37%).

(d) $PhNO_2$.—Repetition of the (a) experiment, with 100 ml of $PhNO_2$ replacing the Dowtherm A gave III-32 in about 50% yield along with substantial amounts of a purple-colored impurity.

(e) *p*-Isopropyltoluene.—Substitution of 100 ml of *p*-isopropyltoluene for the Dowtherm A in (a) gave 2.88 g (80%) yield of III-32.

DMF.—Replacing the Dowtherm A in (a) with 100 ml of DMF and carrying out the reaction under reflux (150–155°) gave III-32 in about 5% yield along with considerable amounts of a purple-colored by-product.

Reaction of *o*-Aminobenzenethiol with Formic Acid. Formation of 2,2′-Dithiodiformanilide.—A mixture of 10.0 g of *o*-aminobenzenethiol and 125 ml of 98–100% HCO_2H was heated under reflux under N_2 for 0.5 hr and concd to dryness. The residue crystallized spontaneously, mp 157–159°. An analytical sample was obtained from *i*-PrOH and melted at 159–160.5°; no absorption in the 2400–2600 cm^{-1} region. *Anal.* ($C_{14}H_{12}N_2O_2S_2$) C, H, N, S.

Method C. 4-{3,7-Dichloro-[5,11-dihydrodibenz[*b,e*][1,4]-oxazepin-5-yl]propyl}-1-piperazineethanol Dimaleate (I-28). (a) 2-Bromo-*p*-chlorotoluene.—To 508.0 g (4.0 mol) of *p*-chlorotoluene and 50 g of powdered Fe at 25–30° was added 880.0 g (5.0 mol) of Br_2 in 3.5 hr, the whole filtered, and the filtrate ($n^{25}D$ 1.5850) distd to give 456.3 g of crude **2-bromo-*p*-chlorotoluene,** bp 95–110° (3 mm), $n^{23}D$ 1.5731. *Anal.* (C_7H_6BrCl) Br. The other principal component in this material was presumed to be **3-bromo-*p*-chlorotoluene** (see below). The residue from the crude 2-bromo-*p*-chlorotoluene distd at 180–185° (0.1 mm) and crystallized spontaneously. Recrystallization from hexane gave 247.5 g of **2,5-dibromo-4-chlorotoluene,** mp 94–95°; its nmr spectrum showed two one-proton singlets at τ 2.38 and 2.51, attributable, resp, to the protons at C_3 and C_6, as well as the 3-proton singlet at τ 7.64 due to CH_3. *Anal.* ($C_7H_5Br_2Cl$)Br, Cl.

(b) 2-Bromo-4-chlorobenzyl Bromide.—To 453 g of crude 2-bromo-*p*-chlorotoluene and 3.0 g of benzoyl peroxide, heated in an oil bath at 120° and irradiated by a uv lamp, was added 360 g of Br_2 in 4.5 hr and the mixture purged with N_2 to give crude 2-bromo-4-chlorobenzyl bromide, $n^{25}D$ 1.6215, used in the next step without purification. The subsequent steps in this synthesis followed the procedure reported[2a] and gave **2-bromo-4-chlorobenzyl 4-chloro-2-nitrophenyl ether (II-8),** the II-8 was reduced with Fe–HCl to the aniline·HCl II-9, and the latter was converted into the formanilide II-10. A mixture of 23.0 g (0.066 mol) of II-10, 51.0 g of K_2CO_3, 1.58 g of Cu bronze, and 450 ml of diethylbenzene was stirred vigorously, heated under reflux for 3 hr, and filtered, and the filtrate was concd to dryness *in vacuo* to give 13.1 g of III-15. The III-15, 150 ml of 95% EtOH, and 10 ml of 25% aq NaOH were heated under reflux for 0.5 hr and concd *in vacuo* to give 9.8 g of III-14. The remainder of the procedure to give I-28 followed that outlined in method A.

Contaminant in the 2-Bromo-4-chlorobenzyl Bromide. By-Products Arising from the 3-Bromo-4-chlorobenzyl Bromide. The mother liquors from the isolation of II-8 were shown to contain a more soluble isomer derived by reaction of 2-nitro-*p*-chlorophenol with 3-bromo-4-chlorobenzyl-bromide; the latter was formed as a by-product from the allylic bromination of the **3-bromo-*p*-chlorotoluene,** present as a minor component in the 2-bromo-*p*-chlorotoluene. The yield was 9.6 g, mp 112–114° after recrystallization from hexane. *Anal.* ($C_{13}H_8BrCl_2NO_3$) C, H, N, Br, Cl. The structure assigned to this isomer was 3-bromo-4-chlorobenzyl 4-chloro-2-nitrophenyl ether. Reduction with Fe–HCl[2a] gave the corresponding aniline·HCl, mp 201–203° after recrystallization from MeCN. *Anal.* ($C_{13}H_{10}BrCl_2NO$·HCl) C, H, N. The aniline·HCl, in turn, gave the formanilide, recrystallized from hexane, mp 102–104°. *Anal.* ($C_{14}H_{11}BrCl_2NO$) C, H, N.

In similar fashion, reaction of *o*-nitrophenol with the 3-bromo-4-chlorobenzyl bromide led to the isolation of the more soluble 3-bromo-4-chlorobenzyl 2-nitrophenyl ether, mp 88–90°, after recrystallization from cyclohexane. *Anal.* ($C_{13}H_9BrClNO_3$) C, H, N. The ether, in turn, gave the aniline·HCl, mp 174–176° *Anal.* ($C_{13}H_{11}BrClNO$·HCl) Br, total Cl], and the formanilide, mp 142–144°, after recrystallization from *i*-PrOH. [*Anal.* ($C_{14}H_{11}BrClNO_2$) N, N-CHO].

2-Bromo-3-chloro-5-[2-(dimethylamino)ethyl]-5,11-dihydrodibenz[*b,e*][1,4]oxazepine Phosphate (I-29).—To 3.1 g (0.01 mol) of III-17, 40 ml of Me_2CO, and 4.3 g (0.04 mol) of 2-dimethylaminoethyl chloride was added 2.4 g (0.06 mol) of granular NaOH and the whole was stirred and heated under reflux for 3 hr. The cooled mixture was filtered and the filtrate concentrated *in vacuo* to dryness. The residue was dissolved in 50 ml of Et_2O and extracted with three 40-ml portions of cold 10% H_3PO_4. On keeping, the extracts deposited the phosphate; however, the mixture was treated with an excess of K_2CO_3 and the oil that sepd was isolated *via* Et_2O extraction. To 3.0 g (0.008 mol) of the oil in 35 ml of MeCN was added slowly 2.1 g of 85% H_3PO_4 in 20 ml of MeCN to give 1.8 g of I-29. The hydrochloride was also prepared but was too hydroscopic to be isolated and purified.

5-[3-(Dimethylamino)propyl]-5,11-dihydro-7-(trifluoromethyl)dibenz[*b,e*][1,4]oxazepine·HCl (I-4).—In a Pyrex combustion tube was placed 10.0 g (0.029 mol) of III-8 and 53.0 g (0.29 mol) of a 25% solution of Me_2NH in C_6H_6, the tube was sealed and heated at 100° for 24 hr. The cooled tube was opened, the mixture washed with H_2O, the C_6H_6 solution concentrated *in vacuo*, the residue dissolved in 100 ml of Et_2O, and the Et_2O solution extracted with two 100-ml portions of 1.5 *N* aq HCl. The acid extracts were washed with Et_2O, treated with an excess of 20% aq NaOH, and extracted with three 50-ml portions of Et_2O. The washed and dried Et_2O solution with Et_2O–HCl gave I-4.

Methyl 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxylate (III-21). (a) Methyl 2-[(*o*-Bromobenzyl)oxy]carbanilate (II-11).—To 21.2 g (0.076 mol) of *o*-(*o*-bromobenzyloxy)aniline in 250 ml of Et_2O was added in 0.5 hr; simultaneously, from two separate dropping funnels, 9.4 g (0.01 mol) of methyl chloroformate in 100 ml of Et_2O and 4.0 g (0.01 mol) of NaOH in 100 ml of H_2O, keeping the internal temp at 15–20° and the pH at 8. Subsequently, the mixture was stirred for 0.5 hr at room temp, the Et_2O layer was sepd, washed with 50 ml of 1% aq NaOH, then aq satd NaCl, dried, and concd to give 22.7 g of II-11.

(b).—A suspension of 6.6 g (0.02 mol) of II-11, 14.0 g of K_2CO_3, 0.4 g of Cu bronze, and 150 ml of Dowtherm A was heated for 2 hr at 165–175°, filtered hot, and the filtrate concd *in vacuo* to dryness. The residual oil solidified when treated with petroleum ether to give 4.0 g of III-21.

7-Chloro-5-[2-(dimethylamino)ethyl]-5,11-dihydrodibenzo-[*b,e*][1,4]thiazepine 10-Oxide (I-52). (a) 7-Chloro-5,11-dihydrodibenzo[*b,e*][1,4]thiazepine 10-Oxide (III-36).—To 16.0 g (0.058 mol) of III-32 in 300 ml of $CHCl_3$ at 20–25° was added a solution

(7) A. J. Collings and K. J. Morgan, *Tetrahedron*, **20**, 2173 (1964).

of 12.0 g (0.058 mol) of *m*-chloroperbenzoic acid (Research Organic/Inorganic Chemical Co.) in 250 ml of $CHCl_3$, the whole stirred 4 hr at room temp, concd *in vacuo*, and the residue treated with Et_2O to give 14.0 g of III-37. A solution of 11.6 g (0.04 mol) of III-37, 450 ml of 95% EtOH, and 90 ml of 25% aq NaOH was stirred and refluxed for 1.5 hr, concd *in vacuo* to about 200 ml, and 500 ml H_2O added to give 10.0 g of III-36.

(b) 7-Chloro-5-[2-(dimethylamino)ethyl]-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine 10-Oxide (I-52).—To 5.2 g (0.02 mol) of III-36 in 30 ml of DMSO with stirring at room temp was added in 0.5 hr 1.8 g (0.04 mol) of 50% NaH dispersion; the internal temp reached 38° during the addition. Subsequently, the mixture was stirred for 2 hr at room temp and 4.5 g (0.04 mol) of 2-dimethylaminoethyl chloride was added dropwise, after which the internal temp was raised to 50°. At this temp, an exothermic reaction occurred and the temp rose spontaneously to 80°. The temp was maintained at 75–85° for 3 hr, the whole mixture was cooled to room temp and poured into 300 ml of H_2O. The aq mixture was extracted with 200 ml of Et_2O, the Et_2O solution was extracted with 100 ml of 2.5% aq HCl, the HCl extracts were cooled, covered with 150 ml of Et_2O, and adjusted to pH 11 with solid K_2CO_3. The Et_2O layer was sepd, dried, and concd to give 2.4 g of I-52.

5-[2-(Dimethylamino)ethyl]-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine 10-Oxide Sesquiphosphate (I-51).—To 11.95 g (0.027 mol) of **38b** in 600 ml of 95% EtOH was added 3.16 g of 31.9% H_2O_2 and the solution was heated under reflux for 17 hr. Concentration *in vacuo* gave a yellow oil which crystallized under Et_2O; it was filtered to give 9.0 g of hydroscopic I-51. No suitable recrystallization solvent was found.

7-Chloro-5-[2-(dimethylamino)ethyl]-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine 10,10-Dioxide (I-53). (a) 7-Chloro-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine-5-carboxaldehyde 10,10-Dioxide (III-39).—The addition, dropwise, of 15 ml of 30% H_2O_2 to a stirred suspension of 10.5 g (0.039 mol) of III-32 in 45 ml of 98–100% HCO_2H resulted in an exothermic reaction. The reaction temp was maintained at 90–95° during the addition and subsequently, by heating, for 4 hr. The cooled reaction mixture was filtered to give 10.5 g of III-39.

(b) 7-Chloro-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine 10,10-Dioxide (III-38).—A suspension of 9.2 g (0.02 mol) of III-39, 320 ml of 95% EtOH, and 54 ml of 25% aq NaOH was stirred and refluxed for 4 hr, cooled, and poured into 500 ml of H_2O to give 7.5 g of III-38.

(c) 7-Chloro-5-[2-(dimethylamino)ethyl]-5,11-dihydrodibenzo[*b*,*e*][1,4]thiazepine 10,10-Dioxide (I-51).—The procedure employed to prepare I-52 was used here, starting with 5.6 g (0.02 mol) of III-38. The yield of crude I-51 was 3.4 g.

4-{3-[7-Chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepin-5-yl]propyl}-1-piperazineethanol Heptanoate (I-22).—To a solution of 8.0 g (0.02 mol) of crystalline I-19 base (prepared by method A) in 120 ml of anhyd C_6H_6 at 75° was added dropwise 4.5 g (0.03 mol) of heptanoyl chloride in 50 ml of anhyd C_6H_6. During the addition a ppt sepd but this had redissolved when the addition was completed. The solution was heated under reflux for 3 hr, concentrated *in vacuo* the residue distributed between 300 ml of Et_2O and 100 ml of H_2O containing 2.0 g of $NaHCO_3$, the Et_2O layer was sepd, washed with satd aq NaCl, dried, and concd to give 11.5 g of crude I-22 base. This was dissolved in 100 ml of MeCN and at the boiling point treated with a hot solution of 4.64 g (0.04 mol) of maleic acid in 50 ml of MeCN with rapid stirring. The product sepd shortly after completion of the addition, the whole was cooled, the solid was filtered, and recrystallized from 550 ml of abs EtOH to give 11.7 g of the dimaleate salt. To 4.0 g of $NaHCO_3$, 50 ml of H_2O, and 200 ml of Et_2O was added 9.7 g of the purified dimaleate and the whole agitated until all the solid had dissolved. The Et_2O layer was sepd, washed with satd aq NaCl, dried, and concd to give 6.35 g of pure I-22 base, as an oil.

5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepine-5-propionitrile (III-4).—To 50.0 g (0.19 mol) of III-1 in 60 ml of redistd acrylonitrile was added in 5 min 0.80 ml of 40% aq Triton B. Subsequently, the mixture was heated for 1 hr under reflux and the product isolated by extraction with C_6H_6 to give 37.5 g of III-4.

5-(3-Aminopropyl)-5,11-dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepine·HCl (I-3). Method A. To 0.06 g (0.016 mol) of LAH in 80 ml of anhyd Et_2O at 0 and 5° was added in 0.25 hr 5.0 g (0.016 mol) of III-4, portionwise; following the addition, the solution was stirred for 1 hr at 0 to 5° and 3.0 ml of H_2O was added cautiously, followed by 0.5 ml of 20% aq NaOH. The Et_2O layer was sepd, washed with H_2O, and extracted with two 50-ml portions of 1.5 *N* aq HCl. The amine was recovered in the usual manner, dissolved in anhyd Et_2O and converted into I-3 with Et_2O–HCl.

Method B. *N*-{3-[5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepin-5-yl]propyl}phthalimide (III-6).—A mixture of 17.9 g (0.097 mole) of potassium phthalimide, 30.0 g (0.088 mol) of III-8, and 210 ml of DMF was heated under reflux for 4 hr and concd *in vacuo*. The residual oil was dissolved in 400 ml of Et_2O, the Et_2O solution was washed with H_2O, dried and concd. The residue was extracted repeatedly with C_6H_6, the C_6H_6 solution was chromatographed on 250 g of alumina (Woelm, Neutral, Grade 1), and eluted with C_6H_6 to give a semicrystalline solid. This was suspended in hexane and filtered and the solid was recrystallized from 95% EtOH to give 8.0 g of III-6. To 25.0 g (0.055 mol) of III-6 in 125 ml of 95% EtOH was added 3.60 g (0.061 mol) of 85% $H_2NNH\cdot H_2O$, the whole was heated under reflux for 3 hr, the suspension was cooled, 9 ml of concd HCl (d 1.18) was added the phthalhydrazide was filtered, the filtrate was concd to dryness *in vacuo* and the residue was dissolved in 350 ml of H_2O. The aq solution was extracted with three 50-ml portions of Et_2O, then made alkaline with 20 ml of 50% aq NaOH, and extracted with three 100-ml portions of Et_2O. The Et_2O solution was washed with saturated aq NaCl, dried, and treated in the usual manner to give 13.8 g of I-3 176–180° alone or as a mixture with the I-3 prepared above.

{3-[5,11-Dihydro-7-(trifluoromethyl)dibenz[*b*,*e*][1,4]oxazepin-5-yl]propyl}guanidine Hemisulfate (I-19).—A suspension of 7.70 g (0.024 mol) of I-3, 3.67 g of 2-methyl-2-thiopseudourea sulfate, 40 ml of 95% EtOH, and 3 ml of H_2O was refluxed for 6 hr, the whole concd *in vacuo*, and the residual gum dissolved in 40 ml of MeOH. The filtered MeOH solution was diluted with 300 ml of anhyd Et_2O to give 6.84 g of I-19. Following recrystallization from MeOH–Et_2O, I-19 was found to have a curious tendency to fly out of the porcelain boat used for holding the material during vacuum drying and yet the solid was *not* electrostatically charged, *i.e.*, it could easily be transferred to a bottle from the boat. The recrystallized material was dried at atmospheric pressure over P_2O_5.

5-(3-Aminopropyl)-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine·HCl (I-3) and *o*-[*N*-(3-Aminopropyl)-*o*-toluidino]phenol. Reduction of III-4 with LAH·$AlCl_3$.—To 1.81 g (0.048 mol) of LAH in 250 ml of anhyd Et_2O was added a solution of 6.37 g (0.048 mol) of anhyd $AlCl_3$ in 60 ml of anhyd Et_2O, the whole was stirred for 5 min to form the insoluble complex and 8.0 g (0.032 mol) of III-4 was added in small portions. Only a mild reflux was observed during the addition and, subsequently, the mixture was stirred for 1 hr at room temp. and hydrolyzed as above. The washed and dried Et_2O solution was treated, while cooling, with 10 ml of 3.4 *N* Et_2O–HCl. The crude hydrochloride (7.1 g) was recrystallized from 120 ml of abs EtOH to give 4.0 g of I-31·HCl; the salt treated with H_2O–$NaHCO_3$ and extracted with Et_2O gave the I-31 base.

The abs EtOH mother liquors from I-31·HCl were concd to dryness to give 3 g of a solid residue; recrystallization from 400 ml of MeCN gave 1.5 g of ***o*-[*N*-(3-aminopropyl)-*o*-toluidino]phenol·HCl,** mp 196–199° dec. *Anal.* ($C_{16}H_{11}ClN_2O$)Cl, N, N, E. The salt by the above procedure, gave the base, mp 137–139°, after recrystallization from cyclohexane. *Anal.* ($C_{16}H_{11}N_2O$), N, N.E., M.W.

5,11-Dihydrodibenz[*b*,*e*][1,4]oxazepine-5-propionamide (III-23).—To 150 ml of 97%·H_2SO_4 was added slowly 23.5 g (0.093 mol) of III-22 while maintaining the internal temp at 25–30°. The deep blue solution was kept at this temp for 1.5 hr and then poured slowly on 1200 g of ice. The pptd solid was filtered, washed well with cold H_2O, and dried to give 22.0 g of III-23.

Reaction of *o*-Aminophenol with *o*-Bromobenzyl Bromide. Formation of *o*-[*N*,*N*-Di(*o*-bromobenzyl)amino]phenol.—To a suspension of 22.0 g (0.2 mol) of recrystallized *o*-aminophenol in 100 ml of abs EtOH, under N_2, was added a solution of 4.6 g (0.2 mol) of Na in 100 ml of abs EtOH. To the clear solution formed was added 51.0 g (0.2 mol) of *o*-bromobenzyl bromide in 0.5 hr and the mixture was stirred and heated under reflux for 1 hr. The cooled mixture was filtered to recover 18.5 g of NaBr (theory 17.8 g) and 45 ml of concd HCl (d 1.18) was added to the filtrate. A solid sepd. By tedious work-up of the solid and the solution there was recovered only one identifiable product, 5.6 g of *o*-[*N*,*N*-di(*o*-bromobenzyl)amino]phenol, mp 148–150°, after

recrystallization from Skellysolve E. *Anal.* ($C_{20}H_{17}Br_2NO$), Br, N, N.E.

5,11-Dihydrodibenzo[*b*,*e*][1,4]thiazepine-5-carboxamide (III-28).—To a solution of 8.2 g (0.046 mol) of III-24, 2.8 g of dry C_5H_5N, and 80 ml of dry PhMe, at −10°, was added dropwise 47 ml of a 15% w/v of $COCl_2$ in PhMe. The work-up of this reaction mixture and the subsequent reaction of the intermediate carbamoyl chloride with EtOH–NH_3 followed the published procedure.[2c] The yield of crude III-27 was 1.45 g; chromatography, in C_6H_6 solution, on 60 g of alumina (Harshaw, Chromatographic Grade), followed by successive elutions with C_6H_6 and *i*-PrOH, and repeated recrystallizations from C_6H_6 were required to give pure III-28.[8]

5-Acetyl-7-chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine (III-10).—A solution of 2.0 g (0.0087 mole) of 7-chloro-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine,[2a] 25 ml of Ac_2O, and 0.4 g of *p*-toluenesulfonic acid was heated under reflux for 2 hr, concd to dryness, and the residue distributed between 50 ml of Et_2O and 25 ml of satd aq $NaHCO_3$. The Et_2O layer was sepd, washed with satd aq NaCl, dried, and concd to give 2.4 g of III-10.

6-[(*o*-Bromobenzyl)oxy]-α,α,α-trifluoro-*m*-acetotoluidide (II-4). A mixture of 20.0 g (0.052 mol) of II-2, 8.6 g (0.11 mol) of anhyd AcONa, and 120 ml of glacial AcOH was heated under reflux for 3 hr, cooled somewhat, and poured into 300 ml of H_2O. The oil, that sepd initially, solidified, and was filtered and dried to give 19.4 g of II-4.

(8) The difficulties encountered in this synthesis are similar to those previously described in the oxazepine series, and are involved in the reaction of the heterocycle with phosgene.[2c]

Synthesis and Hypocholesterolemic Activity of Alkylidenedithio Bisphenols

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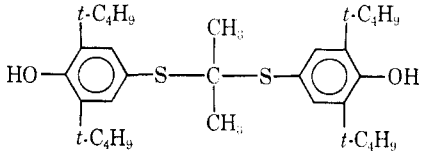
The synthesis and serum cholesterol lowering properties of a new class of alkylidenedithio bisphenols and related compounds are discussed. Maximum activity is shown by 4,4′-(isopropylidenedithio)bis(2,6-di-*t*-butylphenol). A few other members of the class show moderate to good activity and these are produced by substitution of a Me group or an *i*-Pr group for one *t*-Bu group in the phenolic nucleus, or substitution of Et for Me in the isopropylidene moiety. Other reported structural variations resulted in a reduction of activity or, most often, a loss of activity.

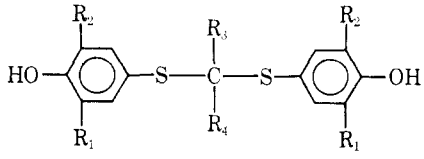
This work represents part of a program on the synthesis of nontoxic oral hypocholesterolemic agents, and is concerned with the structure–activity relationships of a new class of alkylidenedithio bisphenols. Serum cholesterol depressant activity of the most active member of this class has been described.[1,2] Response was shown by mice, rats, monkeys, and humans.

This compound (**1**), 4,4′-(isopropylidenedithio)bis-(2,6-di-*t*-butylphenol), was prepared by acid-catalyzed



condensation of 4-mercapto-2,6-di-*t*-butylphenol with acetone.

A generalized structure for this class of compounds is given below.



The effect of the following variations in structure on hypocholesterolemic activity in mice was examined: (1) size and degree of branching of alkyl groups R_1 and R_2; (2) replacement of R_1 and R_2 by H or Br; (3) substituting H for OH; (4) substitution of H, alkyl groups of increasing molecular weight, Ph, or cycloalkyl for R_3 and/or R_4; (5) replacement of the alkylidenedithio moiety by other S-containing groups.

Hypocholesterolemic Activity.—Good hypocholesterolemic activity in mice is shown by **1** (Table I). Changes in ring substitution have invariably produced a decrease in activity. In fact, one *o*-*t*-Bu must be present for even moderate activity. The unsubstituted compound **2** and compounds substituted with alkyl groups other than *t*-Bu (**6**–**8**, **12**) are inactive. Likewise, the inclusion of one or two *o*-Br substituents in each ring in place of *t*-Bu groups (**10**, **11**) results in compounds inactive in our test. The only other moderately active compounds in this series are those which contain one *t*-Bu and either Me (**4**) or *i*-Pr (**5**). Activity is diminished when Me or *i*-Pr is replaced by H (**3**), and lost when replaced by 1,1,3,3-tetramethylbutyl (**9**).

Maximum activity is observed in a structure consisting of an aromatic ring containing 3,5-di-*t*-Bu substitution and a 4-OH group with respect to the dithioketal linkage. The steric hinderance of the OH group as a result of the vicinal bulky *t*-Bu groups suggested that the OH itself may not contribute to activity. The dehydroxylated analog, 2,2-bis(3,5-di-*t*-butylbenzenethio)propane, showed no activity, indicating that the OH group is essential.

Changes about the central quaternary C also lead, in most cases, to diminished activity (Table II). In fact, if just one of the two central Me groups is re-

(1) J. W. Barnhart, J. A. Sefranka, and D. D. McIntosh, *Fed. Proc.*, **28**, 268 (1969).

(2) J. P. Colmore, A. S. Norrby, D. A. Vloedmon, H. H. Schweem, J. Nakano, and K. M. Dubowski, 4th International Congress of Pharmacology, Basel, July 14–18, 1969, p 405.