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REINVESTIGATION OF APPARENT 1,4-ADDITION AND REARRANGEMENT IN THE REACTIONS OF QUINOLINES WITH ORGANOLITHIUM COMPOUNDS

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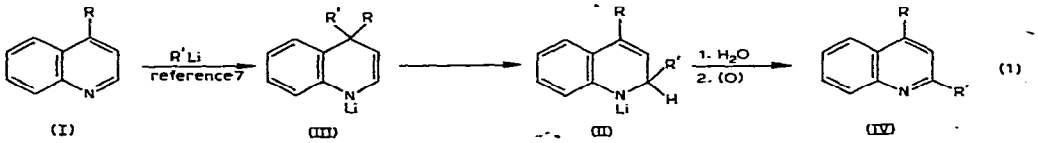
SUMMARY

The recent claim of Otsuji, Yutani and Imoto[7] that both n-butyllithium and phenyllithium gave isolable 1,4-adducts with lepidine (4-methylquinoline) has been reinvestigated. Such adducts were reportedly captured in the form of their *N*-ethoxycarbonyl derivatives. In the present study these same *N*-ethoxycarbonyl derivatives have been prepared and examined by NMR and IR spectroscopy. Moreover, the corresponding *N*-(ethoxycarbonyl)-n-butyldihydro and *N*-(ethoxycarbonyl)phenyldihydro derivatives have now been prepared from 2-deuteriolepidine. An analysis of the spectroscopic data leads to the clear conclusion that all such derivatives are really 2-substituted-1,2-dihydrolepidines. Consequently, all the discussion published in ref. 7, concerning a 1,4-addition of organolithium reagents to the quinoline nucleus and the subsequent rearrangement to the 1,2-adduct, becomes unfounded.

INTRODUCTION

The attack of various organo-lithium[1-3] and -magnesium[4-6] reagents on the quinoline nucleus (I) has been shown to yield, after hydrolysis and oxidation of the intermediate dihydro derivative, principally the 2-substituted quinoline nucleus (IV). Since all previous work[1-6] had assumed such dihydro intermediates to be of the 2-substituted-1,2-dihydro type (II), the recent claim of Otsuji, Yutani and Imoto[7] that such intermediates are really of the 4-substituted-1,4-dihydro type (III) was clearly of unusual significance. According to these workers, if intermediates such as (III)

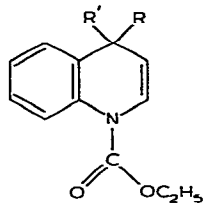


were not trapped in the form of stable derivatives, they underwent rearrangement to yield the usual 2-substituted-1,2-dihydro derivatives (II), which then led to the previously observed products [(IV), eqn. (1)]. Their support for this novel mechanistic proposal depends on the validity of their spectral identification of the *N*-ethoxycar-

bonyl derivatives of presumably intermediate (III), which derivatives were obtained by the addition of ethyl chloroformate to the intermediate. Derivatives assigned the general structure (V) were thus obtained from lepidine and phenyllithium (Va), from lepidine and butyllithium (Vb), and from quinoline and phenyllithium (Vc). The NMR and infrared spectral data were interpreted with the help of published tabulations of $J_{2,3}$ values for certain 1,4-dihydroquinolines[8] and known C=C stretching absorptions[10].

RESULTS AND DISCUSSION

The arresting nature of this mechanistic pathway [eqn. (1)] prompted us to re-examine the structural assignments of products (Va) and (Vb). Accordingly, substances identical in physical properties with those described in the previous work[7]



(Va), R=CH_3 R'=C_6H_5
(Vb), R=CH_3 R'=n-C_4H_9
(Vc), R=H R'=C_6H_5

were prepared in strict conformity with the published procedures. Introduction of lepidine into an ethereal solution of either phenyllithium or butyllithium at room temperature, followed by the addition of ethyl chloroformate, led to ca. 50% of the *N*-ethoxycarbonyl derivatives (VIIa) and (VIIb). Furthermore, 2-deuteriolepidine[9] (>99% homogeneous by NMR and MS data) was converted, by turns, into the corresponding *N*-(ethoxycarbonyl)-phenyldihydro (VIIc) and -butyldihydro (VIId) derivatives. The NMR spectra of the derivatives of undeuterated lepidine (VIIa and VIIb) are reproduced in Fig. 1 and those of the 2-deuteriolepidine in Fig. 2. Although the spectra in Fig. 1 resemble the published spectra of substances assigned[7] structures (Va) and (Vb), respectively, those in Fig. 1 exhibit a cleaner resolution in several of the peaks. Upon analysis of the spectra given in Fig. 1 and 2, the following points can be made: (*a*) the published assignment of the doublet at 5.86 ppm to the 2-H is incorrect; (*b*) the 2-H in (VIIb) occurs as a quartet (*J* 5.75 Hz) at 4.88 ppm, not as a doublet as the previous[7], poorly resolved spectrum of the supposed (Vb) indicates; (*c*) the spectra of the *N*-(ethoxycarbonyl)butyldihydro derivative and its 2-deuterio counterpart are decisively interpretable in favor of the 2-butyl-1,2-dihydro structure [(VIIb), (VIId)] and cannot be brought into accord with the previous assignment as (Vb); (*d*) the 3-H of (VIIb) occurs as the doublet at 5.86 ppm (*J* 5.75 Hz), each of whose components is further split into a quartet (*J* 1.25 Hz) by the 4-CH_3 group; also, the well-resolved spectrum reveals the splitting of the 4-CH_3 group into a doublet (*J* 1.25 Hz); (*e*) the spectra of the corresponding phenyl derivative, the supposed (Va), and its 2-deuterio counterpart confirm the published assignment of the 2-H to the downfield component (at 6.15 ppm) of the AB pattern but the chemical shift and its coupling

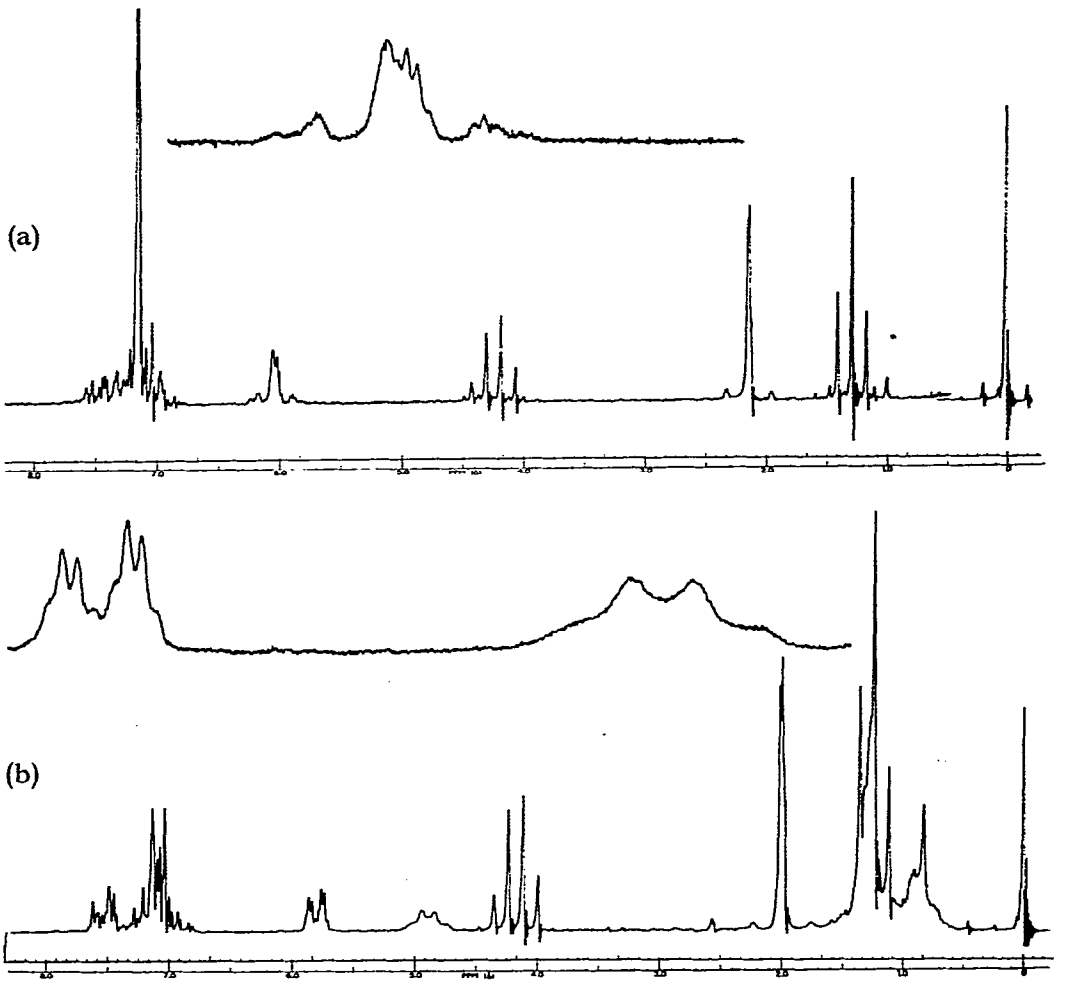


Fig. 1. (a), NMR spectrum of *N*-ethoxycarbonyl-2-phenyl-1,2-dihydroquinoline (VIIa) in CCl_4 with internal TMS (δ-scale). (b) NMR spectrum of *N*-ethoxycarbonyl-2-butyl-1,2-dihydroquinoline (VIIb) in CCl_4 with internal TMS (δ-scale).

constant with 3-H ($J_{2,3}$ 6.5 Hz) do not clearly indicate that 2-H is necessarily a vinylic hydrogen, as the previous workers[7] conclude [the chemical shifts of the saturated $>N-\underset{|}{C}-H$ protons in model compounds such as 5-benzoyl-6-phenyl-5,6-dihydrophenanthridine and the 5-ethoxycarbonyl derivative (VI) are >6.0 ppm and the $J_{2,3}$ of (Va) is within the limits observed for known 1,2-dihydroquinolines[8] ($J_{2,3}$ 4.6 to 6.8 ± 0.5 Hz)]; (*f*) the better resolution in Fig. 1 reveals that the upfield component at 6.00 ppm, due to the 3-H, is further split by the 4-CH_3 group (J 1.0 Hz); and (*g*) the 4-CH_3 group in (VIIa), occurring at 2.08 ppm and exhibiting a doublet (J 1.0 Hz) due to splitting by the 3-H, is very similar in chemical shift and coupling constant to that of the methyl group in lepidine itself (doublet at 2.25 ppm; J 1.0 Hz). Moreover, upon a re-examination of the infrared spectra of (VIIa) and (VIIb), one can discern

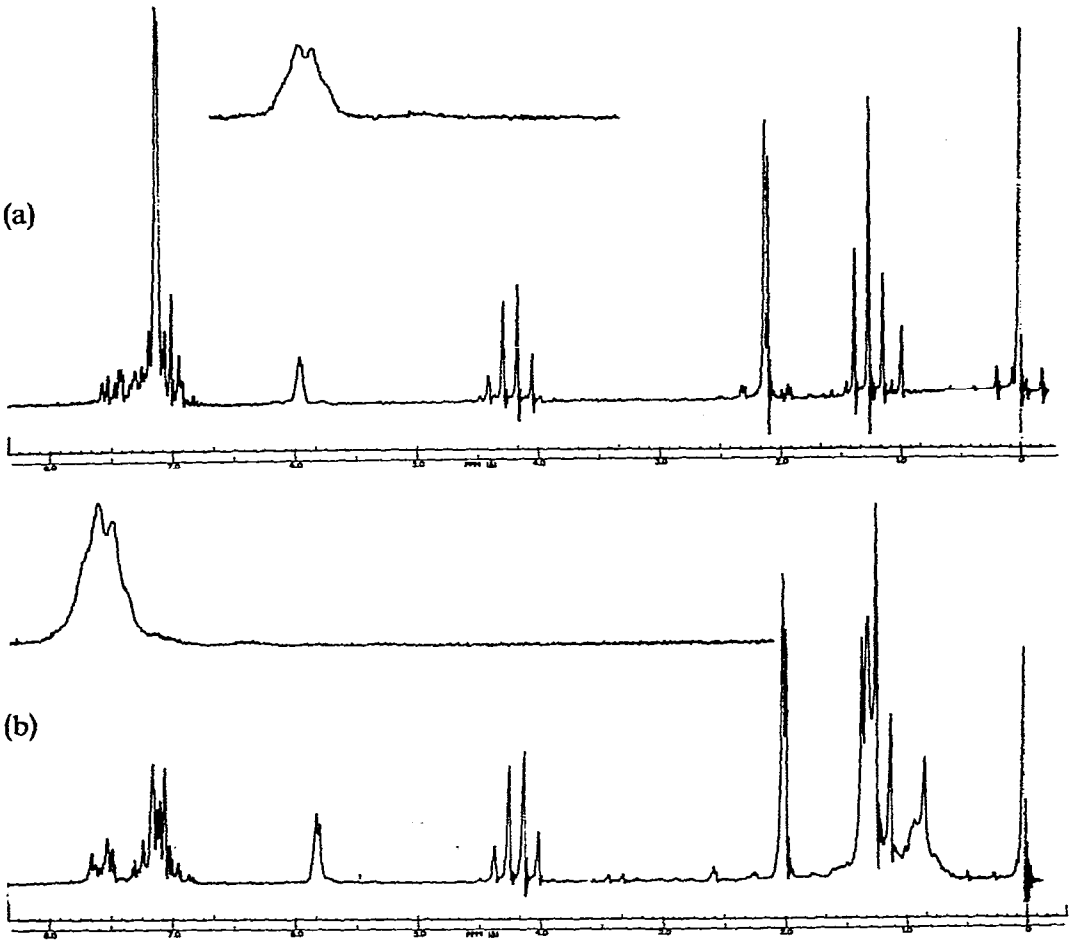
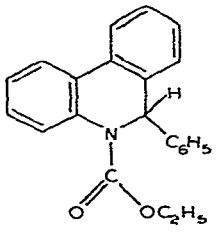


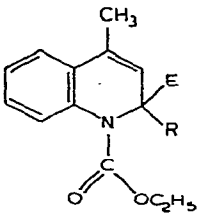
Fig. 2. (a) NMR spectrum of *N*-ethoxycarbonyl-2-deuterio-2-phenyl-1,2-dihydroquinoline (VIIc) *in* CCl_4 with internal TMS (δ-scale). (b) NMR spectrum of *N*-ethoxycarbonyl-2-deuterio-2-butyl-1,2-dihydroquinoline (VIId) *in* CCl_4 with internal TMS (δ-scale).



(VI)

the weak but distinct absorptions present at 1610 and 1580 cm^{-1}, which are characteristic of a C=C stretch conjugated with an aromatic system[10].

The foregoing spectral observations force us to conclude that structures (Va) and (Vb) cannot be correct for the *N*-ethoxycarbonyl derivatives of the addition products of lepidine with phenyllithium and with butyllithium, respectively. Rather



(VIIa), E=H R=C_6H_5
(VIIb), E=H R=n-C_4H_9
(VIIc), E=D R=C_6H_5
(VIId), E=D R=n-C_4H_9

we believe that the spectral properties are in best accord with structure (VIIa) for the phenyl derivative and with structure (VIIb) for the butyl derivative. With this conclusion, all previous discussion[7] of a "rearrangement" occurring to change the supposedly initial product (III) into the final 2-substituted product (IV) becomes unfounded and thus premature. Rearrangements may yet be uncovered in the reactions of quinolines with organometallic reagents; indeed, treatment of (VIIa) with sodium hydroxide dissolved in aqueous dimethyl sulfoxide is claimed[7] to yield 87.5% of 2-phenyllepidine, 7.5% of 2-phenylquinoline and 5% of 4-phenylquinaldine*. Possibly organometallic rearrangements may be instigated in this case by the dimethylsulfinyl carbanion, but the variegated chemical behavior of dimethyl sulfoxide, as oxidant, as methylating agent and as base, leaves the proposal[7] of a simple rearrangement mechanism, even for these hydrolysis products, exposed to many uncertainties. Clearly, the action of alkaline dimethyl sulfoxide solution on substrates such as (VII) requires further study.

EXPERIMENTAL

Starting materials

The lepidine (K and K Laboratories) was redistilled under nitrogen and checked for purity (>99%) by GLP chromatography and NMR spectroscopy before use. 2-Chlorolepidine (Eastman), bromobenzene (Baker), ethyl chloroformate (Aldrich) and anhydrous diethyl ether (Mallinckrodt) were of reagent-grade purity as received, as were all solvents used in spectral measurements.

Procedures

All organometallic reaction solutions were maintained under an atmosphere of dry, oxygen-free nitrogen until they were worked up by final treatment with water. Infrared spectra of samples in chloroform solution were recorded on a Perkin–Elmer spectrophotometer, model 137; mass spectra with a Varian–Atlas instrument, model CH-5; and NMR spectra of samples in $CDCl_3$ or CCl_4 with a Varian spectrometer,

* Our treatment of (VIIc) with sodium ethoxide in ethanol or with potassium tert-butoxide in tert-butyl alcohol led to the recovery of (VIIc), which had undergone little, if any exchange to form (VIIa). Treatment of (VIIc) with potassium tert-butoxide in dimethyl sulfoxide, however, smoothly yielded 2-phenyllepidine.

model A-60. The NMR spectral data are reported in the δ-scale (ppm downfield from internal tetramethylsilane). Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. The melting points were taken in capillaries, sealed under nitrogen where necessary and are uncorrected.

2-Deuteriolepidine

According to a recent procedure for the preparation of 2-deuterioquinoline[9], a suspension of 12.1 g (0.102 g-atom) of powdered tin metal and 14.5 g (0.082 mole) of 2-chlorolepidine in 75 ml of deuterium oxide (99.8%) was stirred at 70° for 15 min. Then 26.0 g (0.17 mole) of phosphorus oxychloride was introduced in a dropwise manner. Usual further heating and distillative work-up provided a 73% yield of 2-deuteriolepidine. The intensity of the mass spectral peak at *m/e* 144 showed that the product was at least 99% monodeuterated. Spectral data: IR, characteristic absorptions at 890, 1090 and 2250 (C–D stretch) cm^{-1}; NMR (CCl_4), 2.3 (doublet, *J* 1.0 Hz, 3H), 6.6 (br, singlet, 1H), 6.9–7.5 (multiplet, 3H) and 7.7–7.9 ppm (complex doublet, 1H).

1-Ethoxycarbonyl-2-n-butyl-4-methyl-1,2-dihydrolepidine (VIIb) and its 2-deuterio derivative (VIId)

The compounds were prepared from lepidine, or 2-deuteriolepidine respectively, by faithful adherence to the published directions[7]. The twice-distilled product was a pale yellow oil, b.p. 124–125°/0.1 mm. The NMR spectra of the samples in CCl_4 solution are reproduced in Fig. 1b and Fig. 2b, respectively. Mass spectra revealed the appropriate parent ions of *m/e* 273 and *m/e* 274, respectively. In addition to the published[7] infrared spectral data, neat spectra of both compounds exhibited weak, but sharp, distinct absorptions at 1580 and 1610 cm^{-1}

1-Ethoxycarbonyl-4-methyl-2-phenyl-1,2-dihydroquinoline (VIIa) and its 2-deuterio derivative (VIIc)

Again, the published directions[7] were followed strictly for both lepidine and 2-deuteriolepidine. Upon recrystallization from an ethanol/water pair, the product formed colorless needles, m.p. 73–75° (and 72–74°). The NMR spectra of the samples in CCl_4 solution are reproduced in Fig. 1a and Fig. 2a, respectively. Mass spectral parent peaks were observed at *m/e* 293 and *m/e* 294, respectively. Again, re-examination of the infrared spectra of samples in $CHCl_3$ uncovered weak, but distinct bands at 1580 and 1610 cm^{-1}.

5-Ethoxycarbonyl-6-phenyl-5,6-dihydrophenanthridine (VI)

A solution of 0.075 mole of phenyllithium in diethyl ether was added dropwise to an ice-cold solution of 9.0 g (0.05 mole) of phenanthridine in 100 ml of anhydrous tetrahydrofuran. The dark-green reaction solution was then allowed to stir for 24 h at room temperature*. After cooling to 0°, the reaction mixture was treated with a solution of 7.8 g (0.072 mole) of ethyl chloroformate dissolved in 50 ml of tetrahydrofuran. After a one-hour stirring period, usual[7] hydrolytic work-up yielded a dark oil.

* Hydrolytic work-up of an identical reaction mixture at the end of this time led to essentially a quantitative yield of 6-phenyl-5,6-dihydrophenanthridine (C. A. Kovacs).

Crystallization from absolute ethanol afforded a colorless solid,m.p. 97–99°. (Found: C, 79.84; H, 5.74. $C_{22}H_{19}NO_2$ calcd.: C, 80.22; H, 5.81%.) The mass spectrum displayed the parent ion at *m/e* 329. The NMR spectrum in CCl_4 showed resonances at 1.28 (triplet, 3H), 4.25 (quartet, 2H), 6.73 (singlet, 1H), 7.02 (singlet, 5H) and 7.1–7.9 ppm (multiplet, 8H).

The NMR spectrum of 5-benzoyl-6-phenyl-5,6-dihydrophenanthridine[11] in $CDCl_3$ also displayed its 6-H at 6.60 ppm.

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