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ANESTHESIA. X. THE IRRITATIVE ACTION OF VOLATILE ANESTHETICS ON THE MUCOUS MEMBRANES AND THE RELATIONSHIP BETWEEN POTENCY AND CHEMICAL CONSTITUTION * †

JOHN C. KRANTZ, JR., PH.D., C. JELLEFF CARR, PH.D., AND WILLIAM E. EVANS, JR., PH.D.

Baltimore, Md.

In this laboratory a new chemical reaction was developed that made it possible to produce hybrid molecules between cyclopropane and aliphatic hydrocarbons (1). As each of these substances elicits anesthetic properties in laboratory animals and man, the availability of these additional compounds made it possible to study two important anesthetic properties of the compounds, namely, irritation and potency, and to relate these in turn to chemical constitution.

METHODS

The potency of these anesthetic agents was studied by measuring the partial pressure in the inspired air required to anesthetize 100 per cent of a population of mice and also by measuring the volume per kilogram required to produce surgical anesthesia in the dog when the agent is administered under standardized conditions (1). Oil-in-water coefficient and the reciprocal of the water solubility have been found to be indicative of relative potency (2). The irritation produced by vapors was studied by the method so frequently employed by the late Dr. Karl Connell. The method consists of filling an Erlenmeyer flask with the desired concentration of the anesthetic vapor and holding the orifice of the flask tightly against the skin around the orbit for definite time periods. The lids are blinked to provide for intimate contact of the vapor with the conjunctiva. The degree of irritation experienced by the subject and the degrees of hyperemia or chemosis produced are noted by another individual. Many of the data herein recorded were determined by Dr. Connell just before his death.

Discussion.—Our observations with the compounds of this series confirm the pharmacologic dictum which holds with a dependability that seldom wavers, namely, that unsaturated hydrocarbon groups confer a greater potency on compounds of this series than do saturated residues.

* From the Department of Pharmacology, School of Medicine, University of Maryland, Baltimore, Md.

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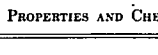
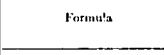
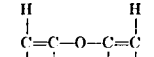
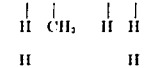
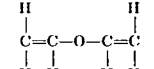
TABLE 1

ANESTHETIC PROPERTIES AND CHEMICAL CONSTITUTION

No.	Name	Chemical Name	Formula	Degree of Irritation*	O/W Coefficient†	I/W Solubility‡	cc./Kg. Induction§ Dog	LD50 Mouse
1	Propethylene	Isopropenyl vinyl oxide		+	86	2.5	0.38	2.5
2	Vinethene	Divinyl oxide		+	41	1.0	0.39	2.5
3	Cyprethylene	Cyclopropyl vinyl oxide		++	67	1.3	0.33	6
4	Ethyl ether	Diethyl oxide	$C_2H_5—O—C_2H_5$	+++	4	0.12	1.0	3
5	Cyprome	Cyclopropyl methyl oxide		++++	6.7	0.14	0.65	4
6	unnamed	Propenyl ethyl oxide	$CH_2.CH_2{:}CH—O—C_2H_5$	++++++	—	2.0	0.45	6
7	Cypreth	Cyclopropyl ethyl oxide		+++++++	16	0.36	0.39	6

* Degree of irritation as measured on the human conjunctiva.

† Oil/water coefficient, the classical figure found in the literature or determined in this laboratory.

‡ I/W solubility is the reciprocal of the water solubility, the cubic centimeter soluble in 100 cc. of water divided into unity.

§ Number of cubic centimeters per kilogram which was required to produce surgical anesthesia when the anesthetic was administered by the technic described by us (1).

Considering the cyclopropyl radical as representing an intermediate degree of unsaturation between a 2-membered ring and a saturated group, we have observed that the cyclopropyl residue is more potent than a saturated chain hydrocarbon, but quite indistinguishable in potency from an unsaturated chain.

It appears again difficult in this series of anesthetics to correlate, except in a very general way, a definite relationship between physical properties and potency. However, the generality of high oil/water coefficient and high potency is evident from the data in table 1. Likewise this same parallelism exists between potency and the reciprocal of the

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water solubility (cubic centimeters soluble in 100 cc. of water divided into unity).

There appears to exist also an interesting relationship between the degree of saturation of the hydrocarbon residue and the irritation of the vapors of the ether containing it. Thus, in this series of ethers, one observes that the unsaturation of the hydrocarbon radicals, with respect to the carbon atom attached to oxygen, favors the blandness of the vapors. However, the 3-membered cyclopropyl residue is inclined to confer irritating properties upon the vapors of ethers containing it. This is exemplified by the fact that the vapors of isopropenyl methyl ether (3) are less irritating than those of its isomer, cyclopropyl methyl ether. However, the inexplicable fact remains that the third isomer of cyclopropyl methyl ether, namely, allyl methyl ether, with the double bond between the second and third carbon atoms, is the most irritating of all of these ethers studied (4).

In this series, those compounds with a degree of irritation above plus are not available as anesthetic agents for man. We confirmed this repeatedly with cypreth (5).

SUMMARY AND CONCLUSIONS

1. An attempt has been made to evaluate the relative capacity of the vapors of several anesthetic agents to irritate human mucous membranes.

2. The relationship between structure, physical properties and potency has been pointed out in a series of new and old volatile anesthetics.

REFERENCES

1. Krantz, J. C., Jr.; Carr, C. J.; Forman, S. E., and Evans, W. E., Jr.: Anesthesia. I. The Anesthetic Action of Cyclopropyl Methyl Ether, J. Pharmacol. & Exper. Therap. 69: 207–220 (July) 1940.
2. Cone, N. M.; Forman, S. E., and Krantz, J. C., Jr.: Relationship between Anesthetic Potency and Physical Properties, Proc. Soc. Exper. Biol. & Med. 48: 461–463 (Nov.) 1941.
3. Krantz, J. C., Jr.; Carr, C. J.; Evans, W. E., Jr., and Forman, S. E.: Anesthesia. VII. The Anesthetic Action of Isopropenyl Methyl Ether, J. Pharmacol. & Exper. Therap. 78: 115–119 (June) 1943.
4. Krantz, J. C., Jr.; Carr, C. J.; Forman, S. E., and Harne, W. G.: Anesthesia. III. The Pharmacology of Methyl Allyl Ether, J. Pharmacol. & Exper. Therap. 71: 126–137 (Feb.) 1941.
5. Kilborn, M. G.; Forman, S. E.; Evans, W. E., Jr., and Krantz, J. C., Jr.: Anesthesia. VI. Studies with Cyclopropyl Ethyl Ether (Cypreth Ether) in Man, Anesthesiology 3: 415–417 (July) 1942.

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