

ALKYL CHAIN LENGTH AND ACUTE ORAL TOXICITY OF *p*-AMINOPHENONES

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Abstract—1. There exists a structure-toxicity relationship between the length of the alkyl chain of *p*-aminopropiophenone homologues and their oral LD₅₀'s in albino mice and rats.

2. The acute oral toxicity decreased in both species with the removal of one carbon atom from the alkyl group, increased with the addition of one and two carbon atoms, and decreased again with the addition of three carbon atoms to the alkyl group.

INTRODUCTION

p-Aminopropiophenone (ethyl *p*-aminophenyl ketone, PAPP) has ferrihemoglobinemia-inducing activity that varies with species (Kiese, 1974). Such activity can sometimes be lethal (Vandenbelt *et al.*, 1944; von Jagow *et al.*, 1966). We are interested in developing vertebrate pest control chemicals and, therefore, explored the possible existence of a structure-toxicity relationship between the length of the alkyl chain of PAPP homologues and their oral LD₅₀'s in albino mice and rats. The results of our study show that such a relationship does exist. The acute oral toxicity decreased in both mice and rats with the removal of one carbon atom from ethyl to methyl in the alkyl group of PAPP, increased with the addition of one and two carbon atoms to propyl and butyl, and decreased again with the addition of three carbon atoms to form the pentyl group.

MATERIALS AND METHODS

p-Aminoacetophenone (PAAP) and PAPP were purchased from a commercial source and recrystallized once from ethanol-water. *p*-Aminobutyrophenone (PABP), *p*-aminovalerophenone (PAVP) and *p*-aminocaprophenone (PACP) were synthesized (Kunckell, 1900) in our laboratory and recrystallized once from ethanol-water. The compounds were confirmed by elemental determination, mass, NMR, and infrared spectroscopy. Young adult male Swiss Webster albino mice (20–30 g) and Sprague-Dawley male albino rats (200–295 g) were acclimatized in our laboratory for 2–3 weeks. Lighting and temperature in the test laboratory were automatically controlled and maintained (i.e. 12 hr light/dark cycle and 23–26°C). The animals were fasted for 17–19 hr before treatment. Water was available *ad libitum*.

The chemicals were prepared in propylene glycol and administered by gavage using a 1-ml tuberculin syringe and 16 or 18 gauge intubation needle of appropriate length. The volume administered to each animal was 0.1 ml/10 g body weight for mice and 0.2 ml/100 g body weight for rats. Five animals were treated at each dose

level and a minimum of three levels per chemical were used. Animals were observed for 7 days posttreatment. The oral LD₅₀'s with 95% confidence limits were calculated by the methods of Thompson (1947) and Thompson & Weil (1952).

RESULTS AND DISCUSSION

The results given in Table 1 and Fig. 1 show large differences in acute oral LD₅₀'s in both mice and rats to the five *p*-aminophenones. In both species PAAP was the least toxic. It is noteworthy that the removal of a single carbon atom from the alkyl group of PAPP decreased the toxicity about 3.5 times in mice and about 1.7 times in rats. However, with the addition of 1 carbon atom to the alkyl group of PAPP to form PABP, the toxicity to the mouse remained unchanged from that of PAPP but increased about 2.6 times in the rat. It is also interesting to note that with the further addition of one more carbon atom on the alkyl group to form PAVP the toxicity to mice increased about 2.5 times, but only slightly in rats. Toxicity decreased in both species with PACP which has five carbon atoms in the alkyl group. PAAP and PABP were more toxic to rats than mice; to mice, PAVP is more toxic than PABP, PAPP, PACP and PAPP; to the rats, PAVP and PABP are of the same toxicity and they are significantly more toxic than PAPP, PACP and PAAP. As a whole, both mice and rats had the same toxicity pattern, and species difference did not exist except in the case of PAAP.

It has been reported that *p*-aminophenones administered i.p. to mice have decreasing LD₅₀'s from PAAP to PACP when expressed in mg/kg, and decreasing from PAAP to PAVP then increasing from PAVP to PACP when expressed in mmol/kg. The authors presumed that all deaths resulted from ferrihemoglobinemia (Lanphier *et al.*, 1947). When large doses of a ferrihemoglobin-inducing chemical were administered, overwhelming toxic ferrihemoglobinemia occurred, and resulted in oxygen deficits in the brain and heart; additional effects can include intravascular hemolysis and the formation of Heinz bodies

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Table 1. Relationship between alkyl chain length and the oral acute toxicity of *p*-aminophenones to albino mice and rats

Compound	Molecular weight	Alkyl group	LD ₅₀ (95% confidence limits) (mg/kg)	
			Mouse	Rat
<i>p</i> -aminoacetophenone	135	Methyl	596 (449–790)	381 (360–404)
<i>p</i> -aminopropiophenone	149	Ethyl	168 (117–243)	221 (197–248)
<i>p</i> -aminobutyrophenone	163	Propyl	133 (89–200)	84 (56–126)
<i>p</i> -aminovalerophenone	177	Butyl	94 (71–125)	84 (56–126)
<i>p</i> -aminocaprophenone	191	Pentyl	299 (183–488)	216 (177–263)

(Smith *et al.*, 1967). The combined effects eventually contribute to death through failure of respiration or circulation (Smith, 1969). Thus, when massive amounts of a ferrihemoglobin-inducing chemical are administered, the concentration of ferrihemoglobin alone cannot account for the death of the animals.

Arylamines are known to be *N*-hydroxylated by the hepatic microsomal mono-oxygenase system into active metabolites (Uehleke, 1972) and it has been shown that the formation of ferrihemoglobin following the injection of PAPP is caused mainly by *p*-hydroxylaminopropiophenone (von Jagow *et al.*, 1966). Graffe *et al.* suggested that *in vivo* *N*-hydroxylation of PAPP proceeded faster than *N*-hydroxylation of aniline and thus a higher concentration of *p*-hydroxylaminopropiophenone than phenylhydroxylamine was quickly attained; with its high activity in the enzymic cycle of ferrihemoglobin formation, a high concentration of ferrihemoglobin was observed after the administration of PAPP (Graffe *et al.*, 1964). The higher toxicity of PABP and PAVP may indicate that PABP and PAVP formed their respective *N*-hydroxyl metabolites faster than PAPP. Since the therapeutic ferrihemoglobinemia property of PAPP against poisoning by cyanide and prevention of damage by high energy radiation is credited to rapid formation of its

N-hydroxyl derivative (Kiese, 1974), it is possible that PABP and PAVP may be more effective than PAPP in this respect.

Martin & Hansch (1971) have related the intensity of pharmacological properties of drugs directly to their hydrophobicity. This may explain the lower toxicity of PAAP than PAPP, since the methyl group in PAAP is shorter than the ethyl group in PAPP. Then, by analogy, the propyl group of PABP and the butyl group of PAVP may have made them more hydrophobic than PAPP; hence the latter two chemicals would be expected to be more toxic than PAPP. However, hydrophobicity fails to explain the decline in toxicity of PACP to rats, since PACP in the pentyl group is longer than all the other alkyl groups studied. Burger (1980) has concluded that there are no absolute ground rules in the relationships of chemical structure and biochemical or biological activity. This is certainly due to the actuality that a chemical in high dose does not induce a single biochemical or biological effect but a number of effects simultaneously. However, the distinct existence of a simple and neat relationship of the alkyl chain length to acute toxicity in mice and rats, as reported here, is intriguing. It compels us to suggest that the size of the *p*-aminophenone molecules, as determined by the length of the alkyl chain, is most likely the major factor in the lethal mode of action of these ferrihemoglobin-forming chemicals, and that the molecular sizes of PAVP and PABP have the best fit to a critical enzyme or other component in the lethal mechanism as yet not well understood.

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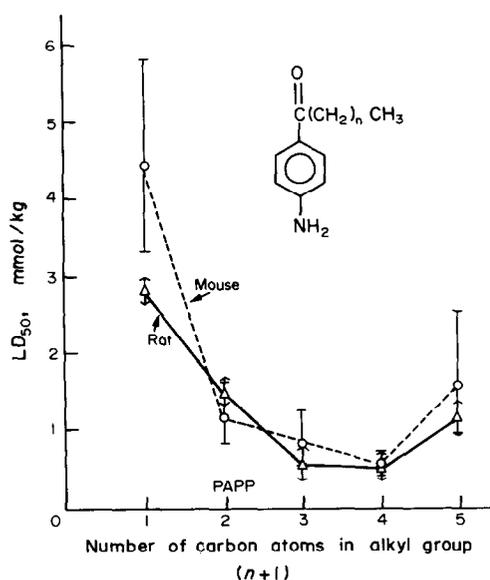


Fig. 1. Oral LD₅₀ of *p*-aminophenones in albino mice and rats vs their respective alkyl chain length.

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