

A Novel Observation on the Lithiation of 2-Iodo-3-hydroxymethylquinoline

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In the metallation of 2-iodo-3-hydroxymethylquinoline (**3**) with BuⁿLi (−78 °C), the halogen–metal exchange is shown to be faster than the hydrogen (of the OH group)–metal exchange.

2-Lithioquinolines are readily obtained by halogen–metal exchange reactions. The 2-lithioquinoline (**2**), for example, was obtained recently in this way from 2-iodo-3-(1,3-dioxolan-2-yl)quinoline (**1**).¹ The halogen–metal exchange reaction is carried out at low temperatures (−60 to −78 °C) to avoid or decrease the extent of the competing nucleophilic substitution reaction leading to 2-butylquinolines.

In connection with another study we required 2-substituted 3-hydroxymethylquinolines. It was planned to obtain these compounds from 2-iodo-3-hydroxymethylquinoline (**3**) by a halogen–metal exchange reaction with BuⁿLi *via* the 2-lithio compounds. It was hoped that the latter, on treatment with appropriate electrophiles, would furnish the target compounds.

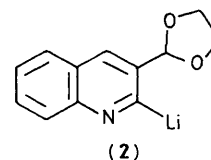
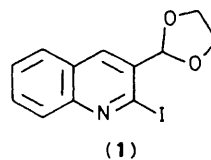
With the above purpose in mind, (**3**) was treated [−78 °C, tetrahydrofuran (THF)] with BuⁿLi (diethyl ether). Two mole equivalents of BuⁿLi were used, one for reaction with the OH group and the other for the exchange reaction. In order to detect the formation of the 2-lithio compound, the metallation mixture was first stirred with D₂O (10 min) and then with H₂O. Surprisingly, however, the expected 2-deuterioquinoline (**12**) was not obtained but only the simple quinoline (**6**) (yield 92%). In this reaction, presumably, the 2-lithioquinoline (**8**) had formed; otherwise, the replacement of iodine by hydrogen would not have occurred.

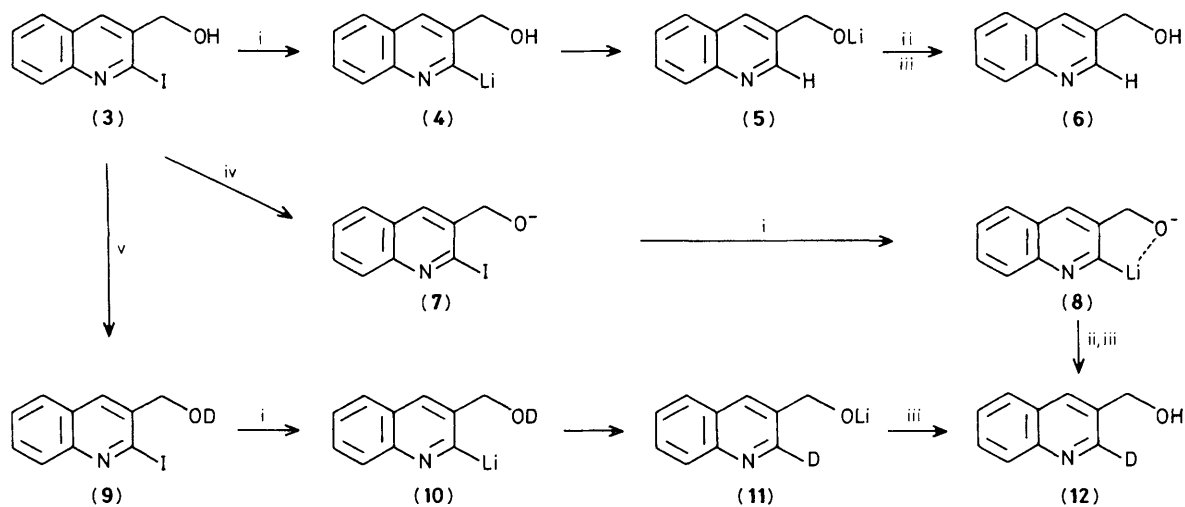
The failure to obtain (**12**) in the above reaction may be due to the reaction of (**8**) with the solvent. Aromatic lithio compounds are known to react with solvents such as THF.² Alternatively, it is possible that the first reaction of BuⁿLi with the substrate is not with the OH group, as normally expected, but with the halogen in a halogen–metal interconversion reaction. Indeed, it is reported that cross-metallation reactions (ArX + BuLi → ArLi + BuBr) are at least as fast and probably faster than the reaction of BuⁿLi with water or ClSiMe₃.³

The results obtained can be rationalised by the following sequence: in the metallation reaction the 2-lithio compound (**4**) is formed first. This then undergoes an intramolecular hydrogen transfer reaction (from the OH group) to give (**5**). At −78 °C the latter does not react further with BuⁿLi, which would then be present only in one mole excess. The last point was checked by an independent experiment. In this, when compound (**6**) was first converted into the alkoxide (**5**) by treatment with NaH (THF, −40 °C, 2 h), and then reacted with one mole of BuⁿLi (−78 °C), workup with water gave only the starting compound (**6**) (recovery 93%).

The above sequence was further established by two experiments. In the first experiment, when compound (**3**) was first converted into the alkoxide (**7**) by treatment with NaH (THF, −40 °C, 2 h) and then reacted with BuⁿLi, further reaction with D₂O first and then with H₂O gave the expected 2-deuterioquinoline (**12**) (83%, 85% D by ¹H n.m.r.). The reaction succeeds because there is no OH group for the intramolecular hydrogen transfer reaction. In the second experiment, when the alcohol (**3**) was first converted into the *O*-deuterated compound (**9**) and then reacted with BuⁿLi, further reaction even with H₂O alone gave (**12**) (91%, 83% D by ¹H n.m.r.). In this case the 2-lithio intermediate (**10**) itself would give the 2-deuterio compound (**12**) by a deuterium transfer reaction (from the OD group).

The study clearly establishes that, in the reaction of 2-iodo-3-hydroxymethylquinoline (**3**) with BuⁿLi, the halo-





Reagents: i, BuⁿLi, THF, -78 °C; ii, D₂O, 10 min; iii, H₂O; iv, NaH, -40 °C, 2 h; v, D₂O.

gen-metal exchange reaction is faster than hydrogen (of the OH group)-metal exchange.

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