Synthetic Applications of *N-N* Linked Heterocycles. Part 7.[1] The Preparation of 4-Alkyl- and 4-Aryl-pyridines by Regiospecific Attack of Grignard Reagents γ to Quaternary Nitrogen in *N*-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium Salts[2]

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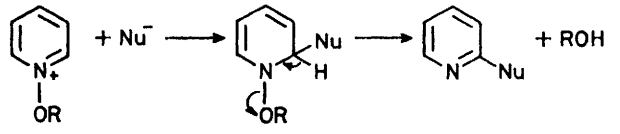
N-(2,6-Dimethyl-4-oxopyridin-1-yl)pyridinium salts (4), new reagents for the regiospecific synthesis of 4-substituted pyridines, give moderate to high yields of 4-alkyl- and 4-aryl-pyridines (8)—(10) on reaction with Grignard reagents. The scope and limitations of the reaction, which proceeds *via* 1,4-dihydro-intermediates (5)—(7), are explored. No 2-substituted pyridines were detected. Some reactions with organolithium compounds are also described.

THE regiospecific synthesis of 4-substituted pyridines *via* displacement of the 4-hydrogen atom with a nucleophile is a desirable synthetic goal. Preparations of these compounds, with the exception of total ring syntheses, have generally been achieved by displacement[3] or modification[4] of a substituent already present, or, with co-production of the 2-isomer, by addition of a nucleophile followed by oxidation of the intermediate dihydropyridine.[5] Quaternary pyridinium salts are considerably more reactive towards nucleophiles, and the presence of a good leaving group on the nitrogen atom[6] permits ready fragmentation of the intermediate dihydropyridine (2) to give the desired product (3) (Scheme 1). Nucleophilic attack on pyridinium salts, however,



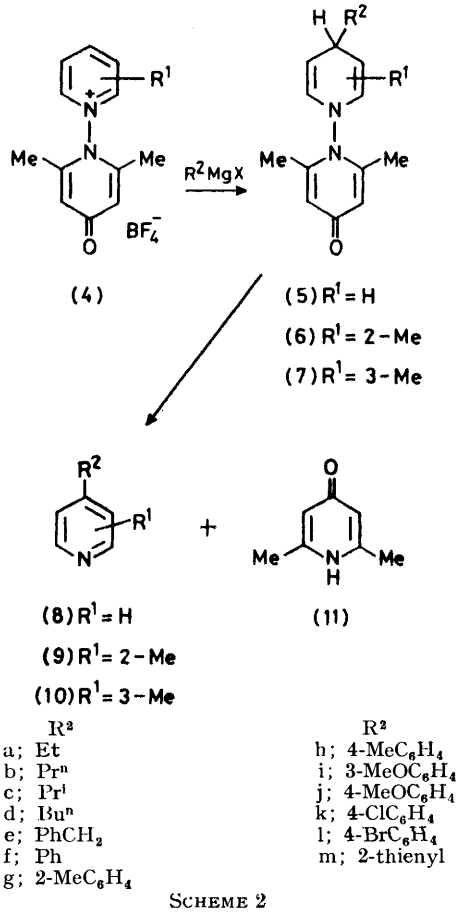
(1) (2) (3)

SCHEME 1

occurs predominantly at the 2-position,[7] and with *N*-alkoxides (1) attack at the alkoxide group, or ring opening, are often major competing reactions.[8]

We designed the 2,6-dimethyl-4-oxopyridin-1-yl substituent [*cf.* (4)] to not only activate the pyridine ring towards nucleophilic attack and to serve as good leaving group as above, but also by sterically shielding the α-positions of the ring to direct the nucleophile into the position γ to the quaternary nitrogen (Scheme 2). The salts (4) may be prepared from pyridines in two high-yield stages,[9] and we recently demonstrated with them the regiospecific synthesis of 4-cyanopyridines.[10] We report now the extension of this strategy to the efficient and regiospecific synthesis of 4-alkyl- and 4-aryl-pyridines by the reaction of the salts (4) with Grignard reagents.

The reactions of Grignard reagents with pyridinium salts normally give products from attack exclusively at the 2-position,[11] though conflicting results have been reported for their reactions with pyridines.[5a,12] 4-Alkylpyridines have been prepared by alkylation of 4-methylpyridine in the presence of organolithium compounds, or sodamide,[13] by reduction of ketones derived from 4-cyanopyridine,[4a] by the Arens procedure,[14] and recently by the action of alkyl halides on pyridine in the presence



R²	R²
a; Et	h; 4-MeC_6H_4
b; Pr^n	i; 3-$MeOC_6H_4$
c; Pr^i	j; 4-$MeOC_6H_4$
d; Bu^n	k; 4-ClC_6H_4
e; $PhCH_2$	l; 4-BrC_6H_4
f; Ph	m; 2-thienyl
g; 2-MeC_6H_4	

SCHEME 2

of magnesium.[15] These methods give low yields, and/or are of limited application. 4-Arylpyridines have been prepared either by multistage ring synthesis from difficulty accessible substituted α-methylstyrenes,[16] or, more usually, as minor components in admixture with 2- and 3-arylpyridines by substitution of pyridine by free radicals derived from diazonium salts.[17]

RESULTS AND DISCUSSION

Reactions of the Salts (4) *with Grignard Reagents.*—The addition of a solution of an arylmagnesium halide in tetrahydrofuran (THF) to an oxopyridinylpyridinium salt (4) gave, after stirring at room temperature for 70 h and work-up with water, a crude intermediate (5)—(7) as an oil. These intermediates were generally too unstable to be isolated in a pure form, though their structures were confirmed from ^{1}H n.m.r. spectra of the crude oils (Table 1), which were entirely consistent with the spectra of intermediates from the addition of cyanide ion to compounds (4).[10] The position of the 4-H proton signal is predictably sensitive to the nature of the 4-substituent. One example, (5f), was purified sufficiently for further characterisation by i.r. spectroscopy. Conversion into 4-arylpyridines (8)—(10) was achieved by one of two methods. *Either* the intermediate oil was heated at 200 °C for 5 min, and the product separated from the pyridone (11) and by-product biaryl by chromatography on alumina (method A); *or* the oil was extracted into acid, the solution basified, and the 4-arylpyridine (8)—(10) back-extracted into $CHCl_3$ and isolated by evaporation (method B). The second method was appropriate for the less-stable 1,4-dihydro-intermediates.

The above procedures were unsuccessful with alkyl

TABLE 1

^{1}H N.m.r. spectra of 1,4-dihydro-intermediates (5; R^1 = H)

		^{1}H N.m.r.(δ) [a]					
		Pyridone ring		1,4-Dihydropyridine ring			
Compound	R^2	2′, 6′	3′,5′	2,6 [b]	3,5	4	R^2
(5a) [c]	Et	*2.41* (s) *2.45* (s)	6.40 (s)	6.0 (d)	4.70 (dd)	3.0 (m)	*0.90* (3 H, t) *1.50* (2 H, m)
(5c) [c]	Pr^i	*2.30* (s)	6.15 (s)	5.90 (d)	4.65 (dd)	3.0 (m)	*1.0* (6 H, d) *1.5* (1 H, m)
(5f)	Ph	*2.35* (s)	6.15 (s)	6.0 (d)	4.8 (dd)	4.3 (m)	7.35 (s)
(5h)	4-MeC_6H_4	*2.4* (s)	6.10 (s)	5.9 (d)	4.7 (dd)	4.2 (m)	7.5 (m) *2.4* (3 H, s)
(5j)	4-$MeOC_6H_4$	*2.2* (s)	6.0 (s)	5.8 (d)	4.75 (dd)	4.2 (m)	7.5 (m) *3.7* (3 H, s)
(5m)	2-Thienyl	*2.5* (s)	6.5 (s)	6.1 (d)	4.8 (dd)	4.5 (m)	6.8—7.4 [d]

[a] Spectra run in $CDCl_3$. Figures in italics are for alkyl substituents. [b] $J_{2,3}$ 8 Hz. [c] Recorded for 3 : 1 mixture of compounds (5) and (8). [d] Complex multiplet.

TABLE 2

^{1}H N.m.r. spectra of 4-alkyl- and 4-aryl-pyridines (8)—(10)

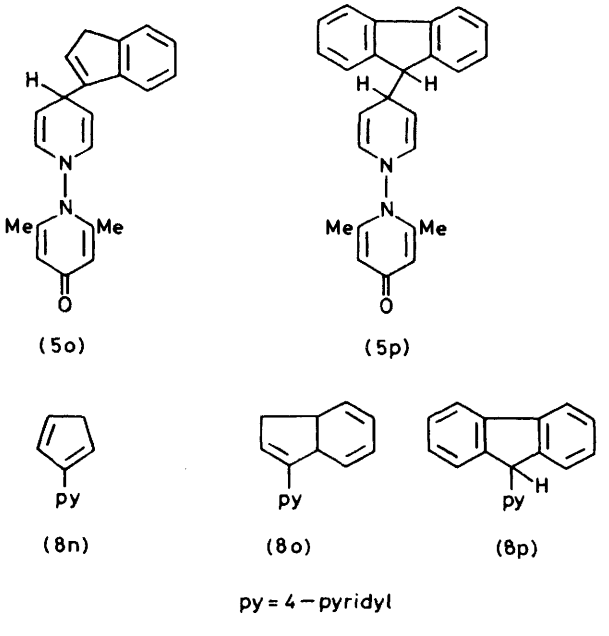
			^{1}H N.m.r. (δ) [a]		
	Substituents		Pyridine ring [b]		
Compound	R^1	R^2	2,6	3,5	4-Substituent
(8a)	H	Et	8.5	7.1	*2.6* (2 H, q), *1.2* (3 H, t)
(8b)	H	Pr^n	8.5	7.1	*2.6* (2 H, t), *1.6* (2 H, m), *0.9* (3 H, t)
(8c)	H	Pr^i	8.5	7.15	*2.8* (1 H, m), *1.25* (6 H, d)
(8d)	H	Bu^n	8.5	7.15	*2.6* (2 H, t), *1.5* (4 H, m), *0.95* (3 H, t)
(8e)	H	$PhCH_2$	8.5	7.1	7.25 (5 H, s), *3.9* (2 H, s)
(8f)	H	Ph	8.7	*c*	7.5 (5 H, m)
(8g)	H	2-MeC_6H_4	8.7	*c*	7.3 (4 H, m), *2.3* (3 H, s)
(8h)	H	4-MeC_6H_4	8.6	*c*	7.4 (4 H, m), *2.4* (3 H, s)
(8i)	H	3-$MeOC_6H_4$	8.6	7.45	7.2 (4 H, m), *3.8* (3 H, s)
(8j)	H	4-$MeOC_6H_4$	8.7	7.4	7.6 [d] (2 H, d), 7.0 [d] (2 H, d), *3.85* (3 H, s)
(8k)	H	4-ClC_6H_4	8.7	*c*	7.5 (4 H, m)
(8l)	H	4-BrC_6H_4	8.65	*c*	7.55 (4 H, m)
(8m)	H	2-Thienyl	8.55	7.4	7.4 (2 H, m), 7.15 (1 H, m)
(9b)	2-Me	Pr^n	8.35 *2.5*	6.9	*2.5* (2 H, t), *1.7* (2 H, m), *0.9* (3 H, t)
(9c)	2-Me	Pr^i	8.35 *2.6*	6.95	*2.8* (1 H, m), *1.25* (6 H, d)
(9f)	2-Me	Ph	8.45 *2.5*	*c*	7.4 (5 H, m)
(10b)	3-Me	Pr^n	8.3	7.0 *2.2*	*2.5* (2 H, t), *1.7* (2 H, m), *0.9* (3 H, t)
(10c)	3-Me	Pr^i	8.35	7.1 *2.3*	*3.1* (1 H, m), *1.2* (6 H, d)
(10f)	3-Me	Ph	8.4	7.0 *2.15*	7.3 (5 H, m)
(10j)	3-Me	4-$MeOC_6H_4$	8.5	*c* *2.25*	7.2 (4 H, m), *3.8* (3 H, s)

[a] Spectra run in $CDCl_3$. Values in italics refer to alkyl substituents. [b] $J_{2,3}$ 4.5—6.0 Hz. [c] Ring protons hidden by aryl signal. [d] J 9 Hz.

Grignard reagents, for reasons which are not apparent. Instead, it was found that addition of a solid salt (4) all at once to a solution of the Grignard reagent in THF led to a vigorous exothermic reaction, during which all the solid dissolved. The oil, isolated after overnight reflux of the solution, proved to be a mixture (*ca.* 3 : 1, by ^{1}H n.m.r. spectroscopy) of the 4-alkylpyridine (8)—(10) and the dihydro-intermediate (5)—(7). All attempts to isolate intermediates in a pure form were unsuccessful. Decomposition of the remaining dihydro-intermediate was achieved by heating the mixture in MeCN solution for 10 h, followed by isolation of the pure product from the pyridone (11) by chromatography on alumina (method C).

^{1}H N.m.r. spectra of alkyl- and aryl-pyridines are presented in Table 2, and physical and analytical data in Table 3. 4-Substituted pyridines which were liquid at room temperature were characterised as picrates. In no case was any 2-substituted pyridine detected.

Optimum yields [average 53% based on the salt (4), or 34% based on pyridine] were obtained by use of 2 mol equivalents of the Grignard reagent, the use of 3 mol giving significantly reduced yields, and 1 mol little or no product. Under optimum conditions, benzylmagnesium chloride gave only 20% of 4-benzylpyridine (8e) together with substantial amounts of bibenzyl and toluene, and the Grignard reagents derived from 1-bromonaphthalene, β-bromostyrene, and phenylacetylene [18] gave products identifiable by ^{1}H n.m.r. spectroscopy as the desired 4-substituted pyridines, but in yields too low to permit isolation. Though 2-thienylmagnesium bromide gave a moderate yield of the product (8m)* reactions attempted with Grignard reagents derived from nitrogen heterocycles were unsuccessful. 1-Indolylmagnesium bromide,[19] and 2-pyridylmagnesium bromide,[20] prepared by titration respectively of indole and 2-bromopyridine with a more active Grignard reagent, gave complex highly coloured, inseparable mixtures on reaction with a salt (4).



* Reported previously in only 2% yield (see Table 3, footnote *l*).

TABLE 3

Preparative data and physical properties of 4-alkyl- and 4-aryl-pyridines (8)—(10)

Compound no.	Substituents R^1	R^2	Method	Yield (%)	M.p.[a] (°C)	Lit. m.p.[a] (°C)	Crystal form[b]	Recrystallisation solvent[b]
(8a)	H	Et	C	74	*168—169*	*169—170* [c]	P	E
(8b)	H	Pr^n	C	90	*130—131*	*131—131.6* [d]	P	E
(8c)	H	Pr^i	C	78	*135—136*	*135* [e]	P	E
(8d)	H	Bu^n	C	85	*112—113*	*112.8—113.8* [d]	P	E
(8e)	H	$PhCH_2$	C	20	*140—141*	*140—141* [f]	N	E
(8f)	H	Ph	A	68	75—76	77—78 [g]	P	H
(8g)	H	2-MeC_6H_4	A	41	*172—173*	*173.5—174* [h]	N	E
(8h)	H	4-MeC_6H_4	A	42	88—89	90—91 [i]	P	H
(8i)	H	3-$MeOC_6H_4$	B	63	*206—207*	*203—204* [j]	N	E
(8j)	H	4-$MeOC_6H_4$	A	73	95—96	95 [j]	P	L
(8k)	H	4-ClC_6H_4	B	40	70	70—71 [k]	P	L
(8l)	H	4-BrC_6H_4	B	53	125—127	129—131 [k]	P	L
(8m)	H	2-Thienyl	B	35	91—92.5	92.5—93.5 [l]	P	L
(9b)	2-Me	Pr^n	C	24	*116*	*117* [m]	P	E
(9c)	2-Me	Pr^i	C	27	*131—132*	*132—134* [n]	P	E
(9f)	2-Me	Ph	B	47	47.5	48 [o]	P	H
(10b)	3-Me	Pr^n	C	57	*137—139*	*136—138* [p]	P	E
(10c)	3-Me	Pr^i	C	61	*107—108*	*q*	N	E
(10f)	3-Me	Ph	B	36	*168—169*	*168—169* [r]	P	E
(10j)	3-Me	4-$MeOC_6H_4$	C	42	*156—158*	*s*	N	E

[a] Figures in italics are for the picrate derivative. [b] P = Plates; N = needles; E = Ethanol; H = heptane; L = light petroleum (b.p. 40—60 °C). [c] Ref. 14*a*. [d] Ref. 14*b*. [e] G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 1941, 41. [f] W. L. C. Veer and S. Goldschmidt, *Rec. Trav. chim.*, 1946, **65**, 793. [g] Ref. 16. [h] Ref. 17*d*. [i] C. J. Schmidle, J. Locke, and R. Mansfield, *J. Org. Chem.*, 1956, **21**, 1194. [j] Ref. 17*c*. [k] Ref. 17*b*. [l] H. Wynberg, T. J. van Bergen, and R. M. Kellogg, *J. Org. Chem.*, 1969, **34**, 3175. [m] R. H. Siddiqui, R. H. Usmani, and S. M. Ali, *J. Indian Chem. Soc.*, 1944, **21**, 245. [n] T. Govindachari, P. S. Santhanam, and V. Sudarsanam, *Indian J. Chem.*, 1966, **4**, 398. [o] J. Bonnier, J. Court, and T. Fay, *Bull. Soc. chim. France*, 1967, 1204. [p] J. P. Wibaut and S. Vromen, *Rec. Trav. chim.*, 1948, **67**, 545. [q] Not previously reported (Found: C, 49.3; H, 4.3; N, 15.2. $C_{15}H_{16}N_4O_7$ requires C, 49.4; H, 4.4; N, 15.4%). [r] Y. S. Dol'skaya and G. Y. Kondrat'eva, *Izvest. Akad. Nauk S.S.S.R.*, 1970, 2123. [s] Not previously reported (Found: C, 53.2; H, 3.7; N, 12.9. $C_{19}H_{16}N_4O_8$ requires C, 53.3; H, 3.7; N, 13.1%).

Reactions of the Salts (4) *with Organo-lithium Compounds.*—An attempt was made to prepare 4-cyclopentadienyl- (8n), 4-inden-3-yl- (8o), and 4-fluoren-9-yl-pyridine (8p), as analogues of the pyridine anhydrobases isoelectronic with sesquifulvalene prepared by Berson and his co-workers,[21] by addition of the salt (4) to a solution of the lithio-derivative [22] of the respective hydrocarbon in THF at 0 °C. The reaction mixture with cyclopentadienyl-lithium turned black immediately, and no identifiable products could be isolated; with both indenyl-lithium and fluoroenyl-lithium, however, the corresponding 1,4-dihydro-intermediates (5o) and (5p) respectively were isolated in *ca.* 40% yields from dark reaction mixtures. The structures of the products were confirmed by ^{1}H n.m.r. and i.r. spectroscopy, compound (5o) being shown to be the inden-3-yl derivative by a broad singlet at δ 3.6 (2 H at C-1) and a double doublet at δ 6.2 (*J ca.* 1 and *ca.* 3 Hz, 1 H at C-2). Attempts to purify the intermediates were unsuccessful. Photolysis of intermediate (5o) in $CHCl_3$ solution for 8 h gave an oil which darkened rapidly in air, and whose u.v. spectrum was consistent with that reported by Berson [21] for the unstable 4-inden-1-ylpyridine. The ^{1}H n.m.r. spectrum confirmed this structure (8o). In contrast, photolysis of the fluorene intermediate (5p) under the same conditions resulted in fragmentation of the molecule to give fluorene as the major product together with a very small amount of the desired pyridine (8p). Reverse fragmentations of this type have been observed by us with dihydro-intermediates derived from other bulky nucleophiles.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 297 instrument as liquid films, or in Nujol, and ^{1}H n.m.r. spectra for solutions in $CDCl_3$ with $SiMe_4$ as internal reference, on a Perkin-Elmer R-12 spectrometer.

Tetrahydrofuran (THF) was redistilled from $LiAlH_4$ before use, and alkyl and aryl halides dried over molecular sieves. The 4-oxopyridin-1-ylpyridinium tetrafluoroborates (4) were prepared as reported previously [9] and dried *in vacuo* before use. Light petroleum refers to the fraction b.p. 40—60 °C.

General Procedures for the Preparation of Alkyl- and Aryl-Pyridines.—Method A. A solution of the Grignard reagent formed from magnesium turnings (7.6 mmol) and the appropriate aryl halide (7.3 mmol) in THF (10 ml) was filtered, and added to a suspension of the tetrafluoroborate salt (2) (3.45 mmol) in THF, all steps being conducted under N_2. The mixture was stirred at room temperature for 70 h and then water (10 ml) was added; the mixture was then extracted with $CHCl_3$ (3 × 50 ml) and the $CHCl_3$ extract dried ($MgSO_4$), filtered, and evaporated to yield an oil comprising a mixture of the dihydro-intermediate (5)—(7) and the product (8)—(10). The oil was heated at 200 °C for 5 min and then cooled, and the product extracted into $CHCl_3$ (3 × 15 ml); the solution was evaporated and the residue taken up in light petroleum and eluted through an alumina column (grade I; neutral) first with light petroleum to remove biaryl, and then with $CHCl_3$. Evaporation of the $CHCl_3$ eluate yielded the 4-arylpyridine (8)—(10) which was recrystallised, or if an oil, converted into the picrate by standard procedures.

Method B. As for method A, except that the $CHCl_3$ extract from work-up of the Grignard reaction was shaken with 3M-HCl (3 × 15 ml); the aqueous layer was neutralised with ammonium hydroxide solution containing ammonium chloride and then extracted with $CHCl_3$ (3 × 15 ml). The $CHCl_3$ solution was dried ($MgSO_4$), filtered, and evaporated to give the 4-arylpyridine (8)—(10), which was recrystallised or converted into its picrate derivative as above.

Method C.—The tetrafluoroborate salt (4) (3.45 mmol) was added all at once to a solution of a Grignard reagent prepared from magnesium turnings (8.6 mmol), and the appropriate alkyl halide (7.72 mmol) in THF (5 ml). After the exothermic reaction had subsided, the solution was heated under reflux overnight, cooled, and treated with water (5 ml). The mixture was extracted with $CHCl_3$ (3 × 30 ml) and the extract dried ($MgSO_4$), filtered, and evaporated. The resulting oil was dissolved in MeCN (50 ml), the solution heated under reflux for 10 h, and evaporated. The product (8)—(10) was purified by chromatography and characterised as described for method A.

Isolation of the 1,4-*Dihydro-intermediate* (5f).—Dropwise addition of phenylmagnesium bromide to *N*-(2,6-dimethyl-4-oxopyridin-1-yl)pyridinium tetrafluoroborate in THF at 0 °C, followed by stirring at room temperature for 48 h gave after work-up with water, extraction with $CHCl_3$, dilution with light petroleum, and cooling in the refrigerator overnight, buff plates of the intermediate (5f), $\nu_{max.}$ 1 680 (enamine C=C), 1 640, and 1 570 cm^{-1} (pyridone ring), which decomposed rapidly on warming or standing.

Reactions with Cyclopentadiene, Indene, and Fluorene Lithio-derivatives.—To a solution of indene (0.38 g, 3.26 mmol) in dry THF (30 ml) at −78 °C was added 1.06M n-butyl-lithium in hexane (2.5 ml, 3.7 mmol). The temperature was raised to 0 °C and the salt (4) (0.86 g, 3.0 mmol) added all at once. The black mixture was stirred for 8 h at room temperature, water (5 ml) was added, and the product extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ extract was dried ($MgSO_4$), filtered, evaporated, and the resulting dark oil triturated with light petroleum to give a greenish solid (0.403 g, 40%). Recrystallisation ($CHCl_3$–light petroleum) gave yellow microcrystals (5o), m.p. 179—182 °C (insufficiently stable for microanalysis); $\nu_{max.}$ ($CHBr_3$) 1 680 (enamine C=C), 1 645, and 1 560 cm^{-1} (pyridone ring); δ ($CDCl_3$) 7.3 (4 H, m), 6.2 (1 H, dd, *J* 1 and 3 Hz), 6.04 (2 H, s), 5.88 (2 H, dd, *J* 8 and 3 Hz), 4.78 (2 H, dd, *J* 8 and 4 Hz), 4.28 (1 H, br), 3.30 (2 H, br), 2.30 (3 H, s), and 2.18 (3 H, s). Likewise, 9-fluorenyl-lithium (prepared at −15 °C) gave the microcrystalline intermediate (5p) (0.52 g; 43%), m.p. 123—126 °C (insufficiently stable for microanalysis); $\nu_{max.}$ ($CHBr_3$) 1 680, 1 645, and 1 560 cm^{-1}; δ ($CDCl_3$) 7.4 (8 H, m), 6.1 (2 H, s), 5.66 (2 H, dd, *J* 8 and 2 Hz), 4.34 (2 H, dd, *J* 8 and 3 Hz), 4.1 (1 H, m), 3.84 (1 H, d), 2.20 (3 H, s), and 1.94 (3 H, s). Cyclopentadienyl-lithium gave a black solution which failed to yield a solid product.

Decomposition of Intermediates (5o) *and* (5p).—Irradiation (medium-pressure Hg lamp; 125 W) of a solution of intermediate (5o) (0.120 g) in $CHCl_3$ (100 ml) for 8 h in the presence of benzoyl peroxide gave, after evaporation, extraction with ether, and re-evaporation, an oil (8o) which darkened rapidly in air; $\lambda_{max.}$ 225, 280sh, and 295sh nm; δ ($CDCl_3$) 8.5 (2 H, dd) (pyridine α-protons), 7.5—7.2 (6 H, m) (pyridine β-protons and benzene ring), 6.7 (1 H, t) (indene 2-H), and 3.5 (2 H, br s) (indene CH_2). Photolysis of the intermediate (5p) under similar conditions gave only fluorene,

and a very small amount of a compound identified tentatively from its ^1H n.m.r. spectrum as compound (8p).

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