6. General agreement between phases of the DEC system and the HLB system was noted.

7. The DEC system was presented as offering values which can be measured directly and which can be reproduced in any laboratory by the use of established procedures.

REFERENCES

(1) Griffin, W. C., *J. Soc. Cosmetic Chemists*, **5**, 249 (1954).
(2) Griffin, W. C., *ibid.*, **1**, 311(1949).
(3) Greenwald, H. L., Brown, G. L., and Fineman, M. N., *Anal. Chem.*, **28**, 1693(1956).
(4) Moore, C. D., and Bell, M., *Soap, Perfumery Cosmetics*, **29**, 893(1956).
(5) Clayton, W., "Theory of Emulsions and Their Technical Treatment," 4th ed., Blakiston, Philadelphia, Pa., 1943.
(6) Chun, A., and Martin, A. N., THIS JOURNAL, **50**, 732(1961).
(7) Davies, J. T., "Proceedings of the 2nd International Congress of Surface Activity," Vol. 1, Butterworths, London, 1957, p. 426ff.
(8) Griffin, W. C., *Offic. Dig., Federation Paint Varnish Prod. Clubs*, **28**, 466(1956).
(9) "Guide to the Use of Atlas Sorbitol and Surfactants in Cosmetics," Atlas Chemical Industries, Inc., Wilmington, Del., 1956.
(10) Chun, A. H. C., Joslin, R. S., and Martin, A. N., *Drug Cosmetic Ind.*, **82**, 164(1958).
(11) Strianse, S. J., and Lanzet, M., *Soap, Perfumery Cosmetics*, **34**, 461(1961).
(12) "Chemmunique," Atlas Chemical Industries, Inc., Wilmington, Del., **9**, No. 3, 1961.
(13) Debye, "Polar Molecules," Dover, N. Y., 1945, p. 7.
(14) Sherrick, P. H., Dawe, G. A., Karr, R., and Ewen, E. F., "Manual of Chemical Oscillometry," E. H. Sargent & Co., Chicago, Ill., 1954.
(15) "Atlas Surfactants," Atlas Chemical Industries, Inc. Wilmington, Del., 1960.
(16) Personal communication, Kessler Co., Philadelphia, Pa., October, 1957.
(17) Maclay, W. N., *J. Colloid Sci.*, **11**, 272(1956).
(18) Miller, C. G., and Maass, O., *Can. J. Chem.*, **38**, 1606(1960).
(19) Becher, P., *J. Soc. Cosmetic Chemists*, **11**, 325(1960).

Antitussive Activity of a Series of Dialkylaminodiphenylbutanol Esters

By JOSEPH A. MILLER, JR., E. BROWN ROBBINS, and DONALD B. MEYERS†

The effect of structural modifications upon the antitussive activity of a series of dialkylaminodiphenylbutanol esters was examined. In an attempt to investigate a possible correlation of pharmacological activities, the compounds were also evaluated for their spasmogenic effect upon the intestine and their analgesic activity. Antitussive activity was determined in guinea pigs by means of SO_2-induced cough. Spasmogenic activity was determined by inserting a balloon into the duodenum of anesthetized dogs. Analgesic activity was determined by the rat-tail heat method. The optimum antitussive structure tested within this series was *α-dl*-2-propionoxy-1,2-diphenyl-3-methyl-4-dimethylaminobutane hydrochloride. The optimum analgesic structure tested in this series was the 2-acetoxy analog of the same compound. Some degree of correlation was shown among the activities, although exceptions were noted.

THE PRIMARY purpose of this study was to investigate the influence of certain structural modifications upon the antitussive activity of dialkylaminodiphenylbutanol esters. Since it had been observed that these compounds exhibited analgesic and spasmogenic activities, the possibility of correlations among these activities also was investigated. The antitussive evaluation was made using a new method which will be described in detail.

The compounds chosen for this study were from a series of dialkylaminodiphenylbutanol esters prepared by Pohland and Sullivan (1) of The Lilly Research Laboratories. All of these compounds were racemic mixtures, and were synthesized by the same general procedure from their corresponding ketones. The compounds used in this study are listed in Table I with their respective melting points.

EXPERIMENTAL

Antitussive Testing Method.—Many problems are associated with the evaluation of antitussive agents and a variety of methods have been employed in an attempt to overcome these difficulties. The major problem is in evoking a reproducible cough. This reproducible cough must be responsive to known antitussive agents, and the method must be sensitive enough to discriminate among varying doses of these compounds. Often this discrimination is not good and results in a flat dosage-response relationship. The numerous disadvantages and problems of most methods led to the development of the following procedure which was used to determine the antitussive activity of the diphenylbutanol esters.

Received August 17, 1962, from Butler University and The Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind.
Accepted for publication September 14, 1962.
Abstracted from a thesis submitted by Joseph A. Miller, Jr., to the Graduate School of Butler University in partial fulfillment of the requirements for the degree of Master of Science.
The authors wish to thank Dr. K. K. Chen, director of the Pharmacology Division, and Dr. F. G. Henderson, head of the Department of Pharmacodynamics, Eli Lilly and Co., for their cooperation.
The authors also wish to thank Mr. William L. Kurtz of The Lilly Research Laboratories who assisted in all of the experimental work.
Presented to The American Society for Pharmacology and Experimental Therapeutics, Rochester, N. Y., meeting, August 1961.
† Present address: Department of Pharmacology, College of Pharmacy, University of Texas, Austin.

TABLE I.—4-DIMETHYLAMINO-1,2-DIPHENYL-2-BUTANOL ESTERS

Compound	M.p.,°C.
dl-2-Acetoxy-1,2-diphenyl-4-dimethylaminobutane HCl	227–228
α-*dl*-2-Acetoxy-1,2-diphenyl-3-methyl-4-dimethylaminobutane HCl	187–188
α-*dl*-2-Acetoxy-1,2-diphenyl-4-dimethylaminopentane HCl	210–211
α-*dl*-2-Acetoxy-1,2-diphenyl-3-methyl-4-pyrrolidinobutane HCl	202–203
α-*dl*-2-Acetoxy-1,2-diphenyl-3-methyl-4-piperidinobutane HCl	215–216
α-*dl*-2-Acetoxy-1,2-diphenyl-3-methyl-4-morpholinobutane HCl	195–196
dl-2-Propionoxy-1,2-diphenyl-4-dimethylaminobutane HCl	188–189
α-*dl*-2-Propionoxy-1,2-diphenyl-3-methyl-4-dimethylaminobutane HCl	170–171
α-*dl*-2-Propionoxy-1,2-diphenyl-4-dimethylaminopentane HCl	210–211
α-*dl*-2-Propionoxy-1,2-diphenyl-3-methyl-4-pyrrolidinobutane HCl	196–197
α-*dl*-2-Propionoxy-1,2-diphenyl-3-methyl-4-piperidinobutane HCl	191–192
α-*dl*-2-Propionoxy-1,2-diphenyl-3-methyl-4-morpholinobutane HCl	190–191

Spotted male guinea pigs weighing 250–400 Gm. were used as test animals. The guinea pigs were restrained in a plastic stock that permitted a face mask to fit flush against the front. The face mask was made by cutting off the bottom of a 6 cm. diam. plastic bottle. The neck of the bottle was fitted with a rubber stopper that had a hole bored in it to accommodate a syringe tip. The cough-producing stimulus was sulfur dioxide obtained from a cylinder. No pressure gauge was necessary, but an estimate of the gas flow was made by allowing the gas to bubble in a beaker of water in an exhaust hood. The gas was passed from the cylinder through a suction flask which served as a water trap for any water which might be siphoned into the tubing when the cylinder valve was closed. This was necessary because the sulfur dioxide within the tubing dissolved in water, resulting in a decreased pressure within the tubing. The apparatus is illustrated in Fig. 1.

Five milliliters of the gas was diluted to 10 ml. with air by means of a 30-ml. syringe, and the 10 ml. of diluted sulfur dioxide was expelled into the plastic mask held over the guinea pig's head. After the gas was administered to the guinea pigs, they were released and observed for cough frequency within the next two minutes.

A responsive colony of guinea pigs was first established by beginning with 3 ml. of gas diluted to 10, then 4 ml. diluted to 10 the next time, and finally 5 ml. diluted to 10 ml. By the third control run, nonresponders were discarded as well as those pigs on subsequent tests that did not respond after having received no treatment.

All assays were of a cross-over design in which each pig received every treatment in a randomized order. All drugs were administered subcutaneously and there were approximately ten pigs used at each dose level. There was at least one day's rest between treatments. The mean number of coughs per pig on a treatment was compared with the mean control response, and the per cent cough depression was calculated by dividing the control value into the difference between treatment and control.

Drugs were evaluated on the basis of their ED_{50}'s. This may be defined as that dose necessary to produce a 50% depression of cough. The ED_{50}'s and their standard errors were estimated by the method of Bliss (2) and are shown in Table II. Although the ED_{50} values were estimated on the basis of individual slopes, when a comparison within the series was to be made it was more appropriate to use a common slope to arrive at an estimate of relative potency. The adjusted ED_{50} of a drug was related to the adjusted ED_{50} of the reference standard.

In all methods of cough stimulation in which the recording is done by measuring the force of expired air, the possibility of false responses must be kept in mind. True cough responses may be confused with gasps, sneezes, and various contractions of the abdominal musculature without the total integrated

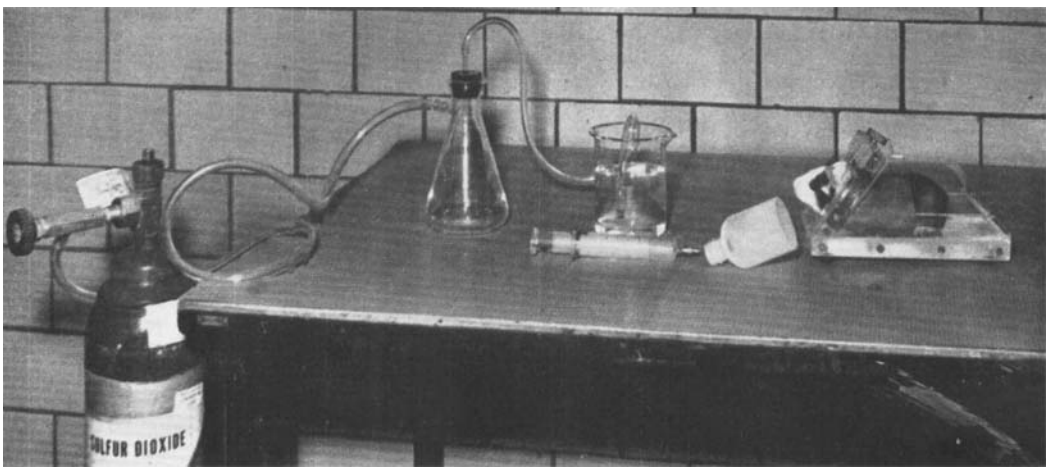


Fig. 1.—The antitussive screening apparatus. The apparatus has since been moved to a closed hood as a precaution against the sulfur dioxide fumes.

cough reflex occurring. This confusion was avoided by recording a response that was seen and heard.

Many electrical methods, due to the necessary surgery, involve acute experiments and the use of anesthetics. Due to their depressant effect on neural conduction, there is the possibility that these anesthetics as well as nonantitussive compounds with anesthetic properties will influence the results.

To avoid inconsistencies in cough response, mechanical methods of cough stimulation must be well controlled so that the stimulus is always applied equally and to the same area. This would be difficult enough to reproduce within the same laboratory using the same animal, but much more so in different laboratories.

None of these problems are encountered with the method described; the simplicity of the method eliminates many variables, and the equipment required is at a minimum. The variance in response due to animals was quite high, but error was greatly reduced by designing cross-over studies in which each animal served as his own control.

In an attempt to criticize and establish confidence in this method, those compounds which would be suspected to yield false positive results were administered, as well as known antitussive agents. Subtoxic doses of phenaglycodol,[1] a central synaptic depressant, secobarbital,[2] a barbiturate, and procaine hydrochloride, a local anesthetic, produced no depression of cough. No significant difference was shown between control (no treatment) and placebo (0.9% saline) when tested on a blind basis. This indicated that the effect of a saline injection was negligible and also showed the reproducibility of the control values in the same animals. On the other hand, morphine sulfate, codeine phosphate, and dextromethorphan hydrobromide[3] produced results (Table II) consistent with clinical findings.

Spasmogenic Testing Method.—Mongrel dogs, 6–12 Kg., anesthetized with an intravenous dose of 140 mg./Kg. phenobarbital, were used as test animals. A tracheal cannula was attached through a two-way valve to a volume-flow gas meter which measured inspired air. The carotid artery was cannulated and connected to a mercury manometer for blood pressure recording. An incision was made in the abdomen to expose the stomach. A cannula of No. PE 350 polyethylene tubing with a small balloon approximately $2^1/_2$ in. long tied around the end was inserted through an incision in the fundus of the stomach. This was passed through the pylorus and down 6 to 8 in. into the duodenum. A purse-string suture was made around the stomach incision to retard bleeding, and the abdominal incision was closed with wound clips. The balloon was inflated with approximately 6 ml. of air and attached to a tambour to record intestinal motility. All injections were made into the exposed femoral vein. A kymograph tracing of duodenal activity, blood pressure, and respiration is shown in Fig. 2.

Analgesic Testing Method.—Female, albino, Harlan strain rats weighing 70–80 Gm. were used as test animals. The method was a modification (3) of that used by Davies and co-workers (4). Mean reaction times of treated rats were compared with mean control values obtained at the same time to arrive at a mean increase in reaction time for each treatment group. A mean increase in reaction time of 1.5 seconds per rat ($ED_{1.5}$) was arbitrarily established as a basis for comparing different drugs. This represented a significant rise in threshold response. Dosage-response curves were calculated for each drug, and using individual slopes, the dose necessary to obtain an increase in reaction time of 1.5 seconds was computed. These figures are to be found in Table II.

The error was estimated by the method used for determining regression coefficients found in most standard statistical texts (5). The error of log dose x was estimated for the special case where y equals 1.5 seconds.

As was done in the case of antitussive evaluations, relative potency figures were estimated on the basis of a common slope and the adjusted $ED_{1.5}$ values were compared with the adjusted $ED_{1.5}$ of the reference standard.

RESULTS

The results of the antitussive, analgesic, and spasmogenic evaluations are summarized in Table II. The minimal toxic dose refers to the dose that produced the first observable signs of toxicity. These consisted of either sedation or tremors. The spasmogenic dose refers to the lowest dose that produced any increase in activity of the duodenum. Explanations of the remaining columns have been given under the appropriate testing methods.

Dotted spaces indicate that no significant effect was seen at subtoxic doses. A dotted space will also be noted after the figure 54.2 ± 26.7 on line 9, under "Analgesic Activity." Although this compound was of a low-order analgesic potency, an estimate of the $ED_{1.5}$ was not impossible. However, due to its poor dosage-response relationship and flat slope, it was not included in the calculation of relative potency. It was felt that inclusion would flatten the common slope of the remaining active compounds, resulting in distorted estimates of relative potency.

DISCUSSION

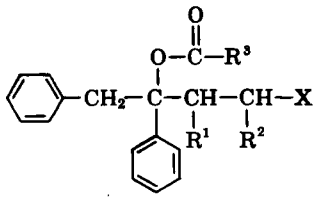
In the following discussion of structure-activity relationships all remarks will be limited to those twelve compounds that were reported in this paper. It must also be emphasized that these were racemic mixtures and that observations and conclusions apply only to these mixtures and not to their optical isomers. From previous reports, it might be expected that there would be a division of activity in the isomers upon resolving the racemate. In the case of the α-*dl*-2-propionoxy-1,2-diphenyl-3-methyl-4-dimethylaminobutane analog (*dl*-propoxyphene), it was demonstrated (6) that all of the analgesic activity resided in the dextrorotatory isomer. Also, this compound was shown to be unique in that the nonanalgesic isomer (*l*) possessed greater antitussive activity than the *d* isomer or the racemic mixture.

No structure-activity study should be considered complete without a study of the optical isomers within that series, and further work in this area should provide additional valuable data.

Antitussive Activity.—In the acetoxy derivatives,

[1] Marketed as Ultran by Eli Lilly and Co.
[2] Marketed as Seconal Sodium by Eli Lilly and Co.
[3] Marketed as Romilar, kindly supplied by Hoffmann-LaRoche, Inc.

TABLE II.—ANTITUSSIVE, ANALGESIC, AND SPASMOGENIC TEST RESULTS



				Antitussive Activity Guinea Pigs, s.c.				Analgesic Activity Rats, s.c.			Intestinal Activity Dogs, i.v. Spasmogenic
R¹	R²	R³	X	ED_{50} ± S.E., mg./Kg.	Relative Potency, % Morphine	Minimal Toxic Dose, mg./Kg.	Peak Effect, minutes	$ED_{1.5}$ ± S.E., mg./Kg.	Relative Potency, %, Morphine	Minimal Toxic Dose, mg./Kg.	Dose, mg./Kg.
H	H	CH_3	$N(CH_3)_2$	25.5 ± 5.0	50	80	60	...	...	160	3.2
CH_3	H	CH_3	$N(CH_3)_2$	8.5 ± 1.8	138	20	30	3.3 ± 0.5	23	12	0.04
H	CH_3	CH_3	$N(CH_3)_2$	12.5 ± 7.6	90	40	90	14.4 ± 1.9	4	40	0.8
CH_3	H	CH_3		5.8 ± 1.2	247	20	60	5.0 ± 1.0	14	20	0.05
CH_3	H	CH_3		23.9 ± 7.5	46	40	30	8.5 ± 1.3	7	20	0.08
CH_3	H	CH_3		...	...	40	30	...	...	320	3.2
H	H	C_2H_5	$N(CH_3)_2$	7.6 ± 3.5	138	160	60	...	...	320	0.1
CH_3	H	C_2H_5	$N(CH_3)_2$	3.5 ± 1.0	292	40	30	6.6 ± 0.6	9	20	0.2
H	CH_3	C_2H_5	$N(CH_3)_2$	23.9 ± 9.7	48	160	60	54.2 ± 26.7	...	160	1.6
CH_3	H	C_2H_5		9.8 ± 1.4	119	80	30	9.6 ± 2.2	7	40	0.4
CH_3	H	C_2H_5		23.3 ± 6.7	53	80	30	...	...	320	3.2
CH_3	H	C_2H_5		...	..	80	30	...	...	640	3.2
Morphine sulfate				9.8 ± 2.1	100	16	30	0.8 ± 0.2	100	4	0.002
Codeine sulfate				25.4 ± 2.9	30	60	30	2.7 ± 0.2	123	20	0.1
Dextromethorphan hydrobromide				18.8 ± 5.8	31	30	30	...	...	64	0.2

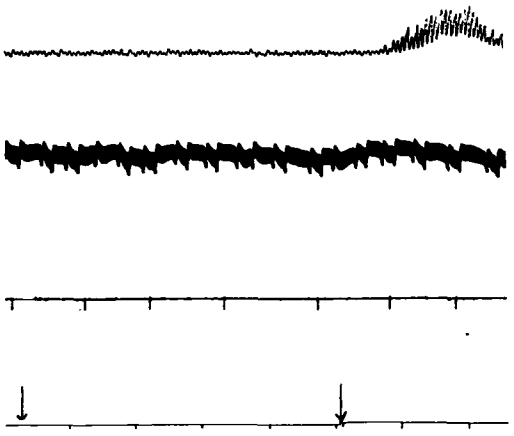


Fig. 2.—The effect of .025 mg./Kg. followed by .05 mg./Kg., i.v. of α-*dl*-2-acetoxy-1,2-diphenyl-3-methyl-4-pyrrolidinobutane hydrochloride on the duodenum of an 8.8 Kg. female dog, anesthetized with 140 mg./Kg. sodium phenobarbital i.v. Top line, duodenal activity; second line, blood pressure; third line, respiratory volume in liters; fourth line, time in minutes.

the compound unsubstituted at R^1 and R^2 possessed weak antitussive activity. Substitution at R^2 with a methyl group enhanced activity, but substitution at R^1 was more effective. The activity of the R^1 methyl-substituted compound was further enhanced by the substitution of a pyrrolidine group for the dimethylamine group. A piperidine substitution at *x* resulted in decreased activity and the morpholine-substituted analog was void of antitussive activity.

In the propionoxy derivatives, results obtained by substituting a methyl group at R^1 and R^2 were inconsistent with the acetoxy analogs. Although both R^1 methyl-substituted analogs were more potent than their corresponding unsubstituted or R^2 methyl-substituted analogs, the R^2 methyl-substituted propionoxy analog was less potent than its unsubstituted (R^1 and R^2 = H) analogs. This was not true in the acetoxy derivative. A pyrrolidine substituent at *x* did not enhance potency as was the case in its acetoxy analog. The piperidine analog was less potent than the acetoxy analog, and in both cases the morpholine analogs were inactive.

From the data it was concluded that the most effective antitussive structure among these compounds was represented by the R^1 methyl-substituted, propionoxy, dimethylamine analog. Pharmacological studies of this compound have been reported previously in the literature (3).

Spasmogenic Activity.—The spasmogenic data on the dog intestine were quite difficult to correlate. The active compounds in the series fell within the range of 0.04 to 0.4 mg./Kg. i.v., which is consistent with other antitussives and analgesics except morphine. The acetoxy derivatives were more active than their corresponding propionoxy analogs, and those compounds which showed weak or no antitussive and analgesic activity were consistently less active in their intestinal effect. If a compound had shown either antitussive or analgesic activity, it was also active upon the intestine. In this respect, it would be concluded that spasmogenic activity paralleled antitussive or analgesic potency, but not in any direct relationship.

Analgesic Activity.—In the compounds tested, it was observed that the acetoxy derivatives were consistently more potent than their propionoxy analogs. This relationship also held true with respect to toxicity resulting in no therapeutic advantage.

The unsubstituted (R^1 and R^2 = H) dimethylaminobutane acetoxy analog produced no analgesia. Substitution with a methyl group at R^2 produced an analgesically active compound and this activity was enhanced by shifting the methyl group to the R^1 position. The substitution of a pyrrolidine group for the dimethylamine moiety resulted in a slight loss of analgesic activity. Activity was further reduced by the substitution of a piperidine group at *x*. The morpholine analog was void of analgesic activity.

In the slightly less active propionoxy analogs, the R^1 methyl-substituted compound was also the most active of the dimethylamine analogs. A progressive loss in activity resulted from shifting the R^1-methyl group to the R^2 position and finally removing it. The effects of the pyrrolidine substitution at *x* were consistent with the acetoxy analog, but the piperidine substitution resulted in a total loss of activity. The morpholine analogs of the acetoxy and propionoxy derivatives were consistently inactive. The ratio of the $ED_{1.5}$ to the minimal toxic dose (therapeutic index) was roughly the same throughout the series.

It was concluded that among these compounds, the acetoxy derivative with a methyl group in the R^1 position and a dimethylamine moiety at *x* represented the optimum analgesic structure.

Correlation.—Only one compound (α-*dl*-2-propionoxy-1,2-diphenyl-4-dimethylaminobutane hydrochloride) exhibited good antitussive activity without analgesic activity. The remaining compounds in which antitussive activity was demonstrated also exhibited analgesic activity. There was only one compound of good analgesic potency which exhibited low antitussive potency (α-*dl*-2-acetoxy-1,2-diphenyl-3-methyl-4-piperidinobutane hydrochloride). All compounds which were active upon the intestine were also active as analgesics and/or antitussives. These observations are suggestive of some degree of correlation between analgesic and antitussive potency, while a strong correlation was shown between antitussive activity and spasmogenic activity although not quantitatively so.

SUMMARY

1. A series of dialkylaminodiphenylbutanol esters was tested for antitussive activity, and this activity was compared with their analgesic potencies and effect upon the intestine.

2. A new method for evaluating antitussive activity was described.

3. The optimum antitussive structure within this series tested was represented by α-*dl*-2-propionoxy - 1,2 - diphenyl - 3 - methyl - 4-dimethylaminobutane hydrochloride.

4. The optimum analgesic structure within this series tested was represented by α-*dl*-2-acetoxy - 1,2 - diphenyl - 3 - methyl - 4 - dimethylaminobutane hydrochloride.

5. Some degree of correlation was shown among the three activities, although exceptions were noted.

REFERENCES

(1) Pohland, A., and Sullivan, H. R., *J. Am. Chem. Soc.*, **75**, 4458(1953).
(2) Bliss, C. I., *Quart. J. Pharm. Pharmacol.*, **11**, 192 (1938).
(3) Robbins, E. B., THIS JOURNAL, **44**, 497(1955).
(4) Davies, O. L., *et al.*, *Brit. J. Pharmacol.*, **1**, 255(1946).
(5) Dixon, W. J., and Massey, F. J., "Introduction to Statistical Analysis," McGraw-Hill Book Co., New York, N. Y., 1951, p. 155.
(6) Robbins, E. B., and Miller, J. A., *Pharmacologist*, **2**, 98(1960).

Chlorpromazine and Dextro-amphetamine as Antidotes in Acute Antihistaminic Toxicity in Rats

By I. H. MAEL† and J. F. BESTER

Acutely toxic oral doses of a number of antihistaminics were determined in adult white rats of both sexes. Toxic symptoms included convulsive seizures which lasted some minutes and were periodically repeated, followed by generalized central depression, terminating in unconsciousness and death. Chlorpromazine and dextro-amphetamine were administered in that order, intraperitoneally, in varying quantities and at varying time intervals. It was found that, if chlorpromazine was administered at the onset of convulsions and dextro-amphetamine at the first signs of depression, the recovery rate of animals was quite high.

THERAPEUTICALLY useful antihistaminics were developed well over 20 years ago, and for most of that time their acutely toxic capabilities have been recognized. Just as the various antihistaminics vary in their potencies, so they vary in the frequency and severity of their toxic manifestations. Such variations are largely quantitative, however; and when they occur, the symptoms of acute toxicity are quite similar regardless of the drug used. Typically, drowsiness followed by nervousness, tremors, muscle twitching, delirium, and convulsions are observed along with respiratory depression and cyanosis and followed by unconsciousness and death (1).

Despite the fact that repeated efforts have been made to find satisfactory methods of treatment of acute poisoning with the antihistaminic drugs, methods of treatment continue to be difficult and not overly successful. The need for uniformly adequate antidoting has not lessened with the years; acute antihistaminic poisoning is not uncommon. Each month, for example, several such intoxications are reported in Arizona, totaling 27 for the year 1961 (2). The Poison Information Center in Los Angeles in the first 6 months of 1961 reported 42 acute poisonings from antihistaminics as such, plus an additional 65 due to antihistaminic-containing nonbarbiturate sedatives (3).

The difficulty in preventing poisoning with these drugs and in coping with them when they arise is complicated by the fact that dose effect relationships are inconsistent. For example, the oral LD_{50} of diphenhydramine in rats has been reported as 500 mg./Kg. (4), and of pyrilamine hydrochloride, subcutaneously in rats, as 150 mg./Kg. (5). Yet 400 mg. of diphenhydramine and 1.3 Gm. of pyrilamine, respectively, caused the deaths of two 2-year-old children (1). Connolloy reported serious intoxication of a $5^1/_2$-year-old child following ingestion of 12 mg. of chlorpheniramine (6).

Because antihistaminics typically cause toxic symptoms of mixed characteristics, single antidotes offer little hope of success. Various drugs and drug combinations have been tried and reported. These include histamine, atropine plus epinephrine, phenobarbital, caffeine, dextro-amphetamine (7), ether (8), phenobarbital plus caffeine and ephedrine (9). Results were generally unsatisfactory.

Chlorpromazine reportedly has shown the ability to cause a definite decrease in motor activity without evidence of hypnosis (10). Dextro-amphetamine has long been recognized as an

Received April 19, 1962, from the School of Pharmacy, University of Southern California, Los Angeles.
Accepted for publication October 23, 1962.
Abstracted from a thesis presented by I. H. Mael to the Graduate School, University of Southern California, Los Angeles, in partial fulfillment of Master of Science degree requirements.
† Present address: Encino Hospital, Encino, Calif.