

Mechanism of Substitution of Quinolines with Organometallic Reagents

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The reactions of quinoline and 4-methylquinoline with organolithium reagents proceed by attack at C-2 to give 1,2-dihydro-1-lithio-intermediates, which can be trapped with ethyl chloroformate, and not 1,4-dihydro-1-lithio-intermediates as suggested recently.

It has been proposed¹ that the commonly observed 2-substitution² of quinolines by organolithium reagents proceeds by initial C-4 addition followed by sigmatropic rearrangement of the substituent to C-2 before standard loss of C-2 hydride (to an oxidant). This proposal was made on the basis of the isolation of three urethanes, which were assigned structures (1a—c), from reactions of 4-methylquinoline with phenyl-lithium and butyllithium and of quinoline with phenyl-lithium followed by treatment with ethyl chloroformate. The urethanes were considered to arise by trapping of the postulated C-4 adducts. Since this mechanism for nucleophilic substitution of quinolines is at variance with the generally accepted view of such reactions,³ and since it seemed that the spectral evidence presented¹ for structures (1a—c) could be interpreted in terms of 1,2-dihydro-systems (2a—c), which would be formed from the traditional² C-2 adducts, we have reinvestigated the three urethanes.

Recently a detailed re-examination⁴ of the n.m.r. spectra of the urethanes has provided strong evidence in favour of structures (2a and b); a detailed account of this work is given in the preceding paper.⁵ † This and the investigation described here prove that the urethanes do indeed have structures (2a—c).

Hydrogenation of the three urethanes in ethanol over platinum proceeded smoothly and rapidly to a dihydro-level to give compounds assigned structures (3a—c) [derivable from (2a—c)] and *not* (3d—f) [as would have been obtained from compounds (1a—c)].

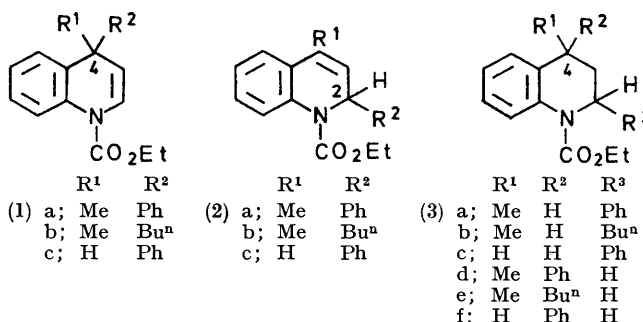
In the n.m.r. spectrum of (3a) the methyl group resonated as a doublet (τ 8.70, J 7 Hz), shown by decoupling to be split by the C-4 proton (τ 7.10—7.40). No such coupling would be possible for structure (3d), in

† Since this work was finished we have learnt of other work which also concludes that the urethanes are 2-substituted (J. J. Eisch and D. R. Comfort, *J. Organometallic Chem.*, 1972, **38**, 209).

¹ Y. Otsuji, K. Yutani, and E. Imoto, *Bull. Chem. Soc. Japan*, 1971, **44**, 520.

² K. Zeigler and G. Zeiser, *Annalen*, 1931, **485**, 174.

which the methyl group would be on a quaternary carbon atom.



In the more complex methyl region in the spectrum of compound (3b) it was not possible to be sure that there was no methyl singlet, though a simplification in this region did result from irradiation at τ 7.45. The structure of compound (2b) has been unambiguously established by the observation^{4,5} of a 6.2 Hz coupling, not evident in the published¹ spectrum, between the C-2 proton and the adjacent methylene group of the butyl substituent.

In order to establish the structure of compound (3c), an authentic sample was prepared by reduction of 2-phenylquinoline followed by ethoxyformylation to give the saturated urethane (3c), identical with that obtained by the alternative route.

The structures now established for the three urethanes are in line with the standard view that attack by organometallic reagents on pyridines and benzopyridines takes place predominantly at a carbon atom adjacent to the

³ For proof of structure of the analogous 1,2-adduct in the pyridine series see R. Foster and C. A. Fyfe, *Tetrahedron*, 1969, **25**, 1489; G. Fraenkel and J. G. Cooper, *Tetrahedron Letters*, 1968, 1825; C. S. Gian and J. L. Stout, *Chem. Comm.*, 1969, 142.

⁴ C. E. Crawforth, O. Meth-Cohn, and C. A. Russell, *J.C.S. Chem. Comm.*, 1972, 259.

⁵ C. E. Crawforth, O. Meth-Cohn, and C. A. Russell, preceding paper.

azomethine nitrogen. It is unnecessary to postulate attack on quinolines at C-4 followed by rearrangement.

EXPERIMENTAL

Hydrogenations.—The urethanes (2a—c) were hydrogenated in ethanol at room temperature over platinum at atmospheric pressure for 20—30 min. In each case the reaction was worked up by filtration, evaporation, and partition between ether and water. The ethereal phase was dried and the ether removed *in vacuo*. The product was purified by dry column chromatography on silica gel.

Ethyl 1,2,3,4-tetrahydro-4-methyl-2-phenylquinoline-1-carboxylate (3a) was a glass, λ_{\max} (EtOH) 239, 268, and 274infr nm, ν_{\max} (film) 1707s cm^{-1} , τ (CCl_4), 2.51 (1H, dd, J 8.5 and 0.75 Hz, 8-H), 2.74—3.04 (8H, m, ArH), 4.77 (1H, dd, J 11 and 8 Hz 2-H), 5.98 (2H, q, J 7 Hz, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$), 7.10—7.40 (1H, m, 4-H), 7.40—7.75 (1H, m, 3-H), 8.70 (3H, d, J 7 Hz, 3H₃), 8.40 to *ca.* 8.80 (1H, m, 3-H), and 8.90 (3H, 7, J 7 Hz, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$), *m/e*, 295 (M^+ , 93%), 222 (100), 218 (28), 206 (45), 146 (27), 144 (28), 130 (45), and 91 (50) (Found: C, 77.1; H, 7.1; N, 5.0. $\text{C}_{19}\text{H}_{21}\text{NO}_2$ requires C, 77.3; H, 7.2; N, 4.7%). **Ethyl 2-butyl-1,2,3,4-tetrahydro-4-methylquinoline-1-carboxylate (3b)** was a glass, λ_{\max} (EtOH), 238, 268, and 274infr nm, ν_{\max} (film) 1702s cm^{-1} , τ (CCl_4) 2.72—3.05 (4H, m, ArH), 5.44 to *ca.* 5.80 (1H, m, 2-H), 5.90—5.93 (2H, 2 overlapping q, J 7 Hz, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$), 7.28 to *ca.*

7.60 (1H, m, 4-H), *ca.* 7.60—7.83 (1H, m, 3-H), 8.20—8.90 (13H, m, 4- CH_3 , $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$, $[\text{CH}_2]_3$, and 3-H), and 9.00—9.24 (3H, m, $[\text{CH}_2]_3\cdot\text{CH}_3$), *m/e* 275 (M^+ , 32%), 219 (27), 218 (100), 174, (22), 146 (66), 132 (39), and 130 (27) (Found: C, 74.1; H, 9.0; N, 4.7. $\text{C}_{17}\text{H}_{25}\text{NO}_2$ requires C, 74.1; H, 9.2; N, 5.1%). **Ethyl 1,2,3,4-tetrahydro-2-phenylquinoline-1-carboxylate (3c)** was a glass, λ_{\max} (EtOH) 239, 268, and 276infr nm, ν_{\max} (film) 1708s cm^{-1} , τ (CCl_4), 2.27 (1H, d, J 8.5 Hz, 8-H), 2.70—3.22 (8H, m, ArH), 4.59 (1H, dd, J 6 and 8 Hz, 2-H), 5.96 (2H, q, J 7 Hz, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$), 7.34 to *ca.* 7.56 (2H, m, 4-H), *ca.* 7.56—7.80 (1H, m, 3-H), 7.96—8.32 (1H, m, 3-H), and 8.87 (3H, t, J 7 Hz, $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$), *m/e* 281 (M^+ , 100%), 208 (98), 206 (43), 132 (46), 130 (57), 105 (48), 104 (34), 103 (33), and 91 (89) (Found: C, 77.3; H, 7.1; N, 4.5. $\text{C}_{18}\text{H}_{19}\text{NO}_2$ requires C, 76.8; H, 6.8; N, 5.0%).

Ethoxyformylation of 1,2,3,4-Tetrahydro-2-phenylquinoline.—The urethane (3c) was prepared by the reaction of ethyl chloroformate with 1,2,3,4-tetrahydro-2-phenylquinoline^{2,6} in pyridine at room temperature. The product was purified by dry-column chromatography, and was identical with that just described.

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⁶ W. Oldham and I. B. Johns, *J. Amer. Chem. Soc.*, 1939, **61**, 3239.