

## The Question of 1,2- or 1,4-Addition of Organolithium Compounds to Quinolines

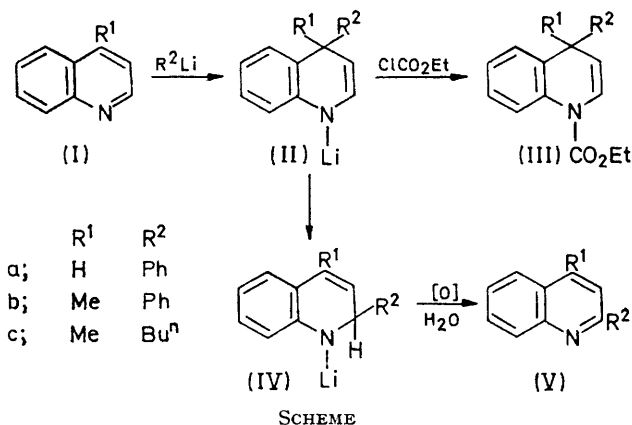
By **Colin E. Crawforth**,\* Department of Chemistry and Biology, Harris College, Preston PR1 2TQ  
**O. Meth-Cohn**, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT  
**C. A. Russell**, The Open University, Walton Hall, Walton, Bletchley, Bucks.

The reactions of quinoline and 4-methylquinoline with organolithium reagents lead to the corresponding 2-substituted 1,2-dihydro-1-lithioquinolines (IV), which upon hydrolysis provide the 2-substituted quinolines (V). Addition of ethyl chloroformate to the reaction mixture prior to hydrolysis gives the ethyl 1,2-dihydroquinoline-1-carboxylates (VI) and not the 1,4-dihydroquinoline analogues (III) as was recently postulated.

REACTIONS of quinolines with organolithium reagents in ethereal solvents have been extensively studied.<sup>1-8</sup> Except in the case of 2-methylquinoline, which undergoes exclusive methyl group lithiation with phenyllithium,<sup>1-3</sup> the usual products, after hydrolysis and oxidation are the 2-substituted quinolines (V). That these nucleophilic substitutions proceed through the 1,2-adducts (IV) has been implicit, though not proved rigorously in the quinoline case, although there is ample evidence for 1,2-adducts in the pyridine series.<sup>9</sup> The report<sup>10</sup> that treatment with *n*-butyl- or phenyllithium of the quinolines (I) initially produced a 1,4-adduct (II), which then rearranged to the 1,2-isomer (IV) giving the quinoline (V) on work-up (Scheme), therefore seemed deserving of further investigation.

The validity of these claims<sup>10</sup> was largely based on spectroscopic data for the *N*-ethoxycarbonyl derivatives, considered to be the trapped 1,4-addition products (III), which were obtained in *ca.* 50% yield by adding ethyl chloroformate to the ethereal suspension of the adducts (II). By carefully following the Japanese workers' pro-

cedure<sup>10</sup> we obtained *N*-ethoxycarbonyl derivatives with physical properties identical with those reported for



	R <sup>1</sup>	R <sup>2</sup>
a;	H	Ph
b;	Me	Ph
c;	Me	Bu <sup>n</sup>

compounds (III); however, a reinvestigation of their n.m.r. spectra led us to reformulate these derivatives as

<sup>7</sup> K. Blaha and O. Cervinka, *Adv. Heterocyclic Chem.*, 1966, **6**, 222.

<sup>8</sup> C. E. Crawforth, Ph.D. Thesis, University of Lancaster, 1971.

<sup>9</sup> R. Foster and C. A. Fyfe, *Tetrahedron*, 1969, **25**, 1489; G. Fraenkel and J. G. Cooper, *Tetrahedron Letters*, 1968, 1825; C. S. Giam and J. L. Stout, *Chem. Comm.*, 1969, 142; R. A. Abramovitch and J. G. Saha, *Adv. Heterocyclic Chem.*, 1966, **6**, 274.

<sup>10</sup> Y. Otsuji, K. Yutani, and E. Imoto, *Bull. Chem. Soc. Japan*, 1971, **44**, 520.

<sup>1</sup> A. M. Jones, C. A. Russell, and S. Skidmore, *J. Chem. Soc. (C)*, 1969, 2245.

<sup>2</sup> A. M. Jones and C. A. Russell, *J. Chem. Soc. (C)*, 1969, 2246.

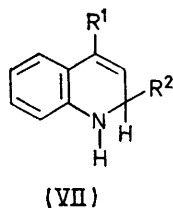
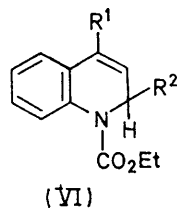
<sup>3</sup> K. Ziegler and H. Zeiser, *Annalen*, 1931, **485**, 174.

<sup>4</sup> H. Gilman and G. C. Gainer, *J. Amer. Chem. Soc.*, 1947, **69**, 877.

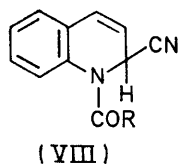
<sup>5</sup> R. A. Abramovitch, K. S. Ahmed, and C. S. Giam, *Canad. J. Chem.*, 1963, **41**, 1752.

<sup>6</sup> D. S. Tarbel, J. F. Bunnett, R. B. Carlin, and V. P. Wystrach, *J. Amer. Chem. Soc.*, 1945, **67**, 1582.

the 1,2-dihydro-compounds (VI).<sup>11\*</sup> We now enlarge on these findings and present some other data which not only confirm the structural assignments but also support the belief that nucleophilic substitution reactions between quinolines and organolithium reagents proceed only through the 1,2-adducts (IV).



	R <sup>1</sup>	R <sup>2</sup>
a;	H	Ph
b;	Me	Ph
c;	Me	Bu <sup>n</sup>
d;	Me	H



R = alkyl or aryl

A comparison of our n.m.r. spectra for the *N*-ethoxycarbonyldihydroquinolines (VI) with those recorded for compounds (III)<sup>10</sup> shows that the chemical shifts are almost identical. However, the fine structure, which was not observed by the Japanese workers, clearly supports our assignments. The *n*-butyl derivative (VIc) shows the 2-H, 3-H, and 4-Me signals as a modified ABX<sub>3</sub> system. The doublet of quartets at  $\tau$  4.17 we assign to 3-H ( $J_{2,3}$  6.2,  $J_{3,4\text{-Me}}$  1.3 Hz) [the previous assignment of this signal as a doublet and due to 2-H of (IIIc) thus becomes untenable<sup>10</sup>] and the methyl signal appears at  $\tau$  7.98 as a pair of overlapping doublets showing allylic coupling to 3-H ( $J_{3,4\text{-Me}}$  1.3 Hz) and homoallylic coupling to 2-H ( $J_{2,4\text{-Me}}$  1.0 Hz). The 2-H signal at  $\tau$  5.12, a broadened quartet confirms structure (VIc) for, in addition to coupling with 4-Me (broadening effect) and 3-H, a large extra coupling with adjacent methylene protons of the 2-*n*-butyl group is evident ( $J_{2,\alpha}$  6.2 Hz). The proposed couplings were confirmed by irradiating in turn at frequencies of the 4-Me, 3-H, and 2-H signals. The definitive coupling between 2-H and the  $\alpha$ -protons of the butyl group was shown by irradiating at  $\tau$  8.74; the 2-H signal was reduced to a broadened doublet ( $J_{2,3}$  6.2 Hz,  $J_{2,4\text{-Me}}$  broadening effect).

In the n.m.r. spectrum of the phenyl derivative the 2-H and 3-H signals overlap. The large downfield shift experienced by the 2-H signal is due to deshielding by an

adjacent phenyl group<sup>12</sup> and therefore strongly suggests structure (VIb). However, apart from the slight coupling to 2-H and 3-H revealed in the expanded methyl signal [which, in itself is substantial proof for the structure (VIb), as the corresponding 1,4-dihydro-compound (III)<sup>10</sup> would show the 4-Me signal as a singlet] little data can be obtained from this deceptively simple ABX<sub>3</sub> spectrum. Complete analysis was made possible however by using the paramagnetic shift reagent, Eu(fod)<sub>3</sub><sup>13</sup> (fod = 1,1,1,2,2,3,3-hepta-fluoro-7,7-dimethyloctane-4,6-dionato). From the 60 MHz spectrum of compound (VIb) in the presence of Eu(fod)<sub>3</sub> (0.035 mol. equiv.) the following conclusions can be drawn. (i) As expected the 2-H signal, now at  $\tau$  3.62 † ( $\Delta$  0.34 p.p.m.), and the 8-H signal,  $\tau$  2.99 ( $\Delta$  0.24 p.p.m.), are shifted downfield to the greatest extent; extrapolated values for a 1:1 molar ratio of (VIb) to Eu(fod)<sub>3</sub> are 2-H,  $\Delta$  8.62; 8-H,  $\Delta$  5.72 p.p.m. (ii) The 4-Me signal is revealed as a distinct triplet ( $\tau$  7.87) showing equivalent allylic and homoallylic couplings with 3-H and 2-H, respectively ( $J_{3,4\text{-Me}} = J_{2,4\text{-Me}} = 1.0$  Hz). (iii) The virtually unmoved 3-H signal ( $\tau$  4.00) is revealed as a doublet of quartets showing coupling with 2-H ( $J_{2,3}$  6.3 Hz) and 4-Me. (iv) The 2-H signal becomes a broadened doublet in which the small coupling with 4-Me is not visible, but which was proved by double irradiation experiments similar to those described for the butyl analogue, as were the other assignments.

If 1,4-addition of organolithium reagents to quinolines were to occur to any extent, that with quinoline itself, which has an unsubstituted 4-position, would be the most likely. The n.m.r. spectrum of the *N*-ethoxycarbonyl derivative obtained from the reaction between phenyllithium and quinoline (1; R = H), which had previously defied analysis,<sup>10</sup> is shown in the Table. However, an easily analysable spectrum which results when Pr(fod)<sub>3</sub> (0.034 mol. equiv.) is added is only attributable to structure (VIa) (see Table). The broadening of the 2-H and 4-H signals indicates that small allylic coupling occurs between these protons which double irradiation experiments show to be  $\leq 0.4$  Hz. The other proposed splittings were similarly proven. The extra coupling of the ethoxy-group methylene protons could be due to rotameric forms of the amidic centre.

These structural assignments are further supported by the similarity between the chemical shifts and coupling constants of the derivatives (VI) and those of known 1,2-dihydroquinoline systems,<sup>14</sup> and also by other spectroscopic data, discussed later. Careful hydrolysis of the *N*-lithio-dihydroquinolines (IV) in the absence of oxygen,

<sup>11</sup> C. E. Crawforth, O. Meth-Cohn, and C. A. Russell, *J.C.S. Chem. Comm.*, 1972, 259.

<sup>12</sup> 'An Introduction to Spectroscopic Methods for the Identification of Organic Compounds,' ed. F. Scheinmann, Pergamon, Oxford, 1970, vol. 1, p. 59.

<sup>13</sup> R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522; 'Perkin-Elmer N.M.R. Quarterly,' 1971, No. 1, p. 2.

<sup>14</sup> (a) R. Bramley and M. D. Johnson, *J. Chem. Soc.*, 1965, 1372; (b) T. W. Bunting and W. G. Meathrel, *Tetrahedron Letters*, 1971, 133.

\* Since completing this work we have been informed that J. J. Eisch and D. R. Comfort have arrived at similar conclusions by studying the 2-deuterio-analogues of (VI) (results to be published in *J. Organometallic Chem.*).

† Our previous assignment<sup>11</sup> of the 2-H signal as that at  $\tau$  1.56 in the presence of 0.25 mol. equiv. Eu(fod)<sub>3</sub> has been shown to be incorrect by decoupling experiments, this signal being due to 8-H.

should yield the hitherto unreported \* dihydroquinolines (VII). This was shown to be true, as evidenced by the similarity between u.v. spectra of compounds (VIIa—c) and those of known 1,2-dihydroquinolines<sup>14a,15</sup> including 1,2-dihydro-4-methylquinoline (VIIId)<sup>16</sup> (see Table). Furthermore, the n.m.r. signals of the parent 1,2-dihydroquinolines (VII) show multiplicities almost identical with those for the corresponding *N*-ethoxycarbonyl derivatives (VI), the slightly lower-field positions of the 2-H and 3-H signals in (VI) being due to the tertiary amide type grouping.

and *n*-butyl bromide. N.m.r. spectra were recorded on a Perkin-Elmer R12 60 MHz spectrometer for solutions in deuteriochloroform, with tetramethylsilane as internal standard. Spin decoupling experiments were carried out with a Varian HA-100 100 MHz spectrometer. In the shift reagent experiments just enough reagent was used to give a clarified spectrum without line broadening becoming too severe. The extrapolated shifts ( $\Delta$ ) were obtained from data for a minimum of three different concentrations of the reagent. I.r. spectra were recorded on a Perkin-Elmer 457 spectrophotometer and u.v. spectra on a Unicam SP 800 spectrophotometer.

Spectral data for compounds (VI) and (VII)

Compd.	$\lambda_{max.}$ (EtOH)/nm ( $\epsilon$ )	$\nu_{max.}/cm^{-1}$		$\tau$ (CDCl <sub>3</sub> )											J/Hz					
		C=C	C=O	Phase	1-H	2-H	3-H	4-H	4-Me	CO <sub>2</sub> Et		ArH	Other	2,3	2,4	3,4	2,4-Me	3,4-Me	Others	
(VIa)	305 * (1940) 265 (5650)		1700	Film			3.26—3.95 (m)			5.74 (q)	8.70 (t)	2.40—3.07 (m)								Et, 7.0
(VIa) †						4.29 (d)	3.94 (dd)	3.48 (d)		6.28 (m)	8.87 (t)	2.70—3.12 (m)		5.9	≤0.4	9.1				Et, 7.0
(VIb)	303 * (1610) 271 (4630)		1695	Nujol			3.96 (m)		7.89 (t)	5.74 (q)	8.71 (t)	2.40—3.10 (m)								Et, 7.0
(VIb) ‡						3.62 (d)	4.00 (dq)		7.87 (t)	5.45 (q)	8.63 (t)	8-H, 2.28 (m); 2.64—3.05 (m)		6.3			1.0		1.0	Et, 7.0
(VIc)	304 * (1540) 272 (5070)		1695	Film		5.12 (q)	4.17 (dq)		7.98 (dd)	5.79 (q)	8.70 (t)	2.37—3.10 (m)	2-Bun, 8.50—9.36 (m)	6.2			1.0		1.3	Et, 7.0; 2 $\alpha$ , 6.2
(VIId)	301 * (1380) 267 (4050)		1695	Film		5.72 (m)	4.23 (m)		7.97 (q)	5.80 (q)	8.71 (t)	2.37—3.05 (m)		4.5			1.5		1.5	Et, 7.0
(VIIa)	352, 337, 300,* 280	1642		Nujol	6.07 (s)	4.34—4.74 (m)		Obs- cured				2.56—3.80 (m)		3.8	1.2	9.2				
(VIIb)	351, 337, 300,* 285	1640		Nujol	6.03 (s)	4.63 (m)		8.02 (t)				2.58—3.80 (m)		5.0			1.2		1.2	
(VIIc) §	344, 300,* 281	1642		Film	6.30 (s)	5.93 (m)	4.66 (m)	8.06 (t)				2.85—3.80 (m)	2-Bun, 8.30—9.30 (m)	5.0			1.5		1.5	2 $\alpha$ , 7.0
(VIIa)	343, 314, 300,* 275	1642		Nujol	6.78 (s)	6.12 (m)	4.81 (m)	8.23 (q)				3.21—4.07 (m)		5.0			2.0		2.0	

\* Infection. † With Pr(fod)<sub>3</sub> (0.034 mol. equiv.). ‡ With Eu(fod)<sub>3</sub> (0.035 mol. equiv.). § Contains 3% 2-butyl-4-methylquinoline.

I.r. spectra of compounds (VI) are not very helpful. The distinct band at 1640—1642 cm<sup>-1</sup> which we observe for the conjugated olefinic bond in the 1,2-dihydroquinolines (VII) is masked by the strong carbonyl absorption. The u.v. spectra are, surprisingly, similar to those reported for 1,4-<sup>14b</sup> or 3,4-dihydroquinolines.<sup>17</sup> However, the Reissert compounds (VIII),<sup>18,19</sup> to which the present compounds (VI) bear a structural resemblance, show similar u.v. spectra,<sup>19</sup> and these compounds (VIII) have been shown to contain the 1,2-dihydroquinoline nucleus.<sup>18</sup>

The preceding evidence points to the mode of addition of organolithium reagents to quinolines being 1,2- rather than 1,4-. In the accompanying paper,<sup>20</sup> independent evidence for this mode of addition is presented.

#### EXPERIMENTAL

4-Methylquinoline was prepared from aniline hydrochloride and methyl vinyl ketone<sup>21</sup> and redistilled prior to use, as were quinoline, ethyl chloroformate, bromobenzene,

\* Analysis figures for 2-*n*-butyl-1,2-dihydroquinoline are given in ref. 3; in other cases the presence of the dihydroquinoline has been assumed.

<sup>15</sup> W. S. Johnson and B. G. Buell, *J. Amer. Chem. Soc.*, 1952, **74**, 4517.

<sup>16</sup> K. W. Rosenmund, F. Zymalkowski, and N. Schwartz, *Chem. Ber.*, 1954, **87**, 1229.

<sup>17</sup> I. Murakoshi, *J. Pharm. Soc. Japan*, 1959, **79**, 72.

*The N-Ethoxycarbonyl Derivatives (VIa—c).*—By carefully following the previously recorded procedures<sup>10</sup> compound (VIa) was obtained as a yellow oil, b.p. 172—174° at 1 mmHg (65%); (VIb) as needles, m.p. 74—75° (from aqueous ethanol) (69%); and (VIc) as a pale yellow oil, b.p. 127—130° at 0.5 mmHg (61%).

*Ethyl 1,2-Dihydro-4-methylquinoline-1-carboxylate (VIId).*—To a stirred ethereal solution of 1,2-dihydro-4-methylquinoline (VIId)<sup>16</sup> (9.0 g, 0.063 mol) was added, dropwise, a solution of ethyl chloroformate (10.85 g, 0.1 mol) in ether. The solvent boiled and a white precipitate was formed. Stirring was continued for 30 min; the mixture was then hydrolysed with water. The resulting ethereal solution was extracted with 2*N*-hydrochloric acid (2 × 50 cm<sup>3</sup>), then dried (Na<sub>2</sub>SO<sub>4</sub>) and fractionated under reduced pressure to give compound (VIa) (10.2 g, 47%), b.p. 109° at 0.2 mmHg (Found: C, 71.6; H, 6.9; N, 6.4. C<sub>13</sub>H<sub>15</sub>NO<sub>2</sub> requires C, 71.8; H, 6.9; N, 6.45%). Spectra are recorded in the Table.

*The 1,2-Dihydroquinolines (VII).*—Except for 1,2-dihydro-4-methylquinoline (VIIId)<sup>16</sup> the 2-substituted 1,2-dihydroquinolines (VII) were prepared (in 80—84% yields) from the appropriate organolithium (0.1 mol) and quinoline (0.1 mol)

<sup>18</sup> W. E. McEwan and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511.

<sup>19</sup> R. F. Collins and T. Henshall, *J. Amer. Chem. Soc.*, 1958, **80**, 159; V. Boekelheide and J. Weinstock, *ibid.*, 1952, **74**, 660; W. E. McEwan, R. H. Terss, and I. W. Elliott, *ibid.*, p. 3605.

<sup>20</sup> A. I. C. Scopes and J. A. Joule, following paper.

<sup>21</sup> K. N. Campbell and I. J. Schaffner, *J. Amer. Chem. Soc.*, 1945, **67**, 86.

in ether at 0° under dried nitrogen. Hydrolysis with water (previously degassed with nitrogen) produced yellow ethereal solutions which were dried ( $\text{Na}_2\text{SO}_4$ ) and distilled under reduced pressure to give pale yellow oils. 1,2-*Dihydro-2-phenylquinoline* (VIIa) gave needles, m.p. 49—50° [from ethanol-water and then from petroleum (b.p. 40—60°)] (Found: C, 86.8; H, 6.3; N, 6.6.  $\text{C}_{15}\text{H}_{13}\text{N}$  requires C, 86.9; H, 6.3; N, 6.75%). Similarly, 1,2-*dihydro-4-methyl-*

*2-phenylquinoline* (VIIb) gave needles, m.p. 62° (Found: C, 86.8; H, 6.75; N, 6.3.  $\text{C}_{16}\text{H}_{15}\text{N}$  requires C, 86.8; H, 6.8; N, 6.3%). The 2-n-butyl derivative (VIIc) was further distilled, b.p. 138—140° at 1 mmHg, but could not be obtained completely free from 2-n-butyl-4-methylquinoline (Vc) [about 3% of (Vc) was indicated by n.m.r.]. Spectra for these compounds are recorded in the Table.

[2/1196 Received, 25th May, 1972]

---