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Notes

Toxicity and Central Depressant Activity of D-1-Phenyl-2-ureidopropane

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D-1-Phenyl-2-ureidopropane was prepared by the method of Toritaku and alternatively, by reacting 1-phenyl-2-aminopropane directly with urea. The LD_{50} of this ureide was found to be 840 mg./Kg. The compound was found to act as a central nervous system (CNS) depressant rather than as a sustained action CNS stimulant, as suggested by Toritaku. Comparison of the structural formula of 1-phenyl-2-ureidopropane with that of the barbiturates and hydantoins supports the experimental evidence that this compound acts as a barbiturate-like central nervous system depressant.

THE PREPARATION of sustained release amphetamine compositions has depended principally upon three approaches: (*a*) the preparation of beads of active ingredient coated with shellac, wax, or other insoluble substance, (*b*) the formation of a complex between amphetamine and an ion exchange resin, and (*c*) the formation of insoluble salts of amphetamine, such as the tannate, which are then slowly converted to soluble amphetamine salts in the acid stomach.

Our attention has been directed toward the search for new amphetamine compounds which would hydrolyze to give sustained amphetamine action or which, in themselves, would provide prolonged stimulation of the central nervous system.

Toritaku (1) has indicated that the urea derivative of amphetamine hydrolyzes *in vivo* to give a sustained amphetamine action. Toritaku's patent described the preparation of the compound but reported no biological tests to demonstrate the amphetamine action. This study was therefore initiated to determine the toxicity and duration of action of D-1-phenyl-2-ureidopropane.

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EXPERIMENTAL

Synthesis.—D-1-Phenyl-2-ureidopropane was prepared from D-1-phenyl-2-aminopropane sulfate and potassium cyanate as described by Toritaku (Fig. 1).

D-1-Phenyl-2-aminopropane sulfate, 60 Gm. and potassium cyanate, 30 Gm., were placed in 350 ml. distilled water and boiled for 30 minutes. After three recrystallizations from water, white needles were obtained which melted at 138.5 to 139°, which agrees with previously reported data (2, 3). The actual yield from the reaction was 55 Gm. or 90 % of the theoretical yield, 58 Gm.

D-1-Phenyl-2-ureidopropane was also prepared by the reaction of D-1-phenyl-2-aminopropane with urea (Fig. 2.). This method was abandoned because of low yield.

Biological Examination.—The intraperitoneal LD_{50} of this compound was determined by the method of Hagan (4). White rats, 200 Gm., both male and female, were used as experimental animals. Following determination of the intraperitoneal LD_{50}, the compound was administered orally to 200-Gm. rats, both sexes, at a dose of twice the intraperitoneal LD_{50}. The experimental animals were compared to the controls by visual examination.

Results.—The data from the intraperitoneal

TABLE I.—INTRAPERITONEAL LD_{50} EVALUATION OF D-1-PHENYL-2-UREIDOPROPANE

Dose, mg./Kg.	Final Dosage Levels and Mortality Ratios[a] Time, hr.										
	1/2	1	1 1/2	2	2 1/2	3	3 1/2	4	4 1/2	5	24
700	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
800	0/6	0/6	0/6	1/6	1/6	1/6	1/6	1/6	2/6	2/6	2/6
900	0/6	0/6	1/6	2/6	3/6	4/6	4/6	4/6	4/6	4/6	4/6

[a] The figures in this table indicate the ratio between the number of animals which succumbed and the number of animals injected.

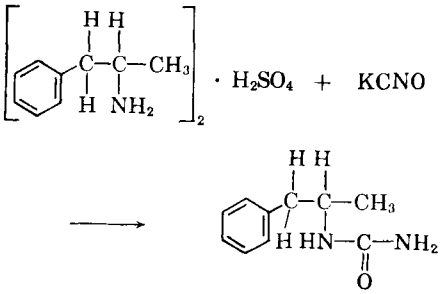


Fig. 1.—Preparation of 1-phenyl-2-ureidopropane from amphetamine sulfate and potassium cyanate.

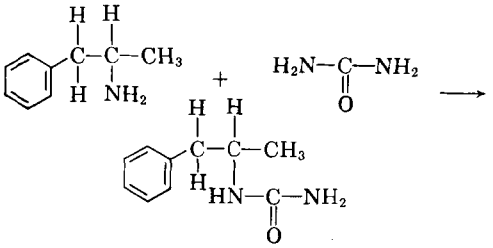
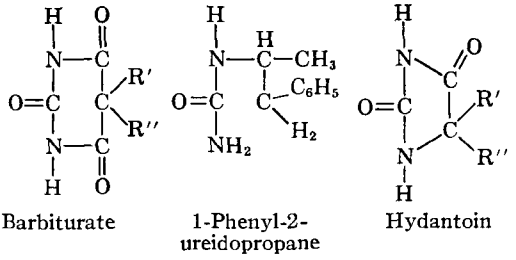


Fig. 2.—Preparation of 1-phenyl-2-ureidopropane from amphetamine and urea.

LD_{50} determination are shown in Table I. The intraperitoneal LD_{50} for 200-Gm. rats appears to be approximately 840 mg./Kg. During this procedure no convulsions or other symptoms of central nervous system stimulation were observed.

When 200-Gm. rats were subjected to an oral dose of this compound equal to two times the intraperitoneal LD_{50} dose the onset of drug activity occurred in approximately 60 minutes and was indicated by general lethargy, loss of irritability, and lack of coordination when walking. Two hours after the administration no voluntary movement of the test animals was observed. At this point shallow breathing was apparent and pulse rates were found to be about one-half of normal. Two of the 12 rats had lost the righting reflex but continued to respond to the tail dip test using water at 160°F. Recovery, indicated by the return of coordinated



Barbiturate 1-Phenyl-2-ureidopropane Hydantoin

Fig. 3.—The structure of 1-phenyl-2-ureidopropane and two typical CNS depressant nuclei.

movement and response to noise, occurred between 6 and 8 hours after administration. All animals survived. It was again observed that no convulsions occurred in the test animals but rather the signs and symptoms of central nervous system depression were apparent.

DISCUSSION

The striking feature of the animal experiment was the absence of any reaction similar to that in rats treated with 1-phenyl-2-aminopropane. In all cases the test animals gave the appearance of having been treated with a central nervous system depressant such as a barbiturate. For example, of 12 animals treated orally, 10 had a marked loss of coordination and the remaining 2 were under light anesthesia, having lost the righting reflex but still responding to pain.

An examination of the structural formula of the compound in question provides an explanation for the observed experimental facts. In Fig. 3 are shown the basic structural components of 1-phenyl-2-ureidopropane, of the barbiturate nucleus, and the hydantoin nucleus. Examination of Fig. 3 will show that the basic components of a central nervous system depressant are present in 1-phenyl-2-ureidopropane and therefore that central nervous system depression from this compound should not have been unexpected.

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