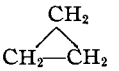
HOMOLOGUES OF CYCLOPROPANE—METHYL CYCLOPROPANE.*,[1]

BY W. A. LOTT, W. G. CHRISTIANSEN AND L. F. SHACKELL.

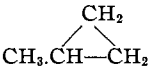
I. PREPARATION OF METHYL CYCLOPROPANE.*

BY W. A. LOTT AND W. G. CHRISTIANSEN.

When it was becoming apparent that despite its somewhat narrow margin of safety, cyclopropane was clinically useful so long as its administration was left in the hands of those familiar with its latent dangers, and when the advisability of supplying it generally was under cautious consideration, it occurred to us that we ought to determine whether homologues of it have any advantages over it for anesthetic purposes. Consideration was given first to the methyl cyclopropanes, the mono- and dimethyl compounds, and experimental work was directed first to the monomethyl cyclopropane which obviously is the one most closely related to cyclopropane. A quantity of it was produced and studied.



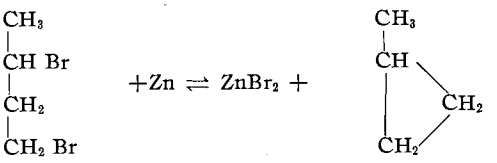
Cyclopropane



Methyl Cyclopropane

It was recognized that if methyl cyclopropane should prove superior to cyclopropane it would have certain additional advantages over cyclopropane due to the fact that its boiling point is 4–5° C. as compared with −34° C. in the case of cyclopropane. This higher boiling point would greatly simplify the liquefaction and packaging procedures; thus, if the liquefaction were to be done by means of pressure much less would be required or if it were to be done at normal pressures much less expensive refrigeration would be necessary. Ice brines for example would be sufficient refrigeration to liquefy methyl cyclopropane at atmospheric pressure. Moreover due to this higher boiling point the container in which it is distributed would not need to withstand more than very moderate pressures and therefore the design and construction of the container could be greatly simplified.

During the spring of 1933 we prepared a quantity of methyl cyclopropane by the reduction of 1,3-dibromobutane with zinc in a medium of 85% alcohol. This was essentially the method of Demjanow (1) excepting, of course, that we modified this method according to the principles already described (2, 3) for the improvement of the yields in reactions of this type, the restraint of side reactions therein and the purification of the gaseous products so that they would be suitable for use as inhalation anesthetics. Thus, in the production of methyl cyclopropane[2] by this reaction,



* Scientific Section, A. PH. A., New York meeting, 1937.

[1] Research Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, New York.

[2] Complete experimental details have previously been described by Lott and Christiansen in the preparation of cyclopropane and propadiene (*loc. cit.*)

the 85% alcohol which was the reaction medium was kept in a vigorous state of agitation during the addition of the zinc dust, and in a vigorous state of ebullition and agitation throughout the gradual addition of the 1,3-dibromobutane. The gaseous methyl cyclopropane was thoroughly scrubbed using activated carbon to remove vapor impurities by adsorption. A yield of 81% of liquefied methyl cyclopropane was obtained by refrigeration and the product characterized by means of the following determinations:

B. p.: 2–5° C., largely 4–5° C.	Recorded 4–5° C.
Molecular weight (Dumas method) 52.2	Theory 56
Assay (H_2SO_4 absorbable): 99.0%	
% isobutylene (bromine titration): 0.68%	

This material was subjected to test as an inhalation anesthetic in monkeys and is compared to cyclopropane from this point of view in the second section of this paper.

At a somewhat later date it occurred to us that we might be able to effect a reduction of the commercially available 1,3-dichloroisobutane with zinc to give methyl cyclopropane.

$$CH_3—CH\begin{matrix}CH_2Cl\\CH_2Cl\end{matrix} + Zn \rightleftharpoons CH_3—CH\begin{matrix}CH_2\\CH_2\end{matrix} + ZnCl_2$$

However, using the same reaction conditions as in the preparation[1] of methyl cyclopropane from 1,3-dibromobutane we obtained practically pure isobutylene. From 900 Gm. of 1,3-dichloroisobutane we obtained 150 Gm. of isobutylene, or 38% of theory. This gas was characterized as isobutylene by means of the following determinations:

B. p.: −6° C. Recorded for isobutylene: −6° C.
Molecular weight: 56. Theory: 56
Absorbable in H_2SO_4 (methyl cyclopropane and isobutylene): 100%
Bromine titration (isobutylene): 98.3%

The product from the dichloroisobutane was further characterized by means of its bromine derivatives.

Merezkosky (4) reported that pure isobutylene reacts with bromine to give a mixture of bromine derivatives of which 62% is isobutylene dibromide and 38% is tribromoisobutane when the temperature is uncontrolled and the reaction mixture allowed to become hot—in the cold the proportion of isobutylene dibromide is considerably larger and the proportion of tribromoisobutane correspondingly smaller. Using the method of Merezkosky we passed 20 liters of our gaseous product through 152 Gm. of bromine dissolved in twice its volume of chloroform in a flask provided with external cooling to maintain the reaction mixture at −15° to −19° C. Only 0.7 liter passed through the bromine unabsorbed. The chloroform solution of the bromine derivatives, after washing and drying, was repeatedly rectified until it was separated into two fractions which were shown to be isobutylene dibromide and tribromoisobutane.

Weight.	Per Cent of Total Brominated Material.	Boiling Point. Found.	Literature.	Specific Gravity at 20° C. Found.	Literature.
124.5 Gm.	84.3%	144–150° C.	147–8° C.*	1.760	1.759*
23.3 Gm.	15.7%	105–112° C/17 mm.	108–9° C/18 mm.**	2.198	2.197**

* Recorded for isobutylene dibromide.
** Recorded for tribromoisobutane.

[1] For experimental details see the papers on Cyclopropane and Propandiene by Lott and Christiansen previously referred to.

Thus we have obtained approximately the same kind and proportion of bromine derivatives with our sample of gas as Merezkosky obtained with his sample of isobutylene under strictly comparable conditions. We therefore can conclude that the gas is practically pure isobutylene containing methyl cyclopropane in an amount ranging from a trace to an upper limit of 1.7%. It should be noted that 1,3-dibromoisobutane in substantially the same reaction is known to give largely methyl cyclopropane (5) contaminated with some isobutylene, *i. e.* the same results as those obtained by using 1,3-dibromo normal butane.

In considering the behavior of the several chloro and bromobutanes it is interesting to recall that under conditions which with 1,3-dibromopropane give high yields of a gas consisting almost entirely of cyclopropane, 1,3-dichloropropane is only slightly reactive, giving a low yield of gas which has a quite considerable propylene content. The results obtained with the several dihalopropanes and dihalobutanes under our experimental conditions are summarized in the following table.

Starting Material.	Total Yield.	Composition of Product. Cyclic.	Olefinic.
1,3-dibromo (*n*) butane	High	99.3	0.7
1,3-dibromo (*iso*) butane	High	Large	Small
1,3-dichloro (*n*) butane	Not investigated		
1,3-dichloro (*iso*) butane		1.7	98.3
1,3-dibromo propane	High	ca 100	Practically none
1,3-dichloro propane	Low	Some	Some

We realize that at the A. C. S. meeting in Florida (Spring of 1934) Hass and McBee reported that cyclopropane can be made satisfactorily and cheaply from 1,3-dichloropropane. Their reaction conditions were not disclosed until the Pittsburgh meeting of the A. C. S. (Fall of 1936) (6). In order to get these results with dichloropropane certain special conditions had to be used. In considering our data on the behavior of the chloro and bromo propanes and butanes it should be kept in mind that special conditions were not used with the chloro compounds; their behavior under conditions giving good yields of the cyclic hydrocarbon from the bromo compounds was determined. Perhaps by means of the special conditions used by Hass, *et al.*, for 1,3-dichloropropane it would be possible to obtain methyl cyclopropane instead of isobutylene from the dichlorobutanes.

Although we would hesitate very much to discuss the mechanism of these differences in rates and direction of reaction on a basis of so little evidence it may not be too venturesome to suggest that there are under the conditions of our reactions two potential changes possible, *viz.* (1) tendency for 1,3-dihalides to change to the more stable isomers, the 1,2-dihalides, and (2) tendency for reduction by removal of two halogens by means of zinc. Furthermore it is known that this loss of two halogens is incurred more rapidly by a 1,2-dihalide than by a 1,3-dihalide, *i. e.*, the formation of propylene from 1,2-dibromopropane is much more rapid than the formation of cyclopropane from 1,3-dibromopropane. Thus it is suggested that the lower total yields of gas, and the higher olefine content obtained from dichlorides is due to the act that the tendency to lose two chlorine atoms is much less than to lose two bromine atoms so that with the chlorine com-

pounds the rearrangement to the 1,2-dihalide followed by loss of two halogens and formation of an olefine proceeds more rapidly than loss of two halogens from the 1,3-dihalide to give a cyclic hydrocarbon. The meager evidence available also suggests that probably the rearrangement of the isobutane 1,3 dihalide to the 1,2-dihalide is more rapid than in the case of the normal butane 1,3-dihalide.[1]

II. Anesthetic Properties of Methyl Cyclopropane.

BY L. F. SHACKELL.

Cyclopropane.—The results of an extended study of cyclopropane anesthesias in monkeys have been published by Shackell and Blumenthal (7). In this study it was found that 17 or 18 per cent of cyclopropane in an anesthetic mixture was sufficient to induce a surgical degree of analgesia with complete muscular relaxation. There was moderate dilatation of the pupils. Salivation was relatively slight. Urine was voided one or more times within an hour after removal of the mask. Consciousness was regained within 1 to 3 minutes after removal of the mask. Heart and respiratory rates in the monkey are depressed by cyclopropane. This was discussed in detail by Shackell and Blumenthal. In Table I have been collected the mean values for heart and respiratory rates of three monkeys which have been used more recently in numerous tests of cyclopropane as well as in the tests of methyl cyclopropane described below. In Table I the highest concentration of cyclopropane for a given monkey would have proved fatal within a few minutes if the mask had not been removed.

Table I.—Mean Values for Heart and Respiratory Rates of Rhesus Monkeys during Anesthesias with Cyclopropane at Various Concentrations.

Cyclopropane %.	Heart Rate.	Respiratory Rate.
	Monkey LH, Female, 4.5 Kg.	
0	196	42
18.7	185	27
22.2	182	26
27.4	183	23
31.8	169	22
	Monkey LS, Female, 5.1 Kg.	
0	199	42
18.2	164	43
22.6	162	41
27.0	161	29
	Monkey RS, Male, 9.7 Kg.	
0	184	40
18.0	145	35
22.7	142	36
26.5	127	29

Anesthesias with cyclopropane are free from the tremors and convulsive seizures that characterize the actions of ethylene and propylene. Repeated

[1] This would be based solely on Faworski's work. It would be interesting to attempt the preparation of methyl cyclopropane from 1,3-dichloro *n*-butane.

anesthesias, even at sublethal concentrations of cyclopropane, apparently cause no damage to the monkey. Three of these animals, more than four years after they were used in the experiments reported by Shackell and Blumenthal, are being subjected to occasional anesthesias in control tests of cyclopropane.

Methyl Cyclopropane.—The three monkeys, LH, LS and RS, referred to in Table I in connection with tests of cyclopropane, were subjected to two anesthesias each with methyl cyclopropane. The first anesthesia in each monkey was at, or somewhat above, the threshold for surgical anesthesia; while the second anesthesia was carried out at increasing concentrations until a sublethal, or at least dangerous, level appeared to have been reached. Following is a summary of the experimental findings:

1. Induction of anesthesia is rapid and is accompanied by relatively little struggling.

2. During induction, and ordinarily after each addition of methyl cyclopropane to the anesthetic mixture, the monkey exhibits involuntary tremors, jerks or generalized convulsive seizures that are strikingly similar to those caused by ethylene and propylene. In contrast with propylene, however, these spasmodic reactions usually persist for only a few minutes. As was pointed out above, such side-effects have not been observed with cyclopropane.

3. The concentrations of methyl cyclopropane and of cyclopropane required to produce complete relaxation appear to be nearly the same, namely, 16 to 18 per cent. The lethal concentrations of the two gases also are nearly the same. The mean lethal concentration of methyl cyclopropane for the three monkeys was 27.7 per cent, while a like value for cyclopropane was 28.4 per cent.

4. It has been shown above that cyclopropane depresses both heart and respiratory rates in the monkey. With methyl cyclopropane the heart rate tends to be slowed; but individual monkeys vary in this respect, especially at different methyl cyclopropane concentrations. The respiratory rate under methyl cyclopropane, however, shows definite acceleration.

Typical data for heart and respiratory rates at different methyl cyclopropane levels are given in Table II.

TABLE II.—MEAN VALUES FOR HEART AND RESPIRATORY RATES OF RHESUS MONKEYS DURING ANESTHESIAS WITH METHYL CYCLOPROPANE AT VARIOUS CONCENTRATIONS.

Methyl Cyclopropane %.	Heart Rate.	Respiratory Rate.
	Monkey LH, Female, 4.5 Kg.	
0	200	34
16.8	185	32
28.4	196	88
	Monkey LS, Female, 5.1 Kg.	
0	205	41
15.8	219	52
22.2	200	67
26.5	253	80
	Monkey RS, Male, 9.7 Kg.	
0	186	34
14.8	163	52
28.2	160	50

5. Salivation is slight with both methyl cyclopropane and cyclopropane. Vomiting has not been observed after either anesthetic.

6. Post-anesthetic depression and loss of appetite appear to be more marked after methyl cyclopropane than after cyclopropane.

SUMMARY.

Methyl cyclopropane has been prepared in a condition of purity suitable for its evaluation as an inhalation anesthetic, by the reduction of 1,3-dibromobutane with zinc. The reduction of 1,3-dichloroisobutane under similar conditions gave almost entirely isobutylene instead of methyl cyclopropane.

Although the effective concentrations as well as the lethal concentrations of methyl cyclopropane and cyclopropane, and hence their margins of safety, are about the same, the methyl cyclopropane does not compare favorably with cyclopropane in a qualitative and quantitative comparison of their several side-effects.

REFERENCES.

(1) Demjanow, *Ber.*, 28, 22 (1895).

(2) Lott and Christiansen, "Preparation of Cyclopropane," JOUR. A. PH. A., 19, 341 (1930).

(3) Lott and Christiansen, "Preparation of Propadiene," *Ibid.*, 20, 207 (1931).

(4) Merezkosky, *J. Russ. Phys.-Chem. Soc.*, 46, 120.

(5) Faworski, *Ann.*, 354, 368.

(6) Hass, McBee, Hinds and Gluesenkamp, *Ind. Eng. Chem.*, 28, 1178 (1936).

(7) Shackell and Blumenthal, *Anesthesia and Analgesia*, 13, 133 (1934).

A PRACTICAL METHOD FOR TESTING NON-PHENOLIC DISINFECTANTS.*[1]

BY WILLIAM C. CLARK.

Jordan (1) defines a disinfectant as a substance that kills the microbes with which it comes into contact. This statement is a very broad and general definition and Reddish (2) clarifies this general statement by asking "What are disinfectants for and why are they used?" and answering "Disinfectants are germicides which are used on inanimate objects for the purpose of killing disease germs which cause epidemiologic diseases. Their primary purpose is to aid in preventing the spread of disease by killing the bacteria which cause them."

Varley (3) recognizes the limitations of the Phenol Coefficient Method and proposes a method for testing disinfectants which are chemically related to Phenol that closely simulates the conditions of use of these disinfectants. His method is adapted to testing odorous disinfectants which may be washed away after a relatively short time. A simpler method was desired for an odorless non-phenolic disinfectant that is recommended for disinfecting floors, woodwork and furniture in the sickroom. Because this disinfectant is colorless and odorless it is not removed from the woodwork by washing, but remains on the wood until the next regular washing of the woodwork.

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* Scientific Section, A. PH. A., New York meeting, 1937.

[1] A contribution from the Bacteriological Laboratory of James F. Ballard, Inc.