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THE COMPARATIVE ANESTHETIC ACTIVITY OF THE ALIPHATIC ETHERS * §

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SINCE the original discovery of the anesthetic activity of ethyl ether by Cordus in 1542 (1) only a few of the aliphatic ethers have been investigated. As early as 1867, Richardson (2, 3) had employed dimethyl ether as an anesthetic twenty-seven times in man and had carried out preliminary experiments with methyl ethyl ether. Although Amiot (4) tried eight of the then forty-five known compounds in man and Brown (5, 6) used ethyl propyl ether extensively, none of these agents is currently used clinically. Leake's (7, 8) success in predicting and later proving the utility of divinyl ether has led Krantz and his co-workers (9–15) to investigate some mixed ethers, but no comprehensive study of the entire field has been undertaken. We have determined the anesthetic activity of all the commonly available ethers of from two to ten total carbon atoms.

SOURCE OF COMPOUNDS

The compounds investigated with some common physical properties are listed in table 1, according to increasing molecular weight with isomers of the same molecular weight listed according to increasing boiling point. We are grateful to Dr. J. C. Krantz, Jr. of the University of Maryland for compounds 4, 5, 8, and 9 and to Dr. Randolph T. Major of Merck and Co., Inc., for compound 3. Compounds 1, 2, 7, 13, 15, 16, 22, 23, 29, 30, and 31 were purchased on the open market. The remaining compounds were synthesized in this laboratory by the method of Bennett and Philip (16). All ethers were purified by their procedure and freshly distilled just prior to use. Their method was used to determine the solubility in water.

METHOD

The method used for determining anesthetic activity is similar to the one employed by Knoefel (17) and Führer (18). In accordance

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§ This paper is based on data included in the thesis "Biochemorphology of Inhalation Anesthesia" of David F. Marsh for the Ph.D. degree at the University of California. Part of the data in this paper was summarized in Federation Proceedings 1: 159 (March) 1942.

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TABLE 1

Ether	Molecular Weight	Boiling Point °C. at 760 mm. Hg.	Vapor pressure at 25 C. in mm. Hg.	Specific Gravity at 20 C.	Solubility in Water Weight Per Cent at 25 C.	Anesthetic Concentration 50%	Anesthetic Concentration 95–99%	Lethal Concentration 1–5%	Lethal Concentration 50%	Therapeutic Index	Certain Safety Factor
1. Dimethyl	46.05	−23.5	>760	—		14	20	35	37	2.6	1.7
2. Methyl ethyl	60.06	7.9	>760	0.73		6	9	14	18	3.0	1.8
3. Divinyl	70.05	28.3	684	0.77	0.78	1.5	1.75	3.7	4.7	3.1	2.1
4. Ethyl vinyl	72.06	35.5	500	0.76	0.6	1.5	1.75	3.5	4.5	3.0	2.0
5. Methyl cyclopropyl	72.06	44	410	0.78	5.1	1.4	1.75	1.4	1.75	1.25	—
6. Methyl isopropyl	74.08	32.5	550	0.74	6.7	2.0	2.5	4.0	5.5	2.75	1.6
7. Diethyl	74.08	34.5	537	0.71	6.3	1.75	2.0	4.0	6	3.4	2.0
8. Methyl propyl	74.08	37	500	0.78	3.25	1.25	1.5	3.0	3.5	2.8	2.0
9. Ethyl cyclopropyl	86.08	68	150	0.78	2.0	0.8	1.0	0.8	1.0	1.25	—
10. Ethyl isopropyl	88.09	53.5	250	0.72	2.4	1.0	1.3	2.0	2.5	2.5	1.5
11. Methyl ter-butyl	88.09	55.2	244	0.74	5.16	1.0	1.2	1.5	1.6	1.6	1.25
12. Methyl sec-butyl	88.09	58	230	0.74	1.10	0.9	1.1	1.5	1.6	1.8	1.4
13. Methyl isobutyl	88.09	60	210	0.74	1.60	1.0	1.1	1.5	1.6	1.6	1.4
14. Ethyl propyl	88.09	61.4	185	0.73	1.87	0.8	1.0	2.0	2.5	3.1	2.0
15. Methyl butyl	88.09	70.3	160	0.74	0.89	0.7	0.8	1.5	2.0	2.9	1.9
16. Di isopropyl	102.11	67.5	170	0.73	0.93	0.7	0.8	1.2	1.5	2.1	1.5
17. Ethyl ter-butyl	102.11	72.8	155	0.74		0.7	0.8	1.0	1.2	1.7	1.25
18. Ethyl sec-butyl	102.11	81.2	98	0.74		0.6	0.7	1.2	1.4	2.3	1.7
19. Ethyl isobutyl	102.11	81.1	98	0.75		0.6	0.7	1.2	1.5	2.5	1.7
20. Propyl isopropyl	102.11	83	85	0.75	0.67	0.55	0.65	1.25	1.5	3.0	1.9
21. Methyl amyl	102.11	88.5	55	0.75		0.4	0.5	1.0	1.3	3.2	2.0
22. Dipropyl	102.11	90.1	60	0.74		0.4	0.5	1.2	1.6	4.0	2.4
23. Ethyl butyl	102.11	91.4	52	0.75		0.5	0.6	1.2	1.5	3.0	2.0
24. Ethyl ter-amyl	116.12	101.0	43	0.77		0.4	0.5	0.5	0.7	1.75	1.0
25. Ethyl isoamyl	116.12	112	30	0.76		0.35	0.45	0.8	1.0	2.8	1.8
26. Ethyl amyl	116.12	119.5	18	0.76		0.35	0.45	0.9*	1.0*	2.8	2.0
27. Di sec-butyl	130.14	121	17	0.76		0.35	0.45	0.8*	1.0*	2.8	1.8
28. Di isobutyl	130.14	122.5	15	0.76		0.5	0.6	1.0*	1.2*	2.4	1.7
29. Dibutyl	130.14	142.4	—	0.77	<0.01	0.4*	0.5*	1.0*	1.3*	3.2	2.0
30. Di isoamyl	158.17	172.5	—	0.78		Not anesthetic					
31. Diamyl	158.17	187.5	—	0.77		Not anesthetic					

* Chamber and contents must be heated to 35 C. for this concentration to be volatilized.

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with the suggestions of Clark (19) recommending dosage in terms of molecules of drug versus numbers of cells affected, all results are given in terms of millimoles per liter of atmosphere that produce a stated effect in a population of animals. This terminology is in agreement with that of earlier workers (7, 8, 17, 18). Millimoles per liter can be roughly converted to "percentage in atmosphere" at ordinary conditions by multiplying by 2.42 (exact for 20 C. and 750 mm. of mercury).

White mice, weight 18 to 24 Gm., were used for the experimental animals since they are available in large numbers, are convenient to handle and keep, are highly inbred and uniform, and the general physiologic responses to anesthesia can be observed with not too great difficulty. The relative concentrations of ethyl ether and vinyl ether that produce anesthesia and respiratory arrest in mice compare favorably with those quoted for man (20).

Twenty liter, wide-mouth, Pyrex jars were flushed out with oxygen and stoppered. A measured quantity of anesthetic agent was introduced and after volatilization had taken place, 4 mice were placed in the jar. The jar was rotated by hand once every thirty seconds for fifteen minutes. Using these conditions, the mice have approximately 2.5 liters of atmosphere available per kilogram of body weight per minute. Any mouse that was unable to right itself for thirty seconds after being rolled on its back was considered anesthetized, and any mouse that developed respiratory collapse and did not recover on exposure to air after the jar was opened was considered dead. No preanesthetic medication was used and no attempt was made at resuscitation after removing the mice from the jar. The experiments were repeated until the quantity of ether was found that would anesthetize 9 to 11 animals out of a total of 20 (AC_{50}), anesthetize 19 of 20 (AC_{95-99}), kill one (LC_{1-5}), and kill 9 to 11 out of 20 (LC_{50}). The dimethyl ether and methyl ethyl ether atmospheres were prepared with the aid of flow-meters. The volume of liquid needed for the other agents was determined by the formula:

$$\text{Milliliters of liquid} = \frac{\text{Millimoles desired} \times \text{molecular weight} \times \text{volume of flask in liters}}{\textit{Specific gravity} \times 1000.}$$

A total of 3562 mice were used over an eight year period. Check runs on the activity of diethyl ether have been used to confirm the uniformity of the mouse population over this period.

Results

The results are summarized in table 1. The ratio of LC_{50}/AC_{50} is given as the therapeutic index and LC_{1-5}/AC_{95-99} as the certain safety factor (21). In general, as the molecular weight or molecular size increases, the potency or activity increases since it requires less agent

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to produce anesthesia in a given percentage of the experimental population. With compounds that have the same total number of carbon atoms or the same molecular weight, the isomers which have the longest possible straight chains or the highest boiling points are the most potent. For example, methyl butyl ether ($CH_3—O—CH_2CH_2CH_2CH_3$) is more active than methyl isobutyl ($CH_3—O—CH_2CH(CH_3)_2$) or methyl secondary butyl ether ($CH_3—O—CH(CH_3)CH_2CH_3$) and these are more active than methyl tertiary butyl ether ($CH_3—O—C(CH_3)_3$). Similarly, the long-chain, high-boiling dipropyl ether is almost twice as active as the compact, low-boiling di-isopropyl ether. The rather close relationship between physical properties and relative anesthetic potency is illustrated in charts 1 and 2. The concentration to produce anesthesia in half an experimental population plotted versus the boiling points of the compounds yields a smooth parabola in chart 1. A similar curve can be plotted for vapor pressure at 25 C. and anesthetic potency. In chart 2, there is a reasonably good fit for the data relating

CHART 1

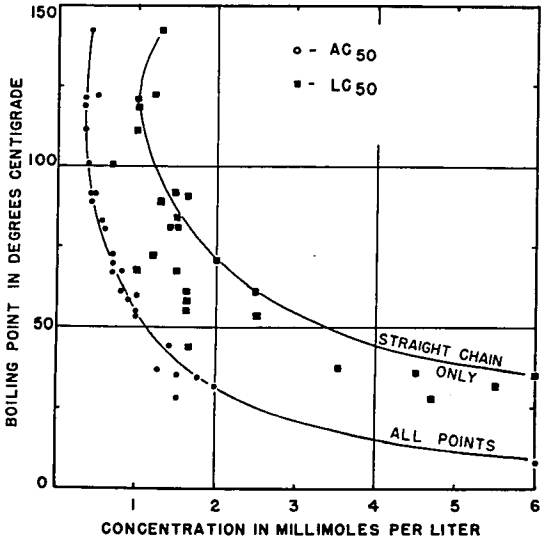

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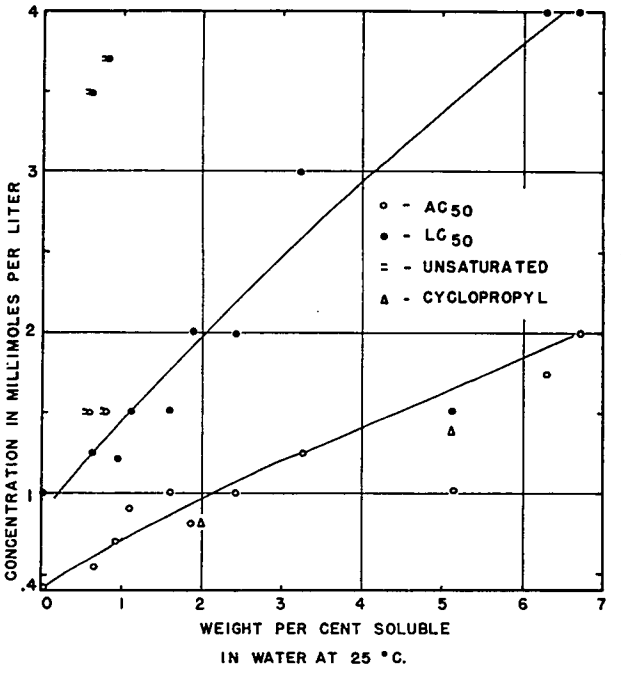
CHART 2



water solubility and anesthetic activity, although the two unsaturated compounds investigated do not fall very near the curve. Perhaps a better correlation would be obtained if the solubilities of the ethers were obtained at 37 instead of 25 degrees.

In general, as the molecular weight increases the toxicity of the compounds also increases, although the relationships are not parallel to those for anesthetic activity. It may be observed in the higher molecular weight groups that isomers of the same molecular weight all require about the same concentration to produce respiratory arrest, although the asymmetric and branched chain compounds are usually more toxic. Compounds 16 through 23 all have the same molecular weight and all require about the same concentration to kill half a given population. In the lower molecular weight groups, the branched chain compounds of the same molecular weight are more toxic. In chart 1

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this is indicated by the lack of correlation between boiling point and toxicity, although it is possible to draw a smooth curve through the ethers that have only straight chains. With the exception of the unsaturated ethers, there is a fairly good relationship between water solubility and toxicity (chart 2). The lack of parallelism of anesthetic activity and toxicity is emphasized by the figures for therapeutic index and certain safety factor, with the higher boiling, straight chain isomers in a given group of ethers having a much greater margin between the concentration that produces anesthesia and that which produces respiratory arrest. For example, the dipropyl ether and ethyl butyl ether have much greater safety factors than the isomeric di-isopropyl ether and ethyl tertiary butyl ether (2.4 and 2.0 versus 1.5 and 1.25). The branch chain compounds and the cyclopropyl ethers are more irritating to the mucous membranes of the mice and produce more salivation; undoubtedly this contributes to the respiratory difficulty.

Ethyl amyl ether, di-secondary butyl ether, and di-isobutyl ether do not have sufficient volatility at room temperature to produce respiratory arrest in the fifteen minute exposure period. If the container is heated in a water bath at 35 C. before adding the agent, sufficient material can be volatilized to produce death. Similarly, the container must be warmed before dibutyl ether is even anesthetic, and the two ten carbon atom ethers investigated were not anesthetic nor lethal although the container was warmed.

Dimethyl ether produces running movements in the mice and induction of anesthesia is very prolonged even at the higher concentrations. The higher boiling compounds appear to produce anesthesia more rapidly than do the lower boiling compounds, although the compounds with boiling points above 100 C. were slower in induction than those with boiling points in the 60 to 90 range. The introduction of unsaturation (divinyl ether and ethyl vinyl ether) causes a slight increase in activity but the rate of onset of anesthesia is increased markedly. Whether or not this relationship between saturated and unsaturated compounds would be true for more complex compounds remains to be demonstrated.

Although the therapeutic index of several of these agents is between 3 and 4, indicating that it requires three to four times as much agent to kill half the population as it does to anesthetize half the population, the certain safety factor is only slightly greater than 2 for the best agents, indicating that it requires only slightly greater than twice the concentration to kill the first individual that it requires to anesthetize all of them.

DISCUSSION

Cone, Forman and Krantz (22) have suggested, as did Richet (23), that anesthetic potency and water solubility can be correlated. Similarly, plotting the boiling point, vapor pressure, and other physical properties versus the anesthetic concentrations or lethal concentra-

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tions often yields smooth curves. Many workers have made similar observations of the general relationship between physical characteristics and anesthetic activity (18). It is questionable that one should imply that the anesthetic activity is dependent on any of these physical properties, any more than it would be reasonable to imply that the physical properties were a function of the anesthetic activity; both are functions of the atomic architecture of the molecule. At present we have no definite knowledge how these molecules interfere with the functioning of the enzyme systems of the central nervous system and thus bring about anesthesia. It is certainly true that they are highly fat-soluble, poorly water-soluble and chemically inert substances and must act more by a physical than a chemical means. The question arises that the limiting anesthetic activities that are measured and are related to the various physical properties may be primarily a function of transport from the lung to the central nervous system rather than the ultimate effect in the central nervous system. Obviously, this is of only minor practical significance since this type of anesthetic agent is given by inhalation and the primary limiting system becomes the most important since it controls the usefulness of any given agent.

The narrow spread of safety factor of the entire group of agents and the general progression of activity with increasing numbers of carbon atoms in the molecule are further indications that the activity of the ethers as anesthetics is a relatively nonspecific physical phenomenon rather than a highly specific chemical phenomenon as is observed with such substances as the vitamins and hormones.

It is seldom possible to apply data obtained in mice to clinical use in man. However, many of the observations with this type of anesthetic in the mouse are quantitatively similar to those obtained in man; it is possible that this is one of the few types of bio-assay that may yield data directly useful for man. For example: the relative anesthetic concentrations for diethyl ether, divinyl ether, and propyl ethyl ether are very similar in man and mouse; agents that are irritant to the mouse, such as cyclopropyl methyl ether and isopropyl methyl ether are irritant to man (9, 14); and agents that produce running movements in mice are only moderately relaxant in man. One can tentatively conclude that this type of mouse assay can be employed with considerable confidence that the data obtained will be useful in man; however, further careful investigation in other species is always indicated as an additional safety factor before an agent becomes available for clinical investigation.

Examination of the results indicates that several of the agents investigated have safety factors as good as those of diethyl ether and divinyl ether. Choice of any given agent for anesthesia would depend on other considerations: high boiling ethers might have promise in tropical areas or even in temperate areas since the higher flash point would diminish the inflammability-explosibility hazard; the more rapid

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induction possible might be desirable. It must be pointed out, however, that the actual volume of agent required with the higher boiling, more potent compounds to carry an anesthetized individual to respiratory collapse is much less. Although the ratio between anesthetic and lethal concentration remains similar to that for diethyl ether, an error of a few drops with diethyl ether is of little importance but with the more potent ethers an error of the same actual volume becomes serious. Only extensive clinical investigation could indicate that a change from the widely used ethyl ether is indicated.

SUMMARY

A series of 31 aliphatic ethers containing two to ten carbon atoms have been investigated as inhalation anesthetics in white mice.

The relationship between physical properties such as boiling point, vapor pressure, and water solubility, and anesthetic activity has been pointed out.

Several compounds, including ethyl vinyl, methyl propyl, ethyl propyl, methyl amyl, dipropyl, ethyl butyl, and ethyl amyl ether, have safety factors of the same order as diethyl ether and divinyl ether. These agents are more potent and more rapidly acting than diethyl ether and might be more useful in general anesthesia in man.

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