ANESTHETIC PROPERTIES OF THE OLEFINE HYDROCARBONS, ETHYLENE, PROPYLENE, BUTYLENE AND AMYLENE.*

BY LLOYD K. RIGGS.

In view of the great numbers of new drugs that have, within recent decades, been introduced into nearly every field of medicine, it is very surprising that, previous to 1923, a period of some sixty years had elapsed during which no new general anesthetic, applicable by inhalation, was introduced which gained any very general recognition by the medical profession. In 1923 Luckhardt and Carter[1] reported experiments carried out at the University of Chicago, which showed that ethylene ($H_2C = CH_2$) gas possesses marked anesthetic properties and that it may be safely applied in surgical operations on animals and man. In the same year Brown[2] working in the University of Toronto reported the anesthetic action of ethylene on laboratory animals. These preliminary announcements have been actively followed by many investigators and clinicians, until now, ethylene is in use as a general anesthetic in many hospitals, clinics, and in the offices of many dentists. There can be no doubt, as shown by Luckhardt and Carter, but that ethylene is a more potent anesthetic than nitrous oxide. It, however, appears to be quite true that relaxation obtained with ethylene is generally less complete, than that obtained with ether or with chloroform.

Prior to the above quoted observations ethylene was known to possess anesthetic properties.[3] It is, however, quite certain that the early workers with ethylene not only failed to appreciate its value, but were quite generally in error in their observations. For example: Richardson[4] (1885), states that 10% to 15% concentrations of ethylene in air produce anesthesia, while it is now well known that ethylene is far from effective in such concentrations.

Propylene ($H_3C.HC:CH_2$), the olefine hydrocarbon next higher than ethylene, resembles ethylene in that it possesses anesthetic properties. That propylene is a more potent anesthetic than ethylene has been shown by a number of observers. Meyer and Hopff,[5] report that 50% propylene and 50% air induces anesthesia in white mice in eight minutes. Halsey, Reynolds and Cook[6] report that propylene is "three times as powerful an anesthetic agent as ethylene." Brown,[7] working on cats, found that anesthesia is induced by 37% to 50% propylene.

Butylene, the olefine hydrocarbon next higher than propylene, occurs in three isomeric modifications, *viz.*, ethyl-ethylene $H_3C\text{-}CH_2CH = CH_2$ (b. p. $-5°$), sym.

---

* Scientific Section, A. PH. A., Buffalo meeting, 1924.

[1] Luckhardt and Carter, *J. A. M. A.*, 80, 765 (March 17, 1923).

[2] Brown, *Canadian M. A. J.*, March, 1923.

[3] Review of early literature of the subject is found in paper by Luckhardt and Carter and Lewis, "Clinical Experiences with Ethylene Oxygen Anesthesia," *J. A. M. A.*, Vol. 81, p. 1851.

[4] Richardson, *Scientific American Supplement*, No. 515, p. 8227, Nov. 14, 1885.

[5] Meyer and Hopff, *Hoppe Seylers Zeitschrift für Physiologische Chemie*, Vol. 126, p. 281 (1923).

[6] Halsey Reynolds and Cook, *New Orleans Medical and Surgical Journal*, July, 1924.

[7] Brown, *Journal of Pharmacology and Experimental Therap.*, July, 1924.

dimethyl-ethylene $H_3C\text{-}CH = CH\text{-}CH_3$ (b. p. $+1°$) and unsym. dimethyl-ethylene $(CH_3)_2\,CH = CH_2$ (b. p. $-6°$). We have not found in our admitedly incomplete survey of the literature any references to the physiologic action of these hydrocarbons, but in view of the fact that other olefine hydrocarbons possess such well-defined anesthetic properties, such physiologic action could be surely predicted for butylene.

The next higher member of the olefine series is amylene which occurs in six isomeric modifications as follows: (1) α-amylene ($H_3C.H_2C.H_2C.HC:CH_2$), b. p. $+39°$; (2) α-isoamylene $(H_3C)_2.CH.HC:CH_2$), b. p. $+21°$; (3) β-amylene ($H_3C.H_2C.HC:CH_2.CH_3$), b. p. $+36°$; (4) γ-amylene $H_3C.\begin{matrix}H_2C\\H_3C\end{matrix}\!\!>\!C:CH_2$, b. p. $+31°$; (5) β-isoamylene ($(H_3C)_2.C:CH.CH_3$), b. p. $+36°$; (6) Tetramethyl-ethylene ($(H_3C)_2.C:C.(CH_3)_2$), b. p. $+73°$.

Amylene, probably isoamylene,[1] was introduced into medical practice by John Snow[2] in 1885 and is characterized by May[3] as resembling chloroform in its narcotic action. Foy[4] states that the condition of insensibility produced by the inhalation of amylene vapor is less persistant than that produced by chloroform, and that muscular spasms are likely to occur under its influence. Richardson[5] considers the anesthetic value of amylene as doubtful on account of the "short but sharp second or spasmodic stage" of anesthesia and because amylene apparently "caused two deaths in 238 administrations."

In striking contrast with the pronounced nervous symptoms or excitement stage produced by amylene, is the absence of excitement stage of ethylene anesthesia in some individuals and its mild character in others.[1]

In view of the information thus briefly outlined, it appeared important that a comparative study of the physiologic properties of various unsaturated hydrocarbons be undertaken. In order to make these studies as strictly comparable as possible it is necessary to have hydrocarbons of high and known purity and also large numbers of standard animals. The pure materials were supplied through the coöperation of Dr. Paul Giesy, Dr. W. E. Tapley and Mr. A. E. Remick of the Brooklyn Research Laboratories of E. R. Squibb & Sons. These chemists supplied propylene, butylene, and amylene of better than 99% purity. The animals chosen were white rats (100 to 150 Gms. weight) of pure strain and great uniformity, supplied by Mr. E. V. B. Douredoure of Germantown, Pa.

Ethylene, propylene and butylene are gases at ordinary room temperatures and the method employed in a study of their physiologic properties was to make mixtures of these gases with oxygen and nitrogen in various proportions in spirometers. The gas mixture of the spirometer was then analyzed and corrected to a desired composition. A wide-mouthed bottle of about five liters capacity, used as a respiration chamber, was then filled, by displacing water with gas from the spirometer, and after an experimental animal had been quickly introduced into the bottle,

---

[1] "Richter's Organic Chemistry," Vol. 1, p. 92 (1899).

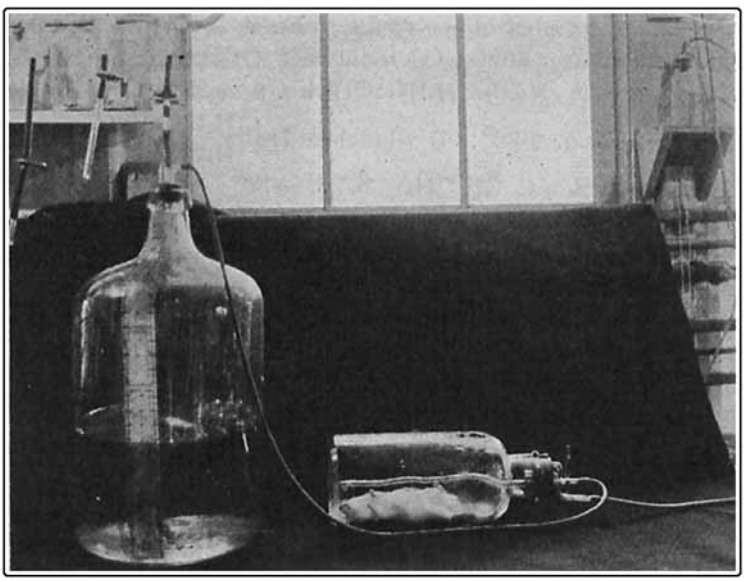
[2] Snow, *Medical Times and Gazette*, Vol. 14, p. 60, et. seg. (1857).

[3] May, "The Chemistry of Synthetic Drugs," London, 1921.

[4] Foy, "Anesthetics Ancient and Modern," London, 1889.

[5] Richardson, *Scientific American Supplement*, No. 515, p. 8227, Nov. 14, 1885.

it was closed with a tightly fitting rubber stopper, equipped with a gas inlet tube extending nearly to the bottom of the bottle and an outlet tube passing just through the stopper. A flow of gas from the spirometer was continued during the experiment. A manometer was also connected with the respiration chamber and atmospheric pressure maintained therein. (See illustration.)



Amylene is an extremely volatile liquid boiling at 37° C., hence the above method was not easily applicable and experiments with this hydrocarbon were carried out by placing an animal in a large-mouthed bottle (5 liters) filled with air. This bottle was then closed with a tightly fitting rubber stopper through which passed a manometer tube and a short glass tube the inside end of which was covered with a rubber diaphragm. A known quantity of amylene was then taken up in a calibrated luer syringe (both syringe and amylene cooled to 15° C.) and the needle forced through the diaphragm. A known quantity of amylene was thus introduced into the bottle without loss. The concentration of amylene in the bottle could then be calculated from the known volume of the bottle and the amount of amylene introduced and also from the temperature and increase of pressure recorded by the manometer. Calculations by these two methods checked within $^1/_4\%$ volume of amylene gas in the bottle.

The behavior of animals exposed to various concentrations of the several hydrocarbons could then be observed.

In arranging and carrying out our experiments we have had especially in mind the establishment of the following bits of information.

1. The symptoms produced in experimental animals by the inhalation of each of the first four hydrocarbons of the olefine series.

2. A quantitative comparison of the anesthetic potencies of these hydrocarbons.

3. The toxic action of each hydrocarbon.

ETHYLENE.

The physiologic action of ethylene is so well known that the experiments which we have carried out were merely for purposes of comparison with the less well-known hydrocarbons. We have confirmed the findings of Luckhardt and Carter[1] that white rats are anesthetized in about 20 minutes by a gas mixture consisting of 90% ethylene and 10% oxygen, and that no excitement stage or at most, only very slight nervous symptoms accompany the induction of anesthesia with this gas mixture. It may be well to point out that the anesthesia induced in white rats by 90% ethylene is very light, *i. e.*, relaxation is incomplete. Animals exposed to a mixture of 95% ethylene and 5% oxygen are deeply anesthetized within a few seconds and are fairly well relaxed. Continued exposure to a gas mixture containing 95% ethylene and only 5% oxygen quickly produces a marked cyanosis and depression. It is, however, impossible from our experiments to say just how much of the obvious toxic action of this gas mixture is due to the effect of ethylene and how much is due to oxygen privation.

PROPYLENE.

When a rat is introduced into a gas mixture of 60% propylene, 25% oxygen and 15% nitrogen the following series of symptoms are noted. The animal very quickly becomes incoördinate. This condition becomes rapidly more pronounced until the animal is unable to stand and make purposeful movements, the wink reflex is retained and the muscle tone is normal or slightly above normal. In this condition the animal surely feels no pain, for it does not respond to such stimuli as clipping off pieces of its tail. It is indeed, in a distinctly analgesic condition, which deepens on continued exposure to the propylene gas mixture, into a profound, rather well relaxed surgical anesthesia. The absence of excitement stage or marked nervous symptoms during the induction of propylene anesthesia is just as marked as in the case of anesthesia induced by ethylene. Propylene is obviously a more potent anesthetic than is ethylene.

In order to compare accurately the anesthetic potencies of two such gases as ethylene and propylene it is necessary to take into account the concentration of the gas tested, the time of exposure, the animals used and a definite easily recognized physiological condition to which reference may be made. The action of 90% ethylene has been chosen as a standard of comparison. This concentration of ethylene with 10% oxygen at 18° to 20° C. and 760 mm. pressure produces light anesthesia in a white rat (100 to 150 grams) in 18 to 22 minutes. A concentration of propylene which mixed with 10% oxygen produces the same physiologic state within the same time may then be said to be of equal anesthetic potency, and if the potency of ethylene be taken as unity, the potencies of ethylene and propylene may then be expressed as the ratio of their equally effective concentrations.

A considerable number of experiments with various concentrations of propylene are summarized in the following table. For purposes of comparison the action of 90% ethylene is described in the first space of this table.

[1] Luckhardt and Carter, *J. A. M. A.*, 80, 765 (March 17, 1923)

TABLE I.

Gas mixture.	Anesthetic properties.	Toxicity.
Ethylene 90% Oxygen 10%	Light anesthesia in 18 to 20 minutes. No excitement stage or hyperexcitability	No toxic symptoms within three hours exposure.
Ethylene 95% Oxygen 5%	Deep anesthesia within 1 minute, well relaxed.	Marked cyanosis and depression.
Propylene 40% Oxygen 25% Nitrogen 35%	Light anesthesia within 15 to 20 minutes. No excitement stage or hyperexcitability.	No toxic symptoms within six hours exposure.
Propylene 40% Oxygen 10% Nitrogen 50%	Light anesthesia within 15 to 20 minutes. No excitement stage or hyperexcitability.	No toxic symptoms within three hours exposure.
Propylene 55% Oxygen 25% Nitrogen 20%	Deep anesthesia in 3 to 6 minutes. No excitement stage or hyperexcitability.	No toxic symptoms. Animals anesthetized for 7.5 hours recover within 2 minutes and show no bad after effects.
Propylene 65% Oxygen 25% Nitrogen 10%	Deep anesthesia in 2 to 5 minutes. No hyperexcitability.	Respiration rate gradually slowed. Respiratory failure after about two hours exposure.
Propylene 70% Oxygen 25% Nitrogen 5%	Deep anesthesia in 1 to 3 minutes. No hyperexcitability.	Respiratory failure in 20 to 25 minutes. Heart action strong.

Reference to the above table indicates that propylene in a concentration of 40%, with either 10% or 25% oxygen, almost exactly duplicates the physiologic properties of 90% ethylene. The two gases, in these concentrations, may then be said to be of equivalent anesthetic potency or the potency of propylene is related to the potency of ethylene as 40 is to 90, *i. e.*, $\frac{90}{40} = 2.25$. The anesthetic potency of propylene is thus shown to be 2.25, when refered to the potency of ethylene as unity.

It is interesting to note that the quantitative relationship between the potencies of ethylene and propylene is apparently (within narrow limits at least), independent of the oxygen content of the gas mixture. This is being investigated.

It will also be noted from Table I that, if a rat (100 to 150 grams) is exposed to a 70% concentration of propylene mixed with 25% oxygen and 5% nitrogen, death due to respiratory failure occurs in about twenty minutes. Death in this case is evidently due to toxic action of propylene on the respiratory center and is not complicated by the factor of oxygen starvation.

BUTYLENE.

The next member of the olefine hydrocarbons studied was butylene made from normal butyl alcohol and hence probably either ethyl-ethylene $H_3C\text{-}CH\text{-}CH = CH_2$ or dimethyl-ethylene $H_3C\text{-}CH = CH\text{-}CH_3$ or a mixture of these two butylenes.

Animals were exposed to various concentrations of butylene, and the observations made, are recorded in the following table, Table II.

TABLE II.

Gas mixture.		Anesthetic properties.	Toxicity.
Butylene Oxygen Nitrogen	15% 25% 60%	Confusion and incoördination only. Marked nervous hyperexcitability.	Very obvious disturbance of nervous mechanism of the animals but no bad after effects.
Butylene Oxygen Nitrogen	20% 25% 55%	Deep anesthesia in 8 to 15 minutes. Definite nervous hyperexcitability.	Respiratory failure after about two hours exposure.
Butylene Oxygen Nitrogen	30% 25% 45%	Very deep anesthesia in 2 to 4 minutes. Nervous hyperexcitability of brief duration.	Respiratory failure after about forty minutes exposure.
Butylene Oxygen Nitrogen	40% 25% 35%	Profound anesthesia in about $^1/_2$ minute. No nervous symptoms observed. Respiration slowed and weakened.	Respiratory failure after 10 to 15 minutes exposure.

It will be noted from Table II that butylene differs from both ethylene and propylene in that the induction of anesthesia by butylene is accompanied by a marked excitement stage, which is shown by marked nervous symptoms, jerking, twitching, spastic contractions of the leg and back muscles and a general heightened response to various external stimuli, such as a sudden rap on the table or respiratory chamber which will cause a sharp contraction of the muscles of an animal which is lightly anesthetized and beginning to slowly relax into the surgical stage of anesthesia.

It may also be pointed out from the above table (Table II) that the nervous reactions produced by butylene are best observed when animals are exposed to the lower effective concentrations of butylene. This of course does not mean that the higher concentrations of butylene fail to produce an excitement stage, but probably that the excitement stage produced by higher concentrations of butylene is of such short duration as to be not readily observed. It may be well to note in passing that we have found that the nervous symptoms produced by any anesthetic may, quite generally, be best observed in animals which are exposed to a minimum effective concentration of the anesthetic.

Butylene does produce a true, fairly well relaxed anesthesia. A concentration of 20% being effective in 10 to 20 minutes. Butylene at 20% is therefore approximately equivalent, in spite of the qualitative differences in its action, to 40% propylene and 90% ethylene. The anesthetic potency of butylene may then be expressed: $\frac{90}{20} = 4.5$, *i. e.*, butylene is 4.5 times as potent an anesthetic as is ethylene.

When animals are exposed to higher concentrations of butylene say 40% butylene mixed with 25% oxygen and 35% nitrogen, death occurs in about twelve minutes. The death mechanism of butylene is apparently respiratory failure, although the heart action appears to be extremely weak at the time that respiratory failure occurs. This contrasts strongly with the fact that heart action appears to be usually quite strong when respiratory failure induced by propylene occurs. A toxic action of butylene on the heart as well as the respiratory center is thus suggested, although further study of the problem is necessary.

AMYLENE.

Isoamyl alcohol was used in the preparation of our amylene which boiled at 35–37° C. and had a specific gravity of 0.655 $(\frac{15}{4})$. The material analyzed 99.6% pure, by the bromine absorbtion method. No further tests for identity were carried out, but the material is probably nearly all β-isoamylene.

Animals were exposed to various concentrations of amylene and the results obtained are recorded in the following table.

TABLE III.—AMYLENE.

Gas mixture.	Anesthetic properties.	Toxicity.
Amylene 5.44% in Air	Incoördination only. Marked hyperexcitability.	No marked toxic symptoms.
Amylene 5.78% in Air.	Light anesthesia in about 20 minutes. Marked nervous hyperexcitability.	Animals are easily thrown into convulsions.
Amylene 6.12% in Air.	Deep anesthesia in 6 to 15 minutes. Marked nervous hyperexcitability.	Respiratory failure after about one hour's exposure. Death in convulsions may, however, intervene within 30 to 45 minutes.

Reference to this table indicates that the physiologic properties of amylene are more like those of butylene than like the properties of propylene and ethylene. The excitement stage produced by amylene is still more marked than that produced by butylene. Some individuals were so markedly hyperexcitable that a sudden rap on the table or respiratory chamber was a sufficient stimulus to throw a lightly anesthetized animal into convulsions, which in two of some two hundred amylene anesthesias terminated in death. This is of course far from being the usual death mechanism for amylene. Long exposure to even moderate concentrations of amylene produces respiratory failure and heart action at the time of respiratory failure is very feeble, in many instances it indeed appears that the heart and respiratory center fail almost simultaneously.

The toxic action of amylene appears to be quite similar to that of butylene except that amylene is more powerful in its toxic actions and appears more definitely, to act on the heart.

In spite of the nervous symptoms produced, fairly well relaxed anesthesia is produced in white rats by 15 to 20 minute exposure to 6% amylene in air. This concentration of amylene is therefore equivalent to 90% ethylene, 40% propylene and 20% butylene. The anesthetic potency of amylene may therefore be expressed by the ratio $\frac{90}{6} = 15.0$. Amylene is fifteen times as potent an anesthetic as is ethylene.

It is apparent from the preceeding data, that the anesthetic potencies of the first four members of the olefine series of hydrocarbons, increases concomittantly with an increase of molecular weight. A similar relationship between the toxicity and molecular weight of alcohols of the paraffin series (Richardson's Law), was announced by Richardson,[1] 1869, and has since been studied by numerous investi-

[1] Richardson, *Medical Times and Gazette*, Vol. 2, p. 705 (1869).

gaters, notably Macht[1] who has summarized previous work on the subject and pointed out that the iso alcohols are less toxic than the normal alcohols. Macht's figures for the toxicity of alcohols are as follows: ethyl 1, propyl 2.5, isopropyl 2.0, butyl 16.6, isobutyl 5.5, amyl 33.2 and isoamyl 19.2. Evidence has been presented above, which indicates that there is an increase of the toxicity as well as the anesthetic potency of the olefine hydrocarbons, with the molecular weight. Only the potencies of the olefines have, however, been related quantitatively and we have no evidence that potency and toxicity are identical functions of the molecular weight. Nevertheless, it is of interest to note that the increase of toxicity of alcohols with their molecular weight, is of the same order as the increase of potency observed for the olefines. It is, of course, quite probable that considerable differences might be observed in the properties of the various isomeric butylenes and amylenes.

Aside from ethylene, propylene is the only olefine studied which apparently deserves further consideration as an anesthetic agent. Both butylene and amylene are more potent than ethylene and propylene, but the nervous symptoms which they induce probably excludes them from consideration. The fact that propylene causes slight, if any, nervous symptoms and is more potent than ethylene, so that it may be administered together with larger amounts of oxygen, seems to favor the introduction of propylene.

It should, however, be noted that none of the hydrocarbons studied produce relaxation comparable to that obtained by ether and chloroform, except when the gas is administered in such concentrations as to produce marked depression.

SUMMARY.

1. The first four hydrocarbons of the olefine series all possess anesthetic properties. Ethylene and propylene cause no marked nervous symptoms or excitement stage. Butylene and amylene produced a marked excitement stage of anesthesia, amylene being more powerful in this respect than butylene.

2. Ethylene 90%, propylene 40%, butylene 20% and amylene 6% induce light anesthesia in white rats (100 to 150 grams) in 15 to 22 minutes and may therefore be said to be of equivalent anesthetic potency. On the basis of the anesthetic potency ethylene as unity, the potencies of the four olefines studied are, ethylene = 1, propylene = 2.25, butylene = 4.5 and amylene = 15.

3. The general mechanism by which the olefines cause death is respiratory failure, *i. e.*, their chief toxic action is on the respiratory center. Butylene and amylene may, however, have an additional toxic action on the heart.

4. Propylene on account of its high anesthetic potency and its failure to cause nervous symptoms is worthy of further consideration as a clinical anesthetic.

The author wishes to express his sincere thanks to Dr. Paul Giesy, Mr. A. E. Remick and Dr. W. E. Tapley for their assistance in the preparation of the hydrocarbons used in these studies; to Mr. Harold D. Goulden and Miss Helen Schipmann for their assistance in the experimental work and to Mr. F. W. Nitardy for numerous helpful suggestions.

RESEARCH LABORATORIES,
E. R. SQUIBB & SONS, NEW BRUNSWICK, N. J.

[1] Macht, *Journal Pharm. and Exp. Ther.*, Vol. XVI, p. 1 (1920).