

Organic Reactions
Volume 4

CHAPTER 8

THE WOLFF-KISHNER REDUCTION

DAVID TODD

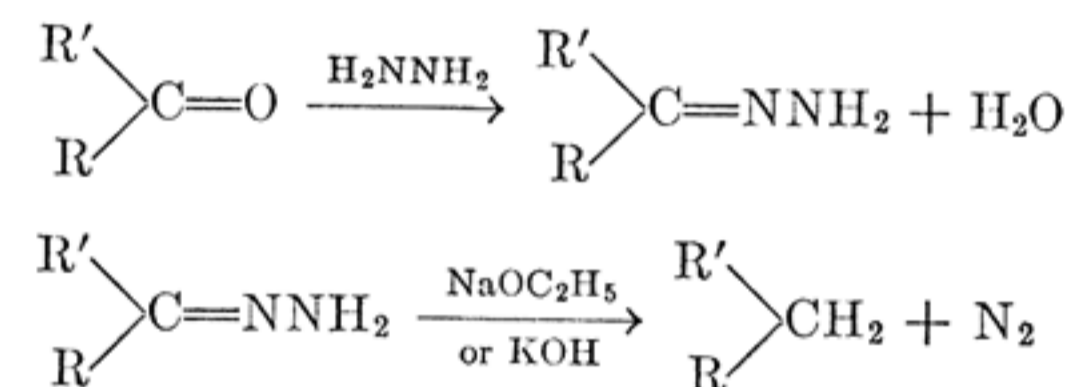
Amherst College

CONTENTS

	PAGE
INTRODUCTION	379
SCOPE AND LIMITATIONS	380
Side Reactions and Abnormal Reductions	380
Variations in the Wolff-Kishner Method	383
Temperature	383
Catalyst	384
Reduction at Atmospheric Pressure	385
Comparison with Other Methods	385
Table I. Comparison of Wolff-Kishner and Clemmensen Reductions	387
EXPERIMENTAL PROCEDURES	388
Wolff Reduction of a Hydrazone	388
Reduction of Camphor	388
Reduction of 1-Keto-8-methyloctahydropyridocoline	389
The Direct Wolff Reduction	389
Reduction of 2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole	389
Kishner Reduction of a Hydrazone	389
Reduction of Ethyl Cyclobutyl Ketone	389
Reduction of 4-Methylacetophenone	389
Kishner Reduction of a Semicarbazone	390
Reduction of <i>cis</i> - β -Bicycloöctanone	390
Wolff-Kishner Reduction without an Alkaline Catalyst	390
Reduction of 2,3-Benzo-1-azafluorenone	390
Reduction of Pyrene-3-aldehyde	390
Direct Wolff-Kishner Reduction at Atmospheric Pressure	391
Reduction of 5-Keto-8-methylnonanoic Acid	391
Reduction of β -(<i>p</i> -Phenoxybenzoyl)-propionic Acid	391
TABLE II. COMPOUNDS REDUCED BY THE WOLFF-KISHNER METHOD	391

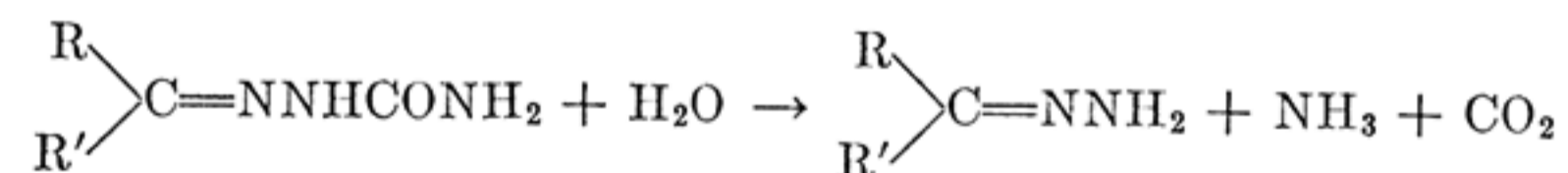
INTRODUCTION

The oxygen atom of the carbonyl group in aldehydes and ketones can be replaced by hydrogen by heating the semicarbazone, the hydrazone, or the azine in the presence of an alkaline catalyst—a reaction known as the Wolff-Kishner reduction. Two slightly different variations of the method were discovered independently by Kishner¹ in 1911 and by Wolff² in 1912. Kishner found that by dropping a hydrazone slowly upon hot potassium hydroxide, with which some platinized porous plate had been mixed, the corresponding hydrocarbon was formed. Wolff accomplished the same result by heating a semicarbazone or hydrazone in a sealed tube to about 180° in the presence of sodium ethoxide. The reduction is illustrated by the following equations. Though the Kishner



method has the obvious advantage of avoiding the necessity of a sealed tube, the Wolff method has been modified to obviate both this necessity and that of isolating the intermediate carbonyl derivative.

The first step in the Wolff reduction of a semicarbazone has been shown to be the conversion of the semicarbazone to the hydrazone.² Wolff pictured this reaction as a hydrolysis.* That hydrazone formation



is the first step in the reduction of a semicarbazone is proved by the isolation of the hydrazone from the semicarbazone if the temperature employed is not sufficiently high to produce reduction. There seems to be no appreciable difference in the yield of hydrocarbon from the two derivatives.

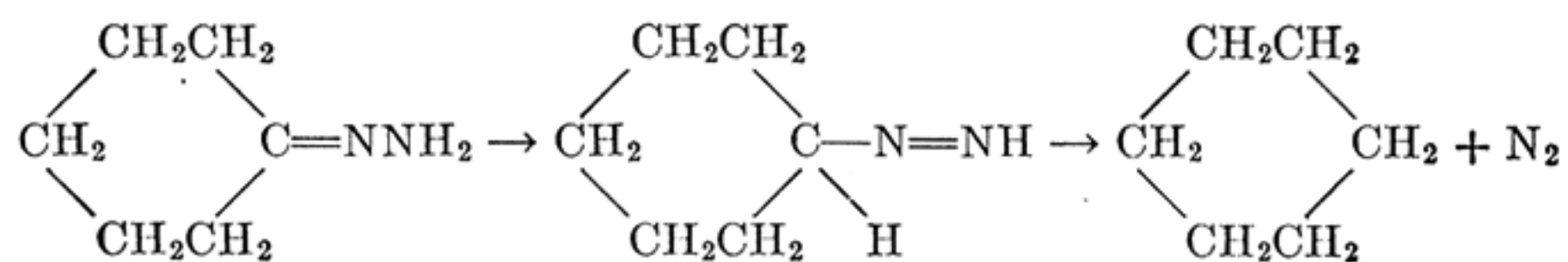
* Because of this conception of the mechanism of semicarbazone decomposition, Wolff suggested the use of 96–98% ethanol in the preparation of sodium ethoxide for the reduction of semicarbazones. For the reduction of hydrazones he used 100% ethanol. However, Eisenlohr and Polenske³ have found that the reduction of *trans*- β -decalone semicarbazone proceeds smoothly in the presence of rigorously dry ethanol. An investigation into the mechanism of this step is certainly in order.

¹ Kishner, *J. Russ. Phys. Chem. Soc.*, **43**, 582 (1911) [*C. A.*, **6**, 347 (1912)].

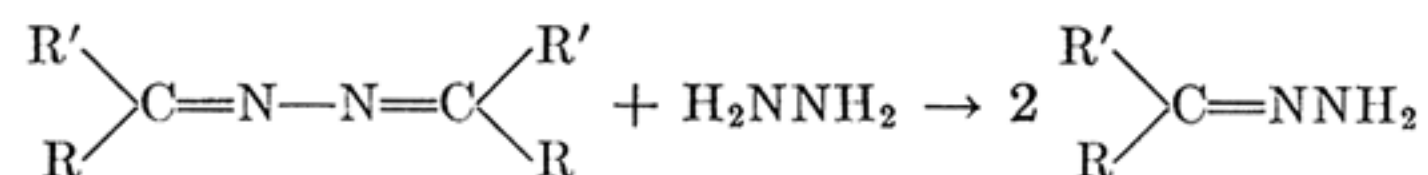
² Wolff, *Ann.*, **394**, 86 (1912).

³ Eisenlohr and Polenske, *Ber.*, **57**, 1639 (1924).

The mechanism of the Wolff-Kishner reduction has been studied by Balandin and Vaskevich.^{3a} A detailed investigation of the kinetics of the decomposition of cyclohexanone hydrazone indicated that two steps are involved, and the isomeric azo compound is suggested as the short-lived intermediate.



Although one can employ the azine for the Wolff-Kishner reduction it is only rarely desirable to do so. Generally the azine is so insoluble that it is brought to react only with great difficulty. When the azine is used it must be treated with alkali in the presence of excess hydrazine hydrate, since it must be first converted to the hydrazone before reduction occurs.

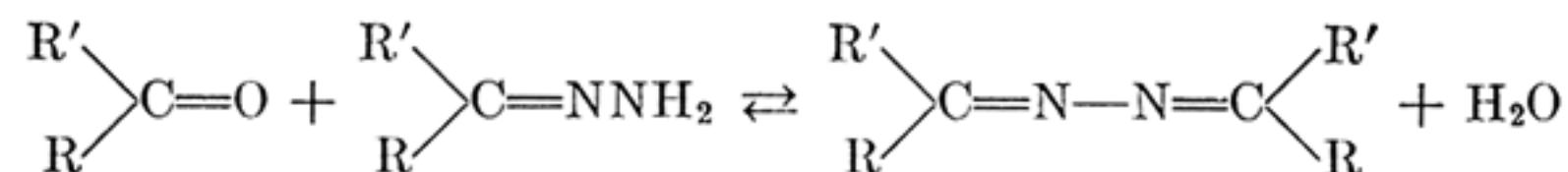


SCOPE AND LIMITATIONS

Although the Clemmensen reduction is the most common method for reducing aldehydes and ketones to the corresponding hydrocarbons,⁴ the Wolff-Kishner method is a valuable complementary tool. For instance, the Clemmensen method cannot be used to reduce pyrrole derivatives since pyrroles are sensitive to acids. The same applies to the furan field. The Wolff-Kishner method generally succeeds with compounds of high molecular weight where the Clemmensen technique fails, presumably because of the insolubility of the carbonyl compound.

Side Reactions and Abnormal Reductions

There are two principal side reactions that may take place when a compound is submitted to the Wolff-Kishner reduction; both are largely preventable by proper precautions. First there is the possibility of azine formation by the reaction of one molecule of hydrazone with one



molecule of the carbonyl compound. Since the ketone can be formed only by hydrolysis of the hydrazone, its formation can be suppressed by the rigid exclusion of water. It was to avoid azine formation that Wolff used sodium ethoxide prepared from absolute ethanol.

The other side reaction is the formation of the secondary alcohol from the ketone, or of the primary alcohol from the aldehyde. This seems to be brought about entirely by hydrolysis of the carbonyl derivative to the free carbonyl compound followed by sodium alkoxide reduction to the carbinol. Alcohol formation may be repressed either by the exclusion of water or by the addition of hydrazine, since water is necessary for hydrolysis and the presence of hydrazine shifts the equilibrium in favor of the hydrazone. Apparently the complete absence of water is more important in some cases than in others. Eisenlohr and Polenske³ obtained a large amount of decalol and only a small amount of decalin when they reduced the semicarbazone of *trans*- β -decalone with sodium and 99.9% ethanol; when 100% ethanol was used the fraction of decalol formed fell to one-fourth of the total product. Dutcher and Wintersteiner⁵ have shown that in the steroid field the often-observed formation of alcohols in Wolff-Kishner reductions can be suppressed by employing excess hydrazine hydrate. Cholestanone semicarbazone with sodium ethoxide at 180° gave only 3(α)- and 3(β)-cholestanol; when hydrazine hydrate was added to the reaction mixture cholestanone was formed in 75% yield. The same authors also showed that the semicarbazone, the hydrazone, and the azine of cholestanone were all converted principally to the carbinol in the absence of hydrazine hydrate.

Aside from the reactions normally expected to take place in the presence of alkali, such as hydrolysis of esters, cleavage of ethers, and dehydration, several abnormal reactions may occur. Complete removal of an acyl group has been observed; for example, the reduction of 2,4-diethyl-3,5-dipropionylpyrrole gives 2,4-diethyl-3-propylpyrrole.⁶ A rather remarkable deacylation was found by Hess and Fink.⁷ Both forms of the hydrazone of cuskhygrin were isolated, and both were submitted to Wolff-Kishner reduction under the same conditions. The α -hydrazone gave the normal product; the β -hydrazone was converted to desacetylcuskhygrin. Removal of an acyl group followed by alkylation by the sodium alkoxide may occur, as in the formation of 2-methylpyrrole from 2-acetylpyrrole when sodium methoxide is used as the reduction catalyst.⁸ Direct reduction of 1-acetylanthracene with

⁵ Dutcher and Wintersteiner, *J. Am. Chem. Soc.*, **61**, 1992 (1939).

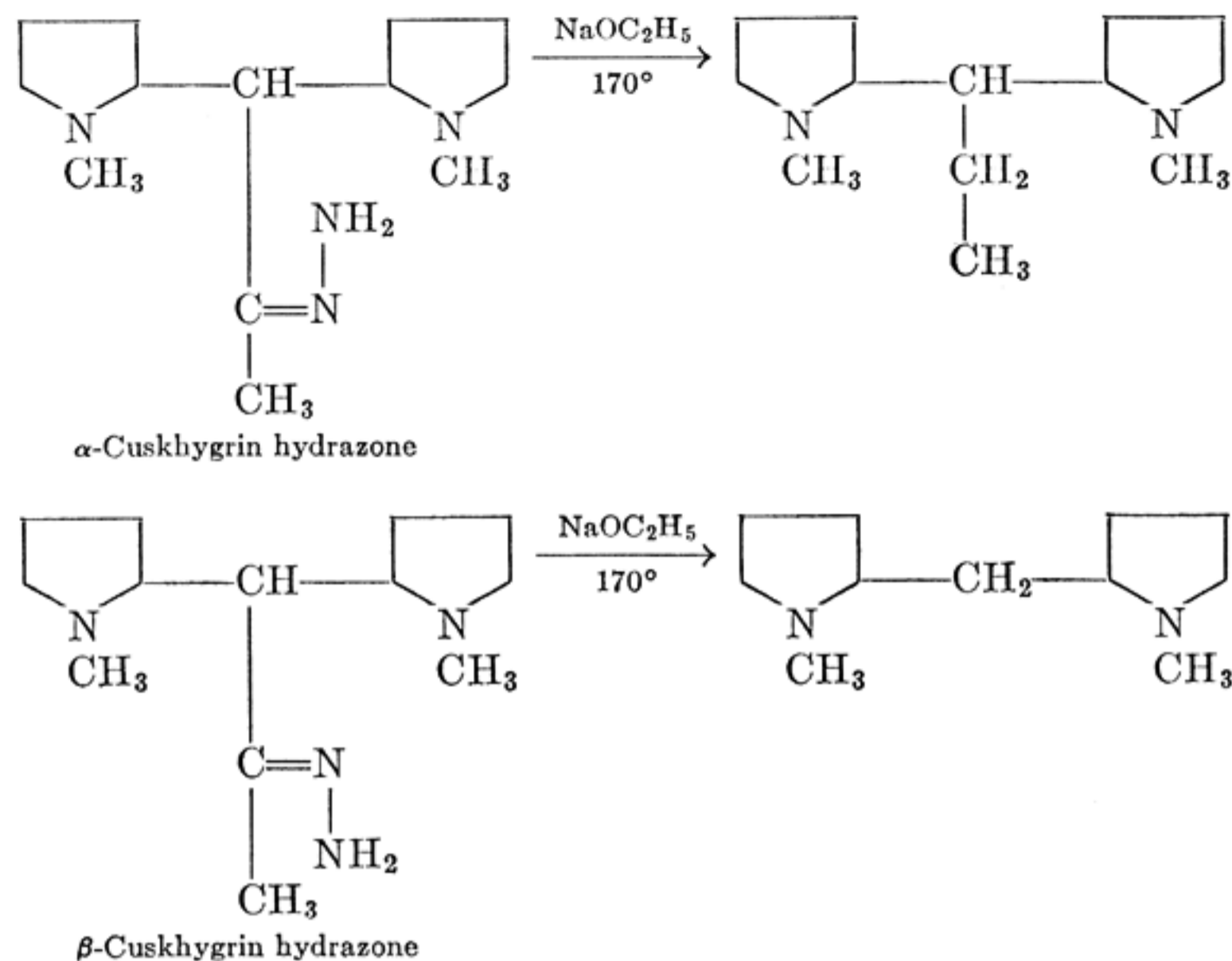
⁶ Fischer, Siedel, and d'Ennequin, *Ann.*, **500**, 137 (1933).

⁷ Hess and Fink, *Ber.*, **53**, 781 (1920).

⁸ Knorr and Hess, *Ber.*, **45**, 2631 (1912).

^{3a} Balandin and Vaskevich, *J. Gen. Chem. U.S.S.R.*, **6**, 1878 (1936) [*C.A.*, **31**, 4575 (1937)].

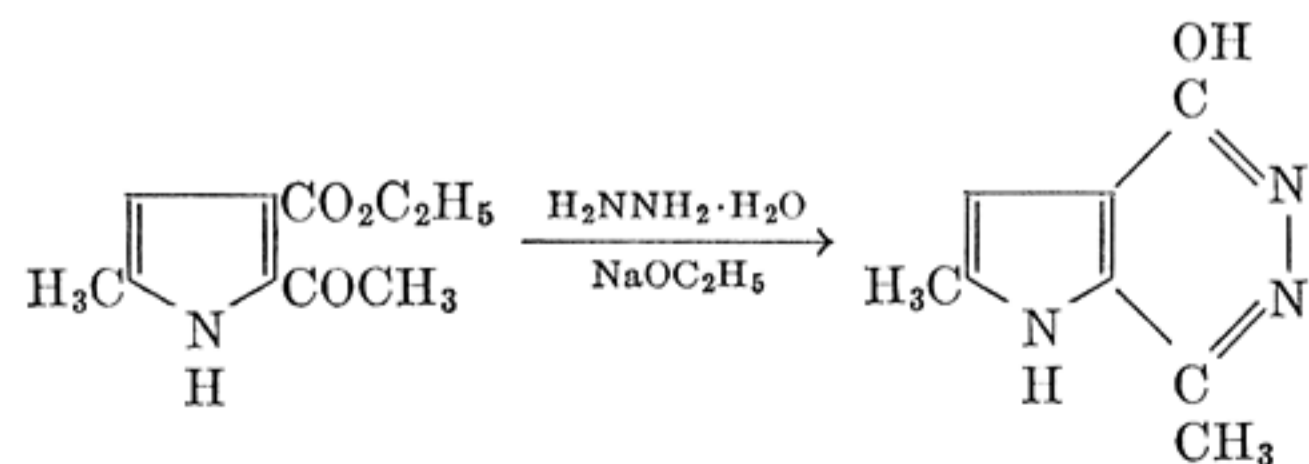
⁴ Martin, *Organic Reactions*, **1**, 155, John Wiley & Sons, 1942.



hydrazine hydrate and sodium ethoxide at 180° for eight hours gives 2-ethylanthracene, whereas reduction of the semicarbazone under the same conditions for only four hours gives the expected 1-ethylanthracene.⁹

Thielepape^{10,11} has found that the Wolff-Kishner reduction of 2-pyridone hydrazone and 2-lepidone hydrazone yields pyridine and lepidine respectively. Presumably the normal products, dihydropyridine and dihydrolepidine, undergo air oxidation to the aromatic products.

Occasionally the intermediate carbonyl derivative will undergo some internal condensation before it has an opportunity to undergo normal reduction. When 5-methyl-3-carbethoxy-2-acetylpyrrole is submitted to direct reduction there is obtained a pyridazine formed by loss of ethyl alcohol from the intermediate hydrazone ester.¹² There is the



⁹ Waldmann and Marmorstein, *Ber.*, **70**, 106 (1937).

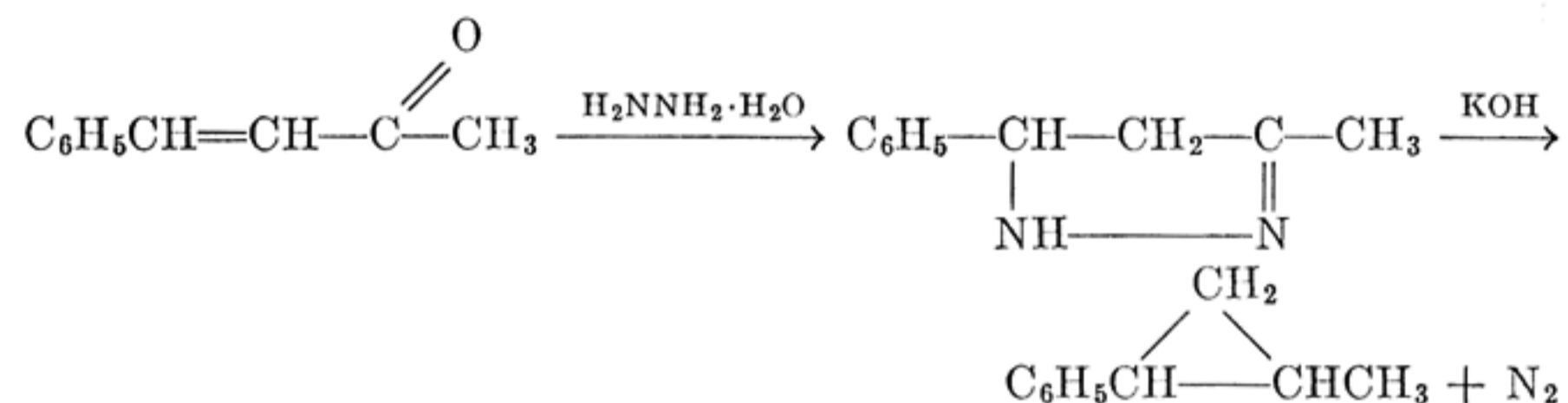
¹⁰ Thielepape, *Ber.*, **55**, 136 (1922).

¹¹ Thielepape and Spreckelsen, *Ber.*, **55**, 2929 (1922).

¹² Fischer, Beyer, and Zaucker, *Ann.*, **486**, 55 (1931).

danger of triazine formation from the monosemicarbazones of α -diketones,¹³ but this can be avoided by employing instead the monohydrazones.¹⁴

α,β -Unsaturated carbonyl compounds require special consideration. These compounds usually react with hydrazine hydrate to form the pyrazoline instead of the normal hydrazone. The pyrazoline on treatment with hot alkali is converted to a cyclopropane derivative.¹⁵ Py-



razoline formation seems to be a necessary step in this synthesis of cyclopropanes. Citral hydrazone when reduced by Kishner's method gives the normal hydrocarbon, 1,7-dimethyl-2,6-octadiene. When the hydrazone is distilled it is converted to the pyrazoline, which under the conditions of the Kishner reduction yields 1-methyl-1-isohexenyl-cyclopropane.¹⁶ Merejkowsky¹⁷ has found that carvenone, carvone, and cyclopentenone-3 react normally instead of forming cyclopropanes, from which it is concluded that cyclopropane formation does not take place if the process requires the formation of one ring within another.

Variations in the Wolff-Kishner Method

In considering variations of the Wolff-Kishner method it should be borne in mind that the minimal conditions for reduction vary greatly with the type of compound to be reduced.

Temperature. In general, heating at 180° for six to eight hours is adequate to achieve complete reduction. The hydrazones of furan derivatives,^{18,19} of substituted benzaldehydes,²⁰ and of substituted acetophenones²¹ undergo rapid reduction at 90 – 100° , but camphor

¹³ Bergstrom and Haslewood, *J. Chem. Soc.*, **1939**, 540.

¹⁴ Ishidate, Kawahata, and Nakazawa, *Ber.*, **74**, 1707 (1941).

¹⁵ Kishner, *J. Russ. Phys. Chem. Soc.*, **44**, 849 (1912) [*C. A.*, **6**, 2915 (1912)].

¹⁶ Kishner, *J. Russ. Phys. Chem. Soc.*, **50**, 1 (1918) [*C. A.*, **18**, 1485 (1924)].

¹⁷ Merejkowsky, *Bull. soc. chim. France*, (4) **37**, 1174 (1925).

¹⁸ Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 249 (1932).

¹⁹ Zelinsky and Shuikin, *Compt. rend. acad. sci. U.R.S.S.*, **1933**, 60 [*C. A.*, **28**, 2002 (1934)].

²⁰ Lock and Stach, *Ber.*, **76**, 1252 (1943).

²¹ Lock and Stach, *Ber.*, **77**, 293 (1944).

hydrazone² must be heated to 190–200° before reduction will occur. When the semicarbazone of 3-hydroxy-6-ketocholanic acid was heated for five hours at 185°, satisfactory reduction took place, whereas no crystalline compound could be isolated after only two hours of heating.²² On the other hand heating the semicarbazone of 7-keto-12-hydroxy-cholanic acid for more than two hours lowers the yield of product.²³ Ruzicka found that the semicarbazone of cyclopentadecanone was in part still undecomposed after being heated for eight hours at 190°.²⁴

Catalyst. It seems to be taken for granted that an alkaline catalyst is necessary to promote the Wolff-Kishner reduction, but it is not at all clear in just which reactions a catalyst is essential. Curtius and Thun early found that distillation of benzil monohydrazone gave an almost quantitative yield of desoxybenzoin.²⁵ Staudinger and Kupfer found that heating fluorenone at 200° with hydrazine hydrate gives fluorene, and that similar treatment of Michler's ketone, benzophenone, and benzaldehyde gives good yields of the corresponding hydrocarbons.²⁶ Pyrene-3-aldehyde can be reduced by the Staudinger-Kupfer method in 90% yield.²⁷ The fluorenones as a group do not seem to require a catalyst,²⁸ and Borsche has been able to reduce α - and β -benzoynaphthalene by heating the ketones for twenty-four hours at 230° with hydrazine hydrate.²⁹

The commonly used catalysts are sodium methoxide and ethoxide in the Wolff variation, and sodium and potassium hydroxides in the Kishner method. Kishner did not begin to use platinized porous plate habitually with his alkaline catalyst until he had found that the reduction of menthone hydrazone would not proceed when either potassium hydroxide or platinized plate was present alone but only when they were present together.³⁰ However, Wolff was able to obtain smooth reduction of menthone hydrazone with sodium ethoxide at 170°.² The Kishner method has frequently been used with good results without any platinum to supplement the alkali.^{31, 32, 33} Palladium-barium sulfate has been used with the alkali in the Kishner method.³⁴

²² Wieland and Dane, *Z. physiol. Chem.*, **212**, 41 (1932).

²³ Wieland and Dane, *Z. physiol. Chem.*, **210**, 268 (1932).

²⁴ Ruzicka, Brugger, Pfeiffer, Schinz, and Stoll, *Helv. Chim. Acta*, **9**, 499 (1926).

²⁵ Curtius and Thun, *J. prakt. Chem.*, [2], **44**, 161 (1891).

²⁶ Staudinger and Kupfer, *Ber.*, **44**, 2197 (1911).

²⁷ Vollmann, Becker, Corell, Streeck, and Langbein, *Ann.*, **531**, 1 (1937).

²⁸ Borsche and Sinn, *Ann.*, **532**, 146 (1937).

²⁹ Borsche, Hofmann, and Kühn, *Ann.*, **554**, 23 (1943).

³⁰ Kishner, *J. Russ. Phys. Chem. Soc.*, **44**, 1754 (1912) [*C. A.*, **7**, 1171 (1913)].

³¹ Cook and Linstead, *J. Chem. Soc.*, **1934**, 946.

³² Barrett and Linstead, *J. Chem. Soc.*, **1935**, 436.

³³ Asahina and Nogami, *Ber.*, **68**, 1500 (1935).

³⁴ Linstead and Meade, *J. Chem. Soc.*, **1934**, 935.

Sodium dissolved in amyl alcohol has been used as a reduction catalyst to help prevent excessive pressure from developing in the bomb tube during the reduction.³⁵

Reduction at Atmospheric Pressure. Although the Kishner reduction has always been carried out at atmospheric pressure, it was not until 1935 that a Wolff reduction was carried out in an open flask with the aid of a high-boiling solvent. Ruzicka and Goldberg³⁶ found that reduction proceeded when the semicarbazone was heated in benzyl alcohol to which some sodium had been added. This method has been extended by Soffer and co-workers,^{37, 38} who bring about direct reduction of the ketone or aldehyde by refluxing the carbonyl compound, hydrazine hydrate, and sodium in any of several high-boiling solvents such as octyl alcohol, triethanolamine, and the ethylene glycols. Whitmore and co-workers³⁹ worked out essentially the same procedure but felt it desirable to prepare the crude hydrazone before adding the alkaline catalyst. Soffer employed excess metallic sodium (12 moles), excess high-boiling solvent, and 100% hydrazine hydrate to offset the temperature-lowering effect of the water formed in the first step. Huang-Minlon⁴⁰ introduced the following simple expedient: after hydrazone formation is complete (one hour), water and excess hydrazine are removed by distillation until a temperature favorable for the decomposition reaction is attained (190–200°). When this is done, no excess of solvent is required, sodium hydroxide or potassium hydroxide (2–3 moles) can be used in place of metallic sodium, cheap aqueous hydrazine is adequate, and the reaction time is reduced from fifty to one hundred hours to three to five hours. The simple procedure is applicable to large-scale reductions, and the yields are excellent.

Comparison with Other Methods

As has been pointed out the Clemmensen method has certain inescapable drawbacks that render it of little practical value for certain types of compounds. In general, compounds of high molecular weight show great resistance to Clemmensen reduction. Neither 8-keto-17-octadecenoic nor 8-keto-16-octadecenoic acid can be reduced by Clemmensen's method whereas reduction proceeds satisfactorily by the Wolff-

³⁵ Ruzicka and Meldahl, *Helv. Chim. Acta*, **23**, 364 (1940).

³⁶ Ruzicka and Goldberg, *Helv. Chim. Acta*, **18**, 668 (1935).

³⁷ Soffer, Soffer, and Sherk, *J. Am. Chem. Soc.*, **67**, 1435 (1945).

³⁸ Sherk, Augur, and Soffer, *J. Am. Chem. Soc.*, **67**, 2239 (1945).

³⁹ Herr, Whitmore, and Schiessler, *J. Am. Chem. Soc.*, **67**, 2061 (1945).

⁴⁰ Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

Kishner method.⁴¹ Similarly Marker found that the former method failed to reduce all five of a series of steroid ketones while the latter method succeeded.⁴² It is well known that the Clemmensen method often unavoidably gives carbinols and unsaturated compounds. Though such by-products are occasionally found in Wolff-Kishner reductions, the reasons for their formation are known and precautions may be taken to prevent such side reactions. In the reduction of a series of alkyl phenyl ketones the Clemmensen method was found to be useless because of the unsaturated compounds and polymers formed;⁴³ here the Wolff-Kishner method made possible the preparation of pure hydrocarbons.

Table I illustrates the different results obtained when both Clemmensen and Wolff-Kishner reductions were applied to the same compounds. The list is not all-inclusive, and, because of improvements in the techniques of both reduction methods, many of the reported yields are doubtless subject to improvement.

A third method, catalytic hydrogenation, is available for the reduction of the carbonyl group to a methylene group. This method is quite limited in its application and suffers from the defect that points of unsaturation elsewhere in the molecule may be reduced simultaneously.^{44, 45} The carbonyl group must be conjugated with an aromatic system to be reduced catalytically.⁴⁶ This method has been used in the pyrrole field in place of the Wolff-Kishner reduction. By the use of copper-chromium oxide and nickel catalysts, carbethoxyacylpyrroles can be reduced to carbethoxyalkylpyrroles whereas the carbethoxyl group is invariably lost during Wolff-Kishner reduction.^{47, 48} By controlling the conditions 2,4-dimethyl-3,5-diacetylpyrrole can be catalytically reduced to either 2,4-dimethyl-3-ethyl-5-acetylpyrrole or to 2,4-dimethyl-3,5-diethylpyrrole.⁴⁷

Hydrogenation with palladium-charcoal catalyst at normal temperature and pressure has been found to be an effective means for the complete reduction of the conjugated carbonyl group.^{44, 46, 49-52}

⁴¹ Kapp and Knoll, *J. Am. Chem. Soc.*, **65**, 2062 (1943).

⁴² Marker et al., *J. Am. Chem. Soc.*, **65**, 1199 (1943).

⁴³ Schmidt, Hopp, and Schoeller, *Ber.*, **72**, 1893 (1939).

⁴⁴ Foster and Robertson, *J. Chem. Soc.*, **1939**, 921.

⁴⁵ Späth and Schläger, *Ber.*, **73**, 1 (1940).

⁴⁶ Zelinsky, Packendorff, and Leder-Packendorff, *Ber.*, **66**, 872 (1933).

⁴⁷ Signaigo and Adkins, *J. Am. Chem. Soc.*, **58**, 709 (1936).

⁴⁸ Fischer and Höfelmann, *Ann.*, **533**, 216 (1938).

⁴⁹ Zelinsky, Packendorff, and Leder-Packendorff, *Ber.*, **67**, 300 (1934).

⁵⁰ Hartung and Crossley, *J. Am. Chem. Soc.*, **56**, 158 (1934).

⁵¹ Miller, Hartung, Rock, and Crossley, *J. Am. Chem. Soc.*, **60**, 7 (1938).

⁵² Ju, Shen, and Wood, *J. Inst. Petroleum*, **26**, 514 (1940) [*C. A.*, **35**, 1386 (1941)].

TABLE I

COMPARISON OF WOLFF-KISHNER AND CLEMMENSEN REDUCTIONS

Compound	Wolff-Kishner Product	Yield	Clemmensen Product	Yield	References*
β -(3-Methoxybenzoyl)-propionic acid	Normal	64.5%	Normal	42%	52a
2-Acetylanthracene	Normal	—	Normal	—	9
β -(3-Acenaphthoyl)-propionic acid	Normal	81%	Normal	50%	52a
β -(<i>p</i> -Phenoxybenzoyl)-propionic acid	Normal	95%	Normal	54%	52a
2-Acetyldihydroretene	Normal	Poor	Normal	79%	53
α -Benzoylcoumarin	Normal	—	Polymer	—	54
β -(2-Chrysenoyl)-propionic acid	Normal	—	Normal	—	55
2,3-Diethyl-1,4-dianisyl-1-butanone	Normal	44%	Normal	72%	56
α -(3,4-Dimethoxybenzoyl)- β -(3',4'-dimethoxybenzyl)-butyrophenone	None	0%	None	0%	57
3,5-Dimethoxyvalerophenone	Normal	85%	Normal	Poor	33
6,7-Dimethoxy-1-veratrylnaphthalene-3-aldehyde	Normal	Small	None	0%	58
α -Diphenyltruxone	Normal	—	α -Diphenyltruxadiol	—	59
Estrone	Normal	35%	Normal	—	60
Isobilanic acid	Normal	—	Normal	Varies	61
α -Isostrophanthic acid	Normal	Poor	Carbinol	—	62
24-Ketocholesterol	Normal	—	Tar	—	63
4-Ketodecahydroquinoline	Normal	33%	Normal	—	64
4-Keto-5,5'-dimethyl-di-(1,2)-pyrrolidine	Normal	65%	Carbinol	—	65
6-Ketolisothobilanic acid	Normal	—	None	0%	66
1-Keto-8-methyloctahydropyridocoline	Normal (A cpd)	74%	Normal (B cpd)	—	64
8-Keto-17-octadecenoic acid	Normal	65%	None	0%	41
2-Ketoöctahydropyrrocoline	Normal	20%	Normal and carbinol	—	67
Ketopinic acid	Normal	62%	Normal	50%	68
2-Ketoquinuclidine	Normal	25%	Normal	—	69
23-Ketosarsasapogenin	Normal	39%	Tetrahydrosarsasapogenin	—	70
3-Ketotetrahydro-1,2-cyclopentenophenanthrene	Normal	—	Hexahydrocyclopentenophenanthrene	—	71
Lupenone	α -Lupenone	28%	β -Lupenone	Small	72
Manogenin	Normal	—	None	0%	42
6-Methoxy- $\Delta^{1,9}$ -2-octalone	Normal	54%	Normal	—	73
2-Methyl-3-acetylpyridine	Normal	63%	Normal	18%	74
2-Methyl-5-acetylthiophene	Normal	40%	Normal	10%	75
2-Methylcyclohexanone	Normal	—	Normal and unsat'd cpds.	—	76
2-Methyl-1-isovaleroylfuran	Normal	—	None	0%	77
Perisuccinoylacenaphthene	Normal	—	None	0%	78
Pregnanol-20(α)-one-3 acetate	Pregnanediol-3(α), 20(α)	85%	Pregnanol-20(α)	—	79
<i>d</i> -Verbanone	Normal	—	<i>o</i> -Menthane	—	80

* References 52a-80 are listed on p. 388.

REFERENCES TO TABLE I

- ^{52a} Private communication from Professor Louis F. Fieser.
⁵³ Nyman, *Ann. Acad. Sci. Fennicae*, **A41**, No. 5 (1934) [*C. A.*, **30**, 2958 (1936)].
⁵⁴ Stoermer, Chydenius, and Schinn, *Ber.*, **57**, 72 (1924).
⁵⁵ Beyer, *Ber.*, **71**, 915 (1938).
⁵⁶ Baker, *J. Am. Chem. Soc.*, **65**, 1572 (1943).
⁵⁷ Haworth, Kelly, and Richardson, *J. Chem. Soc.*, **1936**, 725.
⁵⁸ Haworth and Woodcock, *J. Chem. Soc.*, **1938**, 809.
⁵⁹ Stoermer and Foerster, *Ber.*, **52**, 1255 (1919).
⁶⁰ Danielli, Marrian, and Haslewood, *Biochem. J.*, **27**, 311 (1933).
⁶¹ Borsche and Hallwasz, *Ber.*, **55**, 3324 (1922).
⁶² Jacobs, Elderfield, Grave, and Wignall, *J. Biol. Chem.*, **91**, 617 (1931).
⁶³ Riegel and Kaye, *J. Am. Chem. Soc.*, **66**, 723 (1944).
⁶⁴ Clemo, Cook, and Raper, *J. Chem. Soc.*, **1938**, 1183.
⁶⁵ Clemo and Metcalfe, *J. Chem. Soc.*, **1936**, 606.
⁶⁶ Windaus and Grimmel, *Z. physiol. Chem.*, **117**, 146 (1921).
⁶⁷ Clemo and Metcalfe, *J. Chem. Soc.*, **1937**, 1518.
⁶⁸ Bartlett and Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939).
⁶⁹ Clemo and Metcalfe, *J. Chem. Soc.*, **1937**, 1989.
⁷⁰ Marker and Shabica, *J. Am. Chem. Soc.*, **64**, 813 (1942).
⁷¹ Hawthorne and Robinson, *J. Chem. Soc.*, **1936**, 763.
⁷² Heilbron, Kennedy, and Spring, *J. Chem. Soc.*, **1938**, 329.
⁷³ Cook and Robinson, *J. Chem. Soc.*, **1941**, 391.
⁷⁴ Dornow and Machens, *Ber.*, **73**, 355 (1940).
⁷⁵ Shepard, *J. Am. Chem. Soc.*, **54**, 2951 (1932).
⁷⁶ Cowan, Jeffery, and Vogel, *J. Chem. Soc.*, **1939**, 1862.
⁷⁷ Asano, *J. Pharm. Soc. Japan*, **454**, 999 (1919) [*C. A.*, **14**, 1317 (1920)].
⁷⁸ Fieser and Peters, *J. Am. Chem. Soc.*, **54**, 4347 (1932).
⁷⁹ Marker and Lawson, *J. Am. Chem. Soc.*, **61**, 852 (1939).
⁸⁰ Wienhaus and Schumm, *Ann.*, **439**, 20 (1924).

A recently developed process for accomplishing the desired reduction is the reductive removal of the two —SR groups in thioacetals by means of Raney nickel.⁸¹ This method is practicable for small-scale work only. It has been shown to be very useful in the steroid field.^{82, 83}

EXPERIMENTAL PROCEDURES

Wolff Reduction of a Hydrazone

Reduction of Camphor.² Ten grams of well-dried camphor hydrazone is heated in a sealed tube with 0.8 g. of sodium in 10 ml. of absolute ethanol for eighteen hours at 190°. Crude crystalline camphane separates on the addition of 750 ml. of water to the reaction mixture. The camphane is separated from the small amount of azine present by steam distillation. The steam-distilled camphane melts at 156–157° and boils at 161°/757 mm. The yield is 7 g. (84%).

⁸¹ Wolfram and Karabinos, *J. Am. Chem. Soc.*, **66**, 909 (1944).

⁸² Bernstein and Dorfman, *J. Am. Chem. Soc.*, **68**, 1152 (1946).

⁸³ Hauptmann, *J. Am. Chem. Soc.*, **69**, 562 (1947).

Reduction of 1-Keto-8-methyloctahydropyridocoline.⁶⁴ One-half gram of 1-keto-8-methyloctahydropyridocoline is refluxed eighteen hours with 3 ml. of hydrazine hydrate. The hydrazone is isolated by ether extraction and heated for eighteen hours at 170° in a sealed tube with a sodium ethoxide solution prepared by the addition of 0.4 g. of sodium to 2 ml. of ethanol. Water is added to the reaction mixture; the solution is acidified with concentrated hydrochloric acid, taken to dryness, and the residue made basic with saturated potassium carbonate solution. After extraction with ether the product is distilled. There is thus obtained 0.34 g. (74%) of 8-methyloctahydropyridocoline-A as a colorless oil, b.p. 47–48°/1 mm.

The Direct Wolff Reduction

Reduction of 2,4-Dimethyl-3-acetyl-5-carbethoxypyrrole. Detailed directions for the reduction of 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole to 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole) in 50–58% yield are given in *Organic Syntheses*.⁸⁴

Kishner Reduction of a Hydrazone

Reduction of Ethyl Cyclobutyl Ketone.⁸⁵ The hydrazone is prepared by heating 18 g. of the ketone and 18 g. of 90% hydrazine hydrate in 50 ml. of absolute ethanol for three hours at 110–130° in an oil bath. By the end of this time the ethanol has distilled, and the residue is dried over solid potassium hydroxide. The hydrazone is poured off the potassium hydroxide and dropped slowly from a separatory funnel onto a mixture of 2 g. of potassium hydroxide and two small pieces of platinized porous plate heated to 120–140° in a Claisen flask. The platinized plate is prepared by igniting pieces of plate that have been immersed in chloroplatinic acid solution. The product that distils from the Claisen flask is treated with dilute acetic acid, and the hydrocarbon layer that separates is washed with water. After having been dried over potassium hydroxide, the product is twice distilled from sodium. There is obtained 7 g. (44%) of *n*-propylcyclobutane boiling at 99–100°/736 mm.

Reduction of 4-Methylacetophenone.²¹ The hydrazone is prepared by vigorously refluxing for one hour a mixture of 4-methylacetophenone and twice its weight of 85% hydrazine hydrate. The cooled solution is extracted with ether; the ether solution is dried over potassium hydroxide and distilled in vacuum. There is obtained an 88% yield of the hydra-

⁸⁴ Fischer, *Org. Syntheses*, **21**, 67 (1941).

⁸⁵ Zelinsky and Kasansky, *Ber.*, **60**, 1101 (1927).

zone of boiling point 166–168°/16 mm. It solidifies in the receiver and melts at 34° after crystallization from petroleum ether.

Five grams of the hydrazone is mixed with 2 g. of powdered potassium hydroxide in a flask equipped with a reflux condenser, the top of which is connected with a gas buret. The flask is gently heated to 90–100°, and this temperature maintained until most of the calculated amount of nitrogen has been evolved. The flask is then heated to 150°, cooled, the contents treated with water and extracted with ether. The ether extract is distilled to give 3.25 g. (80%) of 4-ethyltoluene, b.p. 157–160°.

Kishner Reduction of a Semicarbazone

Reduction of *cis*-β-Bicycloöctanone.³¹ Five grams of pure *cis*-β-bicycloöctanone is converted into the semicarbazone, which is thoroughly washed, roughly dried, and heated with a free flame in a distilling flask with 7.5 g. of potassium hydroxide. The mass fuses, and ammonia is given off. At 200–210° a second reaction sets in, nitrogen being evolved, and oily droplets of hydrocarbon begin to distil. There is no charring, the residue being colorless. The distillate is shaken with sodium bisulfite solution, taken up in ether, dried with calcium chloride, and evaporated. The yield of crude *cis*-bicycloöctane is 4.0 g. (90%), 2.8 g. of which boils sharply at 137–138°.

Wolff-Kishner Reduction without an Alkaline Catalyst

Reduction of 2,3-Benzo-1-azafluorenone.⁸⁶ Seven-tenths of a gram of 2,3-benzo-1-azafluorenone and 1 ml. of hydrazine hydrate are heated in a sealed tube for sixteen hours at 180°. The crude crystalline product is almost colorless. On distillation in vacuum the product goes over as a violet fluorescent oil (b.p. 240°/25 mm.) which quickly solidifies. Crystallization from methanol gives colorless prisms, m.p. 140°. The yield is 0.53 g. (80%).

Reduction of Pyrene-3-aldehyde.²⁷ Twenty grams of pyrene-3-aldehyde and 100 g. of hydrazine hydrate are heated at 200° in a 1-l. iron autoclave for eight hours. About 100 atmospheres pressure is developed. The clear solid product is washed, dried, and distilled in vacuum. There is obtained 17 g. (91%) of almost pure 3-methylpyrene melting at 70–71°.

⁸⁶ Borsche and Noll, *Ann.*, **532**, 127 (1937).

Direct Wolff-Kishner Reduction at Atmospheric Pressure

Reduction of 5-Keto-8-methylnonanoic Acid.³⁷ A mixture prepared from a solution of 113 g. of sodium in 1750 ml. of diethylene glycol, 168 g. of 5-keto-8-methylnonanoic acid, and 125 ml. of 85% hydrazine hydrate is refluxed for forty-eight hours. An additional 75 ml. of the hydrazine solution is then added and heating is continued for forty-eight hours. The product is isolated by acidification and extraction with benzene and ether. Distillation at reduced pressure gives 143 g. (92%) of isodecanoic acid, b.p. 93–95/0.3 mm., n_D^{25} 1.4318.

An average yield of 85% was obtained in several repetitions of the reduction carried out in monoethylene glycol without the second addition of hydrazine hydrate.

Reduction of β-(*p*-Phenoxybenzoyl)-propionic Acid.⁴⁰ A mixture of 500 g. (1.85 moles) of the keto acid, 350 g. of potassium hydroxide, and 250 ml. of 85% hydrazine hydrate in 2500 ml. of triethylene (or diethylene) glycol is refluxed for one and one-half hours, the water formed is removed by a take-off condenser, and the temperature of the solution is allowed to rise to 195°, when refluxing is continued for four hours more. The cooled solution is diluted with 2.5 l. of water and poured slowly into 1.5 l. of 6 *N* hydrochloric acid, and the light cream-colored solid is dried. The average yield of material of m.p. 64–66° is 451 g. (95%). The pure product melts at 71–72°.