

(d) The above results apply to dilute solutions within the range covered by the experimental work.

2. The rate of dialysis was determined by removing definite volumes of the dialyzed solution at recorded intervals and inverting one portion of the removed samples to determine the percentage of sucrose calculated from the portion that was inverted.

3. Bertrand's method of analysis was used.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITIES OF TEXAS AND ILLINOIS.]

SYMMETRICAL DI-ISOPROPYL-HYDRAZINE AND ITS DERIVATIVES.

(Preliminary Article.)

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Introduction.

Little work has been done on the purely aliphatic symmetrical hydrazines or hydrazo compounds and, with the exception of the stable azomethane¹ and certain azo derivatives of *isobutyric acid*,² the corresponding azo derivatives are unknown. Harries³ could not isolate azoethane, and Franke⁴ who obtained a small amount of symmetrical di-*isobutyl*-hydrazine, evidently did not have enough material to study this compound at all thoroughly. Busch, in working with the latter hydrazine⁵ does not mention the azo compound. He reports that Stolle and his coworkers made symmetrical hydrazines, but there seem to be no published articles available on this work.

The azines which are so easily prepared from hydrazine through its reaction with aldehydes and ketones, both aliphatic and aromatic, might be expected to yield, on reduction, the corresponding hydrazo compounds and thus furnish a readily available source for these substances. In some cases the reduction proceeds smoothly; *e. g.*, symmetrical benzylhydrazine ($C_6H_5CH_2NHNHCH_2C_6H_5$) is easily prepared from benzalazine, ($C_6H_5CH=N-N=CH-C_6H_5$). However, up to the present the reduction, in this sense, of aliphatic aldazines and ketazines has failed. Curtius, who discovered dimethyl-ketazine⁶ ($(CH_3)_2C=N-N=C$

¹ Thiele, *Ber.*, **42**, 2575 (1909).

² Thiele and Heusser, *Ann.*, **290**, 30 (1896). Thiele and Stange, *Ann.*, **283**, 1 (1894). Bailey and Knox, *THIS JOURNAL*, **29**, 890 (1907).

³ Harries, *Ber.*, **27**, 2279 (1894).

⁴ Franke, *Monatsh.*, **19**, 526 (1898).

⁵ August Busch, "Über *Isobutyl*hydrazine und *Diisobutyl*hydrazine," *Dissertation*, Heidelberg, 1904.

⁶ Curtius, *J. prakt. Chem.*, [2] **44**, 164 (1891).

$\langle(\text{CH}_3)_2\rangle$ tried to reduce it to the symmetrical hydrazine, but he found that it is very easily decomposed into acetone and hydrazine in acid solution while alkaline reducing agents had no effect on the ketazine. Thiele attempted⁷ to reduce this same azine, but obtained negative results with electrolytic methods he found satisfactory for the reduction of benzalazine. He also tried to prepare symmetrical di-*isopropyl*-hydrazine⁸ through the elimination of two molecules of carbon dioxide from *iso*-butyric acid, but did not succeed. Wieland⁹ reports that the purely aliphatic aldazines are not reducible. (Presumably ketazines would be included in this statement.) It remained for Mailhe,¹⁰ quite recently, to reduce ketazines. He used the Sabatier-Senderens method of catalytic reduction over hot nickel. The results obtained are of little interest however, because the main products isolated were mono- and di-*isopropyl*amine.

We have become convinced, through work at the University of Texas and a continuation of this at the University of Illinois, that dimethylketazine does not yield the symmetrical hydrazine with any of the ordinary neutral or alkaline reducing agents, such as aluminum amalgam, iron powder, sodium in alcoholic solution, sodium amalgam in neutral or alkaline solution, and sodium and alcohol in the presence of boric acid.

Recently, in the laboratory of the University of Texas, an exhaustive research on the use of colloidal platinum, according to the method of Skita,¹¹ in the reduction of azines and semicarbazones was begun. The present paper deals with the reduction of dimethylketazine by this method and the process gives, in a yield of over 90%, symmetrical di-*isopropyl*-hydrazine that Curtius, Thiele, and Mailhe were unable to prepare by other methods of reduction. It is now possible to produce this interesting substance with little labor, in any amount desired and, no doubt, an expansion of this reaction will make available a whole series of hydrazo aliphatic hydrocarbons.

From the work of Rupe and Oestreicher¹² it is evident that the reduction of semicarbazones presents difficulties similar to those that were encountered in the case of azines but it appears probable that the Skita method of reduction will also be found effective here.¹³

⁷ Thiele, *Ann.*, **376**, 262 (1910).

⁸ Thiele and Heusser, Ref. 2.

⁹ H. Wieland, "Die Hydrazine," Ferdinand Enke, 1913, Stuttgart.

¹⁰ Mailhe, *Compt. rend.*, **170**, 1265 (1920).

¹¹ Skita and W. A. Meyer, *Ber.*, **45**, 3578, 3589 (1912).

¹² Rupe and Oestreicher, *ibid.*, **45**, 30 (1912).

¹³ Neighbors and Bailey working in the laboratory of the University of Texas find that acetone semicarbazone yields very smoothly, on reduction with colloidal platinum as catalyst, carbon-amido-hydrazo-propane. A description of this phase of the work will appear shortly in THIS JOURNAL.

Although catalytic reduction, using platinum or palladium as catalyst and hydrogen gas as reducing agent, has been known for half a century, the possibilities of this method of reduction were not fully recognized until after the year 1900, and intensive investigation with this form of catalytic reduction really was begun in 1908. During this period three main methods were worked out: (1) the Willstätter method,¹⁴ using platinum black prepared according to Low;¹⁵ (2) the Paal method,¹⁶ using colloidal palladium or platinum protected by the sodium salt of protalbinic or lysalbinic acid, available only for reduction in neutral or alkaline solutions; (3) the Skita method,¹⁷ using gum arabic as protective colloid instead of Paal's protalbinic or lysalbinic acid. The gum arabic stabilizes the colloid in such a way that the reduction may be carried out in neutral, alkaline, or acid solution while at the end of the run the colloid is easily broken by the addition of acetone. Skita furthermore originated the principle of inoculation in catalytic reduction;¹⁸ a small amount of platinic or palladous chloride is reduced separately and a few cubic centimeters of this stock solution can be employed as "seeding" colloid that aids in reducing the main mass of platinum, which, in turn, catalyzes the reduction of the substance in question.

The Skita method was selected as a promising one for the reduction of azines and has proved successful from the start. However, at first it was necessary to employ as much as 100 cc. of 10% chloroplatinic acid for every 100 cc. of ketazine. Even then with this large amount of platinum the yield was only about 80% and several days were required for completion of the reduction. In attempting to improve the yield or, at least, to reduce the amount of platinum used, it was found that partial neutralization of the base formed as the reduction proceeds immensely accelerates the reduction and makes it possible to complete this in a single day with less than a fourth of the platinum formerly used. The extra chloroplatinic acid used in our initial experiments probably owed its main effect to the hydrochloric acid liberated in this reduction rather than to the additional amount of colloidal platinum it added to the reduction mixture. Since then an article, by Skita, has appeared¹⁹ in which he makes the same observation on the effect of hydrochloric acid in a similar

¹⁴ Kauffman, *ibid.*, **51**, 123 (1918). Willstätter, *ibid.*, **51**, 767 (1918).

Rosenmund, *ibid.*, **51**, 580 (1918). Willstätter and E. W. Mayer, *ibid.*, **41**, 1475 (1908).

¹⁵ Low, *ibid.*, **23**, 289 (1890). Willstätter and Hatt, *ibid.*, **45**, 1471 (1912).

¹⁶ Paal and Amberger, *ibid.*, **37**, 124 (1904). Paal, *ibid.*, **45**, 2221 (1912). Borsche, *ibid.*, **52**, 2077 (1919).

¹⁷ Skita and W. A. Meyer, *ibid.*, **45**, 3579, 3589 (1912). Skita, *ibid.*, **45**, 3313 (1912). Rabe, *ibid.*, **45**, 2166 (1912). Skita, *ibid.*, **42**, 1627 (1909); **52**, 1520 (1919).

¹⁸ Skita, *ibid.*, **45**, 3579 (1912).

¹⁹ Skita, *ibid.*, **52**, 1521 (1919).

case. Further experience in these laboratories indicates that addition of hydrochloric acid is always necessary when a base is formed by catalytic reduction.

In experiments now in progress, it is found that addition of the theoretical amount of hydrochloric acid at the beginning of the run in no way diminishes the yield of 90 to 95% (based on the amount of ketazine used) that is obtained by keeping the solution only partially neutralized. Since this seems to indicate that the ketazine is not hydrolyzed appreciably by dilute acid under the conditions of our experiments, the catalytic reduction of a mixture of 1 mol of hydrazine hydrate, 1 mol. of hydrochloric acid, and 2 mols of acetone should give good results while at the same time obviating the isolation, with rather unsatisfactory yields, of dimethyl-ketazine. Three preliminary runs using, in each, 25 g. of hydrazine hydrate in 250 cc. of water gave 78, 80, and 74 g. of the hydrochloride of symmetrical di-*isopropyl*-hydrazine. Although only once recrystallized from alcohol, samples of this salt melted at 197–198°, had a chlorine content of 23.8% (by titration with silver nitrate), and 3 iodine titrations gave an average purity of 95.3% (2 atoms of iodine to 1 mol of the hydrazine) showing that the salt is practically pure and the yield very nearly quantitative (based on the hydrazine hydrate used), while the time required for this reduction is only 3 to 4 hours.

The hydrazo compound formed in the reduction of dimethyl-ketazine is similar to the other symmetrical hydrazines in its physical properties. It is difficult to obtain the base completely anhydrous, and it is very easily oxidized. In all reactions so far observed it is monobasic. The behavior of the base towards mild oxidizing agents is different from that of other compounds of this series.

Work on other reactions of this hydrazine and on its various oxidation products is being continued in this laboratory. It is also planned to reduce other azines of the aliphatic series, especially acetaldazine and methyl-ethyl-ketazine or methyl butyl-ketazine.

Experimental Part.

Reduction of Dimethyl-ketazine.—The initial reductions were carried out on dimethyl-ketazine prepared according to the method of Curtius and Zinkeisen.²⁰ Since the yields of ketazine were only from 60 to 70% of those expected from the amount of hydrazine sulfate used, the isolation of the ketazine has been abandoned and present runs are made on a mixture of hydrazine hydrate, acetone, and hydrochloric acid. The hydrochloric acid was found necessary in case of the initial experiments and its use is essential also in runs as now made.

²⁰ Curtius and Zinkeisen, *J. prakt. Chem.*, [2] 58, 315 (1898).

The Skita apparatus²¹ is used, the container for the reduction mixture being a liter flask. This bottle is charged with 25 g. of hydrazine hydrate (calculated from iodine titration, according to the method of Stolle,²² of a solution of the hydrate) in 100 cc. of water. To this is added a mixture of 0.5 g. of gum arabic dissolved in 50 cc. of water and 10 cc. of chloroplatinic acid. The "seeding" colloid is next prepared by mixing 10 cc. of water, a few drops of gum arabic solution, 5 cc. of chloroplatinic acid, 0.5 cc. of 30% sodium hydroxide, and a few crystals of the hydrochloride of symmetrical di-isopropyl-hydrazine, or some other equally good reducing agent. On heating this mixture, reduction of the platinum begins at once. The hot mixture is rapidly added to the solution in the flask, to which are then added, under thorough shaking of the flask, 100 cc. of 18.5% hydrochloric acid and finally 100 cc. of acetone. The flask is then connected to the apparatus, the system evacuated and filled with hydrogen from a cylinder, until the apparatus is under a total pressure of 2 atmospheres. The hydrogen cylinder should be supplied with a reducing valve to prevent accidents and damage to the apparatus in filling the reservoir and flask.

The room temperature, hydrogen pressure, atmospheric pressure, and gage readings are now recorded and the shaker started. During the few minutes required for the reduction of the chloroplatinic acid the absorption is relatively slow, but as reduction of the platinum proceeds the rate of absorption increases until the gas is used up at the rate of 8 to 12 liters an hour. As reduction proceeds the absorption of hydrogen gradually slows down and comes to a complete stop at the end of 3 to 4 hours, when the theoretical amount of hydrogen has been absorbed. Enough heat is generated to keep the reduction mixture at a temperature of about 45° during the first 2 hours of the run. In case of poisoning of catalyst or other cause of slow reduction an additional 5 cc. of chloroplatinic acid is sometimes required to complete the reduction. As stated in the introductory part of this paper, the yields on 3 consecutive runs using, in each, the amount of hydrazine hydrate given above, gave yields of 78, 80, and 74 g. of hydrochloride of symmetrical di-isopropyl-hydrazine.

This salt is of about 93% purity so that the yield is practically quantitative, as the calculated yield is 76.2 g. of the hydrochloride.

Symmetrical Diisopropyl-hydrazine.—The reaction mixture, from the machine, is treated with acetone until the platinum and gum arabic precipitate together in the form of flakes, then filtered through a pleated filter, the filtrate acidified with hydrochloric acid and the solution evaporated to dryness *in vacuo* on a water-bath. The crude hydrochloride is slightly yellow and hygroscopic, but after recrystallization from alcohol the salt is pure white and nonhygroscopic. The free base is obtained from the salt by treatment with concentrated sodium hydroxide, the yellow oily layer separated, dried for 12 to 15 hours over solid potassium hydroxide, the base again separated and dried for 1 day with aluminum amalgam. The oil is then rapidly filtered from the inorganic material and fractionated. The base is now of a light straw color and distills between 110° and 124.5° as a colorless mobile liquid of ammoniacal, ethereal odor. A complete analysis of the 124° to 124.5° fraction as well as hydrochloric acid and iodine titrations shows this to be the pure symmetrical diisopropyl hydrazine. Even air very readily oxidizes this hy-

²¹ Skita and Meyer, *Ber.*, **45**, 3589 (1912).

²² Stolle, *J. prakt. Chem.*, [2] **66**, 332 (1902).

drazo compound and this property makes aluminum amalgam far superior to barium oxide, which is usually employed as a dehydrating agent for hydrazines.²³ In attempts to dry with barium oxide as much as 50% of the base is often oxidized to the product boiling at 88.8°, and even when an inert gas is kept over the mixture a considerable loss occurs.

The estimation of carbon and hydrogen in symmetrical diisopropyl-hydrazine presents certain difficulties which may be overcome by running the combustion very slowly on a gas furnace under the following conditions. In the beginning with only the burners next to the absorption apparatus lighted, a very slow stream of air (oxygen causes small explosions) is passed through the tube and from time to time, after the liquid in the bulb begins to vaporize, an ice pack is applied to the bedplate immediately under the sample to keep down the tendency of the combustion to run wild. On the other hand when the vaporization does not proceed fast enough a hot tile is held over the sample for a few seconds. Through this alternate cooling and heating the rate of vaporization and combustion is very carefully regulated until all of the liquid has been expelled from the bulb. The tendency of the combustion to run wild is due to the ease with which the hydrazo compound and, to a lesser extent, its derivatives are oxidized, rather than to volatility. Franke⁴ experienced a similar difficulty in the analysis of symmetrical diisobutyl-hydrazine with a boiling point of 170–175°. After the sample has been volatilized as described above, the combustion is completed in the usual manner.

Analyses. Calc. for C₆H₁₂N₂: C, 62.08; H, 13.80; N, 24.14. Found: C, 62.39, 62.17; H, 13.97, 14.31; N, 24°.54, 24.30.

This sample boiled at 124° to 124.5° under 740 mm.; [n]_D^{23°}, 1.4087; d ₄^{31°}, 0.7712.

Since the substance is very easily oxidized, a convenient and rapid check on its purity is obtained by titration with iodine according to Stolle.²²

Hydrochloride of Symmetrical Diisopropyl-hydrazine.—The crude product mentioned above, recrystallized 3 times from alcohol, is obtained in the form of colorless needles melting at 198° (corr.). It is readily soluble in water and alcohol and practically insoluble in ether, acetone and benzene. The salt, like the base, is readily attacked by all common oxidizing agents. A peculiar reaction in this connection is the quantitative oxidation of the dry hydrochloride by dry copper oxide to a product boiling at 88.8° under 740 mm. pressure. A mixture of the substances, after a few minutes, gives the characteristic odor of the oxidation product. After 24 hours it becomes pasty, and finally the greenish-straw colored product is present in such amount that the whole mass may be poured out of the flask. There are reasons for believing that this is the azo compound corresponding to the symmetrical diisopropyl-hydrazine, but work on this product is still in progress and will be reported in a later article.

The hydrochloride of diisopropyl-hydrazine is so easily oxidized that nitrogen determinations may be made by simply oxidizing the salt by means of a dichromate-sulfuric acid mixture and collecting the nitrogen as usual in wet methods. Kjeldahl determinations made in the ordinary manner as well as qualitative nitrogen tests fail because of the ease with which nitrogen is split out.

Analyses. Calc. for C₆H₁₇N₂Cl: Cl, 23.27; N, 18.36. Found: Cl(Carius) 22.99, (titration AgNO₃) 23.77, 23.75, 23.78, 23.69; N, (Dumas) 18.21, (sulfuric-dichromate wet method) 18.15.

Diisopropyl-phenylthio-semicarbazide, (CH₃)₂CHNHN(CSNHC₆H₅)CH(CH₃)₂.—An aqueous solution of the base treated, under cooling, with phenyl mustard oil gives

²³ Harries and Klamt, *ibid.*, 28, 504 (1895). Harries, *ibid.*, 31, 56 (1898).
Knorr and Kohler, *ibid.*, 39, 3259 (1906).

a good yield of a white flaky condensation product. Recrystallized from ether it melts at 129.5° (corr.). It is soluble in acetone, chloroform, benzene and ether and but slightly soluble in water, alcohol and ethyl acetate.

Analyses. Calc. for C₁₃H₂₁N₃S: S, 12.75; N, 16.74. Found: S(Carius) 12.45, 12.45; N, (Dumas) 16.73.

In addition to the compounds studied and analyzed the potassium cyanate and the phenyl-isocyanate condensation products and the oxalic acid salt are obtained as well crystallizing compounds, while the benzoyl compound shows no tendency to crystallize.

Summary.²⁴

1. Dimethyl-ketazine is reduced to the symmetrical diisopropylhydrazine by means of the Skita method of catalytic reduction.

2. The properties of the hydrazine and of some of its salts and derivatives are described.

3. Other derivatives and their reactions are being studied and are to be reported on in a later article.

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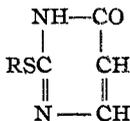
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. XCI. ALKYLATION OF 2-MERCAPTO-PYRIMIDINES.

BY WILLIAM J. HORN.¹

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When a 2-mercapto-6-oxypyrimidine combination is subjected to alkylation in alkaline solution, it is susceptible to attack in three different positions and, at the present time, we have no law, or rule, which will permit one to predict the configuration most likely to be formed.



In most of the cases so far examined² where the radical, R, of the 2-mer-

²⁴ The preparation of symmetrical diisopropyl hydrazine was effected by Bailey and Lochte at the University of Texas and the work was transferred later by Mr. Lochte to the University of Illinois. Professor Bailey prefers the name 2-hydrazopropane.

¹ This paper was constructed from a dissertation presented by William John Horn to the Faculty of the Graduate School of Yale University, in June, 1921, in candidacy for the degree of Doctor of Philosophy. (T. B. Johnson).

² Johnson and Clapp, *J. Biol. Chem.*, **5**, 51 (1908); Johnson and Heyl, *Am. Chem. J.*, **37**, 628 (1907); Wheeler and Johnson, *ibid.*, **42**, 30 (1909); Johnson and Jones, *ibid.*, **40**, 538 (1908); Johnson and Derby, *ibid.*, **40**, 444 (1908); Wheeler and McFarland, *ibid.*, **42**, 101 (1909); Wheeler and Liddle, *THIS JOURNAL*, **30**, 1152 (1908); Johnson and Zee, *Am. Chem. J.*, **49**, 287 (1913).