Reactions of 1,3-Dioxoimidazo[1,5-*b*]isoquinolinium Bromides with Nucleophiles

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Treatment of 10-bromo-1,3-dioxoimidazo[1,5-*b*]isoquinolinium bromides **2**, 1,3-dioxoimidazo-[1,5-*b*]isoquinolinium bromides **4**, and tetrahydro-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromides **7** with selected nucleophiles gave adducts which were respectively 5-substituted 10-bromoimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **3**, 5-substituted imidazo[1,5-*b*]isoquinoline- 1,3(2*H*,5*H*)-diones **5** and 5-substituted 10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **8**. The adduct with cyanide (Reissert compound) **5i** reacted with benzyl chloride to yield 5-benzyl-1,2,3,5-tetrahydro-1,3-dioxo-2-propylimidazo[1,5-*b*]isoquinoline-5-carbonitrile **6**. Both adducts **5i** and the dihydro-Reissert compounds **8l** and **8m** were hydrolysed to the corresponding carboxylic acids. Reaction of isoquinolinium bromide **7a** with phenylmagnesium bromide afforded 2,3,10,10a-tetrahydro-3-hydroxy-2-methyl-3,5-diphenylimidazo[1,5-*b*]isoquinolin-1(5*H*)-one **9**.

Bromination of 10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **1** under various conditions has been shown[1] to yield, *inter alia*, a series of 1,3-dioxoimidazo[1,5-*b*]isoquinolinium salts, *e.g.*, **2**, **4**, or **7** or mixtures of **2** and **4**. The addition reactions of these quaternary salts with selected nucleophiles is now described.

Results and Discussion

Treatment of the 10-bromo-2,3-dihydro-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromides **2a–2d** with methanol or ethanol gave the adducts **3a–3e**. The IR spectra of the products exhibited a characteristic band at or near 1630 cm^{-1} for the 10,10a double bond, which is some 30 cm^{-1} lower than the corresponding band in the non-brominated adducts **5**. In the ^1H NMR, spectra 5-H appeared as a sharp singlet in the range δ 6.40–6.68, comparing favourably with the cited[2,3] values of analogous compounds. The 9-H appeared downfield of the other aromatic protons, presumably reflecting deshielding by the neighbouring bromine atom. The *N*-unsubstituted adducts **3a** and **3b** [in $(CD_3)_2SO$ and $(CD_3)_2CO$], showed no observable signal for the NH moiety, either because of peak broadening by the nitrogen quadruple, or because of a rapid proton exchange with water contained in the solvents; similar observations have been reported for related structures.[4,5] Accurate mass measurement of the molecular ion at *m/z* 324/322 (1:1) in compound **3c** gave the appropriate formula; the base peak occurred at *m/z* 293/291 (1:1) corresponding to the loss of OMe.

N-Alkylisoquinolinium or *N*-acylisoquinolinium salts are well known[3,6] to react with water to give pseudobases and with alcohols to form the corresponding ethers. The latter can also be prepared by reaction of the pseudobase with the appropriate alcohol.

Reaction of the isoquinolinium salts **4b–4d** with methanol or ethanol afforded the corresponding adducts **5a–5d**, which were characterised by IR and ^1H NMR spectroscopy. Their IR spectra showed a band at 1660 cm^{-1} for the 10,10a double bond; the 5-H and 10-H protons appeared as sharp singlets in the ranges δ 6.49–6.63 and 6.83–6.98, respectively.

Ammonia and amines are known[6,7] to add to C-1 of isoquinolinium salts and the factors that influence this addition are similar to those of the addition of water and alcohols.

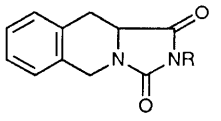
Treatment of the mixture of imidazo[1,5-*b*]isoquinolinium salts **2b**[1] and **4a**[1] with diethylamine, followed by chromatography on silica gel, afforded a yellow solid, which on TLC showed two overlapping spots. The IR and ^1H NMR spectral characteristics of the mixture were in agreement with the expected adducts **3f** and **5e**. The IR spectrum of the mixture exhibited two bands at 1660 and 1635 cm^{-1}, whereas the ^1H NMR spectrum showed the signal for 10-H of compound **5e** as a singlet at δ 6.6 and that for 9-H of compound **3f** at δ 7.76–7.87, downfield of the other aromatic protons. Treatment of the mixture **3f** and **5e** with ethereal hydrogen bromide gave the starting material **2b**/**4a**, indicating that the amination of isoquinolinium salts is reversible in acids.[8] Further elution of the column afforded the pseudobase **5f**. The IR spectrum exhibited two bands at 3440 (OH) and 1660 cm^{-1} (C=C) and the ^1H NMR spectrum [in $(CD_3)_2SO$] showed the 5-OH group resonating as an exchangeable broad singlet at δ 3.28.

Treatment of compound **4b** with triethylamine resulted in the isolation of the pseudobase **5g** as the only identifiable product. The ^1H NMR spectrum (in $CDCl_3$) showed the 5-H and 5-OH as doublets (*J* 6 Hz). Accurate mass measurement of the molecular ion at *m/z* 244 gave the appropriate formula.

Attack of cyanide ion on isoquinolinium salts also occurs at C-1[9,10] to give adducts. Treatment of the isoquinolinium bromides **4b** and **4c** with aqueous potassium cyanide in dichloromethane[11] gave, respectively, the Reissert compounds **5h** and **5i**. The analytical and spectroscopic data were consistent with the assigned structures. The IR spectra showed no detectable absorption for the cyano group in the range 2200–2400 cm^{-1} in common with other Reissert compounds.[12] The mass spectrum of adduct **5h** gave the molecular ion and the principal fragment arose through loss of cyanide radical, which loss is a recognised fragmentation pathway of Reissert compounds.[13] Column chromatography (silica gel) of the ethereal filtrate, after the isolation of adduct **5h**, afforded the pseudobase **5g**.

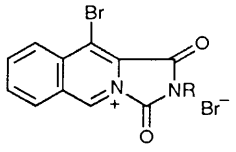
When 5-nitroisoquinoline is treated with potassium cyanide and benzyl chloride in water–dichloromethane, the *N*-acyl pseudobase is formed in high yield, rather than the expected Reissert compound which is formed in less than 2% yield.[3,14] It seems that the effect of the 5-nitro group enhances the 'hardness' of the C-1 centre, thus favouring attack by the hard base water rather than the softer base CN^-.[15,16]

Treatment of the 10-bromoimidazo[1,5-*b*]isoquinolinium bromide **2d** with aqueous potassium cyanide in dichloromethane



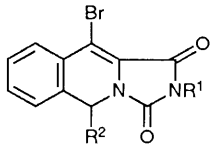
1

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



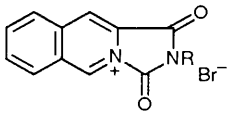
2

a; R = H **b**; R = Me **c**; R = Et **d**; R = Ph



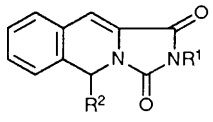
3

a; R^1 = H, R^2 = OMe **b**; R^1 = H, R^2 = OEt **c**; R^1 = Me, R^2 = OMe **d**; R^1 = Et, R^2 = OMe **e**; R^1 = Ph, R^2 = OMe **f**; R^1 = Me, R^2 = NEt_2 **g**; R^1 = Ph, R^2 = OH



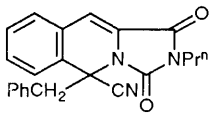
4

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

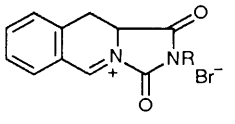


5

a; R^1 = Et, R^2 = OMe **b**; R^1 = Et, R^2 = OEt **c**; R^1 = Pr^n, R^2 = OMe **d**; R^1 = Ph, R^2 = OMe **e**; R^1 = Me, R^2 = NEt_2 **f**; R^1 = Me, R^2 = OH **g**; R^1 = Et, R^2 = OH **h**; R^1 = Et, R^2 = CN **i**; R^1 = Pr^n, R^2 = CN **j**; R^1 = Pr^n, R^2 = $CONH_2$ **k**; R^1 = Pr^n, R^2 = CO_2H

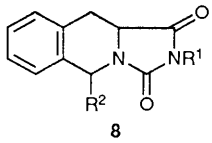


6



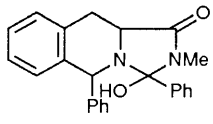
7

a; R = Me **b**; R = Ph

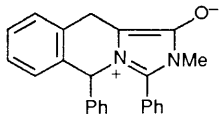


8

a; R^1 = Me, R^2 = OMe **b**; R^1 = Me, R^2 = OEt **c**; R^1 = Ph, R^2 = OMe **d**; R^1 = Ph, R^2 = OEt **e**; R^1 = Ph, R^2 = OPr^i **f**; R^1 = Me, R^2 = SPh **g**; R^1 = Ph, R^2 = SEt **h**; R^1 = Me, R^2 = ON=CHMe **i**; R^1 = Me, R^2 = NMe_2 **j**; R^1 = Ph, R^2 = NEt_2 **k**; R^1 = Me, R^2 = $N[CH_2CH_2]O[CH_2CH_2]$ **l**; R^1 = Me, R^2 = CN **m**; R^1 = Ph, R^2 = CN **n**; R^1 = Me, R^2 = CO_2H **p**; R^1 = Ph, R^2 = CO_2H **q**; R^1 = Me, R^2 = CO_2Me **r**; R^1 = Ph, R^2 = CO_2Me



9



10

afforded the brominated pseudobase **3g** which on refluxing with methanol gave the corresponding ether **3e**. It is possible that the ureido moiety of the isoquinolinium salts **2** and **4** together with the C-10 bromine atom increase the 'hardness' of the C-5 centre, permitting competitive attack by the harder base water.

Reissert compounds usually undergo acid-catalysed hydrolysis to give aldehydes plus the corresponding heterocyclic carboxylic acid.[12] Acid-catalysed hydrolysis of the cyanide adduct **5i** with concentrated hydrochloric acid afforded the corresponding amide **5j** in good yield. The cyano group in adduct **5i** is hindered and hydrolysis to the corresponding acid **5k** is difficult. However, hydrolysis to the acid **5k** was finally achieved by treatment of the amide **5j** with sulphuric acid containing acetic acid[17] and followed the mechanism of ordinary nitriles. The mass spectrum of acid **5k** gave the molecular ion at *m/z* 286 (M^+, 15.6%) and a principal fragment at *m/z* 241 (94.6%) arising through loss of the carboxy group.

Alkylation of Reissert and dihydro-Reissert compounds is known to proceed *via* the corresponding carbanions which, in turn, can effect nucleophilic substitution of alkyl halides[18,19] to give the C-1-substituted derivatives. Treatment of the Reissert compound **5i** with benzyl chloride in dry dimethylformamide (DMF) containing sodium hydride,[20] under nitrogen, afforded the 5-benzyl cyanide adduct **6**. The ^1H NMR spectrum showed the benzylic protons, adjacent to the asymmetric C-5, as an AB quartet (*J* 14 Hz); the 10-H appeared as a singlet at δ 6.16, upfield of the corresponding proton in the parent compound **5i** (δ 6.77). This may be explained by a conformation of compound **6** in which the benzene ring of the C-5 benzyl group is situated underneath the C-10 proton to cause shielding of that proton.

3,4-Dihydroisoquinolinium salts react at C-1 with nucleophiles, in a manner similar to 'fully' aromatic isoquinolinium salts, to give a variety of 1-substituted tetrahydroisoquinolines.[21] Quantitatively the 3,4-dihydroisoquinolinium system is more susceptible to attack than the 'fully' aromatic isoquinolinium system since there is less loss of conjugation energy. The stability of the adducts derived from 3,4-dihydroisoquinolinium salts varies with the nature of C-1 substituent; for the most part, however, treatment with acid results in the loss of the substituent and regeneration of the quaternary salt.

Treatment of the 1*H*-imidazo[1,5-*b*]isoquinolinium bromides **7a** and **7b** with methanol, ethanol, or isopropyl alcohol gave the corresponding adducts **8a**–**8e**. The products were obtained in

Table 1 Analytical data for the 10-brominated adducts **3a–3e**

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found % (Required) C	H	Br	N
3a ($C_{12}H_9BrN_2O_3$)	68	MeOH	236–238	46.85 (46.6	2.9 2.95	25.75 25.85	9.0 9.05)
3b ($C_{13}H_{11}BrN_2O_3$)	65	EtOH	252[a]	48.2 (48.3	3.2 3.45	24.6 24.75	8.65 8.65)
3c ($C_{13}H_{11}BrN_2O_3$)	67	MeOH	142[b]	48.75 (48.3	3.55 3.45	24.75 24.75	9.05 8.65)
3d ($C_{14}H_{13}BrN_2O_3$)	57	MeOH	126–127	49.25 (49.85	3.65 3.9	24.2 23.7	7.95 8.3)
3e ($C_{18}H_{13}BrN_2O_3$)	61	MeOH	199–200	56.05 (56.1	3.5 3.4	20.95 20.75	7.6 7.25)

[a] Over range. [b] Resolidified and then remelted at 250–253 °C.

Table 2 Spectroscopic data for the 10-brominated adducts **3a–3e**

Compound	IR (ν_{max}/cm^{-1})	^{1}H NMR[a] (δ) 5-H	9-H	Other protons
3a[b]	3210 (NH), 1760 (CO), 1710 (CO), 1630 (C=C)	6.40s	7.75m	3.19 (3 H, s, 5-OMe), 7.52–7.62 (3 H, m, ArH)
3b[c]	3190 (NH), 1760 (CO), 1710 (CO), 1630 (C=C)	6.50s	7.83m	1.05 (3 H, t, OCH_2Me), 3.66 (2 H, q, OCH_2Me), 7.35–7.65 (3 H, m, ArH)
3c[d]	1760 (CO), 1710 (CO), 1635 (C=C)	6.45s	7.91–8.02m	3.20 (3 H, s, NMe), 3.36 (3 H, s, 5-OMe), 7.45–7.65 (3 H, m, ArH)
3d	1760 (CO), 1720 (CO), 1630 (C=C)	6.41s	7.89–7.99m	1.30 (3 H, t, NCH_2Me), 3.34 (3 H, s, 5-OMe), 3.74 (2 H, q, NCH_2Me), 7.41–7.60 (3 H, m, ArH)
3e	1765 (CO), 1725 (CO), 1635 (C=C)	6.51s	7.96–8.07m	3.44 (3 H, s, 5-OMe), 7.43–7.66 (9 H, m, ArH)

[a] Spectra were recorded in $CDCl_3$ unless otherwise indicated. [b] Spectrum in $(CD_3)_2SO$. [c] Spectrum in $(CD_3)_2Co$. [d] M^+, 323.9926. $C_{13}H_{11}{}^{81}BrN_2O_3$ requires M, 323.9934; and M^+, 321.9946. $C_{13}H_{11}{}^{79}BrN_2O_3$ requires M, 321.9953.

good yields as white solids and were easily characterised by ^{1}H NMR spectroscopy. All of the adducts showed an ABX pattern arising from splitting of 10a-H, which appeared as double doublets (*J* 6 and 13 Hz), with the C-10 non-equivalent methylene protons which occurred as doublets of quartets. Treatment of compound **7a** with thiophenol afforded the adduct **8f** and reaction of compound **7b** with ethanethiol afforded the adduct **8g**. The adduct **8g** gave a very weak molecular ion at *m/z* 338 (0.1%) and the base peak corresponded to *m/z* 177 (M − SEt). Compound **7a** reacted with acetaldoxime to yield the corresponding adduct **8h** as a semi-solid at room temperature; the analytical and spectroscopic characteristics of the product were consistent with its structure **8h**.

Reaction of salts **7a** and **7b** with dimethylamine, diethylamine and morpholine afforded the adducts **8i–8k**. In the ^{1}H NMR spectra 6-H appeared downfield of the other aromatic protons through deshielding by the neighbouring amino group. Treatment of the morpholino adduct **8k** with DCl, in the NMR tube, shifted the signals downfield and after 12 h gave a yellow precipitate **7b**, indicating the reversibility of the amination reaction of salts **7** in acidic solution.

Treatment of the salt **7a** with an excess of freshly prepared phenylmagnesium bromide gave compound **9** as the only identifiable product. The IR spectrum exhibited two new bands at 3250 (OH) and at 1685 cm^{-1} (CO) but not the usual carbonyl bands of the hydantoin ring.[22] The ^{1}H NMR spectrum showed the signal for 10a-H as a double doublet (*J* 6 and 13 Hz) at δ 3.87, upfield of the analogous proton signal of the hydantoins **8**, reflecting the loss of deshielding by the hydantoin ring; the C-3 hydroxy proton appeared as an exchangeable singlet at δ 5.06. The mass spectrum of the product **9** gave the molecular ion at *m/z* 370 (M^+, 26.4%) and the base peak at *m/z* 352 (M − H_2O), corresponding to the mesoionic structure **10**.[23] Reaction of salts **7a** and **7b** with potassium cyanide in water–dichloromethane afforded the dihydro-Reissert compounds **8l** and **8m**, respectively. Their IR spectra exhibited a very weak band at *ca.* 2240 cm^{-1} for the cyano group. Refluxing of compounds **8l** and **8m** with a mixture of hydrochloric and acetic acid afforded directly the respective acids **8n** and **8p**, which were esterified with freshly prepared diazomethane to the esters **8q** and **8r**.

Experimental

IR spectra were recorded in KCl pellets on a Perkin-Elmer 197 instrument and ^{1}H 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.

Preparation of 5-Alkoxy-10-bromoimidazo[1,5-*b*]*isoquinoline*-1,3-(2H,5H)-*diones* **3a–3e**.—Crude 10-bromo-2,3-dihydro-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **2** (1 mmol) was dissolved in freshly distilled dry methanol or absolute ethanol (5 cm^3) with the aid of heat and the solution was left at room temperature for 3 h. The white solid which formed was collected by filtration, washed with cold dry

Table 3 Analytical data for the adducts **5a–5d**

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found % (Required) C	H	N
5a	62	MeOH	92–93	64.95	5.3	11.0
($C_{14}H_{14}N_2O_3$)				(65.1	5.45	10.85)
5b	58	EtOH	86–87	66.4	6.0	10.1
($C_{15}H_{16}N_2O_3$)				(66.15	5.9	10.3)
5c	58	MeOH	84[a]	66.35	6.05	10.05
($C_{15}H_{16}N_2O_3$)				(66.15	5.9	10.3)
5d	79	MeOH	202–203	70.7	4.6	9.15
($C_{18}H_{14}N_2O_3$)				(70.6	4.6	9.15)

[a] Lit.,[24] m.p. 85 °C; resolidified and then remelted at 205–210 °C.

Table 4 Spectroscopic data for the adducts **5a–5d**

Compound	IR (ν_{max}/cm^{-1})	^{1}H NMR[a] (δ) 5-H	9-H	Other protons
5a	1760 (CO), 1710 (CO), 1660 (C=C)	6.50s	6.85s	1.30 (3 H, t, NCH_2Me), 3.33 (3 H, s, 5-OMe), 3.74 (2 H q, NCH_2Me), 7.47 (4 H, s, ArH)
5b	1760 (CO), 1710 (CO), 1660 (C=C)	6.51s	6.83s	1.06–1.37 (6 H, two overlapping triplets, NCH_2Me and OCH_2Me), 3.54–3.83 (4 H, two overlapping quartets, NCH_2Me and OCH_2Me), 7.43 (4 H, s, ArH)
5c	1770 (CO), 1710 (CO), 1660 (C=C)	6.50s	6.87s	0.96 (3 H, t, NCH_2CH_2Me), 1.74 (2 H, m, NCH_2CH_2Me), 3.32 (3 H, s, 5-OMe), 3.63 (2 H, t, NCH_2CH_2Me), 7.47 (4 H, s, ArH)
5d	1765 (CO), 1720 (CO), 1660 (C=C)	6.58s	6.98s	3.42 (3 H, s, 5-OMe), 7.42–7.56 (9 H, m, ArH)

[a] Spectra were recorded in $CDCl_3$.

methanol or absolute ethanol and recrystallised from the appropriate solvent to give the 5-alkoxy-10-bromoimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **3a–3e** (Tables 1 and 2).

Preparation of 5-Alkoxyimidazo[1,5-b]*isoquinoline*-1,3-(2H,5H)-*diones* **5a–5d**.—A crude *N*-substituted-2,3-dihydro-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **4** (1 mmol) was treated, as described above, with dry methanol or absolute ethanol (5 cm^3) to give the 2-substituted 5-alkoxy-imidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **5a–5d** (Tables 3 and 4).

Reaction of the Mixture of 10-*Bromo*-2,3-*dihydro*-2-*methyl*-1,3-*dioxo*-1H-*imidazo*[1,5-*b*]*isoquinolinium Bromide* and 2,3-*Dihydro*-2-*methyl*-1,3-*dioxo*-1H-*imidazo*[1,5-b]*isoquinolinium Bromide* **2b** and **4a** *with Diethylamine*.—A suspension of the mixture[1] **2b** and **4a** (0.5 g) in dry, ethanol-free chloroform (5 cm^3) was treated with diethylamine (0.25 g) and the resultant yellow solution was shaken occasionally for 0.5 h. The reaction mixture was flooded with anhydrous diethyl ether, and the diethylamine hydrobromide was filtered off, and the filtrate, after concentration, was chromatographed on a silica gel column with chloroform–diethyl ether (1:1) as eluant to give yellow crystals, which on TLC showed two overlapping spots; ν_{max}/cm^{-1} 1760 (CO), 1720 (CO), 1660 (C=C) and 1635 (C=C); δ($CDCl_3$) 0.98 [t, $N(CH_2Me)_2$], 2.44–2.78 [two overlapping quartets, $N(CH_2Me)_2$], 3.11–3.14 (two singlets, NMe), 6.23 (br s, 5-H), 6.60 (s, 10-H), 7.29–7.50 (m, ArH) and 7.76–7.87 (m, 9-H). Treatment of the product with ethereal hydrogen chloride gave a yellow solid whose IR spectrum [1835 (CO) and 1755 cm^{-1} (CO)] was identical with that of the material **2b** and **4a**. Further elution of the column afforded 5-*hydroxy*-2-*methyl*-*imidazo*[1,5-*b*]*isoquinoline*-1,3(2H,5H)-*dione* **5f** (0.06 g), m.p. 189–190 °C (Found: C, 63.25; H, 4.5; N, 12.4%; M$^+$, 230. $C_{12}H_{10}N_2O_3$ requires C, 63.7; H, 4.45; N, 12.4%; M, 230); ν_{max}/cm^{-1} 3440 (OH), 1760 (CO), 1710 (CO) and 1660 (C=C); δ [$(CD_3)_2SO$] 3.02 (3 H, s, NMe), 3.28 (1 H, br s, exchanged with D_2O, 5-OH), 6.59 (1 H, s, 5-H), 6.99 (1 H, s, 10-H) and 7.50 (4 H, s, ArH).

Reaction of 2-*Ethyl* 2,3-*dihydro*-1,3-*dioxo*-1H-*imidazo*[1,5-b]-*isoquinolinium Bromide* **4b** *with Triethylamine*.—A suspension of the salt **4b** (0.307 g, 1 mmol) in dry chloroform (5 cm^3) was treated, as described above, with triethylamine (0.1 g, 1 mmol). Further work-up and column chromatography on silica gel, with chloroform–diethyl ether (4:1) as eluant, gave 2-*ethyl*-5-*hydroxyimidazo*[1,5-b]*isoquinoline*-1,3(2H,5H)-*dione* **5g** (0.04 g), m.p. 144–145 °C (Found: C, 63.55; H, 5.0; N, 11.6%; M$^+$, 244. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.95; N, 11.45%; M, 244); ν_{max}/cm^{-1} 3375 (OH), 1760 (CO), 1710 (CO) and 1665 (C=C); δ($CDCl_3$) 1.28 (3 H, t, NCH_2Me), 3.69 (2 H, q, NCH_2Me), 4.02 (1 H, d, *J* 6, exchanged with D_2O, 5-OH), 6.79–6.85 [2 H, d, *J* 6 (collapsed to a singlet at δ 6.82 on addition of D_2O), 5-H, overlapping with a singlet centred at δ 6.81, 10-H] and 7.39–7.50 (4 H, m, ArH).

Preparation of Reissert Compounds **5h** *and* **5i**.—To a stirred suspension of 2-ethyl-2,3-dihydro-1,3-dioxo-1H-imidazo[1,5-*b*]isoquinolinium bromide[1] **4b** (1.23 g, 4 mmol) in dichlorometh-

Table 5 Analytical data for the (±)-dihydro-adducts **8a–8k**

Compound (Formula)	Yield[a] (%)	Solvent	M.p. (°C)	Found % (Required) C	H	N	S
8a	53	MeOH	107–109	63.0	5.6	11.3	
($C_{13}H_{14}N_2O_3$)				(63.4	5.75	11.35)	
8b	54	EtOH	130–131	64.2	6.35	11.15	
($C_{14}H_{16}N_2O_3$)				(64.6	6.2	10.75)	
8c	48	MeOH	196–198	70.2	5.05	8.95	
($C_{18}H_{16}N_2O_3$)				(70.1	5.25	9.1)	
8d	51	EtOH	143–145	71.1	5.55	8.9	
($C_{19}H_{18}N_2O_3$)				(70.8	5.65	8.7)	
8e	41	Pr^{i}OH	121–123	71.0	5.75	8.05	
($C_{20}H_{20}N_2O_3$)				(71.4	6.0	8.35)	
8f[b]	61	AcOEt	190–191	66.45	5.1	8.85	9.8
($C_{19}H_{18}N_2O_2S$)				(66.65	4.95	8.65	9.9)
8g	51	AcOEt	165.5–167	67.6	5.35	7.95	9.45
($C_{19}H_{18}N_2O_2S$)				(67.45	5.35	8.25	9.45)
8h[c,d]				61.05	5.55	15.15	
($C_{14}H_{15}N_3O_3$)				(61.5	5.55	15.4)	
8i[d]	50	Et_2O	127–128	64.8	6.9	15.95	
($C_{14}H_{17}N_3O_2$)				(64.85	6.6	16.2)	
8j[d]	43	Et_2O	116–118	72.15	6.45	11.65	
($C_{21}H_{23}N_3O_2$)				(72.2	6.65	12.0)	
8k[e]	32	Et_2O	195–197	69.75	5.85	11.2	
($C_{21}H_{27}N_3O_3$)				(69.4	5.8	11.55)	

[a] Yield is based on the appropriate 10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-dione **1**. [b] The (−)-isomer. [c] The product was a semi-solid at room temperature. [d] The products were purified by column chromatography on silica gel, with chloroform–diethyl ether (8:2) as eluant. [e] The product was purified by column chromatography on neutral alumina, with chloroform-diethyl ether (9:1) as eluant.

ane (150 cm^3) was added dropwise a solution of potassium cyanide (0.32 g) in water (4 cm^3). The reaction mixture was stirred until all of the reactants had dissolved and the solution was left overnight before being treated with anhydrous sodium sulphate, filtered and evaporated to give an oil, which on trituration with anhydrous diethyl ether yielded 2-*ethyl*-1,2,3,5-*tetrahydro*-1,3-*dioxoimidazo*[1,5-b]*isoquinoline*-5-*carbonitrile* **5h** (0.26 g, 26%), m.p. 175–176 °C (from MeOH) (Found: C, 66.15; H, 4.2; N, 16.2%; M$^+$, 253. $C_{14}H_{11}N_3O_2$ requires C, 66.4; H, 4.4; N, 16.6%; M, 253); ν_{max}/cm^{-1} 1765 (CO), 1720 (CO) and 1665 (C=C); δ(CDCl$_3$) 1.29 (3 H, t, NCH$_2$*Me*), 3.72 (2 H, q, NC*H*$_2$Me), 6.25 (1 H, s, 5-H), 6.74 (1 H, s, 10-H) and 7.42 (4 H, s, ArH).

Column chromatography of the ethereal filtrate on silica gel, with chloroform–diethyl ether (9:1) as eluant, gave the pseudobase **5g** (0.19 g) (also isolated from the reaction of compound **4b** with triethylamine).

Similar treatment of 2,3-dihydro-1,3-dioxo-2-propyl-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **4c** (1.28 g, 4 mmol) with potassium cyanide (0.32 g) afforded 1,2,3,5-tetrahydro-1,3-dioxo-2-propylimidazo[1,5-*b*]isoquinoline-5-carbonitrile **5i** (0.49 g, 46%), m.p. 159–161 °C (lit.,[24] 160–161 °C) (Found: C, 67.05; H, 4.8; N, 15.45%. Calc. for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.7%); ν_{max}/cm^{-1} 1770 (CO), 1715 (CO) and 1665 (C=C); δ(CDCl$_3$) 0.95 (3 H, t, NCH$_2$CH$_2$*Me*), 1.73 (2 H, m, NCH$_2$C*H*$_2$Me), 3.62 (2 H, t, NC*H*$_2$CH$_2$Me), 6.28 (1 H, s, 5-H), 6.77 (1 H, s, 10-H) and 7.45 (4 H, s, ArH).

Reaction of 10-*Bromo*-2,3-*dihydro*-1,3-*dioxo*-2-*phenyl*-1H-*imidazo*[1,5-b]*isoquinolinium Bromide* **2d** *with Cyanide*.—Treatment of crude 10-bromo-2,3-dihydro-1,3-dioxo-2-phenyl-1*H*-imidazo[1,5-*b*]isoquinolinium bromide[1] **2d** (0.5 g) with potassium cyanide (0.1 g) in water (1 cm^3) and dichloromethane (50 cm^3) gave, after the usual work-up, a white solid (from acetonitrile) which was tentatively assigned as the pseudobase **3g**, ν_{max}/cm^{-1} 3440 (OH), 1760 (CO), 1710 (CO) and 1630 (C=C); δ[(CD$_3$)$_2$SO] 6.68 (1 H, d, *J* 7, after addition of D$_2$O collapsed to a singlet, 5-H), 7.09 (1 H, d, *J* 7, exchanged with D$_2$O, 5-OH), 7.42–7.58 (8 H, m, ArH) and 7.81–7.96 (1 H, m, 9-H). The product was refluxed with dry methanol for 4 h to give the corresponding ether **3e**.

Benzylation of 1,2,3,5-*Tetrahydro*-1,3-*dioxo*-2-*propylimidazo*-[1,5-b]*isoquinoline*-5-*carbonitrile* **5i**.—A suspension of compound **5i** (0.267 g, 1 mmol) in freshly distilled, dry DMF (3 cm^3) was stirred at 0 °C under nitrogen. Benzyl chloride (0.19 g, 1.5 mmol) and sodium hydride (0.036 g, 1.5 mmol) were added successively and the mixture was stirred for 3 h, poured onto crushed ice, then extracted with chloroform and the extracts were dried (MgSO$_4$) and evaporated to afford 5-*benzyl*-1,2,3,5-*tetrahydro*-1,3-*dioxo*-2-*propylimidazo*[1,5-*b*]*isoquinoline*-5-*carbonitrile* **6** (0.16 g, 45%), m.p. 196–197 °C (from MeOH) (Found: C, 73.45; H, 5.15; N, 11.75%; M$^+$, 357. $C_{22}H_{19}N_3O_2$ requires C, 73.9; H, 5.35; N, 11.45%; M, 357); ν_{max}/cm^{-1} 1765 (CO), 1715 (CO) and 1680 (C=C); δ(CDCl$_3$) 0.99 (3 H, t, NCH$_2$-CH$_2$*Me*), 1.75 (2 H, m, NCH$_2$C*H*$_2$Me), 3.21–4.10 (4 H, a triplet centred at δ 3.61, NC*H*$_2$CH$_2$Me, overlapping with an ABq, *J* 14, C*H*$_2$Ph), 6.16 (1 H, s, 10-H) and 6.51–7.63 (9 H, m, ArH).

Reaction of (±)-1,2,10,10a-7-*Tetrahydro*-1,3-*dioxo*-1H-*imidazo*[1,5-b]*isoquinolinium Bromides* **7** *with Various Nucleophiles*.—A suspension of the appropriate (±)-10,10a- tetrahydroimidazo[1,5-*b*]isoquinoline-1,3(2H,5H)-dione **1a** or **1d** (10 mmol) in dry tetrachloromethane (10 cm^3) was treated with a solution of bromine (1.6 g, 10 mmol) in dry tetrachloromethane (5 cm^3)[1]. The resultant crude (±)-1,2,10,10a-tetrahydro-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **7** was treated with dry methanol, absolute ethanol, or isopropyl alcohol (10 cm^3) to give the (±)-2-substituted 5-alkoxy-10,10a-dihydroimidazo[1,5-*b*]isoquinoline-1,3(2*H*,5*H*)-diones **8a–8e**, which were recrystallised from an appropriate solvent.

Treatment, by this procedure, of the salts **7** with thiophenol, ethanethiol, and acetaldoxime in dry, ethanol-free chloroform afforded the corresponding adducts **8f–8h**. Treatment of the salts **7**, under similar conditions, with dimethylamine, diethylamine, and morpholine afforded the adducts **8i–8k**, which were purified by column chromatography on silica or neutral alumina, with chloroform–diethyl ether (9:1) as eluant. The

Table 6 Spectroscopic data for the (±)-dihydro-adducts **8a**–**8k**

Compound	IR (ν_{max}/cm^{-1})	^{1}H NMR[a] (δ) 5-H[b]	10a-H[c]	10-H$_2$[d]	Other protons
8a	1760 (CO), 1710 (CO)	6.02	4.30	2.64 3.38	3.06 (3 H, s, NMe), 3.52 (3 H, s, 5-OMe), 7.18–7.51 (4 H, m, ArH)
8b	1760 (CO), 1710 (CO)	6.10	4.30	2.65–3.33	1.25 (3 H, t, OCH$_2$*Me*), 3.03 (3 H, s, NMe), 3.81 (2 H, q, OC*H*$_2$Me), 7.15–7.50 (4 H, m, ArH)
8c	1770 (CO), 1720 (CO)	6.12	4.49	2.81–3.50	3.60 (3 H, s, 5-OMe), 7.25–7.52 (9 H, m, ArH)
8d	1770 (CO), 1720 (CO)	6.21	4.50	2.82–3.50	1.30 (3 H, t, OCH$_2$*Me*), 3.90 (2 H, q, OC*H*$_2$Me), 7.25–7.51 (9 H, m, ArH)
8e	1780 (CO), 1715 (CO)	6.27	4.50	2.80–3.48	1.20 (3 H, d, *J* 6 Hz, CH-*Me*), 1.40 (3 H, d, *J* 6 Hz, CH*Me*), 4.13–4.29 (1 H, m, C*H*Me$_2$), 7.23–7.48 (9 H, m, ArH)
8f[e]	1770 (CO), 1710 (CO)	6.60	4.37	2.55–3.40	2.90 (3 H, s, NMe), 7.15–7.59 (9 H, m, ArH)
8g[f]	1770 (CO), 1710 (CO)	6.57	4.66	2.86–3.52	1.32 (3 H, t, SCH$_2$*Me*), 2.82 (2 H, q, SC*H*$_2$Me). 7.20–7.48 (9 H, m, ArH)
8i	1770 (CO), 1710 (CO)	5.75	4.15	2.58–3.37	2.29 (6 H, s, 5-NMe$_2$), 3.07 (3 H, s, NMe), 7.18–7.32 (3 H, m, ArH), 7.59–7.70 (1 H, m, 6-H)
8j	1770 (CO), 1710 (CO)	5.99	4.29	2.78–3.47	1.10 [6 H, t, N(CH$_2$*Me*)$_2$], 2.62 [4 H, q, N(C*H*$_2$Me)$_2$], 7.20–7.48 (8 H, m, ArH), 7.63–7.74 (1 H, m, 6–H)
8k[g]	1770 (CO), 1715 (CO)	5.85	4.29	2.82–3.49	2.62–2.75 [4 H, two overlapping triplets N(C*H*$_2$)], 3.69 [4 H, t, O(C*H*$_2$)], 7.24–7.51 (8 H, m, ArH), 7.70–7.81 (1 H, m, 6-H)

[a] Spectra were recorded in $CDCl_3$. [b] Singlet. [c] Doublet of quartets. [d] Double doublets. [e] (−)-Isomer, $[\alpha]_D^{20}$ −62.4° (*c*, 1.0, $CHCl_3$). [f] M^+, 338.1127. $C_{19}H_{18}N_2O_2{}^{32}S$ requires M, 338.1089. [g] Addition of DCl shifted the signals downfield and after 12 h gave a yellow precipitate.

analytical and spectral data of the adducts **8a**–**8k** are given in Tables 5 and 6.

Reaction of (±)-2,3,10-10a-*Tetrahydro*-2-*methyl*-1,3-*dioxo*-1H-*imidazo*[1,5-b]*isoquinolinium Bromide* **7a** *with Phenylmagnesium Bromide*.—To a stirred solution of phenylmagnesium bromide in dry diethyl ether, which was freshly prepared from bromobenzene (3.14 g, 20 mmol) and magnesium turnings (0.53 g, 22 mmol), was added crude powdered compound **7a** (2.36 g, 8 mmol) portionwise. The reaction was continued for 0.5 h and then water (30 cm^3) was added slowly; dil. hydrochloric acid was added until two layers resulted, followed finally by ammonium chloride (1.5 g) and sufficient ammonia to make the aq. phase alkaline. The organic layer was separated, washed with water, and dried (Na_2SO_4). Evaporation of the solvents gave an off-white solid (1.1 g), which was chromatographed on a silica gel column, with chloroform–diethyl ether–methanol (85:10:5) as eluant, to afford (±)-2,3,10,10a-*tetrahydro*-3-*hydroxy*-2-*methyl*-3,5-*diphenylimidazo*[1,5-b]*isoquinolin*-1(5H)-*one* **9** m.p. 188–190 °C (Found: C, 77.35; H, 6.1; N, 7.6%; M^+, 370. $C_{24}H_{22}N_2O_2$ requires C, 77.8; H, 6.0; N, 7.55%; M, 370); ν_{max}/cm^{-1} 3250 (OH) and 1685 (CO); δ($CDCl_3$) 2.50 (3 H, s, NMe), 2.85–3.15 (2 H, dq, 10-H$_2$), 3.87 (1 H,dd, *J* 6 and 13, 10a-H), 5.06 (1 H, s, exchanged with D_2O, 3-OH), 5.78 (1 H, s, 5-H) and 7.05–7.46 (14 H, m, ArH).

Preparation of Dihydro-Reissert Compounds **8l** *and* **8m**.—A suspension of crude (±)-2,3,10,10a-tetrahydro-2-methyl-1,3-dioxo-1*H*-imidazo[1,5-*b*]isoquinolinium bromide **7a**, obtained from the bromination of compound **1b** (2.16 g, 10 mmol) in tetrachloromethane,[1] was treated as described previously for the preparation of Reissert compounds **5h** and **5i** with a solution of potassium cyanide (1 g) in water (5 cm^3) to give (±)-1,2,3,5,10,10a-*hexahydro*-2-*methyl*-1,3-*dioxoimidazo*[1,5-b]*isoquinoline*-5-*carbonitrile* **8l** (0.6 g, 25% based on **1b**), m.p. 230–231 °C (Found: C, 64.5; H, 4.5; N, 17.75%; M^+, 241. $C_{13}H_{11}N_3O_2$ requires C, 64.5; H, 4.6; N, 17.4%; M, 241); ν_{max}/cm^{-1} 2240vw (CN), 1770 (CO) and 1710 (CO); δ($CDCl_3$) 2.70–3.47 (5 H, dq, 10-H$_2$ overlapping with a s centred at δ 3.09, NMe), 4.28 (1 H, dd, *J* 6 and 13, 10a-H), 6.02 (1 H, s, 5-H) and 7.25–7.52 (4 H, m, ArH).

By a similar procedure (±)-1,2,3,5,10,10a-*hexahydro*-1,3-*dioxo*-2-*phenylimidazo*[1,5-*b*]*isoquinoline*-5-*carbonitrile* **8m** was obtained from the salt **7b**, m.p. 229–231 °C (from MeOH) (Found: C, 71.6; H, 4.5; N, 13.7. $C_{18}H_{13}N_3O_2$ requires C, 71.25; H, 4.3; N, 13.85%); ν_{max}/cm^{-1} 2250vw (CN), 1780 (CO) and 1715 (CO); δ($CDCl_3$) 2.85–3.56 (2 H, dq, 10-H$_2$), 4.42 (1 H, dd, *J* 6 and 13, 10a-H), 6.11 (1 H, s, 5-H) and 7.32–7.43 (9 H, m, ArH).

Hydrolysis of Reissert and Dihydro-Reissert Compounds **5i**, **8l** and **8m**.—A solution of the Reissert compound **5i** (0.67 g, 3 mmol) in conc. hydrochloric acid (20 cm^3) was refluxed for 2 h. After cooling, the white product which separated out was

collected by filtration and recrystallised from acetone to give 1,2,3,5-*tetrahydro*-1,3-*dioxo*-2-*propylimidazo*[1,5-*b*]*isoquinoline*-5-*carboxamide* **5j** as a solid (0.64 g, 89.5%), m.p. 287–289 °C (Found: C, 63.65; H, 5.25; N, 14.55. $C_{15}H_{15}N_3O_3$ requires C, 63.35; H, 4.95; N, 14.75%); ν_{max}/cm^{-1} 3395 and 3225 (NH_2), 1775 (CO), 1715 (CO), 1685 (amide I), 1670 (C=C) and 1635 (amide II); δ[$(CD_3)_2SO$] 0.88 (3 H, t, NCH_2CH_2Me), 1.60 (2 H, m, NCH_2CH_2Me), 3.49 (2 H, t, NCH_2CH_2Me), 4.30–4.55 (2 H, br s, exchanged with D_2O, 5-$CONH_2$), 5.22 (1 H, s, 5-H), 6.61 (1 H, s, 10-H) and 7.21–7.65 (4 H, m, ArH).

The amide **5j** (0.3 g) was further hydrolysed by being refluxed for 4 h with a mixture of sulphuric acid, glacial acetic acid and water (15 cm^3; 1:1:1). The resultant clear solution, after cooling to room temperature, was poured onto crushed ice and extracted with diethyl ether; the extract was washed with water, dried (Na_2SO_4), and evaporated to give an oil, which was dissolved in 5% aq. sodium hydroxide and acidified with 6 mol dm^{-3} hydrochloric acid to yield 1,2,3,5-*tetrahydro*-1,3-*dioxo*-2-*propylimidazo*[1,5-*b*]*isoquinoline*-5-*carboxylic acid* **5k** (0.17 g, 57%), m.p. 182–184 °C (Found: C, 62.9; H, 4.95; N, 9.9%; M^+, 286. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.95; N, 9.8%; M, 286); ν_{max}/cm^{-1} 1760 (CO), 1710 (CO) and 1675 (C=C); δ[$(CD_3)_2SO$] 0.87 (3 H, t, NCH_2CH_2Me), 1.62 (2 H, m, NCH_2CH_2Me), 3.50 (2 H, t, NCH_2CH_2Me), 4.35–4.95 (br s, exchange signal of 5-CO_2H with water in solvent), 5.60 (1 H, s, 5-H), 6.72 (1 H, s, 10-H) and 7.25–7.55 (4 H, m, ArH).

Compound **8l** (1.2 g, 5 mmol) was refluxed for 3 h in a mixture of conc. hydrochloric acid (35 cm^3) and glacial acetic acid (15 cm^3). The solution was cooled, extracted with diethyl ether and the extract was washed with water and dried (Na_2SO_4). Evaporation gave an oil, which when triturated with dry diethyl ether afforded (±)-1,2,3,5,10,10a-*hexahydro*-2-*methyl*-1,3-*dioxoimidazo*[1,5-*b*]*isoquinoline*-5-*carboxylic acid* **8n** (0.9 g, 70%), m.p. 189.5–191 °C (Found: C, 60.1; H, 4.95; N, 10.85%. $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.65; N, 10.75%); ν_{max}/cm^{-1} 1770 (CO), 1735 (CO) and 1690 (CO); δ($CDCl_3$) 2.70–3.41 (5 H, dq, 10-H_2 overlapping with a s centred at δ 3.05, NMe), 4.51 (1 H, dd, *J* 6 and 13, 10a-H), 5.70 (1 H, s, 5-H), 7.20–7.34 (3 H, m, ArH), 7.51–7.66 (1 H, m, 6-H), 10.20 (1 H, s, exchanged with D_2O, 5-CO_2H).

By an identical procedure compound **8m** (1.21 g, 4 mmol) gave (±)-1,2,3,5,10,10a-*hexahydro*-1,3-*dioxo*-2-*phenylimidazo*-[1,5-*b*]*isoquinoline*-5-*carboxylic acid* **8p** (0.96 g, 75%), m.p. 246–248 °C (Found: C, 66,75; H, 4.45; N, 8.8%; M^+, 322. $C_{18}H_{14}N_2O_4$ requires C, 67.05; H, 4.4; N, 8.75%; M, 322); ν_{max}/cm^{-1} 1775 (CO), 1735 (CO) and 1700 (CO); δ[$(CD_3)_2SO$] 3.13–3.30 (2 H, m, 10–H_2), 4.68 (1 H, dd, *J* 6 and 13, 10a-H), 5.62 (1 H, s, 5-H) and 7.30–7.69 (9 H, m, ArH).

The acid **8n** (0.53 g, 2 mmol) was treated with a freshly prepared solution of diazomethane in dichloromethane to yield (±)-*methyl* 1,2,3,5,10,10a-*hexahydro*-2-*methyl*-1,3-*dioxoimidazo*[1,5-b]*isoquinoline*-5-*carboxylate* **8q** (0.48 g, 88%), m.p. 118–119 °C (Found: C, 60.9; H, 5.25; N, 9.85. $C_{14}H_{14}N_2O_4$ requires C, 61.3; H, 5.15; N, 10.2%); ν_{max}/cm^{-1} 1775 (CO), 1740 (CO) and 1710 (CO); δ($CDCl_3$) 2.72–3.45 (5 H, dq, 10–H_2 overlapping with a s centred at δ 3.08, NMe), 3.78 (3 H, s, 5-CO_2Me), 4.59 (1 H, dd, *J* 6 and 13, 10a-H), 5.72 (1 H, s, 5-H), 7.20–7.35 (3 H, m, ArH) and 7.53–7.64 (1 H, m, 6-H).

Similar treatment of acid **8p** with diazomethane (0.644 g, 2 mmol) gave (±)- *methyl* 1,2,3,5,10,10a-*hexahydro*-1,3-*dioxo*-2-*phenylimidazo*[1,5-b]*isoquinoline*-5-*carboxylate* **8r** (0.63 g, 94%), m.p. 167–169 °C (from MeOH) (Found: C, 68.25; H, 4.95; N, 8.65. $C_{19}H_{16}N_2O_4$ requires C, 67.85; H, 4.8; N, 8.35%); ν_{max}/cm^{-1} 1780 (CO), 1750 (CO) and 1710 (CO); δ($CDCl_3$) 2.89–3.55 (2 H, dq, 10-H_2), 3.80 (3 H, s, 5-CO_2Me), 4.76 (1 H, dd, *J* 6 and 13, 10a-H), 5.80 (1 H, s, 5-H) and 7.23–7.68 (9 H, m, ArH).

References

1 I. Niopas and G. A. Smail, preceding paper.
2 J. W. Bunting and W. G. Meathrel, *Can. J. Chem.*, 1972, **50**, 917.
3 B. C. Uff, J. R. Kershaw and S. R. Chhabra, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1146.
4 R. A. Corral and O. O. Orazi, *Spectrochim. Acta*, 1965, **21**, 2119.
5 R. H. Barker, G. J. Bourdeaux and S. L. Vail, *Appl. Spectrosc.*, 1966, **20**, 414.
6 C. K. Bradsher, *Quaternary Isoquinolinium Salts*, in *Isoquinolines*, Part 1, ed. G. Grethe, *Heterocyclic Compounds*, John Wiley, London, 1981, vol. 38, p. 381.
7 F. Krohnke and I. Vogt, *Chem. Ber.*, 1957, **90**, 2227.
8 D. Beke, *Adv. Heterocycl. Chem.*, 1963, **1**, 167.
9 M. D. Johnson, *J. Chem. Soc.*, 1964, 200.
10 R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, 1925, **127**, 1434.
11 F. D. Popp and W. Blount, *Chem. Ind. (London)*, 1961, 550.
12 W. E. McEven and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511.
13 F. D. Popp, K. T. Potts and R. Armbruster, *Org. Mass Spectrom.*, 1970, **3**, 1075.
14 R. Chenevert, E. Lemieux and N. Voyer, *Synth. Commun.*, 1983, **13**, 1095.
15 I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, 1976, p. 33.
16 R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 581, 643.
17 C. Schuerch and E. H. Huntress, *J. Am. Chem. Soc.*, 1948, **70**, 2824.
18 R. Piccivili and F. D. Popp, *Can. J. Chem.*, 1969, **47**, 3261.
19 B. C. Uff, J. R. Kershaw and J. L. Neumeyer, *Org. Synth.*, 1977, **56**, 19.
20 M. Makosza, *Tetrahedron Lett.*, 1969, 677.
21 W. J. Gensler, *Heterocyclic Compounds*, ed. R. C. Elderfield, John Wiley, London, 1952, vol. 4, p. 344.
22 S. Cortes and H. Kohn, *J. Org. Chem.*, 1983, **48**, 2246.
23 W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.*, 1976, **19**, 1.
24 E. C. Weir, Ph.D. Thesis, University of Strathclyde, 1979.

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