of activity on the central nervous system, the synthesis of the diamides of terephthalic and isophthalic acids was undertaken.

EXPERIMENTAL

Methods—The best and most general reaction for the preparation of amides has been reported to be the acylation of amines by acyl halides (7). A study of the reaction medium best suited for the synthesis of the desired compounds was undertaken. For this purpose the reaction of terephthaloyl chloride with alkyl amines (propylamine and *N*-di-*n*-butyl amine) was selected for detailed investigation. The results are summarized in Table I.

As a result of these studies anhydrous ether was chosen as the reaction medium. The following procedure was employed for the synthesis of the compounds reported.

A fourfold excess of the amine was dissolved in 100 ml. of anhydrous ether and cooled to 4°. A solution of the chloride (0.05 mole in 150 ml. anhydrous ether) was added slowly with vigorous stirring. The reaction temperature was not allowed to exceed 20° during the addition process. After the addition was complete, the stirring was continued for 15 min. The reaction mixture was stored overnight at 4° during which time the desired product crystallized (if the product failed to crystallize, the ether was removed by evaporation). The crystals or residue obtained were washed with distilled water to remove the amine hydrochloride and recrystallized from 50% ethanol. The melting points, yields, and analytical data for the amides of terephthalic acid are given in Table II, and for the amides of isophthalic acid in Table III.

Pharmacological Survey[1]—The preliminary mouse toxicity study showed that, in general, these compounds are nontoxic and free of any major CNS activity. The *N,N'*-di-*n*-butylterephthalamide and the *N,N,N',N'*-tetra-isopropylisophthalamide were also screened as antidepressants. Although both showed some activity, the activity was not sufficient to warrant further study.

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[1] The authors are indebted to Dr. Warren J. Close, Abbott Laboratories, North Chicago, Ill., for the pharmacological screening.

Multi-Chamber System for Toxicity Studies in Mice at Simulated High Altitude

By I. P. BAUMEL, S. M. ROBINSON, and W. F. BLATT

Plastic desiccators have been adapted to serve as chambers in a simulated high altitude system. The multi-chambered system is convenient for observations of grouped mice or other small animals subjected to decompression. Toxicity data are given for representative drugs at sea level and a simulated altitude of 19,000 ft.

In examining the effects of simulated high altitude on drug toxicity in mice, it was necessary to utilize chambers which could accommodate a group of animals and permit a clear, unobstructed view of them. Accordingly, the authors devised a system incorporating relatively inexpensive plastic desiccators designed for routine laboratory use. The simulated altitude afforded by this system was used to evaluate the lethality to mice of agents representative of various drug classes.

EXPERIMENTAL

Apparatus—The modified spherical desiccators[1] shown in the lower portion of Fig. 1 can be evacuated to below 0.01 μ, a value considerably below that normally required for altitude studies. In single chamber operation, the air valve at the top portion of the chamber was attached directly to a vacuum pump. For air entry, a hole was drilled 2 in. above the level of the porcelain platform in the lower portion of the desiccator, and a suitable tubing adapter was inserted. If desired, additional openings can be made to accommodate separate manometers and/or monitoring equipment.

The operation of several chambers through a multi-port manifold requires the exact duplication of size and length for the air evacuation and entry lines. The $^3/_4$-in. tubing assembly, shown in the top portion of Fig. 1, was devised to serve four chambers. The upper manifold was attached to the pump; the lower section provided for the constant fresh air intake regulated by the control valve. Uniform pieces of thick-walled rubber tubing ($^1/_2$ in.) were used to attach the chambers to the manifold. A $^1/_{12}$-h.p. pump[2] was adequate for establishing a simulated altitude of 19,000 ft. at an air flow of 2.5 L./min. The barometric pressure within the system was monitored by a mercury manometer attached to the end chamber. The unit, during normal operation, is shown in the lower portion of Fig. 1. The speed of ascent was controlled by the air intake valve—more than adequate air flow was maintained at the 1,000

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[1] The Ace Glass Co., Vineland, N.J.

[2] Gelman Co., Ann Arbor, Mich.

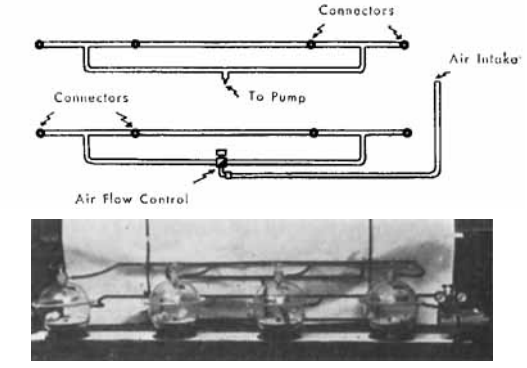

Fig. 1—Four-unit simulated altitude system. Key: top, manifold assembly for chambers showing tubing connections to pump and air entry lines; bottom, assembled system attached to 1/12-h.p. pump.

ft./min. ascent rate utilized in this system. The sufficiency of the air flow obviated a possible problem; the turnover was such that normal room air conditioning could maintain the chambers within one degree of the external ambient temperature.

Drugs and Procedure—Male albino mice (CD_1, Charles River Mouse Farms), approximately 20.0 Gm., were placed in the chambers in groups of four, with 16 mice per dosage level. As part of ongoing studies on the interaction of altitude and drugs affecting the central nervous system (1), the following representative agents were selected for preliminary evaluation: sodium phenobarbital, reserpine, and tranylcypromine sulfate. Drugs were administered intraperitoneally at a constant dosage volume of 0.1 ml./10.0 Gm. of body weight. For the altitude determinations, the mice were then brought to 19,000 ft. at a rate of 1,000 ft./min. The number dead were noted for the 4-hr. period following arrival at the specified altitude. Occasionally an animal succumbed during ascent and as such was discarded from group computation. LD_{50} values and 95% confidence limits were determined by the method of Litchfield and Wilcoxon (2).

RESULTS AND DISCUSSION

Representative data for altitude and comparable sea level determinations are shown in Table I. An increased toxicity was obtained with reserpine in altitude-exposed mice; in contrast, no differences between sea level and simulated altitude could be demonstrated with phenobarbital or tranylcypromine. The observations thus far, while attesting to the feasibility of the system, are too limited to permit speculation on the mechanisms operative in the increased toxicity.

TABLE I—INTRAPERITONEAL LD_{50} DETERMINATIONS OF DRUGS AT SEA LEVEL AND ALTITUDE (19,000 ft.)

Dose, mg./Kg.	Observed/Tested		LD_{50}, mg./Kg.	
	Sea Level	Altitude	Sea Level	Altitude
Na Phenobarbital				
200	0/16	.....	290	273
250	2/16	2/16	(277–303)[a]	(256–286)
275	5/16	8/16		
300	10/16	15/16		
375	16/16	.....		
Reserpine				
75	.....	3/15	188	101
100	1/16	9/16	(138–256)	(80–127)
125	.....	8/16		
200	9/16	.....		
300	14/16	.....		
Tranylcypromine SO_4				
40	1/16	.....	107	122
80	2/16	1/16	(86–134)	(105–142)
100	2/16	3/16		
125	.....	7/12		
160	13/16	.....		
200	16/16	.....		

[a] Figures in parentheses represent values for 95% confidence limits. [b] Solubilized in 20% ascorbic acid.

Although the authors have used this system mainly for acute studies, the apparatus can be used for more protracted periods of exposure. For the latter application, cages containing standard feed and watering devices can be placed within the chamber and, following descent, rapid cleaning made by complete change of cage unit. During prolonged stay at altitude, it is suggested that a safety release valve be inserted within the system to protect against sudden unforeseen increases in altitude.

The apparatus can be expanded to accommodate an increased number of chambers by modification and expansion of the pipe assemblies, holding to the same general principle of equal connecting lengths. It also lends itself, with no major changes, to studies that require varied gas mixtures.

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