

Novel Polycyclic Heterocycles. II. Derivatives of 5,11-Dihydrodibenz[b,e][1,4]oxazepine¹

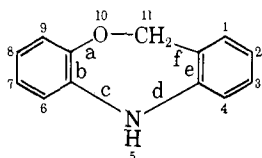
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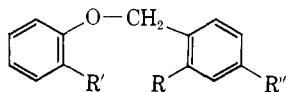
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5,11-Dihydrodibenz[b,e][1,4]oxazepine (I) was prepared by the following sequence: *o*-bromobenzyl *o*-nitrophenyl ether → *o*-(*o*-bromobenzyl)aniline → 2-(*o*-bromobenzyl)formanilide → 5,11-dihydrodibenz[b,e][1,4]oxazepine-5-carboxaldehyde → I. A related synthesis gave 7-chloro-5,11-dihydrodibenz[b,e][1,4]oxazepine (VI). 2-(2,4-Dichlorobenzyl)formanilide (VII) could not be made to cyclize. Alkylation of I and VI with dialkylaminoalkyl chlorides was best carried out with sodium hydride in dimethyl sulfoxide. In addition, I and VI were allowed to react with 3-chloropropionyl chloride and the resulting 5-(3-chloropropionyl) derivatives converted to 5-(3-monoalkyl- and 3-dialkylaminoacyl) derivatives. I and phosgene gave the 5-carbonyl chloride, and this derivative with dialkylamino alcohols and dialkylaminoalkylamines gave the corresponding urethanes and carbamates, respectively. 5-(3-Monoalkylaminopropyl) derivatives of I and VI were prepared by reaction first with *N*-(3-chloropropyl)-*N*-methylformamide and then removal of the blocking formyl group by saponification. Several of the compounds are active as antihistamines and as antipruritic agents.

As part of our program on new heterocycles,^{2,3} we have synthesized 5,11-dihydrodibenz[b,e][1,4]oxazepine (I). The synthesis of I was achieved by the follow-



ing sequence: *o*-bromobenzyl bromide and *o*-nitrophenol in aqueous ethanolic potassium hydroxide gave *o*-bromobenzyl *o*-nitrophenyl ether (II); reduction of II with iron powder in aqueous 2-propanol-hydrochloric acid yielded *o*-(*o*-bromobenzyl)aniline, best isolated as the hydrochloride (III); reaction of III with sodium formate-formic acid gave 2-(*o*-bromobenzyl)formanilide (IV); cyclization of IV with anhydrous potassium carbonate in *N,N*-dimethylformamide led to 5,11-dihydrodibenz[b,e][1,4]oxazepine-5-carboxaldehyde (V); and, saponification of V with aqueous ethanolic sodium hydroxide gave I. It is worth noting that I and V are rapidly decomposed by hot aqueous ethanolic hydrochloric acid. Furthermore, the cyclization of IV must be carried out under the controlled conditions described in the Experimental part.



II,	R = Br; R' = NO ₂ ; R'' = H
III,	R = Br; R' = NH ₂ ·HCl; R'' = H
IV,	R = Br; R' = NHCHO; R'' = H
VII,	R, R'' = Cl; R' = NHCHO
VIII,	R = NH ₂ ; R' = NO ₂ ; R'' = H
IX,	R, R' = NO ₂ ; R'' = H
X,	R, R' = NH ₂ ; R'' = H

The same sequence of reactions, but with the substitution of 2-nitro-4-chlorophenol for the *o*-nitrophenol

(1) Presented in part at the Second Annual Metropolitan Regional Meeting, North Jersey and New York Sections of the American Chemical Society, Newark, N. J., Jan., 1963.

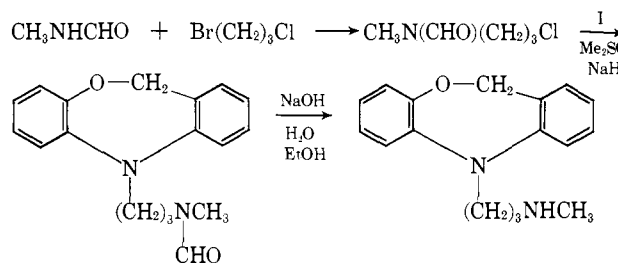
(2) I. F. Sowinski and H. L. Yale, *Arzneimittel-Forsch.*, **14**, 117 (1964).

(3) Part III: F. Sowinski and H. L. Yale, "Derivatives of 10,11-Dihydrodibenz[b,e][1,4]thiazepine," presented at the Third Annual Metropolitan Regional Meeting, New Jersey and New York Sections of the American Chemical Society, New York, N. Y., Jan., 1964. The related 5,11-dihydrodibenzo[b,e][1,4]thiazepine has recently been reported: French Patent 1,176,115 (1959); *Chem. Abstr.*, **55**, 19,972 (1961).

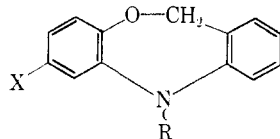
in the above reaction, gave 7-chloro-5,11-dihydrodibenz[b,e][1,4]oxazepine (VI). A similar procedure, starting with 2,4-dichlorobenzyl chloride and *o*-nitrophenol, gave eventually, 2-(2,4-dichlorobenzyl)formanilide (VII), but VII could not be made to cyclize.

In the reactions of I and VI with dialkylaminoalkyl chlorides in toluene or xylene in the presence of sodium hydride poor yields of dialkylaminoalkyl derivatives were obtained; with sodamide, none of the starting material or the desired product was isolated; in tetrahydrofuran, good yields were possible only with dialkylaminoethyl and dialkylaminoisopropyl chlorides, again using sodium hydride as the acid acceptor. The dialkylaminopropyl chlorides gave poor yields in tetrahydrofuran; however, dialkylaminopropyl bromides in tetrahydrofuran afforded good yields of these alkylated derivatives. Finally, in dimethylsulfoxide-sodium hydride, I and VI gave excellent yields of products with all of the dialkylaminoalkyl chlorides, hence this is the solvent of choice for these alkylation reactions.⁴

While 5-(3-monoalkylaminoacyl) derivatives could be prepared (see below), their reduction with lithium aluminum hydride resulted in elimination of the side chain and regeneration of I or VI. Thus, a direct approach to the synthesis of 5-(3-alkylaminopropyl) derivatives was not available. An indirect method, outlined below for the methylamino compound, was found to be generally applicable for the preparation of this class of derivatives.



(4) It is of interest to speculate whether $\text{CH}_3\text{SOCH}_2^-\text{Na}^+$ formed by the reaction of dimethyl sulfoxide with sodium hydride [cf. M. Chaykovsky and E. J. Corey, *J. Org. Chem.*, **28**, 254 (1963); and C. Walling and L. Bollyky, *ibid.*, **28**, 256 (1963)] is, in fact, the condensing agent. In our experience, the yield of **8** (arabic numbers refer to compounds in Table I) was decreased from 87 to 60% by the use of the preformed methylsulfinyl reagent; consequently, the inference is that in our procedure, there is a decreased opportunity for carbanion formation to occur. See Experimental part for details.

TABLE I
 5-[MONO- AND DIALKYLAMINOALKYL- AND -ACYL]-5,11-DIHYDRODIBENZ[b,e][1,4]OXAZEPINES


No.	X	R	Mol. formula	b.p. (mm.) or m.p., °C.	Yield, %	Calcd., %		
						C	H	N
1	H	(CH ₃) ₂ NCH ₂ CH ₂	C ₁₇ H ₂₀ N ₂ O	151-153 (0.5)	98	5.22 ^c
2	H	(C ₂ H ₅) ₂ NCH ₂ CH ₂	C ₁₉ H ₂₄ N ₂ O	161-162 (0.3) ^d	60	76.98	8.16	9.45
3	H	(CH ₃) ₂ N(CH ₂) ₃	C ₁₈ H ₂₂ N ₂ O	167-169 (0.1) ⁱ	84	76.55	7.85	9.92
4	H	(CH ₃) ₂ NCH(CH ₃)CH ₂ ^c	C ₁₈ H ₂₂ N ₂ O	...	74	76.55	7.85	9.92
5	H	(CH ₃) ₂ NCH ₂ CH(CH ₃)CH ₂	C ₁₉ H ₂₄ N ₂ O	170-172 (0.9)	65	76.98	8.16	9.45
6	H	CH ₃ NH(CH ₂) ₃	C ₁₇ H ₂₀ N ₂ O	173-175 (0.05)	41	76.07	7.50	10.43
7	H	CH ₃ NHCH ₂ CH(CH ₃)CH ₂	C ₁₈ H ₂₂ N ₂ O	164-166 (0.1)	28	76.55	7.85	9.92
8	H		C ₂₁ H ₂₇ N ₂ O	194-196 (0.3)	88	74.73	8.06	12.45
9	H		C ₂₀ H ₂₄ N ₂ O	194-196 (0.4)	73	77.88	7.84	9.08
10	Cl	(CH ₃) ₂ NCH ₂ CH ₂	C ₁₇ H ₁₉ ClN ₂ O	...	86	67.43	6.32	8.41
11	Cl	(CH ₃) ₂ NCH(CH ₃)CH ₂ ^c	C ₁₈ H ₂₁ ClN ₂ O	...	85	8.81
12	Cl	(CH ₃) ₂ N(CH ₂) ₃	C ₁₈ H ₂₁ ClN ₂ O	187-189 (0.5) ^f	57	8.81 ^{no}
13	H	(CH ₃) ₂ NCH ₂ CH ₂ CO	C ₁₈ H ₂₀ N ₂ O ₂	78.5-80.0 ^g	45	72.93	6.80	9.45
14	H	CH ₃ NHCH ₂ CH ₂ CO	C ₁₇ H ₁₈ N ₂ O ₂	...	81	72.30	6.42	9.92 ^g
15	H	C ₂ H ₅ NHCH ₂ CH ₂ CO	C ₁₈ H ₂₀ N ₂ O ₂	...	83	9.45
16	H	(CH ₃) ₂ NCH ₂ CH ₂ CO	C ₁₈ H ₁₉ ClN ₂ O ₂	113-114 ^h	52	8.46
17	H	(CH ₃) ₂ NCH ₂ CH ₂ OCO	C ₁₈ H ₂₀ N ₂ O ₃	66-68 ^h	30	69.21	6.45	8.97
18	H		C ₂₃ H ₂₈ N ₂ O ₄	...	14 ^o
19	H	(CH ₃) ₂ NCH ₂ CH ₂ NHCO	C ₁₈ H ₂₁ N ₃ O ₂	135-136	22 ^{oo}	69.42	6.80	13.49

^a Yield calculated on the quantity of base used to prepare salt. ^b See paper for a discussion of the test procedure and discussion of relative potencies. ^c This structure assignment to the least soluble isomer has been discussed previously; see H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957). ^d Base not distilled; analyses on crude base. ^e Basic N by HClO₄ titration. ^f Recryst. from acetone-anhydrous ether. ^g Recryst. from acetone. ^h *n*_D²⁰ 1.5802. ⁱ *n*_D²⁰ 1.5878. The material subsequently crystallized, m.p. 51-52°, after recrystallization from ligroin. ^j *Anal.* Calcd.: Cl, 10.65. Found: Cl, 10.64. ^k Recryst. from acetonitrile-anhydrous ether. ^l The crude base was purified by way of its crystalline phosphate, m.p. 227-228° dec.; while this salt gave unsatisfactory elemental analyses, the base isolated from this salt was pure. ^m *Anal.* Calcd.: Cl, 10.65. Found: Cl, 10.66. ⁿ Re-

With 3-chloropropionyl chloride in boiling toluene, I gave good yields of the 5-(3-chloropropionyl) derivative; this, with monoalkyl- and dialkylamines gave the corresponding alkylamino and dialkylaminoacyl compounds. Phosgene reacted with I in pyridine-tetrahydrofuran at room temperature to give the 5-carbonyl chloride. This derivative reacted with 2-dimethylaminoethanol in boiling chloroform and with the sodium salt of 2-(2-piperidinoethoxy)ethanol in boiling toluene to give the related urethanes, and with N,N-dimethylethylenediamine to give the corresponding carbamate.

The physical properties and analyses for the mono- and dialkylaminoalkyl and mono- and dialkylaminoacyl derivatives are summarized in Table I.

In the course of several earlier unsuccessful efforts to synthesize I, attempts to prepare one key intermediate failed, but several others were synthesized. Thus, in one approach, *o*-aminobenzyl *o*-nitrophenyl ether (VIII) could not be prepared by the reaction between *o*-amino-

benzyl alcohol and *o*-bromonitrobenzene under a variety of conditions. In another approach, *o*-nitrobenzyl bromide and *o*-nitrophenol in ethanolic potassium hydroxide gave *o*-nitrobenzyl *o*-nitrophenyl ether (IX), and IX with hydrazine and Raney nickel gave *o*-(*o*-aminobenzoyloxy)aniline (X), but the diphosphate of X, when heated with polyphosphoric acid was cleaved to give *o*-aminophenol and, presumably, *o*-toluidine.

Pharmacology. Antihistaminic Activity.⁵—Deal strips were mounted in 10-ml. tissue baths and perfused with gassed (5% CO₂-95% O₂) Tyrodes solution at 36°. Each compound in 0.05 ml. of the same solution was added to the bath 2 min. before the addition of 2 γ/ml. of histamine. The concentrations of the compounds ranged from 0.0005-8.0 γ/ml. Compound 1 (Table I) at concentrations ranging from 0.0005-0.125

⁵ These studies were carried out by Drs. B. Rubin and Z. Horowitz of the Pharmacology Section of this institute and will be reported in detail elsewhere.

Found, %			Mol. formula	M.p., °C.	Yield, % ^a	Calcd., %			Found, %			Anti-bistaminic activity ^b
C	H	N				C	H	N	C	H	N	
...	...	5.17	C ₁₇ H ₂₀ N ₂ O·C ₄ H ₄ O ₄	141-142	80 ^f	65.61	6.29	7.29	65.80	6.45	7.50	+++
77.11	8.24	9.64	C ₁₉ H ₂₄ N ₂ O·HCl	179-180	70 ^g	8.41 ^j	8.31	+++
76.25	8.04	9.74	C ₁₈ H ₂₂ N ₂ O·HCl	156-157	75 ^k	67.80	7.27	8.78	67.97	7.42	8.53	+++
76.72	7.99	9.67	C ₁₈ H ₂₂ N ₂ O·C ₄ H ₄ O ₄	132-133	77 ^g	66.30	6.57	7.03	66.56	6.73	7.00	+++
76.97	8.12	9.39	C ₁₉ H ₂₄ N ₂ O·HCl	205-206 dec.	78 ^k	8.41 ^m	8.34	+++
76.06	7.46	10.23	C ₁₇ H ₂₀ N ₂ O·HCl	151-152	68 ⁿ	66.99	6.94	9.19 ^o	66.76	7.11	9.47	+
76.61	7.91	9.72	C ₁₈ H ₂₂ N ₂ O·HCl	182-183	75 ⁿ	67.80	7.27	8.78	67.92	7.38	8.98	++
75.05	8.23	12.29	C ₂₁ H ₂₇ N ₃ O·2HCl	239-240 dec.	89 ^p	61.45	7.12	10.24	61.39	7.07	10.28	+++
77.94	7.87	8.97	C ₂₀ H ₂₄ N ₂ O·HCl	175-176 dec.	32 ⁿ	8.12 ^q	8.09	++
67.33	6.33	8.75	C ₁₇ H ₁₉ ClN ₂ O·HCl	248-249	62 ⁿ	8.25 ^r	8.14	++
...	...	8.48	C ₁₈ H ₂₁ ClN ₂ O·HCl	225-226	52 ^g	7.93 ^t	8.02	++
...	...	8.74	C ₁₈ H ₂₁ ClN ₂ O·HCl	172-173	42 ^g	7.93 ^u	7.84	+
73.10	6.70	9.74	+
72.49	6.53	9.39	C ₁₇ H ₁₈ N ₂ O ₂ ·(CO ₂ H) ₂	174-176 dec.	31 ⁿ	61.27	5.41	7.52	61.19	5.55	7.47	±
...	...	9.12	C ₁₈ H ₂₀ N ₂ O ₂ ·HCl	166-167	56 ^k	64.95	6.36	8.41 ^v	65.02	6.44	8.49	+
...	...	8.18	+
69.29	6.48	8.99	+
...	C ₂₃ H ₂₈ N ₂ O ₄ ·(CO ₂ H) ₂	159-160	80 ^{bb}	61.71	6.21	5.75	61.56	6.34	5.70	-
69.10	7.06	13.63	±

cryst. from acetonitrile. ^o Anal. Calcd.: Cl, 11.63. Found: Cl, 11.58. ^p Recryst. from absolute ethanol-anhydrous ether. ^q Anal. Calcd.: Cl, 10.28. Found: Cl, 10.15. ^r Anal. Calcd.: Cl, 10.45. Found: Cl, 10.55. ^s Recryst. from methanol-anhydrous ether. ^t Anal. Calcd.: Cl⁻, 10.03. Found: Cl⁻, 10.08. ^u Anal. Calcd.: Cl⁻, 10.03. Found: Cl⁻, 10.05. ^v M.p. 47-49° after recrystallization from ligroin. ^w Anal. Calcd.: Cl, 11.20. Found: Cl, 11.31. ^x Recryst. from diisopropyl ether. ^y Anal. Calcd.: Cl, 10.65. Found: Cl, 10.72. ^z Anal. Calcd.: Basic N(HClO₄), 4.96. Found: Basic N(HClO₄), 4.72. ^{aa} Recryst. from hexane. ^{bb} Recryst. from absolute ethanol. ^{cc} Base not analyzed. ^{dd} Recryst. from Skellysolve V.

γ/ml. inhibited the spasmogenic effect of histamine and was found to be 4.9 times as potent and with a duration of activity of about 1-2 times that of pyrilamine maleate.

Inhibition of Dextran-Induced Edema.—Male rats, fasted 1-4 hr., were dosed orally with the compound, suspended or dissolved in agar, 1 hr. before the i.p. administration of dextran (300 mg/kg.). The degree of edema in the snout and each of the legs was rated each hour for the first 4 hr. Compound **1** was at least 12 times as potent as pyrilamine maleate in inhibiting the anaphylactoid edema in the dextran-treated rats.

Antiemetic Activity.—Compound **1** showed little or no antiemetic activity against apomorphine (20 γ/kg., i.v.) induced emesis in dogs.

CNS Stimulant Activity.—Compound **1** had only a slight central nervous system stimulant action in the cat self-stimulation and behavior-EEG test procedures.

Structure-Activity Relationships.—In this area, data

are available only on relative antihistaminic potencies. These are summarized in Table I. Compounds **1-5** and **8** were highly active. The monoalkylaminoalkyl derivatives were less potent than the corresponding dialkylaminoalkyl compounds. Substitution by chlorine in the 7-position causes a decrease in potency. The dialkylaminoacyl derivatives were essentially inactive.

Experimental

All melting points are corrected.

o-(*o*-Aminobenzoyloxy)aniline.—To 29.1 g. (0.44 mole) of potassium hydroxide in 250 ml. of 95% ethanol was added dropwise, first 61.3 g. (0.44 mole) of *o*-nitrophenol in 250 ml. of 95% ethanol, and second, 87.8 g. (0.40 mole) of *o*-nitrobenzyl bromide in 250 ml. of 95% ethanol. The mixture was distilled from a steam bath, the residue was washed with water and dried to give 88.0 g. (61%) of *o*-nitrobenzyl *o*-nitrophenyl ether, m.p. 154-155°.

A mixture of 10.0 g. (0.04 mole) of the ether, 1 l. of absolute ethanol, 42 g. of 85% hydrazine hydrate, and ca. 1 g. of Raney

(6) E. Lellmann and N. Mayer [Ber., 25, 3581 (1892)] report m.p. 154°.

nickel catalyst was heated under reflux for 5 hr., with ca. 1 g. of catalyst being added at hourly intervals. The hot mixture was filtered, the filtrate was treated with Darco and Hyflo, again filtered, and the filtrate was concentrated to dryness. The residue weighed 3.9 g., m.p. 108–110°. Recrystallization from absolute ethanol gave 3 g. (35%) of *o*-(*o*-aminobenzoyloxy)aniline, m.p. 117–118°.

Anal. Calcd. for $C_{10}H_{11}N_2O$: C, 72.86; H, 6.58; N, 13.07. Found: C, 72.71; H, 6.48; N, 13.12.

The diamine formed a diphsophate, m.p. 151–152°.

Anal. Calcd. for $C_{10}H_{11}N_2O \cdot 2H_2PO_4$: N, 6.83; P, 15.09. Found: N, 6.56; P, 15.19.

The phosphate salt was heated in polyphosphoric acid by means of an oil bath at 275–280° for 0.75 hr.⁷ From the work-up of the reaction mixture only *o*-nitrophenol could be isolated and characterized.

5,11-Dihydrodibenz[*b,e*][1,4]oxazepine. A. *o*-Bromobenzyl *o*-Nitrophenyl Ether.—To 119.5 g. (0.5 mole) of *o*-bromobenzyl bromide and 83.6 g. (0.6 mole) of *o*-nitrophenol in 400 ml. of 95% ethanol was added, dropwise, 39.6 g. (0.6 mole) of 85% potassium hydroxide in 200 ml. of water and the reaction mixture subsequently refluxed for 2 hr. The product separated on cooling, was filtered, washed well with water, and air-dried to give 149.6 g. (96%) of product, m.p. 82–83°. The sample for analysis was recrystallized from 95% ethyl alcohol, m.p. 82.5–83°.

Anal. Calcd. for $C_{13}H_{10}BrNO_2$: C, 50.65; H, 3.26. Found: C, 50.59; H, 3.43.

B. *o*-(*o*-Bromobenzoyloxy)aniline Hydrochloride.—To 462 g. (1.5 moles) of *o*-bromobenzyl *o*-nitrophenyl ether in 7 l. of 95% 2-propanol, at 60°, with stirring, was added a total of 1250 g. of iron powder and 200 ml. of concentrated hydrochloric acid in 20 equal portions at approximately 5-min. intervals. The mixture was finally heated under reflux for 1 hr., filtered hot, the filtrate treated with 125 ml. of concentrated hydrochloric acid, concentrated to about 2 l., and cooled. The solid which separated was filtered to give 460 g. (97%) of product, m.p. 191–193°. An analytical sample, recrystallized from 10% aqueous hydrochloric acid, melted at 194–196°.

Anal. Calcd. for $C_{13}H_{12}BrNO \cdot HCl$: C, 49.62; H, 4.16; Cl, 11.27; N, 4.46. Found: C, 49.44; H, 4.03; Cl, 11.02; N, 4.51.

The free base, m.p. 41–42°, was recrystallized from ligroin.

Anal. Calcd. for $C_{13}H_{12}BrNO$: C, 56.12; H, 4.35; N, 5.04. Found: C, 56.00; H, 4.40; N, 4.96.

C. 2-(*o*-Bromobenzoyloxy)formanilide.—A mixture of 78.8 g. (0.25 mole) of the above hydrochloride, 34.0 g. (0.5 mole) of sodium formate, and 460 ml. (10 moles) of 98–100% formic acid was stirred and heated under reflux for 3 hr., cooled somewhat, and poured into 1 l. of ice-water. The solid which separated was filtered and washed with water to give 61.4 g. (80%) of the formanilide derivative, m.p. 113–114°.

Anal. Calcd. for $C_{13}H_{12}BrNO_2$: C, 54.91; H, 3.95; Br, 26.10. Found: C, 54.80; H, 4.12; Br, 26.23.

D. 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxaldehyde.—A mixture of 5.0 g. (0.017 mole) of the above formanilide, 2.8 g. (0.02 mole) of anhydrous potassium carbonate, 0.5 g. of copper powder, and 50 ml. of dimethylformamide was heated and stirred under nitrogen for 2 hr. in an oil bath maintained at 155–160°. The reaction mixture was filtered hot, the filtrate concentrated *in vacuo* to dryness, the residue washed with water, dried, and extracted with Skellysolve V. On cooling, the Skellysolve V extract deposited 2.6 g. of product, m.p. 98–101°; recrystallization from hexane gave 2.1 g. (46%) of the pure product, m.p. 111.5–112.5°.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22; N-formyl, 12.07. Found: C, 74.80; H, 4.88; N, 6.11; N-formyl, 12.74.

E. 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine.—The N-formyl derivative (100 mg.), 10 ml. of 95% ethanol, and 2 ml. of 10% aqueous sodium hydroxide were refluxed for 1 hr., cooled, neutralized, and concentrated to dryness. Recrystallization of the residue from hexane gave the product, m.p. 118–118.5°.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.29; H, 5.67; N, 7.24.

Subsequently, the following procedure was used: 27.0 g. (0.092 mole) of 2-(*o*-bromobenzoyloxy)formanilide, 25.4 g. (0.184 mole) of anhydrous potassium carbonate, 2 g. of copper powder, and 300 ml. of dimethylformamide were allowed to react as described

above, the reaction mixture was filtered hot and freed of dimethylformamide. The residue was dissolved in 235 ml. of 95% ethyl alcohol, treated with Darco, filtered, the filtrate treated with 45 ml. of 25% aqueous sodium hydroxide, and heated 1 hr. under reflux. The cooled mixture deposited 14.5 g. of solid, m.p. 108–109°; concentration of the mother liquors gave an additional 5.1 g. of solid, m.p. 103–105°. Recrystallization of the combined solids from hexane gave 12.4 g. (68%) of pure product, m.p. 118–118.5°.

By employing the above procedures, the following intermediates were prepared.

***o*-Bromobenzyl 4-chloro-2-nitrophenyl ether** had a 61% yield, m.p. 122–124°, after recrystallization from 2-propanol.

Anal. Calcd. for $C_{12}H_9BrClNO_2$: Br, 23.26; Cl, 10.35. Found: Br, 23.60; Cl, 9.71.

2-Amino-4-chlorophenyl *o*-bromobenzyl ether hydrochloride had a 71% yield, m.p. 207–209° dec., after recrystallization from ethyl methyl ketone.

Anal. Calcd. for $C_{12}H_{11}BrClNO \cdot HCl$: Br, 22.90; Total Cl, 20.32; Cl⁻, 10.16. Found: Br, 22.67; Total Cl, 19.92; Cl⁻, 9.93.

2-Amino-4-chlorophenyl *o*-bromobenzyl ether had m.p. 60–62°, after recrystallization from ligroin.

Anal. Calcd. for $C_{12}H_{10}BrClNO$: Br, 25.56; Cl, 11.34. Found: Br, 25.52; Cl, 11.38.

2'-(*o*-Bromobenzoyloxy)-5'-chloroformanilide had a 61% yield, m.p. 140–142°, after recrystallization from 2-propanol.

Anal. Calcd. for $C_{13}H_{10}BrClNO_2$: N, 4.11; N-formyl, 8.52. Found: N, 3.94; N-formyl, 8.55.

7-Chloro-5,11-dihydrodibenz[*b,e*][1,4]oxazepine had a 93% yield, m.p. 150–151°, after recrystallization from benzene.

Anal. Calcd. for $C_{12}H_9ClNO$: Cl, 15.38; N, 6.04. Found: Cl, 15.68; N, 6.32.

2,4-Dichlorobenzyl *o*-nitrophenyl ether had an 82% yield, m.p. 120–122°, after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_8Cl_2NO_2$: C, 52.39; H, 3.04; N, 4.70. Found: C, 52.50; H, 3.14; N, 4.83.

***o*-(2,4-Dichlorobenzoyloxy)aniline hydrochloride** had an 85% yield, m.p. 231–233°, after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_9Cl_2NO \cdot HCl$: Cl⁻, 11.64; N, 4.59. Found: Cl⁻, 11.63; N, 4.41.

***o*-(2,4-Dichlorobenzoyloxy)aniline** had m.p. 56–58°, after recrystallization from ligroin.

Anal. Calcd. for $C_{12}H_9Cl_2NO$: Cl, 26.45; N, 5.23. Found: Cl, 26.25; N, 5.23.

2-(2,4-Dichlorobenzoyloxy)formanilide had a 93% yield, m.p. 146–148°, after recrystallization from 75% 2-propanol–25% water.

Anal. Calcd. for $C_{13}H_{11}Cl_2NO_2$: N-formyl, 9.79; N, 4.72. Found: N-formyl, 9.54; N, 4.83.

The procedures below are typical of those used to prepare 5-dialkylaminoalkyl derivatives, employing dialkylaminoalkyl chlorides.

5-(3-Dimethylamino-2-methylpropyl)-5,11-dihydrodibenz[*b,e*][1,4]oxazepine. Dimethyl Sulfoxide.—A mixture of 9.9 g. (0.05 mole) of 5,11-dihydrodibenz[*b,e*][1,4]oxazepine, 2.8 g. (0.06 mole) of a 50% dispersion of sodium hydride in mineral oil, and 50 ml. of dimethyl sulfoxide was stirred under nitrogen for 1 hr., 10.2 g. (0.075 mole) of 3-dimethylamino-2-methylpropyl chloride added, the mixture heated to 95–100°, and stirring continued for 2.5 hr. The mixture was cooled, treated with 5 ml. of 95% ethanol, poured into 500 ml. of water, and extracted with ether. The ether solution was extracted with 10% aqueous phosphoric acid, the acid solution was neutralized with solid potassium carbonate, and the liberated base again taken up into ether. The dried ether solution was concentrated and the residue distilled to give 9.7 g. (65%) of the base, n_D^{20} 1.5790.

5-(2-Dimethylaminoethyl)-5,11-dihydrodibenz[*b,e*][1,4]oxazepine. Tetrahydrofuran.—Under nitrogen, a mixture of 4.9 g. (0.25 mole) of I, 1.5 g. (0.03 mole) of a 50% dispersion of sodium hydride in mineral oil, and 50 ml. of tetrahydrofuran (dried and distilled over lithium aluminum hydride) was stirred for 0.5 hr. To the mixture was then added 4.0 g. (0.038 mole) of 2-dimethylaminoethyl chloride and the mixture heated under reflux for 3 hr. Stirring was continued for 16 hr., a second portion of 1.2 g. (0.025 mole) of sodium hydride dispersion and 2.7 g. (0.025 mole) of 2-dimethylaminoethyl chloride was added, and refluxing resumed for an additional 3 hr. The reaction mixture was filtered and concentrated to dryness. The residue dissolved in 25 ml. of ether, was extracted with 25 ml. of 10% aqueous phosphoric acid,

(7) This is the procedure used for preparing 10,11-dihydrodibenz[*b,e*][1,4]oxazepine from *o*,*o'*-diaminodibenzyl; cf. U. S. Patent 2,800,470 (1957).

the acid extract made strongly basic, and the base extracted with ether. Concentration of the dried ether extract gave the base.

7-Chloro-5-(3-dimethylaminopropyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine. 3-Dimethylaminopropyl Bromide.—To 103.7 g. (1.0 mole) of 3-dimethylaminopropanol in 250 ml. of dry chloroform was added, at 0°, during 2 hr., 218.0 g. (1.1 moles) of thionyl bromide in 250 ml. of dry chloroform; stirring at 0° was continued for 3 hr. and the mixture was kept 72 hr. The volatiles were removed *in vacuo* and the residue recrystallized from absolute ethanol to give 209.0 g. (85%) of the hygroscopic product.

Anal. Calcd. for $C_8H_{12}BrN \cdot HBr$: Br⁻, 32.35. Found: Br⁻, 32.14.

The base was liberated from the hydrobromide and isolated by the conventional procedure.

A mixture of 9.3 g. (0.04 mole) of 7-chloro-5,11-dihydrodibenzo[b,e][1,4]oxazepine, 2.4 g. (0.05 mole) of a 50% dispersion of sodium hydride in mineral oil, and 100 ml. of dry tetrahydrofuran was stirred for 1 hr., 10.0 g. (0.06 mole) of 3-dimethylaminopropyl bromide added, and the mixture heated under reflux for 2 hr. The heating bath was removed, and stirring continued overnight. A second 2.4 g.-portion (0.048 mole) of the sodium hydride dispersion was added, and after 1 hr., 8.3 g. (0.05 mole) of 3-dimethylaminopropyl bromide. The mixture was again heated under reflux for 2 hr., filtered, concentrated to dryness, and the residue dissolved in ether. The ether solution was then extracted with 200 ml. of cold 10% phosphoric acid, the acid extract made alkaline with solid potassium carbonate, and the base taken into ether. This ether solution was dried, concentrated, and distilled twice to give 7.3 g. (57%) of product, b.p. 187–189° (0.5 mm.), which crystallized spontaneously; recrystallization from ligroin gave the base, m.p. 47–49°.

5,11-Dihydro-5-(2-methyl-3-methylaminopropyl)dibenz[b,e]-1,4]oxazepine. 2-Methyl-3-methylaminopropanol.—To a suspension of 75.9 g. (2.0 moles) of lithium aluminum hydride in 1 l. of anhydrous ether was added under nitrogen, dropwise, a solution of 131.2 g. (1 mole) of methyl 2-methyl-3-methylaminopropionate⁸ in 250 ml. of tetrahydrofuran. The mixture was subsequently stirred and heated under reflux for 2 hr. and worked up to give 64.2 g. (62%) of product, b.p. 45–46° (4 mm.), n_D^{25} 1.4442.

3-Methylformamido-2-methylpropanol.—A solution of 64.2 g. (0.62 mole) of 2-methyl-3-methylaminopropanol in 70.0 g. (1.55 moles) of formamide was heated for 2 hr. in an oil bath maintained at 125°. Fractionation of the mixture gave 82.0 g. (quantitative yield) of the formamido derivative, b.p. 115–116° (2 mm.), n_D^{25} 1.4686.

Anal. Calcd. for $C_8H_{13}NO_2$: C, 54.92; H, 9.98; N, 10.67. Found: C, 54.95; H, 9.91; N, 11.22.

N-(3-Chloro-2-methylpropyl)-N-methylformamide.—To 82.0 g. (0.63 mole) of 3-methylformamido-2-methylpropanol, 54.5 g. (0.69 mole) of pyridine, and 500 ml. of chloroform was added during 0.5 hr., 77.5 g. (0.65 mole) of thionyl chloride. The mixture was heated under reflux for 0.5 hr., cooled, and poured into ice-water. The organic layer was separated, washed with sodium bicarbonate solution until neutral, dried, concentrated, and the residue was distilled to give 53.1 g. (57%) of product, b.p. 120–121° (8 mm.), n_D^{25} 1.4725.

Anal. Calcd. for $C_8H_{12}ClNO$: C, 48.16; H, 8.08. Found: C, 48.24; H, 8.10.

5,11-Dihydro-5-(2-methyl-3-methylaminopropyl)dibenz[b,e]-1,4]oxazepine.—A mixture of 9.9 g. (0.05 mole) of I, 2.8 g. (0.06 mole) of a 50% dispersion of sodium hydride in mineral oil, and 50 ml. of dimethyl sulfoxide was stirred for 0.5 hr., 10.9 g. (0.075 mole) of *N*-(3-chloro-2-methylpropyl)-*N*-methylformamide was added, the mixture heated at 105° for 3 hr., cooled, poured into water, and the mixture extracted with ether. The dried ether extracts were concentrated to give an oily residue of 5,11-dihydro-5-[2-methyl-3-(*N*-methylformamido)propyl]dibenz[b,e][1,4]oxazepine. This residue, 50 ml. of 20% aqueous sodium hydroxide, and 350 ml. of 95% ethanol were refluxed for 2.5 hr., concentrated, and the residue was partitioned between ether and cold 5% aqueous phosphoric acid. The acid phase was separated and treated with an excess of solid potassium carbonate, the base was extracted with ether, the ether solution was dried and concentrated, and the residue was distilled to give the product.

N-(3-Chloropropyl)-N-methylformamide.—The preparation of this derivative was necessary for the synthesis of 5,11-dihydro-

5-(3-methylaminopropyl)dibenz[b,e][1,4]oxazepine. The alkylation was carried out as described directly above.

To a suspension of 23.4 g. (0.6 mole) of sodamide in 400 ml. of dry toluene, kept at 0–5°, was added during 1 hr., a solution of 31.9 g. (0.6 mole) of *N*-methylformamide in 100 ml. of dry toluene. The reaction mixture was stirred for 2 hr. at room temperature, 94.6 g. (0.6 mole) of trimethylene chlorobromide was added over a period of 1 hr., the mixture was heated under reflux for 4 hr., filtered, and concentrated to dryness, and the residue was distilled to give 12.2 g. (15%) of product, b.p. 148–150° (30 mm.), n_D^{25} 1.4722.

Anal. Calcd. for $C_8H_{10}ClNO$: C, 44.28; H, 7.43; N, 10.33. Found: C, 43.92; H, 7.67; N, 10.75.

The preparation of typical hydrochloride, maleate, and phosphate salts are given in the following three examples.

5-(3-Dimethylamino-2-methylpropyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine Hydrochloride.—To 9.1 g. (0.033 mole) of the base in 100 ml. of anhydrous ether was added, dropwise, with cooling, 14.0 ml. (0.035 mole) of 2.5 *N* ethereal hydrogen chloride. The solid which formed was recrystallized first from a mixture of acetone-ether and then from a mixture of acetonitrile and ether.

5-(2-Dimethylaminoethyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine Maleate.—To 6.6 g. (0.025 mole) of the base in 50 ml. of anhydrous ether was added 3.21 g. (0.03 mole) of maleic acid in 10 ml. of acetone. The solid which formed was filtered, dried, and recrystallized from acetone-ether.

5-(3-Dimethylaminopropyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine Diphosphate.—To 0.5 g. of the base in 10 ml. of ether was added 0.2 g. of 85% phosphoric acid in 10 ml. of acetone. The precipitated solid, m.p. 150–152°, was recrystallized from acetonitrile; m.p. 151–153°.

Anal. Calcd. for $C_{18}H_{24}N_2O \cdot 2H_3PO_4$: N, 5.83; P, 12.89. Found: N, 5.66; P, 13.05.

5-(3-Chloropropionyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine.—A mixture of 9.0 g. (0.046 mole) of 5,11-dihydrodibenzo[b,e][1,4]oxazepine, 11.7 g. (0.092 mole) of β -chloropropionyl chloride, and 150 ml. of dry toluene was refluxed for 4 hr., treated with Darco, filtered, and the filtrate concentrated to dryness to give 10.8 g. of a residual gum. The gum crystallized on drying *in vacuo* and, after recrystallization from hexane, melted at 98–99°.

Anal. Calcd. for $C_{16}H_{15}ClNO$: C, 66.78; H, 4.88. Found: C, 66.92; H, 4.78.

5-(3-Ethylaminopropionyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine Hydrochloride.—To 21.2 g. (0.078 mole) of crude 5-(3-chloropropionyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine in 250 ml. of benzene was added 22.6 g. (0.5 mole) of ethylamine and the mixture heated under reflux for 1 hr. The reaction mixture was cooled, a second 22.6-g. portion of ethylamine added, the mixture again heated under reflux for 1 hr., and concentrated. The residue was partitioned between 10% phosphoric acid and ether. The acid solution was made alkaline with potassium carbonate and the liberated base collected in ether. The ether solution was dried and concentrated to give 19.1 g. (83%) of base as a viscous product. To 19.1 g. (0.064 mole) of the base in 250 ml. of anhydrous ether, was added, dropwise, with cooling, 32.5 ml. (0.065 mole) of 2 *N* ethereal hydrogen chloride. The gummy product which separated was triturated with boiling acetone and recrystallized from a mixture of acetonitrile-ether to give the product.

5,11-Dihydro-5-(3-methylaminopropionyl)dibenz[b,e][1,4]oxazepine Hydrogen Oxalate.—To 12.2 g. (0.043 mole) of the base in 125 ml. of anhydrous ether was added 3.9 g. (0.043 mole) of oxalic acid in 20 ml. of hot acetone. The semisolid material which separated was triturated with hot acetone and recrystallized from acetonitrile to give 5.0 g. (31%) of product, m.p. 174–176° dec.

5,11-Dihydrodibenzo[b,e][1,4]oxazepine-5-carbonyl Chloride.—To 19.7 g. (0.1 mole) of 5,11-dihydrodibenzo[b,e][1,4]oxazepine, 7.9 g. (0.1 mole) of pyridine, and 50 ml. of dry tetrahydrofuran was added with stirring and cooling, dropwise, 142 ml. (0.2 mole) of a 14% solution of phosgene in tetrahydrofuran. The mixture was stirred at 0° for 5 hr., allowed to come to room temperature, stirred at that temperature for an additional 16 hr., and concentrated to dryness *in vacuo*. The residue was extracted with 400 ml. of chloroform, the chloroform extract washed with water, and dried. This solution, containing 51 mg. of solid/ml., was used in subsequent reactions, since all attempts to obtain crystalline carbonyl chloride derivative were unsuccessful.

N-(2-Dimethylaminoethyl)-5,11-dihydrodibenzo[b,e][1,4]oxazepine-5-carboxamide.—A mixture of 3.93 g. (0.04 mole) of *N,N*-dimethylaminoethylenediamine and 103 ml. of the above chloro-

(8) R. M. Jacob and J. G. Robert, U. S. Patent 2,837,518 (June 3, 1958).

form extract was heated under reflux for 5 hr. The mixture was concentrated to dryness, partitioned between ether and 10% phosphoric acid, the phosphoric acid solution was neutralized and extracted with ether, and the ether extract was dried and concentrated to give 1.4 g. of product.

2-Dimethylaminoethyl 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxylate.—The procedure described directly above was used in this preparation. From 7.5 g. (0.085 mole) of 2-dimethylaminoethanol and 219 ml. of the chloroform solution was obtained 4.1 g. of ester, m.p. 54–56°. The product was purified by treating a hexane solution with Darco, filtering, and concentrating the filtrate to a small volume.

2-(2-Piperidinoethoxy)ethyl 5,11-Dihydrodibenz[*b,e*][1,4]oxazepine-5-carboxylate.—For this preparation the crude 5-carboxyl chloride was extracted into toluene rather than into chloroform as in the previous example. To 19.0 g. (0.11 mole) of 2-(2-

piperidinoethoxy)ethanol in 125 ml. of dry tetrahydrofuran was added 5.2 g. (0.11 mole) of a 50% dispersion of sodium hydride in mineral oil. When the vigorous reaction had subsided, a toluene solution estimated to contain 13.9 g. (0.08 mole) of the carbonyl chloride was added dropwise; subsequently, the mixture was heated under reflux for 2.5 hr. and worked up as above to give 4.6 g. of oily *base*. This was dissolved in 25 ml. of anhydrous ether and treated with small portions of a saturated solution of oxalic acid in hot acetone until the mixture became acid to Congo red. The resulting gum was crystallized by trituration in hot acetone and recrystallized from absolute ethanol to give 4.5 g. of product.

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Synthesis and Biological Evaluation of Substituted β -Dimethylaminoethyl α -Phenyl-*cis*- and -*trans*-cinnamates^{1a}

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The synthesis and biological evaluation of various nitro- and methoxy-substituted β -dimethylaminoethyl α -phenyl-*cis*- and -*trans*-cinnamates are described. The *cis* acids afford *trans* esters owing to rearrangement during the preparation. This was partially controlled by preparing the acid chlorides at lower temperatures. The compounds were screened for their acute toxicity, anticholinergic, and antihistaminic activities. All of the compounds showed anticholinergic and antihistaminic effects. The unsubstituted *trans* isomer had the highest anticholinergic activity; it appears to be of a competitive antagonist type. When the cardiovascular effects of some of these compounds were investigated, a fall in blood pressure was observed, which is tentatively attributed to a central rather than an adrenolytic action. The *trans* isomers, in general, show more local anesthetic activity than the corresponding *cis* isomers.

A wide variety of pharmacological properties, such as parasympatholytic, local anesthetic, antihistaminic, and tranquilizing, are shared to various degrees by compounds having the general structure $\text{RCOOCH}_2\text{-CH}_2\text{NR}_2'$. Biological evaluations of structural analogs provide some information about the moieties required for potent and specific actions.

A series of β -dimethylaminoethyl α -phenylcinnamates containing substituents in both rings were evaluated. Of the two geometric isomers, the *cis* isomer has two *trans*-related phenyl groups in conjugation, whereas the *trans* isomer contains the *cis*-stilbene moiety. The α -substituent, either carboxyl or phenyl, which is *cis* to the β -phenyl group, has been shown² to occupy a perpendicular conformation with respect to the remaining planar *trans*-stilbene or *trans*-cinnamic acid moieties, respectively. This helps to fix the position of the side chain.

p-Nitro or methoxy groups were selected as substituents in the α -phenyl and/or the β -phenyl rings as representative electron-acceptor and electron-donor groups, respectively. These groups alter the electron density at the carbonyl group and the ether oxygen.

Electron density often plays an important role in

biological activity by altering the binding of the drug to the receptor site.³ Galinsky and co-workers⁴ reported electronic effects of *para* substituents on the local anesthetic activity in β -diethylaminoethyl benzoates, cinnamates, and β -phenylpropionates. Hey³ emphasized the importance of electron density around the ether oxygen for cholinergic activity. Mercier and co-workers⁵ investigated β -diethylaminoethyl esters of α -phenylcinnamic acid, α -phenyl-*p*-methoxycinnamic acid, α,β -diphenylpropionic acid, and α -phenyl- β -(*p*-methoxyphenyl)propionic acid and showed that these compounds are powerful antispasmodics when tested in the isolated rat or rabbit intestine in the presence of acetylcholine (ACh) or barium chloride. The unsaturated esters have nearly the same potency as papaverine hydrochloride in antagonizing the spasmodic action of ACh and barium chloride. With various electron-donating and -accepting substituents, and with different geometric isomers, there exists a possibility of having varying affinities toward "receptors" for different types of biological action, and thereby achieving a separation of these activities.

The electron density of the carbonyl carbon can be determined by measuring the carbonyl stretching frequency in the infrared or by determination of the ionization constants of the corresponding α -phenyl-

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(2) H. E. Zimmerman and L. Abramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959).

(3) P. Hey, *Brit. J. Pharmacol.*, **7**, 117 (1952).

(4) A. M. Galinsky, J. F. Gearson, A. J. Perkins, and S. V. Sasima, *J. Med. Chem.*, **6**, 320 (1963).

(5) F. Mercier, J. Mercier, and M. R. Sestier, *Compt. Rend. Soc. Biol.*, **144**, 551, 1185 (1950).