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The Anesthetic Properties of Certain Unsaturated Ethers.

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From a general consideration of the chemo-pharmacological properties of di-ethyl ether and ethylene, especially in regard to their marked anesthetic power and relatively low toxicity, it seemed possible to predict that compounds combining the chemical characteristics of each would be interesting general anesthetic agents. This prediction might be made more specific by further reference to the theory of the relationship between chemical constitution and pharmacological action. In certain homologous series of absorbable aliphatic compounds (as the monohydric alcohols) toxicity increases (without a comparable increase in *desired* activity), in proportion to the number of carbon atoms in the straight carbon chain. Also related to chemical structure in such a series are certain anesthetically important physical properties, such as boiling points. So, one might venture to anticipate that the higher members of our proposed homologous series of unsaturated ethers would not be found as satisfactory inhalation anesthetic substances as the lower members of the series, because of too high boiling points and too great toxicity.

Through the kindness of Professor Sigmund Fraenkel of Vienna, we obtained vinyl-ethyl ether, allyl-ethyl ether, and di-allyl ether, and through the courtesy of Professor Lauder Jones of Princeton, we secured from Doctor Randolph Major di-vinyl ether, vinyl-ethyl ether, and isopropenyl-ethyl ether. These agents are all volatile colorless liquids with odors varying from the rather pleasant aromatic vapor of di-vinyl ether to the pungent irritation of the allyl compounds. Unfortunately only small quantities of these substances could be supplied (none in excess of 12 cc.), so that only tentative determinations could be made of their partition coefficients and of their action on inhalation in mice.

The partition coefficients (between olive oil and water at 20°C.) of these unsaturated ethers in equimolecular concentrations was estimated, in comparison with ordinary ether, by gravimetric methods, after 15 minutes shaking in small separatory funnels, and after several days standing. The figures obtained by this method were approximated, in the case of substances with relatively low boiling points, by a volumetric technique employing the Van Slyke volu-

TABLE I.
Physico-chemical properties of some unsaturated ethers in comparison with di-ethyl ether.

Substance	Formula	Molecular Weight	Boiling Point	Partition Coefficient, Oil : Water, at 20°C.
Di-ethyl ether	$CH_3—CH_2\diagdown O\diagup CH_2—CH_3$	74	34.5°C.	2.3±0.1
Vinyl-ethyl ether	$CH_2=CH\diagdown O\diagup CH_2—CH_3$	72	34-36°C.	0.5±0.1
Di-vinyl ether	$CH_2=CH\diagdown O\diagup CH=CH_2$	70	36-39°C.	2.5±0.2
Allyl-ethyl ether	$CH_2=CH—CH_2\diagdown O\diagup CH_2—CH_3$	86	68-74°C.	2.0 †
Isopropenyl-ethyl ether	$CH_2=C(CH_3)\diagdown O\diagup CH_2—CH_3$	86	59-63°C.	0.61±0.1
Di-allyl ether	$CH_2=CH—CH_2\diagdown O\diagup CH_2—CH=CH_2$	98	92-98°C.	2.0 †

metric gas apparatus. Our tentative and averaged estimations appear in Table I. The figures given for allyl-ethyl ether and di-allyl ether are not satisfactory because only a single determination was possible. With vinyl-ethyl ether, di-vinyl ether, and isopropenyl-ethyl ether, 3 gravimetric estimations were made and averaged, while 10 gravimetric determinations were made and averaged for di-ethyl ether. Di-vinyl ether alone of the unsaturated ethers studied seems to have a slightly higher partition coefficient than di-ethyl ether. Isopropenyl-ethyl ether, the forked chain isomer of allyl-ethyl ether, seems to have a much lower partition coefficient. We were surprised to find such a low partition coefficient for vinyl-ethyl ether. But if anesthetic power is proportional to partition coefficient, di-vinyl ether might be predicted to be the best anesthetic agent of the series.

In attempting to evaluate the anesthetic action of these compounds, we used mice for economy of material. As a standard we used 2 cc. di-ethyl ether allowed to evaporate completely in a 4 liter jar. This yields a molecular concentration of 0.0048 mols per liter of air. The other agents were measured in such amounts as to give equimolecular concentrations on evaporation in their respective containers. With care taken to avoid any asphyxial complications, individual fresh mice were placed in the containers and watched. Observations were made of respiration, general reactions, especially

such as might indicate irritation, the length of time required to anesthetize, and the period required for recovery after removal from the chamber.

TABLE II.
Average anesthetic effects on mice of equimolecular concentrations of certain unsaturated ethers in comparison with di-ethyl ether.

Substance	Average time for induction of anesthesia in seconds	Average time for recovery from anesthesia in seconds	Irritation of respiratory mucous membranes	Number of mice used
Di-ethyl ether	98	85	+	15
Vinyl-ethyl ether	440	1140	+++	4
Di-vinyl ether	60	80	0	3
Allyl-ethyl ether	182	104	+++	6†
Isopropenyl-ethyl ether	195	380	++	3
Di-allyl ether	288	160	++++	6*

† One died in convulsions 1 hour after recovery from the anesthesia.
* Four died in convulsions within 4 hours after recovery from the anesthesia.

Our experimental observations on mice are summarized in Table II. Every available anesthetic brand of di-ethyl ether seemed to cause some irritation. Di-vinyl ether, however, appeared free from irritating effect in the concentration used. The other unsaturated ethers were all much more irritating to the mucous membranes of the eyes and respiratory tract than was ordinary ether. Di-vinyl ether not only anesthetized more promptly than did di-ethyl ether in the same concentration, but recovery on removal from the chamber was also more rapid. The other unsaturated ethers were, however, much slower than di-ethyl ether in causing anesthesia and recovery was more prolonged. Vinyl-ethyl ether was surprisingly weak in anesthetic power at the concentration used, although this conformed to its low partition coefficient. The prolonged recovery period required for this compound is difficult to explain. Isopropenyl-ethyl ether was also weak in anesthetic action at the concentration employed, again as suggested by its relatively low partition coefficient. Allyl-ethyl ether, the straight chain isomer of isopropenyl-ethyl ether, while a more powerful anesthetic, began to display the predicted greater toxicity of the higher members of the series. In di-allyl ether this toxicity was even more marked, again as was to be expected. Respiration was not greatly altered by the anesthetic concentrations of di-vinyl ether or of di-ethyl ether, but was made very slow and laborious by the other compounds.

In this series of unsaturated ethers a fair degree of correlation seems to exist between their partition coefficients, as we have tentatively estimated them, and their anesthetic power in equimolecular

concentration as judged by the time period required to anesthetize. Except for vinyl-ethyl ether, the general relationship between chemical constitution and pharmacological action, as we could predict from present theory, seems to hold. Since the vinyl-ethyl ether used by us was from two independent sources and was found to have the same properties, to account for its marked failure to conform to theoretical behavior is difficult. At any rate, further study of this interesting series of agents is justified and is cordially invited.

Summary. Of a series of unsaturated ethers, including vinyl-ethyl ether, di-vinyl ether, allyl-ethyl ether, and its isomer isopropenyl-ethyl ether, and di-allyl ether, only di-vinyl ether was found to have a partition coefficient and anesthetic properties on inhalation in equimolecular concentrations in mice approaching or superior to di-ethyl ether. A close correlation was found between the tentative partition coefficients and anesthetic powers of these unsaturated ethers. With the exception of vinyl-ethyl ether, these compounds conformed in general behavior to what was predicted of them on the basis of present theoretical conceptions of the relationship between chemical constitution and pharmacological action.

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Effect of Oxidation-Reduction Potential on Some Enzymic Reactions.

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During the last decade great progress has been made in the study of the intensity factor in oxidation-reduction equilibria. The investigations of Mansfield Clark and others have made possible the quantitative determination of this factor both *in vitro* and *in vivo*.

It has been known for a long time that the activity of the several enzymes essential in life processes is conditioned by a variety of factors, such as temperature, the nature and concentration of electrolytes (notably the hydrogen ion concentration), the dilution of enzyme and of substrate, irradiation.[1, 2, 3, 4, 5, 6, 7, 8, 9] It seems prob-

[1] Compton, A., *Proc. Roy. Soc.*, 1921, **92B**, 1.

[2] Compton, A., *Ann. de l'inst. Pasteur*, 1916, **30**, 497.

[3] Kawakami, T., *J. Pharm. Soc. Japan*, 1929, **49**, 346.

[4] Kita, G., *Mem. Coll. Eng. Kyoto Imperial Univ.*, 1918, **21**, 5.