During the extensive penicillin effort of the 1940's, sodium metaperiodate had been reported by Sykes and Todd[15] to oxidize the sulfide function of benzylpenicillin methyl ester and related systems to sulfoxide,[16] but the method had not found general application. In our hands an adaptation of the sodium metaperiodate procedure of Sykes and Todd to the oxidation of 1-thiacycloöctan-5-one afforded the desired sulfoxide (I) in 91% yield. Encouraged by the success of this conversion, we have now provided additional examples of the oxidation, sufficiently varied (Table I) to demonstrate the generality and selectivity of the method.

On a preparative scale the oxidation is conveniently carried out by addition of the sulfide to a slight excess of 0.5*M* aqueous sodium metaperiodate at ice-bath temperature.[17] The reaction, complete in three to twelve hours, affords pure sulfoxide, usually in better than 90% yield. It appears expedient to use a mixed solvent system—*e.g.*, methanol-water—in those cases where solubility of the sulfide in water is slight. Lower yields may result when water solubility of the product diminishes the efficiency of extraction. The extent and rate of the

$$R_2S + NaIO_4 \longrightarrow R_2SO + NaIO_3 \qquad (1)$$

reaction (1) may be followed quantitatively by the titration methods commonly used in the Malaprade procedure for the periodate oxidation of glycols.[15,18]

When considered with the array of reagents available for the oxidation of sulfides to sulfoxides, sodium metaperiodate possesses certain advantages: over-oxidation can be avoided; mild conditions are employed; the reagent is readily available and is safely and easily handled; and excellent yields are obtainable, even when other functionality is present (periodate-susceptible groupings such as α-glycols being excepted).

EXPERIMENTAL

General method of oxidation. To 210 ml. (0.105 mole) of a 0.5*M* solution of sodium metaperiodate at 0° was added 0.1 mole of sulfide. The mixture was stirred at ice-bath temperature, usually overnight. The precipitated sodium iodate was removed by filtration, and the filtrate was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The sulfoxide was purified by distillation, crystallization, or sublimation.

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(15) P. Sykes and A. R. Todd, Committee on Penicillin Synthesis Reports 526, 677; *The Chemistry of Penicillin*, H. T. Clarke, J. R. Johnson, and R. Robinson, Eds., Princeton University Press, Princeton, N. J., 1949, pp. 156, 927, 946, 1008.

We wish to thank Dr. Peter Sykes, Cambridge University, for suggesting the application of periodate to our problem.

(16) E. H. Flynn, Eli Lilly and Co., Indianapolis, Ind., has recently applied periodate to the synthesis of other sulfoxides in the penicillin series (private communication).

(17) Temperature control is important during the reaction (Table I, footnote *s*). Some over-oxidation was experienced in the case of ethyl sulfide; W. A. Bonner and R. W. Drisko [*J. Am. Chem. Soc.*, **73**, 3699 (1951)] found ethyl sulfide to be oxidized to the sulfone by periodic acid at 60°. Moreover, Sykes and Todd[15] reported that *S*-benzylpenicillamine is oxidized to the corresponding sulfone by sodium metaperiodate at 60°.

(18) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944).

Hydrogenation of Substituted Pyridines with Rhodium on Carbon Catalyst[1]

MORRIS FREIFELDER, RALPH M. ROBINSON, AND GEORGE R. STONE

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Recently we investigated the action of ruthenium dioxide in the hydrogenation of pyridines.[2] While this procedure gives excellent results, it requires pressures in the range of seventy atmospheres. In laboratories where heavier equipment is not available, there is a need for a low pressure method which would eliminate some of the disadvantages of hydrogenation in the presence of platinum catalysts.

The presence of acid is required when Adams' catalyst is used to convert pyridines to piperidines.[3] If the desired base is water soluble, continuous extraction must be employed in order to get good yield. In addition, there are discouraging reports where hydrogen uptake is slow and where more catalyst must be added.[4]

In a description of some hydrogenations with ruthenium and rhodium catalysts, there is a mention of the reduction of pyridine with an equal weight of 5% rhodium on alumina.[5] When we repeated this reaction with a more normal amount of catalyst, we found that, while initial uptake of hydrogen was quite rapid, it slowed down considerably and was 90% complete in 15 hours. In addition, the catalyst was irrevocably poisoned after the reduction and could not be regenerated. We had noted in some previous work that hydrogenation with rhodium on alumina is inhibited by a strong base.[6] Piperidine after conversion from pyridine apparently has a similar effect on this catalyst. This retardation is even more pronounced in the

(1) Presented at the 140th meeting, American Chemical Society, Chicago, Ill., September 1961.

(2) M. Freifelder and G. R. Stone, *J. Org. Chem.*, **26**, 3805 (1961).

(3) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).

(4) J. Overhof and J. P. Wibaut, *Rec. trav. chim.*, **50**, 957 (1931); J. Finkelstein and R. Elderfield, *J. Org. Chem.*, **4**, 365 (1939).

(5) H. Gilman and G. Cohn, *Advances in Catalysis*, Academic Press, New York, **9**, 707–715 (1957).

(6) M. Freifelder, *J. Org. Chem.* **26**, 1835 (1961).

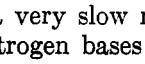
reduction of pyridines with basic side chains, where uptake of hydrogen proceeds at a very slow rate. The inhibitory effect of strong nitrogen bases can be overcome by the use of an appropriate acid[6,7]; except for greater reaction speed, this procedure suffers from the same disadvantages as Adams' catalyst and acid.

A comparison of 5% rhodium on carbon (A) with 5% rhodium on alumina (B) showed that A was better suited for the reduction of the pyridine ring. Further, it was found that when sufficient catalyst was used, the poisoning effect of the piperidine bases could be overcome. Hydrogenations were successful when carried out in the presence of a 40% ratio of rhodium on carbon to compound at 55–60° and 2.7 atmospheres initial pressure. In most instances satisfactory rates were obtained; in a few, uptake of hydrogen was moderately rapid.

The difference in reaction between pyridines substituted in the 2- and 4-position is of interest. A substituent in the 2-position appears to favor the reduction rate rather than retard it, as might be expected, by steric effects. In this position, substitution prevents strong bonding between the nitrogen atom and the catalyst.[8] This effect can be seen in the difference in reduction time between III and IV, V and VII, and VIII and X. The difference is more striking when a lower ratio of the less active B is used. Of further interest in this connection are the reductions of 2- and 4-benzylpyridine. When 4-benzylpyridine was hydrogenated, 4-benzylpiperidine was obtained containing a very small amount of starting material. However, reduction of the 2-derivative was less selective. Vapor phase chromatography showed the presence of 2-cyclohexylmethylpiperidine in addition to III and starting material. As might be suspected, when both *ortho* positions are occupied, steric effect should predominate. This can be seen in the longer reaction time required for the preparation of XIII.

In the hydrogenation of the pyridine carboxylic acids and derivatives, several observations were made. In the reduction of picolinic acid to V, we were able to re-use the catalyst three times without any significant change in reduction time, although for the fifth reduction it was completely poisoned. It appears that the carboxyl group, in lowering the basicity of the resultant piperidine, thereby decreases the usual inhibitory effect of a strong base on hydrogenation with rhodium catalyst. During the reduction of nicotinic acid, considerable decarboxylation occurred. This had been observed before but could be prevented by carrying out the reaction in the presence of an equivalent of sodium bicarbonate.[2] Nicotinamide was converted to XI, using both alcohol and water as solvent. However,

TABLE I



	R	Reduction Time, Minutes	Yield, %
I	2-CH_2CH_2OH	240	[c]
II	2-$CH_2CH_2CH_2OH$	60	76.8[d]
III	2-$CH_2C_6H_5$	140	76 [e]
IV	4-$CH_2C_6H_5$	420	[f]
V	2-COOH[a]	115[b]	93.4[g]
VI	3-COOH[a]	120	42[h]
VII	4-COOH[a]	165[b]	86.8[i]
VIII	2-$COOC_2H_5$	54	[j]
IX	3-$COOCH_3$	110–130	49.6[k]
X	4-$COOCH_3$	100	[l]
XI	3-$CONH_2$[a]	105	86.6[l]
XII	3-$CON(C_2H_5)_2$	800	[m]
XIII	2,4,6-*tri*-CH_3	900	[n]
XIV	4-$CH_2CH_2NHCH_2C_6H_5$	670	56 [o]
XV	4-CH_2NH_2	480–600	70 [p]

[a] Water used as solvent in hydrogenation leading to these compounds. [b] A comparison of the reduction with a 20% ratio of catalyst B is more pronounced. The times are 140 and 480 min., respectively. [c] Vapor phase chromatography indicates 95% of I and 4.6% of starting pyridine. [d] B.p. 248° (756 mm.), n_D^{25} 1.4751. Hydrochloride salt melts at 133–134°. K. Loffler and M. Flugel, *Ber.*, **42**, 3423 (1909), gives same b.p.; m.p. of salt, 128°. V. Boekelheide and S. Rothschild, *J. Am. Chem. Soc.* **70**, 864 (1948), gives $n_D^{21.5}$ 1.4882. [e] Vapor phase chromatography indicates a mixture of 87% III, 4% starting pyridine, and 8% 2-cyclohexylmethylpiperidine. III was obtained free of impurities by converting the mixture to a hydrochloride and recrystallizing the impure salt from absolute alcohol and anhydrous ether, m.p. 136.5–137°. Mixed m.p. with an authentic sample was not depressed. [f] Vapor phase chromatography indicates 98.5% of IV plus 1.25% of starting pyridine. [g] M.p. 270°. R. Willstätter, *Ber*, **29**, 389 (1896), shows 274.5–275.5°. [h] Piperidine (25–35%) was obtained as a result of decarboxylation, see *ref.* 2 for method of determination. [i] M.p. 325° as described by K. Freudenberg, *Ber.* **51**, 1668 (1918). [j] Crude yield almost quantitative. Refractive index of undistilled product compares well with known sample, see ref. 2. Infrared examination shows absence of pyridine ring and vapor phase chromatography indicates only one component. [k] B.p. 84–87.5° (10 mm.), n_D^{25} 1.4630. Hydrochloride salt, m.p. 134°, see ref. 2. In addition, a product distilling at 100–102° (0.2–0.3 mm.), n_D^{25} 1.5343 was obtained. Infrared examination indicated the presence of both ester and amide carbonyl function and absence of aromatic ring. It was probably a product of self condensation of IX, but no satisfactory formula could be evolved from the analytical values. [l] M.p. 107–110°, before recrystallization. H. H. Fox, *J. Org. Chem.* **17**, 543 (1952), finds 110–111°. The yield from reduction of nicotinamide in ethyl alcohol was 74%, m.p. was low, 102–107°. [m] Same as footnote *j*, except that vapor phase chromatography was not carried out. [n] Vapor phase chromatography shows 79.5% of XIII and 19.2% starting pyridine. [o] B.p. 150–153° (1.8 mm.), n_D^{25} 1.5078. *Anal.* Calcd. for $C_{14}H_{22}N_2$: C, 77.00; H, 10.37; N, 12.84. Found: C, 76.45; H, 10.16; N, 13.01. In addition, 30% of XVI, 4-(2-aminoethyl)piperidine was obtained, b.p. 99–100° (10 mm.), n_D^{25} 1.4920 (see ref 2). In this experiment, hydrogen uptake was more than 125% of theory. In another run where we were able to interrupt the reaction at about 110% uptake, vapor phase chromatography indicates only about 10% of XVI. [p] B.p. 89–92° (8.5–9 mm.), n_D^{25} 1.4895. The product absorbed carbon dioxide too rapidly to get a satisfactory analysis. A diacetate salt melting at 172–173° was prepared. *Anal.* Calcd. for $C_8H_{14}N_2 \cdot 2CH_3COOH$: C, 51.26; H, 9.50; N, 11.96; O, 27.28. Found: C, 51.46; H, 9.73; N, 11.76; O, 27.27.

(7) L. E. Brady, M. Freifelder, and G. R. Stone, *in press.*

(8) H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Am. Chem. Soc.*, **56**, 2425 (1934).

reduction in alcohol gave a less pure product and took almost twice as long to complete hydrogen uptake. The much longer reaction time required for the preparation of XII was rather surprising. An examination of a molecular model shows that the starting pyridine makes good contact with the catalyst. However, as hydrogenation proceeds, it appears that there are positions of the molecule where contact with the catalyst is difficult. Under higher pressure, as in reduction with ruthenium,[2] the molecule is apparently forced into the proper configuration to allow uptake of hydrogen to take place rapidly. Under the mild conditions used in this study, there is not enough energy to do the same thing.

Some hydrogenolysis occurred in the preparation of 4-(β-benzylamino) piperidine. From a study of the hydrogen uptake, it seems that debenzylation takes place after the pyridine ring is reduced. In one experiment where the hydrogen uptake was slightly in excess of theoretical, less than 10% of 4-(β-aminoethyl)-piperidine, the product of hydrogenolysis was obtained. In a second run where the uptake of hydrogen was excessive, about 30% of this product was obtained.

The longer reaction time required to obtain XIV and XV is an indication of the inhibiting effect of the basic side chain on the rate of hydrogenation.

From these results, it would appear that the described method should prove useful as a means of carrying out the reduction of most pyridines to a successful conclusion under general laboratory conditions.

EXPERIMENTAL

Selection of catalyst. A solution of 12.3 g. (0.1 mole) of 2-(2-hydroxyethyl)pyridine in 50 cc. of absolute ethyl alcohol was hydrogenated at room temperature under 2.7 atm. pressure in the presence of 2.46 g. of 5% rhodium on carbon.[9] In another run 2.46 g. of 5% rhodium on alumina[9] was used. The two reactions were carried out concurrently in Parr shakers of equal speed for 17 hr. The hydrogen uptake for the experiment with catalyst A was about 70% of theory, for B about 50%. These results were confirmed by vapor phase chromatography which indicated 73% and 54% of I, respectively.

The following is an example of the hydrogenation conditions used, with exceptions noted in the Table.

2-(2-Hydroxyethyl)piperidine. A solution of 12.3 g. (0.1 mole) of 2-(2-hydroxyethyl)pyridine in 50 cc. of absolute ethyl alcohol was hydrogenated under 2.7 atm. pressure at 55–60° with presence of 4.92 g. of 5% rhodium on carbon. The reaction was interrupted at the end of 4 hr. when uptake of hydrogen appeared to be complete. After removal of catalyst the solution was concentrated and the residue identified (see Table I).

Acknowledgment. The authors are greatly indebted to the following for the analyses reported here: P. F. Helgren, vapor phase chromatography; A. Kammer and W. Washburn, infrared examination; and E. F. Shelberg, O. Kolsto, and staff for microanalysis.

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(9) Available from Engelhard Industries, 113 Astor Street, Newark, N. J.

Reaction of α-Diazoacetophenone with *trans*-1,2-Dibenzoylethylene[1a]

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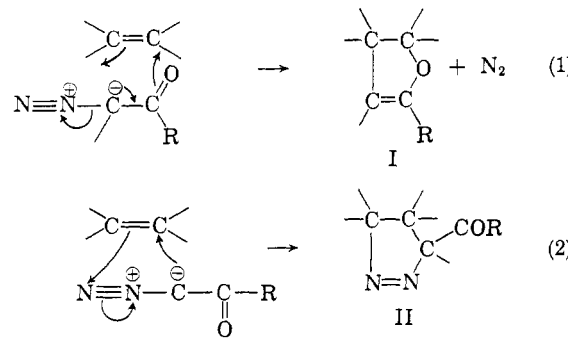
In general there are two possible paths for the uncatalyzed reaction of α-diazo ketones with suitably activated double bonds[2]:



We have recently shown[3] that the reaction of α-diazoacetophenone with ketenes to give products of type I occurs by route (1) rather than by reaction of the ketene with a species $C_6H_5C\ddot{O}CH$.[4,5] No

(1)(a) Aliphatic Diazo Compounds VI; for the preceding paper in this series see P. Yates and B. L. Shapiro, *J. Am. Chem. Soc.*, **81**, 212 (1959). (b) National Science Foundation Pre-doctoral Fellow, 1956–59. (c) Present address: Department of Chemistry, University of Toronto.

(2) *Cf.* A. S. Kende, Ph.D. Thesis, Harvard, 1956.

(3) P. Yates and T. J. Clark, *Tetrahedron Letters*, **No. 13**, 435 (1961).

(4) The *copper-catalyzed* reaction of diazoketones with olefinic compounds, producing cyclopropane derivatives [J. Novák, J. Ratusky, V. Sneberg, and F. Šorm, *Collection Czechoslov. Chem. Communs.*, **22**, 1836 (1957); R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 401 (1957)]; undoubtedly proceeds *via* an intermediate formed by interaction of the diazo compound with the catalyst [*cf.* P. Yates, *J. Am. Chem. Soc.*, **74**, 5376 (1952); W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **78**, 4947 (1956); P. S. Skell and R. M. Etter, *Chem. & Ind. (London)*, 624 (1958); K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *J. Am. Chem. Soc.*, **83**, 2397 (1961)]. The uncatalyzed reaction of α-diazo-4-phenylacetophenone with styrene to give cyclopropane derivatives (R. J. Mohrbacher and N. H. Cromwell, *loc. cit.*) may well proceed *via* pyrazoline formation.

(5) The related thermal reaction of diazoöxides with ketenes proceeds by attack at the carbonyl rather than the ethylenic double bond of the ketene: P. Yates and E. W. Robb, *J. Am. Chem. Soc.*, **79**, 5760 (1957). However, no evidence is available in this instance which distinguishes between attack on the ketene by diazoöxide or by a species $RCO\ddot{C}H$.