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THE ROLE OF NUCLEAR HALOGEN IN THE CYCLISATION OF BENZOYLACETANILIDES TO INDENO[1,2,3-*DE*]QUINOLINONES

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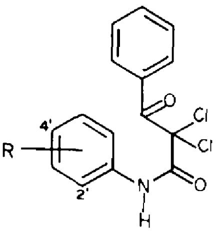
We have found that production of both indenoquinolinone **2** and quinolinone **3** from anilide **1**[2] is markedly dependent on the site of nuclear halogen substitution in **1**. Treatment of the *para*-bromo substrate **1c** with concentrated sulphuric acid at 95° for 15 min gave **2a** in reasonable (43%) yield, practically free of **3**. A comparable result was obtained[2] with the related *para*-chloro anilide **1f**.



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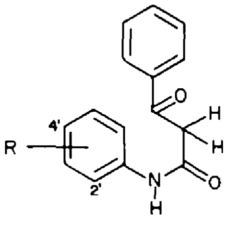
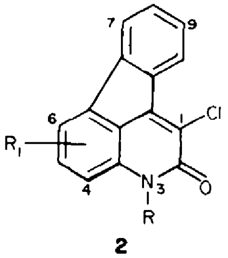


4

a: R = 2'-Br
b: R = 3'-Br
c: R = 4'-Br
d: R = 2'-Cl
e: R = 3'-Cl
f: R = 4'-Cl
g: R = 4'-F
h: R = 4'-I
i: R = 4'-CH_3O
j: R = 4'-NO_2
k: R = 4'-Cl-2',6'-diCH_3
l: R = 3'-Cl-4'-CH_3O
m: R = 2'-Cl-3',4'-diCH_3

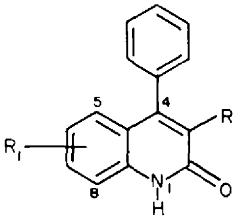


2

a: R = H; R_1 = 6-Br
b: R = $CH_2CH_2N(C_2H_5)_2$; R_1 = 6-Br
c: R = C_2H_5; R_1 = 6-Cl
d: R = C_2H_5; R_1 = 6-Cl-9-Br
e: R = H; R_1 = 5-Br-4,6-diCH_3
f: R = H; R_1 = 4-Br
g: R = H; R_1 = 5-Br
h: R = H; R_1 = 4-Cl
i: R = H; R_1 = 4-Cl-5,6-diCH_3

The identity of **2a** was confirmed by application of a newly established magnetic anisotropic effect in the ^1H NMR spectrum of **2**. For this purpose, **2a** was converted into the chloroform-soluble N-alkyl derivative **2b** by treatment with sodium hydride and 2-chlorotriethylamine. In **2b**, the C-7 and C-10 protons displayed anisotropic deshielding by the neighbouring 6-Br and 1-Cl substituents, and were found downfield near δ 8.2 as a two-proton, eight-line multiplet. This in itself was evidence that the bromine was at C-6. However, in support was the doublet (J_o = 9 Hz) at δ 6.98 attributed to the proton at C-4, with the remaining three aromatic protons appearing as a multiplet in the region δ 7.3–7.5.

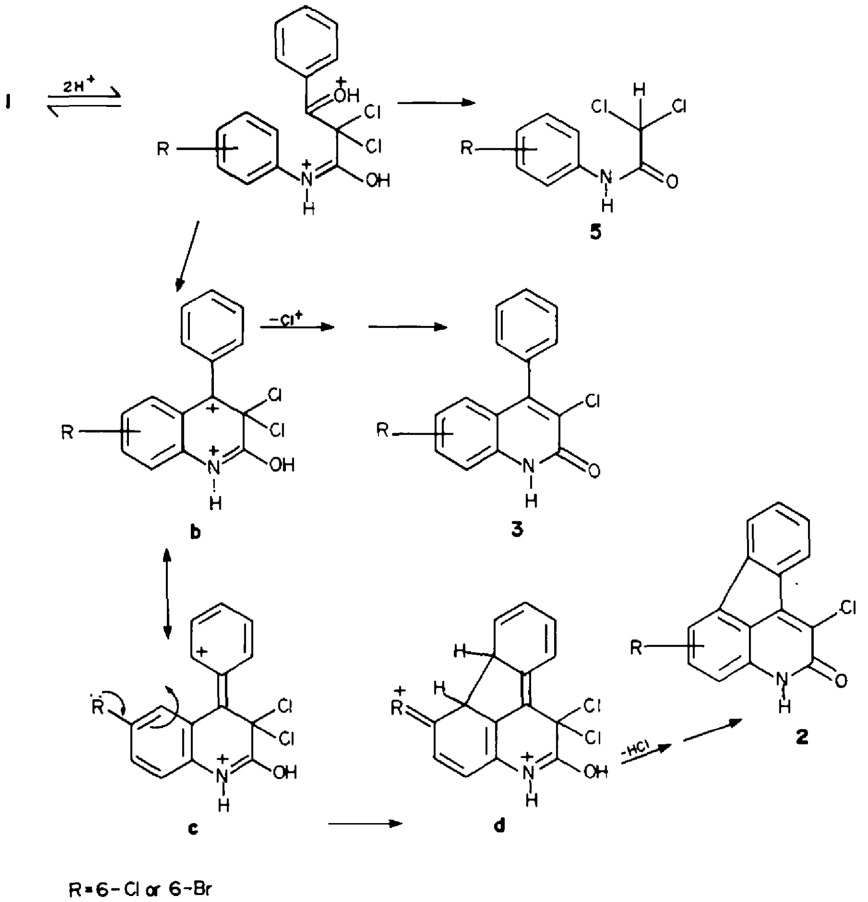
The *ortho*-halogen anilides **1a** and **1d** behaved likewise in giving the corresponding indenoquinolinones **2** as chief cyclisation product, and little quinolinone **3**: however, the **2f** and **2h** were furnished in decidely low (~20%) yields, and were contaminated with chlorinated impurity. Some loss of product **2** resulted from conversion to a water-soluble sulphonated derivative. Indeed, no **2** was isolated on utilisation of a large proportion of acid or of an extended reaction time.



3

a: R = Cl; R_1 = 5- and/or 7-Br
b: R = Br; R_1 = 6-Br
c: R = Br; R_1 = 6, X-diBr
d: R = Cl; R_1 = 6-OCH_3

The fate of the *meta*-halogen substrates **1b** and **1e** in sulphuric acid was significantly different. In each case, reaction afforded predominantly (>50%) quinolinone **3**, and minor (10–15%) indenoquinolinone **2**; moreover, both **2** and **3** contained a substantial proportion of halogenated derivative [*m*/*e* (M + 34)]. The nature of these impurities implied the generation during reaction of an halogenating species, such as the chlorinium ion.[2] This intermolecular halogenation correlates with the production of quinolinones **3**. Thus, in those instances where formation of **3** was minimal (as from **1a**, **1c**, **1d**, and **1f**), the presence of chlorinated impurity was likewise minor, whereas where **3** was the chief product (as from **1b** and **1e**), the proportion of contaminant was appreciable. This pattern, observed also with other anilides,[2] is intimately connected with the role of nuclear halogen in **1** in inducing indenoquinolinone **2** formation, which is suggested to be as follows (Scheme I). The conjugative effect of the *para*-Br (or Cl) substituent is indicated in **c**, and is postulated as helping to promote the ring junction leading to **d**. At any instant species **b** therefore rapidly and preferentially converts to **2**, and concomitant production of **3** is minimal. A similar conjugation is feasible with the *ortho*-halogen anilides **1a** and **1d**, but may be of diminished effect because of spatial and other considerations.[3] Clearly, a *meta*-halogen

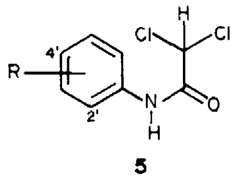


Scheme 1.

substituent, as in **1b** and **1e**, is not able to participate in this manner. In this latter circumstance, species **b** transforms preferentially into quinolinone **3** by loss of Cl^+. Since **2** and **3** are readily substituted by halogen in sulphuric acid,[2] the aforementioned correlation is established.

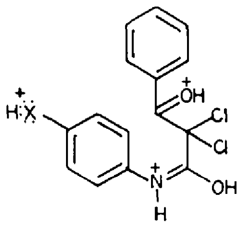
The effect of concentrated sulphuric acid on several other **1** bearing a *para*-substituent formally capable of exhibiting conjugation was examined. In marked contrast to both **1c** and **1f**, the related 4′-fluoro anilide **1g** gave negligible cyclised material **2** or **3**; instead, the cleavage product **5a** was isolated in 81% yield. In comparison, the 4′-iodo anilide **1h** suffered extensive de-iodination, and afforded a tar-like product containing de- and di-iodinated species, and negligible **2**. Of particular interest was the fate of the 4′-methoxy anilide **1i** in view of the participation by methoxyl in a "spiro" intermediate during the cyclisation[4] of 4′-methoxybenzylaminoacetonitrile. However, **1i** in hot acid for 5 min underwent substantial cleavage (benzoic acid was isolated in 56% yield), and provided only a minor yield (~7%) of a mixture of quinolinones **3** free of indenoquinolinone.

The findings with **1g** and **1i** may be rationalised by invoking an extensive protonation of the relevant 4′-substituent, as indicated in **6**. Deactivation of the arylamido moiety in **6** while inhibiting cyclisation to **b** (Scheme 1), apparently is conducive to cleavage of the substrate to **5**. Thus, whereas the 4′-nitro anilide **1j** furnished **5b** in high yield, the relatively activated **1k** under similar conditions was recovered largely unchanged.[2] The aforementioned conjugative effect inducing indenoquinolinone **2** formation is of no consequence in entity **6**.



5

a: R = 4′-F
b: R = 4′-NO_2
c: R = 4′-Br
d: R = 2′-Br

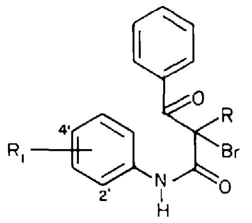


6

X = F or CH_3O

The substrate anilides **1**, including **1c**, were generally derived by heating the appropriate arylamine with ethyl benzoylacetate, and treating the product **4** with sulphuryl chloride. Compound **1c** was also prepared *via* a novel halogen exchange reaction.[5] Thus, the 2,4′-dibromo anilide **7a** and excess sulphuryl chloride were allowed to react in chloroform and provided **1c** in high yield. Even the 2,2,4′-tribromo substrate **7b** was likewise converted to **1c**, and the reaction is being further studied.

In contrast to the related **1c**, the 2,2,4′-tribromo anilide **7b** with sulphuric acid gave no indenoquinolinone **2**, but afforded instead a mixture of the dibromo- and tribromo-quinolinones, **3b** and **3c**, respectively. Under similar conditions, the 2,4′-dibromo substrate **7a** was hardly



7

a: R = H; R₁ = 4'-Br
b: R = Br; R₁ = 4'-Br
c: R = Cl; R₁ = 4'-Br-2',5'-diCH₃

affected and consequently was not the precursor of **3b**. It would seem that **3c** derives from intermolecular bromination of the **3b** initially produced by cyclisation of **7b**, as outlined in Scheme 2. In support, the reaction of **7b** was conducted in the presence of indenoquinolinone **2c** acting as an halogen "trap"; the product was now a mixture of **3b**, **3c**, **2c**, and the brominated derivative **2d**, as shown from its mass spectrum.

The failure of **7b** to yield **2** is attributed to steric hindrance by the C-3 bromines (as in **8**, Scheme 2) preventing attainment of the coplanar conformation prerequisite for indenoquinolinone formation (c.f. **c** in Scheme 2). Quinolinone **3b** arises by supposedly facile loss of Br^+ from **8**. The postulated hindrance is presumably not as effective in the 2-bromo-2-chloro anilide **7c** which cyclises to indenoquinolinone **2e** with liberation of hydrogen bromide.[5]

EXPERIMENTAL

General experimental procedures are reported in an earlier paper.[2]

Benzoylacetanilides **4** *and* **1**. The intermediates **4** were prepared as previously described,[2] and were characterised from their spectral and elemental analyses. Condensation of 4-iodoaniline with ethyl benzoylacetate gave **4h** (m.p. 174–176°) in 1.5% yield. Treatment of **4** with a six-molar proportion[2] of SO_2Cl_2 in $CHCl_3$ formed the corresponding **1**. Compound **4i** under these conditions afforded the 2,2,3'-trichloro derivative **1l**, m.p. 125–126°. The desired **1i** was obtained on utilisation of a three-molar amount of SO_2Cl_2. Relevant details of new **1**, the structures of which were confirmed from their spectral properties, are collected in Table 1.

Cyclisation of para-*halogen anilide* **1c**

6 - *Bromo* - 1 - *chloroindeno*[1,2,3-de]*quinolin* - 2(3H) - *one* (**2a**). Conc H_2SO_4 (2 ml) was added to **1c** (1.0 g) and the (green) mixture, protected from extraneous moisture, was kept at 95° (steam bath) for 15 min with intermittent swirling; reaction occurred with evolution of HCl. Addition of H_2O (50 ml) to the orange soln precipitated a solid which was filtered, washed with H_2O, and extracted with hot EtOH (3 × 20 ml) to give 0.36 g (43%) of sparingly soluble **2a**; yellow crystals (from DMF), m.p. >270°; IR 3170-2880 (H-bonded NH); 1650 cm^{-1} (amide CO); *m/e* 330.940 (M^+, calcd for $C_{15}H_7BrClNO$, 330.940). Evaporation of the EtOH extract afforded **5c**, identified from its mass spectrum, and negligible **3**. Treatment of **1c** (1.0 g) with H_2SO_4 (4 ml) at 95° for 5 min led to **2a** (43%) and unchanged **1c** (20%).

Table 1.

Compound	m.p.°C	Formula	Analysis (%) Calc. (Found) C	 H	 N
1b	120–121	$C_{15}H_{10}BrCl_2NO_2$	46.54 (46.62	2.60 2.45	3.62 3.42)
1e	115–116	$C_{15}H_{10}Cl_3NO_2$	52.58 (52.71	2.94 2.87	4.09 4.21)
1g	102–103	$C_{15}H_{10}Cl_2FNO_2$	55.24 (55.21	3.09 3.10	4.30 4.32)
1h	115–117	$C_{15}H_{10}Cl_2INO_2$	*m/e* 432.912 (M^+, requires 432.909)		
1i[a]	107–108	$C_{16}H_{13}Cl_2NO_3$	56.82 (56.92	3.87 3.92	4.14 4.10)
1l[b]	125–126	$C_{16}H_{12}Cl_3NO_3$	51.57 (51.61	3.25 3.15	3.76 3.52)

[a] NMR ($CDCl_3$) δ 3.74 (s, 3H, $OC\underline{H}_3$), 6.80 (d, J_0 = 9 Hz, 2H, Ar$\underline{H}$), 7.30–7.47 (m, 5H, Ar$\underline{H}$), 7.95 (dd, J_0 = 8 Hz, J_m = 2 Hz, 2H, Ar$\underline{H}$), 8.4 (bs, 1H, N$\underline{H}$). [b] NMR ($CDCl_3$) δ 3.84 (s, 3H, OCH_3). 6.80 (d, J_0 = 9 Hz, 1H, Ar$\underline{H}$), 7.25–7.55 (m, 5H, Ar$\underline{H}$), 7.95 (dd, J_0 = 8 Hz, J_m = 2 Hz, 2H, Ar$\underline{H}$), 8.3 (bs, 1H, N$\underline{H}$).

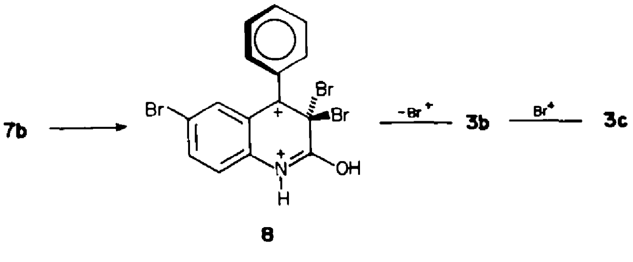
6 - *Bromo* - 1 - *chloro* - 3 - (2 - *diethylaminoethyl)indeno*[1,2,3 - de]*quinolin* - 2 - *one* (**2b**). A suspension of **2a** (0.914 g, 2.76 mmol) and NaH (0.73 g, of a 57% dispersion, 17 mmol; washed free of mineral oil) is dry DMF (30 ml) was stirred at 18° for 45 min under a N_2 atmosphere.

Freshly prepared 2-chlorotriethylamine (1.22 ml, 10 mmol) in dry DMF (15 ml) was added dropwise, over 10 min and stirring was continued for 3.5 hr. The reaction was quenched with ice-water (50 ml), and extracted with Et_2O to afford crude **2b**.

This was treated with dry HCl in Et_2O solution to give 0.71 g (55%) amine hydrochloride; yellow crystals (from aqueous EtOH), m.p. 153–155°. (Found: C, 53.91; H, 4.61; N, 6.16. $C_{21}H_{20}BrClN_2O{\cdot}HCl$ requires: C, 53.87; H, 4.52; N, 6.00%). Addition of 2MNaOH to the **2b** HCl dissolved in warm H_2O, gave the free amine **2b** (0.64 g, 98%); yellow crystals (from EtOH), m.p. 86–89°. (Found: C, 58.61; H, 4.88; N, 6.28. $C_{21}H_{20}BrClN_2O$ requires: C, 58.42; H, 4.67; N, 6.49%). NMR ($CDCl_3$) δ 1.14 (t, J = 8 Hz, 6H, $CH_2\underline{CH_3}$), 2.75 (q, J = 7 Hz, 4H, $N\underline{CH_2}CH_3$), 2.82 (t, J = 8 Hz, 2H, $ArNCH_2\underline{CH_2}$-), 4.42 (t, J = 8 Hz, 2H, $ArN\underline{CH_2}CH_2$-), 6.98 (d, J = 9 Hz, 1H, Ar$\underline{H}$), 7.3–7.5 (m, 3H, Ar$\underline{H}$), 8.1–8.3 (m, 2H, 7-H and 10-H); *m/e* 331 (M^+-$(C_2H_5)_2NCH{=}CH_2$, *via* McLafferty); no M^+ peak, even at 30 eV.

Cyclisation of ortho-*halogen anilides* **1a** *and* **1d**

Reaction of **1a** (1.0 g) with H_2SO_4 (2 ml) as for **1c**, yielded EtOH-insoluble material (~20%). This consisted principally of **2f** [*m/e* 330.939 (M^+, calcd for $C_{15}H_7BrClNO$, 330.940)], contaminated with dichloro material [*m/e* 365 (M + 34)]. Evaporation



Scheme 2.

of the EtOH extract provided cleavage product **5d** [*m/e* 281 (M^+)] and negligible (TLC) quinolinone **3** and unchanged **1a**. Anilide **1d** gave the corresponding products in comparable yields.

Cyclisation of meta-*halogen anilides* **1b** *and* **1e**. Conc H_2SO_4 (2 ml) and **1b** (1.0 g) were reacted as for **1c**, and gave (10–15%) a mixture of **2g** [*m/e* 330.937 (M^+, calcd for $C_{15}H_7BrClNO$, 330.940)] and substantial dichloro derivative [*m/e* 365 (m + 34)]. From the EtOH extract was recovered (>50%) quinolinone **3a** [*m/e* 333 (M^+)] contaminated with dichloro material [*m/e* 367 (M + 34)]. Similar yields of the corresponding products were obtained from anilide **1e**. Utilisation of an increased proportion (8 ml) of the H_2SO_4 for reaction with the substrates **1a**, **1b**, **1d** and **1e**, led to negligible insoluble **2**; the diluted acid mixture was a bright yellow colour indicative of the presence of sulphonated product. Both **1b** and **1e** dissolved in H_2SO_4 to give permanganate-coloured solutions which changed to orange within two min of heating; relatively little HCl was evolved during reaction.

Effect of sulphuric acid on 4'-fluoro-(**1g**), 4' iodo-(**1h**), *and 4'-methoxy-*(**1i**)*-2,2-dichlorobenzoylacetanilides*. A mixture of **1g** (1.65 g) and H_2SO_4 (3.2 ml) was kept at 95° for 5 min and diluted with ice-water (50 ml) to precipitate a colourless solid. This was crystallised from $CHCl_3$ to give 0.91 g (81%) of 2,2-dichloro-4'-fluoroacetanilide (**5a**), m.p. 128–129°. (Found: C, 43.11; H, 2.35; N, 6.43. $C_8H_6Cl_2FNO$ requires: C, 43.27; H, 2.72; N, 6.31%); *m/e* 221 (M^+). Evaporation of the $CHCl_3$ filtrate afforded benzoic acid, identified from its IR spectrum. On similar treatment, anilide **1h** gave, on dilution with H_2O, a tar-like product which contained at least six components (by TLC), while its MS displayed *m/e* values which could be correlated with both de- and di-iodinated species.

A mixture of **1i** (2.27 g) and conc H_2SO_4 (5 ml) was heated at 95° for 5 min; reaction for a longer period led to increased formation of water-soluble products. Dilution with ice-water gave a solid which was chromatographed on silica gel with a graded pet ether-EtOAc eluent to afford benzoic acid (0.45 g, 56%; identified from its IR spectrum) and several quinolinones **3**, including **3d** [2.1%; m.p. >200°; NMR ($CDCl_3$) δ 3.64 (s, 3H, $OC\underline{H}_3$), 6.55 (d, J_m = 2 Hz, 1H, Ar$\underline{H}$), 7.1–7.6 (m, 7H, Ar$\underline{H}$)].

Action of sulphuryl chloride on anilides **7a** *and* **7b**

Halogen exchange reaction. A soln of **7a**[5] [100 mg; m.p. 155–156°; NMR ($CDCl_3$) δ 5.61 (s, 1H, $C\underline{H}Br$), 7.2–7.6 (m, 7H, Ar$\underline{H}$), 7.95 (dd, J_0 = 8 Hz, J_m = 2 Hz, 2H, Ar$\underline{H}$), 8.80 (bs, 1H, $N\underline{H}$); *m/e* 395 (M^+)] and SO_2Cl_2 (0.3 ml) in $CHCl_3$ (10 ml), contained in a stoppered flask, was allowed to remain at 20° for 18 hr. Solvent and reagent were evaporated under reduced pressure below 40°, and the residue was triturated with H_2O and filtered to provide 70 mg of **1c**, identified from its IR and mass spectra. Anilide **7b**[5] [m.p. 132.5–133.5°; NMR ($CDCl_3$) δ 7.40 (s, 7H, Ar$\underline{H}$), 7.95 (dd, J_0 = 8 Hz, J_m = 2 Hz, 2H, Ar$\underline{H}$), 8.55 (bs, 1H, $N\underline{H}$); *m/e* 473 (M^+)] likewise afforded **1c** (65% yield), identified from its IR and mass spectra.

Cyclisation of 2,2,4'-*Tribromobenzoylacetanilide* (**7b**)

A mixture of **7b** (0.4 g) and H_2SO_4 (1 ml) was reacted at 95° for 15 min as for **1c**. Dilution with water gave a solid, free of **7b** and **7a** (by TLC), identified from its mass spectrum as a mixture of **3b** [*m/e* 377 (M^+)] and **3c** [*m/e* 445 (M + 78)]. Repetition of the reaction in the presence of indenoquinolinone **2c** (0.15 g) gave a yellow solid. Mass spectral analysis showed peaks corresponding to **3b**, **3c**, **2c** [*m/e* 315 (M^+)], and **2d** [*m/e* 393 (m + 78)]. Anilide **7a** was recovered largely unchanged (TLC and mass spectrum) after treatment with H_2SO_4 as for **1c**, contaminated with minor **3b** [TLC, blue spot in UV; *m/e* 377 (M^+)].

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