ANESTHESIA. XLI: THE ANESTHETIC PROPERTIES OF CERTAIN FLUORINATED HYDROCARBONS AND ETHERS * †

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In a survey of the literature relative to the narcotic activity of fluorinated hydrocarbons and ethers it was observed that, in general, the substitution of fluorine for chlorine decreased toxicity and anesthetic activity. This is notably true with respect to the chlorinated and fluorinated methanes (1). Organic fluorinated compounds are used as refrigerants and insecticides, but never for medicinal purposes. Robbins (2) studied extensively the anesthetic properties of saturated and unsaturated fluorinated and mixed halogenated hydrocarbons and ethers of the lower members of the aliphatic series up to C_4. Most of these studies were confined to straight chain hydrocarbons. Struck and Plattner (3) reported that although the saturated fluorinated hydrocarbons such as decafluorobutane and decafluorocyclopentane elicit depression in mice, death ensues later owing to their strong irritating effect.

From a study with unsaturated monobrominated and monochlorinated hydrocarbons as general anesthetic agents, Abreu (4) claimed that those in which the halogen was attached to an unsaturated carbon atom were less irritant, less damaging to tissues, more anesthetic and less acutely toxic. Prior to Simpson's use of chloroform it had been empirically observed that a halogen introduced into a simple hydrocarbon molecule increased its narcotic activity. Chemical investigations revealed that halogenation of a hydrocarbon decreases its flammability, although there is also a concomitant decrease in volatility. Further, it still remains unknown how the pharmacologic activity would be influenced by the steric orientation of different halogen atoms in respect to each other in various mixed halogenated compounds.

With this in mind, we investigated the anesthetic properties of certain unsaturated and saturated fluorinated or mixed halogenated low member hydrocarbons and ethers which have not been studied previously. Our investigation also extends to include some of the branched

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TABLE 1

MIXED HALOGENATED HYDROCARBONS

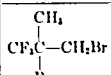
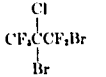
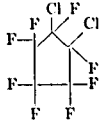
Name	Formula	Animal	Dose or Concentration	Anesthesia	Remarks
			Saturated		
Trifluoro-mono-iodo-methane	CIF_3	1 dog	50%	No	Coughing, choking, retching and convulsion after 30 seconds' inhalation
1,3-dichloro-perfluoro-propane	$CF_2ClCF_2CF_2Cl$	1 dog 1 dog	12 cc. (divided) 10 cc. (divided)	No	Muscular rigidity, tremors of the extremities, slight sedation
1,2,2,3-tetrachloro-perfluoro-propane	$CF_2ClCCl_2CF_2Cl$	1 dog	3.5 cc. (divided)	No	Muscular rigidity, opisthotonus, pulmonary edema, tremors, incoordination, later marked depression; died within 24 hours
2,3-dibromo-1-trifluoro-2-methyl-propane		2 rats	2 cc.	Yes	Postanesthetic analgesia, pulmonary edema, rapid recovery
1,2-dibromo-2-chloro-perfluoro-propane		2 rats	1 cc.	No	Violent respiratory depression and failure, convulsion; both died
1,2-dichloro-perfluoro-cyclo-pentane		2 rats	2 cc.	No	Extreme depression, analgesia, respiratory depression and failure; both died within 18 hours

TABLE 1—*Continued*

Name	Formula	Animal	Dose or Concentration	Anesthesia	Remarks
1,2-dibromo-perfluoro-propane		3 rats	2 cc.	No	Marked salivation, prolonged convulsions lasting until death
	Unsaturated				
1,2-dichloro-perfluoro-propylene-1		4 dogs	Av. 6 cc. (divided)	Yes	Induction quiet, recovery uneventful, like ethyl ether, heart slowed although no fall of blood pressure, E.K.G. changes: inversion of T-wave, bradycardia, prolongation of Q–R interval
2-chloro-perfluoro-propylene		1 dog	75%	No	Marked struggle and gasping, respiratory arrest, revived by artificial respiration
1,1,2-trichloro-3-trifluoro-propylene		1 dog	3.5 cc. (divided)	No	Muscular rigidity, opisthotonos, pulmonary edema, incoordination, marked depression later; died within few hours
2,3-dichloro-perfluoro-butene-2		4 rats	2 cc.	Yes	2 rats had convulsions at the point of anesthesia; all rats had postanesthetic analgesia, died within 18 hours
1,2-dichloro-3-trifluoro-propylene		2 rats	2 cc.	No	Depression, slight analgesia, respiratory depression, failure; one animal could not be revived, the other recovered quickly
1,1-difluoro-perchloro-propylene-2		2 rats 1 rat	2 cc. 3 cc.	No Yes (light)	Depression, analgesia, pulmonary edema, irritation to eyes, convulsions and death within one hour

TABLE 2

FLUORINATED HYDROCARBONS

Name	Formula	Animal	Dose or Concentration	Anesthesia	Remarks
1-methyl-1-trifluoro-methyl-cyclobutane		1 dog	7 cc. (divided)	Yes	Induction rapid and smooth, some extensor rigidity in front legs and some tremors in hind legs, relaxation fair, recovery rapid and uneventful
Trifluoroisobutene	$CF_3C{=}CH_2$ $\vert$ CH_3	3 dogs	75%	Yes	Marked struggle, extensor rigidity, tremors throughout body and extremities, relaxation poor, stertorous respiration, recovery prompt, extreme salivation
Perfluoro-2-butine	$CF_3C{\equiv}CCF_3$	1 dog	75%	No	Animal died within a few hours of pulmonary edema
Perfluoropropylene	$CF_3CF{=}CF_2$	2 dogs	50% 75%	No No	No demonstrable effect; tremors, respiratory irritation
1,1,1-trifluoropropylene	$CF_3CH{=}CH_2$	2 dogs	50%	No	Tremors, incoordination

TABLE 3

FLUORINATED ETHERS

Name	Formula	Animal	Dose or Concentration	Anesthesia	Remarks
Perfluorodiethyl ether	$C_2F_5—O—C_2F_5$	1 dog 2 rats	75% air in jar displaced by compound	No No	No deleterious effects No deleterious effects
Pentafluoropropyl methyl ether	$CF_3CF_2CH_2—O—CH_3$	1 dog 1 dog	6 cc. 10 cc.	No Yes	Labored respiration, cardiac irregularities, slow recovery Extensor rigidity of hind legs, tremors throughout body, respiratory depression, slow recovery
Trifluoroethyl methyl ether	$CF_3CH_2—O—CH_3$	1 dog 1 dog 1 dog	10 cc. 10 cc. 12 cc.	No No Yes	Rigidity of extremities, marked salivation and irritation to mucous membranes Tremors of extremities, marked salivation and irritation to mucous membranes No tremors or rigidity, marked salivation and irritation to mucous membranes
Methyl heptafluorobutyl ether	$CF_3CF_2CF_2CH_2—O—CH_3$	1 rat 1 rat	2 cc. 2 cc.	Yes No	Threatened respiratory arrest, quick recovery Pulmonary edema, deep depression, respiratory failure, convulsions, death
Trifluoroethyl vinyl ether	$CF_3CH_2—O—CH=CH_2$	2 rats 6 dogs	1 cc. av. 5.5 cc. (divided)	Yes Yes	No untoward symptoms Good relaxation, little struggle during induction, rapid recovery, no abnormal changes of E.K.G., average anesthetic index in 4 dogs = 2.5
Pentafluoropropyl vinyl ether	$CF_3CF_2CH_2—O—CH=CH_2$	2 rats	3 cc.	No	Irritation of eyes, peripheral vasodilatation, pulmonary edema, opisthotonus, threatened respiratory collapse, quick recovery

chain isomers, triple bond compounds and certain halogenated cyclo-hydrocarbons.

The results are summarized in tables 1, 2 and 3.

DISCUSSION

An examination of table 1, "Mixed Halogenated Hydrocarbons," indicates that these compounds containing fluorine atoms and other halogens that we studied were not suitable as anesthetic agents. Most of them produced marked respiratory irritation, muscular rigidity and violent incoordinated muscular activity of the extremities.

By unsaturating these mixed substituted halogenated hydrocarbons containing fluorine, anesthetic properties appeared to manifest themselves in certain of the compounds, namely, 1, 2-dichloro-perfluoro-propylene-1 in table 1. This compound elicited anesthetic action, but the changes produced in the myocardium were serious and obviated its possible clinical use.

By the removal of the other halogens from the fluorinated hydrocarbons, anesthetic properties appeared to diminish, and although certain of these agents produced anesthesia, the induction was stormy, accompanied by marked struggle and extensor rigidity.

Our most promising results were obtained by the fluorination of ethers, as shown in table 3. Four out of six of these compounds exhibited anesthetic properties. Most amazing to us was the fact that perfluorodiethyl ether was completely devoid of any pharmacologic effect, even in concentrations of 75 per cent.

The best responses obtained in this series were those elicited by trifluoroethyl vinyl ether, the analogue of which we studied some years ago (5) as an anesthetic agent. As shown in table 3, this substance has promise as an anesthetic agent and it is our plan to study further the possibilities of this partially fluorinated unsaturated ether as a volatile anesthetic agent. It is of interest to note that the flammability of this compound is not as marked as that of its nonfluorinated analogue, for it burns quietly with a sooty flame.

SUMMARY

Our studies with certain mixed halogenated and fluorinated hydrocarbons indicate that these compounds offer little promise as volatile anesthetics.

Our studies with partially fluorinated ethers reveal that trifluoroethyl vinyl ether gives promise of being a useful anesthetic agent.

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PRELIMINARY PROGRAM

1953 ANNUAL MEETING

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

OLYMPIC HOTEL, SEATTLE, WASHINGTON

October 5-9, 1953

WEDNESDAY, OCTOBER 7, 1953

MORNING: GENERAL SCIENTIFIC SESSION:

Controlled Induced Hypotension—Donald E. Hale, M.D.

Clinical Appraisal of Hypotensive Anesthesia—Paul H. Lorhan, M.D.

Studies Concerning the Prolongation of Activity of Succinylcholine—H. Jennings Hampton, M.D., David M. Little, Jr., M.D., and William H. Chaffee, M.D.

Co_2 Homeostasis During Anesthesia—E. S. Brown, M.D., and James O. Elam, M.D.

Cardiac Rhythm and Endotracheal Intubation: A Clarification—J. S. Denson, M.D., and S. I. Joseph, M.D.

Some Observations of the Use of Nitrous Oxide, Oxygen, and Trichlorethylene in Dental Anesthesia—Robert Patrick Bergner, M.D., Richard M. Herd, D.D.S., Charles E. Hutton, D.D.S., Kenneth K. Kline, D.D.S., and Duard Lawrence, D.M.D.

A Biochemical Study of Benzimidazole in Relation to its Clinical Use for Muscle Relaxation—O. F. Denstedt, Ph.D., Esau Hosein, Ph.D., and Harold R. Griffith, M.D.

Postoperative Anesthesiology—Curtis W. Caine, M.D.

AFTERNOON: GENERAL SCIENTIFIC SESSION:

Supplementation of Nitrous Oxide Anesthesia With Opiates and a New Opiate Antagonist—William Hamilton, M.D., and Stuart C. Cullen, M.D.

Our Method of Selective Antalgic Block for the Therapy of Intractable Pain—A. M. Dogliotti, M.D.

Some Anesthesia Problems in a Southern City Hospital—Mary F. Poe, M.D.

Animal and Clinical Studies in the Use of Pyribenzamine for Regional and Spinal Analgesia—W. K. Nowill, M.D., C. R. Stephen, M.D., and R. C. Martin, M.D.

Effect of Azotemia Upon Intravenous Barbiturate Anesthesia—R. E. Richards, M.D., and J. W. Dundee, M.D.

(Continued on page 489)