(50 ml) was stirred for 16 hr. The temperature of the reaction mixture rose spontaneously to a maximum of 65°. The mixture was poured into  $H_2O$  (375 ml) and extracted with five 100-ml portions of  $C_6H_6$ . The  $C_6H_6$  solution was washed twice with 20-ml portions of  $H_2O$ , dried (MgSO<sub>4</sub>, charcoal), and evaporated to a yellow syrup at 100° (0.2 mm), yield 21.2 g (89%),  $n^{25}D$  1.5749. Anal. ( $C_{11}H_{14}N_2O_2S$ ) C, H, N.

1,4-Bis[2-(2-pyridylthio)ethyl]piperazine (14) Tetrahydrochloride.—A mixture of 13a (4.23 g, 10.0 mmoles) and 50% aqueous NaOII (20 ml) was stirred for 16 hr. The resulting mixture was extracted with  $C_6H_6$  (10 ml), and the  $C_6H_6$  solution was dried (MgSO<sub>4</sub>). Removal of the solvent at 100° (0.3 mm) left a viscous oil, which did not react with H<sub>2</sub>S in cold MeOH and was treated with dry HCl in EtOH to give 14 · 4HCl, yield 1.12 g (44%), melting point indefinite. Anal. ( $C_{18}H_{24}N_4S_2 \cdot 4HCl$ ) C, H, N. The mass spectrum of the oil showed a peak at a massto-charge ratio of 360 corresponding to that expected for the molecular ion of 14.

S-[2-(2-Pyridylthio)ethylamino]ethanethiol Dihydrochloride (15b).—The thiol 15b, mp 129–131° (Mel-Temp), was prepared from 15a in 95% yield by the procedure used for the preparation of 10a. Recrystallization was unnecessary. Anal. (C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>S<sub>2</sub>· 2HCl) C, H, N, S; SH: calcd, 11.51; found, 10.4.

2- $\{2-[3-(2-Pyridylthio)propylamino]ethyl\}$ -2-thiopseudourea Trihydrobromide (15c).—A solution of 13b (2.00 g, 4.58 mmoles) and thiourea (349 mg, 4.58 mmoles) in EtOH (20 ml) was refluxed under N<sub>2</sub> for 30 min and evaporated to dryness *in vacuo*. Trituration of the gummy residue with EtOH (4 ml) gave a white crystalline solid, which was collected, washed (EtOH), and dried in vacuo  $(P_2O_5)$ ; yield 2.11 g (90%), mp 174-176° (Mel-Temp). Anal.  $(C_{11}H_{18}N_4S_2\cdot 3HBr) C, H, N, S.$ 

3-[2-(2-Benzothiazolylthio)ethyl]-2-oxazolidinone (17).—A mixture of 16 (16.7 g, 0.100 mole), 1a (15.0 g, 0.100 mole), and DMF (80 ml) was stirred at 80° for 2.5 hr and poured into H<sub>2</sub>O (400 ml). The resultant mixture was refrigerated for 2.5 days, and the crystalline 17 that had precipitated was collected, washed (cold H<sub>2</sub>O, 100 ml), and dried *in vacuo* (P<sub>2</sub>O<sub>3</sub>); yield 26.4 g (94%), mp 86°. Anal. (C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>) C, H, N, S.

2,2'-[Dithiodiethylenebis(iminoethylenethio)]dibenzothiazole (19).—A solution of NaOMe prepared from Na (0.432 g, 18.8 mg-atoms) and anhydrous MeOH (30 ml) was saturated with H<sub>2</sub>S at 0°. While H<sub>2</sub>S was bubbled slowly through the solution, 18 (3.00 g, 6.27 mmoles) was gradually added over 20 min. The solution was stirred at 0° for 1 hr in a stream of H<sub>2</sub>S and warmed to 25°. The resulting solution, after standing 16 hr in a stoppered flask, was evaporated to dryness. The gummy residue was stirred with H<sub>2</sub>O (30 ml) containing FeCl<sub>3</sub> (about 2 mg) and exposed to the air until a negative SH test (nitroprusside) was obtained. The tan precipitate obtained after 2 days of stirring was collected, washed (H<sub>2</sub>O), and dried *in vacuo* (P<sub>2</sub>O<sub>5</sub>); yield 1.54 g (80%), mp 90-95°. Anal. (C<sub>22</sub>H<sub>26</sub>N<sub>4</sub>S<sub>6</sub>) C, H, N, S.

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## Aryl-Substituted Triazines with Antidepressant Activity

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A series of 1,4,5,6-tetrahydro-as-triazines that possessed 3-aryl substituents, including dihydrodibenzocycloheptenyl, benzhydryl, naphthyl, phenethyl, diphenylethyl, and phenylisopropyl, was synthesized and tested for potential antidepressant activity. Structure-activity relationships are discussed.

Practically all of the clinically active nonmonoamine oxidase inhibiting antidepressants are composed of a basic moiety, such as amino, alkylamino, dialkylamino, cycloalkylamino, or pyridyl, attached by an aliphatic side chain to a lipid-soluble, electron-donating benzenoid-containing moiety. Examples of these moieties are dibenzazepine, dibenzocycloheptene, dihydrodibenzocycloheptene, dibenzoxepin, benzothiazepinone, benzhydrol, and naphthalene. In two review articles<sup>1</sup> summarizing structure-activity relationships of antidepressant drugs, Biel discusses the effects on pharmacological and clinical activity produced by alterations in the tricyclic moiety and the amine group in thymoleptic and neuroleptic agents. In changing the tricyclic moiety from phenothiazine to dibenzazepine to dihydrodibenzocycloheptene as in promazine, imipramine, and amitriptyline, the clinical activity spectrum changes from tranquilizing to tranquilizing-antidepressant to antidepressant. Changing the amine group from tertiary to secondary as in imipramine-desimipramine and amitriptyline-nortriptyline also changes the pharmacodynamic and clinical profile. In general the secondary amine congeners appeared to be less of a central depressant. This is analogous to the pressordepressor change in the series norepinephrine-epinephrine-methepinephrine and also the loss of central stimulant activity N,N-dimethylamephetamine as compared to methamphetamine.

This paper reports the results of a study in our laboratories on structure-activity relationships of some new substituted 1,4,5,6-tetrahydro-as-triazines synthesized and tested for antidepressant activity. These new compounds are structurally similar to known antidepressant drugs in that they are composed of the basic 1,4,5,6-tetrahydro-as-triazine ring attached either directly or by means of an alkyl chain to a lipid-soluble benzenoid or benzenoid-containing moiety. These moieties include dihydrodibenzocycloheptenyl, benzhydryl, naphthyl, phenethyl, diphenylethyl, and phenylisopropyl. The 1,4,5,6-tetrahydro-as-triazine was chosen as the basic moiety because of the variety of amino group types that it afforded. This interested us because of the demonstrated difference in activity profile of secondary and tertiary amine derivatives in CNS active compounds. A variation in the amino groups using the 1,4,5,6-tetrahydro-as-triazine heterocycle was accomplished by altering the degree of substitution on the three ring nitrogen atoms. Aziridine (Ia), 2-

 <sup>(</sup>a) J. H. Biel, "Molecular Modification in Drug Design," Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D. C., 1964, pp 115-129;
(b) J. H. Biel, "Annual Reports in Medicinal Chemistry, 1965," Academic Press, New York, N. Y., 1966, pp 12-29.

methylaziridine (Ib), or 1-(β-hydroxyethyl)aziridine (Ic) was allowed to react with hydrazine (IIa) or methylhydrazine (IIb) to give 2-aminoethylhydrazine (IIIa), 1-(2-aminoethyl)-1-methylhydrazine (IIIb), 1-(2-aminopropyl)-1-methylhydrazine (IIIc), or 1-(2-β-hydroxyethylaminoethyl)-1-methylhydrazine (IIId).



The desired substituted 1,4,5,6-tetrahydro-*as*-triazines listed in Table I were obtained by either treating one of the four  $\beta$ -aminoethylhydrazines III with an imino ester or imino thioester hydrohalide or allowing a nitrile to condense with 1-(2-hydroxyisobutyl)-1methylhydrazine (IV) in concentrated H<sub>2</sub>SO<sub>4</sub>. The 16 new triazines prepared using these three methods are listed in Table I.



**Pharmacology.**—The ability of a compound to prevent reserpine-induced ptosis and to potentiate *d*amphetamine toxicity in the mouse was used as an indication of antidepressant activity. Prolongation of hexobarbital sleep time was used as a first test to suggest potential tranquilizing activity. Protection against maximal electric shock was used to indicate anticonvulsant activity. The behavior of the 16 new *as*-triazines and desmethylimipramine, imipramine, amitriptyline, and *d*-amphetamine in these tests was determined. The results are recorded in Table I. The test methods are described in the Experimental Section.

A number of *as*-triazines were active in these tests; *e.g.*,  $3 \cdot (\alpha, \beta$ -diphenylethyl)-1,4,5,6-tetrahydro-*as*-triazine (10) compares favorably in all four tests with the standard drugs. Triazines 1, 10, 13, and 14 have a greater milligram potency than imipramine and amitriptyline in the reserpine ptosis test. 3-(Phenylisopropyl)-1,4,5,6-tetrahydro-*as*-triazine (13) is extremely potent in the *d*-amphetamine toxicity test; it has an ED<sub>50</sub> of 0.19 (0.13–0.3) and *d*-amphetamine has an ED<sub>50</sub> of 7.6 (6.9–8.4) mg/kg.

Using the benzhydryltriazines  $(1 \ 5)$  as a point of departure, the relationship of structure to activity in the reserpine test is that 1 in which the triazine possesses two secondary amine functions and bears no substituents other than the benzhydryl is the most active. Addition of a methyl at N-1 (2) and addition of methyls at N-1 and N-4 (3) greatly reduced the milligram potency. Addition of a third methyl group (4) or addition of a hydroxyethyl (5) practically abolished all activity. This is similar to previously observed more potent antireserpine activity for secondary amine structures than for tertiary amine structures (imipramine vs. desmethylimipramine).

Considering the benzenoid portion of the molecule, substitution of chloride in the *para* position (6-8)diminishes activity. Fusing together the two phenyl rings of the benzhydryl moiety to give 3-(1-naphthylmethyl)-1,4,5,6-tetrahydro-*as*-triazine (14) produced one of the most potent antireserpine compounds of the series. (As in the benzhydryl compounds (1-5), methylation of the triazine ring (15) abolished antireserpine activity.) Connection of the two phenyl groups of the benzhydryl moiety by an ethylene bridge (16) yielded an inactive compound.

Extension of the side chain by insertion of a CH<sub>2</sub> between the benzhydryl and the triazine ring (**9**) abolished antireserpine activity. When one of the phenyl groups is moved one carbon closer to the triazine ring, 3- $(\alpha,\beta$ -diphenylethyl)-1,4,5,6-tetrahydro-*as*-triazine (**10**), a compound with potent antireserpine activity, results. Removal of this  $\alpha$ -phenyl by methyl (**13**) results in only moderate diminution of antireserpine activity.

In general, activity in the potentiation of amphetamine aggregate toxicity test parallels activity in the reserpine ptosis test. For example, the benzhydryltriazines (1-5) show a decrease in activity in both tests with increase in methyl substitution on the triazine ring. Triazine 1 which has two secondary amine functions and 2 which has one secondary amine function are the most potent. Exceptions are 7 and 12, inactive in the reserpine ptosis test but both having marked activity in the potentiation of amphetamine aggregate toxicity test.

Unlike amitriptyline most of these compounds are inactive or only moderately active in the hexobarbital sleep time and maximal electric shock tests. An exception is **10** which prolongs hexobarbital sleep time greater than twofold at a dose of 17 mg/kg. In the maximal electric shock test this compound has an  $ED_{50}$  of 10 mg/kg.

## **Experimental Section**

**Chemistry.**—Melting points were determined in open capillary tubes using the Thomas–Hoover Uni-Melt and are uncorrected. The elemental analyses were done by Midwest Microlaboratories, Indianapolis, Ind. Where analyses are indicated by only symbols of the elements or functions, analytical results obtained for those elements or functions were within  $\pm 0.4 \frac{C_c}{C_c}$  of the theoretical values.

Preparation of aminoalkylhydrazines IIIa, b and 1-methyl-hydrazino-t-butyl alcohol (IV) have been reported.<sup>2,3</sup>

(2) D. L. Trepanier, J. E. Richman, and A. D. Rudzik, J. Med. Chem., 10, 228 (1967).

(3) D. L. Trepanier and V. Spranemanis, J. Org. Chem., 29, 673 (1964).

No.	Y-1A	Я	Rı	$\mathbf{R_2}$	Mp, °C	Method <sup>a</sup>	Yield, %	Formula	Analyses	Mouse LD‰, mg/kg ip	Screening dose, mg/kg ip	Potentiate $d$ -amphet toxic. $^b$	Reserpinc ptosis <sup>c</sup>	Hexo- barbital sleep time <sup>d</sup>	Max elec shock <sup>e</sup>
Т	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH	Н	Η	Η	159-160	Α	42	$C_{16}H_{17}N_3$	С, Н, N	83	25	12 (8–18)	$23\ (17{-}30)$	59/32	0/10
51	$(C_6H_5)_2CH$	$CH_3$	Η	Н	121-122	Α	19	$C_{17}H_{19}N_3$	C, H, N	383	78	14 (8 - 26)	49(39-60)	109/41	2/10
<u></u>	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH	CH3	Η	CH <sub>3</sub>	16-68	Υ	17	$C_{18}H_{21}N_3$	С, Н	215	65	21(13-34)	$46 \ (36 - 57)$	170/57	0/10
4	$(C_6H_5)_2CH$	CH <sub>3</sub>	Н	(CH <sub>3</sub> ) <sub>2</sub>	138 - 139	В	22	$C_{19}H_{23}N_{3}$	С, Н	383	115	71 (31 - 153)	2/10	94/37	1/10
ι¢	$(C_6H_5)_2CH$	$CH_3$	$HO(CH_2)_2$	Η	179 - 181	V	13	$C_{19}H_{23}N_{3}O$	C, H, N	681	204	0/10	3/10	111/32	4/10
9	4-ClC <sub>6</sub> H <sub>4</sub> (C <sub>6</sub> H <sub>5</sub> )CH	Η	Η	Η	176-178	C	44	C <sub>16</sub> H <sub>16</sub> CIN <sub>3</sub>	C, H, N	178	53	23(17-31)	3/10	86/28	3/10
2	4-ClC <sub>6</sub> H <sub>4</sub> (C <sub>6</sub> H <sub>5</sub> )CH	$CH_3$	Н	Η	140 - 141	C	38	C <sub>17</sub> H <sub>18</sub> CIN <sub>3</sub>	C, H, N	681	204	7 (3-16)	5/10	150/36	138(97 - 180)
∞	4-ClC <sub>6</sub> H <sub>4</sub> (C <sub>6</sub> H <sub>5</sub> )CH	$CH_3$	Н	$CH_3$	123 - 125	С	40	C <sub>18</sub> H <sub>20</sub> CIN <sub>3</sub>	С, Н, N	261	78	56 (49-64)	2/10	92/36	0/10
6	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CHCH <sub>2</sub>	Н	Н	Н	104-105	Υ	33	C17H19N3	С, Н, N	129	39	1/10	1/10	46/24	
10	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> (C <sub>6</sub> H <sub>5</sub> )CH	Н	Н	Η	107-108	V	21	$C_{17}H_{19}N_3$	C, H, N	38	17	6~(4-9)	$10 \ (6-18)$	66/26	10(7-15)
Π	C6H5CH2CH2	Η	Η	Η	114-115	Α	45	$C_{11}H_{15}N_3$	С, Н, N	147	44	3/10	0/10	49/39	
12	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	CH3	Η	Η	145 - 146'	Α	32	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> ·HCl	С, Н, N	121	36	3.5(1.8-6.7)	1/10	74/33	0/10
13	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> (CH <sub>3</sub> )CH	Η	Н	Н	160-161/	Α	30	C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> ·HCl	С, Н, N	178	53	0.2(0.13-0.3)	$19\ (10{-}36)$	63/39	0/10
14	1-Naphthyl-CH2	Н	Η	Η	249–250° dec	C	19	C14H15N3.HBr	C, H, N	147	44	24(17-35)	12 (8-18)	62/28	1/10
15	$1-Naphthyl-CH_2$	$\mathrm{CH}_{3}$	Н	Η	100-101	C	13	$C_{15}H_{17}N_3$	C, H, N	147	44	35 (32 - 39)	0/10	52/43	
16	8-	CH3	Η	Н	145-1470	Ö	15	C <sub>19</sub> H <sub>21</sub> N <sub>3</sub> ·HBr	C, H, N	147	44	0/10	0/10	105/43	4/10
17	Desmethylimipramine									68	20	4(3-5)	1.7(0.8 - 3.7)	72/23	
18	Imipramine									95	53	50(30-83)	35 (26-47)	95/27	28 (18-41)
19	Amitriptyline									100	33	14 (11–19)	46(26-83)	144/36	8 (7-9)
20	d-Amphetamine									100	33	7.6(6.9 - 8.4)	$1.8(0.8^{-3.8})$	25/27	17(14-20)
															•

Substituted 1,4,5,6-Tetrahydro-as-triazines

TABLE I

 $\operatorname{Ar} - Y - \bigvee_{N - NR} R_z$ 

March 1969

<sup>a</sup> See Experimental Section. <sup>b</sup> Results are expressed either as a ratio of number of mice dead to number of mice treated with screening dose, or as ED<sub>26</sub> values (mg/kg) and their 95% confidence limits. <sup>a</sup> Results are expressed either as a ratio of number of mice protected to number of mice treated, or as ED<sub>26</sub> values (mg/kg) and their 95% confidence limits. <sup>a</sup> Results are expressed as a ratio of duration of sleeping times of treated group to the control group. <sup>e</sup> Results are expressed either as ratio of number exposed to name expressed as a ratio of duration of sleeping times of treated group to the control group. <sup>e</sup> Results are expressed either as ratio of number protected to number exposed to maximal electroshock, or as ED<sub>26</sub> values (mg/kg) and their 95% confidence limits. <sup>J</sup> Hydrochloride. <sup>e</sup> Hydrobromide.

1-(2- $\beta$ -Hydroxyethylaminoethyl)-1-methylhydrazine (IIIc).---To a stirred mixture of 995 g of methylhydrazine and 1 g of NH<sub>4</sub>Cl, heated to reflux temperature, was added, dropwise, over a period of 2 hr, 206 g of 1-( $\beta$ -hydroxyethyl)aziridine. The mixture was stirred and heated at reflux temperature for 18 hr, the excess methylhydrazine was removed by distillation at atmospheric pressure, and the residue was distilled *in vacuo* to give 211 g (67%) of colorless liquid, bp 152-154° (17 mm). Anal. (C<sub>5</sub>H<sub>15</sub>N<sub>3</sub>O) C, H, N.

Methods Used to Prepare the Compounds Listed in Table I. Method A.—An ethyl imino ester hydrochloride was condensed with a  $\beta$ -aminoalkylhydrazine in refluxing ethanol.<sup>4</sup>

Method B.—A  $\beta$ -hydroxyalkylhydrazine was added to a solution of a nitrile in concentrated H<sub>2</sub>SO<sub>4</sub> and processed by a method described earlier.<sup>5</sup>

Method C.—A mixture of 0.10 mole of methyl imino thioester hydriodide, 0.10 mole of  $\beta$ -aminoalkylhydrazine, and 250 ml of absolute EtOH was heated at reflux temperature for 4 hr and concentrated *in vacuo*, the residue was dissolved in CHCl<sub>3</sub>, and the CHCl<sub>3</sub> solution was washed (Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O), dried (MgSO<sub>4</sub>), and evaporated *in vacuo*. The residual oil was purified either by crystallization with Et<sub>2</sub>O and recrystallization with an appropriate solvent, chromatography on alumina followed by recrystallization, or by conversion to a hydrobromide and recrystallization of the salt.

(*p*-Chlorophenyl)phenylthioacetamide.—A mixture of 23 g (0.1 mole) of (*p*-chlorophenyl)phenylacetonitrile, 100 ml of pyridine, and 50 ml of Et<sub>8</sub>N was treated with H<sub>2</sub>S for 1 hr. After standing at ambient temperature for 2 days, the mixture was evaporated *in vacuo*, and the residue was recrystallized (MeOH) to give 23.5 g (90%) of a white crystalline solid, mp 165–167°. The analytical sample melted at 166-167.5°;  $\lambda_{\rm mylol}^{\rm mylol}$  2.93, 3.05, 3.17 (NH<sub>2</sub>), 6.15  $\mu$  (C=S). Anal. (C<sub>14</sub>H<sub>12</sub>CINS) C, H, Cl, S.

**5-Thiocarboxamide-10,11-dihydro-5H-dibenzo**[a,d]**cycloheptene** was obtained in 53% yield. Recrystallization from CHCl<sub>3</sub> gave an off-white solid, mp 187–188°. *Anal.* (C<sub>16</sub>H<sub>15</sub>NS) C, H, N.

**i-Naphthenethioacetamide** was obtained in 51% yield, mp 170–171°, from MeOH–CHCl<sub>3</sub> (1:1). Anal. (C<sub>12</sub>H<sub>11</sub>NS) C, H, N.

Methyl (*p*-Chlorophenyl)phenylthioacetimidate Hydriodide.—A mixture of 22 g (0.084 mole) of (*p*-chlorophenyl)phenylthioacetamide, 12 g (0.084 mole) of MeI, and 150 ml of Me<sub>2</sub>CO was allowed to stand at ambient temperature for I day and cooled; the crystallized from EtOH-Et<sub>2</sub>O; mp 197-200° dec (inserted at 190°);  $\lambda_{\text{max}}^{\text{widd}}$  3.18 (NH), 6.31, 6.40  $\mu$  (C–N). Anal. (C<sub>15</sub>H<sub>14</sub>ClNS ·HI) C, H, S.

Methyl 10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5-thiocarboximidate hydriodide was obtained in 80% yield. Recrystallization from MeOH-Et<sub>2</sub>O gave a white solid, mp 194-195° dec. Anal. (C<sub>17</sub>H<sub>17</sub>NS·HI) C, H, N. Methyl 1-naphthalenethioacetimidate hydriodide was obtained in 91% yield, mp 141–143° (from Me<sub>2</sub>CO-Et<sub>2</sub>O 1;5). Anal. (C<sub>13</sub>H<sub>13</sub>NS·HI) C, II, N.

**Pharmacology** Acute Toxicity in Mice.—Adult male mice, in groups of four, were given the test compound, intraperitoneally, using at least three dose levels, and observed for 24 hr.  $LD_{50}$ 's were calculated by the method of Litchfield and Wilcoxon.<sup>6</sup>

**Hexobarbital Sleep Time Test.**—Adult male mice were injected intraperitoneally with the test compound (dose *ca*.  $0.3 \text{LD}_{50}$  as noted in Table I) 30 min prior to the intraperitoneal injection of 100 mg/kg of hexobarbital. The time in minutes between injection of the hexobarbital and the regain of the righting reflex was taken as the duration of sleeping time. The results are expressed as a ratio of the treated group over the control group.

Antagonism to Reserpine-Induced Ptosis in Mice.—Adult male mice were given test compound intraperitoneally (this screening dose was ca.  $0.3 \text{LD}_{50}$ ) 30 min prior to a reserpine (5 mg/kg ip) challenge. Observation for ptosis was made 45 min after reserpine. Results are given as the ratio of number of mice protected to number of mice tested. When 6/10 or more mice were protected at this screening dose, additional tests were made to determine the ED<sub>50</sub>. In these cases, the ED<sub>50</sub> values and their 95% confidence limits (calculated according to the method of Litchfield and Wilcoxon<sup>5</sup>) are listed instead of the protection ratios.

Potentiation of Amphetamine Toxicity in Aggregated Mice. Adult male mice, in groups of ten, were given test compound intraperitoneally  $(0.3 \text{LD}_{io})$ , saline control, or amphetamine (5 mg/kg) "positive" control. All animals were dosed with amphetamine (5 mg/kg) 30 min later and aggregated by placement in cubic wire mesh cages 16 cm on a side. They were then kept in a walk-in incubator (30°, for both noise and temperature control) for 5 hr at which time the dead were counted. If three or more dead were found in the saline control group or six or less in the amphetamine control group the entire experiment was arbitrarily discounted. Results are given as a ratio of number of mice dead to number of mice in group. When 6/10 mice were found dead at this screening dose, additional tests were made to determine the ED<sub>50</sub>. In these cases the ED<sub>50</sub> values and their 95% confidence limits are listed instead of the lethality ratios.

**Maximal Electroshock Test.**—Groups of ten mice were given the test compounds intraperitoneally 1 hr prior to being subjected to supramaximal electroshock delivered through corneal electrodes.<sup>7</sup> The results are expressed as a ratio of the number of mice protected from the tonic hind limb extensor phase of the seizure to the number shocked. When 6/10 mice were protected at the screening dose, additional tests were made to determine the ED<sub>50</sub>. In these cases the ED<sub>50</sub> values and their 95<sup>°</sup><sub>e</sub> confidence limits are listed instead of the protection ratios.

<sup>(4)</sup> For a discussion and examples of this reaction see ref 2.

<sup>(5)</sup> For a description of this reaction see D. L. Trepanier, E. R. Wagner, G. Harris, and A. D. Rudzik, J. Med. Chem., 9, 881 (1966), method B.

<sup>(6)</sup> J. T. Litchfield and F. Wilcoson, J. Pharmacol. Expl. Therap., 96, 99 (1949).

<sup>(7)</sup> E. A. Swinyard, W. C. Brown, and L. S. Goodman, *ibid.*, **106**, 319 (1952).