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PRODUCTS FROM METALLATION AND ATTEMPTED METALLATION OF 1-ALKYL-4,6-DIPHENYL-2-PYRIDONES AND SUBSEQUENT REACTION WITH ELECTROPHILES

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Summary The title pyridones form products in which either their own carbanion, or an alkylcarbanion, has added to the 3-position, followed by an electrophile to the 4-position.

In a dipole-stabilized carbanion (1),[1] the carbanionic-carbon is attached to a hetero-atom Y which is itself joined to an electron-accepting group Z. Hence mesomeric dipolar canonicals (2) contribute. Numerous acyclic and alicyclic examples are known,[1] but carbanions derived from sp^3-CH groups attached to the nitrogen atom of a heteroaromatic ring were previously unreported.

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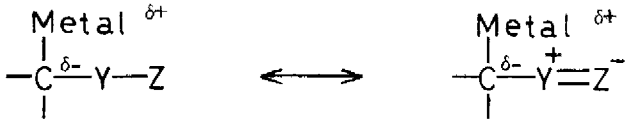

$$\overset{\text{Metal}^{\delta+}}{-\overset{|}{\underset{|}{C}}}\overset{\delta-}{—}Y—Z \longleftrightarrow \overset{\text{Metal}^{\delta+}}{-\overset{|}{\underset{|}{C}}}\overset{\delta-}{—}\overset{+}{Y}=Z^{-}$$

2

As part of a wide-ranging investigation of heterocycle-stabilized organolithiums, we studied 1-substituted-4,6-diphenyl-2-pyridones (3). 1-Benzyl derivatives (3a) readily form stable organolithiums (4a), which give expected reactions with electrophiles.[2] However, the 1-alkyl analogues, such as 3b and 3c, can afford derivatives of three distinct types, two of them of unexpected structure, as is explained in the present paper.

(A) Products Derived from One Mole of Pyridone and One Mole of Electrophile. We found that the normal expected products could be obtained by adding lithium di-isopropyl-amide (LDA) to the pyridone and a suitable electrophile premixed in tetrahydrofuran (THF) solution. Thus the 1-methyl-2-pyridone (3b) with methyl benzoate and benzophenone yielded 3e and 3f, respectively. Similarly, the 1-ethyl-2-pyridone 3c gave products 3g and 3h with methyl benzoate and benzophenone.

(B) Products Derived from Two Moles of Pyridone and One Mole of Electrophile. Metallation of the 1-methylpyridone (3b) with LDA at -78° followed by the addition of methyl iodide, p-toluoyl chloride, or water gave, in each case, a crystalline product which elemental analysis indicated had been formed according to the stoichiometry of eqn (1).

$$3b + 3b + RX \longrightarrow \text{product} + HX \quad .... (1)$$

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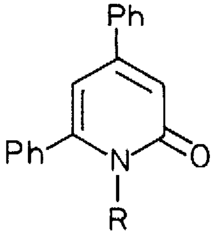

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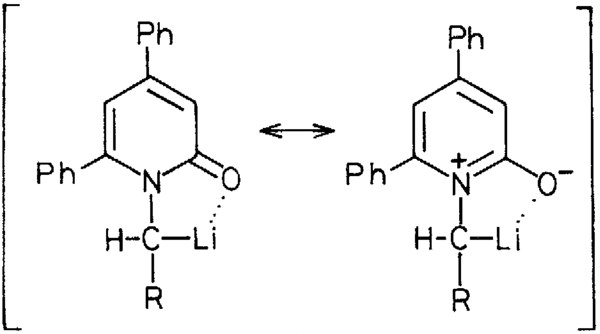

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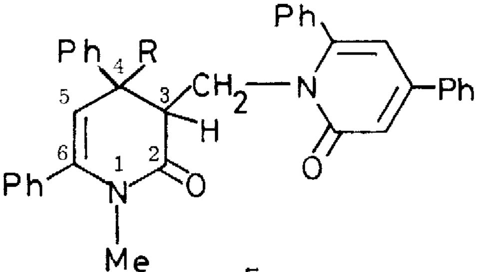
In 3	a	b	c	d	e	f	g	h
R =	CH_2Ph	Me	Et	Bu^n	CH_2COPh	$CH_2C(OH)Ph_2$	CH(Me)COPh	$CH(Me)C(OH)Ph_2$

In 4	a	b	c
R =	Ph	H	Me

The mass spectra gave in all cases an intense ion m/e 522, this is M^+ for 5c and corresponds to (M^+ - R + H) for the other compounds. The base peaks were at m/e 274.

The ^1H NMR spectra of each of the three products show that, of the original pyridone signals, all the phenyls are intact, as is one N-methyl (near δ 2.8) and one pair of 3,5-pyridone ring protons (near 6.75 and 6.2). The four remaining protons appear as a finely split doublet near δ 5.6 (evidently a modified ring proton) and an ABC system with chemica shifts respectively near 2.8, 3.1, and 4.8. The splittings correspond to $J_{A,B}$ = 5 Hz, $J_{A,C}$ = $J_{B,C}$ = 12.5 Hz. The assignment, which was confirmed by decoupling experiments, indicates that in the ABC system the remaining two protons from the N-methyl group are coupled with one of the original pyridone ring protons, and this leads directly to structures of general type 5a-c. Each product shows additionally the expected signals for the protons of the electrophile: in 5a these appear as a singlet.



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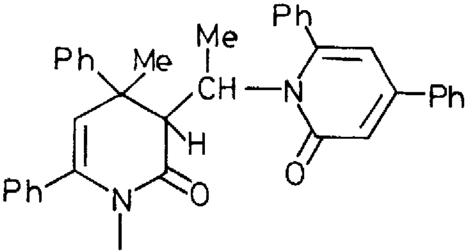

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	a	b	c
R =	Me	$p\text{-}MeC_6H_4CO$	H

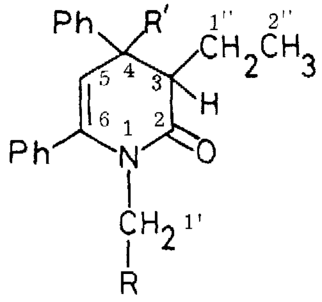
Structure 5 is supported by the off-resonance ^{13}C NMR spectra. Thus for 5a, the aromatic carbons give overlapping resonances from δ 127-149, the undisturbed pyridone ring shows the C-2' C=O at δ 163.7 (singlet), C-3' and C-5' as 112.1 and 101.2 doublets, whilst C-4' and C-6' resonate in the aromatic region. In the other ring, C-2 gives a δ 169.8 singlet (more deshielded), C-5 a 118.9 doublet, and C-6 appears in the aromatic region. C-3 and C-4, give respectively, a doublet at δ 52.5 and a singlet at 40.1. The methylene carbon gives a δ 42.1 triplet, and the N- and C-methyl groups respectively 32.0 and 27.6 quartets.

Reaction of the 1-ethylpyridone (3c) with LDA, followed by methyl iodide, at -78°, similarly gave the product (6), with spectra analogous to 5. In the ^{1}H spectrum the prochiral N-ethyl group gave an ABX_3 system at δ 2.75, 3.88 and 0.81; $J_{A,B}$ = 14 Hz; $J_{A,X}$ = $J_{B,X}$ = 7 Hz.

(C) Products Derived from One Mole each of Pyridone, Alkyl-lithium, and Electrophile. Attempts to generate the pyridone carbanions 4b and 4c from the respective pyridones 3a and 3b and ethyl-lithium (n-butyl-lithium gives analogous products) in THF at -78 °C gave, *after the addition of p-chlorobenzoyl chloride or methyl iodide* electrophile, products derived according to the stoichiometry of eqn (2).

$$\text{3a (or 3b)} + R'Li + RX \longrightarrow \text{product} + LiX \quad \dots\dots\dots\dots \quad (2)$$

The mass spectra showed moderately intense molecular ions with (M - ArCO) as base peaks. The ^{1}H NMR spectra of the products derived from the N-ethylpyridone 3c and ethyl-lithium all showed two ethyl patterns (a) an ABX_3 system with δ 3.0, 4.1, and 0.8 respectively; $J_{A,B}$ = 14 Hz; $J_{A,X}$ = $J_{B,X}$ = 7 Hz, typical for a prochiral N-Et group and (b) as part of an $ANMX_3$ system with δ 3.2, 1.5, 1.45, and 0.9 respectively; $J_{A,N}$ = 11 Hz, $J_{A,M}$ = 5 Hz; $J_{N,M}$ ≈ 14 Hz; $J_{N,X}$ = $J_{M,X}$ = 7.5 Hz, which is typical for a prochiral CHEt group. This leads to structures 7. These assignments were supported by decoupling experiments.



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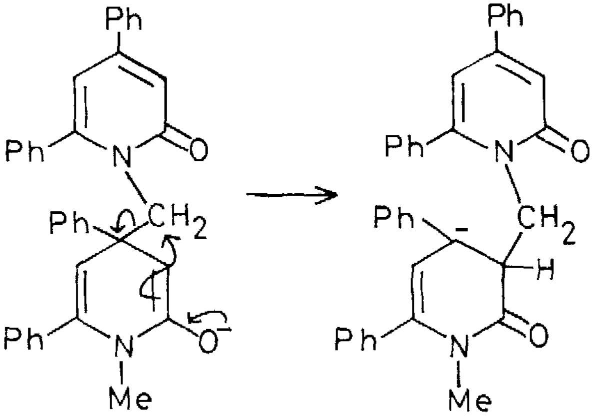
a; R = Me, R' = p-MeC_6H_4CO

b; R = Pr^n, R' = p-ClC_6H_4CO



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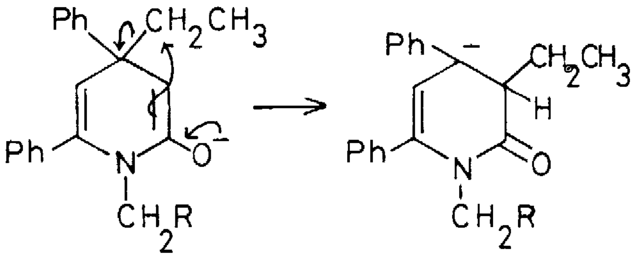
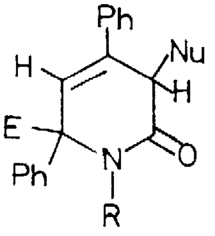
These structures are supported by the off-resonance ^{13}C NMR spectrum of 7a showing carbonyl singlets at 195.5 and 172.3 for the ketone and C-2 respectively. The overlapping aromatic resonances, δ 144-126 also include C-6, but C-5 forms a doublet at 110.0. The quaternary C-4 gives a δ 59.4 singlet, and the methine C-3 a 52.7 doublet, similarly to 5b. The N-substituent gives a δ 37.7 triplet (C-1') and 13.7 quartet (C-2'), whilst the C-ethyl group gives higher field absorbances of 19.6 triplet (C-1'') and 11.9 quartet (C-2''). The terminal carbon of the ethyl group gives the expected δ 21.5 quartet.

The Mechanism of Formation of the Anomalous Products. In products of both types (B) and (C), a nucleophile has added to the 3-position and an electrophile to the 4-position of a 2-pyridone ring. This is the reverse of the usual orientation.[3] We suggest that the nucleophile first adds to the 4-position and then the product rearranges 8 → 9 and 10 → 11. Addition of the electrophile now gives structures 5 and 7.



10 11



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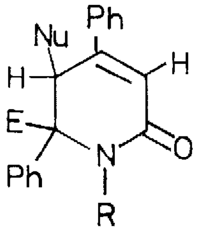

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Possible Alternative Structures. A mechanism of the type just suggested could also give rise to structures of type 12 or of type 13. It is difficult to distinguish definitively between such structures and those suggested above on infrared evidence.[4] However, the ^{13}C NMR shifts of the quaternary ring carbon atoms (at ca. 50 ppm)[*] support the structures assigned: the quaternary ring carbon atoms in 12 and 13, adjacent to a nitrogen atom, would be expected to possess chemical shifts at δ ≫ 60 ppm.[5]

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1 P. Beak and D.B. Reitz, Chem. Rev., 78, 275 (1978).

2 A.R. Katritzky, J. Arrowsmith, Zakaria bin Bahari, C. Jayaram, T. Siddiqui, and S. Vassilatos, J. Chem. Soc. Perkin I, in the press.

3 Cf., e.g. A.R. Katritzky and J.M. Lagowski, The Principles of Heterocyclic Chemistry, p.31. Academic Press, New York (1968).

4 As will be discussed in the full paper.

5 K. Ramalingam, K.D. Berlin, N. Satyamurthy and R. Sivakumar, J. Org. Chem., 1979, 44, 471.

[*] In 5a and 5c· in the 4-aroyl compounds 5b and 7 the shift is larger.

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