

absorption methods and the compression method.

The results of a few of these tests are given in Table II. Under yield is given the quantity of liquid condensed by use of the compressor described above. This figure is to be looked upon as an upper limit. The yield on the large scale will be less than the figure given, owing to leakage, evaporation losses, imperfect cooling, etc. The combustions were made over mercury, using oxygen and a heated platinum spiral. In almost every case the figure for hydrogen is slightly greater than that corresponding to a paraffin of the formula C_nH_{2n+2} . This is undoubtedly due to experimental error, as it is well established that natural gas does not contain free hydrogen. The density of the gas calculated from the empirical formula agrees fairly well with the observed D.

SUMMARY

I. A few simple empirical tests are given whereby the approximate quantity of gasoline obtainable from natural gas can be determined.

II. A small testing compressor is described.

III. Some typical analyses and tests are given.

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THE CHEMISTRY OF ANAESTHETICS, V.: ETHYL CHLORIDE¹

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CHEMICAL HISTORY

Ethyl chloride ("sweet spirit of salt;" *aethylum chloratum*; *aethylis chloridum*; *aether chloratus*; *aether hydrochloricus seu muriaticus*; "hydrochloric ether;" chlorhydric ether; chloro-ethane; mono-chlorethane; chlorethyl; *chloräthyl*; *chlorwasserstoffäther*; *leichter salzäther*; *chlorure d'éthyle*; *ether chlorhydrique*; "chelen" or "chelene;" "kelen" or "kelene;" "anodynone;" "antidolorin;" "ethylol;" "loco-dolor;" etc.) was first obtained in alcoholic solution by Basil Valentine (*pseudo*-).² "Sweet Spirit of Salt" was well known to the later chemists. Glauber, for example, referred to it in 1648.

Ludolff stated, in 1749,³ that on heating alcohol with sulfuric acid and sodium chloride, a distillate was obtained which, when treated with lime, yielded an "ether;" but he endeavored in vain to obtain a similar compound by the action of hydrogen chloride ("muri-

¹ Read at the regular June meeting of the New York Section of the American Chemical Society, 1913.

² He described its preparation thus ("*Wiederholung des grossen Steins der uralten Weisen*," ed. *Petraeus*, p. 72): "This I also say that, when the spirit of common salt unites with spirit of wine, and is distilled three times, it becomes sweet and loses its sharpness." In his *Last Testament* ("*Basilius Valentinus*," ed. *Petraeus*, p. 786) he also says: "Take of good spirit of salt which has been well dephlegmated and contains no watery particles, one part; pour to this, half a part of the best and most concentrated *spiritus vini* which also contains no phlegma or vegetable mercury." Valentinus goes on to state that this mixture must be repeatedly distilled, and then "placed in a well-closed bottle and allowed to stand for a month or until it has all become quite sweet and has lost its acid taste. Thus is the *spiritus salis et vini* prepared and may be readily extracted."

In 1739, Johann Pott demonstrated that "sweet spirit of salt" could be obtained by the action of "butter of arsenic" or "butter of antimony" (arsenic or antimony trichloride) on spirit of wine, and other chemists found that other metallic chlorides might be employed for the same purpose. Rouelle, in 1759, found that ethyl chloride resulted from the action of sulfur chloride, phosphorus pentachloride, aluminum chloride, ferric chloride, stannic chloride, etc., on alcohol.

³ *Die in der Medicin siegende Chemie* Erfurt, 1746-9.

atic gas") on alcohol. Baumé was also unsuccessful in this direction, but Woulfe¹ obtained the preparation in this way, and it was afterwards prepared and sold by an apothecary in Germany under the name of "Basse's hydrochloric ether" (1801).

HISTORY OF ITS USE AS AN ANAESTHETIC

Flourens² drew attention to the anaesthetic properties of ethyl chloride in 1847, and Heyfelder, in the following year, first administered the vapor for surgical purposes. Unsatisfactory symptoms often accompanied its administration at that time, these effects being attributed to imperfections in the manufacture and the consequent presence of impurities. The use of the agent as a general anaesthetic was abandoned until 1895, since which time it has rapidly gained in favor. This is principally attributable to the improved methods of administration, and to an increase in the knowledge of its properties and physiological action; and last, but not least, to improvements in its manufacture.³

Ethyl chloride may be regarded as ethyl alcohol (CH_3CH_2OH), in which the OH has been replaced by Cl, hence the formula CH_3CH_2Cl , which was established by Colin and Robiquet.⁴

"Alcoholic (or 'alcoholized') muriatic ether" is a solution of ethyl chloride in an equal amount of alcohol by volume. It has been used as an internal stimulant in doses of 0.6 to 1.8 cc.

USES

So far ethyl chloride has not been used technically, although Palmer⁵ called attention to its advantages (and disadvantages) as an industrial refrigerating agent. In medicine it is used for (a) general anaesthesia (by inhalation); (b) local anaesthesia (by external application, in effect refrigeration); and (c) diagnostic and therapeutic purposes.

PREPARATION

As noted, ethyl chloride may be regarded as ethyl alcohol (C_2H_5OH), in which the hydroxyl has been replaced by chlorine. Ethyl alcohol is the raw product from which it is usually made, although ethyl chloride results in the regulated chlorination of ethane,⁶ on treating acetic and other ethers with hydrogen chloride, by the action of hydrochloric acid on ether in sealed tubes,⁷ and by the action of chlorine on ethyl iodide. In actual practice, ethyl alcohol is mixed

¹ *Phil. Trans.*, 1767, 520.

² Hewitt, "*Anaesthetics*," 1907, 11.

³ In 1880, a committee of the British Medical Society reported that ethyl chloride was not safe to employ as a general anaesthetic, owing to its liability to produce respiratory failure and convulsions. In 1898, it was stated in *Sajous' Annual*: "We would also warn against its (ethyl chloride) use for the purpose of inducing general anaesthesia, as the dangers incurred therefrom are too great." Interest in its use was revived in the same year, however, by the reports of Lotheisen, and in 1901 by McCardie, who cited a large number of successful cases in general anaesthesia. To quote Dodge [*Boston Med. Surg. J.*, 1909, 234 (February 25)]: "It is believed that the bad results obtained earlier were due partly to impure preparation of the drug, as well as improper methods of administration."

Ware (*J. Am. Med. Assn.*, November 8, 1902) directed attention to the fact that preparations marketed in this country in 1902 contained methyl chloride to facilitate evaporation.

⁴ *Ann. chim. phys.*, [2], 1, 343.

⁵ *Eng. Digest*, 5, 262.

⁶ *Darling, Ann.*, 150, 216; Schorlemmer, *Compt. rend.*, 58, 703.

⁷ Berthelot.

with hydrogen chloride, which acts as a desiccating agent itself,¹ or dehydrating agents, as zinc chloride² or phosphorus pentoxide,³ are added to remove the water produced. If these agents were not added, the reversible reaction would reach an equilibrium. This equilibrium may be avoided by increase of pressure.⁴ It is also manufactured by mixing concentrated sulfuric acid (2 parts) with 96 per cent. alcohol (1 part), and, after standing, diluting with water (1/2 part), adding potassium chloride, and distilling.

IMPURITIES FROM MATERIALS USED

If pure hydrogen chloride is used, there is little danger of impurities being introduced from that source. The quality of the alcohol used, however, is very important. If denatured alcohol, especially if wood alcohol be the denaturant or one of the denaturing substances,⁵ then methyl chloride will likely be produced. This gas (b. p. —23.7° C.), while very soluble in ethyl chloride, may easily be removed by rectification. Aldehydes form compounds with hydrogen chloride. Any acetic acid present is liable to form acetyl chloride, and the higher alcohols, as propyl, butyl and amyl, produce their corresponding halogen derivatives. It is desirable, therefore, to use only absolute alcohol of the highest degree of rectification.

An examination of seven different makes of ethyl chloride obtainable in London in 1905 showed that all the branded samples were pure, as was also one unbranded sample. The report of this investigation⁶ states that ethyl chloride should be free from water, foreign chlorides, acids, aldehydes, ether, alcohol, and organo-metallic substances.

¹ Ethyl chloride may be prepared by distilling ethyl alcohol (5 parts), sulfuric acid (2 parts) and sodium chloride (12 parts) together, or by passing dry hydrogen chloride into absolute alcohol; but it is said that the action of hydrochloric acid upon alcohol gives a poor yield of chloride unless zinc chloride is added to the alcohol before passing in hydrochloric acid [Groves, *J. Chem. Soc.*, **27**, 637 (1874)]. Groves found that when hydrochloric acid gas was passed into a boiling solution of zinc chloride (2 parts) in 95 per cent ethyl alcohol (3 parts), the yield was nearly theoretical. He purified the product by washing with water.

² Kruger (*J. prakt. Chem.*, [2], **14**, 193) recommended that a mixture of one part of zinc chloride in 82 parts of ethyl alcohol should be saturated with hydrochloric acid gas in the cold and then heated to the boiling point. Hydrochloric acid gas being conducted into the mixture during distillation, as the process is carried out, a reflux condenser prevents the alcohol vapor from coming over and the zinc chloride is said to act by abstracting water from the alcohol, the nascent ethylene combining with hydrogen chloride to form ethyl chloride, according to Schorlemmer (*J. Chem. Soc.*, **1875**, 308). On the action of hydrochloric acid on alcohol, alone and in the presence of zinc chloride, see also Robiquet and Colin, *Ann. chim. phys.*, [2], **1**, 343; Regnault, *Ibid.*, [2], **71**, 355; Kuhlmann, *Ann.*, **33**, 108; and Lowig, *Pogg. Ann.*, **45**, 346. On velocity of the reaction, see Kailan, *Monatsh.*, **28**, 559 (1907). The formation of ethyl chloride in this process is partly due to the action of hydrogen chloride upon alcohol and partly to the union of this nascent ethylene with hydrogen chloride.

³ The practice of some American manufacturers is to use phosphorus pentoxide as the dehydrating agent.

⁴ The process of Mennet and Cartier (French Patent 206,574, June 23, 1890) relates to the production of ethyl chloride. An autoclave of 150 liters capacity is used, into which a mixture of 95 kg. of hydrochloric acid (21° Be.) and 34 kg. of 93-95 per cent. ethyl alcohol is maintained at 50 atmospheres pressure and at 130° C. for about 28 hours. The pressure is then diminished to 42 atmospheres and finally the autoclave is cooled. See also Hager's "*Handbuch d. Pharm. Praxis*," **1**, 189 (1910).

⁵ The Commissioner of Internal Revenue ruled in 1907 that the use of alcohol would be allowed tax free in the manufacture of ethyl chloride in accordance with Section 40, Part VI, of the revised regulations, after September 1, 1907, provided the finished product contained no alcohol. The following formula was authorized for use in the manufacture of ethyl chloride: To 100 gallons of ethyl alcohol add 5 gallons of approved wood alcohol.

⁶ *Lancet*, **1905**, ii, 1631.

PURIFICATION

Ethyl chloride is purified¹ by passing the vapor through water, dilute caustic solution and then concentrated sulfuric acid. The treatment is intended to free it from alcohol,² hydrogen chloride,³ and water. Re-distillation is sometimes practised. This rectification serves to remove other alkyl chlorides, the methyl going off in the first fractions of the distillate and the higher compounds remaining in the residue.

PROPERTIES

Ethyl chloride is a colorless mobile liquid at low temperatures and is extremely volatile. It possesses a slightly saccharine taste and a penetrating and pungent, yet fragrant, "ethereal" odor. It is inflammable, burning, when ignited, with a smoky green-edged flame, producing fumes of hydrogen chloride; hence, care must be exercised in using it near an open flame or a hot cautory. It decomposes even when very close to a hot bulb or an incandescent electric light.

Ethyl chloride has a melting point of —142.5° C.; it possesses a boiling point of +12.5° C.,⁴ and its specific gravity is 0.92138 at 0°,⁵ 0.9176 at +8°,⁶ 0.8510 at +12°,⁷ and at +25°⁸ the vapor has a specific gravity of 0.91708. Its vapor density is 2.22.

Water dissolves about one-fiftieth of its weight of ethyl chloride and acquires a sweetish, ethereal taste. Ethyl chloride is readily soluble in ethyl alcohol and ethyl ether, and neither solution should give a reaction with silver nitrate at ordinary temperatures. Ethyl chloride dissolves phosphorus, sulfur, fats, oils, and many resins. It combines with many metallic chlorides—for example, antimony pentachloride and ferric chloride—to form crystalline compounds. It is decomposed at a red heat into ethylene and hydrogen chloride.

STORAGE AND CONTAINERS

Owing to its extreme volatility, ethyl chloride cannot be kept in ordinary bottles, except at a temperature below +10° C., and even then the stopper must be tight-fitting and very well secured, and the bottles should preferably be stored in an inverted position. Ethyl chloride is now supplied on the market in sealed or mechanically capped glass or metal tubes of convenient forms, wherein the ethyl chloride is held under pressure. Automatic closing tubes are preferable for local anaesthesia, and there are at least five different types of these on the American market, each manufacturer using his special form of container. Ethyl chloride is also furnished by certain manufacturers in plain capped tubes.

Containers of ethyl chloride should be kept in a dark, cool place, remote from lights or fire; and no empty tubes should be refilled with a fresh lot of the compound, since such an economy may result in spreading infection.

¹ *Pharm. J.*, [4], **15**, 694.

² Acetyl chloride decomposes into acetic and hydrochloric acids with water.

³ And other bodies forming acids with water.

⁴ Regnault, *Jahresber.*, **1863**, 67.

⁵ Pierre, *Compt. rend.*, **27**, 213. Darling (*Jahresber.*, **21**, 328) found a density of 0.9252 at this temperature.

⁶ Linnemann, *Ann.*, **160**, 195.

⁷ Ramsay, *J. Chem. Soc.*, **35**, 470.

⁸ Perkin, *J. prakt. Chem.*, [2], **31**, 481.

GLASS VS. METAL CONTAINERS

It is maintained by some that ethyl chloride decomposes when exposed to air and sunlight, hence that the drug should be kept in metal containers. It is further claimed that inasmuch as ethyl chloride is inflammable, there is less danger of breaking in accidentally dropping the metal container. In opposition to this, it may be said that in filling any container, no air remains in it on account of the great volatility of ethyl chloride. Furthermore, in drawing off a portion of the contents of a tube, pressure is produced within the tube which is constant for each temperature, it matters not how much liquid ethyl chloride is present, so long as there is some liquid there; hence no backward pressure is created, whereby air may be drawn into the tube. Undoubtedly light facilitates the decomposition of ethyl chloride by oxygen, but the authors have found that light produces no apparent change in pure ethyl chloride when oxygen is absent.¹ Assuming that the ethyl chloride is pure, there is another objection to the use of a metal container, namely,

TABLE I—THE RESULTS OF AN EXAMINATION OF AMERICAN ETHYL CHLORIDES

Sample	Description	Odor (U. S. P. test): sulfur compounds, etc.	Residue (B. P. test)	Reaction with litmus (B. P. and P. H. tests)	Hydrochloric acid (U. S. P. test)	Metallic chlorides	Alcohol (U. S. P. test)
1.....	"Antidolorin," contained in a nickel-plated tube	No foreign or unpleasant odor	None	Negative	Absent	Absent	Absent
2.....	"Gebauer's Ethyl Chlorid C. P." contained in nickel-plated tube	"	"	"	"	"	"
3.....	"Kelene," contained in a colorless glass tube	"	"	"	"	"	"
4.....	"Ethyl Chloride Squibb," contained in colorless glass tube	"	"	"	"	"	"

inability to tell how much of the preparation is within the tube and how much has been or is being used in the anaesthesia. This has been met by having a graduated (3 cc. capacity) dropper made of glass which may be attached to the metal container.

IMPURITIES WHICH MAY DEVELOP IN ETHYL CHLORIDE

Uncertain results have been encountered by several who have used ethyl chloride for general anaesthesia and these have been attributed in some cases to impurities that were present and have been detected chemically.²

The original product must not have been properly purified, for the conditions essential for the decomposition of ethyl chloride itself involve oxygen, and, as animadverted, oxygen has no opportunity to enter the receptacles in which ethyl chloride is dispensed. The presence of small amounts of water may bring about a reverse change in ethyl chloride, with the formation of ethyl alcohol and hydrogen chloride. The latter may readily be detected by spraying some of the drug into a clear silver nitrate solution.

¹ Five samples of "Kelene" and "Ethyl Chloride Squibb," both of which were contained in colorless glass tubes, securely capped, as delivered to the trade, were suspended, at room temperature, inside of a window having direct southern exposure for a period of 21 months, at the end of which time no apparent decomposition had occurred. The exposed samples complied in full with the various pharmacopoeial requirements (see *infra*).

Five samples of "Kelene" and "Ethyl Chloride Squibb" were also exposed, under exactly the same conditions, for a period of 8 months, and the results were the same as above. In samples from which varying amounts of ethyl chloride had been withdrawn, no decomposition occurred for the same periods.

² Hawley, *J. Am. Med. Assn.*, 47, 502 (1906).

DETECTION OF IMPURITIES IN ETHYL CHLORIDE

The impurities likely to occur in ethyl chloride are (a) those which it brings with it from the manufacturer, and (b) those resulting through careless storage. While the exact nature of all these is unknown, yet ethyl chloride complying with the requirements of the pharmacopoeias, as given below, is entirely suitable for the purposes for which it is intended. On account of its volatility, the examination of ethyl chloride presents more difficulties than are encountered in the cases of ethyl ether and chloroform; and it is indeed fortunate that it may be easily prepared in a state of comparative chemical purity.

The *Pharmacopoeia of the United States*¹ prescribes the following tests for purity:

1. "If 10 cc. of ethyl chloride, while cold, be dissolved in alcohol, and a few drops of silver nitrate T. S. be added, no turbidity should be produced (*absence of hydrochloric acid*)."

2. "If 10 cc. of ethyl chloride be agitated with 10 cc. of cold water and the supernatant stratum of

ethyl chloride be evaporated spontaneously, and if a few drops of potassium dichromate T. S. be added to the remaining aqueous liquid, followed by some diluted sulfuric acid, and the mixture be boiled, no odor of aldehyde should be developed, and a greenish or purplish color should not be produced in the liquid (*absence of alcohol*)."

3. "On allowing ethyl chloride to evaporate from clean, odorless blotting paper, which has been saturated with it, no unpleasant odor should remain upon the paper (*absence of sulfur compounds, etc.*)."

The *British Pharmacopoeia* requires that it should leave no residue on evaporation and that an aqueous or alcohol extract should have no acid reaction with blue litmus paper. The *Deutsches Arzneibuch*² requires also that "during evaporation, and thereafter, no garlic odor should be apparent (phosphorus compounds)." The *French Codex*,³ while giving the incorrect specific gravity, states that it should be free from ethyl bromide and iodide. The *Pharmacopoeia Helvetica*⁴ requires that when its vapors are led through water, the water must not give an acid reaction with litmus nor a reaction with silver nitrate.

All the pharmacopoeial tests seek to eliminate acids.

In the opinion of the authors, ethyl chloride intended

¹ 8th Decennial Revision, p. 32.

² 1910, p. 37.

³ 1908, p. 249.

⁴ 1907, p. 27.

for anaesthetic purposes should comply with the following requirements:

1. *Boiling Point*.—Ethyl chloride should possess a boiling point of $+12.5^{\circ}$ C.

2. *Odor*.—On allowing 30 cc. of ethyl chloride to evaporate from a filter paper $12\frac{1}{2}$ cm. in diameter, no foreign or unpleasant odor, especially a garlic odor (indicating phosphorus compounds), should be apparent either during or subsequent to evaporation.

3. *Residue*.—When 60 cc. of ethyl chloride are allowed to evaporate in a platinum dish at room temperature, there should be left no weighable residue.

4. *Alcohol*.—When 10 cc. of ethyl chloride are agitated with 10 cc. of distilled water, both of which are at about 10° C., in a glass stoppered tube, and the supernatant layer of ethyl chloride is allowed to evaporate spontaneously from the opened tube at room temperature, and then 3 drops of potassium dichromate T. S. are added to the remaining water, followed by 5 drops of dilute sulfuric acid, and the mixture is then boiled, no odor of acetaldehyde should be apparent and no greenish or bluish color should be produced in the liquid.

5. *Hydrochloric Acid and Metallic Chlorides*.—On dissolving 10 cc. of ethyl chloride in 10 cc. of 95 per cent alcohol U. S. P., and then adding 3 drops of silver nitrate T. S., no turbidity, even faint, should result, and no precipitate should form.

A simple combination test for the purity of ethyl chloride consists in attaching a 30 cc. ethyl chloride container to a glass tube vial containing 35 cc. of water kept at 40° C. A slow stream of ethyl chloride is passed through the water until the container is emptied, and then 10 cc. of the water are tested with litmus paper, to which it should impart no acid reaction; 10 cc. with silver nitrate T. S., as in *test 5* above; and 10 cc. are finally tested for alcohol as in *test 4* above.

THE PURITY OF THE ETHYL CHLORIDES ON THE AMERICAN MARKET

Recently the authors examined the products of four American manufacturers, in order to ascertain whether the grades in use complied with the requirements of the various pharmacopoeias above cited. The results are presented in Table I. It will be seen that all the samples examined were of official grade. American manufacturers appear to take the necessary simple precautions to guard against the presence of organic impurities.

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A RAPID VOLUMETRIC METHOD FOR DETERMINING *o*-*m*- AND *p*-CRESOLS, THYMOL AND PHENOL

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This method determines by one titration rapidly and accurately:

- A. Ortho-, meta- and para-cresols or phenol.
- B. The meta-cresol in the presence of *o*- and *p*-cresol.
- C. Phenol in the presence of *o*- and *p*-cresol.

D. The meta-cresol, the phenol and the sum of the *o*- and *p*-cresols in any mixture of these compounds.

Three methods have been proposed for determining the cresols separately: (1) gravimetric,¹ weighing the ortho- and para-cresol as the dibrom-cresol-bromide, the meta-cresol as tribrom-cresol-bromide; (2) volumetric,¹ by Koppeschaar's solution, titrating back the unabsorbed bromine; (3) volumetric, by using a solution of iodine² in sodium acetate and titrating back the unabsorbed iodine with thiosulfate. This latter method does not serve for the quantitative determination of *m*-cresol.

A special method has been devised for determining *m*-cresol^{3,4} in the presence of ortho- and para-cresol, by weighing the *m*-cresol as trinitro-*m*-cresol. The *o*- and *p*-cresol are oxidized away by strong nitric acid and trinitro-phenol is soluble if present in small amounts, *i. e.*, up to 10 per cent. The method, therefore, is reliable in the presence of *o*- and *p*-cresol and less than 10 per cent of phenol. H. Ditz⁵ has given the following equations whereby the *m*-cresol present in a mixture consisting only of the three *o*-cresols may be determined

$$x + y = a \quad (1)$$

$$\frac{3\text{Br}.x + 2\text{Br}.y}{108.064} = b \quad (2)$$

x = meta-cresol.

y = *o*- and *p*-cresol.

a = Wt. of mixture of cresols taken.

b = Wt. of Br disappearing.

Br = 79.97 grams.

The same equations will apply to a mixture of the *o*- or *p*-cresols and phenol. The equation (2) is modified for the formula weight of the phenol⁶ as follows:

$$\frac{3\text{Br}.x}{94.048} + \frac{2\text{Br}.y}{108.064} = b \quad (3)$$

x = the amount of phenol in the mixture taken.

Siegfried and Zimmermann⁷ have criticized H. Ditz and Cedivoda's method and have shown that variable results from 2–20 per cent are obtained by brominating the cresols in an acid bromine solution. Their method varies from that of Koppeschaar's for determining phenol, only in the fact that one hour's time is allowed after the KI is added before the thiosulfate is run into the solution. F. Russig and G. Fortmann⁸ have also criticized Ditz and Cedivoda's method adversely. Ditz replied⁹ to their objections and H. Ditz and F. Bardach⁹ have published results at variance with Russig and Fortmann's conclusions.

Recently Pence¹⁰ has shown that Koppeschaar's solution in an acid menstruum will determine quanti-

¹ Ditz and Cedivoda, *Z. angew. Chem.*, **12**, 1873 (1899). Ditz and Bardach, *Biochem. Z.*, **37**, 272 (1911). Siegfried and Zimmermann, *Biochem. Z.*, **29**, 368 (1910).

² Pence, *THIS JOURNAL*, **4**, 518 (1912).

³ F. Raschig, *Z. angew. Chem.*, **13**, 759 (1900).

⁴ F. Russig and G. Fortmann, *Ibid.*, **14**, 157 (1901).

⁵ H. Ditz, *Ibid.*, **13**, 1050 (1900). H. Ditz and F. Bardach, *Biochem. Z.*, **37**, 272 (1911).

⁶ Siegfried and Zimmermann, *Biochem. Z.*, **29**, 368 (1910).

⁷ *Biochem. Z.*, **37**, 272 (1911).

⁸ *Z. angew. Chem.*, **13**, 1050 (1900).

⁹ *Biochem. Z.*, **37**, 272 (1911).

¹⁰ *THIS JOURNAL*, **4**, 518 (1912).