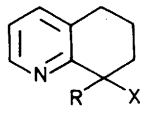
Applications of Organolithium and Related Reagents in Synthesis. Part 3.[1] A General Study of the Reaction of Lithium Alkyls with Pyridine Ketones

Jan Epsztajn * and Adam Bieniek
Department of Organic Chemistry, Institute of Chemistry, University, 90–136 Łódź, Narutowicza 68, Poland

The reaction of MeLi and PhLi with acetylpyridines (**1a**—**c**) and their annelated derivatives (**2a**), (**2b**), (**3**), and (**4**) has been examined. The 3- and 4-pyridyl ketones (**1b**), (**1c**), (**3**), and (**4**) gave similar results to acetophenone and 3,4-dihydronaphthalen-1(2*H*)-one. In the case of the 2-pyridyl ketones (**1a**), (**2a**), and (**2b**) unexpectedly low yields of products resulted from the addition of RLi to the carbonyl group; the reaction was efficiently enhanced by initially adding an additional amount of LiBr. These results were accounted for by the chelation of RLi or LiBr by the 2-pyridyl ketones.

The observed antiulcer and antisecretory activity[2] of compounds of type (**A**) [X = $O(CH_2)_nNHR$ or NHC(S)NHR] have promoted a widespread interest in their synthesis. We

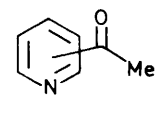


(**A**)

were particularly interested in using the reaction of the corresponding pyridine ketones with lithium alkyls as the first step (X = OH) towards the desired products. However, we could find no general investigation of this reaction in the literature which reported all the products and yields. Nearly all the literature reports involved only specific compounds, and generally gave only the isolated yields of the major product. This was somewhat surprising, not only because of the wide use of lithium alkyls in organic synthesis, but also because of the large number of analogous studies reported for the corresponding aryl alkyl ketones or 3,4-dihydronaphthalen-1(2*H*)-ones.[3] All we could conclude was that in the case of the pyridine ketones there are two competing centres of reactions: the carbonyl group (addition, enolization, and reduction)[3] and the pyridine nucleus (1,2- or 1,4-addition).[3b,4]

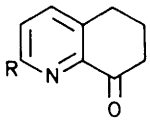
For this reason, we investigated the reaction of lithium hydrocarbons with the acetylpyridines (**1**) and their annelated derivatives (**2**)—(**4**) and we report the results here. We have determined all the products and their yields, and have attempted to establish the conditions necessary to obtain the maximum yield from the desired reaction at the carbonyl group. The lithium hydrocarbons used were MeLi and PhLi, which were selected because they are contrasting examples of the various lithium reagents (*i.e.* aliphatic *vs.* aromatic).

The annelated pyridine ketones were most conveniently prepared by oxidation (CrO_3–$HClO_4$–AcOH) of the corresponding alcohols; this was applied successfully to give the 8-oxo-5,6,7,8-tetrahydroquinolines (**2a**) and (**2b**), and 5-oxo-5,6,7,8-tetrahydroisoquinoline (**4**). 5-Oxo-5,6,7,8-tetrahydroquinoline (**3**) was obtained in the condensation of prop-2-ynal with 3-aminocyclohex-2-en-1-one.[5]



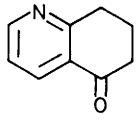
(**1**)

a; 2-pyridyl
b; 3-pyridyl
c; 4-pyridyl

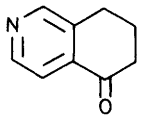


(**2**)

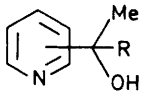
a; R = H
b; R = Ph



(**3**)

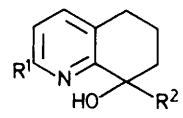


(**4**)



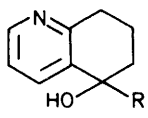
a; R = Me
b; R = Ph

(**5**) 2-pyridyl
(**6**) 3-pyridyl
(**7**) 4-pyridyl

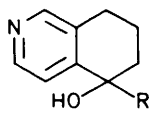


(**8**)

a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = Ph
c; R^1 = Ph, R^2 = Me
d; R^1 = R^2 = Ph



(**9**)



(**10**)

a; R = Me
b; R = Ph

Results and Discussion

The detailed results of the reaction of MeLi and PhLi with the pyridine ketones (**1**)—(**4**) are reported in Table 1. An examination of the data reveals the following: firstly, the only products obtained from the reaction with RLi (1 equiv.) were the corresponding alcohols (**5**)—(**10**), together with recovered ketone. It has been suggested[6] that the recovered starting ketones are in fact products of the enolization reaction. However, the observed increase in yield from the addition reaction at the carbonyl group with longer reaction times, or with an excess of RLi in the case of MeLi or PhLi with the 2-pyridyl ketones (**1a**) and (**2**) (see below), suggests that at least a part of

Table 1. Reactions of the pyridine ketones (**1a**—**c**), (**2a**), (**2b**), (**3**), and (**4**) with MeLi and PhLi in ether for 1.5 h at 25 °C

Expt. no.	Ketone	RLi	Ratio of ketone:RLi	Product yields[a] (%) % Addition to C=O			Recovered ketone		Overall yield (%)	
1	(**1a**)	MeLi	1:1	(**5a**)	45	(49)	34	(42)	79	(91)
2	(**1a**)	MeLi	1:2	(**5a**)	78	(83)	5	(8)	83	(91)
3	(**1a**)[c]	MeLi	1:1	(**5a**)		(75)		(20)		(95)
4	(**1a**)	PhLi	1:1	(**5b**)	63	(67)	19	(24)	82	(91)
5	(**1a**)	PhLi	1:2	(**5b**)	75	(78)	14	(18)	89	(96)
6[b]	(**1a**)	PhLi	1:1	(**5b**)		(80)		(16)		(96)
7	(**1a**)[c]	PhLi	1:1	(**5b**)		(96)	Trace			(96)
8	(**1b**)	MeLi	1:1	(**6a**)	88		6		94	
9	(**1b**)	MeLi	1:2	(**6a**)	89		4		93	
10	(**1b**)	PhLi	1:1	(**6b**)	77		13		90	
11	(**1b**)	PhLi	1:2	(**6b**)	49		12		61 and (**11**)[d]	
12	(**1c**)	MeLi	1:1	(**7a**)	87		7		94	
13	(**1c**)	MeLi	1:2	(**7a**)	89		3		92	
14	(**1c**)	PhLi	1:1	(**7b**)	92		5		97	
15	(**1c**)	PhLi	1:2	(**7b**)	28		9		37 and (**12**)[e]	
16	(**2a**)	MeLi	1:1	(**8a**)	43	(46)	42	(45)	85	(91)
17	(**2a**)	MeLi	1:2	(**8a**)	55	(58)	33	(37)	88	(95)
18	(**2a**)[c]	MeLi	1:1	(**8a**)		(75)		(20)		(95)
19	(**2a**)	PhLi	1:1	(**8b**)	41	(45)	45	(52)	86	(97)
20	(**2a**)	PhLi	1:2	(**8b**)	62	(67)	20	(25)	82	(92)
21[b]	(**2a**)	PhLi	1:1	(**8b**)		(49)		(48)		(97)
22	(**2a**)[c]	PhLi	1:1	(**8b**)		(74)		(21)		(95)
23	(**2b**)	MeLi	1:1	(**8c**)[f]		(58)		(38)		(96)
24	(**2b**)	MeLi	1:2	(**8c**)		(79)		(17)		(96)
25	(**2b**)	PhLi	1:1	(**8d**)	5	(7)	85	(89)	90	(96)
26	(**2b**)	PhLi	1:2	(**8d**)	31	(35)	58	(62)	89	(97)
27	(**2b**)[c]	PhLi	1:1	(**8d**)		(44)		(53)		(97)
28	(**3**)	MeLi	1:1	(**9a**)	85		8		93	
29	(**3**)	MeLi	1:2	(**9a**)	88		4		92	
30	(**3**)	PhLi	1:1	(**9b**)	80		14		94	
31	(**3**)	PhLi	1:2	(**9b**)	82[g]		13		95	
32	(**4**)	MeLi	1:1	(**10a**)	81		10		91	
33	(**4**)	MeLi	1:2	(**10a**)	82		9		91	
34	(**4**)	PhLi	1:1	(**10b**)	69		15		84 and (**14**)[h]	
35	(**4**)	PhLi	1:2	(**10b**)	15		Trace		15 and (**14**) + (**15**)[i]	

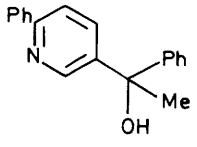
[a] All yields represent isolated pure materials. Data in parentheses represent yields identified in the cases of (**1a**) and (**2a**) by ^{1}H n.m.r. spectroscopy, and in the case of (**2b**) by i.r. spectroscopy. Values are within ±5% of the reported data. [b] The reaction time was extended to 150 h. [c] With LiBr. [d] Adduct (**11**) (26%). [e] Adduct (**12**) (54%). [f] The alcohol (**8c**) was not isolated preparatively. [g] Quenching with D_2O showed the transformation of the alcohol (**9b**) into the lithiated alcohol (**13b**) (95% ^{2}H). [h] Adduct (**14**) (9%). [i] Adducts (**14**) (42%) and (**15**) (34%).

the isolated residual ketones had not reacted. Products from the reduction of the carbonyl group or addition to the pyridine nucleus were not detected. This has previously been observed with *N,N*-dimethylpyridinecarboxamides,[7] where treatment with one equivalent of MeLi, Bu^{n}Li, and PhLi gave only the corresponding ketones, and no adducts to the pyridine nucleus were observed. The high overall yields obtained apparently show that condensation reactions were also minimized.

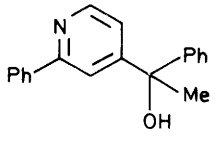
Secondly, it was found that the position of the carbonyl group on the pyridine ring appears to significantly affect the reaction. The 2-pyridyl ketones gave a lower yield of the corresponding alcohols than expected from the reported reactions of the carbonyl group with lithium hydrocarbons, and than those obtained from 3- and 4-pyridyl ketones.

This last observation suggests that the ketones examined may be divided into two groups. The first group comprises ketones with the carbonyl group attached the 3- and 4-positions of the pyridine ring [(**1b**), (**1c**), (**3**), and (**4**)]. The second consists of ketones with the carbonyl group at the 2-position [(**1a**), (**2a**), and (**2b**)].

3- *and* 4-*Pyridyl Ketones.*— The ketones (**1b**), (**1c**), (**3**), and (**4**) reacted with MeLi or PhLi (1 equiv.) to give good yields of

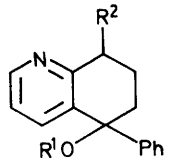


(**11**)



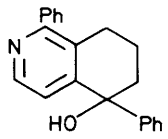
(**12**)

corresponding alcohols (**6**), (**7**), (**9**), and (**10**), together with recovered ketone. The results obtained showed the reactions of the 3- and 4- pyridyl ketones to be similar to those of acetophenone and 3,4-tetrahydronaphthalen-1(2*H*)-one.[3,8] Only in the reaction of compound (**4**) with PhLi was the alcohol (**10b**) accompanied by products from addition to the pyridine ring, (**14**) and (**15**). The use of an excess of MeLi (2 equiv.) did not change the ratio of the products, and no others were observed. However, with an excess of PhLi, the ketones (**1b**), (**1c**), and (**4**) gave the alcohols (**6b**), (**7b**), and (**10b**) together with significant quantities of the products from 1,2-addition to the pyridine nucleus [(**11**), (**12**), (**14**), and (**15**), respectively]. These adducts were formed from the 1,2-addition of PhLi to the pyridine nucleus of the lithium alcoholate intermediates from the initial

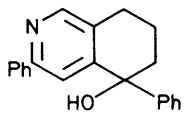


(13)

a; $R^1 = R^2 = Li$
b; $R^1 = R^2 = D$



(14)



(15)

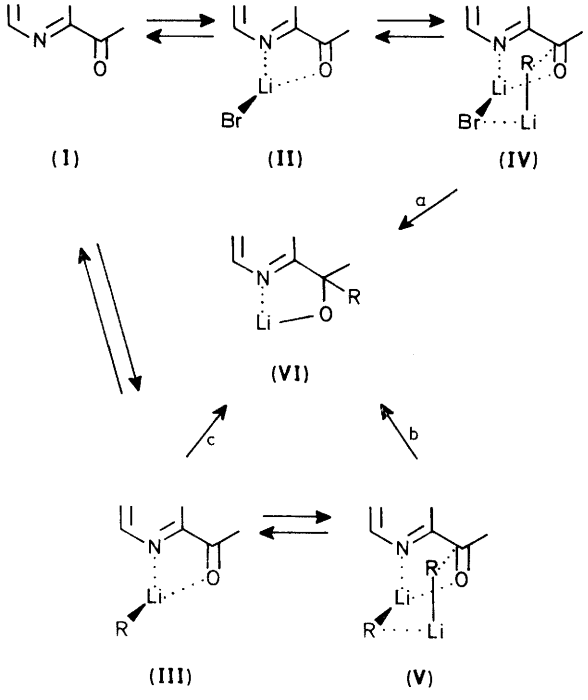
reaction of the 3- or 4-pyridyl ketone with the first molecule of RLi. In the case of the ketone (**3**), the lithium alcoholate formed initially with PhLi, was then lithiated by the same base at the methylene attached to the 2-position on the pyridine ring to give the di-lithiated compound (**13a**).

2-Pyridyl Ketones.—The 2-pyridyl ketones (**1a**), (**2a**), and (**2b**) reacted with MeLi or PhLi (1 equiv.) with a very low degree of conversion into the corresponding alcohols (**5a**), (**5b**), and (**8a—d**); the extent of conversion increased noticeably with an excess of RLi (2 equiv.).

In contrast with the observed 1,2-addition to the pyridine nucleus of the alcoholate intermediates derived from the 3- and 4-pyridyl ketones, the 2-pyridyl ketones did not give such adducts with an excess of RLi. This is probably due to the chelation of the lithium counter ion by the alcoholate [*e.g.* alcoholate (**VI**) in the Scheme] which makes the pyridine nitrogen atom inaccessible for complexation with RLi (the first step of the addition).[3b,4]

Longer reaction times (150 h) altered the product ratio from the reaction of compound (**1a**) with PhLi in the favour of the alcohol (**5b**), but had no effect in the case of (**2a**). The conversion of 2-pyridyl ketones into the corresponding alcohols was efficiently increased when the amount of LiBr was increased (to 3 equiv.). This is probably due to the initial complexation of LiBr by the 2-pyridyl ketone.

Although the complexation of pyridines and ketones with lithium halides has been investigated,[9] it was not known whether the 2-pyridyl ketones (**1a**) and (**2**) form complexes with LiBr. In an attempt to clarify this problem, the products from the reaction of (**1a**) and (**2**) with LiBr were isolated from ethereal solution and characterized by i.r. spectroscopy and analytical results. Thus, on complexation of the ketone (**2a**) with LiBr in $CHCl_3$, the C=O stretch was shifted from 1 696 to 1 685 cm^{-1} and the skeleton band from 1 583 to 1 590 cm^{-1}, and the band at 1 566 cm^{-1} disappeared. In the case of the complex of compound (**1a**) with LiBr in $CHCl_3$, no differences from the parent compound were observed in the i.r. spectrum. However, in Nujol suspension two new bands appeared at 1 703 and 1 676 cm^{-1} in the C=O stretching region, the band at 1 698 cm^{-1} [of (**1a**)] disappeared, and the skeleton bands were shifted from 1 566 and 1 548 cm^{-1} to 1 602 and 1 585 cm^{-1}, respectively. The weaker band of higher frequency in the spectrum of (**1a**)·LiBr probably results from Fermi resonance between the C=O band and the overtone of a longer wavelength



Scheme.

band at 850 cm^{-1}. The analytical data showed (Experimental section) that the donor-to-acceptor ratio of the complexes obtained was 1:1. Therefore, the shifts of the carbonyl stretch and the skeleton bands indicate that the 2-pyridyl ketones chelate the LiBr to form complexes of type (**II**) (Scheme).

In connection with the unexpectedly poor conversion of the 2-pyridyl ketones into the corresponding alcohols and the great improvement on pre-adding additional LiBr, the following should be considered: (i) Ashby and co-workers[10] have shown that the addition of various metallic salts (*e.g.* LiBr, LiI, $LiClO_4$, $LiOBu^t$) efficiently enhances the rate of reaction of RLi with a carbonyl group in ether. They suggested that complexation between the salt and the carbonyl group takes place; this increases the rate of subsequent attack by RLi as the complexed carbonyl group is probably highly polarized, as in other acid-catalysed reactions of carbonyl compounds. (ii) It has been proposed,[11] that the addition of halide-free RLi to the carbon–heteroatom multiple bond proceeds through a monomer which is in rapid equilibrium with the oligomeric species. The addition of LiBr or LiI does not change the kinetic order in this system. (iii) It has been found,[12] that 2-acetylpyridine (**1a**) exists predominantly in the twisted ($\varphi \simeq 155°$) *anti* form (> 85%). (iv) The annelated ketones (**2**) are the fixed, planar, *syn* conformers. In the case of compound (**2b**), the twist angle (φ) was found from *X*-ray data to be 1.4°.[13]

Although the observed behaviour of the 2-pyridyl ketones in the reaction with lithium alkyls cannot be unequivocally explained, two pathways (a) and (b) (Scheme) can be proposed on the basis of the significant effect of pre-adding LiBr (→ complexation between LiBr and the 2-pyridyl ketone), or with an excess of MeLi or PhLi. Moreover, in the transformation of compound (**1a**) (originally the *anti* conformer) into the alcohol (**5b**), the significant increase in yield after longer reaction times (150 h) suggests that an equilibrium between (**1a**)·PhLi and (**1a**)·LiBr occurs which may be summarized as follows:

$$[(\mathbf{1a})\text{·PhLi} + \text{LiBr} \rightleftharpoons (\mathbf{1a})\text{·LiBr} + \text{PhLi}]$$

Thus, as a result of the competing reaction the 2-pyridyl ketones (**I**) are converted into the chelates (**II**) and/or (**III**) which are probably in equilibrium. These chelates then react with a free or an added molecule of RLi to give, *via* intermediate (**IV**) or (**V**), the alcoholates (**VI**). If this is the case, the unexpectedly poor conversion of the 2-pyridyl ketones into the corresponding alcohols would be due to the 2-pyridyl nitrogen atom; this provides a strong bidentate ligand for lithium and thus consumes at least some of the lithium hydrocarbon by the formation of the chelate (**III**) [which is particularly stable in the case of (**2b**)-PhLi].

This explanation disagrees with the commonly accepted model,[14] that the addition reaction proceeds *via* the complex (**III**) involving both the carbonyl oxygen atom and an adjacent Lewis basic centre [pathway (c)]. However, in work[15] on a transition state model, the extent to which the presence of the lithium halide affects the reaction of the carbonyl group with the lithium hydrocarbon is not discussed, although in a number of the experiments MeLi and PhLi were prepared from the corresponding halides in ether.

While the results might be explained by some combination of the two pathways we prefer not to speculate until more information is available.

Experimental

M.p.s were determined using a Boetius hot-stage apparatus and are uncorrected. Spectra were recorded for solutions in $CHCl_3$ or Nujol mulls: a Zeiss-Jena Specord 71-IR or a Perkin-Elmer 325 i.r. spectrometer was used for the i.r. spectra, a Unicam SP800 or a Unicam SP1700 u.v. spectrometer for the u.v. spectra, and a Varian EM-360 (60 MHz), a Telsa BS-467 (60 MHz), or a Tesla BS-847C (80 MHz) n.m.r. spectrometer for the n.m.r. spectra.

Compounds were purified until observed as single spots on t.l.c. (Kieselgel GF-254 type 60). Ether and benzene free of thiophene were used freshly distilled from $LiAlH_4$ and sodium. Ether refers to diethyl ether. All ketones were purified by distillation, chromatography on alumina ($CHCl_3$), and redistillation or recrystallization before use. The acetylpyridines (**1a**—**c**) are commercially available. The annelated ketones (**2a**), (**2b**), (**3**), and (**4**) were obtained by the known methods; in the case of new compounds or methods, the synthesis is given.

5-*Oxo*-5,6,7,8-*tetrahydroquinoline* (**3**).—Condensation of 3-aminocyclohex-2-en-1-one (11.1 g, 0.1 mol) with prop-2-ynal (5.4 g, 0.1 mol) in DMF yielded the ketone (**3**) (5.9 g, 41%), b.p. 151—152 °C at 41 hPa (lit.,[5] b.p. 131—132 °C at 12 mmHg); $\nu_{max.}$(neat) 1 702 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$; Me_4Si) 8.63 (1 H, dd, *J* 2 and 5.5 Hz, 2-H), 8.18 (1 H, dd, *J* 2 and 8 Hz, 4-H), 7.23 (1 H, dd, *J* 5.5 and 8 Hz, 3-H), 3.1 (2 H, m, CH_2), 2.68 (2 H, m, CH_2), and 2.17 (2 H, m, CH_2).

5-*Oxo*-5,6,7,8-*tetrahydroisoquinoline* (**4**).—(*a*) 5,6,7,8-*Tetrahydroisoquinoline* 2-*oxide*. 5,6,7,8-Tetrahydroisoquinoline (13.3 g, 0.1 mol) and hydrogen peroxide (15 ml) in AcOH (60 ml) were heated for 12 h at 70—80 °C; then hydrogen peroxide (30 ml) was added and heating continued for 12 h. After the reaction, the mixture was evaporated to one-quarter of the starting volume, water (50 ml) was added, and the mixture was evaporated again to the same volume. To the residue $CHCl_3$ (50 ml) was added and the solution was neutralized with K_2CO_3. The solvent was evaporated under reduced pressure, the residue distilled, and the fraction containing the product (10.1 g, 68%) was collected, b.p. 166—175 °C at 1.6 hPa (lit.,[16] b.p. 170—173 °C at 3 mmHg).

(*b*) 5-*Hydroxy*-5,6,7,8-*tetrahydroisoquinoline*. To boiling Ac_2O (12 ml) was added dropwise a saturated solution of crude 5,6,7,8-tetrahydroisoquinoline 2-oxide (8.9 g, 0.06 mol) in Ac_2O during 30 min and the mixture was then heated for an additional 30 min till boiling. The excess of Ac_2O was distilled off under reduced pressure and oily residue distilled to give a fraction (7.4 g) with b.p. 112—115 °C at 0.8 hPa. The distillate was dissolved in 12% HCl (40 ml) and boiled for 4 h. The acidic solution obtained was made alkaline with NaOH and extracted five times with $CHCl_3$. The combined extracts, after removal of the solvent, gave an oily residue. The residue was distilled to give a fraction (4.5 g, 50%) with b.p. 130—132 °C at 0.5 hPa which solidified. The solid crystallized from hexane as colourless crystals of 5-*hydroxy*-5,6,7,8-*tetrahydroisoquinoline*, m.p. 89.5—91 °C (Found: C, 72.5; H, 7.4; N, 9.4. $C_9H_{11}NO$ requires C, 72.3; H, 7.5; N, 9.3%); $\nu_{max.}$(Nujol) 3 210 cm^{-1} (OH); δ_H (60 MHz; $CDCl_3$; Me_4Si) 8.2 (2 H, m, 1- and 3-H), 7.4 (1 H, d, *J* 5 Hz, 4-H), 6.1 (1 H, s, OH), 4.7 (1 H, m, 5-H), 2.7 (2 H, m, CH_2), and 2.0 (4 H, m, CH_2).

(*c*) 5-*Oxo*-5,6,7,8-*tetrahydroisoquinoline* (**4**). 70% $HClO_4$ (4 ml) was added to 5-hydroxy-5,6,7,8-tetrahydroisoquinoline (14.9 g, 0.1 mol) dissolved in AcOH (70 ml) and CrO_3 (1 g, 0.01 mol) in water (3 ml) and AcOH (16 ml) were added dropwise during 10 min at 15 °C. The mixture was kept for 3 days at room temperature, then the mixture was evaporated to one-quarter of the starting volume, and water (75 ml) was added to the residue and again evaporated to the same volume. The solution was made alkaline with KOH (pH *ca.* 10) and continuously extracted with $CHCl_3$ for 20 h, then chromatographed over basic alumina ($CHCl_3$). The solvent was evaporated and the oily residue distilled to give compound (**4**) (11.8 g, 80%) as a colourless liquid, b.p. 115—117 °C at 2.0 hPa (lit.,[17] b.p. 113—115 °C at 4 mmHg), which solidified. The solid product crystallized from light petroleum as colourless crystals, m.p. 42—44 °C (Found: C, 73.3; H, 6.4; N, 9.3. Calc. for C_9H_9NO: C, 73.5; H, 6.2; N, 9.5%); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$; Me_4Si) 8.35 (2 H, m, 1- and 3-H), 7.4 (1 H, d, *J* 5 Hz, 4-H), and 3.2—1.9 (6 H, m, CH_2).

8-*Oxo*-5,6,7,8-*tetrahydroquinoline* (**2a**) *and* 8-*Oxo*-2-*phenyl*-5,6,7,8-*tetrahydroquinoline* (**2b**).—The ketones (**2a**) (10.3 g, 70%) and (**2b**) (15.4 g, 69%) were prepared as described for compound (**4**) from 8-hydroxy-5,6,7,8-tetrahydroquinoline[18] (14.9 g, 0.1 mol) and 8-hydroxy-2-phenyl-5,6,7,8-tetrahydroquinoline[18] (22.5 g, 0.1 mol). In the case of (**2b**), the perchlorate was precipitated, and crystallized from Ac_2O, m.p. 221.5—224 °C (decomp.). An equimolecular amount of KOH dissolved in MeOH was added to the saturated solution of perchlorate in MeOH. After 30 min an inorganic precipitate was filtered off and filtrate evaporated until dry and crystallized. The ketone (**2a**) had m.p. 102—104 °C (Pr^i_2O) (lit.,[19] m.p. 96—98 °C) (Found: C, 73.6; H, 6.3; N, 9.5. Calc. for C_9H_9NO: C, 73.5; H, 6.2; N, 9.5%); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$; Me_4Si) 8.62 (1 H, dd, *J* 1 and 5 Hz, 2-H), 7.75 (1 H, dd, *J* 1 and 7.5 Hz, 4-H), 7.45 (1 H, dd, *J* 1, 5 and 7.5 Hz, 3-H), and 1.9 (6 H, m, CH_2). The ketone (**2b**) had m.p. 140—142 °C (water–methanol) (Found: C, 80.6; H, 5.9; N, 6.3. $C_{15}H_{13}NO$ requires C, 80.6; H, 5.9; N, 6.3%); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$; Me_4Si) 8.3—7.2 (7 H, m, 3-, 4- and Ph-H), 3.2—2.6 (4 H, m, CH_2), and 2.4—1.8 (2 H, m, CH_2).

Organolithium Reagents and General Conditions.—The organolithium reagents were prepared in ether before use by usual methods; the solids were allowed to settle, and the clear solutions were forced under argon pressure through a plug of glass wool into a calibrated dropping funnel (with equalizer), stopped with a serum cap equipped with an additional syringe needle allowing samples for titrations to be withdrawn. The generator for lithium alkyls was connected with a dropping

Table 2. Physical properties and analytical data of compounds (**5**)—(**15**)

Compound[a] (Formula)	B.p. (°C/hPa)	M.p. (°C)	Crystallization solvent	Found (%) (Required) C	H	N
(**5a**)	96—98/40			70.1	8.0	10.0
($C_8H_{11}NO$)				(70.0)	(8.1)	(10.2)
(**5b**)	106—107/0.13	37—39	Light petroleum	78.4	6.5	7.1
($C_{13}H_{13}NO$)				(78.4)	(6.6)	(7.0)
(**6a**)	111—112/2.6			70.2	8.2	10.1
($C_8H_{11}NO$)				(70.0)	(8.1)	(10.2)
(**6b**)	172—174/2.6	81—83	Light petroleum	78.3	6.7	7.1
($C_{13}H_{13}NO$)				(78.4)	(6.6)	(7.0)
(**7a**)		134—136	Benzene	70.3	8.2	10.3
($C_8H_{11}NO$)				(70.0)	(8.1)	(10.2)
(**7b**)		146—148	Acetone	78.3	6.7	6.9
($C_{13}H_{13}NO$)				(78.0)	(6.6)	(7.0)
(**8a**)		72—73.5	Light petroleum	73.7	8.3	8.7
($C_{10}H_{13}NO$)				(73.6)	(8.0)	(8.6)
(**8b**)		104—106[h]	Light petroleum	80.0	6.9	5.9
($C_{15}H_{15}NO$)				(80.0)	(6.7)	(6.2)
(**8d**)		91–93	Light petroleum	83.6	6.4	4.6
($C_{21}H_{19}NO$)				(83.7)	(6.4)	(4.7)
(**9a**)		108—110	Light petroleum	73.6	8.3	8.5
($C_{10}H_{13}NO$)				(73.6)	(8.0)	(8.6)
(**9b**)		151—153[i]	Light petroleum	79.7	6.9	6.4
($C_{15}H_{15}NO$)				(80.0)	(6.7)	(6.2)
(**10a**)		85—86	Pr^i_2O	73.8	8.2	8.8
($C_{10}H_{13}NO$)				(73.6)	(8.0)	(8.6)
(**10b**)		180—182	Light petroleum	80.0	6.8	6.2
($C_{15}H_{15}NO$)				(80.0)	(6.7)	(6.2)
(**11**)		126—128	Benzene	83.0	6.4	5.3
($C_{19}H_{17}NO$)				(82.9)	(6.2)	(5.1)
(**12**)		131—133	Benzene	82.6	6.3	5.0
($C_{19}H_{17}NO$)				(82.9)	(6.2)	(5.1)
(**14**)		156—158	Benzene	83.4	6.4	4.7
($C_{21}H_{19}NO$)				(83.7)	(6.4)	(4.7)
(**15**)		202—204	Benzene	83.5	6.2	4.8
($C_{21}H_{19}NO$)				(83.7)	(6.4)	(4.7)

[a] Solvent used for elution: (**5b**) and (**8b**), benzene–acetone (9:1); (**6a**), ethyl acetate; (**6b**), (**7a**), (**7b**), (**8a**), (**8d**), (**9a**), (**9b**), (**10a**), (**10b**), (**11**), (**12**), (**14**), and (**15**), benzene–acetone (8:2). [b] Lit., b.p. 85—90 °C at 10 mmHg (G. B. Bachman and D. D. Micucci, *J. Am. Chem. Soc.*, 1948, **70**, 2381). [c] Lit., m.p. 40 °C (A. G. Davies, J. Kenyan, and K. Thaker, *J. Chem. Soc.*, 1956, 3394). [d] Lit., b.p. 110 °C at 5 mmHg (M. Mallet and F. Marsais, *C. R. Acad. Sci.*, 1972, **275**, 1439). [e] Lit., m.p. 76—77 °C [E. M. VanHeyningen, U.S.P., 3 396 224 (*Chem. Abstr.*, 1968, **69**, 96485k)]. [f] Lit., m.p. 136 °C (B Emmert and E. Asendorf, *Ber.*, 1939, **72**, 1188). [g] Lit., m.p. 146—147 °C (see footnote *f*, Table 2). [h] Lit., m.p. 103—105 °C [N. Lodde and E. Reimann, *Arch. Pharm. (Weinheim)*, 1979, **312**, 940]. [i] Lit., m.p. 146—147 °C (Ref., 19).

funnel by a Teflon-tube sealed with serum caps containing syringe needles (generator and dropping funnel). The dropping funnel was assembled in a round-bottomed flask (250 ml), equipped with a Teflon-coated magnetic stirring bar, and a condenser stopped with a mercury bubbler. One arm of the flask was stopped with a serum cap with two syringe needles, one connected to an argon-filled manifold, and a second one for introducing the solution of ketone and if needed the solution of LiBr. The apparatus was flushed for 2 h with argon before the experiment (generation of MeLi or PhLi) was started and kept under a positive pressure of inert gas during each run. MeLi and PhLi were assayed by double titration.[20] The concentration of the lithium alkyls varied in the range 0.85—0.95 mol/l for MeLi and 0.65—0.75 mol/l for PhLi.

Reaction of Lithium Alkyls with Ketones.—An ethereal solution (0.01 or 0.02 mol) of the organolithium reagent was added at 25 °C during 3 min to the ketone (0.01 mol) dissolved in C_6H_6 (30 ml) and ether (30 ml). The mixture was stirred for 1.5 h (or a longer reaction time, 150 h) and water or deuterium oxide (10 ml) was added. The layers were separated and the aqueous one continuously extracted for 3 days with $CHCl_3$. The combined organic solutions were dried ($MgSO_4$) and the solvents removed under reduced pressure to give an oily residue. In these experiments with the greater amount of LiBr, the ethereal solution of the salt (0.03 mol) was added before the organolithium reagent. The ethereal solution of LiBr was prepared from lithium shot with dibromoethylene[21] and standardized to give a 1 mol l^{-1} solution. In the reactions of the ketones (**1a**—**c**) with MeLi, the products were separated by fractional distillation. In the case of (**1a**), the alcohol (**5a**) obtained was contaminated with a trace of the parent ketone, after double distillation. In other cases, the products were separated by chromatography on silica gel. The yields of the reactions and overall yields are summarized in Table 1, the physical properties, the i.r. and ^1H n.m.r. data, the eluants, and the analytical data are given in Tables 2 and 3. The yields and ratios of the products from the reactions of ketones (**1a**), (**2a**), and (**2b**) with MeLi and PhLi were obtained as follows. In the case of the ketones (**1a**) and (**2a**), they were determined by ^1H n.m.r. ($CDCl_3$; internal reference Me_4Si) spectroscopy utilizing the peak areas of the methyl and 2-pyridine protons. The chemical shifts of the methyl protons of (**1a**) and the 2-pyridine protons of (**1a**) and (**2a**) are δ 2.68, 8.68, and 8.62; those of the

Table 3. I.r. bands[a] and ^{1}H n.m.r. data[b] of compounds (**5**)—(**15**)

Compound	$\nu_{max.}$(OH) (cm^{-1})	δ_H (p.p.m.)
(**5a**)	3 450[c]	8.35 (1 H, d, *J* 5 Hz, Py 6-H), 7.70—6.85 (3 H, m, Py 3-, 4-, and 5-H), 5.0 (1 H, s, OH), 1.40 (6 H, s, CH_3)
(**5b**)	3 350	8.20 (1 H, d, *J* 5 Hz, Py 6-H), 7.60—6.65 (8 H, m, Py 3-, 4-, and 5-H and Ph-H), 5.95 (1 H, s, OH), 1.85 (3 H, s, CH_3)
(**6a**)	3 200	8.55 (1 H, d, *J* 1.5 Hz, Py 2-H), 8.20 (1 H, dd, *J* 1.5 and 5 Hz, Py 6-H), 7.80 (1 H, m, Py 4-H), 7.15 (1 H, m, Py 5-H), 6.10 (1 H, br s, OH), 1.50 (6 H, s, CH_3)
(**6b**)	3 200	8.35 (1 H, d, *J* 1.5 Hz, Py 2-H), 8.05 (1 H, dd, *J* 1.5 and 5 Hz, Py 6-H), 7.65 (1 H, m, Py 4-H), 7.50—6.80 (6 H, m, Py 5-H and Ph-H), 6.0 (1 H, s, OH), 1.75 (3 H, s, CH_3)
(**7a**)	3 200	7.50 (2 H, d, *J* 5 Hz, Py 2- and 6-H), 7.45 (2 H, d, *J* 5 Hz, Py 3- and 5-H), 4.10 (1 H, m, OH), 1.60 (6 H, s, CH_3)
(**7b**)	3 200	8.35 (2 H, dd, *J* 1.5 and 5.5 Hz, Py 2- and 6-H), 7.55—7.0 (7 H, m, Py 3- and 5-H and Ph-H), 3.80 (1 H, s, OH), 1.9 (3 H, s, CH_3)
(**8a**)	3 500	8.40 (1 H, dd, *J* 1.5 and 5 Hz, 2-H), 7.40 (1 H, dd, *J* 1.5 and 8 Hz, 4-H), 7.10 (1 H, m, 3-H), 4.5 (1 H, br s, OH), 3.05—2.75 (2 H, m, CH_2), 2.20—1.85 (4 H, m, CH_2), 1.50 (3 H, s, CH_3)
(**8b**)	3 500	8.42 (1 H, dd, *J* 1.5 and 5 Hz, 2-H), 7.60—6.95 (7 H, m, 3-, 4-H and Ph-H), 4.55 (1 H, br s, OH), 3.0—2.70 (2 H, m, CH_2), 2.35—2.10 (2 H, m, CH_2), 1.95—1.45 (2 H, m, CH_2)
(**8d**)	3 500	8.05—6.90 (12 H, m, 3-, 4-H and Ph-H), 4.85 (1 H, br s, OH), 3.0—2.60 (2 H, m, CH_2), 2.45—2.10 (2 H, m, CH_2), 2.0—1.45 (2 H, m, CH_2)
(**9a**)	3 250	8.15 (1 H, m, 2-H), 7.95 (1 H, m, 4-H), 7.10 (1 H, m, 3-H), 4.85 (1 H, s, OH), 3.0—2.60 (2 H, m, CH_2), 2.10—1.80 (4 H, m, CH_2), 1.45 (3 H, s, CH_3)
(**9b**)	3 250	8.35 (1 H, m, 2-H), 7.70—6.80 (7 H, m, 3-, 4-H and Ph-H), 3.85 (1 H, br s, OH), 3.20—2.80 (2 H, m, CH_2), 2.40—1.55 (4 H, m, CH_2)
(**10a**)	3 200	8.15 (1 H, d, *J* 5.5 Hz, 3-H), 8.06 (1 H, br s, 1-H), 7.45 (1 H, d, *J* 5.5 Hz, 4-H), 5.3 (1 H, br s, OH), 2.80—2.50 (2 H, m, CH_2), 2.10—1.80 (4 H, m, CH_2), 1.45 (3 H, s, CH_3)
(**10b**)	3 200	8.30 (1 H, s, 1-H), 8.15 (1 H, d, *J* 5 Hz, 3-H), 7.30—6.90 (6 H, m, 4-H and Ph-H), 3.80 (1 H, br s, CH), 3.0—2.75 (2 H, m, CH_2), 2.30—1.50 (4 H, m, CH_2)
(**11**)	3 300	8.55 (1 H, br s, Py 6-H), 8.05—7.0 (12 H, m, Py 3-, 4-H and Ph-H), 3.05 (1 H, s, OH), 1.90 (3 H, s, CH_3)
(**12**)	3 300	8.50 (1 H, br s, Py 6-H), 8.10—7.0 (12 H, m, Py 3-, 4-H and Ph-H), 3.40 (1 H, br s, OH), 1.90 (3 H, s, CH_3)
(**14**)	3 250[d]	8.35 (1 H, d, *J* 5 Hz, Py 3-H), 7.60—7.40 (10 H, m, Ph-H), 6.90 (1 H, d, *J* 5 Hz, Py 4-H), 3.7 (1 H, br s, OH), 2.80—1.75 (6 H, m, CH_2)
(**15**)	3 100	7.77 (1 H, br s, Py 1-H), 7.27—7.10 (11 H, m, Py 4-H and Ph-H), 5.3 (1 H, br s, OH), 2.50—1.35 (6 H, m, CH_2)

[a] Recorded in $CHCl_3$. [b] Recorded in $CDCl_3$ with Me_4Si as internal standard. [c] Neat. [d] Recorded in Nujol.

methylated and phenylated derivatives are δ 1.40, 1.85, 8.35, 8.20, 8.40, and 8.42 respectively. In the case of the ketones (**2b**), the yields of the products were calculated from the amount of unchanged starting material, estimated by the intensity of the carbonyl absorption at 1 715 cm^{-1} in the i.r. spectrum ($CHCl_3$). Samples for identification were obtained by dissolving the oily residue in the appropriate solvent to make stock solutions, which were diluted before the measurements were carried out. The oily residues were column chromatographed on silica gel to remove small quantities of polar contaminants before samples for ^{1}H n.m.r. or i.r. measurements were prepared. In the case of the ketone (**1a**) with MeLi, the oily residue was distilled to give 93% of distillate.

Complexes of the Ketones (**1a**) *and* (**2a**) *with Lithium Bromide.*—An ethereal solution of LiBr[21] (0.01 mol) was added to the ketone (0.01 mol) dissolved in ether (50 ml). The precipitated complexes were filtered off and washed with ether in a glove box, dried, and stored in a vacuum desiccator. For analysis the complex (1 g) was decomposed by dissolution in distilled water (5 ml). The ketones were analysed by u.v. spectroscopy, at 232 nm for (**1a**) and 235 nm for (**2a**); the LiBr was analysed by argentometric titration. The composition of the complexes was found to be (**1a**)·LiBr 1:1.09, and (**2a**)·LiBr 0.97:1.

References

1 Part 2, J. Epsztajn, A. Bieniek, J. Z. Brzeziński, and A. Jóźwiak, *Tetrahedron Lett.*, 1983, 4735.
2 D. E. Beattie, R. Crossley, A. C. W. Curran, G. T. Dixon, D. G. Hill, A. E. Lawrence, and R. G. Sheperd, *J. Med. Chem.*, 1977, **20**, 714; D. E. Beattie, R. Crossley, A. C. W. Curran, D. G. Hill, and A. E. Lawrence, *ibid.*, 1977, **20**, 718.
3 (*a*) T. Eicher in 'The Chemistry of the Carbonyl Group,' ed. S. Patai, Interscience Publishers, New York, 1966, vol. 1, p. 621; (*b*) B. J. Wakefield, 'The Chemistry of Organolithium Compounds,' Pergamon Press, 1974, pp. 109, 122.
4 (*a*) R. A. Abramovitch and J. G. Sacha, *Adv. Heterocycl. Chem.*, 1966, **6**, 229; (*b*) R. E. Lyle in 'Pyridine and Its Derivatives,' ed. R. A. Abramovitch, John Wiley, New York, 1974, Part 1, p. 137; (*c*) R. A. Abramovitch and G. H. Singer in 'Pyridine and Its Derivatives,' ed. A. R. Abramovitch, John Wiley, New York, 1974, Part 1, p. 1.
5 H. J. Rimek and F. Zymalkowski, *Arch. Pharm. (Weinheim)*, 1961, **294**, 759.
6 J. D. Buhler, *J. Org. Chem.*, 1973, **38**, 904.
7 Ref. 12 in J. Epsztajn, Z. Berski, J. Z. Brzeziński, and A. Jóźwiak, *Tetrahedron Lett.*, 1980, 4739.
8 W. J. O'Sullivan, F. M. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, 1961, **26**, 2306; J. Freeman and M. F. Hawthorne, *J. Am. Chem. Soc.*, 1956, **78**, 3366.
9 I. S. Perelygin, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, 1976, **19**, 827.
10 E. C. Ashby and S. A. Nading, *J. Org. Chem.*, 1979, **44**, 4371.
11 T. Holm, *Acta Chem. Scand.*, 1969, **23**, 24; 1971, **25**, 833; S. G. Smith, L. F. Charboneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.*, 1972, **94**, 7059; L. F. Charboneau and S. G. Smith, *J. Org. Chem.*, 1976, **41**, 808.

12 L. Lunazzi, D. Macciantelli, and G. Cerioni, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1791; J. S. Kwiatkowski and M. Swiderska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1977, **25**, 325; J. G. John, G. L. D. Ritchie, and L. Radom, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1601; W. Pietrzycki, P. Tomasik, and A. Sucharda-Sobczyk, *J. Mol. Struct.*, 1981, **73**, 49.
13 J. Epsztajn, A. Bieniek, J. Z. Brzeziński, and A. Stepień, unpublished data.
14 J. J. Eisch, *J. Organomet. Chem.*, 1980, **200**, 101.
15 D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, 1963, **85**, 1245; C. Zioudrou, I. Moustakali-Mavridis, P. Chrysochou, and G. J. Karabatsos, *Tetrahedron*, 1978, **34**, 3181.
16 E. Ochiai and M. Ikehara, *J. Pharm. Bull. Jpn*, 1954, **2**, 109 (*Chem. Abstr.*, 1956, **50**, 1014).
17 N. Sugimoto, K. Hiroshi, and T. Tadashi, *J. Pharm. Soc. Jpn*, 1956, **76**, 1308 (*Chem. Abstr.*, 1957, **51**, 5076).
18 W. E. Hahn and J. Epsztajn, *Rocz. Chem.*, 1963, **37**, 403.
19 E. Reimann and H.-L. Ziegon, *Liebigs Ann. Chem.*, 1976, 1351.
20 H. Gilman, *Bull. Soc. Chim. Fr.*, 1963, 1356; R. R. Turner, A. G. Altenan, and T. C. Heng, *Anal. Chem.*, 1970, **42**, 1835.
21 T. V. Talalaeva and K. A. Kocheshkov, *Dokl. Akad. Nauk SSSR*, 1955, **104**, 260.

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