[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Heterogeneous Bimolecular Reduction. I. General Considerations of Mechanism. The Emmert Reaction[*,1]

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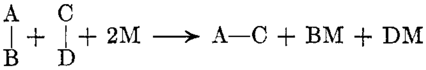
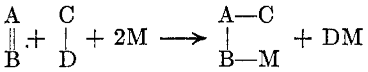
Heterogeneous bimolecular reduction has been defined as a general category of reactions. It has been discussed as to its applications, variations, and limitations in specific cases. The coreduction of carbonyl compounds and pyridine with metals to give pyridyl alcohols has been studied critically as an example of this type of reaction.

The classification of organic reactions into general types serves not only to correlate known reactions, but also to suggest new reactions and to simplify mechanism studies. The purpose of this research has been to investigate the general type of reaction in which two different kinds of molecules are coupled under reductive conditions. We will refer to this as Heterogeneous Bimolecular Reduction (Het BR) to distinguish it from reactions in which like molecules are so coupled, which will be called Homogeneous Bimolecular Reduction (Hom BR).

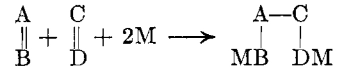
Het BR reactions may occur in various ways. Three subtypes may be illustrated by the following equations in which A, B, C, and D are atoms of any element, but usually are carbon, oxygen, nitrogen, halogen, or sulfur, and M is a reducing agent.



$$\overset{A}{\underset{B}{|}} + \overset{C}{\underset{D}{|}} + 2M \longrightarrow A{-}C + BM + DM \qquad (1)$$



$$\overset{A}{\underset{B}{\|}} + \overset{C}{\underset{D}{|}} + 2M \longrightarrow \begin{array}{c}A{-}C\\ |\\ B{-}M\end{array} + DM \qquad (2)$$



$$\overset{A}{\underset{B}{\|}} + \overset{C}{\underset{D}{\|}} + 2M \longrightarrow \begin{array}{cc}A & {-}C\\ | & |\\ MB & DM\end{array} \qquad (3)$$

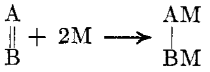
Familiar examples of these types include:

Type (1): the Wurtz,[3] and Wurtz-Fittig[4] and Grignard reactions; with A and C carbon, and B and D halogen.

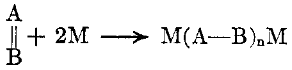
Type (2): the Reformatskii reaction;[5,6] with A and C carbon, B oxygen, and D halogen.

Type (3): the pinacol reduction of unlike ketones,[7,8] with A and C carbon, and B and D oxygen; the oxo or hydroformylation reaction[9] with A, B, and C carbon, and D oxygen; the coreduction of aldehydes and nitro compounds to dialkyl amines,[10] with A carbon, C nitrogen, and B and D oxygen.

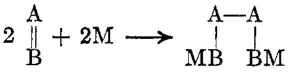
Because of its apparently greater applicability in organic chemistry the third of the above types has attracted our attention first. Casual reflection will reveal that this type of reaction is likely to be accompanied by other reactions including: (4) monomolecular reduction, (5) telomerization, and (6) Hom BR.



$$\overset{A}{\underset{B}{\|}} + 2M \longrightarrow \overset{AM}{\underset{BM}{|}} \qquad (4)$$



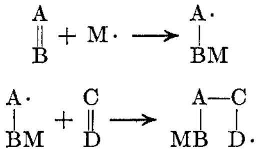
$$\overset{A}{\underset{B}{\|}} + 2M \longrightarrow M(A{-}B)_nM \qquad (5)$$



$$2\,\overset{A}{\underset{B}{\|}} + 2M \longrightarrow \begin{array}{cc}A & {-}A\\ | & |\\ MB & BM\end{array} \qquad (6)$$

All of the factors which influence the relative extent of (3) versus (4), (5), and (6) have not been determined although it would be expected that the natures of A=B, C=D, M, and any solvent employed would be important.

Another less obvious factor would be the mechanism by which the reaction proceeds, *i.e.*, the nature of the intermediates involved. Thus the overall reaction (3) might involve a free radical intermediate (7) or an anionic intermediate (8) depending on whether the reducing agent M supplies one or two electrons at a time.



$$\overset{A}{\underset{B}{\|}} + M\cdot \longrightarrow \overset{A\cdot}{\underset{BM}{|}} \qquad (7)$$

$$\overset{A\cdot}{\underset{BM}{|}} + \overset{C}{\underset{D}{\|}} \longrightarrow \begin{array}{cc}A & {-}C\\ | & |\\ MB & D\cdot\end{array}$$

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[*] This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Contains material from the Ph. D. theses of M. Hamer, August, 1953; E. Dunning, August, 1954; and R. M. Schisla, June, 1957; all at Purdue University.

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(c) Indiana Elks Fellow, 1954–55; Allied Chemical Dye Corp. Fellow, 1955–56. Present address: Monsanto Chemical Co., Dayton, Ohio.

(3) C. A. Wurtz, *Ann.*, **96**, 364 (1855).

(4) R. Fittig and B. Tollens, *Ann.*, **131**, 303 (1864).

(5) S. N. Reformatskii, *Ber.*, **20**, 1210 (1887).

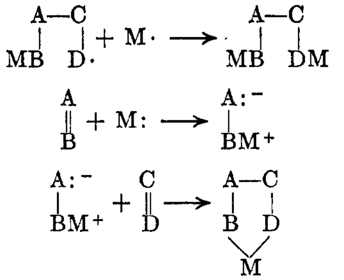
(6) R. L. Schriner, *Org. Reactions*, **I**, 1 (1942).

(7) N. V. Elagina and N. D. Zelinskii, *Doklady Akad. Nauk S.S.S.R.*, **71**, 293 (1950).

(8) R. C. Fuson, *Record Chem. Progr.* **12**, 1 (1951).

(9) H. H. Storch, N. Golumbic and R. B. Anderson, *The Fischer-Tropsch and Related Syntheses*, John Wiley and Sons, Inc., New York, 1951, p. 441.

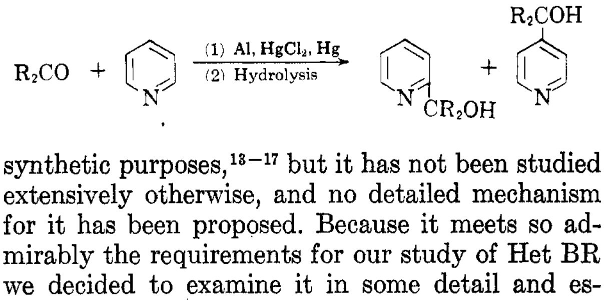
(10) W. S. Emerson and H. W. Mohrmann, *J. Am. Chem. Soc.*, **62**, 69 (1940).



(8)

Since reducing agents possessing two or more electrons do not necessarily supply them in pairs it is not possible to decide *a priori* whether a given M will follow mechanism (7) or (8). If however, a C=D compound could be found which was known to be more readily attacked by anions than by free radicals, then in this case it should be possible to demonstrate a preference for mechanism (8). Such a substance is available in pyridine which resists substitutive attack by cations, is slowly attacked by free radicals, and is readily attacked by anions. Furthermore pyridine is preferentially attacked by anions at the 2- and 4-positions while it is attacked by free radicals at all positions.[11] This latter fact serves to sharpen the differentiation of free radical from anion attack which would otherwise be dependent on rate differences only.

The coreduction of aldehydes or ketones and pyridine with magnesium or aluminum produces pyridyl alcohols.[12] The reaction has been used for synthetic purposes,[13–17] but it has not been studied extensively otherwise, and no detailed mechanism for it has been proposed. Because it meets so admirably the requirements for our study of Het BR we decided to examine it in some detail and especially to determine the effect on it of variations in the reactants and conditions.



The nature of the reaction. Small amounts of the carbonyl compound and pyridine are heated with the amalgamated metal at reflux until the reaction begins as evidenced by the formation of color (usually green, changing to brown). The remainder of the reactants are added slowly to prevent too rapid reaction, and the mixture is finally heated at reflux until the metal has disappeared, or until no further change is noted. The reaction mixture is then cooled, hydrolyzed with base, the organic products acid extracted, basified, and the nitrogenous products fractionally distilled.

The nature of the reducing agent. The metals magnesium and aluminum seem to be specifically suitable reducing agents and give yields of products up to about 50%.[18] In spite of careful attempts by ourselves and the previous workers to find other isomers, only the 2- and 4-pyridyl alcohols were found. The ratio of the two isomers averages about 4/1 for aluminum while magnesium produces the 2-isomer only. From these facts it would appear that the reaction involves an anion intermediate as in (8).

Numerous attempts were made to produce pyridyl alcohols with reducing agents known to be capable of supplying only one electron at a time. Sodium, lithium, binary mixture ($Mg + MgI_2$),[19] chromous acetate $Cr(OCOCH_3)_2$,[20] vanadous chloride (VCl_2),[20] and hypophosphorous acid[21] gave Hom BR of the carbonyl compound only or at best traces of Het BR. Sunlight converts a mixture of benzophenone and 2-propanol to benzopinacol apparently by a free radical (single electron) process.[22] However we found that a similar mixture containing pyridine gave a 66% yield of benzopinacol and no pyridyl alcohol on illumination. From these unsuccessful attempts we conclude that agents supplying electrons by single-electron processes are incapable of causing the Emmert reaction to occur.

A series of bivalent metals beside magnesium were investigated. Those with low reduction potentials (zinc, 0.76 v.; manganese, 1.1 v.) did not react. One with a high reduction potential but a poor coördinating power[23] (calcium, 2.87 v.) reacted but gave the pinacol and no pyridyl alcohols.

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(11) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, pp. 401–410.

(12) B. Emmert and E. Asendorf, *Ber.*, **72**, 1188 (1939); B. Emmert and E. Pirot, *Ber.*, **74**, 714 (1941).

(13) G. B. Bachman and D. D. Micucci, *J. Am. Chem. Soc.*, **70**, 2381 (1948).

(14) C. H. Tilford, R. S. Shelton, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **70**, 4001 (1948).

(15) H. L. Lochte, P. F. Kruse, Jr., and E. N. Wheeler, *J. Am. Chem. Soc.*, **75**, 4477 (1953).

(16) C. H. Tilford and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **76**, 2431 (1954).

(17) F. J. McCarty, C. H. Tilford, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **79**, 472 (1957).

(18) Yields on the reaction have been calculated by different authors on different bases, *i.e.*, on the metal or on either of the other reagents. When calculated on the metal the basis may be the total valence of the metal or some fraction thereof depending on the assumed mechanism of the reaction. We have in general used the total reducing-power approach and calculated yields on the basis of one molecule of product resulting from each pair of valence electrons in the metal atom, *i.e.*,

$$\%\ \text{yield} = \frac{\text{moles products} \times 100}{\text{gram atoms metal} \times \text{metal valence}/2}$$

(19) M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

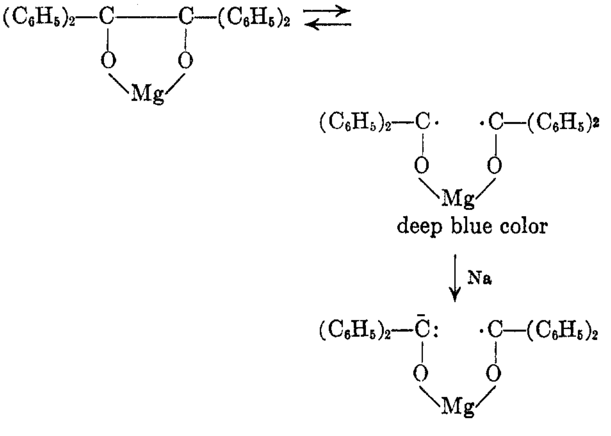
(20) J. B. Conant and H. B. Cutter, *J. Am. Chem. Soc.*, **48**, 1016 (1926).

(21) T. Moeller, *Inorganic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 641.

(22) W. E. Bachmann, *Org. Syntheses*, **Coll. Vol. II**, 71 (1944).

(23) A. A. Grinberg and K. B. Yatsimirsky, *Bull. acad. sci. U.R.S.S.*, **2**, 239 (1952), on the basis of the heats of formation of chelates between metal ions and bases, arranges the metals in the following order of complexing ability: Be > Cu > Hg > Ni > Zn > Co > Fe > Cr > Mg > Mn > Cd > Ca.

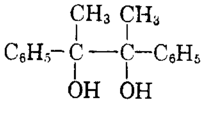
One with a high reduction potential and a high coordinating power (beryllium, 1.69 v.) gave a very low yield (2%) of the 2-pyridyl alcohol and a good yield of pinacol. We conclude that while a minimum reduction potential and coordinating power are important, the essential factor in the reducing agent is an ability to transfer two electrons at a time to the carbonyl compound. Magnesium (2.4 volt) and aluminum (1.7 volt) seem to combine these characteristics better than any other metals although beryllium is apparently able to function this way to a minor extent.[24] A combination of zinc (low reduction potential, high coordinating power) and sodium (high reduction potential, low coordinating power) gave the same results as sodium alone. However, separately prepared magnesium benzopinacolate, which alone did not react with pyridine, did give a pyridyl alcohol when sodium was added. A possible rationalization of this latter result is,



The same reaction would not be expected to occur with magnesium acetone pinacolate because it does not dissociate readily at the central C-C bond.

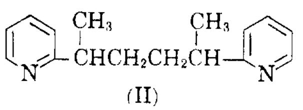
Nature of the pyridine compound. The introduction of a substituent in the 2-position of the pyridine ring might be expected to increase the relative extent of reaction at the 4-position and a compound like 2,6-lutidine might be expected to react at the 4-position only. However steric effects interfere and 2-picoline gives only about 5–15% yields of the 2,6-isomer,[12,14,15] while 2,6-lutidine gives only pinacols and no pyridyl alcohols.[12] We conclude that the product before hydrolysis consists of a cyclic coordination compound with metal attached to nitrogen and that groups in the 2-position interfere with its formation. Very good yields are obtained with 3-picoline[12,15] and 4-picoline[14,15] and fair yields with quinoline.[12]

Vinylogs of pyridine, such as 2-vinylpyridine, 2-isopropenylpyridine, and 2-stilbazole, react with ketones and aluminum to give Hom BR products from both reactants. Thus 2-isopropenylpyridine, acetophenone, and aluminum give I and II as well as about equal amounts of the monomolecularly reduced product 2-isopropylpyridine. Similar results were obtained with the other two vinylogs except that 2-vinylpyridine gave much polymer. We conclude from these experiments that the postulated cyclic coordination compound obtained with pyridine is less probable with pyridine vinylogs because of the increased size of the ring (IV).

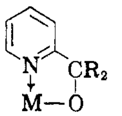


$C_6H_5-C(CH_3)(OH)-C(CH_3)(OH)-C_6H_5$

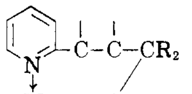
(I)



(II)

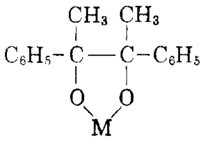


(III)

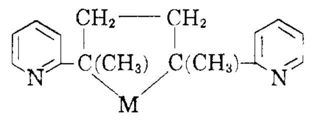


(IV)

Instead a different pair of 5-membered rings, V and VI, form



(V)



(VI)

These lead to the dimeric forms I and II on hydrolysis. α,β-Unsaturated carbonyl compounds also are reported[12] not to react satisfactorily to give pyridyl alcohols probably for a similar reason. Assuming conjugate addition of the pyridine and the metal to the unsaturated ketone a seven-membered ring would again have to form.

Nature of the carbonyl compound. Simple dialkyl, diaryl, alkyl aryl, and cycloalkyl ketones react satisfactorily with pyridine to give pyridyl alcohols. However ortho substituents sterically inhibit the reaction with aryl compounds.[14] Thus *o*-methylacetophenone gives a moderate yield while *o*-methoxy- and *o*-chloroacetophenone gives zero yields. This hindrance is less apparent in *ortho*-substituted benzaldehydes, since *o*-chloro- and *o*-methoxybenzaldehydes give fair yields of the corresponding pyridyl alcohols.

Groups in the *para*-position of the benzene ring exert electronic influences which may assist or hinder the reaction. Thus methyl and methoxyl groups assist, while the chloro group hinders the reaction. These results suggest that electron-supplying groups assist by increasing the negativity of the intermediate anion and hence by increasing the ease with which it attacks the pyridine ring.

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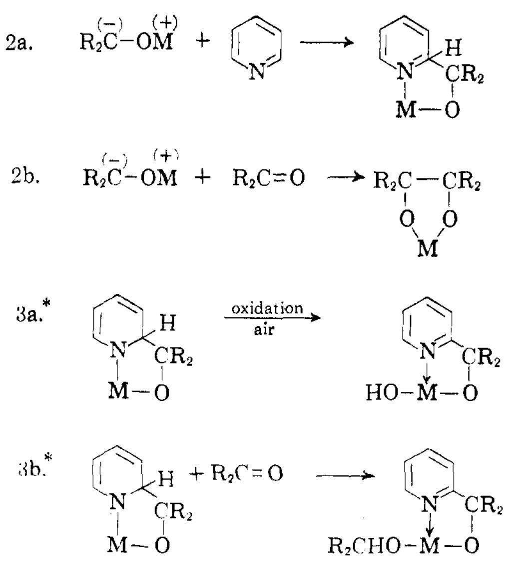
[24] Investigations by R. Muller, F. Holzl, W. Knaus, F. Planiszig, and K. Prett, *Monatsh.*, **44**, 205 (1923), on the electrodeposition of metals from pyridine solutions of their salts show that the reduction potentials of the metals are not the same in pyridine as in water. Thus magnesium and sodium are electrodeposited from pyridine, while aluminum is not. Hence, reduction potentials in water cannot be taken as an exact measure of reduction potentials in pyridine, although it is reasonable to suppose that there is a rough correlation between the two.

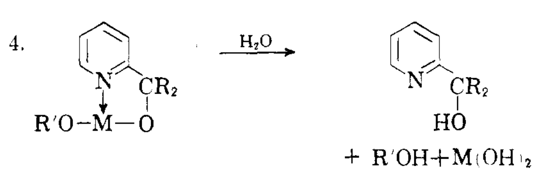
Electron withdrawing groups have the opposite effect. An alkyl group in a ketone similarly reinforces (by hyperconjugation) the negativity of the anion to a greater extent than the hydrogen of an aldehyde group. This may account for the generally better yields obtained with simple ketones than with simple aldehydes.

The nature of the medium. Moisture hinders or prevents the Het BR reaction of pyridine and carbonyl compounds. Scrupulous care must be used to dry the reagents thoroughly. Similarly, solvents which can supply protons through ionization cannot be used. This includes carboxylic acids and alcohols. Apparently these solvents either prevent the formation of the carbanion intermediate or neutralize it before it can attack the pyridine nucleus. It is interesting to compare these results with the effects of pH changes in the electroreduction of ketones. Using a polarograph it was observed by Pasternak[25] that benzophenone is reduced monomolecularly by a two-electron process at pH 4–9 to the alcohol (benzhydrol), while at pH 1.3 and below it is reduced bimolecularly by a single-electron process to benzopinacol. Here also the higher proton concentration apparently interferes with the two-electron or anionic process but not with the one-electron or free radical process.

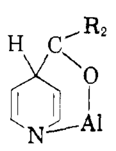
Mechanism of the reaction. The above studies of factors influencing the Het BR reaction of carbonyl compounds and pyridine with metals are summarized in Table I. They suggest the following series as a rational explanation of the overall synthesis:

1. $R_2C{=}O + M{:} \longrightarrow R_2\overset{(-)}{C}-\overset{(+)}{OM}$





The adaptation of these equations to a trivalent metal like aluminum would be cumbersome but not complicated. The fact that aluminum gives some of the 4-isomer while magnesium does not may depend on the greater size of the aluminum atom which more readily permits a transannular bridge between the hetero atom and the 4-position.



(Note, however, our remarks concerning the nonformation of IV). Step 3 (a and b) represents oxidations of the assumed dihydropyridine intermediate which results in restoration of the full resonance of the pyridine ring and as such should proceed very readily.[26] To the extent that this step involves unreacted carbonyl compound the potential yields based on this reagent are reduced. However only minor amounts of the corresponding alcohol are found in the products indicating that other oxidizing agents are also involved. The fact that no hydrogenated pyridines are found in the products suggests that air may be the primary oxidizing agent.

Conclusions. For success the Emmert reaction requires: (*a*) a two-electron transferring agent of strong reducing power (> Mn) and strong coordinating power (> Ca), (*b*) a heterocyclic base containing a —N=ring member, an unsubstituted α-position, and freedom from steric interference (by α-substituents) to chelation of the nitrogen atom to a metal atom, (*c*) a carbonyl compound capable of accepting two electrons to form a carbanion and no groups which by resonance stabilization or steric hindrance interfere with its ability to attach itself to the pyridine ring, and (*d*) a reaction medium which is not able to furnish protons in sufficient concentration to hamper the formation of the carbanion or to neutralize it before it can react with the pyridine.

An important implication of this analysis is that metals differ in their relative capacities to react with carbonyl compounds by one-electron and two-electron processes, and that in pyridine there exists a suitable reagent for detecting this difference. It is our intention to pursue this conclusion further and to study other examples of Het BR.

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(25) R. Pasternak, *Helv. Chim. Acta*, **31**, 753 (1948).

* Each of these processes probably involves more than one step.

(26) See reference (11), p. 621.

TABLE I. COREDUCTION OF HETEROCYCLIC AND CARBONYL COMPOUNDS

Expt. No.	Heterocyclic Compound	Carbonyl Compound	Reducing Agent	Procedure Used	Products, % Yield[a]	
					Pyridyl Alcohol	Others
1	Pyridine	Acetone[12, 15]	Al	A	*2*-, 31–39	
2	Pyridine	Benzaldehyde[14]	Mg	A	*2*-, 14	
3	Pyridine	Benzaldehyde	VCl_2	C	0	Hydrobenzoins
4	Pyridine	Acetophenone[12, 14]	Al	A	*2*-, 32 *4*-, 4	
5	Pyridine	Acetophenone	$Mg + MgI_2$	A	0	[b]
6	Pyridine	Acetophenone	Li	B	0	[b]
7	Pyridine	Acetophenone	Zn	A	0	[b]
8	Pyridine	Acetophenone	Zn + Na	A	0	Pinacol
9	Pyridine	Acetophenone	Mn	A	0	[b]
10	Pyridine	Acetophenone	Ca	A	0	Pinacol
11	Pyridine	Phenylacetone[14]	Al	A	*2*-, 29	
12	Pyridine	2,3-Dimethoxyphenylacetone	Al	A	0	Tar
13	Pyridine	4-Hydroxy-3-methoxyphenylacetone	Al	A	0	Tar
14	Pyridine	4-Chlorophenylacetone	Al	A	0	Tar
15	Pyridine	α-Dimethylaminoacetophenone	Al	A	0	[b]
16	Pyridine	Benzophenone[12]	Mg	A	*2*-, 22	[b]
17	Pyridine	Benzophenone	Na	B	*4*-, 2[c]	Tar
18	Pyridine	Benzophenone	$(CH_3)_2CHOH$, sunlight	E	0	Pinacol, 66
19	Pyridine	Fluorenone	Al	A	0	Pinacol
20	Pyridine	Magnesium acetone pinacolate	...	F	0	[b]
21	Pyridine	Magnesium benzpinacolate	...	F	0	[b]
22	Pyridine	Magnesium benzpinacolate	Na	F	*2*-, 10	
23	Pyridine	Benzaldehyde	H_3PO_2, H^+	G	0	[b]
24	Pyridine	Benzaldehyde	H_3PO_2, OH^-	G	0	[b]
25	Pyridine	Benzaldehyde	H_3PO_2, pH 7	G	0	[b]
26	2-Picoline	Benzaldehyde	Mg	A	*2,6*-, 5[d]	[b]
27	2-Picoline	Benzaldehyde	Al	A	0	[b]
28	2-Picoline	*p*-Methoxybenzaldehyde	Mg	A	0	
29	2-Picoline	p-Methoxybenzaldehyde	Al	A	0	
30	2-Picoline	Phenylacetone	Al	A	0	[b] Tar
31	4-Picoline	Acetophenone[14]	Al	A	*2*-, 30	
32	4-Picoline	Acetophenone	Be	A	*2*-, 2	Pinacol, 54.5
33	4-Picoline	Phenylacetone	Al	A	*2*-, 56[e]	
34	2,6-Lutidine	Acetophenone	$Cr(OCOCH_3)_2$	D	0	[b]
35	2,6-Lutidine	Acetophenone	Al	A	0	[b]
36	2,6-Lutidine	Acetophenone	Mg	A	0	[b]
37	2,6-Lutidine	Benzophenone	Al	A	0	[b]
38	2,6-Lutidine	Benzophenone	Mg	A	0	[b]
39	Ethyl nicotinate	Acetophenone	Mg	A	0	Tar
40	2-Vinylpyridine	Acetophenone	Al	A	0	2-Ethylpyridine, 10[f], 10[f,g] Pinacol, 20[a]
41	2-Isopropenylpyridine	Acetophenone	Al	A	0	2-isopropylpyridine, 33[h] II, 24[i,j] Pinacol, 13.5[a]
42	2-Stilbazole	Acetone	Al	A	0	[b]
43	2-Stilbazole	Acetone	Mg	A	0	[b]
44	2-Stilbazole	Benzaldehyde	Al	A	0	2-Phenethylpyridine, 19.5[k] Isohydrobenzoin, 5[a], 33[g,i,k]
45	2-Stilbazole	Acetophenone	Al	A	0	2-Phenethylpyridine, 25–34[k] Pinacol, 12[a], 29[g,i,k]
46	2-Stilbazole	Phenylacetone	Al	A	0	2-Phenethylpyridine, 44[k] 33[g,i,k]
47	Quinoline	Acetophenone	Al	A	*2*-, 14–20	
48	Quinoline	Phenylacetone	Al	A	0	Tar
49	Isoquinoline	Acetophenone	Al	A	0	Tar
50	Quinaldine	Acetophenone	Al	A	0	Tar
51	2-Phenoxyquinoline	Acetophenone	Al	A	0	Tar

[a] Yield based on metal. [b] Recovered starting material. [c] M.p. 234–235°, lit. m.p. 234° and 235°.[29] [d] M.p. 87–88.5°, hydrochloride m.p. 174–175°. *Anal.* Calcd. for $C_{13}H_{13}NO$: N, 7.03. Found: N, 6.97. This material was oxidized with $KMnO_4$ in H_2SO_4 to pyridine-2,6-dicarboxylic acid (m.p. 228–230° d.). [e] M.p. 76–77°. *Anal.* Calcd. for $C_{15}H_{17}NO$: C, 78.64; H, 7.50; N, 6.10. Found: C, 78.96; H, 7.62; N, 6.19. [f] Yield based on 2-vinylpyridine; picrate, m.p. 106–107°, lit. m.p. 107.8–108.3°.[27] [g] Dimer like II. [h] Yield based on 2-isopropenylpyridine; picrate m.p. 116.5°, lit. m.p. 118.1–118.7°.[27] [i] See experimental. [j] Calcd. for $C_{16}H_{20}N_2$: M R_D, 73.73; found M R_D, 73.65. [k] Yield based on 2-stilbazole; methiodide m.p. 190°, lit. m.p. 190–191°.[28]

EXPERIMENTAL

The following experimental details are provided to illustrate the various procedures listed in Table I.

Procedure A. Bimolecular reduction of 4-picoline and acetophenone. Granular (30 mesh) aluminum (27 g., 1 mole), 0.5 g. of mercuric chloride and a few drops of mercury were preheated together for 0.5 hr at 100° in a 1-l. three-necked flask fitted with a dropping funnel, condenser, and mercury sealed stirrer. A mixture of 25 g. each of 4-picoline and acetophenone was added in one portion and stirred until the reaction began. The beginning of the reaction was accompanied by an evolution of heat and a color change to dark green. The remaining picoline (290 g., 3.5 moles total) was added in one portion, and 185 g. acetophenone (1.75 moles total) was added dropwise. The temperature was kept at 130° during the addition with the aid of a heating mantle. The ketone addition required 5.5 hr.; the temperature was kept at 130° for an additional 3.5 hr., rapid stirring being maintained during this time. The reaction mixture was then cooled and decomposed by pouring into 1 l. of 3*N* sodium hydroxide solution. The separating oil was extracted successively with 200 ml. portions of 6*N* hydrochloric acid. The acid extract was made basic with sodium hydroxide. The separating organic layer was dried over calcium sulfate and distilled. The fraction boiling 130–135° (0.8 mm) yielded a total of 85 g. (30% yield) of the pyridyl alcohol. Recrystallization from petroleum ether (b.p. 60–70°) gave a colorless solid, m.p. 69.5–70°. This compound is reported to melt at 70–71°.[14] It should be noted that larger amounts of $HgCl_2$ (0.2 mole per 1 mole of metal) were used with all the other bivalent metals (*i.e.*, Zn, Mn, Mg, Ca, and Be) listed in Table 1 where procedure A is employed.

Procedure B. Bimolecular reduction of pyridine and benzophenone with sodium. A mixture of pyridine (40 g.), benzophenone (90 g.), and toluene (500 ml.) was placed in a 3-necked flask fitted with a stirrer, dropping funnel, and condenser. The pyridine and toluene used were thoroughly dried over CaH_2. The flask was flushed with dry nitrogen, and a nitrogen atmosphere was maintained throughout the reaction. Sodium dispersion (40 g. National Distillers Co. sample, dispersed in xylene, 50% by weight) was added dropwise under nitrogen. The first drop gave a dark blue color which intensified as more was added. Reaction was slightly exothermic. The reaction mixture was allowed to stand at room temperature under nitrogen for 5.5 days, after which the color was dark brown. The reaction mixture was then oxidized by passing moist air through the flask. The oxidation procedure required 4 hr., and was exothermic but not vigorous. The light-orange solution was then decomposed with 6*N* hydrochloric acid, and the acid extract made basic with 3*N* sodium hydroxide. An ether extract of the basic layer gave no crystals on evaporation. A solid substance which precipitated from the basic solution showed m.p. 227–231° when recrystallized from benzene, and 232.5–234° when recrystallized from ethyl acetate. Literature values are 234° and 235° for 4-pyridyldiphenylcarbinol.[29] The crystals were insoluble in ether and gave a positive phenyl test with $AlCl_3$ and chloroform. The yield of the 4-pyridyl alcohol was less than 2%.

A mixture of benzophenone (61 g.), pyridine (26.3 g.), and toluene (50 ml.) was added slowly to sodium dispersion (30 g.), the temperature being maintained at 75–85° by means of a heating mantle during the addition and for 1 hr. thereafter. The solution was air-oxidized and decomposed with water. After cooling, 0.55 g. (0.75% yield) of the 4-isomer separated. No other condensation product could be isolated. Tar formation was greater than in the previous experiment.

Other variations in the reaction conditions included extended heating, rapid addition of the reactants, and allowing the reaction mixture to stand for two weeks at room temperature, but in no case was a yield better than 2% obtained, and the 2-isomer was never isolated.

Procedure C. Reaction between vanadous ion, pyridine and benzaldehyde. A solution of vanadous chloride prepared from 25 g. V_2O_5, 37.5 g. of zinc metal (amalgamated), 100 cc. water, and 140 cc. concentrated hydrochloric acid according to the procedure of Conant and Cutter,[20] was filtered through glass wool into a three-necked flask previously swept out with CO_2 gas. A solution of benzaldehyde (11 g.), ethanol (40 cc.), pyridine (32 g.), and hydrochloric acid (50 g.) was added dropwise with rapid stirring. After the addition was complete (3 hr.) the solution was stirred for 1 hr. The reaction mixture was then extracted eight times with ether, giving, after drying with Drierite and evaporating the solvent, 11 g. of a non-basic crystalline material, with a wide melting range. Oxidation of this material with permanganate yielded benzoil. These results parallel those which Conant and Cutter[20] obtained in the absence of pyridine.

Procedure D. Reaction of chromous ion with 2,6-lutidine and acetophenone. Chromous acetate (7.8 g.), acetophenone (15 g.), and 50 ml. of benzene were added in one portion to a refluxing mixture of 17 g. of 2,6-lutidine. The mixture was refluxed for 24 hr., during which time it turned from red-brown to green. The solution was cooled to room temperature, filtered, and the inorganic salts removed by extraction with water. Distillation of the residue gave 16 g. of 2,6-lutidine and no condensation product.

A three-necked flask containing a mixture of 17 g. of 2,6-lutidine and 15 g. of acetophenone was flushed out with nitrogen. Chromous acetate (7.8 g.) was added in one portion, and the temperature raised to 140° for 6 hr. The reaction mixture was cooled, filtered, extracted, and distilled. Only unreacted starting material could be isolated.

Procedure E. Irradiation of mixtures of benzophenone, acetophenone, and pyridine. A mixture of pyridine (26 g.), benzophenone (61 g.), and isopropyl alcohol (344 g.) was placed in a flask and a cork stopper was wired in place. The flask was exposed to sunlight for 7 days, after which the crystals which had formed were filtered off and purified. Forty-one grams (66% yield) of benzopinacol were found. Distillation of the liquid filtrate yielded 20 g. of pyridine and a small amount of a non-distillable tar.

Another reaction identical with the above except that acetophenone was used in place of the benzophenone resulted in the recovery of the starting materials.

Procedure F. Reaction of magnesium benzpinacolate with pyridine in the absence and presence of sodium. Benzpinacol[19] (24 g., 0.66 mole) in ether was added to 154 cc. of 0.4*M* Et_2Mg solution[30] in a 3-necked flask under nitrogen, giving first a cherry red color, and then a deep blue. The solution was allowed to stand at room temperature for 1 hr., and then pyridine (21.2 g., 0.25 mole) was added, and the solution was heated at 100° for 8 hr. The reaction mixture was cooled and decomposed with ammonium chloride solution and extracted with toluene. The toluene layer was dried and evaporated, giving 21 g. (89%) recovered benzopinacol. The aqueous layer was made basic and extracted with benzene, and the benzene extracts were evaporated. No bimolecular reduction product could be found.

Another reaction mixture containing magnesium benzopinacolate, which was prepared by adding benzopinacol (18.3 g., 0.05 mole) in ether dropwise to an ethereal solution of Et_2Mg (116 cc., 0.05 mole), was allowed to stand for 2 hr. under nitrogen, and then pyridine (21.2 g., 0.25 mole) was added rapidly to the mixture. Finally sodium (5 g., 0.22 mole) was added in small pieces over a period of 1 hr.

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There was no color change, but a metallic luster appeared. The reaction mixture was allowed to stand at room temperature for 73 hr. At the end of this time the metallic luster which was present at the beginning of the reaction had disappeared but the color was still deep blue. The reaction mixture was decomposed by adding 3*N* hydrochloric acid dropwise to the reaction mixture, allowing the slight evolution of gas to subside after each addition. The mixture was then filtered, ether was added, and the layers were separated. The residue from the filtration was a small amount of an orange-red solid, insoluble in acid, base, water, acetone, and ethanol. The aqueous layer was made basic, filtered, and extracted with toluene, and the toluene extracts were dried and allowed to evaporate. The crystals which were left were recrystallized from ethanol, yielding 1.3 g. (10%) of 2-pyridyldiphenylcarbinol, m.p. 102–103°, lit. m.p. 104–105°.[14] Hydrochloride, m.p. 178–179°, mixed m.p. with an authentic sample, 177–179°.

Procedure G. Reaction of hypophosphorous acid with pyridine and benzaldehyde. Three reactions were set up involving H_3PO_2, pyridine, and benzaldehyde, in acidic, basic, and neutral (pyridine) solutions. The mixtures contained:

(*a*)	Pyridine,	10 g. (0.13 mole)
	C_6H_5CHO,	14 g. (0.13 mole)
	H_3PO_2,	32 g. (0.5 mole)
(*b*)	Pyridine,	16 g. (0.2 mole)
	NaOH,	8 g. (0.2 mole)
	C_6H_5CHO,	10.6 g. (0.1 mole)
	Water	20 cc.
	H_3PO_2,	6.6 g. (0.1 mole)
(*c*)	Pyridine,	32 g. (0.4 mole)
	C_6H_5CHO,	10.6 g. (0.1 mole)
	H_3PO_2,	6.6 g. (0.1 mole)

Each mixture required the addition of a little ethanol to obtain a homogeneous solution. All were refluxed for 11 hr. except for (*b*) which was allowed to stand at room temperature for 24 hr. The (*a*) was extracted with ether, while the (*b*) and (*c*) were first acidified with HCl and then ether extracted. The ether extracts were extracted with sodium bisulfite and gave, on evaporation, non-basic materials with a very wide melting range. Oxidation of these products with nitric acid gave benzoic acid as the only insoluble product.

The (*a*), (*b*), and (*c*) were basified with sodium hydroxide. Extraction of these basic solutions with ether followed by evaporation of the ether gave no basic material other than pyridine.

Determination of the structure of the dimer of 2-isopropenylpyridine with the aid of infrared analysis. The structure II was assigned to the dimer obtained from the attempted coreduction of 2-isopropenylpyridine and acetophenone on the basis of the following characteristic absorption peaks: (*a*) 12.73 μ and 13.40 μ-strong bands corresponding to monosubstitution at the 2-position of the pyridine nucleus,[31] and (*b*) a weak band in the region 9.52–9.62 μ corresponding to the linkage $CH_3—\overset{|}{\underset{|}{C}}H$. Bands corresponding to disubstitution on the pyridine nucleus were absent.[32] Bands corresponding to an olefinic linkage were also absent. Dimeric forms containing gem-dimethyl groups were eliminated by the absence of an absorption peak in the range 8.35–8.40 μ—a characteristic peak for this grouping.[33] Finally, any dimeric form containing a cyclobutane ring was eliminated by the absence of absorption bands in the range 10.9–11.52μ—a region which has been reported to exhibit characteristic absorption peaks for mono-alkyl-cyclobutanes (10.9–11.0 μ)[34] and more highly substituted cyclobutanes (11.28–11.52 μ).[35] Of the possible simple dimers of 2-isopropenylpyridine only II meets all of these requirements of spectral analysis. The dimers of 2-stilbazole and 2-vinylpyridine were assumed by analogy to possess structures similar to II.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Heterogeneous Bimolecular Reduction. II. Direct Acylation of Pyridine and Its Homologs and Analogs*,[1]

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Heterogeneous bimolecular reduction of pyridine and acid derivatives with metals has been found to yield *C*-acylated pyridines. The general applicability of this reaction has been studied and a series of new heterocyclic ketones has been prepared. Intermediate steps in the synthesis have been postulated.

Pyridine, quinoline, and related heterocyclic bases have never been directly and substitutively acylated.[3] Apparently the ring member =N— is sufficiently electrophylic in nature to deactivate the remainder of the ring to attack by cations. Hence the Friedel-Crafts and related reactions fail.

It occurred to us that acylation of pyridine might be achieved satisfactorily if acyl anions could be

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(1) From the Ph.D. thesis of R. M. Schisla, June 1957, Purdue University.

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