Reactions of 2*H*,5*H*-Imidazo[1,5-*b*]isoquinoline-1,3-diones† with Bromine

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Treatment of 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **1** with one molar proportion of bromine in glacial acetic acid gave complex mixtures. The major component of each mixture was the corresponding 1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromide **4**; other constituents shown to be present included the 1,3-dioxo-10-bromoimidazo[1,5-*b*]isoquinolinium bromides **5**, 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **3**, isocarbostyryl derivatives **9**, dihydroisocarbostyryl derivatives **10**, and 3-carbamoylisoquinolines **8**. Reaction of the 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **1** in glacial acetic acid with excess of bromine afforded 1,3-dioxo-10-bromoimidazo[1,5-*b*]isoquinolinium bromides **5** as principal products. Bromination of compounds **1** in carbon tetrachloride yielded mainly 1,3-dioxo-2*H*-imidazo[1,5-*b*]isoquinolinium bromides **12**.

A number of 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **1** have been synthesized[1] and some have been shown to exhibit positive inotropic activity.[2] The insolubility of these compounds in water presented difficulties in their pharmacological evaluation and methods were sought to increase their solubility in aqueous media through derivatisation with appropriate functional groups as salt-forming sites.

Gabriel[3] has shown that bromination of 5-phenylhydantoin in acetic acid yields 5-bromo-5-phenylhydantoin and that the bromohydantoin reacts with alcoholic ammonia to give 5-amino-5-phenylhydantoin. Although all 5-monosubstituted hydantoins brominate at C-5, the nature of the C-5 substituent dictates the final product since appropriate substituents permit elimination of hydrogen bromide following the initial bromination.[4] Thus, 5-(*p*-hydroxybenzyl)hydantoin reacts with bromine to give 5-(*p*-hydroxybenzylidene)hydantoin.[5] Alkylidene- and aralkylidene-hydantoins may react further with bromine; 5-benzylidenehydantoin with bromine gives 5-bromo-5-(α-bromobenzyl)hydantoin which eliminates hydrogen bromide to yield 5-(α-bromobenzylidene)hydantoin.[6] However, elimination of hydrogen bromide does not necessarily occur, as illustrated by the reported isolation of 5-bromo-5-isopropyl-3-methyl-1-phenylhydantoin.[7] Bromination of the 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **1** was therefore expected to give a number of products of which the 10a-bromo derivatives **2** and the 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **3** in particular offered routes to derivatisation of the parent nucleus **1**, the latter through residual enamine character.[8]

Results and Discussion

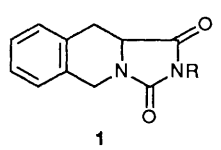
Bromination reactions of hydantoins **1** under various conditions gave complex mixtures from which a series of various components were isolated. Especially, **1a** gave **5a**; **1b** gave **3b**, **4b**, **5b**, **6b**, **7b**, **8b**, **10b**, **11b** (R^2 = H or Me) and **12b**; **1c** gave **3c**, **4c**, **5c**, **8c**, **9c** and **10c**; **1d** gave **4d**, **8d** (R^1 = H) and **9d**; and **1e** gave **3e**, **4e**, **5e**, **6e**, **10e** and **12e**, respectively.

Treatment of hydantoins **1** with one molar equivalent of bromine in glacial acetic acid at 95 °C led to the isolation of 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **3** in low yield. The IR spectra of these products retained the characteristic bands of the hydantoin ring[9,10] at 1760 and 1710 cm^{-1} and showed a new band at 1665 cm^{-1} for the 10,10a double bond. In the ^1H NMR spectra of compounds **3** the 5-H_2 signal was a singlet (δ *ca.* 5.1) and not the AB quartet as shown for the corresponding protons of compounds of **1**. Accurate mass measurement of the molecular ion at *m/z* 214 gave the appropriate formula for **3b**. The products are thus sufficiently stable for characterisation, although the ethyl derivative **3c** when left for a few hours showed (TLC) a second component.

Bromination of compounds **1** with 1 molar equivalent of bromine in glacial acetic acid at 95 °C gave either pure 1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromides **4** or mixtures of salts **4** and 10-bromo-1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromides **5** as yellow, chloroform-insoluble solids. Microanalyses of these mixtures **4** and **5** consistently gave values for bromine 10–20% higher than those required for pure salts **4**. The IR spectra of compounds **4** and **5** exhibited bands at 1835 cm^{-1}, *ca.* 70 cm^{-1} higher than the corresponding band in compounds **1**, reflecting the influence of the quaternary nitrogen on the adjacent carbonyl group. The ^1H NMR spectra of compounds **4** [trifluoroacetic acid (TFA)] showed 5-H and 10-H singlets at δ *ca.* 10.2 and 9, respectively. In the ^1H NMR spectrum of compound **4d** [$(CD_3)_2SO$–D_2O] 5-H and 10-H appeared as singlets at δ 6.52 and 6.93, respectively, corresponding to pseudobase **6d**; it is known[11,12] that pseudobase formation from heteroaromatic cations results in large upfield shifts of comparable protons. The solution of pseudobase **6d** was kept in the NMR tube at room temperature for 66 h. The ^1H NMR spectrum which resulted was that of 3-[deuterio(propyl)carbamoyl]isoquinoline **8d** (R^1 = D). The 1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromides **4** and their 10-bromo derivatives **5** undergo addition reactions.[13] Thus, treatment of the mixture **4b** and **5b** with methanol afforded the adduct **6b**, whose spectral characteristics were similar to those of related adducts,[13] and the adduct **7b**, which was identical in m.p. and spectral characteristics with that of a sample prepared from the reaction of pure 10-bromo-2-methyl-1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromide **5b** with methanol.[13]

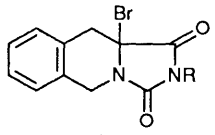
The 2*H*,5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **3** may be regarded as 2,3-disubstituted 1,2-dihydroisoquinolines. 1,2-Dihydroisoquinolines are enamines and are regarded as unstable and difficult to isolate.[14] Exposure to air can result in polymerisation or oxidation to isocarbostyryls.[15] In acidic solution, disproportionation to an isoquinolinium salt and a 1,2,3,4-tetrahydroisoquinoline has been observed.[14,16] Disproportionation of partially saturated compounds **3** to saturated **1** and unsaturated products **4**, in the presence of hydrogen

† 10,10a-Dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones.



1

a; R = H d; R = Pr^n
b; R = Me e; R = Ph
c; R = Et



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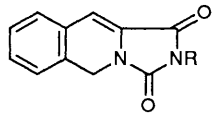
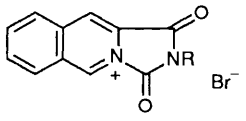


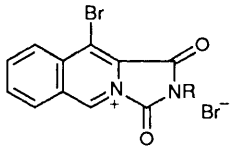
3

b; R = Me e; R = Ph
c; R = Et



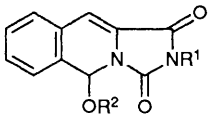
4

b; R = Me d; R = Pr^n
c; R = Et e; R = Ph



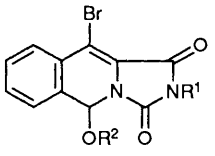
5

a; R = H c; R = Et
b; R = Me e; R = Ph



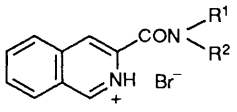
6

b; $R^1 = R^2$ = Me
d; $R^1 = Pr^n$, R^2 = D
e; R^1 = Ph, R^2 = Me



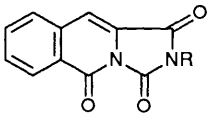
7

a; R^1 = H, R^2 = D
b; $R^1 = R^2$ = Me



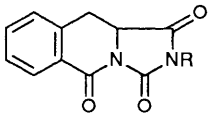
8

b; R^1 = H, R^2 = Me
c; R^1 = H, R^2 = Et
d; R^1 = H or D, $R^2 = Pr^n$



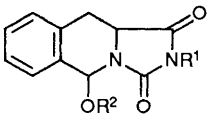
9

c; R = Et
d; R = Pr^n



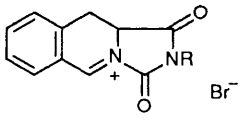
10

b; R = Me e; R = Ph
c; R = Et



11

b; R^1 = Me, R^2 = H or Me
e; R^1 = Ph, R^2 = D



12

b; R = Me
e; R = Ph

bromide liberated in the reaction **2** ⟶ **3**, followed by further bromination, dehydrobromination and disproportionation reactions (Scheme 1) rationalises the formation of the various products.

Evidence for the proposed reaction sequence (Scheme 1) was provided by treatment of compound **3c** with hydrogen bromide in glacial acetic acid at 95 °C. The resultant mixture afforded the chloroform-insoluble salt **4c** and the presence of compound **1c** was detected by TLC of the filtrate, remaining from the isolation of the salt **4c**, using authentic compound **1c** as a standard.

3-Alkylcarbamoylisoquinoline hydrobromides **8** were obtained in small amounts from the chloroform filtrates which had been left for a few days. It is assumed that these products arose from interaction of salts **4** with traces of water in the reaction solvents. The IR spectra showed bands at 3210 (NH) and 1670 cm^{-1} (amide) and the absence of bands characteristic of the hydantoin ring.

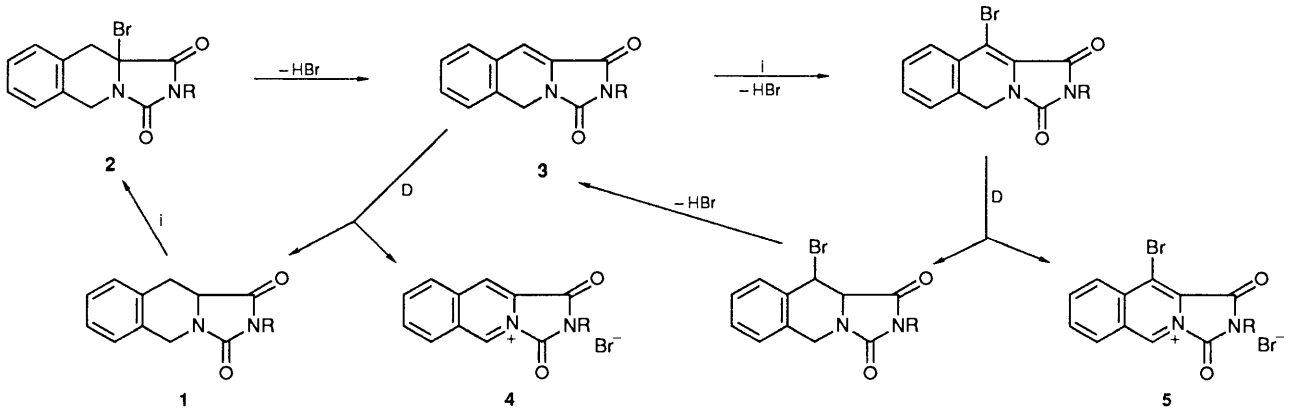
Small amounts of isocarbostyryl derivatives **9** were isolated. Their IR spectra showed an additional band at 1800 cm^{-1}. The UV spectra of these compounds **9** showed several maxima concordant with the UV spectra of related compounds.[17] Their ^{1}H NMR spectra showed 6-H resonating as double doublets (δ 8.5, *J* 2 and 8 Hz) separated from the other aromatic protons and consistent with the signals observed in related structures.[18] The oils remaining after the isolation of compounds **3**, **4** and **5** also afforded the dihydroisocarbostyryl derivatives **10**. Their IR spectra had a band at 1800 cm^{-1}, their UV spectra exhibited several maxima, and their ^{1}H NMR spectra showed 6-H resonating as a double doublet (δ 8.15, *J* 2 and 8 Hz) still well separated from the other aromatic protons;[19] 10a-H gave a double doublet (δ 4.62, *J* 6 and 13 Hz) and 10-H a doublet of quartets (δ 2.94–3.51). These isocarbostyryls are probably formed by oxidation by air at C-5 since 1,2,3,4-tetrahydroisoquinolines have been shown to oxidise in air to dihydroisocarbostyryls.[20]

Bromination of the imidazo[1,5-*b*]isoquinoline-1,3-diones **1** with excess of bromine in glacial acetic acid at 95 °C gave 10-bromo-1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromides **5**. Their IR spectra showed the characteristic band at 1835 cm^{-1}. The products were too insoluble in appropriate inert solvents to permit NMR characterisation but were readily identified by their adducts **7** formed by reaction with alcohols.[13] However, compound **5a** [in $(CD_3)_2SO$–D_2O] gave the ^{1}H NMR spectrum of the corresponding pseudobase **7a** in which 5-H appeared as a singlet at δ 6.50 and 9-H at δ 7.72–7.83, downfield of the other aromatic protons, presumably reflecting deshielding by the neighbouring bromine atom.

Bromination of 1,2,3,4-tetrahydroisoquinolines with *N*-bromosuccinimide (NBS) occurs at C-1 initially,[21,22] and the products were converted into 3,4-dihydroisoquinolines. 1,2-Dihydroisoquinolines on treatment with NBS give isoquinolinium salts.[23] The observations on the bromination of simple hydantoins and of 1,2,3,4-tetrahydroisoquinolines indicate that in compounds **1** C-5, in addition to C-10a, may be susceptible to attack by bromine.

Treatment of compound **1b** with bromine in carbon tetrachloride gave the chloroform-insoluble mixture of products **4b** and **5b**. The filtrate was concentrated and chromatographed on a column of silica gel with chloroform–diethyl ether (7:3) followed by chloroform–methanol (9:1) as eluants to give dihydrocarbostyryl **10b**, pseudobase **11b** (R^2 = H), and the adduct **11b** (R^2 = Me). Repetition of the bromination of compound **1b** in an atmosphere of nitrogen gave the mixture **4b** and **5b** and from the chloroform filtrate 2,3,10,10a-tetrahydro-2-methyl-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **12b** was isolated. Bromination of the *N*-phenyl compound **1e** under identical conditions afforded the mixture **4e** and **5e** as well as compound **12e**. The ^{1}H NMR spectrum of **12e** in $CDCl_3$ showed 5-H resonating as a singlet at δ 7.6; addition of D_2O converted the spectrum into that of the pseudobase **11e** in which the signal for 5-H had shifted to δ 6.38. Products **12** were characterised by the adducts **11** formed on their treatment with alcohols.[13] Compounds **11b** (R^2 = H and Me) isolated from the silica gel column obviously arose by addition of water and methanol, respectively, to the salt **12b**, and compound **10b** by oxidation of the salt **12b** by air.

Treatment of the hydantoins **1** with bromine in carbon tetrachloride proceeds by a route different from that with bromine in acetic acid. The first step appears to be attack by



Scheme 1 *Reagents:* i, Br_2, −HBr, D = Disproportionation

bromine at C-5 to give the salts **12**. The formation of products **4** and **5** may be attributed to disproportionation[24] of the salts **12** to compounds **4** and **1** followed by the reaction sequence of Scheme 1.

Experimental

IR spectra were recorded in KCl pellets on a Perkin-Elmer 197 instrument, and ^1H NMR spectra were obtained with a Perkin-Elmer R32 (90 MHz) spectrometer, with tetramethylsilane as internal standard. *J* Values are given in Hz. Mass spectra were run on a AEI-MS 902 double-focussing, high-resolution spectrometer. M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Light petroleum refers to the fraction boiling in the range 40–60 °C.

Bromination of 10,10a-*Dihydroimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*diones* **1** *with Bromine (1 Mol Equiv.) in Acetic Acid*

Bromination of (±)-10,10a-*Dihydro*-2-*methylimidazo*[1,5-b]-*isoquinoline*-1,3(2H,5H)-*dione* **1b**.—A solution of (±)-10,10a-dihydro-2-methylimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione **1b** (2.16 g, 10 mmol) in glacial acetic acid (10 cm^3), containing acetic anhydride (0.1 cm^3), was heated to 90–95 °C under reflux and protected from moisture by a calcium chloride drying tube. A solution of bromine (1.6 g, 10 mmol) in glacial acetic acid (3 cm^3) was added dropwise and the reaction was allowed to continue for 1 h. Evaporation to dryness gave a reddish yellow residue, which was dispersed in dry ethanol-free chloroform and the yellow insoluble material was collected by filtration to afford mixed salts **4b** and **5b** (0.75 g), m.p. >390 °C; ν_{max}/cm^{-1} 1835, 1755 and 1605; δ(TFA) 3.50 (s, NMe), 8.25–8.90 (m, ArH), 9.00 (s, 10-H) and 10.23 (s, 5-H). A solution of the product in water–acetone was acidic and gave a positive reaction on treatment with aq. silver nitrate.

Concentration of the chloroform filtrate and addition of light petroleum gave 2-*methylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **3b**, which crystallised from ethanol as light yellow material (0.25 g, 11.5%), m.p. 221–222 °C (Found: C, 66.7; H, 4.7; N, 13.15%; M^+, 214.0739. $C_{12}H_{10}N_2O_2$ requires C, 67.25; H, 4.7; N, 13.1%; M, 214.0742); ν_{max}/cm^{-1} 1755, 1705 and 1665; δ($CDCl_3$) 3.10 (3 H, s, NMe), 5.07 (2 H, s, 5-H_2), 6.57 (1 H, s, 10-H) and 7.05–7.40 (4 H, m, ArH); R_f [$CHCl_3$–Et_2O (7:3)] 0.38 (fluorescence). After some days white crystals which had formed in the filtrate were collected by filtration to give the carbamide **8b** (0.1 g), ν_{max}/cm^{-1} 3210 and 1670; δ[$(CD_3)_2SO$–D_2O] 2.98 (3 H, s, NMe), 7.85–8.45 (4 H, m, ArH), 8.70 (1 H, s, 4-H) and 9.52 (1 H, s, 1-H).

5-*Methoxy*-2-*methylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **6b** *and* 10-*bromo*-5-*methoxy*-2-*methylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **7b**. The mixture of isoquinolinium bromides **4b** and **5b** (0.5 g) was dissolved in hot, dry methanol (15 cm^3) and, after cooling, the white solid which separated was collected by filtration (0.21 g); ν_{max}/cm^{-1} 1760, 1720, 1660 and 1630. Recrystallisation from dry methanol gave 10-bromo-5-methoxy-2-methylimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione **7b**, m.p. 142 °C (lit.,[13] 142 °C); ν_{max}/cm^{-1} 1760, 1710 and 1660. The mother liquor, after concentration, was chromatographed on silica gel with chloroform–diethyl ether (4:1) as eluant to give 5-methoxy-2-methylimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione **6b**; ν_{max}/cm^{-1} 1760, 1710 and 1660; δ($CDCl_3$) 3.18 (3 H, s, NMe), 3.32 (3 H, s, OMe), 6.49 (1 H, s, 5-H), 6.85 (1 H, s, 10-H) and 7.46 (4 H, s, ArH).

Bromination of (±)-2-*Ethyl*-10,10a-*dihydroimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **1c**.—Bromination of compound **1c** (2.3 g, 10 mmol) with bromine (1.6 g, 10 mmol) under similar conditions to those described for **1b** gave 2-*ethyl*-2,3-*dihydro*-1,3-*dioxo*-1H-*imidazo*[1,5-b]*isoquinolinium bromide* **4c** (1.12 g, 36.5%), m.p. 243–245 °C (Found: C, 50.4; H, 3.4; Br, 26.4; N, 9.4. $C_{13}H_{11}BrN_2O_2$ requires C, 50.85; H, 3.6; Br, 26.0; N, 9.1%) [Found: M^+, 227.0823. $(C_{13}H_{11}N_2O_2)^+$ requires M, 227.0820]; ν_{max}/cm^{-1} 1835, 1760 and 1610; δ(TFA) 1.47 (3 H, t, NCH_2Me), 4.06 (2 H, q, NCH_2Me), 8.25–8.90 (4 H, m, ArH), 8.99 (1 H, s, 10-H) and 10.22 (1 H, s, 5-H).

From the chloroform filtrate after addition of light petroleum was isolated 2-*ethylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **3c** (0.3 g, 13%), m.p. 186–190 °C (from EtOH) (Found: C, 67.35; H, 5.5; N, 12.0. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%); ν_{max}/cm^{-1} 1755, 1710 and 1665; δ($CDCl)_3$) 1.27 (3 H, t, NCH_2Me), 3.69 (2 H, q, NCH_2Me), 5.02 (2 H, s, 5-H_2), 6.60 (1 H, s, 10-H) and 7.27 (4 H, s, ArH); R_f [$CHCl_3$–Et_2O (9:1)] 0.27. After 4 h, TLC of the product exhibited two components, R_f 0.27 and 0.18 (very low intensity).

From the chloroform–light petroleum filtrate stored for some days was isolated compound **8c** (0.05 g), m.p. 221–225 °C; ν_{max}/cm^{-1} 3225 and 1670; δ[$(CD_3)_2SO$] 1.20 (3 H, t, $NHCH_2Me$), 3.42 (2 H, quintet, collapsed to a quartet on addition of D_2O, $NHCH_2Me$), 7.30 (1 H, br s, exchanged with D_2O, NH), 7.80–8.42 (4 H, m, ArH), 8.74 (1 H, s, 4-H), 9.13 (1 H, br s, exchanged with D_2O, NH^+) and 9.52 (1 H, s, 1-H). The filtrate was kept for several weeks, then evaporation of the solvents gave an oil, which after repeated recrystallisation from ethanol gave (±)-2-*ethyl*-10,10a-*dihydroimidazo*[1,5-b]*isoquinoline*-1,3,5(2H)-*trione* **10c** (0.32 g, 13%), m.p. 199–200 °C (Found: C, 64.25; H, 5.0; N, 11.1. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.95; N, 11.45%); ν_{max}/cm^{-1} 1800 and 1740; δ($CDCl_3$) 1.26 (3 H, t, NCH_2Me), 2.94–3.51 (2 H, dq, 10-H_2), 3.66 (2 H, q, NCH_2Me), 4.62 (1 H, dd, *J* 6 and 13, 10a-H), 7.25–7.72 (3 H,

(Found: C, 64.25; H, 5.0; N, 11.1. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.95; N, 11.45%); ν_{max}/cm^{-1} 1800 and 1740; δ($CDCl_3$) 1.26 (3 H, t, NCH_2Me), 2.94–3.51 (2 H, dq, 10-H_2), 3.66 (2 H, q, NCH_2Me), 4.62 (1 H, dd, *J* 6 and 13, 10a-H), 7.25–7.72 (3 H, m, ArH) and 8.15 (1 H, dd, *J* 2 and 8, 6-H); λ_{max}(EtOH)/nm 213, 238, 334 and 350; R_f [$CHCl_3$–Et_2O 4:1)] 0.20.

Repetition of the bromination reaction of compound **1c** gave, *inter alia*, from the chloroform-light petroleum, compound **9c** as a white solid (0.2 g), m.p. slow melting from 223 °C EtOH); ν_{max}/cm^{-1} 1800, 1740 and 1600; δ(TFA) 1.34 (3 H, t, NCH_2Me), 3.86 (2 H, q, NCH_2Me), 7.40 (1 H, s, 10-H), 7.81–7.98 (3 H, m, ArH) and 8.54 (1 H, dd, *J* 2 and 8, 6-H).

Reaction of 2-*Ethylimidazo*[1,5-b] *dione* **3c** *with Hydrogen Bromide in Glacial Acetic Acid.*—A solution of compound **3c** in glacial acetic acid was saturated with a continuous stream of hydrogen bromide and the mixture was heated at 95 °C for 0.5 h. Evaporation of the acetic acid under reduced pressure gave a yellow residue, which after dispersion in dry, ethanol-free chloroform (20 cm^3) and filtration gave a yellow solid (0.05 g) whose IR spectrum was identical with that of 2-ethyl-2,3-dihydro-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **4c**. TLC of the chloroform filtrate [$CHCl_3$–Et_2O (9:1)] showed components with R_f 0.27 **3c**, 0.22 **1c** and 0.18 **8c**.

Bromination of (±)-10,10a-*Dihydro*-2-*propylimidazo*[1,5-b]-*isoquinoline*-1,3(2H,5H)-*dione* **1d**.—Bromination of compound **1d** (2.44 g, 10 mmol) by the procedure described for compound **1b** with bromine (1 mol equiv.) gave 2,3-*dihydro*-1,3-*dioxo*-2-*propyl*-1H-*imidazo*[1,5-b]*isoquinolinium bromide* **4d** (1.1 g, 34%), m.p. 228–232 °C (Found: C, 51.9; H, 3.9; Br, 25.5; N, 8.4. $C_{14}H_{13}BrN_2O_2$ requires C, 52.3; H, 4.1; Br, 24.9; N, 8.7%); ν_{max}/cm^{-1} 1835, 1760 and 1610; δ(TFA) 1.03 (3 H, t, NCH_2CH_2Me), 1.89 (2 H, m, NCH_2CH_2Me), 3.95 (2 H, t, NCH_2CH_2Me), 8.25–8.91 (4 H, m, ArH), 8.99 (1 H, s, 10-H) and 10.21 (1 H, s, 5-H); δ[$(CD_3)_2SO$–D_2O] 0.86 (3 H, t, NCH_2CH_2Me), 1.61 (2 H, m, NCH_2CH_2Me), 3.50 (2 H, t, NCH_2CH_2Me), 6.52 (1 H, s, 10-H), 6.93 (1 H, s, 5-H) and 7.49 (4 H, s, ArH); after storage for 66 h in the NMR tube, the spectrum of compound **8d** (R^1 = D) was observed; δ 0.82 (3 H, t, $NDCH_2CH_2Me$), 1.52 (2 H, m, $NDCH_2CH_2Me$), 3.35 (2 H, t, $NDCH_2CH_2Me$), 7.80–8.40 (4 H, m, ArH), 8.70 (1 H, s, 4-H) and 9.48 (1 H, s, 1-H).

The chloroform filtrate from the isolation of compound **4d** was kept for several weeks to afford 3-(propylcarbamoyl)-isoquinoline hydrobromide **8d** (R^1 = H) (0.15 g), m.p. 206–212 °C; ν_{max}/cm^{-1} 3210 and 1670; δ[$(CD_3)_2SO$] 0.86 (3 H, t, $NHCH_2CH_2Me$), 1.55 (2 H, m, $NHCH_2CH_2Me$), 3.36 (2 H, q, collapsed to a triplet on addition of D_2O, $NHCH_2CH_2Me$), 5.41 (br s, exchanged with D_2O, NH), 7.85–8.42 (4 H, m, ArH), 8.76 (1 H, s, 4-H), 9.08 (1 H, br s, exchanged with D_2O, NH^+) and 9.52 (1 H, s, 1-H). Evaporation of the solvents gave a yellowish oil which solidified and from which, after repeated recrystallisation from absolute ethanol, was obtained 2-propylimidazo[1,5-*b*]isoquinoline-1,3,5(2*H*)-trione **9d** (0.28 g, 11%), m.p. 215–220 °C; ν_{max}/cm^{-1} 1800, 1740 and 1600; λ_{max}(EtOH)/nm 234, 255, 265, 309, 321, 335 and 352; δ($CDCl_3$) 0.95 (3 H, t, NCH_2CH_2Me), 1.75 (2 H, m, NCH_2CH_2Me), 3.60 (2 H, t, NCH_2CH_2Me), 7.31 (1 H, s, 10-H), 7.53–7.70 (3 H, m, ArH) and 8.50 (1 H, dd, *J* 2 and 8, 6-H); R_f [$CHCl_3$–Et_2O (9:1)] 0.17.

Bromination of (±)-10,10a-*Dihydro*-2-*phenylimidazo*[1,5-b]-*isoquinoline*-1,3(2H,5H)-*dione* **1e**.—Bromination of compound **1e** (2.78 g, 10 mmol) by the method described for compound **1b** with bromine (1.6 g, 10 mmol) gave the chloroform-insoluble yellow material **4e** and **5e** (1.45 g), m.p. 260–265 °C; ν_{max}/cm^{-1} 1840, 1770 and 1605; δ(TFA) 7.59 (s, Ph), 8.26–8.94 (m, ArH), 9.08 (s, 10-H) and 10.27 (s, 5-H).

Concentration of the chloroform filtrate and addition of light petroleum gave 2-*phenylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **3e** (1 g, 36%), m.p. slow melting from 115 °C (Found: C, 73.55; H, 4.2; N, 9.85. $C_{17}H_{12}N_2O_2$ requires C, 73.9; H, 4.3; N, 10.15%) ν_{max}/cm^{-1} 1775, 1715 and 1665; δ($CDCl_3$) 5.10 (2 H, s, 5-H_2), 6.69 (1 H, s, 10-H) and 7.10–7.57 (9 H, m, ArH); λ_{max}(EtOH)/nm 231, 240sh, 249, 305sh and 319; R_f [$CHCl_3$–Et_2O (9:1)] 0.47.

Chromatography on neutral alumina with chloroform–Et_2O (7:3) as eluant yielded *inter alia* a white product which, from its spectroscopic characteristics, was tentatively characterised as (±)-10,10a-dihydro-2-phenylimidazo[1,5-*b*]isoquinoline-1,3,5(2*H*)-trione **10e**, m.p. 245–247 °C; ν_{max}/cm^{-1} 1800, 1740 and 1600; δ($CDCl_3$) 3.10–3.68 (2 H, dq, 10-H_2), 4.80 (1 H, dd, *J* 6 and 13, 10a-H), 7.16–7.56 (8 H, m, ArH) and 8.19 (1 H, dd, *J* 2 and 8, 6-H); λ_{max}(EtOH)/nm 222, 294sh, 319sh, 335 and 350; R_f [$CHCl_3$–Et_2O (8:2)] 0.20.

Bromination of 10,10a-*Dihydroimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*diones* **1** *with Excess* (*5 Mol Equiv.*) *of Bromine in Acetic Acid*

Bromination of (±)-10,-10a-*Dihydroimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **1a**.—Bromination of compound **1a** (2.02 g, 10 mmol) in glacial acetic acid (30 cm^3) and acetic anhydride (0.2 cm^3) with bromine (8 g, 50 mmol) at 90–95 °C gave 10-*bromo*-1,3-*dioxo*-2,3-*dihydro*-1H-*imidazo*[1,5-b]*isoquinolinium bromide* **5a** (2.8 g, 78%), m.p. > 300 °C over range (Found: C, 35.6; H, 1.8; Br, 45.1; N, 8.1. $C_{11}H_6Br_2N_2O_2$ requires C, 36.9; H, 1.7; Br, 44.65; N, 7.85%); ν_{max}/cm^{-1} 1845 and 1780; δ[$(CD_3)_2SO$–D_2O] 6.50 (1 H, s, 5-H), 7.32–7.62 (3 H, m, ArH) and 7.72–7.83 (1 H, m, 9-H).

Bromination (under similar conditions) of compounds **1b**, **1c** and **1e** gave the corresponding bromoisoquinolinium bromides **5b**, **5c** and **5e**. Attempts to obtain pure samples for microanalysis were unsuccessful. The products were insufficiently soluble for ^1H NMR characterisation and gave adducts of type **7** on treatment with different nucleophiles.[13]

Bromination of 10,10a-*Dihydroimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*diones* **1** *with Bromine in Carbon Tetrachloride*

Bromination of (±)-10,10a-*Dihydro*-2-*methylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **1b**.—A solution of bromine (3.2 g, 20 mmol), in dry carbon tetrachloride (10 cm^3) was added dropwise to a rigorously stirred suspension of compound **1b** (4.32 g, 20 mmol) in dry carbon tetrachloride (30 cm^3). After completion of the addition the reaction mixture was stirred overnight at room temperature and evaporated to dryness to afford a yellow residue, which was dispersed in dry chloroform (150 cm^3). The yellow insoluble mixture **4b** and **5b** (1.5 g) was collected by filtration and had the same spectroscopic characteristics as the product obtained from the bromination (1 mol equiv.) of compound **1b** in acetic acid. The filtrate obtained after concentration was chromatographed on silica gel with chloroform–diethyl ether (7:3) as eluant and yielded the starting material **1b** (0.2 g recovery), R_f 0.30; and (±)-10,10a-*dihydro*-2-*methylimidazo*[1,5-b]*isoquinoline*-1,3,5(2H)-*trione* **10b** as a white solid (0.1 g), m.p. 240–241 °C (Found: C, 62.2; H, 4.25; N, 11.8%; M^+, 230.0669. $C_{12}H_{10}N_2O_3$ requires C, 62.6; H, 4.35; N, 12.15%; M, 230.0691); ν_{max}/cm^{-1} 1800 and 1740; δ($CDCl_3$) 2.96–3.51 (5 H, dq, 10-H_2 overlapping with a singlet centred at δ 3.11, NMe), 4.67 (1 H, dd, *J* 6 and 13, 10a-H), 7.26–7.73 (3 H, m, ArH) and 8.15 (1 H, dd, *J* 2 and 8, 6-H); λ_{max}(EtOH)/nm 212, 243, 293sh, 307sh, 319sh, 334 and 349; R_f [$CHCl_3$–Et_2O (7:3)] 0.22.

$C_{12}H_{12}N_2O_3$ requires C, 62.05; H, 5.2; N, 12.05%; M, 232.0848); ν_{max}/cm^{-1} 3430, 1765 and 1705; δ($CDCl_3$) 2.63–3.40 (5 H, dq, 10-H_2 overlapping with a singlet centred at δ 3.05, NMe), 4.19 (1 H, d, *J* 5, exchanged with D_2O, OH), 4.33 (1 H, dd, *J* 6 and 13, 10a-H), 6.41 (1 H, d, *J* 5, collapsed to a singlet with D_2O, 5-H), 7.25–7.41 (3 H, m, ArH) and 7.53–7.63 (1 H, m, 6-H). Further elution of the column with chloroform–methanol (9 : 1) as eluant afforded (±)-10,10a-*dihydro*-5-*methoxy*-2-*methylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **11b** (R^2 = Me) (1.5 g), m.p. 107–109 °C (from MeOH) (Found: C, 63.0; H, 5.6; N, 11.3. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.75; N, 11.35%); ν_{max}/cm^{-1} 1770 and 1710; δ($CDCl_3$) 2.67–3.40 (5 H, dq, 10-H_2 overlapping with a singlet centred at δ 3.10, NMe), 3.56 (3 H, s, OMe), 4.31 (1 H, dd, *J* 6 and 13, 10a-H), 6.03 (1 H, s, 5-H) and 7.15–7.55 (4 H, m, ArH).

Repetition of the bromination of compound **1b** (2.16 g, 10 mmol) with bromine in carbon tetrachloride under nitrogen gave the yellow insoluble material (0.7 g), and evaporation to dryness of the chloroform filtrate afforded (±)-2,3,10,10a-*tetrahydro*-2-*methyl*-1,3-*dioxo*-1H-*imidazo*[1,5-b]*isoquinolinium bromide* **12b** (2.22 g, 75%), m.p. 118 °C (over range); ν_{max}/cm^{-1} 1775 and 1710; δ($CDCl_3$) 2.98–3.53 (5 H, dq, 10-H_2 overlapping with a singlet centred at δ 3.08, NMe), 4.44 (1 H, dd, *J* 6 and 13, 10a-H), 7.15–7.57 (4 H, m, ArH) and 7.61 (1 H, s, 5-H); after addition of D_2O the singlet at δ 7.61 (5-H) shifted to δ 6.38; $\lambda_{max}(CHCl_3)$/nm 252 and 352 (Found: M^+, 215.0787. $[C_{12}H_{11}N_2O_2]^+$ requires M, 215.0820).

Bromination of (±)-10,10a-*Dihydro*-2-*phenylimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **1e**.—Bromination of compound **1e** (1.878 g, 10 mmol) under similar conditions afforded the yellow insoluble mixture of the salts **4e** and **5e** (0.5 g), which was obtained from the bromination of compound **1e** in acetic acid, and (±)-2.3,10,10a-*tetrahydro*-1,3-*dioxo*-2-*phenyl*-1H-*imidazo*[1,5-b]*isoquinolinium bromide* **12e** (2.9 g, 81%), m.p. 181–183 °C; ν_{max}/cm^{-1} 1785 and 1720; δ($CDCl_3$) 3.01–3.66 (2 H, dq, 10-H_2), 4.63 (1 H, dd, *J* 6 and 13, 10a-H), 7.24–7.65 (9 H, m, ArH) and 7.70 (1 H, s, 5-H); after addition of D_2O the singlet at δ 7.70 (5-H) shifted to δ 6.46; $\lambda_{max}(CHCl_3)$/nm 247, 335sh and 350sh.

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