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ADDUCTS OF 4-ALKOXYPYRIDINES WITH GRIGNARD REAGENTS

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SUMMARY

The reaction of ethyl and phenyl Grignard reagents with 4-alkoxypyridines gives adducts of the formula $(4\text{-RO-Py})_2MgBr_2$, for which a tetrahedral structure is proposed. The IR and NMR data are discussed.

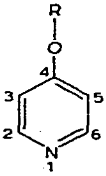
INTRODUCTION

The reactions of Grignard solutions with pyridine and its derivatives have been extensively studied. Some authors reported the alkylation of pyridine by Grignard solutions[1-6], but the results are often contradictory. The reaction of 3-pyridyl ketones, 3,5-dicyanopyridines and esters of pyridine-3,5-dicarboxylic acid with Grignard reagents led to the formation of dihydropyridines, but some attack on the substituents by the Grignard reagent is sometimes observed[7].

Kuthan[8] isolated the primary adducts formed from methylmagnesium iodide and 3,5-dicyanopyridines, and found they were 1-magnesiodihydropyridines of variable composition. Other authors[9-12] described the use of pyridine as a precipitating agent for Grignard solutions, and the structure and properties of the complexes obtained from diorganomagnesium compounds and pyridine have also been investigated[10-12]. We have now investigated the interaction of Grignard reagents and 4-alkoxypyridines.

RESULTS AND DISCUSSION

Mixing the Grignard solutions [(A), (B)] with 4-alkoxypyridines [(I)–(IV)] at room temperature, gave insoluble amorphous precipitates. The structure of the products was studied through their IR spectra in Nujol or perfluorolube suspension, their NMR spectra, and their Mg and Br contents.



(I) $R=CH_3$
(II) $R=CH_2CH_3$
(III) $R=CH_2Ph$
(IV) $R=Ph$

$(A)=CH_3CH_2MgBr$
$(B)=PhMgBr$

TABLE 1

ANALYTICAL DATA FOR THE ADDUCTS

Adduct	*% Mg*		*% Br*	
	Found	*Calcd.*[a]	*Found*	*Calcd.*[a]
(I)/(A)	6.24	6.041	39.72	39.72
(I)/(B)	5.88	6.041	39.47	39.72
(II)/(A)	5.69	5.648	37.21	37.13
(II)/(B)	5.81	5.648	36.83	37.13
(III)/(A)	4.54	4.383	28.90	28.82
(III)/(B)	4.25	4.383	28.95	28.82
(IV)/(A)	4.64	4.616	30.41	30.35
(IV)/(B)	4.67	4.616	30.66	30.35
(II) + $MgBr_2(Et_2O)_x$	5.53	5.648	36.83	37.13

[a] Calculated for $(4\text{-RO-Py})_2MgBr_2$.

The adduct obtained by mixing (II) with an ethereal solution of $MgBr_2$-etherate shows the same characteristics as the adducts (II)/(A)* and (II)/(B). The analysis of the adducts (Table 1) indicates that the empirical formula of the adducts is [(4-alkoxypyridine)$_2$MgBr$_2$].

NMR spectra

The NMR spectra (Table 2) of the pyridine derivatives (I)–(IV) show, for the protons on the pyridine ring, an A_2B_2 system which is degenerated to two only slightly

TABLE 2

COMPARISON OF CHARACTERISTIC NMR RESONANCES FOR THE 4-ALKOXYPYRIDINES AND THE CORRESPONDING ADDUCTS[a]

Compound	H_2, H_6[b]	H_3, H_5[b]	*R*	
(I)	1.63 d	3.14 d	$-CH_3$: 6.18 s	
(I)/(A)	1.41 d	3.01 d	6.11 s	
(I)/(B)	1.41 d	3.03 d	6.11 s	
(II)	1.65 d	3.17 d	$-CH_2-$: 5.92 q	$-CH_3$: 8.65 t
(II)/(A)	1.42 d	3.07 d	5.86 q	8.64 t
(II)/(B)	1.44 d	3.06 d	5.84 q	8.64 t
(III)	1.63 d	3.08 d	$-CH_2-$: 4.87 s	–Ph: 2.59 m
(III)/(A)	1.40 d	2.95 d	4.81 s	2.59 m
(III)/(B)	1.40 d	2.96 d	4.81 s	2.59 m
(IV)	1.58 d	3.17 d	–Ph: 2.71 m	
(IV)/(A)	1.34 d	3.06 d	2.66 m	
(IV)/(B)	1.36 d	3.08 d	2.64 m	

[a] All data's are in τ-values; s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. [b] $J_{2,3}$ and $J_{5,6}$ have the value of 7 Hz for the pyridines and the adducts.

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* In this article we use the abbreviation (I)/(A) to denote the adduct formed by the reaction of (I) (4-methoxypyridine) with (A) (ethylmagnesium bromide).

perturbed doublets. The resonance patterns for the R groups of (I)–(IV) are as expected. The NMR spectra of the adducts show the same patterns as the corresponding 4-alkoxypyridines, although the positions of the peaks are slightly changed. This means that no substitution has occurred in the nucleus or in the 4- substituents.

In all cases, the change in chemical shift on adduct formation has the same sign. Thus, the doublet of the H_2,H_6 resonance on adduct formation shows a deshielding of 22 Hz, the H_3,H_5 resonance one of 11 Hz, and the peaks of the hydrogen atoms on the carbon attached to the ether oxygen one of 6 Hz, while those arising from protons in the β-position to the ether oxygen do not show any shift at all. Since the "adduct shift" decreases with the distance to the nitrogen atom, we conclude that there is an electron-attracting group near that part of the pyridine nucleus, and this can be assumed to be $MgBr_2$.

However, when we mix the solution of the adduct in CH_3CN with that of the corresponding 4-alkoxypyridine [*e.g.* (II)/(A) with (II), both in CH_3CN] the extent of the deshielding is diminished for all the peaks, the effect being greatest for the H_2,H_6 peak, but the fine structure of the peaks is unchanged. This decrease of deshielding is proportional to the quantity of 4-alkoxypyridine added. We conclude that when the adduct is dissolved in acetonitrile it becomes less stable because of the high polarity of the solvent. The decrease in the deshielding on adding 4-alkoxypyridine to a solution of the adduct is, we suggest, due to exchange of 4-alkoxypyridine molecules.

IR spectra

The significant parts of the IR spectra of the CH_3 derivative and the adduct are shown in Figs. 1 and 2.

3200–2700 cm^{-1} region. The weak absorption band appearing at about 3170 and 3140 cm^{-1} for the CH_3 derivative may be due to overtones or combinations of the fundamental ring stretching vibrations. The other absorption bands appearing in this region are caused by the stretching modes of the pyridine ring system and the alkyl group. (The absorptions due to the different R groups will not be discussed, although some differences are observed on forming the adduct.) A great change in the spectrum of the CH_3 derivative occurs in the region 3070–3000 cm^{-1}; this is because the stretching modes of the pyridine ring system, which appear in this region, are

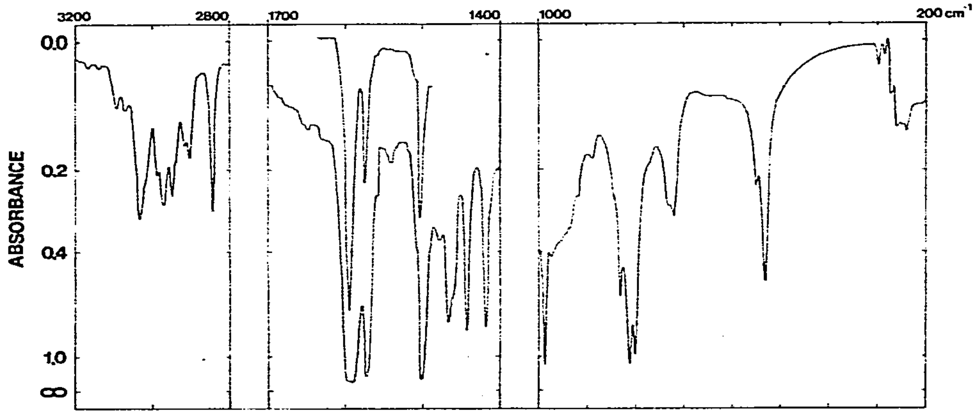

Fig. 1. IR spectrum of 4-methoxypyridine.

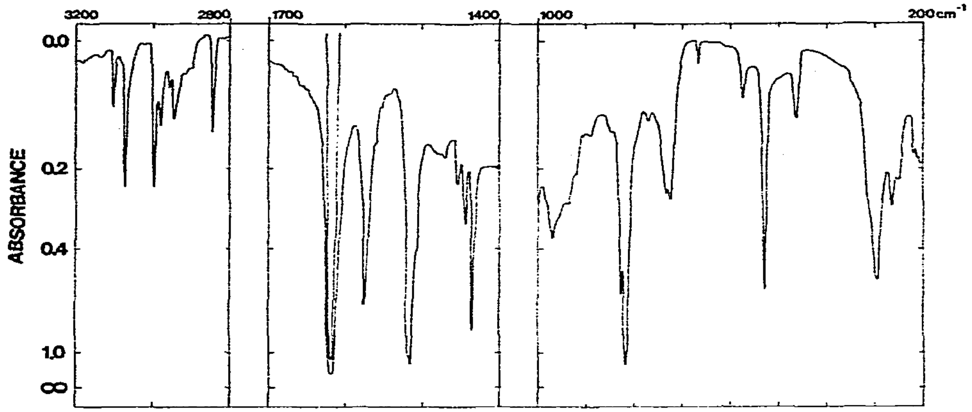

Fig. 2. IR spectrum of bis(4-methoxypyridine)magnesium dibromide.

very sensitive to the environment. Such changes of position and intensity for the CH bands in this region were also found with the other derivatives.

1700–1350 *cm*$^{-1}$ *region.* In this region appear the four typical bands of the pyridine ring system which result from the interaction of the C=C and C=N stretching modes[8,13]; the absorptions for the different R groups are given in Table 3, and are found to be in good agreement with the literature data. The first band at around 1595 cm^{-1} shifts to 1615 cm^{-1} and becomes more intense on forming the adduct. The second at around 1570 cm^{-1} is weaker, and undergoes almost no change. The third, situated around 1500 cm^{-1}, behaves like the first band, becoming more intense and shifting to a higher frequency. The fourth band, which should appear around 1420 cm^{-1} according to the literature[8,13], was difficult to detect, because it was obscured by the CH bending modes of the different R groups, which appear in the same region, but we did identify a medium strong band around 1419 cm^{-1} which (except in the case of the

TABLE 3

CHARACTERISTIC IR FREQUENCIES FOR THE 4-ALKOXYPYRIDINES AND THE CORRESPONDING ADDUCTS IN THE REGION 1700–1350 cm^{-1}

Adduct	*Characteristic frequencies (cm^{-1})*			
4-MeOPy	1594 vs	1574 s	1503 s	1419 m
adduct	1618 vs	1575 m	1516 s	1435 m
4-EtOPy	1595 vs	1569 s	1501 s	1418 m
adduct	1622 1611 } vs	1567 s	1513 s	1436 s
4-BzOPy	1592 vs	1574 m	1499 m	1418 m
adduct	1612 vs	1569 m	1514 s	1434 m
4-PhOPy	1583 vs	1577 1583 } s	1489 s	1417 m
adduct	1612 vs	1583 s	1503 s	(1417 m)?

phenyl derivative) moves to 1435 cm^{-1} in the adducts. The changes in intensity and frequency for those typical bands can be explained by assuming that the nitrogen coordinates with a magnesium atom; this should lead to a change in the electron availability at the nitrogen atom, and thus to shifts and intensity changes for the ν(C=C) and ν(C=N) bands.

1000–200 cm^{-1} region. The strong band shown by the methyl derivative at 985 cm^{-1}, which disappears on forming the adduct, may be due to the skeletal ring vibrations of the pyridine system[14]. Analogous bands appear for the ethyl and benzyl derivative at 998 cm^{-1} and 990 cm^{-1} respectively, and these also disappear on forming the adduct. The ring breathing mode could not be detected for the phenyl derivative. For all the compounds a broad band which appears around 930 cm^{-1}, can be attributed to ν(C–O). The δ(C–O) band seems to be situated at 532 cm^{-1} for the methyl, at 539 cm^{-1} for the ethyl, at 529 cm^{-1} for the benzyl, and at 530 cm^{-1} for the phenyl derivative. The absorptions due to the CO group are practically unchanged on forming the adducts. The CH out-of-plane deformations[15] and the in-phase "umbrella" modes of the pyridine ring system appear as strong bands in the 850–700 cm^{-1} region. A

TABLE 4

CHARACTERISTIC IR FREQUENCIES (in cm^{-1}) OF THE 4-ALKOXYPYRIDINES AND THE CORRESPONDING ADDUCTS IN THE REGION 700–200 cm^{-1}

4-MeOPy	*Adduct*	*4-EtOPy*	*Adduct*
550 m	664 mw	640 w	640 w
532 vs	572 m	570 vw	609 mw
460 (sh), w	527 vs	534 vs	555 (sh)
296 vw	461 mw	460 w	530 vs
271 vw	310 (sh)	430 w	443 m
261 vw	292 vs	380 w	402 (sh)
	280 (sh)	355 mw	378 ms
	263 m	260 mw	310 (sh)
	24[illegible] w		292 vs
			271 vs
			250 (sh)
4-BzOPy	*Adduct*	*4-PhOPy*	*Adduct*
731 (br), vs	730 (br), vs	691 vs	695 vs
694 vs	694 vs	663 w	688 vs
624 mw	632 m	655 w	665 vw
533 s	625 w	616 mw	631 mw
503 w	540 m	561 mw	610 vw
445 w, (br)	529 vs	521 s	573 m
264 w	499 m	477 mw	530 m
	437 m	401 vw	515 s
	320 mw	391 w	508 s
	303 (sh)	244 vw	480 m
	290 vs		390 w
	270 (sh)		340 mw
	264 vw		295 m
	250 m		283 s
			242 m

change comparable with that shown in Fig. 1 for the methyl derivative was also observed in the case of the other systems.

We could not identify the other ring vibrations, situated below 600 cm^{-1}. Indeed very little is known about these remaining ring deformation modes, because they are generally weak and hard to detect[16].

The strong absorptions in the 700–200 cm^{-1} region which appear in the adducts are listed in Table 4; they are due to the Mg–N and Mg–Br absorptions. Zeil[17] identified the 146 cm^{-1}, 307 cm^{-1}, 821 cm^{-1} and 861 cm^{-1} bands as Mg–Br frequencies by assuming a D_{2h} structure for the dimeric form Mg_2Br_4. Randall[18] located the frequencies for the linear $MgBr_2$ at 490 cm^{-1} for the asymmetric stretching mode and 178 cm^{-1} for the bending mode; this is in agreement with the findings of Büchler[19] for $MgCl_2$ (frequencies 597 cm^{-1} and 295 cm^{-1}, respectively). Kuthan[8] found absorptions due to ν(Mg–N) and ν(Mg–C) in the 430–570 cm^{-1} region in the case of the adduct of methylmagnesium iodide and cyanopyridines. With no other useful data available, we can only conclude that the new absorption appearing for all the derivatives at 630 cm^{-1}, 500 cm^{-1}, 295 cm^{-1}, 270 cm^{-1} and 250 cm^{-1} may be due to the antisymmetric and symmetric Mg–Br and Mg–N frequencies and the Br–Mg–Br and N–Mg–N bending modes.

Conclusion

The spectroscopic results obtained are consistent with a tetrahedral structure for the adducts $(4\text{-RO-Py})_2MgBr_2$. The changes in the NMR spectra of the adducts reveal that the electron cloud of the pyridine molecules is attracted towards the magnesium, but the N–Mg bond must be rather weak in acetonitrile solution, as the rapid exchange of pyridine molecules show.

The shifts of the IR bands can also be explained by coordination of N to Mg, which changes the π-orders of the ring bonds. The wholly new absorption bands which appear in the low IR frequency region can be identified as Mg–N and Mg–Br stretching and deformation modes.

A theoretical explanation for the proposed tetrahedral structure can be found in papers by Hamelin[20,21] and Ashby[22], but in our opinion their discussions do not present definitive evidence for any particular steric arrangement. The present work is being extended to other pyridines and Grignard reagents with the intention of examining the reactivity of these adducts in substitution reactions.

EXPERIMENTAL

Syntheses

Synthesis of the 4-alkoxypyridines. The 4-alkoxypyridines were usually prepared from 4-nitropyridine oxide and sodium alcoholate, with subsequent reduction by H_2 and Raney nickel, as described by Ochiai[23]. However, for the preparation of 4-phenoxypyridine we used another method, starting from *N*-pyridyl-4-pyridinium chloride hydrochloride and phenol[24].

Synthesis of the Grignard solutions. The ethyl- and phenylmagnesium bromide solutions were prepared in the usual way[25].

Synthesis of the adducts. A solution of 1 mmole of 4-alkoxypyridine in 20 ml of super dry ether was added with stirring to 1.25 mmoles of the Grignard reagent in dry apparatus. The addition caused immediate flocculation. The precipitate was handled under dry N_2 in a Schlenk apparatus[26]; it was filtered, washed with anhydrous ether, and dried *in vacuo*. White amorphous powders were obtained in 90% yield, except in the case of the 4-phenoxypyridine derivative, which gave only a 50% yield. Refluxing of the mixture after complete addition, use of reverse addition (Grignard to pyridine derivative) or use of an excess of the Grignard reagent did not change the structure of the obtained product.

Synthesis of $MgBr_2$-etherate and its reaction with 4-alkoxypyridines. $MgBr_2$-etherate was prepared by Braur's method[27], and was dissolved in dry diethyl ether; the solution was mixed with a solution of 4-alkoxypyridine in diethyl ether. An adduct was immediately precipitated. The analysis and spectra of the adducts prove that they are the same as those obtained from the Grignard solutions and the 4-alkoxypyridines.

Analyses

Magnesium. Samples of the adducts were decomposed with dilute sulphuric acid, and the solutions were diluted to 100 ml with distilled water. The magnesium was determined complexiometrically[8,28] by neutralizing to Methyl Red a 10 ml sample with 40% aqueous sodium hydroxide, adding 10 ml of an ammoniacal buffer solution of pH 10, and titrating with 0.02 *M* EDTA to Eriochrom Black T.

Bromine. Samples of ca. 1 g of the adduct were dissolved in 25 ml of 6 *N* acetic acid, and the volume was made up to 100 ml with distilled water. To a 10 ml sample was added 5 drops of an eosin solution (0.1 g eosin in 100 ml 70% ethanol) and 25 ml of distilled water and the bromine content was determined by titration against 0.050 *N* $AgNO_3$ the end-point being the persistence of a red colour in the precipitate[28].

Measurements of spectra

IR spectra. The IR spectra were recorded on a Perkin-Elmer 225 apparatus. Since the adducts are very sensitive to moisture, we could not record spectra in KI pellets while solution spectra could not be obtained because of the low solubility in IR solvents. Perfluorolube suspensions were used for the 4000–1350 cm^{-1} region and Nujol suspensions for the 1000–200 cm^{-1} region. The suspensions were prepared[8] by introducing perfluorolube and steel balls under nitrogen into a vessel containing the dried product and shaking the mixture until a high degree of homogeneity was obtained. The use of CsI windows made possible measurements down to 200 cm^{-1}.

NMR spectra. All the NMR spectra were recorded on a Jeol JNM PS 100 apparatus. As the adducts are very sensitive to moisture and do not dissolve in the usual NMR solvents, we used the following procedure: solutions of adducts containing 40 mg adduct per 1 ml acetonitrile (absolutely dry by distillation over CaH_2) were prepared in a Schlenk apparatus, and transferred to an NMR tube previously flushed with dry nitrogen. Another tube filled with CH_3CN and TMS was used for calibration. The samples for the reference spectra of the 4-alkoxypyridines were similarly prepared. There was no shift due to dilution effects for 4-alkoxypyridines at concentrations ranging from 0.05 g to 0.750 g of 4-alkoxypyridine per 1 ml of CH_3CN.

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REFERENCES

1 E. Bergmann and W. Rosenthal, *J. Prakt. Chem.*, 135 (1932) 267.
2 W. L. C. Veer and S. Goldschmidt, *Recl. Trav. Chim. Pays-Bas*, 65 (1946) 793.
3 R. A. Benkeser and D. S. Holton, *J. Amer. Chem. Soc.*, 73 (1951) 5861.
4 F. W. Bergstrom and S. H. Mc Allister, *J. Amer. Chem. Soc.*, 52 (1930) 2845.
5 N. Goetz-Luthy, *J. Amer. Chem. Soc.*, 71 (1949) 2254.
6 H. Gilman, J. Eisch and T. Soddy, *J. Amer. Chem. Soc.*, 79 (1957) 1245.
7 U. Eisner and J. Kuthan, *Chem. Rev.*, 72 (1972) 1.
8 J. Kuthan, A. Kohoutova and L. Helesic, *Collect. Czech. Chem. Commun.*, 35 (1970) 2776.
9 A. C. Cope, *J. Amer. Chem. Soc.*, 60 (1938) 2215.
10 G. J. Dubsky and Jacot-Guillarmod, *Helv. Chim. Acta*, 52 (1969) 1735.
11 G. J. Dubsky and Jacot-Guillarmod, *Helv. Chim. Acta*, 53 (1970) 1965.
12 G. J. Dubsky and Jacot-Guillarmod, *Helv. Chim. Acta*, 54 (1971) 1571.
13 A. R. Katritzky, *Quart. Rev. Chem. Soc.*, 13 (1959) 353.
14 A. R. Katritzky and J. N. Gardner, *J. Chem. Soc.*, (1958) 2198.
15 J. K. Wilmhurst and H. J. Bernstein, *Can. J. Chem.*, 35 (1957) 1183.
16 F. F. Bentley, L. D. Smithson and A. L. Rozek, *Infrared spectra and characteristic frequencies in the region* 700–300 *cm*$^{-1}$, Interscience, New York, 1968, p. 72.
17 W. Zeil, *Z. Elektrochem.*, 56 (1952) 789.
18 S. P. Randall, F. T. Green and J. L. Margrave, *J. Phys. Chem.*, 63 (1959) 758.
19 A. Büchler and W. Klemperer, *J. Chem. Phys.*, 29 (1958) 121.
20 R. Hamelin, *Bull. Soc. Chim. Fr.* (1961) 684.
21 A. Kirrmann, R. Hamelin and S. Hayes, *Bull. Soc. Chim. Fr.*, (1963) 1395.
22 E. C. Ashby, *Quart. Rev. Chem. Soc.*, 21 (1967) 259.
23 E. Ochiai, *Aromatic Amine Oxides*, Elsevier, Amsterdam, 1967, pp. 189, 380.
24 D. Jerchel, H. Fischer and K. Thomas, *Ber.*, 89 (1956) 2921.
25 M. S. Kharash and O. Reinmuth, *Grignard reactions of nonmetallic substances*, Prentice-Hall, New York, 1954, pp. 25, 28.
26 D. F. Shriver, *The manipulation of air-sensitive compounds*. McGraw-Hill, New York, 1969, p. 145.
27 G. Brauer, *Handbuch der Präparativen Anorganischen Chemie I*, Enke, Stuttgart, 2nd ed., 1960, p. 803.
28 A. I. Vogel, *A Textbook of Quantitative Inorganic Chemistry*, Longmans, London, 3rd. ed., 1964, pp. 261, 415.