Reaction of 1,2,3,4-Tetrahydro-2-methylisoquinoline with BrCN.—To a solution of BrCN (7.50 g, 70.80 mmol) in 50 ml of anhydrous C_6H_6, a solution of 1,2,3,4-tetrahydro-2-methylisoquinoline (**21**) (6.00 g, 40.75 mmol) in 100 ml of anhydrous C_6H_6 was added slowly over a period of 2 hr. Essentially the same procedure was previously employed to obtain N-CN compound was utilized to give a colorless viscous residue which crystallized into fine needles, **22** (3.52 g, 22.25 mmol, 54.60%), mp 43–44°; ir (neat): 2220 cm^{-1} (C≡N). *Anal.* ($C_{10}H_{10}N_2$) C, H, N.

Acknowledgment—The authors gratefully acknowledge the support of this project by McNeil Laboratories, Inc., Fort Washington, Pa.

Studies of Piperidine Derivatives. I

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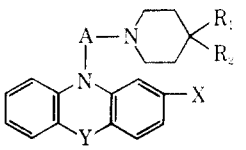
Received December 8, 1969

Some tricyclic compounds having a 4,4-disubstituted piperidine substituent were synthesized. The phenothiazines thus prepared showed potent CNS depressant action, while the iminodibenzyls, iminostilbenes, and 9,9-dimethylacridans exhibited coronary vasodilating effects. Phenothiazines as well as iminostilbenes possessed potent antiinflammatory activity.

The spectrum of biological activities of tricyclic psychotropic drugs depends to a large extent upon the nature of the amino group. We have synthesized and examined the biological properties of some new 4,4-disubstituted piperidine derivatives represented by formula **1**. Tables I, II, III, and IV display the



1

A = CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CHMeCH_2$
R_1 = H, OH, $CONH_2$, $CONC_4H_8$, NMe_2, CH_2NHAc, CN, Ac, OMe, CO_2Et
R_2 = C_6H_5, *p*-Cl or *m*-Cl or *p*-Me or *p*-MeO or *p*-F-C_6H_4, $CH_2C_6H_5$, NMe_2, NC_4H_8, NC_5H_{10}
Y = S, CH_2CH_2, CH=CH, CMe_2
X = H, Cl, Me, OMe, CF_3, SMe, SBu, Ac

resulting phenothiazines, iminodibenzyls, iminostilbenes, and 9,9-dimethylacridanes, respectively.

These compounds were evaluated pharmacologically with respect to inhibition of locomotor activity, suppression of fighting episodes, coronary vasodilation, and antiinflammatory action. Recent reports, moreover, claim that some of the same or similar tricyclic compounds have coronary vasodilating[1-6] and antiinflammatory actions.[7-11]

(1) Sandoz Ltd., Netherlands Patent 6,706,369 (1967).
(2) J. R. Geigy Chem. Corp., South African Patent 6,603,362 (1966).
(3) J. R. Geigy Chem. Corp., Netherlands Patent 6,608,101 (1966); *Chem. Abstr.*, **67**, 11503 (1967).
(4) Sterling Drug Co., Netherlands Patent 6,801,093 (1968).
(5) Boehringer and Soehne G. m. b. H., British Patent 1,134,589 (1967); *Chem. Abstr.*, **71**, 22041*g* (1969).
(6) K. P. F. Brocades Stehman and Pharmacia, Netherlands Patent Application 6,608,741 (1966); *Chem. Abstr.*, **67**, 11438*h* (1967).
(7) American Home Products Corp., U. S. Patent 3,320,245 (1967); *Chem. Abstr.*, **67**, 100146 (1967).
(8) G. D. Searle & Co., U. S. Patent 3,320,246 (1967); *Chem. Abstr.*, **67**, 90823 (1967).
(9) J. R. Geigy Chem. Corp., U. S. Patent 2,965,639 (1960); *Chem. Abstr.*, **55**, 12437*g* (1961).
(10) J. R. Geigy Chem. Corp., British Patent 1,111,733 (1968); *Chem. Abstr.*, **69**, 67224 (1968).
(11) G. D. Searle & Co., U. S. Patent 3,350,402 (1967); *Chem. Abstr.*, **68**, 105239 (1968).

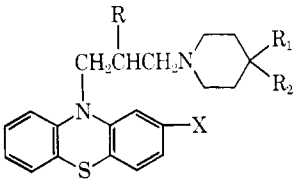
The inhibitory effect of each of the test compounds on locomotor activity was examined with d,d-strain mice by the photocell method described by Dews.[12] The rate of inhibiting fighting episodes was determined by giving electric stimuli, according to the technique of Tedeschi,[13] to the test animals previously treated with the test compound. The effect on the coronary blood flow was assessed by the technique of Yago,[14] using dogs anesthetized with 30 mg/kg of secobarbital iv. The antiinflammatory effect was estimated by the method of Winter, *et al.*,[15] using Donryu male rats previously given 1% carrageneen or 1% dextran as a phlogistic agent. The LD_{50} value was calculated from the lethality rate in 2 days after the treatment by the Litchfield–Wilcoxon method.

The results obtained are shown in Table V. Each of compounds **11**, **12**, **14**, **21**, and **26** exhibited potent inhibition of locomotor activity and suppression of fighting episodes. Compound **26** showed high toxicity, however. Compound **21** was one-third as active as chlorpromazine in inhibition of fighting activity and 6 times as potent in suppressing locomotor activity. Compound **22** showed high toxicity. These phenothiazine derivatives were regarded as potent CNS depressants.

On the other hand, the compounds of iminodibenzyl and iminostilbene increased coronary blood flow. Compounds **34**, **40**, **41**, **45**, and **46**—most of them belonging to the iminostilbene series—exhibited 10–20 times greater potency than prenylamine.[16] The iminostilbene derivatives also inhibited locomotor activity. Compound **46** which possesses mild locomotor supression may serve as a candidate antianginal drug. Considerable antiinflammatory action was found in the phenothiazines and iminostilbenes such as **11**, **12**, **43**,

(12) P. B. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953).
(13) R. E. Tedeschi, D. H. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *J. Pharmacol. Exp. Ther.*, **125**, 28 (1959).
(14) N. Yago, *Nippon Yakurigaku Zasshi*, **57**, 380 (1961).
(15) C. A. Winter, E. A. Resley, and G. W. Nuss, *J. Pharmacol. Exp. Ther.*, **141**, 369 (1963).
(16) *N*-(3,3-Diphenylpropyl)-α-methylphenethylamine. Farbwerke Hoechst.

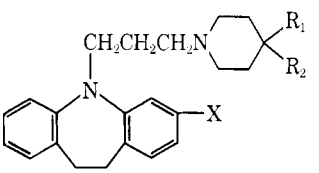
Table I



No.	X	R	R_1	R_2	Method[a]	Recrystn solvent	Yield,[b] %	Mp, °C	Formula[c]
1	Cl	H	CN	C_6H_5	A_1	*d*	49	120	$C_{27}H_{27}Cl_2N_3S \cdot EtOH$
2	Me	H	CN	C_6H_5	A_1	*e*	52	105 dec	$C_{28}H_{30}ClN_3S \cdot H_2O$
3	MeS	H	CN	C_6H_5	A_3	*e*	43	110 dec	$C_{28}H_{30}ClN_3S_2 \cdot H_2O$
4	Ac	H	CN	C_6H_5	A_3	*e*	46	106 dec	$C_{29}H_{30}ClN_3OS \cdot H_2O$
5	H	H	CN	C_6H_5	A_2	*f*	34	235	$C_{27}H_{28}ClN_3OS \cdot 0.5MeOH$[g]
6	Cl	H	CH_2NHAc	C_6H_5	A_3	*e*	51	137–140	$C_{29}H_{33}Cl_2N_3OS$
7	MeO	Me	CH_2NHAc	C_6H_5	A_3	*e*	62	135	$C_{31}H_{38}ClN_3O_2S \cdot H_2O$
8	Cl	H	$CONC_4H_8$	$C_6H_4Cl(m)$	A_1	*e*	43	120	$C_{31}H_{34}Cl_3N_3OS \cdot H_2O$
9	Cl	H	$CONH_2$	C_6H_5	A_3	*e*	62	104–110	$C_{27}H_{29}Cl_2N_3OS \cdot H_2O$
10	*n*-BuS	H	CO_2Et	C_6H_5	A_1	*e*	53	82–84	$C_{33}H_{41}ClN_2O_2S_2 \cdot 0.5H_2O$
11	Cl	H	Ac	C_6H_5	A_3	*e*	51	105–110	$C_{28}H_{36}Cl_2N_2OS \cdot 2H_2O$
12	Cl	H	OH	C_6H_5	A_3	*h*	55	115	$C_{26}H_{28}Cl_2N_2OS$
13	CF_3	H	OH	C_6H_5	A_3	*e*	66	75–80	$C_{27}H_{28}ClN_2F_3OS \cdot H_2O$
14	Cl	H	OH	$C_6H_4Cl(p)$	A_2	*h*	56	196	$C_{26}H_{27}Cl_3N_2OS$
15	MeO	Me	OH	$C_6H_4Cl(p)$	A_3	*e*	47	150–160	$C_{28}H_{32}Cl_2N_2O_2S \cdot 0.5H_2O$
16	Cl	H	OH	$C_6H_4Me(p)$	A_1	*h*	61	185	$C_{27}H_{30}Cl_2N_2OS$
17	Cl	H	OH	$C_6H_4CF_3(m)$	A_3	*e*	51	115–120	$C_{27}H_{27}Cl_2N_2F_3OS \cdot H_2O$
18	Cl	H	OMe	C_6H_5	A_2	*e*	58	125–130	$C_{27}H_{30}Cl_2N_2OS \cdot H_2O$
19	Cl	H	H	NC_4H_8[i]	A_3	*h*	70	287	$C_{24}H_{32}Cl_2N_2S$
20	Cl	H	H	NC_5H_{10}[i]	A_3	*f*	43	217 dec	$C_{33}H_{40}ClN_3O_8S$[j]
21	Cl	H	$CONH_2$	NC_5H_{10}[i]	A_3	*f*	42	263	$C_{26}H_{33}Cl_3N_4OS \cdot MeOH$
22	Me	H	$CONH_2$	NC_5H_{10}[i]	A_3	*k*	59	248	$C_{27}H_{33}Cl_2N_4OS \cdot H_2O$
23	MeO	H	$CONH_2$	NC_5H_{10}[i]	A_3	*d*	39	252	$C_{27}H_{33}Cl_2N_4O_2S$
24	MeS	H	$CONH_2$	NC_5H_{10}[i]	A_3	*k*	34	247	$C_{27}H_{33}Cl_2N_4OS_2 \cdot 0.5H_2O \cdot EtOH$[l]
25	CF_3	H	$CONH_2$	NC_5H_{10}[i]	A_3	*k*	48	256	$C_{27}H_{33}Cl_2N_4F_3OS \cdot 0.5H_2O$
26	Ac	H	$CONH_2$	NC_5H_{10}[i]	A_3	*k*	51	247	$C_{28}H_{33}Cl_2N_4O_2S \cdot 0.5H_2O \cdot EtOH$[m]
27	H	H	$CONH_2$	NC_5H_{10}[i]	A_3	*k*	39	256	$C_{26}H_{36}Cl_2N_4OS \cdot H_2O$
28	MeO	Me	$CONH_2$	NMe_2	A_3	*h*	57	210	$C_{25}H_{36}Cl_2N_4O_2S \cdot 0.5H_2O$

[a] See Experimental Section. [b] Most of the yields indicated in this and subsequent tables are based on a single run and they do not necessarily reflect the optimum attainable. [c] All compounds were analyzed for C, H, N. [d] EtOH. [e] EtOH–Et_2O. [f] MeOH. [g] Nmr(CF_3CO_2H) τ 6.05, equivalent to 0.5 mole of MeOH. [h] MeOH–Et_2O. [i] NC_4H_8, pyrrolidino; NC_5H_{10}, piperidino. [j] Acid maleate. [k] 90% EtOH. [l] Nmr(CF_3CO_2H) quartet τ 5.90, 6.01, 6.12, 6.25, triplet 8.54, 8.65, 8.75, equivalent to 1 mole of EtOH. Karl Fisher titration H_2O = 1.5%. [m] Nmr(CF_3CO_2H) quartet τ 5.89, 6.00, 6.11, 6.24, triplet 8.52, 8.63, 8.73, equivalent to 1 mole of EtOH. Karl Fisher titration H_2O = 1.6%.

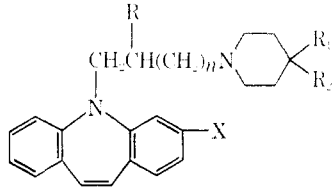
Table II



No.	X	R_1	R_2	Method[a]	Recrystn solvent	Yield,[b] %	Mp, °C	Formula[k]
29	H	CH_2NHAc	C_6H_5	A_3	*c*	75	75–80	$C_{31}H_{38}ClN_3O \cdot 0.5H_2O$
30	H	OH	C_6H_5	A_3	*d*	67	226	$C_{28}H_{33}ClN_2O$
31	H	OH	$C_6H_4Cl(p)$	A_3	*e*	70	128–136	$C_{28}H_{32}Cl_2N_2O \cdot 0.5H_2O$
32	H	OH	$C_6H_4CF_3(m)$	A_3	*c*	64	112–114	$C_{29}H_{32}ClF_3N_2O \cdot 0.5MeOH$
33	H	$CONH_2$	NC_5H_{10}[f]	A_3	*g*	81	260	$C_{28}H_{40}Cl_2N_4O \cdot H_2O$
34	H	$CONH_2$	NMe_2	A_3	*g*	83	265	$C_{25}H_{36}Cl_2N_4O$
35	H	H	NC_5H_{10}[f]	A_1	*g*	78	300	$C_{27}H_{39}Cl_2N_3$
36	Cl	$CONH_2$	NC_5H_{10}[f]	A_3	*h*	47	259	$C_{28}H_{39}Cl_3N_4O \cdot 0.5H_2O$
37	Cl	$CONH_2$	NMe_2	A_3	*i*	32	145–150	$C_{33}H_{41}ClN_4O_9$[j]

[a] See Experimental Section. [b] See Table I, footnote *b*. [c] MeOH–Et_2O. [d] AcOEt. [e] EtOH–Et_2O. [f] NC_5H_{10}, piperidino. [g] 90% MeOH. [h] MeOH. [i] EtOH. [j] Acid maleate. [k] See Table I, footnote *c*.

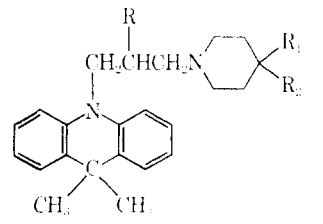
TABLE III



No.	X	*n*	R	R_1	R_2	Method[a]	Recrystn solvent	Yield,[b] %	Mp, °C	Formula[a]
38	H	1	H	CN	C_6H_5	A_1	*c*	70	209	$C_{29}H_{30}ClN_3 \cdot H_2O$
39	H	1	H	$CONH_2$	C_6H_5	A_3	*d*	53	260	$C_{29}H_{32}ClN_3O \cdot {}^1/_6DMF^f$
40	H	1	H	Ac	C_6H_5	A_3	*e*	63	194	$C_{30}H_{33}ClN_2O$
41	H	1	H	OMe	C_6H_5	A_3	*e*	56	188	$C_{29}H_{33}ClN_2O \cdot 0.5H_2O$
42	H	1	H	OH	$CH_2C_6H_5$	A_3	*f*	59	100	$C_{29}H_{33}ClN_2O \cdot H_2O$
43	H	1	H	OH	C_6H_5	A_3	*g*	52	230	$C_{28}H_{31}ClN_2O \cdot EtOH$
44	H	1	H	OH	$C_6H_4Cl(p)$	B	*h*	58	199	$C_{28}H_{30}Cl_2N_2O \cdot i\text{-}PrOH$
45	H	1	H	OH	$C_6H_4CF_3(m)$	A_2	*g*	63	141–143	$C_{29}H_{30}ClF_3N_2O \cdot EtOH$
46	H	1	H	OH	$C_6H_4Me(p)$	A_3	*h*	63	158	$C_{29}H_{33}ClN_2O \cdot i\text{-}PrOH$
47	H	1	H	OH	$C_6H_4OMe(p)$	B	*i*	53	176–177	$C_{29}H_{33}ClN_2O_2$
48	H	1	H	$CONH_2$	NC_5H_{10}[k]	A_3	*f*	59	235	$C_{28}H_{38}Cl_2N_4O \cdot 0.5H_2O$
49	H	1	H	$CONH_2$	NMe_2	A_3	*l*	51	225	$C_{27}H_{34}Cl_2N_4O \cdot 0.5H_2O$
50	Cl	1	H	CN	C_6H_5	A_3	*j*	41	201–203	$C_{29}H_{29}Cl_2N_3$
51	Cl	1	H	OH	$C_6H_5Me(p)$	A_3	*e*	41	130–140	$C_{29}H_{32}Cl_2N_2O$
52	Cl	1	H	$CONH_2$	NC_5H_{10}[k]	A_3	*i*	48	182–185	$C_{36}H_{43}ClN_4O_9$[m]
53	Cl	1	H	$CONH_2$	NMe_2	A_3	*h*	45	140–145	$C_{33}H_{39}ClN_4O_9$[m]
54	H	1	Me	OH	$C_6H_4CF_3(m)$	A_3	*i*	59	236	$C_{30}H_{32}ClF_3N_2O$
55	H	0	H	OH	$C_6H_4CF_3(m)$	A_3	*e*	61	191	$C_{28}H_{28}ClF_3N_2O$
56	H	1	Me	NMe_2	C_6H_5	A_3	*h*	53	229	$C_{31}H_{39}Cl_2N_3$

[a] See Experimental Section. [b] See Table I, footnote *b*. [c] AcOEt. [d] DMF. [e] Ir(KBr) 1660 cm^{-1} weak sharp peak, nmr(CF_3CO_2H) τ 6.65, 6.77 weak doublet. [f] EtOH–Et_2O. [g] 90% EtOH. [h] *i*-PrOH. [i] MeOH. [j] MeOH–Et_2O. [k] NC_5H_{10}, piperidino. [l] 90% MeOH. [m] Acid maleate. [n] See Table I, footnote *c*.

TABLE IV



No.	R	R_1	R_2	Method[a]	Recrystn solvent	Yield,[b] %	Mp, °C	Formula[a]
57	H	CN	C_6H_5	A_3	*c*	48	190	$C_{31}H_{34}ClN_3 \cdot 0.25H_2O$[d]
58	H	H	$C_6H_4OMe(p)$	A_3	*c*	53	188	$C_{30}H_{37}ClN_2O$
59	H	OH	$C_6H_4CF_3(m)$	A_3	*f*	52	259	$C_{30}H_{34}ClF_3N_2O \cdot 0.25H_2O$[e]
60	H	OH	$C_6H_4F(p)$	A_3	*h*	44	218	$C_{29}H_{34}ClFN_2O$
61	H	$CONH_2$	NC_5H_{10}[f]	A_3	*c*	46	263–265	$C_{29}H_{42}Cl_2N_4O_4 \cdot 0.25H_2O$[f]
62	Me	$CONH_2$	NC_5H_{10}[f]	A_3	*c*	55	187	$C_{38}H_{50}N_4O_9 \cdot 0.5H_2O$[g]
63	H	$CONH_2$	NMe_2	A_3	*c*	61	259	$C_{26}H_{38}Cl_2N_4O \cdot 0.25H_2O$[h]
64	H	H	NC_4H_8	A_3	*l*	55	220	$C_{35}H_{45}N_3O_8$[g]
65	H	H		A_3	*m*	45	279	$C_{28}H_{43}Cl_2N_4 \cdot 0.5H_2O$

[a] See Experimental Section. [b] See Table I, footnote *b*. [c] 90% MeOH. [d] Karl Fisher titration H_2O = 0.9%, ir(KBr) 3400 cm^{-1} broad medium. [e] EtOH. [f] DMF–Et_2O. [g] K. F. titration H_2O = 0.8%. [h] *i*-PrOH. [i] NC_5H_{10}, piperidino. [j] K. F. titration H_2O = 0.8%, ir(KBr) 3400 cm^{-1} broad strong. [k] K. F. titration H_2O = 0.9%, ir(KBr) 3300 cm^{-1} broad strong. [l] 90% EtOH. [m] Me_2CO–H_2O. [n] See Table I, footnote *c*.

and **45** which were found more potent than phenylbutazone.[17]

It was concluded that compounds belonging to the iminodibenzyl and iminostilbene groups were very potent in inhibiting inflammation and in increasing the coronary blood flow with some action on CNS, whereas the 9,9-dimethylacridans were somewhat less potent than the iminodibenzyls and iminostilbenes in these tests. The specific action on the CNS and the remarkable spasmolytic potency of compound **33**[18] was described in detail in an earlier report.[19]

(17) 1-Butyl-1,2-diphenyl-3,5-pyrazolidinedione, Geigy Chem. Corp.

(18) Carpipramine, Defekton®.

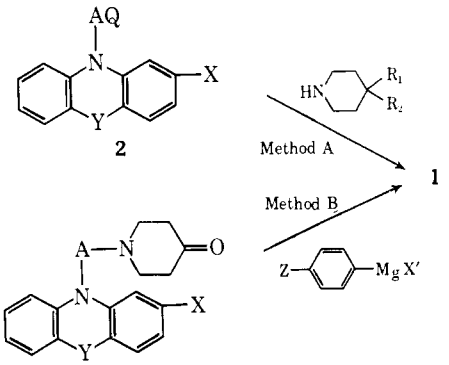
(19) M. Nakanishi, T. Tsumagari, T. Okada, and K. Kasé, *Arzneim. Forsch.*, **18**, 1435 (1968).

Experimental Section

Melting points were determined in an open capillary tube in a H_2SO_4 bath apparatus and are not corrected. Ir and nmr spectra were obtained on Nihon Bunko IRG and C-60 instruments, respectively.

The synthesis of these compounds followed that shown in Scheme I.

Scheme I



A = $(CH_2)_2$, $(CH_2)_3$, $CH_2CHMeCH_2$
Q = Br, Cl, OMe, OTs
X = H, Cl, Me, OMe, CF_3, SMe, SBu, Ac
Y = S, CH_2CH_2, CH=CH, CMe_2
R_1 = H, OH, $CONH_2$, $CONC_4H_8$, NMe_2, CH_2NHAc, CN, Ac, OMe, CO_2Et
R_2 = C_6H_5, *p*- or *m*-Cl or *p*-Me or *p*-MeO or *p*-FC_6H_4, $CH_2C_6H_5$, NMe_2, NC_4H_8, NC_5H_{10}
Z = Cl, MeO
X' = Br, Cl

Method A.—For condensing a 4,4-disubstituted piperidine with a halogen or an aryl and alkyl sulfonyloxyalkyl derivative of **2**,[20-26] the following three methods were employed. (1) The components were dissolved in alcohol and heated to 100–170° in a sealed tube. (2) Components were stirred in DMF solution at 100° in the presence of a basic reagent. (3) The components were refluxed in EtOH in the presence of a basic compound.

Method B.—Compound **1** was prepared from **3**[27] and a substituted PhMgBr in THF.

The compounds thus obtained were purified by column chromatography or recrystallization. Some of the compounds showed a tendency to form solvates. Representative procedures to obtain compounds listed in Tables I–IV are given below.

3-Chloro-10-[3-(4-*p*-chlorophenyl-4-hydroxypiperidino)-propyl]phenothiazine Hydrochloride (14).—In 50 ml of EtOH were dissolved 1.8 g of 3-chloro-10-(3-chloropropyl)phenothiazine and 2.3 g of 4-*p*-chlorophenyl-4-hydroxypiperidine, and the solution was heated in a sealed tube at 120–130° for 7 hr. After cooling, EtOH was distd off. The oily residue was treated with 100 ml of H_2O, and extracted with 100 ml of C_6H_6. After drying, C_6H_6 was removed under vacuum. The oily residue, after crystallizing as a hydrochloride, yielded 1.7 g (56%) of the product, mp 196°. *Anal.* ($C_{26}H_{26}Cl_3N_3OS$) C, H, N.

5-[3-(4-Acetylaminomethyl-4-phenylpiperidino)propyl]-5*H*-10,11-dihydrodibenzo[*b*,*f*]azepine Hydrochloride (29).—In 60 ml of abs EtOH were dissolved 2.7 g of 5-(3-chloropropyl)-5*H*-10,11-dihydrodibenzo[*b*,*f*]azepine and 1.7 g of 4-acetylaminomethyl-4-phenylpiperidine, followed by the addition of 3.0 g of K_2CO_3. The mixture was heated under reflux on a steam bath for 40 hr. After the reaction was completed, the base was extracted with C_6H_6, and the C_6H_6 layer was purified by column chromatography (Wako alumina gel 300 mesh, eluant, C_6H_6). The oil thus obtained, after crystallizing as a hydrochloride and recrystd from MeOH–Et_2O, yielded 3.6 g (75%) of the product, mp 75–80°. *Anal.* ($C_{31}H_{38}ClNO \cdot 0.5H_2O$) C, H, N.

5-[3-(4-Hydroxy-4-*m*-trifluoromethylphenylpiperidino)-propyl]-5*H*-dibenzo[*b*,*f*]azepine Hydrochloride (45).—5-(3-Chloropropyl)-5*H*-dibenzo[*b*,*f*]azepine (6 g) and 6.0 g of 4-hydroxy-4-*m*-trifluoromethylphenylpiperidine were mixed in 100 ml of DMF. After the addition of 6 g of K_2CO_3, the mixture was stirred and heated at 100° in an oil bath for 10 hr. It was filtered hot, and the filtrate was coned under vacuum. The oily residue was dissolved in 50 ml of C_6H_6, and crystallized as a hydrochloride by the addition of EtOH–HCl. Recrystallization from 95% EtOH yielded 7.9 g (63%) of yellow crystals, mp 141–143°. *Anal.* ($C_{29}H_{30}ClF_3N_2O \cdot C_2H_5OH$) C, H, N.

9,9-Dimethyl-10-[3-(4-carbamoyl-4-piperidinopiperidino)-propyl]acridan Dihydrochloride (61).—9,9-Dimethyl-10-(3-chloro-

Table V

Pharmacological Evaluation

No.	Inhibition of fighting behavior[a]	Suppression of locomotor activity[b]	Coronary vasodilatory activity[c]	Anti-inflammatory activity[d]	LD_{50} mg/kg (ip)
8	−	−	±	±	>320
11	++	+		++	>320
12	+++	+			>320
14	++	+			≥320
18	−	−			>320
21	++	+++	++	++	80
22	−	++			40
26	++	++			60
29	±	±	+	±	>320
30	±	+	+	±	>80
31	±	±			120
32	+	±			>80
33	−	+	++	−	136
34	−	±	+++	−	>80
35	−	−			>80
36	+	++			160
37	±	+			60
38	−	−	±	−	>500
39	−	±			>320
40	+	−	+++	−	320
41	+	−	+++	−	240
42	+	+	++		120
43	+	+	+++	+	60
45	±	+	+++	++	120
46	±	++	+++	±	120
48	±	+	++	±	60
49	−	+	±	±	120
52	±	++			80
53	±	+			160
59	−	−			320
61	−	+	++		320
62	−	±			≤320
63	−	±	±	±	100
64	−	±	+		150
65	−	+	+		120

The potency of each activity is represented under the criterion as below. [a] As ED_{50} values (mg/kg *p.o.*) <10; +++, 10–40; ++, 41–100; +, 101–150; ±, >151; −. ED_{50} of chloropromazine = 6.3 mg/kg. *p.o.* [b] As ED_{50} values (mg/kg *i.p.*) <5; +++, 5–10; ++, 11–40; +, 41–100; ±, >100; −. ED_{50} of chloropromazine = 1.2 mg/kg *i.p.* [c] As ED_{50} values (mg/kg *i.v.*) <0.5; +++, 0.5–1; ++, 2–10; +, >10; ±. ED_{50} of prenylamine lactate = 3.6 mg/kg *i.v.* [d] As ED_{50} values (mg/kg *p.o.*) <50; ++, 50–100; +, 101–250; ± >250; −. ED_{50} of phenylbutazone = 380 mg/kg *p.o.*

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(26) J. R. Geigy Chem. Corp., Netherlands Patent Appl., 6,603,826 (1966); *Chem. Abstr.*, **66**, 55412 (1967).

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propyl)acridan (19 g) was dissolved in 100 ml of EtOH. After the addition of 14 g of 4-carbamoyl-4-piperidinopiperidine and 19 g of K_2CO_3, the mixture was refluxed on a steam bath for 48 hr. EtOH was removed under vacuum, the residue was dissolved in C_6H_6 and treated with EtOH–HCl. The pptd crystals were collected. Recrystallization from MeOH–H_2O yielded 16.6 g (46%) of material, mp 263–265°. *Anal.* ($C_{29}H_4Cl_2N_4O \cdot 0.25H_2O$) C, H, N.

5-[3-(4-Hydroxy-4-*p*-methoxyphenylpiperidino)propyl]-5*H*-dibenzo[*b*,*f*]azepine Hydrochloride (47).—A 14.5-g sample of 5-[3-(4-oxopiperidino)propyl]-5*H*-dibenzo[*b*,*f*]azepine was added to a solution of *p*-$MeOC_6H_4MgBr$ (prepared from 15.5 g of *p*-$MeOC_6H_4Br$ and 2.2 g of Mg in 100 ml of THF) at 10–20°. The mixture was stirred at room temp for 1 hr, and then refluxed for 3 hr. The resulting reaction mixture was decompd with 150 ml of satd aq NH_4Cl solution. The THF layer was sepd and concd. The residue was dissolved in 50 ml of $CHCl_3$ and shaken with 10% of aq HCl. The sepd crystals were filtered off. Recrystallization from MeOH yielded 10.9 g (53%) of yellow crystals, mp 176–177°. *Anal.* ($C_{29}H_{33}ClN_2O_2$) C, H, N.

Synthesis and Pharmacological Activity of New Basic Carbamates

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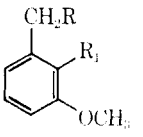
Received August 25, 1969

A series of bicarbamates of *N*-phenethyldiethanolamine, 2-diethylamino- and 2-piperidino-1,3-propanediol, and *N*-methyldiethanolamine, were synthesized and their nonoxalate soluble salts were evaluated in a primary mouse screen. In secondary studies, bis(*N*-butylcarbamoylethyl)-2,3-dimethoxyphenethylamine maleate (**17**) showed mild CNS depressant activity while another compound, bis-(*N*-phenylcarbamoylethyl)-2-*n*-butoxy-3-methoxyphenethylamine hydrochloride (**5**), exhibited antidepressant activity. Both decreased blood pressure.

The carbamoyl radical, which constitutes the principal characteristic of the compounds described in the present paper, is responsible for numerous pharmacological properties. Several basic carbamates[1b-3] have shown interesting pharmacodynamic activity as local anesthetics.[3] We have undertaken an exploration of the activity of the bicarbamates of some aminoalcohols, such as *N*-β-phenethyldiethanolamine, 2-diethylamino- and 2-piperidino-1,3-propanediol, and *N*-methyldiethanolamine.

Chemistry.—We have synthesized (1) bisphenylurethans of *N*-phenethyldiethanolamine (I), with or without substituents on the nucleus, and of N-substituted 2-amino-1,3-propanediol (II); (2) bisalkyl- (Et, *n*-Pr, *n*-Bu) urethans of I and of *N*-methyldiethanolamine (III); and (3) bicarbamates of I, II, and III unsubstituted on the carbamic N. The bisalkyl- and bisphenylurethans were prepared by the reaction of the amino alcohols with the corresponding alkyl[4] and phenyl isocyanate.[3] Bicarbamates unsubstituted on the carbamic N were synthesized from the amino alcohol and carbamoyl chloride.[1b,2,5] Other methods, re-

TABLE I



R	R_1	Yield, %	Bp, °C (mm)	Formula	Analyses[a]
$COOCH_3$	OCH_3	32[b]	159 (10)	$C_{11}H_{14}O_4$	C, H
$COOC_2H_5$	OCH_3	65[c]	155–157 (10)	$C_{12}H_{16}O_4$	C, H
$COOCH_3$	OC_2H_5	32[b]	167 (18)	$C_{12}H_{16}O_4$	C, H
$COOC_2H_5$	OC_2H_5	50[c]	170–172 (25)	$C_{13}H_{18}O_4$	C, H
$COOCH_3$	O-*n*-C_3H_7	26	171 (16)	$C_{13}H_{18}O_4$	C, H
$COOCH_3$	O-*n*-C_4H_9	20	166 (13)	$C_{14}H_{20}O_4$	C, H
CH_2OH	OC_2H_5	74	170 (18)	*d*	
CH_2OH	O-*n*-C_5H_7	93	174–180 (13)	*e*	
CH_2OH	O-*n*-C_4H_9	54	167–169 (14)	*f*	
CH_2Cl	OC_2H_5	60	150–152 (19)	$C_{11}H_{15}ClO_2$	C, H, Cl
CH_2Cl	O-*n*-C_3H_7	78	149–152 (15)	$C_{12}H_{17}ClO_2$	C, H, Cl
CH_2Cl	O-*n*-C_4H_9	78	150 (10)	$C_{13}H_{19}ClO_2$	Cl

[a] Where analyses are indicated by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [b] Method B; yield calculated as to aldehyde. [c] Method A; yield calculated as to nitrile. [d] Phenylurethan: mp 81° (EtOH); *Anal.* ($C_{18}H_{21}NO_4$) C, H, N. [e] 3,5-Dinitrobenzoic ester: mp 105° (EtOH); *Anal.* ($C_{19}H_{20}N_2O_8$) C, H, N. [f] 3,5-Dinitrobenzoic ester: mp 93° (EtOH); *Anal.* ($C_{20}H_{22}N_2O_8$) C, H, N.

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