

Organometallic Compounds of Group II. Part VII.^{1,2} Preparation of 4-Alkylpyridines by Reactions of Some Light Metals with Alkyl Halides in Pyridine

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Ether-free alkylmagnesium halides and alkyl-lithium compounds react with pyridine in the absence of the free metals to form 2-alkylpyridines; but in the presence of the free metals, 4-alkylpyridines are also formed. The reaction of an alkyl halide with the metal *in situ* in pyridine gives the 4-alkylpyridine essentially free from the 2-isomer. The use of alkyl chlorides and magnesium provides the best combination. Allyl chloride reacts with magnesium in pyridine to give 4-n-propylpyridine. The reactions of n-butyl chloride and magnesium in 2-picoline, 4-picoline, and collidine give a mixture of 2-n-pentylpyridine and 4-n-butyl-2-methylpyridine, 4-n-pentylpyridine, and a mixture of 'bicolindinyls,' respectively. It is suggested that the key step in the new 4-alkylation reaction involves abstraction of an alkylmetallic species by an intermediate derived from pyridine by electron transfer from the free metal.

PYRIDINE has long been known readily to undergo nucleophilic addition of organolithium compounds. The adducts form the corresponding alkylpyridines either by thermal elimination of lithium hydride or by hydrolysis followed by oxidation.³ In almost all cases the 2-substituted products are formed, although one or two instances of attack at the 4-position have been reported.^{4,5}

In contrast with the well defined behaviour of organolithium compounds in these reactions, that of Grignard reagents has appeared unclear and erratic. The literature contains several reports of 2-alkylation and -arylation of pyridine or quinoline,⁶⁻¹⁰ and of 4-alkylation of pyridine.^{11,12} Benkeser and Holton re-examined the conflicting reports in refs. 8 and 12 on the reaction of pyridine with benzylmagnesium chloride, and obtained both 2- and 4-benzylpyridines, the latter predominating.¹³ Goetz-Luthy could not confirm the reported⁷ ethylation by ethylmagnesium bromide.¹⁴ Pyridine has been used as a halide precipitant in the preparation of dialkylmagnesium compounds from Grignard reagents: no alkylation of the pyridine was reported.¹⁵ The object of the present work has been to elucidate the situation by an investigation of the reaction variables, using the experimentally convenient n-butylation as a typical case.

The reaction of ethereal n-butylmagnesium chloride with an excess of pyridine was incomplete (apart from an initial exothermic solvation reaction) after 8 h at 42–44 °C, and gave only 5% of a 10 : 1 mixture of 2-

and 4-n-butylpyridines. The yield and isomer ratio were unaffected by the presence of residual free magnesium. Avoidance of ether by the use of unsolvated n-butylmagnesium iodide prepared in toluene¹⁶ gave the results summarised in Table 1. These results show

TABLE 1
Reactions of non-ethereal n-butylmagnesium iodide with pyridine; ^a influence of free magnesium

Expt. no	Excess (atom %) of Mg used to prepare reagent	Yield of butylpyridines (%)	Isomer ratio (2- : 4-)
1	0 ^b	22	>100 : 1
2	50	16	7 : 1
3	50 ^c	18	>100 : 1
4	100	9	3 : 1
5	100 ^d	12	9 : 1
6	150	9	2 : 1

^a For standard conditions used, see Experimental section.

^b About 10 atom % of free magnesium remained after preparation of the reagent: the yields of n-butylmagnesium iodide were only 75–80% owing to side-reactions.¹⁷ ^c The reagent was centrifuged to remove free magnesium and magnesium iodide prior to the reaction with pyridine. ^d Excess of magnesium added to centrifuged solution.

that in the absence of free magnesium (experiments 1 and 3) the alkylation product is 2-n-butylpyridine essentially free from the 4-isomer, but that the presence of increasing amounts of residual free magnesium leads to the formation of increasing proportions of the 4-isomer. Comparison of experiments 2 and 3 shows that the prior removal of free magnesium and magnesium iodide prevented the formation of the 4-isomer. Comparison of experiments 1 and 3 shows that this effect is

⁹ H. Gilman and G. C. Gainer, *J. Amer. Chem. Soc.*, 1949, **71**, 2327.

¹⁰ H. Gilman, J. Eisch, and T. S. Soddy, *J. Amer. Chem. Soc.*, 1959, **81**, 4000.

¹¹ H. Gilman, J. Eisch, and T. S. Soddy, *J. Amer. Chem. Soc.*, 1957, **79**, 1245.

¹² W. L. C. Veer and S. Goldschmidt, *Rec. Trav. chim.*, 1946, **65**, 793.

¹³ R. A. Benkeser and D. S. Holton, *J. Amer. Chem. Soc.*, 1951, **73**, 5861.

¹⁴ N. Goetz-Luthy, *J. Amer. Chem. Soc.*, 1949, **71**, 2254.

¹⁵ A. C. Cope, *J. Amer. Chem. Soc.*, 1938, **60**, 2215.

¹⁶ D. Bryce-Smith and G. F. Cox, *J. Chem. Soc.*, 1961, 1175; D. Bryce-Smith, *Bull. Soc. chim. France*, 1963, 1418.

¹⁷ D. Bryce-Smith and G. F. Cox, *J. Chem. Soc.*, 1958, 1050.

¹ Part VI, D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc. (C)*, 1966, 154.

² Preliminary communication, D. Bryce-Smith, P. J. Morris, and B. J. Wakefield, *Chem. and Ind.*, 1964, 495.

³ B. J. Wakefield, 'The Chemistry of Organolithium Compounds,' Pergamon, Oxford, 1974.

⁴ H. Gilman and H. E. McNinch, *J. Org. Chem.*, 1962, **27**, 1889; R. A. Abramovitch and G. A. Poulton, *J. Chem. Soc. (B)*, 1969, 901.

⁵ T. Taguchi, M. Nishi, K. Watanabe, and T. Mukaiyama, *Chem. Letters*, 1973, 1307.

⁶ B. Oddo, *Gazzetta*, 1907, **37**, 568.

⁷ F. W. Bergstrom and S. H. McAllister, *J. Amer. Chem. Soc.*, 1930, **52**, 2845; T. T. Tsai, W. E. McEwen, and J. Kleinberg, *J. Org. Chem.*, 1961, **26**, 318.

⁸ E. Bergmann and W. Rosenthal, *J. prakt. Chem.*, 1932, **135**, 267.

not attributable to the removal of magnesium iodide, and experiment 5 demonstrates the promotion of 4-alkylation by magnesium metal. The use of non-etheral n-butylmagnesium chloride¹⁰ under the conditions of experiment 1 gave results similar to those listed for the iodide, except that *ca.* 10% of a mixture of butyltoluenes was also obtained; these were clearly formed during the preparation of n-butylmagnesium chloride by a Friedel-Crafts type side reaction catalysed by 'active' magnesium chloride.^{16,18}

The evident promotion of 4-alkylation of pyridine by magnesium metal suggested that 4-alkylation might be caused to predominate under conditions which provide

when the whole reaction was performed at 118 °C. Evidently heating caused rearrangement of allyldihydropyridines to the isomeric n-propylpyridines (*cf.* refs. 10 and 19).

Use of Metals Other than Magnesium.—Addition of pyridine to metal-free n-butyl-lithium in n-pentane at 40 °C gave, after hydrolysis, 2-n-butylpyridine in which the 4-isomer was not detectable by g.l.c., but when free lithium was present, traces of the 4-isomer were also produced. On the other hand, a one-step reaction between n-butyl chloride and lithium in pyridine at 40 °C gave 4-n-butylpyridine containing less than 1% of the 2-isomer. Sodium reacted similarly. Calcium,

TABLE 2

Variations of solvent and reaction temperature for the reaction of n-butyl chloride with pyridine (6 mol. equiv.) and magnesium (1.65 atom equiv.)

Expt. no.	Solvent ^a	Reaction temp. (°)	Reaction time (h)	(%) Yield of n-butylpyridines	2-:4- Isomer ratio
1	Pyridine	122	3	57	≤1:100
2	Diethyl ether	45—50	6	9	1:1
		45—55	20	14	1:10
3	Di-n-propyl ether	93	6	15	1:5
4	Di-n-butyl ether	125—127	3	35	<1:100
5	n-Pentane	45—50	6	3	1:5
		45—55	20	21	1:15
6	n-Hexane	72—76	3	9	1:10
7	Benzene	83—84	3	14	1:15
		83—84	12	25	1:50
8	Methylcyclohexane	98—99	3	42	<1:100
9	Toluene	111	3	49	<1:100
10	Xylene	132	2	36	<1:100
11	Cumene	141—145	2	29	<1:100

^a Little if any n-butylation occurred with triethylamine, decahydronaphthalene, or dimethylformamide as solvent.

a great excess of magnesium. This prediction was confirmed by reactions of n-butyl halides and magnesium *in situ* in boiling pyridine, which gave 4-n-butylpyridine virtually free from the 2- or 3-isomer. The best yield (57%) was obtained from the chloride, since this quaternised the least readily with pyridine in a competing side-reaction (as discussed below, the quaternary salts are not involved in the main alkylation route). This synthetically useful yield is comparable with those typically obtained in the 2-alkylation of pyridine by organolithium compounds.³ A series of experiments showed that the optimum molar ratio of n-butyl chloride to magnesium was 1.65:1. The main side-product in the 4-alkylation reactions was 4,4'-bipyridyl. The use of solvents other than an excess of pyridine led to lower yields and, in the cases of the lower boiling solvents, to appreciable proportions of the 2-isomers; these results are summarised in Table 2. The use of *s*- and *t*-butyl chlorides in the 4-alkylation reaction gave rather low yields of the corresponding 4-alkylpyridines, containing *ca.* 10% of the 2-isomers. The use of allyl chloride at 40 °C gave a 20:1 mixture of 4- and 2-allylpyridines. When the reaction mixture was heated to 118 °C before hydrolysis, the product was a 20:1 mixture of 4- and 2-n-propylpyridines, and a similar result was obtained

zinc, and aluminium were relatively unreactive, although traces of butylpyridines were detected: these may have

TABLE 3

n-Butylation of pyridine with metals and n-butyl halides

Metal	Halide	Temp. (°C)	Yield of n-butylpyridines (%)	2-:4- Isomer ratio
Li ^a	Cl	115—120	10	1:25
	Cl	40 ^b	9	<1:100
Na ^c	I	<i>ca.</i> 130	5	1:25
	Cl	<i>ca.</i> 118	8	1:2
Ca	Cl	40 ^b	6	1:65
	Cl	115	0	
Zn ^e	I	<i>ca.</i> 130	8	1:1
	Cl	115	0	
Al ^f	I	120	Trace	2:1
	Cl	115	Trace	
	I	117	4	1:2

^a Chips cut directly into pyridine. ^b 24 h reaction, followed by 3 min at 118 °C. ^c Wire. ^d Filings prepared under nitrogen. ^e Powder. ^f Mercury(II) chloride added as catalyst.

been formed by reaction of the metal with n-butylpyridinium chloride (see below).

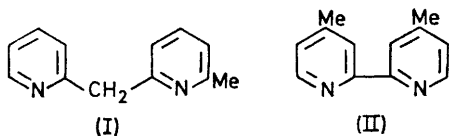
n-Butylation of Methylpyridines.—Reaction of n-butyl chloride with magnesium in 2-methylpyridine gave a 1:5 mixture of 2-n-pentylpyridine and 4-n-butyl-2-methylpyridine. The former probably arose *via* metalation of the 2-methyl group to give 2-picolylmagnesium chloride, which then coupled with n-butyl chloride. The use of 4-methylpyridine gave 4-n-pentylpyridine as the

¹⁸ D. Bryce-Smith and W. J. Owen, *J. Chem. Soc.*, 1960, 3319; E. T. Blues and D. Bryce-Smith, *Proc. Chem. Soc.*, 1961, 245.

¹⁹ J. J. Eisch and D. R. Comfort, *J. Org. Chem.*, 1975, **40**, 2288.

sole alkylation product. 2-Methylpyridine but not, surprisingly, the 4-isomer, has been shown to undergo α -metallation by organomagnesium reagents;²⁰ with organolithium compounds the relative susceptibilities to metallation of 2- and 4-methyl groups appear finely balanced.²¹ The present work may provide inferential evidence for the formation of a 4-picolylmagnesium species (but see below). The reaction of magnesium and n-butyl chloride with 2,4,6-trimethylpyridine (collidine) at *ca.* 120 °C led to the evolution of n-butane in quantitative yield, so no alkylation could have occurred. The product was apparently a mixture of 'bicollidinyls.'

The reaction of 2-methylpyridine with ether-free n-butylmagnesium iodide in toluene gave n-butane quantitatively, together with 2-methyl-6-(2-pyridylmethyl)pyridine (I). The formation of this compound



can be rationalised in terms of the initial formation of 2-picolylmagnesium iodide, followed by nucleophilic addition of this intermediate to the 6-position of 2-methylpyridine. The corresponding reaction of 4-methylpyridine again gave n-butane quantitatively, together with 4,4'-dimethyl-2,2'-bipyridyl (II). This compound could have been formed by metallation to give the 2-iodomagnesium derivative, followed by 1,2-addition of this intermediate to 4-methylpyridine. The formation of 2,2'-bipyridyl in the reactions of 2-lithio-1,3-dithians⁵ and lithium di-isopropylamide²² with pyridine has been reported, and an analogous mechanism has been proposed.²²

Since 4-methylpyridine appears to be resistant to metallation at the methyl group by organomagnesium compounds, the explanation for the formation of 4-pentylpyridine by the '*in situ*' reaction remains in doubt; it is possible that the metallating reagent is a reactive 'nascent' organomagnesium compound (*cf.* ref. 23) and conceivable that radical or single electron transfer processes are involved (see below).

Mechanism of the Direct 4-Alkylation of Pyridine.*— Since the reaction of pyridine with preformed n-butyl-lithium or ether-free n-butylmagnesium halides leads to almost exclusive 2-butylation, the 4-butylation which results with similar exclusivity by the *in situ* reaction must proceed by a different mechanism. The 2-alkylations are normally considered to involve straightforward nucleophilic 1,2-addition, in many respects similar to the Chichibabin reaction.

* It is assumed that any dihydropyridine products either eliminate metal hydride thermally or are oxidised on work-up (*cf.* ref. 3). No attempt has been made to detect dihydropyridine intermediates in our 4-alkylation reactions, although they have been reported as products of the reaction of lithium with trimethylsilyl chloride and pyridine,²⁴ and the formation of n-propyl derivatives by use of allyl chloride is difficult to rationalise other than in terms of a dihydro-intermediate.

The possibility that alkylpyridinium salts are intermediates in the 4-alkylation reactions may first be considered. These salts were certainly formed to some extent, particularly when alkyl iodides were used, and they are well known to rearrange to a mixture of 2- and 4-alkylpyridines at 300 °C (Ladenburg rearrangement). Control experiments showed that neither n-butylpyridinium chloride nor the iodide rearranges in boiling pyridine during the periods used for the 4-alkylation reactions. It was also found that although pyridine solutions of these quaternary salts react readily with magnesium at 100 °C, the products include only very low yields of 2- and 4-n-butylpyridines, in ratios of 3 : 1 (chloride) or 1 : 8 (iodide). Clearly such reactions do not occur to a significant extent under the conditions of the present 4-alkylation reaction, particularly when n-butyl chloride is used.

It is known that free alkyl radicals may be formed in reactions of alkyl halides with magnesium.^{17,25} However, when n-butyl radicals were generated in pyridine by photolysis of di-n-butylmercury, a low yield of n-butylpyridines was obtained; the 2- : 3- : 4-isomer ratio was 4.5 : 2 : 3 (ratios of *ca.* 5—6 : 2—3 : 1.5 have been reported for the attack of methyl radicals on pyridine²⁶). Furthermore, no 2,3-dimethyl-2,3-diphenylbutane was obtained from the reaction of n-butyl chloride with magnesium and pyridine in the presence of isopropylbenzene (*cf.* ref. 27). The intermediacy of *free* butyl radicals can therefore be excluded.

In a control experiment, 2-n-butylpyridine was shown not to rearrange to the 4-isomer under the conditions of the 4-alkylation reaction.

The reaction of n-butyl chloride and magnesium in toluene can produce high yields of butyltoluenes by a Friedel-Crafts type of reaction involving 'active' magnesium chloride;¹⁸ but the resemblance to the present systems is only formal since pyridine does not undergo Friedel-Crafts alkylation and in any case tends to give 3-substituted products with electrophiles: it also rapidly deactivates 'active' magnesium chloride.

Elimination of the foregoing possibilities leads us to propose the following mechanism for 4-alkylation as best in accord with the observed facts. The case of lithium is considered, for convenience in formulation, but the mechanism may readily be extended to magnesium and the other metals.

²⁰ N. Marekov, *Compt. rend. Acad. bulg. Sci.*, 1956, **9**, 35; E. Profft and H. W. Linke, *Chem. Ber.*, 1960, **93**, 2591.

²¹ E. M. Kaiser, G. J. Bartling, W. R. Thomas, S. B. Nichols, and D. R. Nash, *J. Org. Chem.*, 1973, **38**, 71; E. M. Kaiser and W. R. Thomas, *ibid.*, 1974, **39**, 2659; A. M. Jones, C. A. Russell, and S. Skidmore, *J. Chem. Soc. (C)*, 1969, 2245; W. B. Edwards, III, *J. Heterocyclic Chem.*, 1975, **12**, 413.

²² A. J. Clarke, S. McNamara, and O. Meth-Cohn, *Tetrahedron Letters*, 1974, 2373.

²³ D. Bryce-Smith and B. J. Wakefield, *Tetrahedron Letters*, 1964, 3295.

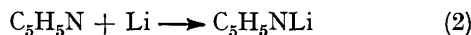
²⁴ R. A. Sulzbach, *J. Organometallic Chem.*, 1970, **24**, 307.

²⁵ H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron Letters*, 1972, 281; *Tetrahedron*, 1973, **29**, 719.

²⁶ R. A. Abramovitch and K. Kenaschuk, *Canad. J. Chem.*, 1967, **45**, 509.

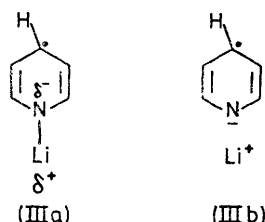
²⁷ D. Bryce-Smith, *J. Chem. Soc.*, 1955, 1712.

It is envisaged that the metal is consumed in two competing reactions, (1) and (2). The first of these

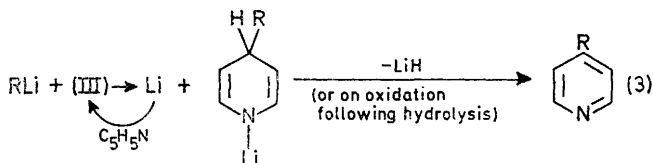


requires no justification. The second is also of a known type,^{28,29} and produces a radical (or the corresponding radical anion) of which (IIIa and b) represent canonical forms. E.s.r. measurements³⁰ and the formation of 4,4'-bipyridyl as the main product when pyridine reacts with lithium or magnesium in the absence of alkyl halide are consistent with the unpaired electron being located at the 4- rather than the 2- and 6-positions.

The intermediate represented by (III) could give rise to the 4-alkylpyridine in several ways, of which three are most likely to be significant. (i) The intermediate (III)



could react with the alkyl halide, by analogy with known reactions of radical anions.²⁹ (ii) The first stage in the formation of organomagnesium (and organolithium) compounds from magnesium and alkyl halides is believed to involve electron transfer from the metal surface to the alkyl halide.^{25,31} The 4-alkylpyridine could thus be formed following coupling of the intermediate (III) and the radical anion of the alkyl halide at the metal surface. (iii) The intermediate (III) could react with an organolithium compound [reaction (3)]. Routes (i) and (ii)



appear at first sight more likely, but they cannot be the only ones followed, since 4-alkylation occurs in the absence of residual alkyl halide (see Table 1). Route (iii) must therefore be followed to some extent. Although route (iii) may on first sight appear less probable, an analogous reaction (of the anthracene radical anion with *n*-butyl-lithium) has been reported.³² Moreover, if reaction (iii) takes place at the metal surface it could well involve an electron-deficient, 'nascent' intermediate. Indeed, routes (i)—(iii) may be regarded as special cases of a continuum, in which the intermediate (III) reacts

²⁸ R. Weil and N. Collignon, *Bull. Soc. chim. France*, 1974, 253.

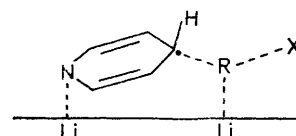
²⁹ N. L. Holy, *Chem. Rev.*, 1974, **74**, 243.

³⁰ C. L. Talcott and R. J. Myers, *Mol. Phys.*, 1967, **12**, 549.

³¹ R. G. Rogers, H. L. Mitchell, Y. Fujiwara, and G. M. Whitesides, *J. Org. Chem.*, 1974, **39**, 857.

³² H. J. S. Winkler, R. Bollinger, and H. Winkler, *J. Org. Chem.*, 1967, **32**, 1700.

with some species involved in the formation of the organolithium compound [equation (1)]. The Figure shows a possible pictorial representation of the process,



FIGURE

in which the dotted lines represent bonds which are made or broken in the course of the reaction.

The reaction of the metal with alkyl halide and pyridine may be regarded as a type of Barbier synthesis.³³ There has recently been a revival of interest in such reactions, which normally give the same products as those given by pre-formed Grignard reagents or organolithium compounds.³⁴ Our results indicate that in some cases the Barbier approach may give different products, and suggest that even when the same products are obtained they may be formed by a different mechanism (*cf.* ref. 35).

EXPERIMENTAL

All alkylation reactions were carried out under an atmosphere of dry oxygen-free nitrogen. Magnesium powder (Magnesium Elektron Ltd.) was sieved and the material passing the 170 mesh sieve was used. Pyridine and methylpyridines were dried by distillation from potassium hydroxide. Solvents were dried over sodium wire or calcium hydride. Alkyl halides were dried over calcium chloride. Authentic 2-*n*-butylpyridine was prepared from *n*-butyl-lithium and pyridine,³⁶ and 4-*n*-butylpyridine from 4-picolyl-lithium and 1-bromopropane.³⁷ Mixtures of 2- and 4-*n*-butylpyridine were analysed by g.l.c. (180 cm × 3 mm column; 7% dinonyl phthalate on Celite; 110 °C), with the authentic compounds as standards.

Non-etheral n-Butylmagnesium Halides.—(a) Magnesium powder (3.65 g, 0.15 g atom) was suspended in toluene (50 ml). 1-Iodobutane (12 drops) was added, and the mixture was heated to reflux temperature *without stirring*. After *ca.* 10 min under reflux, the reaction started. 1-Iodobutane (the remainder of 11.5 ml, 0.10 mol) in toluene (50 ml) was added dropwise with stirring during 30 min. The mixture was stirred under reflux during 2 h.

(b) In order to obtain the reagent free from magnesium metal, the mixture was allowed to settle for *ca.* 12 h. The supernatant was decanted, under a rapid stream of nitrogen, into a 100 ml polypropylene tube which had been flushed with nitrogen. The tube was fitted with a gas-tight cap and centrifuged at *ca.* 6 000 rev. min⁻¹ during 20 min. The clear supernatant liquid was decanted under nitrogen into the reaction vessel.

(c) *n*-Butylmagnesium chloride was prepared as described

³³ P. Barbier, *Compt. rend.*, 1899, **128**, 110.

³⁴ M. P. Dreyfus, *J. Org. Chem.*, 1963, **28**, 3269; P. J. Pearce, D. H. Richards, and N. F. Scilly, *J.C.S. Perkin I*, 1972, 1655; N. F. Scilly, *Synthesis*, 1973, 160; F. Huet and G. Emptoz, *J. Organometallic Chem.*, 1975, **101**, 139.

³⁵ C. Blomberg and F. A. Hartog, Seventh International Conference on Organometallic Chemistry, Venice, 1975, Abstract 54.

³⁶ J. C. W. Evans and C. F. H. Allen, *Org. Synth.*, 1938, **18**, 70.

³⁷ C. Osuch and R. Levine, *J. Amer. Chem. Soc.*, 1956, **78**, 1723.

in (a), from magnesium (2.43 g, 0.10 g atom) and 1-chlorobutane (10.5 ml, 0.10 mol).

Reactions of n-Butylmagnesium Halides with Pyridine.—(a) *In diethyl ether.* Pyridine (50 ml) was added dropwise during 30 min to a solution of n-butylmagnesium chloride, from 1-chlorobutane (10.5 ml, 0.10 mol) and magnesium (4.86 g, 0.20 g atom), in diethyl ether (100 ml). The mixture was heated under reflux during 8 h. Saturated aqueous ammonium chloride (100 ml) was added. The organic layer was separated. The aqueous layer was basified (sodium hydroxide) and extracted with ether (4 × 100 ml). The combined organic layers were dried (Na₂SO₄). Material of b.p. < 120° (ether and pyridine) was distilled (column packed with Fenske helices). G.l.c. of the residue (0.7 g) showed it to consist mainly of 2- and 4-n-butylpyridines (9 : 1), together with traces of bipyridyls.

Similar results were obtained in experiments with 2.43 g (0.10 g atom) and 3.65 g (0.15 g atom) of magnesium.

(b) *In the absence of ethers.* The n-butylmagnesium halide, prepared as described above, was stirred and maintained at 16 °C as pyridine (50 ml) was added during 30 min; a yellow precipitate was formed. The mixture was heated rapidly to reflux temperature, and stirred under reflux during 2 h. A Gilman test for organomagnesium compounds³⁸ was then negative. The mixture was allowed to cool, saturated aqueous ammonium chloride (100 ml) was added, and the organic layer was separated. The aqueous layer was basified (4N-sodium hydroxide) and extracted with ether (4 × 100 ml). The organic layer and ethereal extracts were combined and dried (Na₂SO₄), and the ether, toluene, and pyridine were distilled off through a column packed with Fenske helices. The residue was transferred to a smaller flask and distilled. The fraction of b.p. 180—220° was analysed for butylpyridines as described above. Further distillation gave a mixture of bipyridyls, b.p. 270—305° (see below). The yields and 2- : 4-isomer ratios of the products obtained from reagents containing various amounts of free magnesium and/or magnesium iodide are recorded in Table 1. The product from experiment 3 was essentially pure 2-n-butylpyridine, b.p. 189—190° (lit.,³⁷ 188—192°) (Found: C, 79.9; H, 9.6; N, 10.45. Calc. for C₉H₁₃N: C, 79.95; H, 9.7; N, 10.35%); picrate, m.p. 94.5—95.5° (lit.,³⁷ 96.7—97.6°).

The fraction of b.p. 180—220° from the reaction with n-butylmagnesium chloride was shaken with 6N-hydrochloric acid (3 × 2 ml). The combined acidic extracts were washed with ether (10 ml) and the ether was added to the organic layer. Distillation gave a mixture of butyltoluenes (10% based on a 75% yield of organomagnesium compound), identified by g.l.c. and i.r. spectroscopy. The acidic extracts were made alkaline with saturated aqueous sodium carbonate and extracted with ether (4 × 10 ml). The extracts were dried and distilled, to give 2-n-butylpyridine (23%).

The One-step 4-n-Butylation Process.—(a) Pyridine (15 ml) and magnesium (4.0 g, 0.165 g atom) were placed in a flask fitted with two addition funnels, containing respectively 1-chlorobutane (10.5 ml, 0.10 mol) and pyridine (65 ml). 1-Chlorobutane (12 drops) was run into the flask, the mixture was heated to ca. 110 °C, and a crystal of iodine was added. After 2—3 min, reaction commenced.

³⁸ H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.

³⁹ J. F. Arens and J. P. Wibaut, *Rec. Trav. chim.*, 1942, **61**, 59.

⁴⁰ C. R. Smith, *J. Amer. Chem. Soc.*, 1924, **46**, 414.

The stirrer was started, and the reagents were added dropwise. In the earlier stages of the reaction, the mixture became dark mauve and viscous, and the pyridine was then added more rapidly. The mixture was stirred under reflux during 3 h. It was then allowed to cool, and saturated aqueous ammonium chloride (100 ml) was added. The product was worked up as described above for the reactions of non-ethereal n-butylmagnesium halide, to give 4-n-butylpyridine (57%), b.p. 207—209° (lit.,³⁹ 207—209°) (Found: C, 79.7; H, 9.5; N, 10.4. Calc. for C₉H₁₃N: C, 79.95; H, 9.7; N, 10.35%); picrate, m.p. 112.2—112.7° (lit.,³⁷ 111.5—112.4°); and bipyridyls (50%), b.p. 270—310° (see below).

Numerous experiments were performed with variations in the proportion of magnesium, the proportion of pyridine, the time of addition of the halide, and the time of reaction. The procedure described above represents the optimum conditions.

(b) Similar reactions, with 1-bromobutane or 1-iodobutane in place of 1-chlorobutane, gave 4-n-butylpyridine in 25 and 15% yields, respectively, with large amounts of tar.

(c) For the reactions whose results are recorded in Table 2, neat pyridine (15 ml) was run into the flask for the initiation of the reaction. After initiation a mixture of pyridine (25 ml) and the appropriate solvent (40 ml) was added rapidly.

In the experiment where the solvent was isopropylbenzene, ether and pyridine were distilled from the combined organic products, and the residue was extracted with 6N-hydrochloric acid (5 × 50 ml). Distillation of the remaining organic layer gave isopropylbenzene (27 ml), b.p. 150—154°, with no significant residue. The combined extracts were basified and worked up as before.

Examination of the Bipyridyl Fractions.—The bipyridyl fractions were dissolved in ethanol and examined by g.l.c. (2 m × 3 mm column; 1.5% silicone gum rubber on Chromosorb W; 180 °C). In all cases, peaks with retention times corresponding to 2,2', 2,4', and 4,4'-bipyridyls were observed. In the products from the organomagnesium reagents free from metallic magnesium, the peak corresponding to 2,2'-bipyridyl predominated. When magnesium metal had been present, the 4,4'-isomer was the main component of the mixture. The product from the 4-butylation with 1-chlorobutane, described above, consisted almost entirely of 4,4'-bipyridyl; the crude fraction had m.p. 86—90°, raised on recrystallisation from light petroleum (b.p. 60—80°) to 113—113.5° (lit.,⁴⁰ 114°) (Found: C, 76.65; H, 5.35; N, 17.5. Calc. for C₁₀H₈N₂: C, 76.9; H, 5.15; N, 17.95%).

Other 4-Alkylation Reactions of Pyridine.—(a) *With magnesium and 2-chlorobutane.* A reaction carried out as described above for 1-chlorobutane gave a mixture (18%) of 2- and 4-s-butylpyridines (1 : 12), b.p. 170—195°. A similar experiment, in which the 2-chlorobutane was added during 1 h and the mixture was subsequently heated during 30 min gave a mixture (12%) of 2- and 4-s-butylpyridines (1 : 85). Fractional distillation gave essentially pure 4-s-butylpyridine, b.p. 189—191° (lit.,⁴¹ 187°; lit.,⁴² 195.5°); picrate, m.p. 140—141° (lit.,^{41,42} 142°).

(b) *With magnesium and 2-chloro-2-methylpropane.* A

⁴¹ A. E. Tschitschibabine, *Bull. Soc. chim. France*, 1936, **3**, 1607.

⁴² R. Lukes and I. Ernest, *Coll. Czech. Chem. Comm.*, 1950, **15**, 107.

reaction carried out as described for 1-chlorobutane gave a mixture (8%) of 2- and 4-t-butylpyridines (1:8), b.p. 165–200°. A similar experiment in which the halide was added during 1 h and the mixture was subsequently heated during 30 min gave a mixture (5%) of 2- and 4-t-butylpyridines (1:22). Fractional distillation gave a specimen of 4-t-butylpyridine, b.p. 195–196° (lit.,⁴³ 196.3°); picrate, m.p. 130–131° (lit.,⁴³ 130.9–131.4°).

(c) *With magnesium and 3-chloropropene.* A reaction carried out as described for 1-chlorobutane gave a mixture (20%) of 2- and 4-n-propylpyridines (1:8), b.p. 160–190° (no peaks at ν_{\max} 1640 and 915 cm^{-1}). A similar experiment, in which the halide was added during 1 h and the mixture was subsequently heated during 30 min gave a mixture (18%) of 2- and 4-n-propylpyridines (1:20). Fractional distillation gave a specimen of 4-n-propylpyridine, b.p. 189–191° (lit.,³⁹ 189°); picrate, m.p. and mixed m.p. 131.8–132.5° (lit.,³⁹ 131.0–131.6°).

In another experiment, the halide was added at 40 °C during 1 h, and the mixture was stirred at 40 °C during 24 h and then at 118 °C during 3 min. The product (14%) was virtually identical with that from the preceding experiment.

In another experiment otherwise similar to the preceding one, the period of heating at 118 °C was omitted. The product (11%) was a mixture of 2- and 4-allylpyridines (1:20), b.p. 160–190°, with an i.r. spectrum (ν_{\max} 1640 and 915 cm^{-1}) virtually identical with that of a mixture of 2- and (mainly) 4-allylpyridines, prepared as described in ref. 11.

(d) *With metals other than magnesium and n-butyl halides.* The reactions were carried out essentially as described for magnesium and 1-chlorobutane. The reagents, temperatures, and products are recorded in Table 3.

n-Butylation of Methylpyridines.—(a) *With magnesium and 1-chlorobutane.* 2-Methylpyridine (10 ml) was added to magnesium (4.0 g, 0.165 g atom), a few drops of 1-chlorobutane were added, and the mixture was heated to reflux. After initiation (iodine; ca. 5 min induction period), 1-chlorobutane (remainder of 10.5 ml, 0.10 mol) was added dropwise to the dark mauve slurry, followed by a mixture of 2-methylpyridine (30 ml) and toluene (40 ml). The mixture was heated under reflux during 3 h, and hydrolysed and worked up to give a mixture (1.8 g), b.p. 100–125° at 15 mmHg, of 2-methyl-4-n-butylpyridine and 4-n-pentylpyridine (5:1) (Found: C, 80.1; H, 10.2; N, 9.55. Calc. for $\text{C}_{10}\text{H}_{15}\text{N}$: C, 80.5; H, 10.1; N, 9.4%).

A similar reaction with 4-methylpyridine gave 4-n-pentylpyridine, b.p. 114–116° at 15 mmHg (lit.,³⁷ 115–120° at 21 mmHg); picrate, m.p. and mixed m.p. 104.2–104.8° (lit.,³⁷ 104.6–105.0°).

A similar reaction with 2,4,6-trimethylpyridine gave a mixture (three main components by g.l.c.) (2.7 g), b.p. 90–110° at 0.05 mmHg [Found: C, 79.55; H, 8.5; N, 12.1%; *M* (Rast), 247. Calc. for $\text{C}_{16}\text{H}_{20}\text{N}_2$: C, 79.95; H, 8.4; N, 11.65%; *M*, 240]. From a trap cooled in solid carbon dioxide-acetone was obtained n-butane (5.8 g, 0.10 mol), identified by b.p. and i.r. spectrum.

(b) *With ether-free n-butylmagnesium iodide.* To a clear, stirred solution of n-butylmagnesium iodide (0.077 mol) in toluene (100 ml), 2-methylpyridine (50 ml) was added dropwise during 30 min. The temperature of the mixture

was maintained at ca. 14 °C during the addition, and then raised to 118 °C under reflux during 2 h. During this period butane (4.5 g, 0.077 mol) was collected in a cold trap. Hydrolysis and work-up gave 2-methyl-6-(2-pyridylmethyl)pyridine (I) (4.3 g, 34%), b.p. 95–96° at 0.1 mmHg, λ_{\max} (EtOH) 263, 268, and 273sh nm (ϵ 7.38, 7.43, and $5.34 \times 10^3 \text{ cm}^2 \text{ mol}^{-1}$), τ (CCl_4) 1.60 (1 H, s, 6'-H), 2.2–3.2 (6 H, m, other pyridyl H), 5.71 (2 H, s, CH_2), and 7.43 (3 H, s, CH_3); no colour with Fe^{2+} ; orange colour with Cu^+ [Found: C, 78.3; H, 6.8; N, 14.9%; *M* (Rast), 176. $\text{C}_{12}\text{H}_{12}\text{N}_2$ requires C, 78.25; H, 6.55; N, 15.2%; *M*, 184].

A similar reaction was carried out with 4-methylpyridine. After toluene and 4-methylpyridine had been distilled from the product, the black, tarry residue (14.2 g) was washed with cold acetone to leave 4,4'-dimethyl-2,2'-bipyridyl (7.0 g, 49.5%), white needles from light petroleum, m.p. 172–173° (lit.,⁴⁴ 171–172°), red colour with Fe^{2+} [Found: C, 78.25; H, 6.5; N, 15.4%; *M* (Rast), 184. Calc. for $\text{C}_{12}\text{H}_{12}\text{N}_2$: C, 78.25; H, 6.5; N, 15.2%; *M*, 184].

Reactions of Magnesium with n-Butylpyridinium Halides.—Pyridine (80 ml) and 1-chlorobutane (10.5 ml, 0.10 mol) were heated under reflux until the chloride ion content of the solution (determined by the Volhard method in 1.0 ml samples) was constant (ca. 8 h; 75% yield). The mixture was cooled to room temperature, magnesium (4.0 g, 0.165 g atom) was added, and the mixture was heated to ca. 100 °C, when a vigorous reaction occurred. The mixture was heated under reflux during 3 h and hydrolysed and worked up as usual, to give a mixture of 2- and 4-n-butylpyridines (0.51 g, 3.8%) in the ratio 3:1, and a mixture of bipyridyls (8.46 g, 55%) in which the 4,4'-isomer was predominant.

In a similar experiment with 1-iodobutane (11.5 ml, 0.10 mol) quaternisation was virtually complete by the time the mixture had been heated to reflux. The products of the reaction with magnesium were a mixture of 2- and 4-n-butylpyridines (0.47 g, 3.5%) and a mixture of bipyridyls (4.50 g, 29%) in which the 4,4'-isomer was predominant.

A similar reaction of n-butylpyridinium iodide in pyridine with lithium (1.15 g, 0.165 g atom) gave a mixture of 2- and 4-n-butylpyridines (3%) in the ratio 1:20, and a mixture of bipyridyls (40%) with the 4,4'-isomer predominant.

When the butylpyridinium halides were prepared as described above, and the resulting mixtures were heated during 12 h (chloride) or 3 h (iodide), and hydrolysis and work-up were carried out as usual, no butylpyridines or bipyridyls were detected.

Free Radical n-Butylation of Pyridine.—A solution of di-n-butylmercury (6.4 g) in pyridine (180 ml) was irradiated during 3 h by a Hanovia S500 mercury vapour lamp in a stirred reactor,⁴⁵ without water cooling. The temperature rose to 100 °C during 1 h and to its maximum, 105 °C, during 2 h. The mixture was cooled, and the mercury formed was recovered, dissolved in nitric acid, and determined as mercury zinc thiocyanate.⁴⁶ The yield of mercury corresponded to the formation of 0.0104 mol of n-butyl radicals. Most of the pyridine (together with diethyl ether used to wash the mercury) was distilled off through a 12 in Dufton column. The residue was extracted with 6*M*-hydrochloric acid (4 × 25 ml) and the extract was washed with ether (4 × 100 ml), made alkaline with sodium carbonate, and

⁴⁵ J. M. Blair, D. Bryce-Smith, and B. W. Pengilly, *J. Chem. Soc.*, 1959, 3174.

⁴⁶ A. I. Vogel, 'Quantitative Inorganic Analysis,' Longmans, London, 1957, p. 423.

⁴³ H. C. Brown and W. A. Murphy, *J. Amer. Chem. Soc.*, 1951, **73**, 3308.

⁴⁴ F. H. Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2574.

extracted with ether (4×100 ml). Ether and pyridine were distilled from the final extract, to leave a mixture (0.46 g) consisting mainly of 2-, 3-, and 4-n-butylpyridines in the ratio of 4.5 : 2.0 : 3.0. The yield of n-butylpyridines was 33%, based on the quantity of dibutylmercury decomposed.

Attempted Rearrangement of 2-n-Butylpyridine.—A mixture of 2-n-butylpyridine (1.88 g), magnesium (2.0 g), and

pyridine (40 ml) was heated, and a crystal of iodine was added. Reaction commenced after a few minutes at *ca.* 100 °C, and the mixture was heated under reflux during 3 h. Hydrolysis and work-up as before gave 2-n-butylpyridine (1.10 g; no 4-isomer detectable by g.l.c.) and a bipyridyl fraction (5.22 g).

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