

5. Defects in the standard Fehling solution method for the determination of the carbonyl group are pointed out.

6. Acetone-phenylhydrazone formation can be forced almost to completion by adjusting the final Sørensen value of the solution to between 5 and 7, and at the same time salting out the hydrazone. If the hydrazone is now extracted by a selective solvent immiscible with water the reaction can be made practically quantitative.

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AN ACCURATE GENERAL IODIMETRIC METHOD FOR THE QUANTITATIVE DETERMINATION OF THE CARBONYL GROUP IN ORGANIC COMPOUNDS

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There are to be found in the literature¹ a number of methods for the quantitative determination of individual aldehydes^{2,3,4,5} and ketones^{2,4,6,7}. Owing to the greater reactivity of aldehydes as a class as compared with ketones more quantitative methods have naturally been proposed for the former. A few of these methods are applicable to the determination of a limited number of aldehydes and ketones. There are only two, however, that can in any sense be called general methods.

The one general method for the quantitative determination of the carbonyl group which has been considered by all chemists to be dependable is that of Benedikt and Strache.⁸ This method, in which the excess of phenylhydrazine is oxidized by Fehling's solution and the liberated nitrogen measured, unfortunately gives only approximately correct results. The method, furthermore, is tedious and cumbersome. Its accuracy has been improved by Smith,⁹ but even his results are merely close approximations. With *p*-nitrobenzaldehyde he obtained consistent results 4.3% low, and with hydroxybenzaldehyde his results were consistently 2.7% high.

¹ Houben-Weyl, "Die Methoden der organischen Chemie," Georg Thieme, Leipsic, 2nd edition, 1921, vol. 1, pp. 188 and 220.

² Lautenschläger, *Arch. Pharm.*, **256**, 84 (1918).

³ Pauly, Schübel and Lockemann, *Ann.*, **383**, 288 (1911). Welmans, *Pharm. Ztg.*, **1898**, p. 634. Meyer, *Monatsh.*, **24**, 833 (1903). Burzepe, *Analyst*, **29**, 78 (1904).

⁴ Ripper, *Monatsh.*, **21**, 1079 (1900).

⁵ Lockemann and Croner, *Z. anal. Chem.*, **54**, 11, 22 (1915).

⁶ Messinger, *Ber.*, **21**, 3366 (1888). Ardagh, *Ind. Eng. Chem.*, **16**, 1133 (1924).

⁷ Sy, *THIS JOURNAL*, **29**, 786 (1907).

⁸ Benedikt and Strache, *Monatsh.*, **14**, 270, 373 (1893).

⁹ Smith, *Chem. News*, **93**, 83 (1906).

We subjected Smith's modification to a careful test with acetone and obtained results within only about 5% of the correct value.

E. von Meyer's method¹⁰ has also been recommended as a reliable general method for the carbonyl group. Using acetone, we found that von Meyer's method gave much lower results even than Smith's modification of the Benedikt and Strache method.

These two are the only known methods for the determination of the carbonyl group that are looked upon as general methods. Our method resembles that of von Meyer in so far as the iodimetric determination of phenylhydrazine is concerned, but differs from von Meyer's in every other respect.

It is fairly obvious that the use of a hydrazine giving virtually insoluble hydrazones would largely solve the difficulties. We prepared a number of hydrazines in the hope of finding one that would give an insoluble acetone-hydrazone. We were not so fortunate as to discover such a one. We note, however, that Bülow¹¹ has recently succeeded in isolating a very insoluble acetone-hydrazone (acetone-2,4-dinitrophenylhydrazone) and has applied it to the detection and estimation of small amounts of acetone in urine.

The study of the conditions for the maximum formation of acetone-phenylhydrazone given in the preceding paper enabled us to develop a general method for the determination of the carbonyl group.

Attention is drawn in that paper to the necessity of preventing oxidation of phenylhydrazine through contact with air. Boiled distilled water must be used in the preparation of all solutions as well as for making up samples to a definite volume. An inert atmosphere must be kept in contact with the solutions at all stages. Furthermore, the hydrogen ion concentration must be kept within certain limits. Finally the hydrazine \rightleftharpoons hydrazone reaction is reversible, so that theoretically complete reaction is impossible. However, by adjusting all the influencing conditions enumerated above to an optimum, and at the same time introducing the principle of salting out, together with extraction of the hydrazone by a selective solvent, the hydrazine \rightarrow hydrazone reaction can be forced for all practical purposes to completion.

To maintain the Sørensen (P_H) value of the solutions between 5 and 7 any suitable buffer salt can be used. For our general method we selected disodium phosphate; the Sørensen value of the 0.1 *N* solution is 9.2 and that of the 0.1 *N* monosodium phosphate solution is 4. The hydrochloric acid liberated in the hydrazine \rightarrow hydrazone reaction would result in a Sørensen value somewhere between these limits.

The partition coefficient of the phenylhydrazine hydrochloride be-

¹⁰ von Meyer, *J. prakt. Chem.*, [2] **36**, 115 (1887).

¹¹ Bülow, *Science*, **61**, 344 (1925).

tween ether and water was determined by experiment to be 0.5. The addition of one equivalent of disodium phosphate increases this to 1.9, and six equivalents to 6.2.

Such high values necessitate so large a correction that, in order to work out a reliable analytical method, some more suitable solvent should be employed. This we found in petroleum ether.

Under certain circumstances it is obvious that the hydrazone reaction must of necessity be carried out in some organic solvent. Herein petroleum ether has the additional advantage of being practically immiscible with alcohol-water solutions of high alcoholic content. Forty per cent. by volume alcohol shows no change in volume on shaking with petroleum ether, and even with 70% by volume the change is very small.

The petroleum ether that we used was purchased from the J. T. Baker Chemical Company, who state that it is the fraction obtained between 40° and 60°. It had been distilled presumably from Pennsylvania crude oil. We shook it with bromine water until no more of this reagent was bleached by five minutes' shaking, then with water, then with 0.1 *N* sodium thio-sulfate solution, and finally with water several times. A distillation test following the treatment with bromine water showed first drops over at 34° and the rest came over steadily with steadily rising temperature to 58°, except for a residue of less than 10%, of which half distilled very slowly with temperature rising to 67° and the remaining 5% did not distil even with the water boiling in the water-bath. This residue was miscible with petroleum ether but had a specific gravity slightly greater than water. It was probably brominated hydrocarbons.

As an extracting solvent petroleum ether is ideal in its low partition coefficient for phenylhydrazine. With a solution of 20 cc. of 0.5 *M* phenylhydrazine hydrochloride, 20 cc. of 0.5 *M* disodium phosphate solution, 40 cc. of saturated sodium chloride solution, made up to 100 cc., the partition coefficient was 0.055. This value changes very little with appreciable variation of conditions; using the same amount of phenylhydrazine hydrochloride and disodium phosphate, 30 cc. of 95% by volume alcohol, 10 cc. of saturated sodium chloride solution and then making up to 100 cc., the value obtained was 0.052. In making a determination 25 cc. was vigorously shaken with 4-5 cc. of petroleum ether for two minutes. A period of two minutes was taken, because it was found that one minute of shaking does not suffice to extract the hydrazone from aqueous liquids.

The following is a detailed description of our general analytical process.

Distilled water boiled and cooled under a nitrogen atmosphere is used throughout. The carbonyl compound is weighed out; if liquid, by being sucked into a tared glass bulb which is then broken under water (or a mixture of alcohol and water) and the liquid made to a known volume. Approximately 0.5 *M* phenylhydrazine hydrochloride is made from recrystallized hydrochloride carefully dried and kept in the dark. Al-

ternatively it can be made by carefully neutralizing a phenylhydrazine solution with hydrochloric acid. The 0.5 *M* sodium phosphate solution begins to crystallize at about 25°; hence a slightly weaker solution is advisable, somewhat more being taken.

For a determination 20 cc. of phenylhydrazine solution, 20 cc. of phosphate and sufficient carbonyl compound to react with about half the phenylhydrazine are mixed in a 100cc. flask (flushed out with nitrogen) made up to the mark with saturated sodium chloride solution and allowed to stand, stoppered, at room temperature. Generally 30 minutes is sufficient for complete reaction. If a solid precipitate separates it should be filtered off as quickly as possible. Twenty-five cc. of the aqueous solution is now placed in a cylindrical separatory funnel of about 75–100cc. capacity (flushed out with nitrogen) and 4–5 cc. of petroleum ether is added. After two minutes of vigorous shaking, the petroleum ether is allowed two minutes to separate, and then some of the aqueous layer is run into a calibrated 25cc. cylinder. Ten cc. of this is now pipetted into a 250cc. ground glass-stoppered Erlenmeyer flask (again in a nitrogen atmosphere), two drops of 0.1% methyl orange solution are added and then dilute acid—sulfuric or hydrochloric—drop by drop until the indicator just turns pink. Sufficient 0.1 *N* iodine solution is now added to give an excess of about 5 cc. and the stoppered flask allowed to stand for five minutes to insure complete reaction between the phenylhydrazine and iodine. Freshly prepared starch solution is added and an excess (about 3–4 cc.) of 0.1 *N* thio-sulfate solution run in. About 5 cc. of diethyl ether is now added and the whole shaken to dissolve iodine from the drops of iodobenzene. A final back-titration is now made with the 0.1 *N* iodine solution. The nitrogen atmosphere is especially necessary to prevent oxidation of hydriodic acid. The remainders of the aqueous and ethereal solutions are then run into the measuring cylinder and the volumes determined.

A blank under similar conditions is carried out on the phenylhydrazine alone. The partition coefficient can be determined by shaking for two minutes with petroleum ether and testing the aqueous layer. The rest is a simple calculation; 108 parts by weight of phenylhydrazine react with 28 parts by weight of the carbonyl group.

Details of Calculation for Acetaldehyde

The sample was taken from a bottle of Merck's absolute that had not been previously opened.

Wt. of bulb + acetaldehyde = 4.4516 g.

Wt. of bulb = 1.4773 g.

Acetaldehyde = 2.9743 g.

Volume of glass fragments = 0.5 cc.

Therefore, concn. of acetaldehyde is 2.9743 g. in 99.5 cc.

The iodine solution was 0.0995 *N*; the thiosulfate was exactly equivalent.

Amounts taken: 25 cc. of 0.5 *M* phenylhydrazine hydrochloride soln.

20 cc. of 0.5 *M* disodium phosphate soln.

10 cc. of acetaldehyde soln.

45 cc. of satd. sodium chloride soln.

100 cc.

A dense, white emulsion immediately separated, later forming a solid. After 30 minutes at room temperature the solution was filtered and 25 cc. of the filtrate extracted with petroleum ether. This gave an aqueous layer of 24.9 cc. and a petroleum-ether layer of 3.2 cc. Ten cc. of the aqueous layer was taken, 30 cc. of iodine added, the mixture allowed to stand as described and then 12 cc. of thiosulfate solution was run in; 2.65 cc. of iodine solution was now required to produce a blue color with starch. The net amount of iodine required was, therefore, 20.65 cc. The blank on the phenylhydrazine

alone was 47.55 cc. of iodine. The partition coefficient for the phenylhydrazine in water-petroleum ether was 0.055.

The corrected value for iodine required by the 10cc. aliquot portion extracted = $([24.9 + (3.2 \times 0.055)]/25.0) \times 20.65 = 20.70$ cc.

The weight of hydrazone formed and removed by filtration (calculated) = 1.040 g. (say, 1.0 cc.). Correcting the iodine value for this gives $99/100 \times 20.70 = 20.45$ cc.

The iodine value for 1 cc. of acetaldehyde is, therefore, $47.55 - 20.45 = 27.10$ cc. of 0.0995 *N* iodine solution.

$\text{CH}_3\text{CHO} \equiv \text{C}_6\text{H}_5\text{NHNH}_2 \equiv 2\text{I}_2$. Therefore, 44.04 g. of acetaldehyde \equiv 40 liters of 0.1 *N* iodine solution, or 1 cc. of 0.1 *N* iodine solution indicates 0.001101 g. of acetaldehyde.

Acetaldehyde found per cc. = $27.1 \times 0.995 \times 0.001101$ g. = 0.02969 g.

Acetaldehyde taken per cc. = $2.9743/99.5 = 0.02989$ g.

The corrections for partition coefficient and change in aqueous volume when petroleum ether is employed are so small that for many purposes they can be safely ignored.

This simplification eliminates both the determination of the partition coefficient and of the change in volume of the aqueous layer. In consequence it greatly shortens the necessary figuring, especially when we also leave out of our calculations the correction for volume of glass fragments and volume of hydrazone filtered off. In this way the time required to carry out the determination and to make the calculation is greatly cut down.

The determination of acetaldehyde described above is shortened under this simplified procedure to the following.

Blank on phenylhydrazine	47.5 cc. of 0.995 <i>N</i> iodine soln.
Aqueous extract	20.6 cc.
	26.9 cc.
Iodine equivalent of acetaldehyde in 10 cc.	26.9 cc.

$26.9 \times 0.995 \times 0.001101 = 0.02947$ g. of acetaldehyde per cc. Error due to simplified procedure: $0.2969 - 0.2947 = 0.0022$ g. or 0.74% of the amount of acetaldehyde found by the long method.

For the sake of space further calculations have been omitted. The solvent for the benzaldehyde was 60% by volume alcohol, while for the acetophenone 40% by volume alcohol was employed.

The examples given serve to show in what manner the authors' general method can be modified. It will be seen that when the substance to be analyzed is not soluble in water, alcohol of suitable strength can be substituted for the water. In the compounds determined petroleum ether and water, or alcohol-water, sufficed. But the principles of the method are quite general and hence one is not restricted to petroleum ether as the hydrazone solvent or to alcohol-water as the solvent for the carbonyl compound. Any solvent that will extract hydrazones from other solvents can be used.

Following the general practice the authors have employed phenylhydrazine hydrochloride which necessitates the use of a buffer salt to

control the Sørensen value. It will be realized from the first paper that in normal cases solutions of the phenylhydrazine base itself can be used. This may in certain cases offer decided advantages; for example, when a high percentage of organic solvent is necessary to keep the ketone or aldehyde in solution.

Table I gives the results obtained with a few additional compounds. The last three substances in the table were not specially purified samples.

TABLE I
TYPICAL RESULTS

Compound	Acetone	Benzaldehyde	Acetophenone	Diethyl ketone	Ethyl aceto-acetate	Citral
Wt. taken, g.	0.02980	0.05227	0.0675	0.0291	0.0545	0.0603
Wt. found, g.	.02991	.05222	.0672	.0287	.0560	.0600

In the case of benzophenone the reaction proceeds at an exceptionally slow rate. Trials were made using alcohol-water and allowing the mixture to stand for periods of time up to 24 hours and also heating on the water-bath for one hour. The characteristic needle-like crystals of benzophenone-phenylhydrazone were obtained, but the extent of formation was only 10-15%. Butyl alcohol was also tried without success. Further work will be done on this compound. The presence of one phenyl group in a ketone (acetophenone) slowed down the rate of reaction considerably (two hours at room temperature was required). It appears that ketones with two aromatic radicals react very slowly indeed, and it may require particular conditions of high concentration and temperature and possibly also control of the Sørensen value within narrower limits to secure a high degree of reaction in a reasonable time.

The slow rate of reaction in the case of such compounds as acetophenone and benzophenone may reasonably be attributed at least in part to steric hindrance. The senior author proposes in the near future to carry out a series of investigations upon the rate of hydrazone formation under various conditions, and also upon the application of the general method to the determination of aldehydes and ketones in the presence of one another and its application to the analysis and valuation of many substances of commercial importance.

Summary

1. A general method of a high degree of accuracy for the determination of the carbonyl group in organic compounds has been worked out.
2. Further interesting fields to which this general method can be applied have been pointed out.

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