Reactions of Aryl Grignard Reagents with Pyridine 1-Oxide. The Structure of the Addition Products

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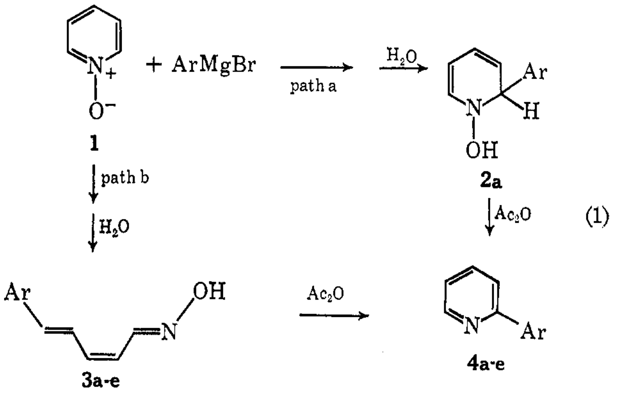
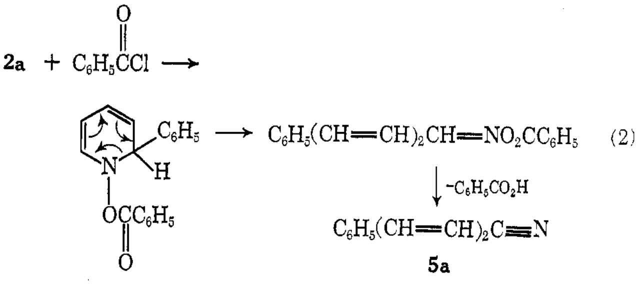
Addition of phenyl Grignard reagent to pyridine 1-oxide (**1**) leads to an addition product to which Kato and Yamanaka assigned 1,2-dihydropyridine structure **2a** (eq 1, path a).[1] This structural assignment appeared to be supported by the conversion of presumed **2a** to 2-phenylpyridine (**4a**) upon treatment with acetic anydride. Kato and coworkers[2] have also shown that the addition product is a useful intermediate for the synthesis of some *ring-opened* conjugated systems suggested to be formed along the general lines detailed in eq 2 for nitrile **5a** (which, after having been worked up, was identical with the presumed *all-trans*-**5a** prepared by another route).



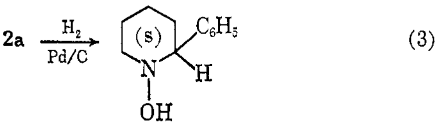
a, Ar = phenyl
b, Ar = perdeuteriophenyl
c, Ar = 4-tolyl
d, Ar = 4-anisyl
e, Ar = 2-thienyl



We have been interested in 1,2-dihydropyridines[3a,b] and in the synthesis of arylpyridines[3c] and hence were led to use the Grignard addition to **1** described by Kato and Yamanaka. Although able to duplicate fully the results of these authors, we offer evidence here that the additions of phenyl, perdeuteriophenyl, 4-tolyl, 4-anisyl, or 2-thienyl Grignard reagents to pyridine 1-oxide lead not to 1,2-dihydropyridines **2** but rather to ring-opened products **3a–e** (eq 1, path b) and that subsequent transformations of **3** give 2-arylpyridines **4** as well as nitriles **5**.

Results

Phenyl, 4-tolyl, 4-anisyl, and 2-thienyl Grignard reagents with **1** give addition products in 10–45% yield. No attempt was made to increase yields. The addition products all have the same general spectral features indicating like structural arrangement. Several details concerning the adduct of phenyl Grignard reagent and **1** militate against the proposed 1,2-dihydropyridine structure **2a**. Complete hydrogenation of **2a** should give **6** (eq 3). Kato and Yamanaka[1] obtained a compound, mp 57–58°; authentic **6** has mp 111–112°.[4]



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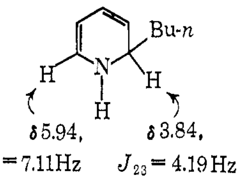
The nmr spectrum of supposed **2a** shows one proton at δ 8.5 (J = 10 Hz) which is suggested to be 2 H.[1] Comparison with known 1,2-dihydropyridines **7–9**[5–7] shows this J value to be unreasonably large for J_{23} and the absorption to be shifted too far downfield for a dihydropyridine, even assuming that it arises from the 6 rather than the 2 proton.



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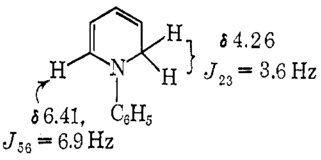

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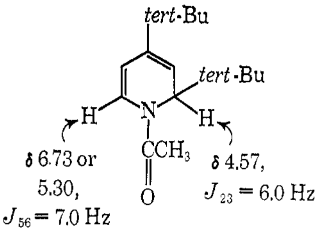

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Our structural assignment of 5-phenyl-2(*cis*),4-(*trans*)-pentadienal (*syn*)-oxime (**3a**) to Kato and Yamanaka's addition product is based primarily on the nmr spectrum. Other spectral data are also in full agreement with this structure. To simplify the nmr spectrum of the addition product, Grignard addition to **1** was carried out using bromobenzene-d_5. A product, mp 127.5–129°, was obtained whose 100-Mc nmr spectrum is shown in Figure 1 along with the computer-simulated spectrum derived using the spectral param-

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[1] T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965), and references to earlier work contained therein.

[2] T. Kato, H. Yamanaka, T. Adachi, and H. Hiranuma, *ibid.*, **32**, 3788 (1967).

[3] (a) R. M. Kellogg, T. J. van Bergen, and H. Wynberg, *Tetrahedron Lett.*, 5211 (1969); (b) T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.*, **36**, 978 (1971); (c) H. Wynberg, T. J. van Bergen, and R. M. Kellogg, *J. Org. Chem.*, **34**, 3175 (1969).

[4] J. Thesing and H. Mayer, *Chem. Ber.*, **89**, 2159 (1956); J. Thesing and H. Mayer, *Justus Liebigs Ann. Chem.*, **609**, 46 (1957).

[5] G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).

[6] M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).

[7] G. Fraenkel, J. W. Cooper, and C. M. Fink, *Angew. Chem.*, **82**, 518 (1970).

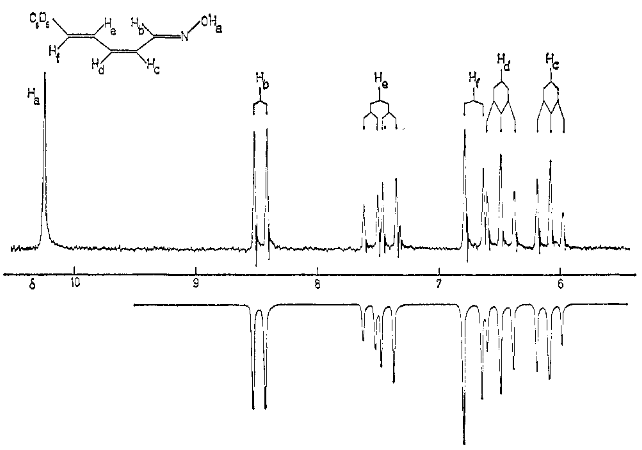
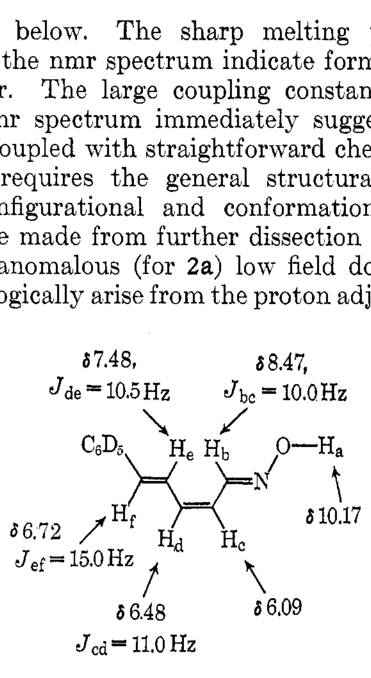


Figure 1.—100-Mc nmr spectrum (upper) of **3b** at *ca.* 37° in C_3D_6O. The negative signal spectrum (lower) is computer simulated using the parameters given in the text.

eters shown below. The sharp melting point and cleanness of the nmr spectrum indicate formation of a single isomer. The large coupling constants derived from the nmr spectrum immediately suggest olefinic units; this, coupled with straightforward chemical considerations, requires the general structural unit **3b**. Detailed configurational and conformational assignments can be made from further dissection of spectral data. The anomalous (for **2a**) low field doublet at δ 8.47 should logically arise from the proton adjacent to N



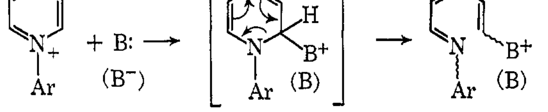
(H_b); H_b was shown furthermore to be coupled to a proton absorbing at δ 6.09 which must be H_c. The other simple doublet at δ 6.72 must come from the proton H_f adjacent to phenyl and the magnitude of the coupling constant (J = 15.0 Hz) requires that H_f and H_e define a trans double bond (Δ^4).[8] The Δ^2 double bond defined by H_d and H_c should be cis on the basis of J_{cd} = 11.0 Hz.[8] This assignment is also supported by absorptions at 845 and 785 cm^{-1} in the ir.[9] Finally, the values of J_{de} and J_{cd} are consistent for a transoid conformation as shown in **3b**.[10-12] This entire configurational and conformational assignment is strengthened further by the observation of a nuclear Overhauser effect (NOE) between H_b and H_e. Irradiation of H_b enhances the absorption of H_e 20% while other integrations are not affected. The closest approach of the nuclear centers of H_b and H_e in **3** is 1.8 Å measured from models.

Chemical considerations require the presence of the oxime functionality which explains the downfield shift of the absorption for H_b which is perfectly reasonable for an oxime.[13] Assignment of the syn configuration[14a] is based on the value $\delta_{OH} - \delta_{H_b}$ in DMSO.[14b] For a considerable sample of aliphatic oximes the chemical shift difference between the OH and vinylic protons is 3.04–3.18 for *syn*-oximes and 3.82–4.23 for *anti*-oximes. For two aromatic oximes the respective differences are 2.95–3.01, syn; 3.96–4.61, anti. For **3** (phenyl or perdeuteriophenyl) $\delta_{OH} - \delta_{H_b}$ is 2.56 and for the 4-anisyl, 4-tolyl, and 2-thienyl derivatives the value varies from 2.58 to 2.75. This strongly suggests syn configuration for the oxime functionality.

The net conclusion is that Grignard additions to pyridine 1-oxide result in ring opening leading stereospecifically to a Δ^2-*cis*,Δ^4-*trans*-pentadienal *syn*-oxime; the 1,2-dihydropyridine isomer is not formed in isolable amounts.

Discussion

The well-known ring openings (eq 4) of various *N*-arylpyridium salts on reaction with hydroxide ion or



(4)

other bases serve as obvious precedent for the reactions of **1**.[15] For the special case that the nucleophile is an aryl amine, ring opening is followed by ring closure resulting in a new pyridium salt and elimination of $ArNH_2$ (Ar is usually substituted with electron-withdrawing groups).[16-18] The ring closure, which takes place only with the neutral form of the open precursor,

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[8] A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **87**, 3445 (1965).

[9] See, for example, K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, and references cited therein.

[10] D. P. Kelly, *J. Mol. Spectrosc.*, **28**, 204 (1968).

[11] J. A. Elvidge and L. M. Jackman, *Proc. Chem. Soc., London*, 89 (1959).

[12] A. L. Segre, L. Zetta, and A. Di Corato, *J. Mol. Spectrosc.*, **32**, 296 (1969).

[13] G. C. Kleinspehn, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967).

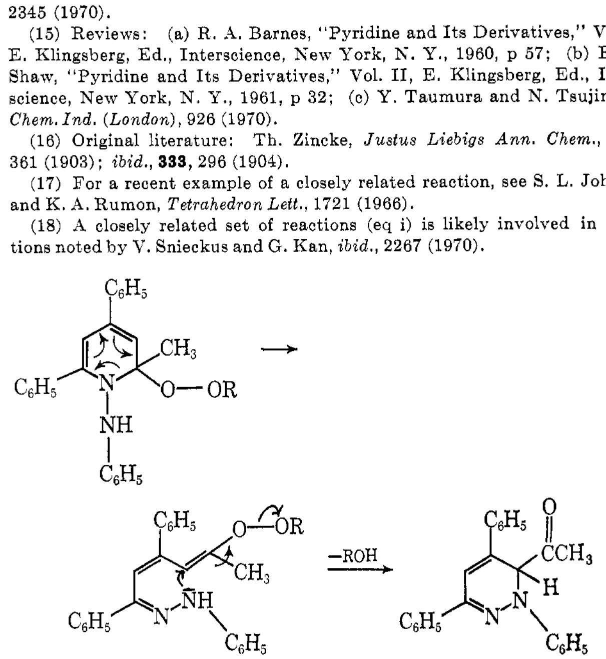
[14] (a) A review of oxime chemistry: C. G. McCarty in "The Chemistry of the Carbon Nitrogen Double Bond," S. Patai, Ed., Interscience, New York, N. Y., 1970, pp 383–392. (b) F. A. Neugebauer, *Tetrahedron Lett.*, 2345 (1970).

[15] Reviews: (a) R. A. Barnes, "Pyridine and Its Derivatives," Vol. I, E. Klingsberg, Ed., Interscience, New York, N. Y., 1960, p 57; (b) E. N. Shaw, "Pyridine and Its Derivatives," Vol. II, E. Klingsberg, Ed., Interscience, New York, N. Y., 1961, p 32; (c) Y. Taumura and N. Tsujimoto, *Chem. Ind. (London)*, 926 (1970).

[16] Original literature: Th. Zincke, *Justus Liebigs Ann. Chem.*, **330**, 361 (1903); *ibid.*, **333**, 296 (1904).

[17] For a recent example of a closely related reaction, see S. L. Johnson and K. A. Rumon, *Tetrahedron Lett.*, 1721 (1966).

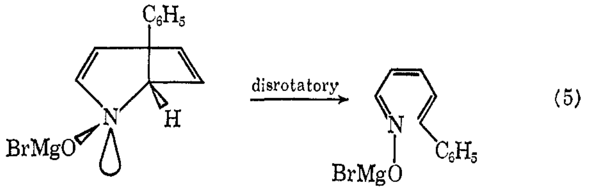
[18] A closely related set of reactions (eq i) is likely involved in reactions noted by V. Snieckus and G. Kan, *ibid.*, 2267 (1970).



(i)

is suggested to be an electrocyclic reaction on the basis of detailed mechanistic studies.[19]

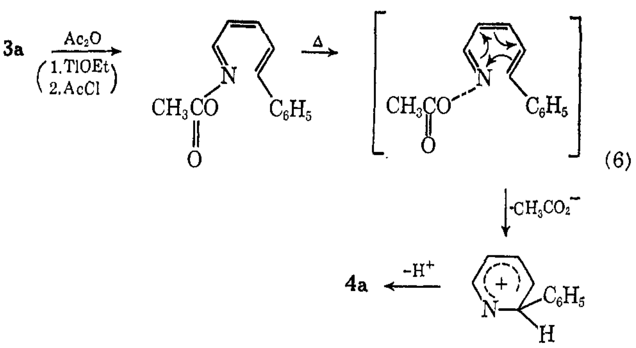
Although ring openings of pyridine 1-oxides seem not to have been noticed previously, such behavior should not occasion surprise.[20] An important driving force for ring opening is likely the potentially greater delocalization of charge in the open-chain structure. It is tempting to suppose that, subsequent to addition to Grignard reagent perpendicular to the pyridine ring, immediate disrotatory opening[21] of conformation **2a** occurs (at a rate faster than conformational equilibrium) leading directly to the observed stereochemistry (eq 5). The possibility that the *anti*-oxime as its magnesium salt isomerizes spontaneously to the syn form cannot be disregarded, however.



2a **3a**

The facile ring closure of compounds **3** upon treatment with acetic anhydride (a small amount of nitriles **5** is also formed) may be viewed as a Beckmann-like reaction (eq 6). Treatment of the thallium salt of **3a** gives the acetate[22,23] which undergoes smooth ring closure in dioxane solution; hence the reaction sequence as depicted in eq 6. A minor variation on eq 6 would involve electrocyclic cyclization of **3** with subsequent loss of acetic acid.[19,24,25]

Possible synthetic utility of the products **3** is obvious particularly since an otherwise difficult to obtain cis double bond can be secured selectively. Considerable care in subsequent manipulations is called for, however, because of the possibility of rapid cis–trans isomerism in these types of compounds.[26] In this connection, Kato, *et al.*,[2] isolated from **3a**, on treatment with benzoyl chloride, two compounds, mp 78.5–79.5 and 157–158°. They suggest that the lower melting compound is the benzoylated derivative of **2a** and the higher melting isomer to be a derivative of (presumably) *all-trans*-**3a**. Most likely the former compound is actually a derivative of Δ^2-*cis*,Δ^4-*trans*-**3a** while the latter is a derivative of Δ^2-*trans*,Δ^4-*trans*-**3a**.



Experimental Section

Melting points were measured on a calibrated melting point block. Nmr spectra (60 Mc) were taken with a Varian A-60 instrument. Ultraviolet spectra were run on a Zeiss PMQ-II spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Model 21 instrument. Microanalyses were performed by the analytical department of this University under direction of Mr. W. Hazenberg. Bromobenzene-d_5 was obtained from Merck AG, Darmstadt, Germany.

5-Aryl-2(*cis*),4(*trans*)-pentadienal (*syn*)-oximes (**3a–e**) were obtained by adding dropwise a solution of 6.0 g (0.07 mol) of **1** in 50 ml of dry tetrahydrofuran (THF) to a well-stirred Grignard reagent (0.10 mol), held at room temperature and prepared from the aryl bromide or iodide in 50–75 ml of dry THF. Stirring was continued for 1 hr after all the pyridine *1*-oxide had been added. The reaction mixture was poured out into concentrated ammonium chloride solution and the aqueous portion was extracted twice with THF.

The combined organic layers were concentrated by evaporating the solvent, and the residue was dissolved in methylene chloride and was dried over Na_2SO_4. Filtration and removal of the solvent yielded an oily residue from which the solid oxime separated upon crystallization from benzene, toluene, or methylcyclohexane. Crystalline **3d** was obtained only with difficulty by this procedure. A second recrystallization was necessary in all cases to obtain analytical samples. See Table I for physical and other data.

5-(Phenyl-d_5)-2(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3b) was isolated from the reaction of the Grignard reagent, prepared from 7.3 g of bromobenzene-d_5 and 1.4 g of magnesium in 25 and 40 ml of dry THF, respectively, with 2.7 g of **1** in 25 ml of the same solvent. By following the procedure described above, 1.7 g of **3b** was obtained.

5-Aryl-2,4-pentadiene nitriles (**5a–e**) were isolated from the reaction of an ice-cooled solution of 2.8 mmol of the oxime in 10 ml of dry pyridine and 2.8 mmol (0.5 g) of tosyl chloride. The solution was stored overnight in a refrigerator. Most of the pyridine was removed at reduced pressure. The residue was dissolved in methylene chloride, extracted three times with water, dried (Na_2SO_4), filtered, and concentrated by chromatography on a silica gel column with a 1:1 mixture of benzene and diethyl ether as the eluent. Further purification was effected by distillation or crystallization from methylcyclohexane. For physical constants and other data see Table II.

Ring closure of 5-phenyl-2(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3a) to 2-phenylpyridine was observed when 0.5 g of **3a** in 7 ml of acetic anhydride was refluxed for 1 hr. The solvent was evaporated and the residue dissolved in diethyl ether. This solution was extracted with water, dried (Na_2SO_4), filtered, and

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[19] (a) E. N. Marvell, G. Caple, and I. Shahidi, *Tetrahedron Lett.*, 277 (1967); (b) E. N. Marvell, G. Caple, and I. Shahidi, *J. Amer. Chem. Soc.*, **92**, 5641 (1970); (c) E. N. Marvell and I. Shahidi, *ibid.*, **92**, 5646 (1970).

[20] For example, F. Binns and H. Suschitzky, *Chem. Commun.*, 750 (1970), report that methylmagnesium bromide adds to 2,3,4,5-tetrachloropyridine 1-oxide to give a 1,2-dihydropyridine which loses MgBrCl to give 2-methyl-3,4,5-trichloropyridine 1-oxide. No ring opening is observed. We are grateful to Professor Suschitzky for correspondence on this problem.

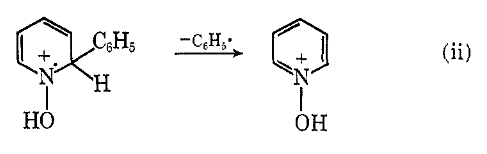
[21] R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

[22] E. C. Taylor, G. H. Hawks, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968); E. C. Taylor, C. W. McLay, and A. McKillop, *ibid.*, **90**, 2422 (1968).

[23] Oxime acetates from ketoximes are formed spontaneously at room temperature upon treatment with acetic anhydride: E. J. Corey and J. E. Richman, *ibid.*, **92**, 5276 (1970), and references cited therein.

[24] This represents a drastically improved route to 2-(2′-thienyl)pyridine (**4e**) obtained only with difficulty by other methods.[8c]

[25] Analogous behavior may occur in the mass spectrometer. The 100% peak from **3a** is seen at *m/e* 96 consistent with the process detailed in eq ii, whereby, subsequent to ionization at nitrogen, ring closure occurs followed by expulsion of a phenyl radical giving the observed fragment. For the mass spectra of dihydropyridines, see G. Schroll, S. P. Nygaard, S. O. Lawesson, A. M. Duffield, and C. Djerassi, *Ark. Kemi*, **29**, 525 (1969).



[26] (a) G. Gamboni, V. Theus, and H. Schinz, *Helv. Chim. Acta*, **38**, 225 (1955); (b) E. E. Boehm and M. C. Whiting, *J. Chem. Soc.*, 2541 (1963).

Table I

Physical Properties of 5-(Aryl)-2(*cis*),4(*trans*)-pentadienal (*syn*)-Oximes (**3a–e**)

				Uv[b]		Nmr[c]					Calcd			Found		
Compd	Mp, °C	Yield, %	Ir,[a] cm^{-1}	mμ	Log ε	δ_{H_a}	δ_{H_b}	δ_{H}[j]	δ_{CH_3}	$J_{H_bH_c}$ in Hz	C	H	N	C	H	N
3a	128.5–130.5[d]	28	845, 785	237	4.13	11.09	8.53	5.80–7.80		10.0	76.29	6.40	8.09	76.43	6.15	8.24
				302 (s)[g]	4.51									76.59	6.44	8.13
				315	4.61											
				328 (s)	4.57											
3b	127.5–129[d]	27	840, 790	237	4.17	11.16	8.56	5.80–7.70		10.5	74.13	3.40	7.86	74.15	3.49	7.83
				300 (s)	4.52							D[i]		74.31	3.57	7.89
				314	4.62							5.65			D[i]	
				327	4.52										5.24	
															5.35	
3c	128–130[e,f]	45	870, 780	241	4.07	11.11	8.52	5.80–7.70	2.30	10.0	76.98	7.00	7.48	77.11	6.90	7.36
				310 (s)	4.45									77.29	6.96	7.27
				320	4.53											
				332	4.45											
3d	119–121[d]	10	860, 775	245	4.05	11.11	8.53	5.80–7.70	3.69	10.0	70.91	6.44	6.89	71.15	6.30	6.89
				328	4.59									71.10	6.32	6.89
3e[h]	110–112[e]	48	860, 785	250	4.29	11.16	8.41	5.85–7.60		10.0						
				332	4.71											
				345	4.67											

[a] KBr pellet. [b] In 96% ethanol. [c] In dimethyl sulfoxide-d_6. [d] Recrystallized from benzene. [e] Recrystallized from toluene. [f] Recrystallized from methylcyclohexane. [g] Shoulder. [h] Repeated attempts to obtain a good analysis failed. [i] Deuterium. [j] For aromatic and vinylic protons.

Table II

Physical Properties of 5-(Aryl)-2,4-pentadieneonitriles (**5**)[a]

				Uv[b]		Nmr[c]				Calcd, %				Found, %			
Ar	Mp or bp (mm), °C	Yield, %	Ir, cm^{-1}	mμ	Log ε	δ_{H_a}	δ_{other}	δ_{CH_3}	$J_{H_aH_b}$ in Hz	C	H	N	S	C	H	N	S
5a	104–105	80	2200	232	4.04	5.18	6.60–7.60		8.0	85.13	5.85	9.03		84.95	5.89	8.92	
	(0.3)			307	4.50									85.06	5.77	8.95	
5b	105–107	67	2210	232	4.08	5.18	6.60–7.50		8.0	82.48	2.51	8.74		82.55	2.53	8.65	
	(0.3)			307	4.56						D[e]			82.67	2.53	8.76	
											6.30				D[e]		
															6.32		
															6.32		
5e	25.0–26.3	80	2210	236	3.97	5.13	6.70–7.40		8.0	67.04	4.38	8.69	19.88	66.87	4.38	8.81	19.95
				337	4.44									66.96	4.40	8.83	19.93
5c	54.5–55.5	85	2200[d]	237	4.05	5.16	6.70–7.50	2.37	9.0	85.16	6.55	8.28		84.73	6.51	8.49	
				244	3.95									84.91	6.58	8.48	
				318	4.50												

[a] Probably cis-trans mixtures. [b] In 96% ethanol. [c] In carbon tetrachloride. [d] KBr pellet. [e] Deuterium.

concentrated. The remaining oil was purified by chromatography over a silica gel column. Elution with benzene yielded 59 mg (13%) of an oil spectroscopically identified as **5a**. Elution with diethyl ether gave 272 mg (60%) of 2-phenylpyridine (**4a**) as confirmed by comparison with an authentic sample.[27]

Ring closure of 5-(2-thienyl)-2(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3e) to 2-(2′-thienyl)pyridine was performed as described above with the modification that the reflux period was 15 min. Starting with 0.7 g of **3e**, 104 mg (17%) of **5e** (identified spectroscopically) and 309 mg (49%) of a solid, mp 60–61.5° (recrystallized from petroleum ether, bp 40–60°), identical with 2-(2′-thienyl)pyridine **3e**, were isolated.

Acetylation of 5-phenyl-2-(*cis*),4(*trans*)-pentadienal (*syn*)-oxime (3a) was achieved *via* the thallium salt of **3a** which was prepared by adding a 4.9-g solution of thallium ethoxide[22] in 20 ml of dry diethyl ether to a 3.5-g solution of **3a** in 50 ml of the same solvent. The precipitated yellow salt, mp 137–140°, was collected in an almost quantitative yield by filtration and subsequent washing with diethyl ether.

To a well-stirred suspension of 2.0 g of this compound was added dropwise a solution of 420 mg of freshly distilled acetyl chloride over a 1-hr period maintaining the temperature at 5°. The color changed slowly to a pale yellow. Stirring was continued for 15 min. After all the acetyl chloride had been added, the thallium chloride was filtered off and the filtrate was concentrated at room temperature at reduced pressure to avoid decomposition of the product. The residue, 1.05 g (90%) of the almost pure acetylated oxime, could not be obtained in crystalline form and was immediately used for further reaction.

The oxime acetate had uv max (96% EtOH) λ_{max} 237 mμ (log ε 3.94) and 319 (4.49); ir 1770 (C=O) and 1010 cm^{-1} (NO); nmr (CCl$_4$) δ 2.11 (s, 3, CH$_3$), 6.00–7.50 (m, 9, aromatic and vinylic H), 8.48 (d, 1, J = 10.0 Hz, CH=N).

Ring closure of acetylated 3a to 2-phenylpyridine was observed when 445 mg of the acetate was concentrated by flash evaporation and the residue was purified by preparative thick layer chromatography (silica gel and benzene). A trace of 5-phenyl-2,4-pentadienenitrile and 133 mg (41%) of an oil identical with authentic 2-phenylpyridine[27] were isolated.

Reactions of *tert*-butylmagnesium bromide and methylmagnesium iodide with 1 were carried out in respectively THF and diethyl ether as described for the aryl compounds. Although a reaction undoubtedly took place, no products could be isolated.

Phenyllithium was allowed to react with **1** in THF at different temperatures in the same manner as described for the Grignard reagents. Only tarry mixtures were obtained in which no oxime could be detected and from which only a small amount of biphenyl was isolated.

Registry No.—**1**, 694-59-7; **3a**, 28541-47-1; **3b**, 28541-48-2; **3c**, 28541-49-3; **3d**, 28541-50-6; **3e**, 28541-51-7; **5a**, 14164-31-9; **5b**, 28541-53-9; **5c**, 28541-54-0; **5e**, 28541-55-1.

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[27] K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).