UNSATURATED MONO HALOGENATED HYDROCARBONS AS GENERAL ANESTHETIC AGENTS * †

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INTRODUCTION

IN the selection of compounds for use in general anesthesia it is necessary to consider such pharmacological properties as toxicity and anesthetic potency and such chemical and physical properties as inflammability, volatility and stability. The search for new anesthetic agents in the group of halo-olefins has been influenced by the biochemorphic predictions of Leake (1) which resulted in the discovery of divinyl oxide. He predicted that a compound such as divinyl oxide would be a more potent anesthetic agent than the two compounds represented in its structure, viz., ethylene and diethyl ether. This was amply confirmed in the studies which followed (2). In general, unsaturation results in an increase in the pharmacological activity of compounds. Prior to Flourens' use of chloroform it had been empirically discovered that halogen introduced into a simple hydrocarbon molecule increases its narcotic potency. Chemical investigations had shown that halogenated hydrocarbons were less inflammable than the parent hydrocarbon, but there was also a concomitant decrease in volatility. Other chemical studies, chiefly those of Pogorzelski (3), von Braun (4), Clarke (5), Tronov (6), and Wiezevich (7), indicated that unsaturated halogenated compounds of the type R–C=C–X were more stable *in vitro* than their corresponding saturated analogues.

On the basis of this evidence, Leake and Knoefel suggested that halogenated unsaturated compounds of the type R–C=C–X and $R–\overset{X}{\overset{|}{C}}=C$ might possess the following attributes: (*a*) potent anesthetic properties, (*b*) lower inflammability, (*c*) decreased capability of hydrolysis *in-vivo,* and therefore less potentiality for producing tissue damage.

ANESTHETIC POTENCY AND ACUTE TOXICITY OF MONO-BROM AND MONO-CHLOR UNSATURATED HYDROCARBONS

Peoples and Leake (8) demonstrated that vinyl chloride is less toxic but possesses an anesthetic potency of the same order as ethyl chloride. A preliminary survey (9) of the anesthetic potency and acute toxicity

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in white mice of a number of saturated and unsaturated halogenated compounds has shown that previous assumptions with respect to unsaturation, based on the findings with divinyl oxide and ethylene, may not hold in other series of compounds. Increase in anesthetic potency could not be uniformly correlated with unsaturation. Of the monohalogenated unsaturated compounds investigated, the agent 1 chloro-2-methyl-propene was found to possess the widest margin of safety and was selected for an extended investigation (10). The *Certain Safety Factor* (11) was found to be 2.7, and in a study of chronic toxicity, no significant liver damage was observed. However, some alveolar damage resulted, indicating that it was a local irritant. Another study (12) of unsaturated compounds was undertaken in which the types R–C=C–X and R=C–C–X were compared. The agents 1 chloro-propene,

TABLE 1

Compound	Certain Anesthetic Conc. mM./L.	Highest Tolerated Conc. mM./L.
1 chlor ethene	5.0	9.0
1 chlor propene	2.2	2.7–3.0
2 chlor propene	2.5	3.0–3.5
1 chlor 2 methyl propene	1.0	2.5
1 chlor *n*-butene	1.5	1.75
2 chlor *n*-butene	1.5	2.0
1 brom ethene	3.5	7.0
1 brom propene	1.1	2.0–2.4
2 brom propene	1.2	2.5
1 brom 2 methyl propene	0.75	1.37

1 chloro-2-methyl-propene, 3 chloro-propene and 3 chloro-2-methyl-propene were considered. Those in which the halogen was attached to an unsaturated carbon atom were less irritant, less damaging to tissue, more anesthetic and less acutely toxic.

Other biochemorphic generalizations may be drawn from the studies which have been made of the halogenated hydrocarbons. Table 1 contains the minimal certain anesthetic concentrations and the highest tolerated concentrations of the mono-brom and mono-chlor unsaturated hydrocarbons investigated to date. Both series obey Richardson's Law in that there is a progressive increase in anesthetic potency and acute toxicity with an increase in the length of the carbon chain. Further, support for the finding that brominated compounds are more active than their chlorinated analogues is found in this group. The brominated agents are effective as general anesthetics and are more acutely toxic in lower concentrations than the corresponding chlorinated compounds. Marsh and Emerson (13) and Marsh (14) have supported these conclusions, extending the series to the pentenes. Later studies (15) of the 1 and 2 chloro and bromo propenes in dogs have shown that these

compounds are somewhat irritant, but are potent anesthetic agents and do not produce any of the intense biochemical changes which are characteristic of diethyl ether. Histological studies are now in progress in this laboratory in which attempts are being made to demonstrate whether or not the cleavage products of the unsaturated and saturated monohalogenated hydrocarbons, i.e., the aldehydes, alcohols and acids are responsible for tissue damage.

INFLAMMABILITY

Marsh (16) has compiled from the literature the inflammability limits of a number of halogenated saturated and unsaturated compounds. In addition, he has determined these limits for still other compounds. The monohalogenated compounds were found to be inflammable in concentrations which were anesthetic, but the lower limits of inflammability were higher in all cases than those of the parent hydrocarbon or olefin. The lower limits of inflammability were higher for the bromine containing compounds than for the corresponding chlorine derivatives. With an increase in the number of halogen atoms in a molecule, there was a uniform decrease in inflammability.

In-Vivo AND *In-Vitro* HYDROLYSIS

Previously cited chemical studies indicate that compounds of the type R–C=C–X are more stable than the type R–C–C–X. It has been generally assumed that the hydrolysis of halogenated compounds to halogen acid and a hydrocarbon residue explained their potential tissue damaging properties. After the administration of bromoform to rabbits, Binz (17) found an increase in urinary inorganic bromide. Dreser (18) found that rabbits, after exposure to ethyl bromide vapor, excreted large amounts of inorganic bromide in their urine. Henderson (19) has stated that chemical decomposition of such compounds as chloroform, bromoform, ethyl bromide, methylene bromide, trimethylene bromide and ethylene bromide, is the basis of their secondary chronic toxicity to the liver and other tissues. Lucas (20) found a positive correlation between the increase in urinary and tissue bromide and the production of pathological effects after the administration of a number of saturated and unsaturated brominated hydrocarbons to rabbits. Recent experiments (21) demonstrate that there is a correlation between structure and *in-vivo* hydrolysis. Compounds of the type R–C–C–X invariably liberate more inorganic bromide *in-vivo* than

those of the type R–C=C–X or R–C=C.

There is, however, no positive evidence to indicate that halogen acid *per se* can alone be the cause of the damage. Dickens (22) and Michaelis and Schubert (23) have shown that iodoacetic acid may exert its effects on certain enzyme systems by combining with amino or

sulfhydryl groups. Morrison (24) suggests that there may be some possibility of the other mono halogen acetates acting in the same manner. Marsh, in the study of bromo and chloro pentenes, believes that because of the relatively great stability of these compounds, it is conceivable that their tissue damaging properties may be due alone to direct combinations of the same type as seen with the halogenated organic acids. As yet no evidence has been adduced which would give some indication as to the type of combination which occurs. Winter (25) has shown that carbon tetrachloride produces an inhibition in the utilization of fatty acids. It is possible that enzyme systems concerned with the metabolism of fat could also readily be inhibited by such combinations thus resulting in similar types of damage.

SUMMARY

1. The mono-brom and mono-chlor olefins offer possibilities as agents for use in general anesthesia.

2. Compounds containing bromine are more potent anesthetic agents and more acutely toxic than those containing chlorine.

3. Methods by which halogenated hydrocarbons may produce tissue damage are discussed.

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THESES ON ANESTHESIA

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