PHARMACOLOGY

A *Cyclo*butane possessing Hypotensive Activity

A NUMBER of non-quaternary bases have been found to possess ganglionic blocking and hypotensive properties[1–5]. In investigating the pharmacological properties of a new series of *cyclo*butanes[6], one of them, 3-dimethylamino-2,2,4,4-tetramethyl-*cyclo*butanol, was found to exhibit a lowering activity of the blood pressure of long duration. The pharmacological properties of the *cis* isomer of this tertiary amine were qualitatively similar to those of the *trans* isomer. The *cis* isomer appeared, however, to be slightly less active when tested for hypotensive activity. Beard and Burger[7] have recently reported the synthesis of the *cis* and *trans* isomers of 3-dimethylamino *cyclo*butanol. They found the antispasmodic activity of the *cis* isomer of the diphenylacetic acid ester of 3-dimethylamino *cyclo*butanol to be slightly less than that of the *trans* isomer.

Oral administration of doses as low as 10 mg/kg of the *trans* isomer produced in anæsthetized cats a fall in blood pressure within 5–10 min. Although this material was at least as active as hexamethonium bromide in lowering blood pressure on intravenous injection in anæsthetized cats, it was only one-half as active in blocking the contraction of the nictitating membrane elicited by preganglionic nerve stimulation.

The oral acute toxicities of the *cis* and *trans* isomers of 3-dimethylamino-2,2,4,4,-tetramethyl-*cyclo*butanol in mice were not significantly different. Hexamethonium bromide was found to be four times more toxic by the oral route of administration. Chronic feeding of the *trans* isomer to dogs at dose-levels of 200 mg/kg for a period of three weeks was well tolerated. Sedation and ptosis were evident at doses well below the lethal level.

A complete report on the pharmacological activity of 3-dimethylamino-2,2,4,4-tetramethyl-*cyclo*butanol and related members of the series will be presented elsewhere.

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Effect of Sensory Stimuli on Amphetamine Toxicity in Aggregated Mice

THE increased toxicity of amphetamine in aggregated mice has been reported by several workers[1–3]. Among the factors which have been found to contribute to the enhancement of toxicity in aggregated mice are cage floor area, environmental temperature, and body-weight[2–4]. The present investigation has examined the effect of type of sensory contact between mice as a factor influencing amphetamine toxicity.

Male Swiss albino mice weighing 20–28 g were used. Food and water were supplied *ad lib.* except during the experimental period. Animals were housed in groups of ten prior to use. Environmental temperature was maintained at 24° ± 1° C. D-Amphetamine sulphate was administered intraperitoneally in a dose of 25 mg/kg. Injection volume was maintained at 5 c.c./kg of body-weight. Mortality was determined by recording the number of dead mice at intervals of 1, 2, 3, and 24 h after administration of drug.

Two types of experimental containers were used in this study. One was a metal container 30 cm long, 17 cm wide, and 5 cm high. The other was a transparent plastic container 35 cm long, 17 cm wide, and 6·5 cm high. Each container was divided into 12 compartments of equal volume. The partitions dividing the metal container were adjustable and could be raised or removed depending on the experimental conditions being examined.

Table 1. EFFECT OF SENSORY STIMULI ON AMPHETAMINE* TOXICITY IN MICE

Sensory stimulus	Container	No. of mice per group	Total No. of mice used	Cumulative percentage mortality (h) 1	2	3	24
Unlimited	Metal container	10	30	27	90	93	100
Limited	Metal container divided into compartments (7·5 × 5·7 × 5 cm) separated by partitions with 0·6 cm space at bottom	10	30	7	23	47	80
Visual	Transparent plastic container divided into compartments (8·8 × 5·7 × 6·5 cm)	10	20	0	5	45	55
Visual and olfactory	Transparent plastic container divided into compartments (8·8 × 5·7 × 6·5 cm). Partitions between compartments have opening (0·6 cm diameter) in centre	10	20	0	5	15	40
None	Metal container	1	12	0	0	0	20
None	Metal container divided into compartments (7·5 × 5·7 × 5 cm)	1	10	0	0	0	0

* 25 mg/kg intraperitoneally.

The experiments were designed to emphasize one or more types of sensory stimulation and minimize others. The effects of unlimited sensory contact, limited sensory contact, visual contact, visual and olfactory contact, and absence of sensory contact (isolation) were studied in mice that received amphetamine. The results are summarized in Table 1. Maximal sensory stimulation, that is, unlimited contact between mice, was found to produce the highest per cent mortality. Body contact appeared to be the most important contributor to amphetamine toxicity in aggregated mice since the per cent mortality steadily declined as the degree of body contact decreased. In the case of isolated mice, the area available to each mouse appeared to have only a slight effect on mortality. This study further emphasizes the importance of environment as a factor in the complex mechanism of amphetamine toxicity in aggregated mice.

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HÆMATOLOGY

Effect of Adenosine Diphosphate on Circulating Platelets in Man

IN 1960 Hellem[1] reported that platelet adhesiveness *in vitro* was increased by a dialysable substance derived from red cells, and that he had observed transient thrombocytopenia in rabbits after intravenous injections of this material. The active fraction was afterwards identified as adenosine diphosphate (ADP)[2]. The specific aggregation of platelets *in vitro* by ADP, and the inhibition of this action by adenosine, its monophosphate (AMP) and its triphosphate (ATP), have been demonstrated by other