the case serves to indicate a close correlation between the mineral elements of the ash and the chemical changes occurring in the leaf. As is well known, the principal seat of the changes taking place in the life and growth of the plant is in the leaf, and here we find a great concentration of the ash constituents, as compared with the sap. As compared with the leaf, the woody stem of the plant is of slower growth and in a sense at least secondary to it, in order of development. In the stem, therefore, while we find considerable concentration of the ash constituents of the sap, it is by no means as high, in most cases at least, as in the leaf. It will be observed, of course, that the organic matter contained in the stem is nearly as great as that found in the leaf. It should be borne in mind, however, that the greater amount of this represents woody fiber and reserve material which has been translocated from the leaf and hence there has been less concentration of the ash constituents of the sap in the stem than in the leaf, where the organic matters are largely the product of photosynthesis.

It is a matter of common experience that if pruned just before budding and after the sap has begun to flow freely, and especially if much bleeding or loss of sap occur, the grape vine will suffer considerable injury, due to loss of reserve materials, mineral matter and water required for the development of the new growth. Hence the common practice of pruning such vines in the late fall or early spring, before the rise of the sap. All of these considerations, therefore, serve to emphasize the importance of the sap in the life and growth of the plant. The fact that a soil solution is being continually imbibed by the plant roots, while pure water is being driven off in such large amounts from the foliage, with corresponding concentration of the several mineral constituents in the various tissues of the plant, renders a study of the sap, such as we have described above, of great interest to students of plant physiology. We propose therefore to considerably extend the scope of this investigation as soon as the necessary materials can be obtained so as to include in our comparisons, the soil solution, the sap from various portions of the plant and several plant tissues which we have not as yet been able to examin.

[CONTRIBUTION FROM THE HARRIMAN RESEARCH LABORATORY (ROOSEVELT HOSPITAL), NEW YORK CITY.]

# PHENOLPHTHALEIN AND ITS COLORLESS SALTS.[1]

[THIRD PAPER.]

## PREPARATION OF MONOBASIC PHENOLPHTHALATES.

BY P. A. KOBER AND J. THEODORE MARSHALL, with the assistance of E. N. ROSENFELD.

Received May 6, 1912.

*Introduction.*—For many years, until it was disproven by Meyer and

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[1] Read in part before the Section on Organic Chemistry, Eighth International Congress of Applied Chemistry, Sept. 10, 1912, New York City.

Spengler[1] the colored salts of phenolphthalein were generally assumed to be monobasic, and theories of indicators were based on phenolphthalein's functioning as a monobasic acid.

Green and Perkins[2] determined from the titration of the tribasic salts in solution, that the carbinol form could exist as a monobasic salt in solution; but after many attempts they failed to isolate either the monobasic or the tribasic carbinol salts.

Recently we described[3] the isolation and purification of the tribasic salts and it is now our object to describe the preparation and properties of the monobasic salts, and also to discuss certain recent views in relation to the "phenolphthalein problem."

*Discussion.*—In our first paper,[4] after following the fading of phenolphthalein quantitatively, using a colorimeter and an unchangeable standard (special tints),[5] we came to the conclusion "that hydration begins with the smallest amount of alkali." This was shown by the tables giving the total amount of fading with a certain strength of alkali; *i. e.*, in a 0.1 $N$ solution of potassium hydroxide over 90% of the phenolphthalein[6] had lost color with the formation of phthalates, whereas in a 0.125 $N$ solution over 50% of the color had faded.

We are glad to note that about the same time or a little later, Thiel[7] came to a similar conclusion independently, as follows: "Schon in ziemlich schwach alkalischer Lösung ist ein grosser Teil des Salz in Carbinolform vorhanden, wie man aus den Versuchen von Acree und Slagle leicht berechnen kann." We also set up a series of equilibria expressing our views on the behavior of phenolphthalein when dissolving in alkali. Thiel in his paper also gives most of the same equilibria.

We believe the equilibria will help to explain, to a larger extent than the purely chemical theories alone, the various phenomena observed with phenolphthalein and its derivatives. Thiel, however, does not come to any conclusion as to whether the quinoid or the carbinol form is primary. We believe we can dispose of that question, if the law of mass action is accepted as correct.

Gomberg,[8] who is inclined to assume the formation of the colored dibasic salt through the carbinol form, gives the following equation:

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[1] *Ber.*, 41, 2446.

[2] *Proc. Chem. Soc.*, 20, 50.

[3] Kober and Marshall, THIS JOURNAL, 33, 1780.

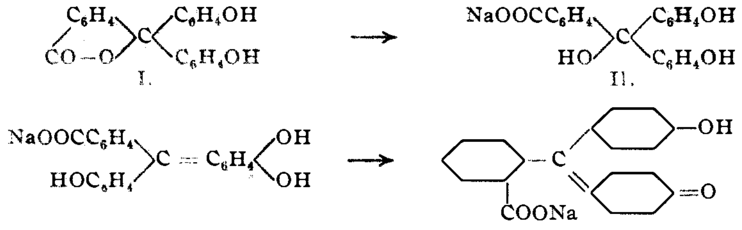
[4] *Ibid.*, 33, 62.

[5] Eimer and Amend, Lovibond tints.

[6] The total amount of phenolphthalein was 0.001258 gram in 100 cc. solution.

[7] Thiel, *Sammlung Chemischer und Chem. Technische Vorträge*, 16, 388.

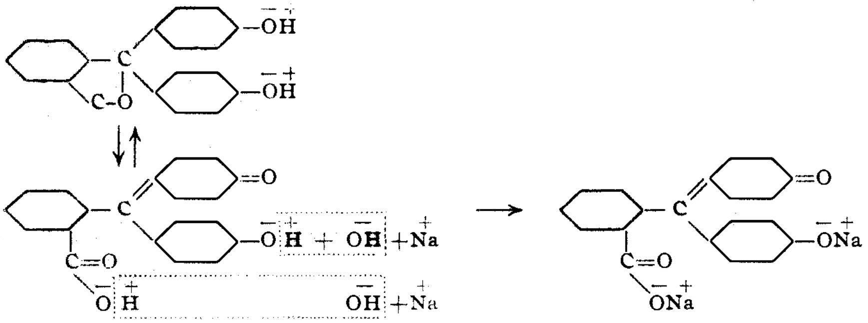
[8] *Ber.*, 40, 1880.



I. II. III. IV.

This plausible theory, however, does not agree with facts. Disregarding the omission of another atom of sodium in the molecule—for phenolphthalein is dibasic—the equation practically means that when phenolphthalein is dissolved in weak alkali, a semi-stable colored quinoid salt (IV) is produced. Furthermore it means—and this is its weakest point—that in an excess of alkali the full color of phenolphthalein is never reached, or in other words most of the phenolphthalein will remain in the carbinol form (II) because of the fact that the carbinol (the colorless form) is the stable form in excess of alkali hydroxide. A glance at our former curves and figures[1] will convince that the reverse is true. In making tribasic salts with saturated alkali hydroxide, a very dark, almost black, solution, having a bronze metallic lustre, is produced, after which hydration and fading take place. We believe that we can safely conclude that *in ordinary phenolphthalein the quinoid dibasic salt is essentially primary*, and the carbinol form essentially secondary.

We explain the facts in this way, giving an equilibrium from our first paper:[1]



As may be observed, the only assumption necessary in this equation, is that a lactone is in equilibrium with its acid, or an acid with its lactone. Similar equations are given by Stieglitz in his theory of indicators, and by Acree, McCoy, Hildebrand, and Wegscheider. Meyer[2] and Spengler believed that the quinoid group is not essential to the color of phenol-

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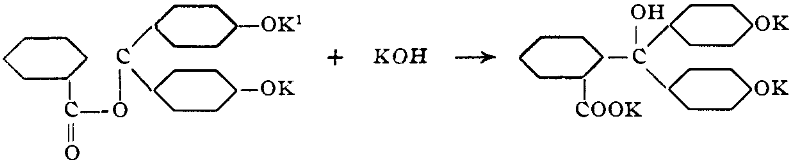
[1] This Journal, 33, 68.

[2] *Ber.*, 38, 1318.

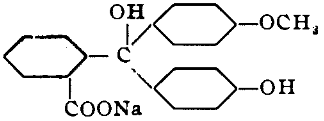
phthalein; and like Gomberg they held that the splitting open of the lactone ring involved the formation of the carbinol group.



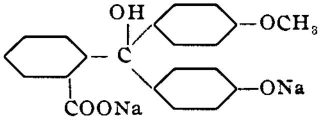
The underlying idea seems to be that the hydroxyl ion of the alkalin hydroxide satisfies the valence set free when the lactone ring is severed. This assumption is unnecessary and has been abandoned by Meyer[2] himself.

Why Green and King[3] found much support for the quinone theory in the behavior of the two esters—the methyl ester and the lactoïd methyl ester—on treatment with alkali, we fail to understand. The statement that the methyl ester does not fade, or is unattacked by excess of hydroxide, seems to us to support the ideas of Gomberg and Meyer and Spengler fully as much as it does the quinoid theory. It seems, however, doubtful that the ester cannot be converted into the carbinol form. If the hydration is somewhat slower than that of phenolphthalein it could easily have escaped the attention of Green and King; and in view of lack of accurate measurements, with a spectrophotometer or with a colorimeter using a permanent tint (the amount of color being very deceptive even to the practiced eye), the question remains open.

Green and King also stated that the lactoid ester formed a colorless salt, a monobasic carbinol ester.



We believe that this was meant for a dibasic salt:



and we explain its formation with the help of the following equation:

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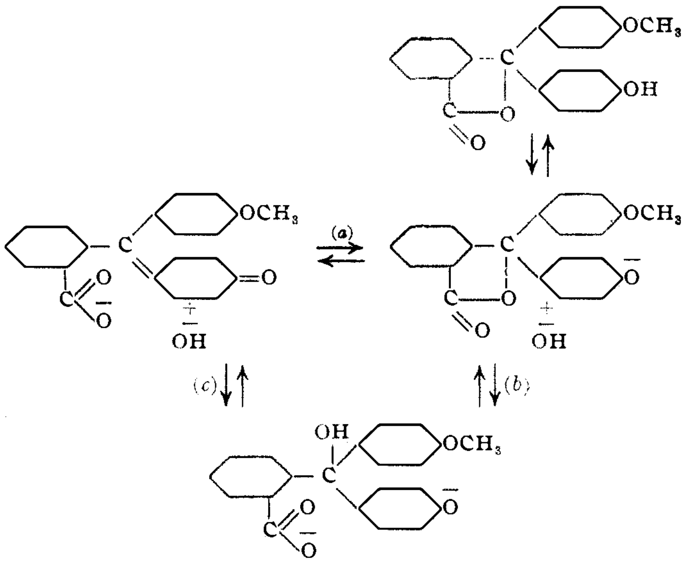
[1] Acree and Slagle believed that the lactoid form can exist as a colorless salt, but our experiments show that very little, if any, can exist as such.

[2] *Ber.*, 42, 2832.

[3] *Ibid.*, 39, 2365.



The first equation gives the ionization of the lactoid ester, the equation (*a*) represents the equilibrium between lactone and acid, and equation (*b*) indicates the carbinol formation directly. As can easily be seen, the only assumption necessary to explain the behavior of the lactone methyl ester is that the speed of hydration directly (*b*) is greater than the speed of formation of the quinoid acid. For the speed of hydration to be greater than the speed of quinoid acid formation is not unexpected. The formation of a quinoid acid in this case is dependent on the change of position of an electric charge, or on the mobility of the hydrogen atom of a phenol group. Since ordinary phenolphthalein has two phenol groups, both of which are probably active, to one phenol group in the lactoid ester, its speed of quinoid acid formation should be the greater. The dibasicity of phenolphthalein means that the speed of the salt formation of its phenol group is about the same as that of its carboxyl group. And therefore any decrease in the speed of carboxyl formation will result in the increased neutralization of the phenol group.

To sum up, it may be said that the mass law holds also for intramolecular changes: if the speed of quinoid acid formation is dependent on phenol groups, the speed of reaction will certainly be greater when there are two such groups in a molecule than when there is only one.

Determination of the basicity of this ester, as well as the quantitative study of the amount of color, would help to clear up the matter. If the salt is monobasic and gradually becomes dibasic, it would indicate a slow action of (*b*). If dibasic, it would indicate rapid acition of (*b*).

## Preparation of Monobasic Phthalates.

The preparation of monobasic phthalates, besides its theoretical interest, is of importance practically. Abel and Rowntree[1] have demonstrated the value of phenolphthalein and its tetrachlor derivatives, as subcutaneous purgatives, when administered in olive oil. The bulkiness of the injection (20 cc. in oil solution) stands in the way of its general adoption.

The dibasic sodium salt cannot be used, it seems, as it is highly irritating, owing to hydrolysis of the salt,[2] or perhaps to the presence of the quinoid group.[3] Abel and Rowntree showed that lactoid phenolphthalein is not irritative, but have not shown the source of irritation in the dibasic salts. They are inclined to ascribe it to the sodium's forming NaOH on hydrolysis. On studying the action of tribasic phthalates Rowntree[4] found that about 50% of the animals developed irritation. The large amount of alkali salts, resulting from neutralization with acetic acid probably, played an important role in producing irritation.

Therefore it was of considerable pharmacological interest to prepare in pure condition monobasic phthalates, since such salts would contain only from 5–9% of alkali metal, would have no quinoid group, and would in all probability be neutral salts. Green and Perkins found that the tribasic phenolphthalates could be titrated with acetic acid, and found that one atom of alkali metal was not attacked. This shows that the monobasic salt in solution hydrolyzes very little, is practically neutral, and that its acid is decidedly stronger than acetic acid.

We succeeded over a year ago in developing a technique for making these monobasic salts, but were unable until recently to come to a conclusion as to the amount of water, alcohol or acetone in the crystallized product.

In general these monobasic salts are beautiful crystallin products, of definit crystallin form, belonging probably to the mono- or triclinic system. Like the tribasic salts they are colorless and dissolve with great rapidity, even in cold water. The pure salts, when freshly prepared, have not even a trace of color. On standing in aqueous solution color develops slowly, and after some time phenolphthalein separates according to the following equation.

If additional proof were needed that phenolphthalein is dibasic, the fact just mentioned would be an excellent proof. That a solution of these monobasic salts can never be very alkalin is quite obvious.

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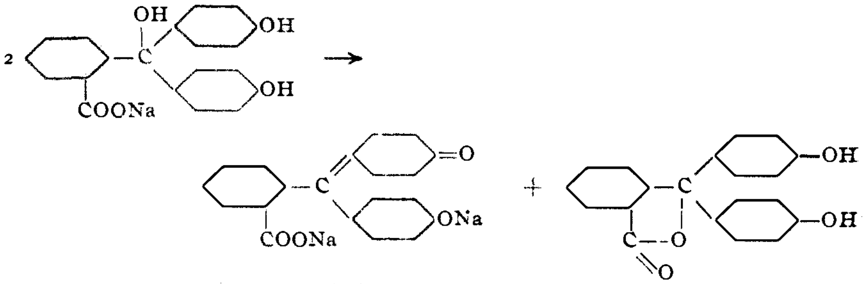
[1] *J. Pharm. and Exp. Therap.*, 1, 231.

[2] *Loc. cit.*

[3] Dresbach, *Ibid.*, 3, 161, finds that phenolphthalein oxime, which does not change to a quinoid form, has no irritative or laxative action on animals.

[4] *Ibid.*, 2, 469.



Colored dibasic phenolphthalein.

Precipitated phenolphthalein.

Since the formation of the dibasic salt, which in turn produces on hydrolysis only a small amount of free sodium hydroxide, is slow, and is accompanied by the formation of an equal amount of free phenolphthalein, the amount of free alkali at the start cannot be very large. In addition to this are the free phenol groups of undecomposed carbinol salts, which can neutralize any free alkali. It is doubtful if these salts produce any irritant action in the animal body through hydrolysis.

We hope, in the near future, to make a more extensive study of the behavior of these compounds, especially a study of their ionization and the dynamics of their reaction, as well as of their pharmacological behavior.

The starting materials in these preparations are the tribasic phthalates, which were made for the most part according to the directions given in our second article. Although we have not yet succeeded in getting a purer sodium salt than that described before, we have improved the method so that the preparation of the sodium salt is now no more difficult than that of the potassium salt. The method of purification to obtain a fairly good product, although a little slower, is also less troublesome. The details follow:

The tribasic preparations can be made at any room temperature, but the purification should be done in *cold dry air*. The tribasic sodium salt is best made as follows: 150 grams of good commercial phenolphthalein are put into the porcelain pan of a vacuum still, and heated over the steam bath for about one-half hour. To this is then added 75 cc. hot water, which on stirring leaves the mass of phenolphthalein in the form of a stiff paste. A solution containing 200 grams of pure sodium hydroxide in 160 cc. water is poured, while still very hot, on the paste, which, with considerable evolution of heat, forms a deep red solution having a beautiful bronze and metallic luster. A vacuum (any good water pump giving 20 to 30 mm. vacuum is sufficient) is then applied, and the air entering the pan is purified with a calcium chloride and soda lime tube.

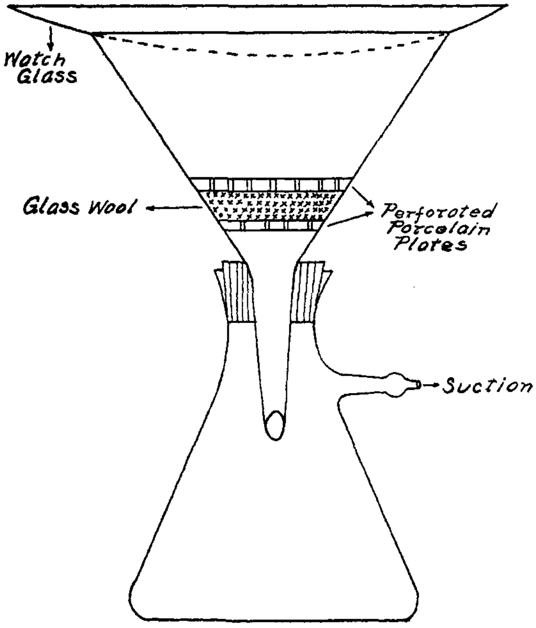
The distillation, which is slow, is continued for two or three hours, at the end of which time the crystallization is very nearly complete. While still hot, the crystals are filtered off with suction. We have found this arrangement advantageous.

After the tribasic sodium salt has been filtered until nearly dry, it is purified in portions of not more than ten grams, which are washed successively with the following solutions. After each washing the salt is filtered rapidly, a hardened filter paper and a Buchner funnel with suction being used:

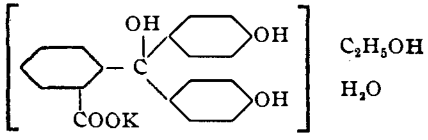
1. Absolute alcohol, temperature —5° to —10° C.
2. Absolute alcohol 2 parts, absolute ether 1 part, temperature —5° to —10° C.
3. Absolute alcohol 1 part, absolute ether 1 part, temperature —5° to —10° C.
4. Absolute alcohol 1 part, absolute ether 2 parts, temperature —5° to —10° C.
5. Absolute ether.

To make monobasic salts a weak acid must be used, which will neutralize the two sodium atoms of the phenol groups, without attacking the sodium of the carboxyl group. Acetic and carbonic acids are well adapted to this purpose, and are easily obtainable, but only carbonic acid was used in this investigation because its salt, sodium carbonate, is insoluble in absolute alcohol, acetone, and ether. This fact enabled us to separate the sodium carbonate formed in the process from the monobasic salts.

One method consists in using absolute alcohol to dissolve the tribasic salt, while a second method uses acetone to dissolve the monobasic salt as it is formed. The latter method is not suitable for the potassium salt, but is practicable for the sodium salt.



Potassium salt



Twenty-five grams of tripotassium phenolphthalate were dissolved in 400 grams absolute alcohol, and 10–15 grams of anhydrous sodium sulfate were added to remove some of the water contained as water of crystallization in the tribasic salt. We are not certain that this purpose was accomplished. After passing carbon dioxide through the solution for 2 hours, it was filtered, concentrated by vacuum distillation, and precipitated with absolute ether. The crystallin precipitate was washed with ether, air dried, and placed in a desiccator.

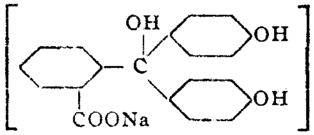
The determination of the amount of phenolphthalein and alkali metal was made with each salt as follows: About 0.5 gram of the salt was weighed accurately in a weighed beaker. After dissolving it in 20 to 25 cc. of water, hydrochloric acid was added until the solution was permanently decolorized. Then it was carefully evaporated to dryness, and the beaker, containing the phenolphthalein and the alkali metal as chloride, was weighed. The amount of chlorine was determined by titration by Volhard's method, or gravimetrically as silver chloride. The amount of phenolphthalein was determined by subtracting the amount of sodium chloride from the weight of the dried residue. The only impurity possible in this case is sodium carbonate, and the relation of sodium to phenolphthalein would quickly show its presence if it were there.

The alcohol content was determined by carefully distilling the salt in a neutral solution, and determining the amount of alcohol in the distillate by specific gravity estimations.

ANALYSIS.

| Sample, | 0.5152 gram. | | 0.5002 gram. | | 0.5087 gram. | | |
|---|---|---|---|---|---|---|---|
| | Gram. | Per cent. | Gram. | Per cent. | Gram. | Per cent. | Theory. Per cent. |
| Phenolphthalein | 0.3728 | 72.4 | 0.3616 | 72.3 | 0.3673 | 72.2 | 72.6 |
| Potassium....... | 0.0470 | 9.1 | 0.0456 | 9.1 | 0.0456 | 9.0 | 8.9 |
| Alcohol[1]........ | 0.0546 | 10.6 | 0.0530 | 10.6 | 0.0539 | 10.6 | 10.5 |
| $OH^-$ and $H_2O$ by difference..... | 0.0408 | 7.9 | 0.0400 | 8.0 | 0.0419 | 8.2 | 8.0 |

Sodium salt



$C_2H_5OH$

$H_2O$

The sodium salt was made in the same way as the potassium salt. The methods of purification and analysis were identical with those described under the potassium salt, and gave the following results:

| Sample, | 0.5028 gram. | | 0.5040 gram. | | |
|---|---|---|---|---|---|
| | Gram. | Per cent. | Gram. | Per cent. | Theory Per cent. |
| Phenolphthalein............ | 0.3749 | 74.5 | 0.3823 | 75.8 | 75.4 |
| Sodium....................... | 0.0278 | 5.5 | 0.0286 | 5.7 | 5.4 |
| Alcohol[2]..................... | 0.0578 | 11.6 | 0.0580 | 11.6 | 10.9 |
| $OH^-$ and $H_2O$ by difference... | 0.0423 | 8.4 | 0.0351 | 7.0 | 8.3 |

The monobasic salts, prepared with alcohol, crystallize in long, usually clear, colorless prisms, with truncated ends and an hexagonal outline. They dissolve rapidly in water, slightly less so in alcohol, to form colorless solutions. At room temperature the salts hydrolyze slowly with development of color and the precipitation of phenolphthalein.

It seems that acetone, alcohol, and water, can be used interchangeably without producing much difference in the crystal form. The following monobasic salts were made with acetone, which replaces wholly or in part the alcohol of the salt as just described.

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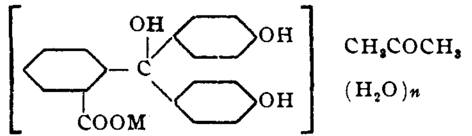
[1] Only one quantitative determination of alcohol was made, using 5.00 grams of the salt.

[2] Only one quantitative determination of alcohol was made, using 1.476 grams of material.



(For Na, $n = 2$)

M = K or Na

The sodium salt crystallized from acetone only, gave the following analysis:

| | I. Per cent. | II. Per cent. | Average. | Theory. |
|---|---|---|---|---|
| Phenolphthalein[1] | 72.9 | 72.7 | 72.8 | 70.3 |
| Sodium | 5.0 | 5.3 | 5.2 | 5.1 |
| Acetone | 14.4 | 10.1 | 12.2 | 12.8 |
| $OH^-$ and $H_2O$ by difference | 8.7 | 11.9 | 10.3 | 11.8 |

When the salt is precipitated with alcoholic ether (3%) the analysis is slightly different, part of the acetone being replaced by alcohol.

| | I. | II. | Average. |
|---|---|---|---|
| Phenolphthalein | 71.2 | 69.3 | 72.0 |
| Sodium | 5.1 | 5.0 | 5.4 |
| $^1/_2$ molecule acetone, $^1/_2$ molecule alcohol | 11.6 | 11.6 | 10.7 |
| $OH^-$ and $2H_2O$ by difference | 12.1 | 10.4 | 11.9 |
| Acetone (alone) | 6.5 | 6.3 | .... |

## Summary.

I. The dynamics of phenolphthalein reactions have been discussed, and it is shown that they explain some of the recently observed phenomena.

II. A description is given for the first time of a method for the isolation of monobasic phenolphthalates.

III. Monosodium and monopotassium phenolphthalates are described.

NEW YORK CITY.

## NEW BOOKS.

**Annual Reports on the Progress of Chemistry for 1911.** Issued by the Chemical Society (London). By J. C. CAIN, D.Sc., PH.D., editor. Vol. VIII. London: 1912. Gurney and Jackson. New York: D. Van Nostrand Co. pp. 319. Price, $2 net.

The general character of these Reports is so well known that no comment is required in connection with this, the eighth volume, the plan of which is essentially the same as those of its predecessors. It is obvious that the summarizing of a year's progress tends to increase in difficulty with multiplicity of workers, and of organs of publication, and with the broadening of the fields of investigation. The individual reporters in the subdivisions of the science find it impossible to command an intimate

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[1] The per cent. of phenolphthalein is too high, owing possibly to the presence of a little free phenolphthalein precipitated from some decomposed dibasic salt. Analysis No. I was made immediately after isolating the salt, whereas analyses No. II was made only after 9 days.