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DOUBLE MIGRATION OF METHYL AND BROMINE ACCOMPANYING INDENO[1,2,3-*de*]QUINOLINONE FORMATION

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Abstract—The migration of two substituents, methyl and bromine, around an aryl ring is described, and interpreted in terms of consecutive 1,2-shifts. The diagnostically useful shielding of the C-5 proton in 3-chloro-4-phenylquinolinones is reported.

We recently reported[2] that migration of two substituents, Me and Cl, around an aryl ring, accompanied the cyclisation of anilide **1a** to indeno[1,2,3-*de*]quinolin-2(3H)-one **2a**. This "double" migration, for which there appear to be few precedents, has now been demonstrated for Me and Br using the related bromo substrate **1b**.

Concentrated sulphuric acid converted **1b** into a yellow, high-melting product [$C_{17}H_{11}BrClNO$, by elemental and mass spectral analysis; $\nu_{C=O}$ 1640 cm^{-1} (amide CO), ν_{C-H} 750 cm^{-1} (four adjacent aromatic protons)] in ~50% yield, which by analogy with the earlier work[2] was assigned structure **2b**. Moreover, this is the most plausible assignment considering that the synthesis proceeds via a "direct" cyclisation mechanism.[1] Product **2b** was contaminated with negligible dichloro impurity, while minor peaks in the mass spectrum were correlated with both debrominated and dibrominated indenoquinolinones, indicative of disproportionation of bromine during reaction.

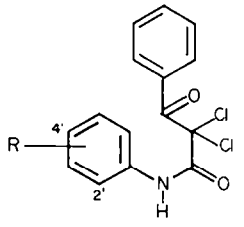
H-bonding in the product precluded sufficient solubility in ^{1}H NMR-useful solvents. A satisfactory spectrum was obtained with the chloroform-soluble 2-chloro derivative **3** (from **2b** and thionyl chloride-dimethylformamide). This displayed a deshielded one-proton double doublet near δ 8.0 for the C-10 proton, arising from the anisotropic effect of the neighbouring C-1 chlorine substituent,[1] and multiplets for the remaining three aromatic protons in the region δ 7.2–7.5. The spectrum unequivocally confirmed the absence at C-6 of a bromine substituent.

In the absence of an X-ray crystal structure determination, confirmation of assignment **2b** was sought by the method[2] of comparing the product with that derived from the isomeric anilide **1c**. It was expected that **1c** would give rise to indenoquinolinone **2b** by a "direct" cyclisation, with no migration of substituents. Accordingly, **1c** was treated with sulphuric acid to furnish **2b** in 22% yield. Infrared and mass spectral comparison showed this material to be identical with that derived from **1b**; minor differences in the spectra stemmed from the presence of high-melting impurities in the specimens. Finally, the separate 2-chloro derivatives likewise proved to be the same **3**.

The "double" migration of Me and halogen is currently envisaged as consecutive 1,2-migrations commencing from **b** (Scheme 1) and leading to **2**. The postulated initial transfer of Me, as in **b**→**c**, as well as the subsequent preferential migration of halogen, **c**→**d**, may occur *via* a σ or π complex. Finally, expulsion of H^+ from **d** results in the rearranged product **2**. Disproportionation of bromine during the cyclisation of **1b** may result by loss of Br^+ from an entity such as **c** or **d**, leading to **2c** and **2d**. The sequence in Scheme 1 is an improvement over our earlier speculations[2] on the "double" migration.

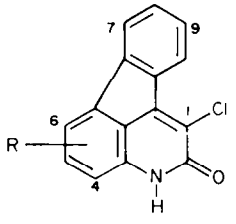
Whereas negligible quinoline **4** accompanied **2b** from **1b**, it was the chief product from **1c**. Thus, the substituted 4-phenylquinolin-2(1H)-one, **4a**, identified from its spectral characteristics, was isolated in 61% yield. This striking disparity in quinolinone **4** production from **1** bearing a *para*-halogen vs **1** bearing a *meta*-halogen is a consequence of the conjugative effect of the former halogen promoting indenoquinolinone **2** formation,[1] as indicated in **a** (Scheme 1).

Of interest in the ^{1}H NMR spectrum of **4a** was the diagnostically-useful shielding of the C-5 proton which appeared as a singlet upfield at δ 6.78 ($CDCl_3$). This effect is attributed to the influence of the 4-phenyl substituent which is forced out of plane to the rest of the molecule by steric interaction with the C-3 Cl atom; the C-5 proton consequently lies in the shielding cone of the twisted ring. In support, the C-5 proton appeared as a singlet for **4b** (δ 6.94), derived by N-ethylation of **4a**, and



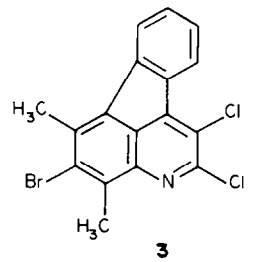
1

a: R = 4'-Cl-2',5'-diCH$_3$
b: R = 4'-Br-2',5'-diCH$_3$
c: R = 3'-Br-2',4'-diCH$_3$



2

a: R = 5-Cl-4,6-diCH$_3$
b: R = 5-Br-4,6-diCH$_3$
c: R = 5-H-4,6-diCH$_3$
d: R = 5,9-diBr-4,6-diCH$_3$



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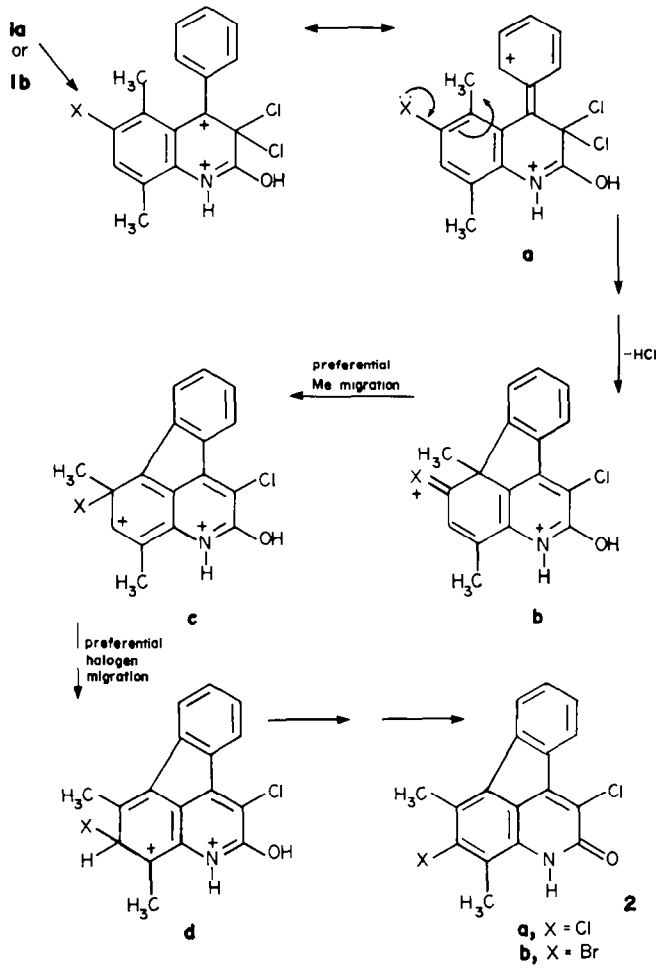
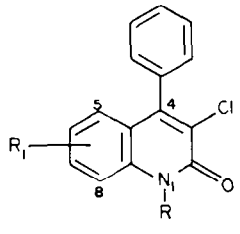


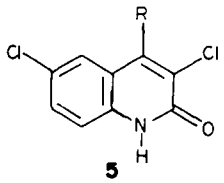
Scheme 1.

as a doublet (J = 2 Hz) for **4c** (δ 6.83; DMSO-d_6) and **4d** (δ 6.55). In the absence of the postulated steric hindrance, the C-5 proton in **5a** (DMSO-d_6) and **5b** (CF_3COOD) was shown as a *meta*-coupled doublet near δ 7.9, while in 4-phenylquinolin-2 (1H)-one itself, it formed part of a multiplet in the region δ 7.6–8.1 (DMSO-d_6). The chemical shift assigned to the C-5 proton was, as expected, solvent dependent. Thus for **4a** the singlet at δ 6.78 ($CDCl_3$) was displaced to δ 6.66 (DMSO-d_6).



4

a: R = H; R_1 = 7-Br-6,8-diCH_3
b: R = C_2H_5; R_1 = 7-Br-6,8-diCH_3
c: R = H; R_1 = 6-Cl
d: R = H; R_1 = 6-OCH_3



5

a: R = CH_3
b: R = CH_2OH

EXPERIMENTAL

General experimental procedures are reported in a previous paper.[2] In all cases the correct isotope abundance ratios were observed in the mass spectra (Varian CH5 spectrometer, 70 eV) of the various halogen-containing compounds. Chemical shifts (Hitachi Perkin Elmer instrument) are relative to TMS, and are reported as δ ppm (multiplicity, coupling constant, number of protons, assignment). Silica gel 60 (particle size 0.063–0.2 mm, E. Merck) was the adsorbent for column chromatography. The petroleum ether (pet ether) used as eluent had b.p. 60–80°.

Starting materials. In view of the rearrangement phenomenon encountered in this work, all precursor arylamines and anilides **1** were unequivocally identified from their NMR and mass spectra.

3-Bromo-2,4-dimethylaniline was prepared from 2,6-dimethylaniline by the following route: Sandmeyer reaction yielded 2-bromo-1,3-dimethylbenzene [b.p. 42° (1 mm)]; NMR (neat) δ 2.20 (s, 6H, $\underline{CH_3}$), 6.73 (s, 3H, Ar$\underline{H}$). Acetyl nitrate[3] was constituted

by slow addition of fuming (100%) HNO_3 (E. Merck; 30 ml) to Ac_2O (700 ml) with vigorous stirring while the temp. was kept below 25°. Introduction of the 2-bromo-substrate (57.0 g) caused the temp. to rise to about 50°, and stirring was continued for 1.25 hr at ±50°. Extra fuming HNO_3 (15 ml) in Ac_2O (100 ml) was added and GLC revealed the completion of the reaction after a further 1 hr at 50°. The mixture was diluted with H_2O (2 l), stirred at 20° for 3 hr, and extracted with CH_2Cl_2 to yield an oil. This was washed successively with 2 M NaOH and H_2O, and finally dried to provide 60.5 g (85%) 2-bromo-1,3-dimethyl-4-nitrobenzene, free of dinitro impurity; crystals (from EtOH), m.p. 53° (lit.[4] m.p. 57–58°); NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.04 (d, J = 8 Hz, 1H, ArH), 7.50 (d, J = 8 Hz, 1H, ArH); *m/e* 229 (M^+).

The nitro derivative (24.2 g, 0.106 mol) was hydrogenated (9.8 l H_2; calcd uptake 9.1 l H_2) over prehydrogenated platinum oxide (1.07 g) in absolute EtOH (70 ml) at 1 atm. The mixture was filtered through celite and the solvent evaporated to yield crude 3-bromo-2,4-dimethylaniline. This was purified by crystallisation of its hydrochloride from 2 M HCl, and obtained (17.0 g, 81%) as colourless crystals (from aqueous MeOH), m.p. 47–47.5° (lit.[4] m.p. 47–48°); NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.60 (s, 2H, NH_2, D_2O-exchangeable), 6.46 (d, J = 8 Hz, 1H, ArH), 6.84 (d, J = 8 Hz, 1H, ArH); *m/e* 201 (M + 2, 97%), 199 (M^+, 100).

4-Bromo-2,5-dimethylaniline [m.p. 95–96° (lit.[5] m.p. 96°)] was prepared by bromination of 2',5'-dimethylacetanilide;[5] NMR (CCl_4)[6] δ 2.05 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.32 (s, 2H, NH_2, D_2O-exchangeable), 6.38 (s, 1H, ArH), 7.05 (s, 1H, ArH).

3'-Bromo-2',4'-dimethylbenzoylacetanilide was derived (87%) from 3-bromo-2,4-dimethylaniline and ethyl benzoylacetate; colourless crystals (from EtOH), m.p. 152–153°; (Found: C, 59.24; H, 4.70; N, 3.92. $C_{17}H_{16}BrNO_2$ requires: C, 58.93; 4.66; N, 4.05%); NMR ($CDCl_3$) δ 2.34 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.06 (s, ~2H, CH_2), 6.94–7.88 (m, 7H, ArH), 9.10 (bs, 1H, NH); *m/e* 345 (M^+).

3' - Bromo - 2,2 - dichloro - 2',4' - dimethylbenzoylacetanilide (**1c**) was formed (88%) from the aforementioned substrate and a six-molar proportion of SO_2Cl_2; colourless crystals (from EtOH), m.p. 149–150°. (Found: C, 49.30; H, 3.43; N, 3.50. $C_{17}H_{14}BrCl_2NO_2$ requires: C, 49.19; H, 3.40; N, 3.38%); NMR ($CDCl_3$) δ 2.42 (coincident s, 6H, CH_3), 7.05–7.6 (m, 5H, ArH), 8.12 (dd, J_o = 8 Hz, J_m = 2Hz, ArH), 8.3 (bs, 1H, NH); *m/e* 413 (M^+), 225 (Ar-N=C=O), 188 ($C_6H_5C(OH)=CCl_2$), 105 (C_6H_5CO); the fragmentation pattern[6] helped verify structure **1c**.

Anilide **1b** was prepared in like manner from 4' - bromo - 2',5' - dimethylbenzoylacetanilide[6] [m.p. 188–189°; NMR (CF_3COOH) δ 2.25 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.55 (s, 2H, CH_2), 7.2–8.0 (m, 7H, ArH), 9.65 (bs, 1H, NH)] and SO_2Cl_2; colourless crystals (from EtOH), m.p. 121–121.5°; NMR ($CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 7.2–7.6 (m, 5H, ArH), 8.0 (dd, J_o = 8 Hz, J_m = 2 Hz, 2H, ArH), 8.22 (bs, 1H, NH); *m/e* 413 (M^+), 225 (Ar-N=C=O), 188 ($C_6H_5C(OH)=CCl_2$), 105 (C_6H_5CO).

5 - Bromo - 1 - chloro - 4,6 - dimethylindeno[1,2,3 - de]quinolin - 2(3H) - one (**2b**)

(A) *From anilide* **1c**. Conc. H_2SO_4 (4 ml) was added to **1c** (2.0 g) and the purple mixture, protected from extraneous moisture, was kept at ~95° (steam-bath) for 5 min with intermittent swirling; reaction occurred with evolution of HCl, while molecular halogen was detected with KI-starch paper. (Heating for 15 min led to a water-soluble (sulphonated) derivative). Dilution with ice-water (50 ml) precipitated a solid which was washed with H_2O, and freed of any unchanged **1c**, cleavage product, or quinolinone **4** by extraction with hot EtOH (3 × 20 ml). The residual **2b** (0.38 g, 22%) gave yellow crystals (from DMF), m.p. > 350°. (Found: C, 56.15; H, 2.83; N, 3.75. $C_{17}H_{11}BrClNO$ requires: C, 56.62; H, 3.08; N, 3.88%): IR 3160 (w), 3000 (w), 2920 (w), 1650 (s), 1585 (m), 1030 (s), 950 (m), 750 cm^{-1} (s); *m/e* (%) 363 (M + 4, 45%) 361 (M + 2, 100%), 359 (M^+, 100%), 280 (M − Br, 96%); halogenated impurities at 437 (M + 78) and 393 (M + 34).

The EtOH extract was evaporated to give crude **4a** mixed with tri-halogenated material [(*m/e* 395 (M + 34)]. Chromatography on silica gel with pet ether-EtOAc (1.5:1) as eluent afforded 1.07 g (61%) of *7 - bromo - 3 - chloro - 6,8 - dimethyl - 4 - phenylquinolin - 2(1H) - one* (**4a**); m.p. > 250°; IR 3160–3020 (w); 1650 (s), 780 (m), 710 cm^{-1} (s); NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 6.78 (s, 1H, 5-H), 7.2–7.5 (m, 5H, ArH); *m/e* 360.986 (M^+, calcd for $C_{17}H_{13}BrClNO$, 360.986).

N-Ethylation of **4a**. A mixture of **4a** (0.123 g, 0.341 mmol) and NaH (0.063 g of a 80% dispersion, 2.1 mmol; washed free of mineral oil) in dry DMF (5 ml) was stirred at 18° for 30 min under a N_2 atm. EtBr (82 mg, 0.75 mmol) was added and stirring was continued for 3 hr. Dilution with H_2O and extraction with $CHCl_3$ gave a solid which was chromatographed on silica gel with pet ether-EtOAc (1.5:1) as eluent to yield 0.067 g (51%) of the N-ethyl derivative, **4b**; m.p. 85–88°; NMR ($CDCl_3$) δ 1.54 (t, J = 7 Hz, 3H, CH_2CH_3), 2.39 (s, 3H, $ArCH_3$), 2.85 (s, 3H, $ArCH_3$), 4.62 (q, J = 7 Hz, 2H, CH_2CH_3), 6.94 (s, 1H, 5-H), 7.2–7.5 (m, 5H, ArH); *m/e* 389.017 (M', calcd for $C_{19}H_{17}BrClNO$; 389.018).

(B) *From anilide* **1b**. Addition of conc. H_2SO_4 (4 ml) to **1b** (2.0 g) gave a green mixture, and reaction as for **1c**, furnished indenoquinolinone **2b** in 50.3% crude yield; yellow crystals (from DMF), m.p. > 350°. (Found: C, 56.34; H, 3.20; N, 3.92. $C_{17}H_{11}BrClNO$ requires: C, 56.62; H, 3.08; N, 3.88%); *m/e* (300°) 358.969 (calcd for $C_{17}H_{11}BrClNO$, 358.971), minor peaks at *m/e* 437 (M + 78), 393 (M + 34), and 281 (M–78). Evaporation of the EtOH extract afforded a residue containing negligible quinolinone **4** (by TLC).

5 - Bromo - 1,2 - dichloro - 4,6 - dimethylindeno[1,2,3 - de]quinoline (**3**). A mixture of 0.837 g of **2b** (derived from **1b**), $SOCl_2$ (freshly distilled, 26 ml), and DMF (0.15 ml) was refluxed for 2 hr. The excess reagent was evaporated and the residue eluent to give **3** (0.758 g, 86%); yellow needles (from DMF), m.p. 280–285°. (Found: C, 53.65; H, 2.71; N, 3.60. $C_{17}H_{10}BrCl_2N$ requires: C, 53.86; H, 2.66; N, 3.70%); NMR ($CDCl_3$) δ 2.60 (s, chromatographed on silica gel with pet ether-benzene (9:1) as 3H, CH_3), 2.66 (s, 3H, CH_3), 7.2–7.5 (m, 3H, ArH), 8.0 (dd, J_o = 9 Hz, J_m = 2.5 Hz, 1H, 10-H); *m/e* 377 (M^+).

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