(15) Weiss, R., Robins, R. K., and Noell, C. W., *J. Org. Chem.*, **25**, 765(1960).
(16) Roblin, R. O., Jr., *et al.*, *J. Am. Chem. Soc.*, **67**, 290 (1945).
(17) Israel, M., and Day, A. R., *J. Org. Chem.*, **24**, 1455 (1959).
(18) McCormack, J. J., and Mautner, H. G., *ibid.*, **29**, 3370(1964).
(19) Taylor, E. C., and Loux, H. M., *J. Am. Chem. Soc.*, **81**, 2474(1959).
(20) Chatterjee, S. Trites, D. H., and Modest, E. J., *Nature*, **203**, 970(1964).
(21) Yannoni, N. F., and Silverman, J., *ibid.*, **202**, 484 (1964).
(22) Benson, F. R., Hartzel, L. W., and Savell, W. L., *J. Am. Chem. Soc.*, **72**, 1816(1950).
(23) Wagner, E. C., and Meyer, J. F., *Ind. Eng. Chem., Anal. Ed.*, **10**, 584(1938).
(24) Brown, D. J., and Jacobsen, N. W., *J. Chem. Soc.*, **1962**, 3172.
(25) Montgomery, J. A., *J. Am. Chem. Soc.*, **78**, 1928 (1956).

Pharmacological Evaluation of a Series of 3,6-Substituted Pyridazine Derivatives

By BARRY DUBINSKY, WILLIAM J. KINNARD, and JOSEPH P. BUCKLEY

A series of 3,6-substituted pyridazine derivatives were tested for central pharmacologic activity. On the basis of their effects on gross behavior, spontaneous, and forced motor activity of albino mice, the alkoxy-pyridazine derivatives were characterized as CNS depressants, while the alkoxy-2-dimethylaminoethoxy-pyridazine derivatives produced initial stimulation followed by a depression of spontaneous activity. The latter compounds also shortened hexobarbital sleeping time in mice and induced a low-voltage fast-wave activity in the electrocorticogram of the cat. None of the compounds produced any alteration of avoidance escape responding in mice or rats or caused a significant inhibition of convulsions produced by chemo- or electrostimulation in rats. A substudy indicated that there was little or no species difference in the learning ability or the response to chlorpromazine of mice and rats in the conditioned avoidance response test (pole climbing).

PYRIDAZINE, pyrimidine, and pyrazine are six-membered ring structures, which include two nitrogen atoms in the *ortho*, *meta*, and *para* positions, respectively. Pyrazine and, in particular, pyrimidine furnish a number of important derivatives useful in medicine; however, as noted by Wilson (1), fewer derivatives of pyridazine have been found to be useful. The pharmacological spectrum of pyridazine derivatives is very broad, ranging from sulfa drugs having antibacterial action (2), to drugs having neuromuscular blocking activity (3), central nervous system stimulating activity (4), and sedative activity (5). Thus, while a number of compounds with therapeutic potential have been synthesized and investigated, it is still not possible to describe with certainty the unique contribution of the pyridazine ring to a series of its derivatives.

The major purpose of the current investigation was to study the pharmacology of pyridazine and a series of closely related pyridazine derivatives synthesized by Drs. P. Coad and R. A. Coad, Department of Chemistry, Chapman College, Orange, Calif.[1]

The testing procedure for evaluation of psychopharmacologic agents involves the use of both mice and rats; and, while these species are closely related phylogenetically, there may be differences in behavior which are neglected in the transition from the use of mice in preliminary tests to the use of rats in the more sophisticated studies of learned behavior. It appeared then that there was a need to compare acquisition of a learned behavior and drug effects on an on-going behavior in the two species. Such a comparison could serve to bridge the gap between the use of mice in preliminary screening of centrally acting compounds and the use of rats in more intensive tests.

METHODS

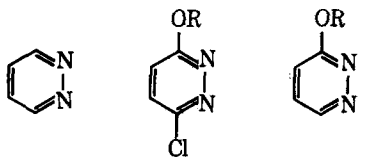
Pyridazine and 15 of its derivatives (Table I) were examined for potential central nervous system activity. Pyridazine (I), the parent compound, and the other compounds were grouped according to Coad *et al.* (6). The compounds of group III had an alkoxy substituent as R and a chloro substituent. The compounds of group IV are either bis-alkoxy or bis-dimethylaminoethoxy derivatives, and the compounds of group V have an alkoxy substituent

Received June 4, 1965, from the Department of Pharmacology, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pa.
Accepted for publication August 19, 1965.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
This investigation was supported in part by research grant MH-03029 from the National Institute of Mental Health, U. S. Public Health Service, Bethesda, Md.

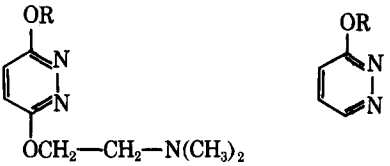
[1] Present address: Department of Medicinal Chemistry Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

TABLE I.—STRUCTURES OF THE EXPERIMENTAL COMPOUNDS[a]

Basic Structures



Pyridazine (I) Group III Group IV



Group V Group VI

Substituents (R)

a = methyl	*e* = *n*-amyl
b = *n*-propyl	*f* = isoamyl
c = isopropyl	*g* = cyclohexyl
d = *n*-butyl	*h* = dimethylaminoethyl

[a] Compounds tested: I, III*c*, III*e*, IV*c*, IV*d*, IV*f*, IV*h*, V*a*, V*b*, V*c*, V*d*, V*e*, V*g*, VI*c*, VI*f*, and VI*h*.

as R and a dimethylaminoethoxy substituent. In group VI, R is represented by an alkoxy or a dimethylaminoethoxy substituent.

Effects on General Behavior of Albino Mice.—Graduated doses of each of the experimental compounds were injected intraperitoneally into male Swiss-Webster albino mice, weighing between 20 and 40 Gm. Their gross behavior was studied and compared to animals receiving the solvent as a control injection. All compounds were either dissolved or emulsified in a 0.9% sodium chloride solution, using 0.025 ml. of polysorbate 20 per ml. of saline. Methylcellulose, 3% solution, was used to suspend III*c* and III*e*, which were water insoluble.

Effects of Spontaneous and Forced Motor Activity of Albino Mice.—Spontaneous activity of naive male albino Swiss Webster mice, weighing between 20 and 40 Gm., was measured using the Actophotometer (Metro Co., Mineola, Long Island, N. Y.), and forced motor activity of the mice was measured using the rotarod. The protocols for both tests were previously described by Furgiuele *et al.* (7). All drugs were given intraperitoneally, and both types of activity were measured 1 hr. after drug administration.

Anticonvulsant Activity of the Experimental Compounds.—*Antagonism of Pentylenetetrazol-Induced Convulsions.*—Saline, chlordiazepoxide, and six experimental compounds, which were representative of the total series of pyridazine derivatives, were injected intraperitoneally into eight groups of six male albino Swiss Webster mice in doses approximating the dose required to depress spontaneous activity by 50%. Pentylenetetrazol, 100 mg./Kg., was administered subcutaneously to the same mice 60 min. later. The onset of clonic convulsions and death were recorded.

Antagonism of Strychnine-Induced Convulsions.—Sixty minutes following the administration of the previously mentioned test compounds, strychnine was administered subcutaneously in a dose of 1.5 mg./Kg. to a series of eight groups of mice. Onset of tonic convulsions and/or death were recorded.

Antagonism of Maximal Electroconvulsive Seizures.—The technique employed by Toman *et al.* (8) and Swinyard *et al.* (9) was employed. Saline, chlordiazepoxide, and the experimental compounds were administered intraperitoneally to groups of six mice 1 hr. before testing. Diphenylhydantoin was administered 3 hr. before testing, since Swinyard *et al.* (9) had determined that 3 hr. are required before peak anticonvulsant activity is obtained in mice. Electroconvulsive seizure was produced by applying current to the corneas of the mice through the use of an electroseizure apparatus (Hans Technical Associates, model 2-C, Palo Alto, Calif.). The stimulus intensity was 50 ma. applied for 0.2 sec. The number of animals protected from tonic hind-limb extension was recorded.

Effects on Hexobarbital Sleeping Time.—Several of the experimental compounds, notably group V, produced a mixed stimulant and depressant effect in studies on general behavior. Thus, the following experimental design was followed to further distinguish the classes of compounds producing depression alone from the class producing both stimulation and depression.

Saline, chlordiazepoxide, and six representative pyridazine derivatives, including pyridazine, were given intraperitoneally to 16 groups ($N = 10$) of male Swiss Webster albino mice, weighing between 20 and 24 Gm. Because latency for stimulant effects was short, the dose of saline, chlordiazepoxide, and experimental compounds were given to one-half the groups at the same time as hexobarbital, 100 mg./Kg. i.p. The remaining groups received hexobarbital 1 hr. after dosing. All solutions were injected intraperitoneally, in total volumes of 0.1 ml., and sleeping time was recorded as the duration of the loss of the righting reflex.

Electroencephalographic Studies.—Two of the more potent pyridazine derivatives, compounds IV*f* and V*g*, were tested in the unanesthetized, curarized cat for changes in electrocortical activity. Electrodes were placed subdurally on the right and left anterior sigmoid and the posterior ectosylvian gyri. Recordings were obtained on a Medcraft model B electroencephalograph (Medcraft Electronic Corp., Babylon, N. Y.). Experimental compounds were dissolved in propylene glycol and administered intravenously. All incisions in the animal were procainized.

Effects on Conditioned Avoidance Escape Responding.—The substudy was designed to determine the behavioral profile of mice and rats in respect to acquisition of a conditioned avoidance response and the effects of chlorpromazine and the experimental compounds on the acquired response. The automatic pole-climbing apparatus and the basic scheme for its use with albino rats was previously described by Aceto *et al.* (10). A similar apparatus was built in dimensions to conform with the size of mice in order to compare the two species of animals. The cage in which the mice were trained to avoid or escape an electric shock was constructed of 0.25-in. thick clear Plexiglas. The inner dimensions of the cage were 5 in. deep, 5 in. wide, and 11 in. high. The grid floor was

made of 1/8-in. stainless steel bars placed 3/8 in. from each other and was wired to a high-voltage shock delivery and scrambling device. The grid floor was placed 2 in. above the floor of the cage. A removable drawer, 1.25 in. below the grid floor, served to catch fecal material. A 7.5 by 1/8-in. uncharged stainless steel pole was suspended by two springs from the roof of the cage to within 3/8 in. of the grid floor. The tension on the pole was adjusted by turning a steel bolt placed through the cage top so that the weight of the mouse on the pole was sufficient to trip a microswitch, the arm of which made contact with the top of the pole. The steel pole passed through a 4 1/8 by 4.5-in. Plexiglas partition which separated the mechanical components of the apparatus from the actual test chamber. A hole, 1 9/16 in. in diameter, was bored in this partition to permit the attachment of a 3.2-ohm 0.05-w. speaker for the generation of the tone.

Training and testing of the effects of chlorpromazine and the experimental compounds were conducted simultaneously in the two species according to the following schedule. Ten male albino Wistar rats, weighing between 150 and 200 Gm., and 10 male albino Swiss Webster mice, weighing between 20 and 25 Gm., were given a dose of saline or drug intraperitoneally 1 hr. before initiation of a training or testing sequence (10 trials) on a particular day. Each dose of the test drug was given on the day following a dose of saline; at least 3 days were allowed to elapse between doses of test drugs.

RESULTS

Effects on General Behavior of Albino Mice.—Pyridazine produced no behavioral or physiological effects in doses ranging from 25 to 200 mg./Kg. i.p. Compounds III*c* and III*d* required doses of 150 to 200 mg./Kg. to produce ataxia and generalized depression. All of the compounds in group IV produced purely depressant activity; however, it required doses in excess of 100 mg./Kg. i.p. to produce major depressant effects. Compound IV*f* was the most potent of the group. All of the compounds in group V, in doses greater than 100 mg./Kg., produced initial central nervous system stimulation, as evidenced by tremors and convulsions. This was then followed by mild depression of the animal. Compounds VI*c* and VI*f* produced depression to the extent of loss of righting reflex in higher doses. However, high doses of VI*h* produced stimulation; that is, tremors and clonic convulsions. VI*h* is distinguished from VI*c* and VI*f* by its being a dimethylaminoethoxy-substituted rather than an alkoxy-substituted derivative.

Effect on Spontaneous and Forced Motor Activity of Albino Mice.—All of the compounds, except pyridazine (in doses up to 200 mg./Kg. i.p.), produced a depression of spontaneous motor activity. The only compounds that produced a depression of forced motor activity were those in group IV. Compounds IV*c*, IV*d*, and IV*f* produced a 50% depression of forced motor activity at doses above 160 mg./Kg. i.p. The dose that produced a 50% depression of spontaneous and forced motor activity can be seen in Table II.

Anticonvulsant Activity of the Experimental Compounds.—*Antagonism of Pentylenetetrazol-Induced Convulsions.*—None of the experimental compounds (I, III*c*, IV*f*, IV*h*, V*a*, and VI*f*) blocked clonic convulsions. One of the bis-alkoxypyridazine derivatives, IV*f*, doubled the onset time of clonic convulsions compared to saline-treated animals, which had an onset time of 1.61 ± 0.25 min. The increase was significant at the 0.05 probability level. Chlordiazepoxide, in a dose of 25 mg./Kg. i.p., protected all of the mice against clonic convulsions and death ($N = 6$). Compounds IV*f* and VI*f* protected one animal from tonic convulsions and

TABLE II.—DOSE OF EXPERIMENTAL COMPOUND NECESSARY TO DEPRESS SPONTANEOUS MOTOR AND FORCED MOTOR ACTIVITY BY 50%

Compd.	SMA_{50}[a, c] (mg./Kg. i.p.)	FMA_{50}[b, c] (mg./Kg. i.p.)
I	...	...
III*c*	125	...
III*e*	145	...
IV*c*	82	160
IV*d*	69	160
IV*f*	100	160
IV*h*	133	...
V*a*	82	...
V*b*	77	...
V*c*	100	...
V*d*	59	...
V*e*	64	...
V*g*	160	...
VI*c*	145	...
VI*f*	59	...
VI*h*	80	...

[a] SMA_{50} = depression of spontaneous motor activity by 50%. [b] FMA_{50} = depression of forced motor activity by 50%. [c] Four groups of 5 animals in each case.

TABLE III.—EFFECTS OF CHLORDIAZEPOXIDE AND THE EXPERIMENTAL COMPOUNDS ON MOUSE SLEEPING TIME WHEN ADMINISTERED WITH HEXOBARBITAL (100 mg./Kg.)

Compd.	Dose (mg./Kg. i.p.)[a]	Sleeping Time ± S.E. (min.)
Saline		19.85 ± 2.23
Chlordiazepoxide	25	97.03 ± 11.49[b]
I	200	9.13 ± 1.84[b]
VI*f*	70	24.63 ± 1.73
III*c*	120	57.35 ± 5.47[b]
V*a*	80	9.47 ± 2.35[b]
IV*h*	150	19.65 ± 1.60
IV*f*	100	29.57 ± 6.31

[a] Ten mice employed in each case. [b] Change significant at 0.05 level.

TABLE IV.—EFFECTS OF CHLORDIAZEPOXIDE AND THE EXPERIMENTAL COMPOUNDS ON MOUSE SLEEPING TIME WHEN ADMINISTERED 1 HR. PRIOR TO HEXOBARBITAL (100 mg./Kg.)

Compd.	Dose (mg./Kg. i.p.)[a]	Sleeping Time ± S.E. (min.)
Saline		22.22 ± 1.41
Chlordiazepoxide	25	79.20 ± 7.18[b]
I	200	31.68 ± 3.28[b]
VI*f*	70	40.85 ± 3.06[b]
III*c*	120	26.38 ± 2.05[b]
V*a*	80	20.83 ± 3.07
IV*h*	150	38.52 ± 4.77[b]
IV*f*	100	28.27 ± 3.14[b]

[a] Ten mice employed in each case. [b] Change significant at 0.05 level.

death, while compound V*a* protected two animals out of six from tonic convulsions and death.

Antagonism of Strychnine-Induced Convulsions.—Chlordiazepoxide, in a dose of 25 mg./Kg. i.p., protected four out of the six mice from death, following the dose of strychnine. The average onset time of convulsions in the saline-pretreated mice was 4.56 ± 0.34 min. The only compounds which significantly altered this onset time were VI*f*, 70 mg./Kg.; III*c*, 120 mg./Kg.; and IV*f*, 100 mg./Kg. The average onset times were, respectively, 6.70 ± 0.69, 7.29 ± 0.49, and 7.79 ± 0.79 min. All of these were significantly different from the saline results when compared at the 0.05 level. None of the compounds held any major protection against strychnine-induced tonic convulsions and death.

Antagonism of Maximal Electroconvulsive Seizures.—Neither the experimental compounds nor chlordiazepoxide protected mice from the hind-limb extensions induced by electroshock. Four out of six mice pretreated with 12.5 mg./Kg. i.p. of diphenylhydantoin and all the mice pretreated with 25 mg./Kg. of diphenylhydantoin were protected from the hind-limb extension.

Effects on Hexobarbital Sleeping Time.—Tables III and IV summarize the effects of the hexobarbital studies. When given simultaneously with hexobarbital, three compounds significantly altered hexobarbital sleeping time. Chlordiazepoxide and compound III*c* prolonged sleeping time, while compounds I and V*a* significantly shortened sleeping time. When the compounds were given 1 hr. prior to hexobarbital, five of the experimental compounds significantly altered sleeping time. Chlordiazepoxide, compounds I, VI*f*, III*c*, IV*h*, and IV*f* prolonged the sleeping time of the animals. Compound V*a* did not alter the sleeping time.

Electroencephalographic Studies.—Compound IV*f*, when administered in divided doses totaling 100 mg./Kg., produced mainly slow-wave high-voltage synchronous firing. Occasional spindling could be noted in the animal. The test animal was purposely kept in a semiaroused state through the use of room light and noise, so that any depression could be noted. When compound V*g* was administered in divided doses totaling 100 mg./Kg., low-voltage fast asynchronous firing was seen in all leads; and spontaneous spindle bursts were abolished. When 5 mg./Kg. of sodium pentobarbital was administered intravenously to produce high-voltage spindle bursts, this was also abolished by the injection of 10 mg./Kg. of V*g*.

Effects on Conditioned Avoidance-Escape Responding.—The acquisition of the conditioned avoidance response by mice and rats is compared in Fig. 1. Mice appeared to be inferior to rats as learners for the first 4 days; however, no difference between the species could be demonstrated for the remaining acquisition trials. The effects of chlorpromazine on conditioned avoidance behavior in mice and rats are seen in Table V and Fig. 1, and no significant difference between chlorpromazine-treated mice and rats was demonstrated when the data were treated by the analysis of variance ($F = 2.63, df = 1/9, p < 0.05$). When the Student t test for significant difference between means was applied to the data generated by the chlorpromazine studies, the lowest dose of chlorpromazine which produced a significant interference with conditioned avoidance behavior was found to be 4.5 mg./Kg. in mice ($T = 2.97, p < 0.01$), and 3.0 mg./Kg. in rats ($T = 2.53, p < 0.05$). Compounds IV*f* and V*a*, in doses of 100 to 200 mg./Kg., had no significant effect on the conditioned avoidance behavior of mice or rats.

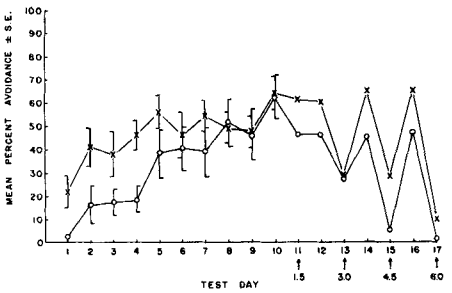


Fig. 1.—Conditioned avoidance responding in mice and rats (acquisition and drug effects). Key: ○, mice; ×, rats; ↑, dose of chlorpromazine (mg./Kg. i.p.).

DISCUSSION

The series of 3,6-substituted pyridazine derivatives were tested for central nervous system pharmacologic activity. All of the compounds except pyridazine depressed spontaneous motor activity; however, pyridazines containing both alkoxy and dimethylaminoethoxy substituents and one containing only a single dimethylaminoethoxy substituent (VI*h*) produced tremors and clonic convulsions in mice, which were followed by decreased spontaneous motor activity. Further evidence of CNS stimulation was shown by the observation that when hexobarbital and compound V*a* were given concurrently, the average sleeping time of mice was significantly shorter than the control values. When compound V*g*, another in this series, was administered to the cat, the electroencephalographic tracings indicated the possibility of central nervous system stimulation, as evidenced by the low-voltage fast-frequency cortical activity produced by the drug.

TABLE V.—EFFECTS OF CHLORPROMAZINE ON A CONDITIONED AVOIDANCE RESPONSE (POLE CLIMBING) IN MICE AND RATS

Mice[a]					Rats[a]				
Saline Test Day	Av.[b] % Avoidance	Dose CPZ[c] (mg./Kg.)	Av.[b] % Avoidance	p	Saline Test Day	Av.[b] % Avoidance	Dose CPZ[c] (mg./Kg.)	Av.[b] % Avoidance	p
1	62	1.5	46	<0.40	1	64	1.5	61	<0.90
2	46	3.0	27	<0.30	2	60	3.0	29	<0.025
3	45	4.5	5	<0.01	3	65	4.5	28	<0.005
4	47	6.0	1	<0.005	4	65	6.0	10	<0.001

[a] $N = 10$. [b] Average of 10 trials on a particular day. [c] Chlorpromazine hydrochloride.

It would appear that compounds of group V and compound VI*h* initially produced stimulation of motor areas of the cerebral cortex leading to tremors or clonic convulsions and that depression then spread over the cortex with a decrease in spontaneous motor activity being observed. It was noted that as the length of the alkoxy side chain of the dimethylaminoethoxy-substituted compounds is increased, the dose required to produce tremors and convulsions is decreased. A single dimethylaminoethoxy substituent, with or without an alkoxy side chain on the pyridazine ring, is essential for central nervous system stimulant activity. However, double substitution, as in the case of the bis-dimethylaminoethoxy derivative (IV*h*), produced only depression. The other pyridazine derivatives appeared to be minor depressants. Compound IV*f* did have a greater degree of anticonvulsant activity than the other compounds and did show some depressant activity on the EEG of the unanesthetized cat. When compound IV*f* was tested against a single classical cat flexor preparation (11, 12), it had no effect on polysynaptic reflex activity, in spite of the fact that it did prolong the onset of strychnine convulsions. When the two major compounds were tested on conditioned avoidance response, they produced no effect on the test animals. It would appear, therefore, that the pyridazine derivatives tested have little possibility of therapeutic potency within the present framework of experimental evidence.

The effects of chlorpromazine on the conditioned avoidance response in mice and rats are similar. However, the dose of chlorpromazine necessary to produce a significant blockade of avoidance responding was lower in rats than in mice. A consistently higher but not a significant number of avoidance responses on saline test days was given by rats than by mice. Mice appeared inferior to rats as learners, until the end of the fifth training day. Therefore, when time available for training is limited, it may be preferable to use rats rather than mice. Rats may also be more desirable than mice for testing tranquilizing activities, since rats were shown to be more sensitive to the tranquilizing effects of chlorpromazine.

SUMMARY

1. All of the experimental compounds having one dimethylaminoethoxy substituent (V*a*, V*b*, V*c*, V*d*, V*e*, V*g*, and VI*h*) produced mixed central nervous system stimulant and depressant effects; the other compounds had purely depressant activity.

2. All of the compounds investigated, except pyridazine, produced a depression of the spontaneous motor activity of mice as measured by the photocell activity cage. The only compounds capable of decreasing forced motor activity by 50% were IV*c*, IV*d*, and IV*f*. The other compounds produced only a minor degree of depression.

3. IV*f*, V*a*, and VI*f*, protected one out of six, two out of six, and one out of six mice, respectively, from the tonic phase of pentylenetetrazol-induced convulsions; none of the compounds blocked the clonic phase of convulsions.

4. None of the compounds blocked the tonic extensor phase of strychnine-induced convulsions; however, III*c*, IV*f*, and VI*f* significantly increased the latency for onset of convulsions.

5. None of the compounds blocked electroshock-induced convulsions in mice.

6. Hexobarbital sleeping time was significantly shortened by I and V*c*, while it was significantly potentiated by III*c* when the test drugs were given concurrent to the dose of the barbiturate; I, III*c*, IV*f*, IV*h*, and VI*f* significantly potentiated hexobarbital sleeping time when given 1 hr. prior to the dose of the barbiturate.

7. IV*f* produced slow synchronous electrocortical activity indicative of depression in the cat cerebral cortex. However, V*g* produced low-voltage fast asynchronous electrocortical waves with intermittent spiking and abolished spindle bursts produced by the prior administration of pentobarbital.

8. Little difference between mice and rats, in their ability to learn a conditioned avoidance response (pole climbing), could be demonstrated. Likewise, no significant difference between the performance of mice and rats in saline test trials or in the effects of chlorpromazine on the learned behavior could be demonstrated.

REFERENCES

(1) Wilson, C. O., in "Textbook of Organic Medicinal and Pharmaceutical Chemistry," 3rd ed., Wilson, C. O., and Gisvold, O., Lippincott Co., Philadelphia Pa., 1956, p. 228.

(2) Overend, W. G., and Wiggins, L. F., *J. Chem. Soc. London*, **1947**, 549.

(3) Steck, E. A., Brundage, R. P., and Fletcher, L. T., *J. Am. Chem. Soc.*, **76**, 4454(1954).

(4) Staehelin, A., U. S. pat. 2,835,671(1958).

(5) Druey, J., Meier, K., and Staehelin, A., Ger. pat. 1,112,078(1961).

(6) Coad, P., *et al.*, *J. Med. Chem.*, **8**, 129(1965).

(7) Furgiuele, A. R., Kinnard, W. J., and Buckley, J. P., *J. Pharm. Sci.*, **50**, 252(1961).

(8) Toman, J. E. P., Swinyard, E. A., and Goodman, L. S., *J. Neurophysiol.*, **9**, 231(1946).

(9) Swinyard, E. A., Brown, W. C., and Goodman, L. S., *J. Pharmacol. Exptl. Therap.*, **106**, 319(1952).

(10) Aceto, M. D. G., Kinnard, W. J., and Buckley, J. P., *Arch. Intern. Pharmacodyn.*, **144**, 214(1963).

(11) Berger, F. M., *J. Pharmacol. Exptl. Therap.*, **96**, 213 (1949).

(12) *Ibid.*, **112**, 413(1954).