ative of cinchophen to the original cinchophen is 0.754. If desired this compound can then be reconverted to cinchophen by treatment with alkali and extracted as directed in Method 1.

TABLE I.—RESULTS OBTAINED BY USING METHODS 1 AND 2.

Method.	Quantity of pure cinchophen taken. Mg.	Quantity of hydrobromide obtained.	Quantity of cinchophen recovered. Mg.
1	100		95.5
			100.0
			99.7
1	200		
			200.2
			200.5
1	500		
			498.3
			498.5
2	100	132.8	101.1
		132.2	99.7
		132.0	99.5
2	200	263.8	198.9
2	500	660.5	498.6

SUMMARY.

Two new methods for the quantitative determination of cinchophen are described. One depends on the extraction of cinchophen as such from an acid solution with an immiscible solvent; the other depends on the conversion of cinchophen to a bromine addition compound of its hydrobromide, which is extracted with ether and determined as the hydrobromide. Data showing results obtained by the respective methods are given.

Determinations by electrometric and indicator methods show that phenol red, brom-thymol blue and cresol red are suitable indicators for the titration of cinchophen.

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FURTHER STUDIES ON THE PHYSIOLOGIC ACTION OF PROPYLENE.*

BY LLOYD K. RIGGS AND HAROLD D. GOULDEN.

At the Buffalo (August 1924) meeting of this association one of us (1) presented a preliminary report of studies on the physiologic action of several hydrocarbons of the olefine series. A later communication (2) reported further studies on the physiologic action of unsaturated hydrocarbons of the acetylene and diene series. Other papers by Riggs and Goulden (3), Halsey and his co-workers (4) and (5) and by Brown (6) reported more detailed studies on the physiologic action of propylene, the only one of the series of hydrocarbons studied, which gave promise of being of any practical value as an anesthetic. It should in this connection be remembered that one of the olefine hydrocarbons ethylene, had pre-

* Scientific Section, A. PH. A., Philadelphia meeting, 1926.

viously, due to the excellent researches of Luckhardt and his co-workers and of Brown, been introduced and gained a considerable popularity as an anesthetic in general and dental surgery. Acetylene has already been introduced into the practice of anesthesia through the researches of Wieland and Gaus in Germany and of the Drs. Goldman in America.

As a preliminary to the studies which we now wish to report a very brief summary of previous findings on propylene should be presented.

Halsey and his co-workers making use of rats, mice, rabbits, etc., Brown making use of cats and Riggs and Goulden making use, very largely, of white rats all reported that propylene was an effective anesthetic in concentrations of 40 to 60 per cent by volume. None of these authors reported either any immediate or delayed toxic action of this hydrocarbon.

It appeared, therefore, that propylene might be with safety tried out in actual surgical practice.

It should be pointed out that in all of these studies only freshly prepared propylene was employed. Later, propylene in sufficient quantities for experimental studies was prepared and distributed to several research workers through the courtesy of E. R. Squibb & Sons of New York.

A group of research workers in New Orleans under the leadership of Prof. Halsey of Tulane University were the first to undertake clinical trials of propylene. These studies were reported in a brief private communication from Prof. Halsey, read before the Philadelphia joint meeting of the Eastern and Western Associations of Anesthetists October 26–30, 1925.

Two cases of appendectomy were reported, one of which was characterized by marked irregularity of the heart which developed toward the end of the period of anesthesia which was maintained for a little over thirty minutes.

An editorial in the February 1926 issue of *Current Researches in Analgesia and Anesthesia* states that "one case, operated on recently under anesthesia with the new gas (propylene) developed very alarming and rather prolonged circulatory collapse seven hours after operation," and issues a general warning to all using propylene experimentally or clinically to watch out for deleterious by-effects on the circulation.

Dr. James Gwathmey of New York reported[1] the use of propylene as an anesthetic in about one hundred short dental operations. No unfavorable heart symptoms were observed by Dr. Gwathmey.

Caine and Reynolds (7) undertook electrocardiographic studies on the action of propylene and other anesthetic gases. They found that non-anesthetic concentrations of propylene (25%) caused ectoptic ventricular beats which promptly disappeared when the concentration of propylene was lowered and that higher concentrations of propylene caused more frequent ectoptic ventricular beats and runs of ventricular tachycardia of longer or shorter duration.

Chapman (8) studied the action of propylene and of ethylene upon isolated turtle and frog hearts. His method was to place the isolated heart *in situ* in bottles containing a small amount of frog Ringer solution and gas mixtures. His

[1] Joint meeting of Eastern and Mid-Western Association of Anesthetists, October 26–30, 1925.

results "indicate that propylene in narcotic dosage is somewhat less depressing to these cold blooded hearts than is ethylene."

In view of the above evidence it appeared to be important that we pursue further our studies on the physiologic action of propylene giving special attention to its action upon the heart. In carrying out these studies it appeared to us that we should study the mechanism of death due to propylene, *i. e.*, we should push propylene anesthesia to the death of the experimental animal watching carefully the time of cessation of respiration and of the heart beat. We had previously found (3) that in white rats respiration failed first and that the heart continued to beat for some time after respiratory failure. We now employ cats, dogs, guinea-pigs and rabbits. While our series of experiments is not extensive our results tend strongly to confirm our previous observations, *viz.*, that the primary toxic action, of propylene is upon the respiratory center and quite secondarily upon the heart. We noted, however, one strikingly exceptional case, a cat in which failure of the heart and the respiratory centers occurred practically simultaneously.

These studies could, of course, have been made much more valuable by the use of an electrocardiograph, but such an instrument was not available. Our results were, however, sufficiently clear cut as to give us a feeling of relative safety in so far as the action of propylene upon the heart is concerned.

In the course of these studies we did, however, note that periods of muscular rigidity occurred in some of our animals. We also noted the occurrence of an occasional clonus which might be elicited by sharply striking one leg of the anesthetized animal, and in some instances either by striking the table upon which the animal was resting, or by lifting the animal (cat) by means of a cord passed into a bell jar under which it was subjected to a flow of the anesthetizing propylene (40–50%), oxygen (20%), nitrogen (30–40%) mixture. These symtoms which we interpreted as being due to a disturbance of the central nervous system were occasionally varied by the occurrence of rhythmic movements of both fore feet as if the animal were creeping or swimming. Occasional general spasticity of the animal occurred. When this occurrence was observed the animal either curled up (white rat and cat) or tossed its head back and became quite rigid (dog).

This spasticity was usually accompanied, or immediately preceded by a marked contraction of the oculomotor muscles which gave the eyes a characteristic appearance (stare), noted when the eyelids were held open. These symtoms usually occurred during the induction stage of anesthesia and disappeared when the concentration of propylene was either increased or diminished markedly.

In these experiments propylene which had been prepared some time previously and stored in a liquid condition in steel cylinders was employed. Such symptoms, did not appear with anything like the same frequency when freshly prepared uncompressed propylene was used.

This observation, taken together with the further observation that more frequent and more nervous symptoms appeared in our animals when the last portions of propylene from a nearly empty cylinder were employed, tends to fix attention upon the necessity for physico-chemical studies of freshly prepared and of stored propylene. Such studies are under way and will be reported at a later date.

In view of the foregoing considerations it appeared quite safe and desirable

to proceed with electrocardiographic studies on the human subject under propylene anesthesia. Such studies required the services of an expert electrocardiographer. We feel that we were especially fortunate in that Dr. Morris H. Kahn the eminent heart specialist of New York City, offered his services in this connection. We wish to express our sincere appreciation not only to Dr. Kahn but also to the Beth Israel Hospital of New York City, the facilities of which institution were made available for this investigation.

The method employed in this investigation was for one of us (L. K. R.) to submit to general anesthesia while the electrocardiograph leads either 2 or 3 were attached. Nine experiments were carried out. Anesthesia was complete in each instance and varied in duration from one to about sixteen minutes.

A detailed report of these studies will be made at a later date by Dr. Kahn. The electrocardiographic effects of propylene shown by the studies may be summarized in Dr. Kahn's words as follows:

A preliminary electrocardiographic study was made before each experiment to ascertain the normal status of the individual. This proved to be entirely normal with a moderate voltage, showing all the waves upright in the three leads, of normal duration and normal time relations.

A comparison of the pulse rate at the beginning of the anesthesia with that when the patient aroused from it shows, in each of the experiments, a very slight reduction in rate varying about 2–10 beats. This takes into consideration, however, the sinus arrhythmia which was fairly marked before the anesthetic was administered. During the progress of the anesthesia, the sinus arrhythmia became less distinct. I would consider this, as is shown by the graph, as a quite definite effect of propylene. In no experiment was there evidence of any sudden change of rate, except that resulting from a change in the amount of sinus arrhythmia.

The pulse rate and its sinus rhythm returned to their previous status within a few minutes after recovery from anesthesia. The character of the waves and the voltage remained unchanged. No aberrant conduction tract was noted in any case, no premature beats and no other form of irregularity.

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ABSTRACT OF DISCUSSION.

In reply to questions, the author stated that studies are under way for the estimation of propylene and various gases in the blood. He had experienced no nausea from administration of propylene. He had with him about 50 electro-cardiographic tracings.

THE INFLUENCE OF DIGITALIS ON THE RESISTANCE OF GUINEA-PIGS TO POISONING BY DIPHTHERIA TOXIN.*

BY CHARLES C. HASKELL.

It has been stated that digitalis is contraindicated in diphtheria and other infections. In the experiments reported on, diphtheria was selected for the tests and it was found that the administration of tincture of digitalis, apparently, does not hasten the death of guinea-pigs that were coincidentally given a dose of diphtheria toxin.

The question of employment of digitalis in the treatment of the acute involvement of the heart which occurs in the course of certain infectious diseases is a cause of dispute among clinicians. A certain number contend that the drug is indicated here; others believe that, instead of being beneficial, in such cases it actually does harm. The discussion has been waged especially in regard to pneumonia, due either to infection with the pneumococcus or to other organisms; but, unfortunately, no positive evidence has been presented in support of either view as to the rôle of the drug in these conditions, although Jamieson has shown that the resistance of cats suffering from experimental pneumonia does not seem to be lowered to the toxic action of ouabain.

In 1919, Bush reported experiments which seemed to show that poisoning by diphtheria toxin increased the susceptibility of frogs and of dogs to the toxic action of digitalis. Two years later, McCulloch pointed out that the changes in the human electrocardiogram encountered in clinical diphtheria strongly resembled the changes produced by the toxic action of digitalis. On the basis of this observation, he contended that digitalis should never be administered to patients suffering from diphtheria.

As a matter of fact, it is rarely, if ever, that the administration of digitalis clinically in diphtheria is considered. However, if it could be clearly demonstrated that the drug acted deleteriously in this form of intoxication, it would suggest the possibility, at least, that it would have an unfavorable influence in those bacterial infections where its use is recommended by competent authorities. Diphtheria toxin is easily administered to animals and its potency is relatively constant from day to day; in these respects, it is decidedly superior to bacterial cultures, where exact dosage is difficult and where the virulence decreases rapidly under conditions of artificial cultivation.

In Bush's experiments, conditions quite unlike those existing clinically were present. His animals were given a single large dose of the toxin and, after 24 or

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* Scientific Section, A. PH. A., Philadelphia meeting, 1926.