[CONTRIBUTION FROM THE SCHOOL OF ENGINEERING RESEARCH, UNIVERSITY OF TORONTO]

A STUDY OF CERTAIN PROPERTIES AND REACTIONS OF PHENYLHYDRAZINE

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RECEIVED SEPTEMBER 14, 1931 PUBLISHED FEBRUARY 5, 1932

Part I

Determination of Phenylhydrazine.—The need for a simple and dependable method for the quantitative determination of phenylhydrazine arose as a result of the use of this reagent by Ardagh and Williams[2] in the quantitative determination of the carbonyl group in organic compounds. The present paper should be read in conjunction with the two just referred to, since it is impossible, due to lack of space, to repeat much of the detail given there.

In the quantitative determination of acetophenone and benzophenone we employed ethyl alcohol + water as solvent for these ketones since they are too sparingly soluble in water alone for practical purposes.

The method recommended by Ardagh and Williams for the determination of phenylhydrazine[2] by titration with iodine in slightly acid solution, the course of which reaction is represented by the equation given at the end of this paragraph, gives low results when more than 10% by volume of alcohol is present. This is particularly the case when the phenylhydrazine is very dilute, say, 0.01 *M*.

$$C_6H_5HN{\cdot}NH_2 + 2I_2 \longrightarrow C_6H_5I + 3HI + N_2$$

To accelerate the rate of the reaction between the ketone and the phenylhydrazine, heating the mixture to 60° under an atmosphere of nitrogen is very effective. At this temperature some phenylhydrazine is always destroyed when alcohol is present even in solutions as acid as P_H 2, but if the P_H does not exceed 4 the destruction of phenylhydrazine is reduced practically to a constant (about 2% of the amount present after heating to 60° for three hours, and 5% for nine hours) even though the alcohol present may make up half the total volume, as shown in the accompanying graph (Fig. 1).

The effects of considerable quantities of alcohol on the figures obtained for phenylhydrazine may be summed up as follows.

(1) On heating the solution containing the phenylhydrazine to 60° for three hours, the decomposition of phenylhydrazine in faintly acid solution (P_H about 4) is independent of the proportion of alcohol present and is roughly a constant at 2% of the amount of phenylhydrazine present. It is most important that the alcohol be free from aldehydes and traces of

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[2] Ardagh and Williams, THIS JOURNAL, 47, 2976, 2983 (1925).

other impurities which will react with iodine. Sometimes absolute alcohol is prepared by the use of calcium carbide. In this case traces of acetylene will be present.

(2) When alcohol and buffer are both present (we used NaH_2PO_4), numerous factors appear to affect the iodine–phenylhydrazine reaction, *e. g.*, rate of addition of iodine, excess of reagents, time allowed for reaction, etc.

(3) When alcohol without buffer is present, the titration gives more trouble than when buffer without alcohol is present, but either is less uncertain than when both alcohol and buffer are present.

(4) The phenylhydrazine content of the solution to be titrated should not fall below approximately 0.05 *M*, especially if alcohol is present.

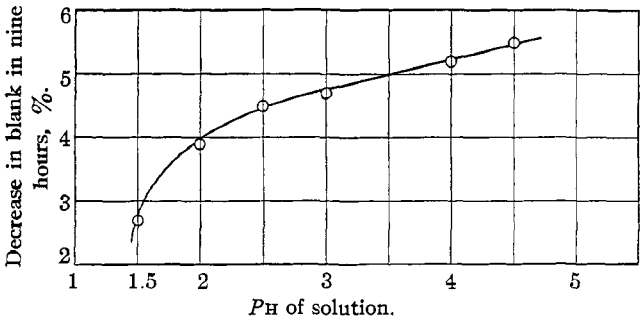

Fig. 1.—Change in phenylhydrazine value with P_H of solution of $C_6H_5NHNH_2 \cdot HCl$ heated for nine hours at 60° (50% alcohol).

(5) The phenylhydrazine solution should be added to an excess of the standard iodine and the mixture allowed to stand for five minutes before titrating the excess iodine.

(6) When alcohol is present the end-point is improved by adding 2 to 3 cc. of thiosulfate in excess and shaking gently to remove the iodine dissolved in the droplets of iodobenzene. If these droplets are very minute a more certain end-point is secured by omitting the ether formerly recommended.[2]

Owing to the inconvenience as well as the instability of the phenylhydrazine base, we prepared the hydrochloride, which we used in all our work. To obtain the salt free from impurity, the base, after redistilling at 16 mm. under nitrogen followed by diluting with alcohol, must be added slowly with constant stirring to an excess of the acid, also diluted with alcohol. If the reverse method is followed a product containing aniline hydrochloride and even ammonium chloride is likely to be obtained as a result of the reaction shown here, especially if the mixture is allowed to become warm.[3]

$$2C_6H_5HN \cdot NH_2 + C_6H_5HNNH_2 \cdot HCl \longrightarrow 3C_6H_5NH_2 + NH_4Cl + N_2$$

[3] M. Busch, *J. prakt. Chem.*, **116**, 39 (1927).

Proceeding in the manner described we had no difficulty in preparing beautiful, lustrous, white scales of the hydrochloride which, after washing, first with alcohol, then with diethyl ether, and drying to constant weight over porous calcium chloride in a desiccator filled with nitrogen, required for titration the precise proportion of 0.1 *N* iodine calculated for the pure salt.

Experiment proved that 25 cc. of a 0.25 *M* solution in water of the hydrochloride diluted to 100 cc. when exposed to air turned brown and turbid in a few days, as a result of oxidation.

In our attempts to find an inhibitor against oxidation we tried adding 0.1 g. of each of the following to 100 cc. batches of the above: pyridine, quinoline, *o*-toluidine, *m*-phenylenediamine and β-naphthylamine. None of these appeared to exercise any inhibitory effect. The addition of 0.5 cc. of 6 *N* hydrochloric acid to a 100-cc. batch appeared, on the contrary to be most effective. Doubtless this was due to the resulting increase in hydrogen-ion concentration.

In our work we preferred to prepare our phenylhydrazine solutions from day to day from the pure, dry hydrochloride. This practice we considered to be more free from possible sources of error than any other method.

Part II

$$C_6H_5CH_3C{=}O + C_6H_5HNNH_2{\cdot}HCl \rightleftharpoons C_6H_5CH_3C{=}NNHC_6H_5 + HCl + H_2O$$

Optimum Conditions for the Preparation of Acetophenone Phenylhydrazone.—In the earlier work referred to, the authors' object was the development of an analytical method for the quantitative determination of aldehydes and ketones; in Part II and Part III of the present article the purpose is to discover the conditions that will result in a high yield of hydrazone in a short time.

Ardagh and Williams found that the conditions necessary to give a high percentage yield of hydrazone in a reasonable time from acetophenone and from benzophenone must be maintained within narrower limits than are required in the case of the aldehydes and ketones of the aliphatic series, and furthermore that the rate of hydrazone formation is too slow at room temperature to be satisfactory. This is particularly the case with benzophenone.[4]

At 60° the reaction proceeds much more rapidly. The hydrogen-ion concentration of the solution, as one would expect, also has an important influence upon the rate.

The accompanying graph (Fig. 2) constructed from our results shows the effect of the hydrogen-ion concentration upon the rate of the formation of acetophenone phenylhydrazone at 60°. The optimum P_H evidently lies between the limits 4 and 5.

The following method we found to be very successful.

[4] Ref. 2, p. 2988.

To a 100-cc. ground-glass stoppered graduated flask were added 25 cc. of 0.25 *M* $C_6H_5HNNH_2 \cdot HCl$, 25 cc. of buffer solution (0.5 *M* NaH_2PO_4), to which enough phosphoric acid had been added to give the buffer a P_H of 4.6, 10 cc. of acetophenone (1 cc. contained 0.0246 g. of acetophenone) dissolved in 40% alcohol by volume and 40 cc. of sodium chloride containing 370 g. per liter (saturated). The air was displaced by nitrogen and the tightly stoppered flask immersed in a water-bath at 60°. The yield was 100% of the theoretical in less than thirty minutes. The time required to obtain 100% yield at room temperature as shown in graph V was twelve hours in a solution having a P_H of 6.1. No doubt the time required would have been materially reduced if the P_H had been adjusted to between 4 and 5.

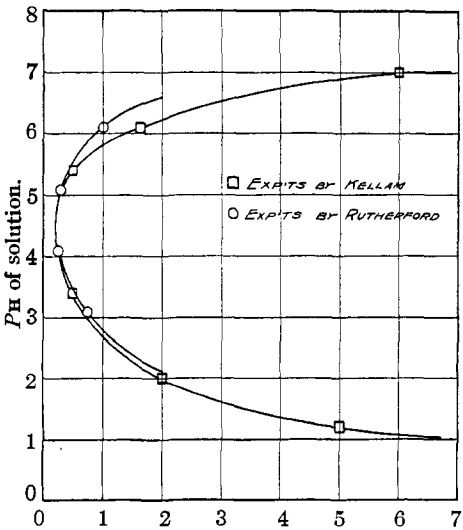

Fig. 2.—Relation between P_H of solution and time required to produce 100% yield of acetophenone phenylhydrazone.

Figures 3 and 4 show the rate of reaction at 60° at a P_H of 7.0 and of 7.8, respectively. These rates are quite obviously very much slower than for lower P_H's. In fact it is possible that at P_H 7.8 the reaction might never arrive at completion.

All the determinations of phenylhydrazine were made by the method described in the earlier paper referred to,[5] with such modifications as have herein been shown to be necessary in the presence of alcohol.

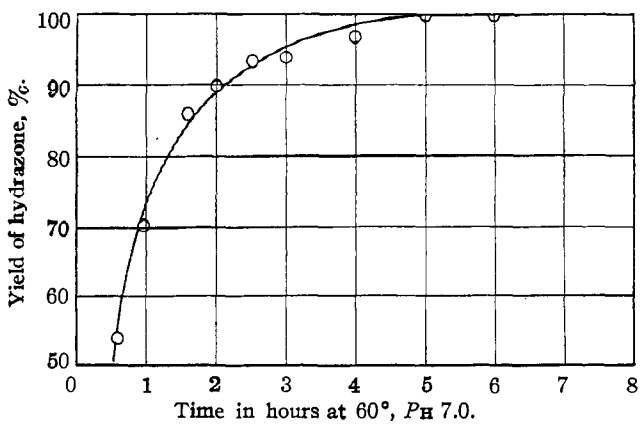

Fig. 3.—Acetophenone phenylhydrazone, time–yield, P_H 7.0.

In each determination we added 10 cc. of the phenylhydrazine solution to an excess of the 0.1 *N* iodine, usually 30 cc.

[5] Ref. 2, p. 2986.

Part III

$$(C_6H_5)_2C{=}O + C_6H_5HNNH_2{\cdot}HCl \rightleftharpoons (C_6H_5)_2C{=}NNHC_6H_5 + HCl + H_2O$$

Optimum Conditions for the Preparation of Benzophenone Phenylhydrazone.—To secure 100% yield of this hydrazone from the ketone in a reasonable time necessitates very careful control of conditions. To keep

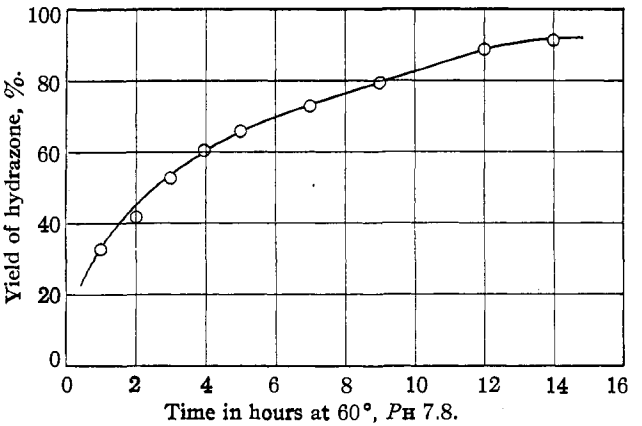

Fig. 4.—Acetophenone phenylhydrazone, time–yield, P_H 7.8.

the ketone in solution, the alcoholic content of the mixture must be not much below 50% by volume. Even at 60° and with 50% alcohol the reaction proceeds much more slowly than for acetophenone.

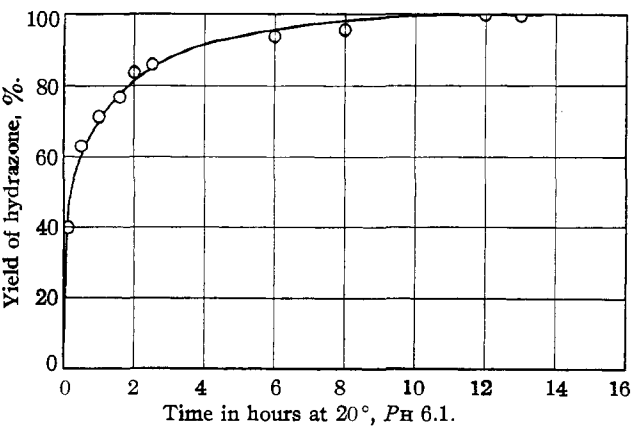

Fig. 5.—Acetophenone phenylhydrazone, time–yield, P_H 6.1.

In the formation of the hydrazone, water is split off. One would expect, therefore, that by using absolute alcohol the rate of reaction would rise. The solubility of the hydrazone would, however, increase with increase in alcohol concentration. As a result the yield of hydrazone would tend to

diminish above a certain alcoholic concentration in spite of the increase in the rate of its formation. We had not time to determine experimentally,

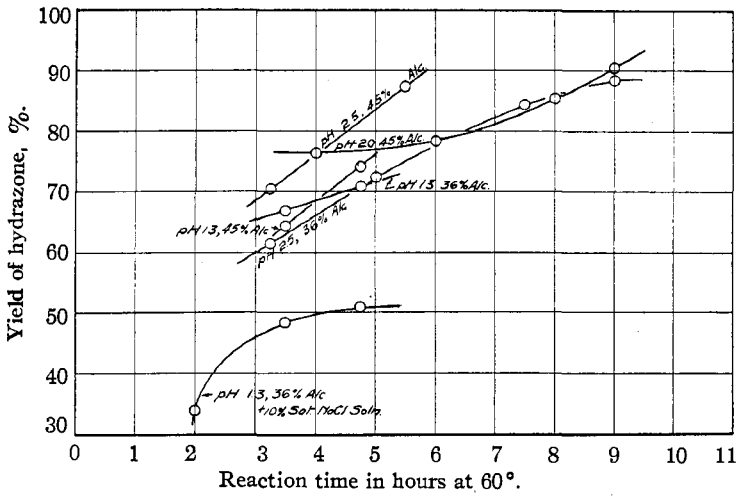

Fig. 6.—Yields of benzophenone phenylhydrazone in solutions of different composition, %.

from the viewpoint of both time and yield, the most effective alcoholic concentration. In any case the opinion of the experimenter would also have an important bearing upon the interpretation of the word *effective*. An increase in alcohol content would, unfortunately, add to our analytical troubles, and since the study was originally undertaken for the purpose of developing an analytical method, we have endeavored for this reason to keep the alcohol concentration down to a convenient figure. Figure 6 gives some indication of the influence at 60° of the hydrogen-ion concentration and of the alcoholic content upon the rate of the reaction.

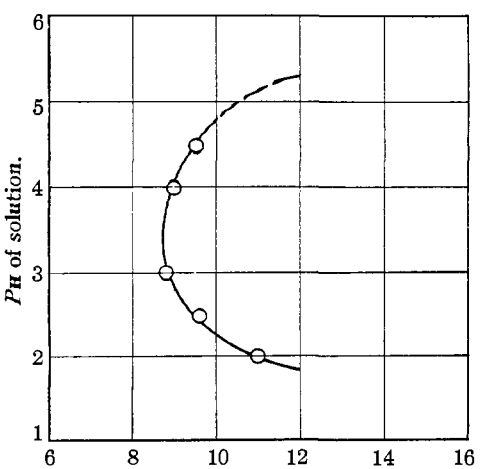

Fig. 7.—Relation between P_H of solution (50% alcohol) and time required to produce 100% yield of benzophenone phenylhydrazone.

Figure 7 shows the effect of the hydrogen-ion concentration on the rate of the reaction at 60° when the alcoholic content of the solution is 50% by volume. The optimum hydrogen-ion concentration evidently

lies between P_H 3 and 4, which is very close to the hydrogen-ion concentration of 0.25 *M* phenylhydrazine hydrochloride itself (P_H 3.5).

It seems strange that the addition of saturated sodium chloride retards the rate of formation of this hydrazone, since in all the other hydrazones we prepared the reverse is the case.

One peculiar phenomenon observed in dealing with both the acetophenone and benzophenone phenylhydrazones was that, while both hydrazones are capable of supersaturation to a high degree during formation, nevertheless when they were forced out of solution as soon as they were formed (by constant agitation) the rate of formation was not increased. In the case of the benzophenone phenylhydrazone it even seemed that the longer the elapsed time before the crystals of hydrazone appeared (depending on the menstruum employed), the higher was the final yield.

Summary

1. The conditions requisite for obtaining satisfactory results in the iodimetric determination, more particularly in the presence of ethyl alcohol, have been worked out.

2. The effect of hydrogen-ion concentration upon the minimum time required to secure a high yield of the hydrazones of acetophenone and benzophenone has been determined.

3. Details of a method by which very pure phenylhydrazine hydrochloride can be prepared have been worked out.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

RESEARCHES ON PYRIMIDINES. CXXIII. THE REARRANGEMENT OF 2,6-DIMETHOXY-4-CHLOROPYRIMIDINE AND 2,4,6-TRIMETHOXYPYRIMIDINE IN THE PRESENCE OF METHYL IODIDE[1]

BY HARRY J. FISHER AND TREAT B. JOHNSON

RECEIVED SEPTEMBER 16, 1931 PUBLISHED FEBRUARY 5, 1932

Hilbert and Johnson[2] showed that 2,6-dimethoxypyrimidine I in the presence of methyl iodide was quantitatively rearranged at room temperature to 2-oxy-3-methyl-6-methoxypyrimidine III.

$$\overline{N{=}C(OCH_3){-}N{=}C(OCH_3)CH{=}CH} + CH_3I \longrightarrow$$

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[1] This paper is constructed from a portion of a Dissertation presented by Harry Johnstone Fisher to the Graduate School of Yale University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1931.

[2] Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930); Johnson and Hilbert, *Science*, **69**, 579 (1929).