Conversion of Pyridines and Quinolines into Pyridazines and Pyrazoles

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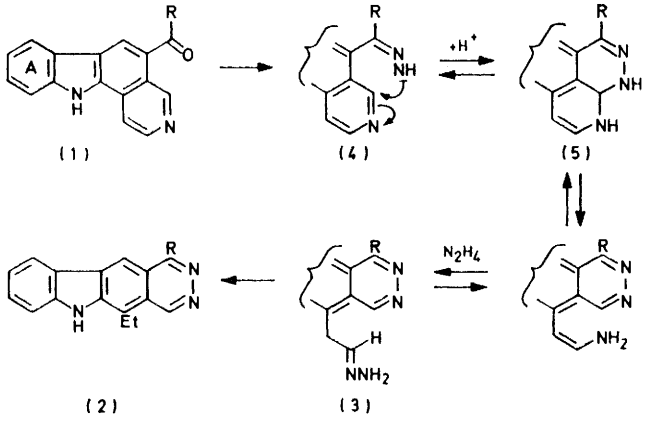
3-Phenacylpyridinium and 3-phenacylquinolinium methiodides are shown to react with hydrazine–potassium hydroxide and hydrazine respectively to give 4-alkyl-6-phenylpyridazines and 4-(2-aminobenzyl)-6-phenylpyridazines respectively. 3-Benzoylpyridinium methiodide gives 3-phenyl-4-propylpyrazole with hydrazine–potassium hydroxide, then catalytic reduction.

RECENTLY we recorded [1] the transformation of a 5-acyl-11*H*-pyrido[4,3-*a*]carbazole (1) (and ring-A-tetrahydro-derivatives) into a pyridazo[4,5-*b*]carbazole (2) (and tetrahydro-derivatives) by reaction with hydrazine and



SCHEME 1

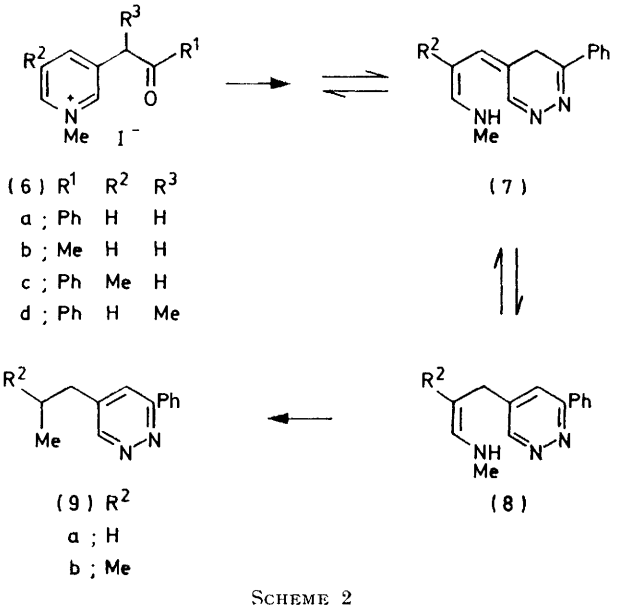
alkali. The rearrangement was envisaged as proceeding by the novel sequence shown in Scheme 1, the series of equilibria being taken to completion by the irreversible Wolff–Kishner reduction step (3) ⟶ (2). We have now examined further the generality of the process by looking at simpler analogues, in particular at 3-phenacylpyridines and -quinolines.

3-Phenacylpyridine [2] treated with hydrazine and alkali in the same way as was successful for the transformation of (1) into (2) led only and cleanly to standard Wolff–Kishner reduction and thus the formation of 3-(2-phenethyl)-pyridine. Reasoning that, in the monocyclic system, the ring-closure step, intramolecular nucleophilic addition, (4) ⟶ (5), would be considerably less favoured, a greater loss of aromatic resonance energy being involved than in the polycyclic system, we sought to favour this over the competing step in the Wolff–Kishner sequence by quaternising the nitrogen and so rendering the ring more susceptible to addition.

3-Phenacylpyridinium methiodide (6a) was treated with hydrazine and potassium hydroxide and now the corresponding pyridazine (9a) was indeed formed. Scheme 2 shows how we envisage that the intermediate (7) aromatises [to (8)] by tautomerism and then, as in Scheme 1, this step is followed by an irreversible Wolff–Kishner reduction. Attempts to achieve a comparable transformation, as had been successful in the polycyclic series,[1] with a methyl ketone, 3-acetonylpyridine methiodide (6b), were completely without success. Accordingly all subsequent experiments detailed below were carried out using benzoyl compounds. Thus, for example, benzoylation of 3,5-dimethylpyridine and the sequential treatment of the ketonic product with methyl iodide [to (6c)] and then hydrazine–potassium hydroxide gave the isobutylpyridazine (9b). Disappointingly, although 3-ethylpyridine was readily benzoylated and the ketone quaternised [to (6d)] no pyridazine could be obtained from hydrazine–base treatment, a multi-component mixture being formed instead.

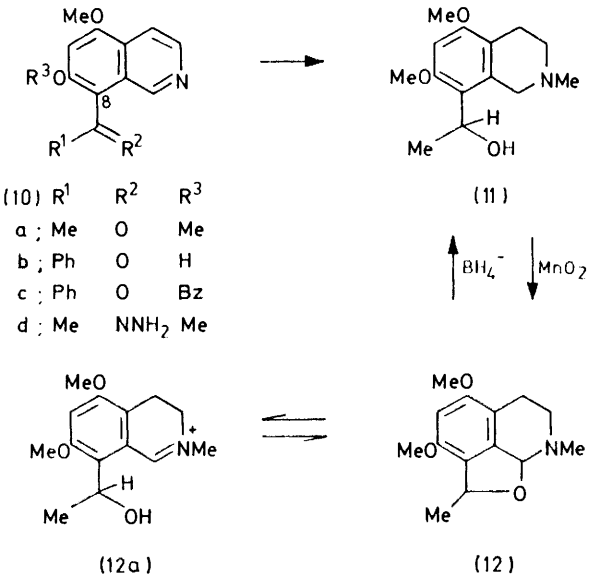
The operation of the novel sequence had now been demonstrated in a monocyclic, pyridine system and also in an isoquinoline system, albeit as part of a fused ring system in (1). We next sought to examine the operability of the rearrangement in a simpler isoquinoline context. For this purpose an 8-acylisoquinoline was required. Such ketones are not easily available; the most obvious way to make one seemed to be the acylation of a benzene-ring-activated isoquinoline.

5,7-Dimethoxyisoquinoline [3] could not be formylated with the usual Vilsmeier conditions, but it was acylated in very good yield with either acetyl chloride [to (10a)] or benzoyl chloride [to (10b) or (10c) according to length of reaction] and aluminium chloride. In order to confirm the predicted 8-substitution, the ketone (10a) was quaternised with methyl iodide and the salt reduced



SCHEME 2

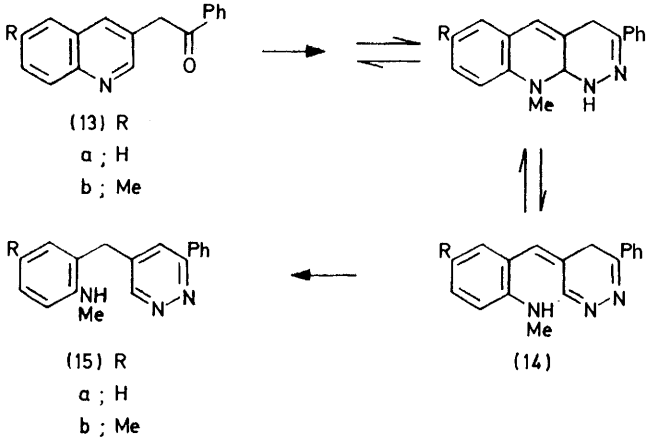
with sodium borohydride to the tetrahydroisoquinoline alcohol (11). Oxidation of this with manganese dioxide gave the cyclic carbinolamine ether (12), τ 5.40 for the C-1-proton, a structure only possible from an 8-acylated



isoquinoline. The ether, which was shown by u.v. spectroscopy in ethanol, to be in equilibrium, in that solvent, with a ring-opened immonium form (12a), could be efficiently reconverted to the alcohol (11) by reduction with sodium borohydride.

The ketone (10a) was transformed, with difficulty, presumably because of steric factors, into the hydrazone (10d), but attempted transformation to a benzopyridazine met with total failure. Quaternisation of the pyridine nitrogen and treatment with hydrazine–alkali also failed to bring about reaction in the desired sense, only water-soluble products being formed. Using the methiodide of the benzoyl ketone (10b), again no success was achieved in attempts to effect transformation to a benzopyridazine.

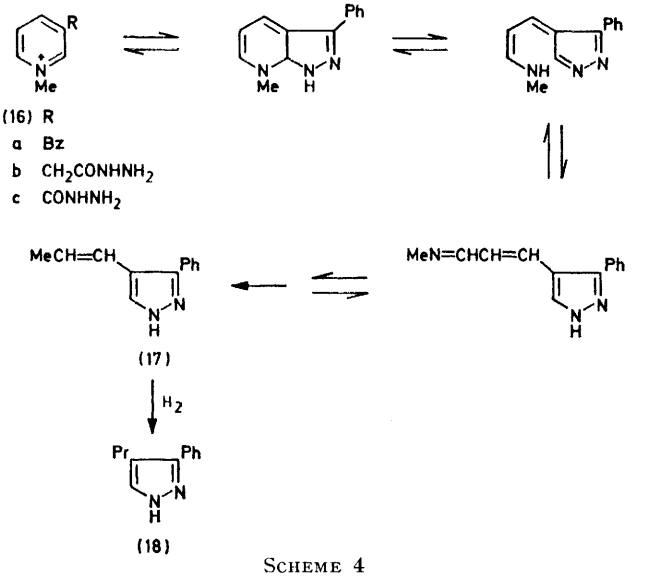
Examination of an extrapolation (Scheme 3) of the proposed mechanistic sequence (Scheme 1) for the



SCHEME 3

pyridazine-forming process, readily reveals that for a 2,3-benzopyridine, *i.e.* for a quinoline, no reductive step would seem to be necessary, the postulated intermediate ring-closure–ring-opening product (14) being a tautomer of an aromatic pyridazine, with the ' enamine ' double bond now being part of the carbocyclic aromatic ring. In the event, this prediction was fully borne out, in what turned out to be the most efficient examples of the operation of the new ring transformation. 3-Methylquinoline [4] was benzoylated on the side chain and the methiodide of the product ketone (13a) treated with hydrazine alone: the phenyl aminobenzyl pyridazine (15a) was formed easily, in high yield. 3,6-Dimethylquinoline [4] was shown to deprotonate and thus benzoylate selectively on the hetero-ring methyl group, by the subsequent conversion of this ketone (13b), again very efficiently, into the pyridazine (15b).

Finally, at this stage of our studies in this area, we have demonstrated that an exactly analogous sequence, to produce pyrazoles, is feasible. Thus we transformed, albeit in poorer yield than for the corresponding pyridazine, 3-benzoylpyridine methiodide (16a) with hydrazine–potassium hydroxide, into an unstable substance, which could not be easily purified or characterised but which we believe to be the pyrazole (17) on the



SCHEME 4

basis of a mass-spectral molecular ion and principally its catalytic reduction in good yield to fully characterised 3-phenyl-4-propylpyrazole (18). Scheme 4 indicates a reasonable sequence of steps.

Attempts to bring about the ring transformation at a higher oxidation level to give pyridazinones or pyrazolones starting with the hydrazide salts (16b) and (16c) were unsuccessful, only water-soluble products being produced.

EXPERIMENTAL

General.—Organic extracts were dried with anhydrous magnesium sulphate. Extracts and reaction mixtures were

evaporated under reduced pressure (*ca.* 20 mmHg) using a rotary evaporator and a bath temperature of *ca.* 60 °C. Unless otherwise specified, u.v. spectra were measured in ethanol, i.r. spectra in chloroform, and n.m.r. spectra in deuteriochloroform solutions. Only clearly distinguished and unambiguously assignable absorptions are given for i.r. and n.m.r. spectra, in particular those which are of greatest importance for establishment of structure. Only ions of greater than 10% of base peak are given for mass spectra, except where a less intense ion is of particular importance for structure establishment.

3-Phenethylpyridine.—3-Phenacylpyridine [2] (110 mg) was treated with hydrazine hydrate (1.1 g) in refluxing diethylene glycol (12 ml) for 0.75 h. The mixture was cooled and potassium hydroxide (powdered, 400 mg) added. After a further period (2 h) under reflux the mixture was cooled, diluted with water, and extracted with ether to give the *phenethylpyridine* (100 mg), m.p. 24—25 °C, $\lambda_{max.}$ 222, 258, 264, and 270 nm (log ε 3.92, 3.42, 3.48, and 3.36), $\lambda_{max.}$ (EtOH–HCl) 232 and 267 nm (log ε 3.96 and 3.79), *m/e* 183 (M^+, 87%), 92 (47), and 91 (100) (Found: *M*, by mass spectrometry, 183.1051. $C_{13}H_{13}N$ requires *M*, 183.1048).

1-Methyl-3-phenacylpyridinium Iodide (6a).—3-Phenacylpyridine [2] (650 mg) was quaternised in ethyl acetate at reflux for 2 h with methyl iodide (4.7 g). The resulting precipitate was filtered off and crystallised from ethanol to give the *methiodide* (6a) (1.02 g), m.p. 119 °C, $\lambda_{max.}$ 247, 270sh, and 286sh nm (log ε 4.24, 3.89, and 3.19); $\lambda_{max.}$ (EtOH–NaOH) 248 and 374 nm (log ε 4.21 and 4.47) (Found: C, 49.4; H, 4.1; I, 37.8; N, 3.9. $C_{14}H_{14}INO$ requires C, 49.56; H, 4.1; I, 37.5; N, 4.1%).

6-Phenyl-4-propylpyridazine (9a).—The iodide (6a) (250 mg) in diethylene glycol (10 ml) was treated with hydrazine hydrate (1.5 g) at reflux for 2 h. Powdered potassium hydroxide (400 mg) was then added to the cooled solution and the mixture was refluxed for 2.5 h. The cooled reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was thoroughly washed with water, dried, and evaporated to give an oil which was crystallised from hexane to give the pyridazine (9a) (80 mg), m.p. 69—70 °C, $\lambda_{max.}$ 219 and 252 nm (log ε 3.96 and 4.03); $\lambda_{max.}$ (EtOH–HCl) 220, 241, and 262 nm (log ε 3.99, 4.01, and 4.02); τ 1.04 (1 H, d, *J* 2 Hz, 3-H), 7.37 (2 H, t, *J* 8 Hz, pyridazinyl-CH_2), 8.28 (2 H, sextet, *J* 8 Hz, $CH_2CH_2CH_3$), and 9.03 (3 H, t, *J* 8 Hz, CH_3CH_2); *m/e* 198 (M^+, 100%), 170 (38), 141 (38), and 102 (90) (Found: C, 78.8; H, 7.1; N, 14.1%; *M*, by mass spectrometry, 198.1160. $C_{13}H_{14}N_2$ requires C, 78.8; H, 7.1; N, 14.1%; *M*, 198.1157).

3-Acetonyl-1-methylpyridinium Iodide (6b).—3-Acetonylpyridine [5] (550 mg), prepared using the recently described [2] method, was quaternised with methyl iodide (5.78 g) in ethyl acetate (12 ml) at reflux for 5 h. The solvent was decanted and the residue dried under high vacuum, to give the *iodide* (6b) (1.09 g) as a foam, $\lambda_{max.}$ 248 and 267 nm; $\nu_{max.}$ 1 720 cm^{-1}; τ (D_2O) 1.2 (2 H, br s, pyridine-α-H), 1.56 (1 H, br s, pyridine-γ-H), 1.79 (1 H, t, *J* 6 Hz, pyridine-β-H), 5.57 (3 H, s, N^+CH_3), and 7.45 (3 H, s, CH_3CO).

5-Methyl-3-phenacylpyridine.—3,5-Dimethylpyridine (1.34 g) was deprotonated using lithium di-isopropylamide [prepared from di-isopropylamine (1.27 g) and n-butyllithium (1.8M; 7.2 ml) in THF at 0 °C] at 0 °C for 0.5 h. HMPA (2.25 g) and then methyl benzoate (1.98 g) were added and the mixture stirred at room temperature for 2 h when the product was extracted into dilute hydrochloric acid. After washing the aqueous layer with ethyl acetate it was basified and then extracted with ether to give an oil from which the *pyridine ketone* (1.41 g) was obtained by distillation at 100—103 °C at 0.5 mmHg and then crystallisation of the distillate from hexane, m.p. 54—55 °C; $\lambda_{max.}$ 245, 268sh, and 278sh nm (log ε 4.16, 3.57, and 3.17); $\lambda_{max.}$ (EtOH–HCl) 250 and 278sh nm (log ε 4.32 and 3.34); $\nu_{max.}$ 1 681s cm^{-1}; τ 1.7 (2 H, br s, pyridine-α-H), 5.8 (2 H, s, CH_2), and 7.7 (3 H, s, CH_3); *m/e* 211 (M^+, 21%), 192 (12), 151 (42), 106 (14), 105 (100), and 77 (65) (Found: C, 79.4; H, 6.4; N, 6.5%; *M*, by mass spectrometry, 211.0991. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.6%; *M*, 211.0997).

1,5-Dimethyl-3-phenacylpyridinium Iodide (6c).—5-Methyl-3-phenacylpyridine (190 mg) was quaternised with methyl iodide (1.28 g) in refluxing ethyl acetate (5 ml) for 4 h. The solid was filtered off and recrystallised from ethanol to give the *iodide* (6c) (282 mg), m.p. 147—149 °C, $\lambda_{max.}$ 247, 271sh, and 288sh nm (log ε 4.2, 3.96, and 3.31); $\lambda_{max.}$ (EtOH–NaOH) 253 and 373 nm (log ε 4.19 and 4.38); $\nu_{max.}$ 1 688s cm^{-1}; τ (D_2O) 1.37 (2 H, br s, pyridine-α-H), 1.70 (1 H, br s, pyridine-γ-H), 5.6 (3 H, s, N^+CH_3), and 7.5 (3 H, s, CH_3) (Found: C, 50.6; H, 4.6; I, 35.9; N, 3.8. $C_{15}H_{16}INO$ requires C, 51.0; H, 4.5; I, 36.0; N, 4.0%).

4-Isopropyl-6-phenylpyridazine (9b).—A solution of the iodide (6c) (100 mg) in diethylene glycol (6 ml) was refluxed with hydrazine hydrate (0.7 g) for 1.5 h. After cooling, powdered potassium hydroxide (180 mg) was added and the whole refluxed for 2 h. The cooled, diluted (water) mixture was extracted with ethyl acetate. After washing the organic layer thoroughly with water it was dried and evaporated to give an oil which was crystallised from hexane to give the *pyridazine* (9b) (32 mg), m.p. 62 °C; $\lambda_{max.}$ 222 and 254 nm (log ε 3.96 and 4.08); $\lambda_{max.}$ (EtOH–HCl) 223, 242, and 264 (log ε 4.00, 4.03, and 4.07); τ 1.07 (1 H, d, *J* 2 Hz, 3-H), 7.45 (2 H, d, *J* 7.5 Hz, pyridazinyl-CH_2), 8.0 [1 H, m, $CH_2CH(Me)_2$], and 9.05 [6 H, d, *J* 7.5 Hz, $(CH_3)_2CH$]; *m/e* 212 (M^+, 100%), 170 (41), 141 (43), and 102 (76) (Found: C, 78.7; H, 7.8; N, 12.8%; *M*, by mass spectrometry, 212.1312. $C_{14}H_{16}N_2$ requires C, 79.2; H, 7.6; N, 13.2%; *M*, 212.1313).

1-Phenyl-2-(3-pyridyl)propan-1-one.—Lithium di-isopropylamide was prepared by treating di-isopropylamine (1.265 g) in THF (5 ml) with n-butyl-lithium (1.8M; 7.3 ml) in hexane at 0 °C for 0.5 h. After the addition of HMPA (2.25 g), 5-ethylpyridine (1.33 g) was added and the mixture set aside at room temperature for 2 h. To the resulting dark brown solution, methyl benzoate (1.7 g) in THF (7.5 ml) was added in one portion. After 3 h at room temperature the pyridine was extracted into dilute hydrochloric acid which was then washed thoroughly with ethyl acetate, basified, and extracted with ether to give an oil which was distilled at 102 °C and 0.5 mmHg. After chromatography over silica and elution with ethyl acetate the *pyridine ketone* (1.29 g), was obtained, m.p. 66—67 °C; $\lambda_{max.}$ 247 and 269sh nm (log ε 4.12 and 3.56); $\lambda_{max.}$ (EtOH–HCl) 252 and 271sh nm (log ε 4.22 and 3.69); $\nu_{max.}$ 1 682s cm^{-1}; τ 1.44 (1 H, br s, pyridine-α-H), 5.28 (1 H, q, *J* 8 Hz, CHMe), and 8.45 (3 H, d, *J* 8 Hz, CH_3CH); *m/e* 211 (M^+, 7%), 106 (11), 105 (100), and 77 (58) (Found: C, 79.4; H, 6.2; N, 6.5%; *M*, by mass spectrometry, 211.0995. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.6%; *M*, 211.0997).

1-Phenyl-2-(3-pyridyl)propan-1-one Methiodide (6d).—1-Phenyl-2-(3-pyridyl)-propan-1-one (250 mg) was quaternised with methyl iodide (1.7 g) in ethyl acetate (8 ml) at reflux for 4 h. The solvent was decanted from the brown

amorphous salt produced and traces of remaining solvent removed under high vacuum to give the *iodide* (6d) (401 mg) as a foam, $\lambda_{max.}$ 250 and 272sh nm; $\lambda_{max.}$ (EtOH–NaOH) 251 and 372 nm; $\nu_{max.}$ 1 680s cm^{-1}; τ (D_2O–[$^2H_6$]DMSO) 0.98 (1 H, br s, pyridine-α-H), 1.7 (1 H, d, *J* 6 Hz, pyridine-α-H), 1.39 (1 H, d, *J* 6 Hz, pyridine-γ-H), 4.64 (1 H, q, *J* 8 Hz, C*H*Me), 5.52 (3 H, s, N^+CH_3), and 8.31 (3 H, d, CH_3CH).

8-*Acetyl*-5,7-*dimethoxyisoquinoline* (10a).—A solution of 5,7-dimethoxyisoquinoline [3] (550 mg) in dry nitrobenzene (15 ml) was added to resublimed aluminium chloride (2.2 g) with stirring during 5 min at room temperature. After a further 15 min at room temperature acetyl chloride (550 mg) was added slowly to the mixture and the whole heated at 55 °C for 1 h. The mixture was poured onto ice with stirring, made strongly basic with sodium hydroxide, and extracted with ethyl acetate; the basic product was obtained by extraction from the organic layer with dilute hydrochloric acid followed by basification of the aqueous layer after washing with ether, and finally extraction with ethyl acetate to give a solid product which was recrystallised from ethyl acetate to give the *ketone* (10a) (598 mg), m.p. 139—140 °C; $\lambda_{max.}$ 221, 241, 290sh, 300, and 350 nm (log ε 4.29, 4.52, 3.84, 3.88, and 3.84); $\lambda_{max.}$ (EtOH–HCl) 224, 262, 305, and 388 nm (log ε 4.39, 4.53, 3.73, and 3.82); $\nu_{max.}$ 1 675s cm^{-1}; τ 0.7 (1 H, br s, 1-H), 1.6 (1 H, d, *J* 7 Hz, 3-H), 2.14 (1 H, d, *J* 7 Hz, 4-H), 3.3 (1 H, s, 6-H), 5.99 and 6.30 (6 H, 2 × s, 5-OCH_3 and 7-OCH_3), and 7.37 (3 H, s, CH_3CO); *m/e* 231 (M^+, 75%), 226 (100), 201 (35), 173 (20), 158 (30), 145 (24), 130 (35), 115 (33), 102 (31), and 75 (33) (Found: C, 67.5; H, 5.7; N, 6.1%; *M*, by mass spectrometry, 231.0887. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.6; N, 6.1%; *M*, 231.0895).

8-*Benzoyl*-7-*hydroxy*-5-*methoxyisoquinoline* (10b).—A solution of 5,7-dimethoxyisoquinoline [3] (60 mg) in dry nitrobenzene (4 ml) was added to freshly sublimed aluminium chloride (240 mg) during 5 min with stirring at room temperature. After a further 12 min at this temperature benzoyl chloride (90 mg) was added dropwise and the whole heated at 56 °C for 1 h. The mixture was poured onto ice, made basic with sodium hydroxide, and extracted with chloroform. The basic product was re-extracted into dilute hydrochloric acid and recovered from the ether-washed aqueous phase by basification and extraction with chloroform to give a solid which was recrystallised from ethyl acetate to give the phenolic ketone (10b) (53 mg), m.p. 233—235 °C; $\lambda_{max.}$ 241, 285, and 358 nm (log ε 4.36, 3.64, and 4.62); $\lambda_{max.}$ (EtOH–HCl) 259, 300, and 387 nm (log ε 4.43, 3.73, and 3.62); $\lambda_{max.}$ (EtOH–NaOH) 255, 296, and 413 nm (log ε 4.43, 3.87, and 3.63); $\nu_{max.}$ 3 661w and 1 636s cm^{-1}; τ −2.80 (1 H, br s, HO), 1.4 (1 H, br s, 1-H), 1.7 (1 H, d, *J* 6 Hz, 3-H), 2.14 (1 H, d, *J* 6 Hz, 4-H), 3.34 (1 H, s, 6-H), and 5.96 (3 H, s, 5-OCH_3); *m/e* 279 (M^+, 99%), 278 (100), 264 (36), 235 (12), 216 (13), 202 (52), 189 (26), 176 (43), 161 (42), 105 (18), and 77 (30) (Found: *M*, by mass spectrometry, 279.0889. $C_{17}H_{13}NO_3$ requires *M*, 279.0895).

8-*Benzoyl*-7-*benzoyloxy*-5-*methoxyisoquinoline* (10c).—A solution of 5,7-dimethoxyisoquinoline [3] (100 mg) in dry nitrobenzene (6 ml) was added to freshly sublimed aluminium chloride (400 mg) with stirring at room temperature during 5 min. After a further 10 min at room temperature benzoyl chloride (150 mg) was added dropwise and the whole heated at 56 °C for 1.25 h. The cooled reaction mixture was poured onto ice, basified with sodium hydroxide, and extracted with chloroform; re-extraction of the organic phase with dilute hydrochloric acid, and then rebasification of the aqueous phase, after washing with ether, and extraction with chloroform gave a white solid which was recrystallised from ethyl acetate to give the *benzoyloxy-ketone* (10c) (104 mg), m.p. 177—178 °C, $\lambda_{max.}$ 240, 299, and 335 nm (log ε 4.28, 3.53, and 3.49), $\lambda_{max.}$ (EtOH–HCl) 245, 310, and 361 nm (log ε 4.29, 2.49, and 3.50); $\nu_{max.}$ 1 740s and 1 665s cm^{-1}; τ 0.86 (1 H, s, 1-H), 1.44 (1 H, d, *J* 7 Hz, 3-H), 1.96 (1 H, d, *J* 7 Hz, 4-H), 3.03 (1 H, s, 6-H), and 5.95 (3 H, s, 5-OCH_3); *m/e* 383 (M^+, 11%), 278 (10), 105 (100), and 77 (40) (Found: C, 75.1; H, 4.5; N, 3.6%; *M*, by mass spectrometry, 383.1152. $C_{24}H_{17}NO_4$ requires C, 75.2; H, 4.44; N, 3.66%; *M*, 383.1157).

8-*Acetyl*-5,7-*dimethoxy*-2-*methylisoquinolinium Iodide*.—The ketone (8a) (30 mg) was quaternised with methyl iodide 180 mg) in refluxing ethyl acetate (4 ml) for 4 h. The resulting salt was filtered off and recrystallised from ethanol to give yellow crystals of the *iodide* (40 mg), m.p. 204—205 °C (decomp.); $\lambda_{max.}$ 225, 264, 305, and 390 nm (log ε 4.56 4.52, 3.74, and 3.76); τ (D_2O) 0.36 (1 H, s, 1-H), 1.37 (1 H, d, *J* 8 Hz, 3-H), 1.54 (1 H, d, *J* 8 Hz, 4-H), 5.4 (3 H, s, N^+CH_3), 5.7 (6 H, s, 5-OCH_3 and 7-OCH_3), and 7.17 (3 H, s, CH_3CO) (Found: C, 45.2; H, 4.4; I, 34.0; N, 3.5%. $C_{12}H_{14}INO_3$ requires C, 45.0; H, 4.3; I, 34.0; N, 3.8%).

1,2,3,4-*Tetrahydro*-8-(1-*hydroxyethyl*)-5,7-*dimethoxy*-2-*methylisoquinoline* (11).—8-Acetyl-5,7-dimethoxy-2-methylisoquinolinium iodide (140 mg) was reduced with sodium borohydride (excess) in ethanol (5 ml) at room temperature for 2 h. The mixture was diluted with water and extracted with ethyl acetate, which gave a solid which was recrystallised from ethyl acetate to give the *alcohol* (11), m.p. 147—148 °C; $\lambda_{max.}$ 228 and 285 nm (log ε 3.87 and 3.36); $\nu_{max.}$ 3 550w cm^{-1}; τ 3.62 (1 H, s, 6-H), 5.12 (1 H, q, *J* 8 Hz, C*H*Me), 6.12 and 6.20 (6 H, 2 × s, 5-OCH_3 and 7-OCH_3), 7.53 (3 H, s, NCH_3), and 8.5 (3 H, d, *J* 8 Hz, CH_3CH); *m/e* 251 (M^+, 7%), 250 (14), 233 (100), 218 (48), 193 (31), 190 (31), 161 (16), 160 (17), and 91 (12) (Found: C, 66.5; H, 8.3; N, 5.3%; *M*, by mass spectrometry, 251.1516. $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.6%; *M*, 251.1521).

Cyclic Ether (12).—The alcohol (11) (100 mg) was oxidised with manganese dioxide (1 g) in dry ether (25 ml) with stirring at room temperature for 1 day. The oxidant was filtered off, washed with chloroform and the combined organic solutions evaporated to give material which was purified by column chromatography [silica, eluting with $CHCl_3$–EtOH (1 : 1)] to give the ether (12) (34 mg), m.p. 124—126 °C; $\lambda_{max.}$ 232, 283, 305, and 385 nm (log ε 3.94, 3.38, 3.06, and 2.19); $\lambda_{max.}$ (EtOH–HCl) 230, 304, and 390 nm (log ε 4.10, 3.92, and 3.24); $\lambda_{max.}$ (EtOH–NaOH) 232 and 283 nm (log ε 4.00 and 3.40); τ 3.7 (1 H, s, 6-H), 4.7 (1 H, q, *J* 7 Hz, C*H*Me), 5.40 (1 H, br s, OCHN), 6.2 (6 H, s, 5-OCH_3 and 7-OCH_3), 7.56 (3 H, s, NCH_3), and 8.45 (3 H, qd, *J* 7 Hz, CH_3CH); *m/e* 249 (M^+, 22%), 248 (95), 234 (98), 218 (29), 206 (100), 191 (39), 190 (21), 178 (29), 163 (28), 161 (15), 160 (15), 149 (17), 148 (14), 117 (13), and 91 (13) (Found: *M*, by mass spectrometry, 249.1361. $C_{14}H_{19}NO_3$ requires *M*, 249.1364).

8-*Acetyl*-5,7-*dimethoxyisoquinoline Hydrazone* (10d).—The ketone (8a) (29 mg) was heated with hydrazine hydrate (290 mg) in ethanol (4 ml) at reflux for 22 h. After concentration, a precipitate formed; this was filtered off to give the *hydrazone* (10d) (17 mg), m.p. 174—176 °C; $\lambda_{max.}$ 214, 239, 291sh, 300, and 349 nm (log ε 4.38, 4.44, 3.77, 3.79, and 3.67); $\lambda_{max.}$ (EtOH–HCl) 220, 261, 310, and 388 nm (log ε

4.39, 4.43m, 3.71, and 3.57); $\nu_{max.}$ 3 360—3 260w cm^{-1}; τ 0.8 (1 H, s, 1-H), 1.65 (1 H, d, *J* 8 Hz, 3-H), 2.15 (1 H, d, *J* 8 Hz, 4-H), 3.25 (1 H, d, 6-H), 4.58 (2 H, br s, NH_2), 6.01 and 6.10 (6 H, 2 × s, 5-OCH_3 and 7-OCH_3), and 7.84 (3 H, s, CH_3); *m/e* 245 (M^+, 91%), 244 (96), 230 (26), 229 (57), 214 (88), 213 (76), 199 (65), 198 (50), 189 (100), 174 (22), 160 (11), 128 (22), and 115 (50) (Found: *M*, by mass spectrometry, 245.1160. $C_{13}H_{15}N_3O_2$ requires *M*, 245.1164).

3-*Phenacylquinoline* (13a).—3-Methylquinoline [4] (3.5 g) was deprotonated at 0 °C for 30 min with a solution of lithium di-isopropylamide prepared, as described above, from di-isopropylamine (5.06 g), THF (20 ml), and n-butyl-lithium (1.8M in hexane; 28 ml) with the subsequent addition of HMPA (9 g). Methyl benzoate (3.8 g) in THF (30 ml) was added and the resulting mixture stirred at room temperature for 3.5 h. Extraction of the product into dilute hydrochloric acid followed by thorough washing with ether, basification, and extraction with ethyl acetate gave an oil which was crystallised from hexane to give 3-*phenacylquinoline* (13a) (3.12 g), m.p. 70—71 °C; $\lambda_{max.}$ 233, 245sh, 280, 303, and 317 nm (log ε 4.41, 4.15, 3.59, 3.40, and 3.40); $\lambda_{max.}$ (EtOH–HCl) 238, 310sh, and 317 nm (log ε 4.56, 3.76, and 3.79); $\lambda_{max.}$ (EtOH–NaOH) 232, 242, 283, 320, 360, and 420 nm (log ε 4.30, 4.15, 3.78, 3.58, 3.83, and 3.72); $\nu_{max.}$ 1 680s cm^{-1}; τ 1.17 (1 H, d, *J* 3 Hz, 2-H) and 5.55 (2 H, s, CH_2); *m/e* 247 (M^+, 17%), 142 (5), 115 (13), 105 (100), and 77 (58) (Found: C, 82.7; H, 5.3; N, 5.5%; *M*, by mass spectrometry, 247.0990. $C_{17}H_{13}NO$ requires C, 82.6; H, 5.3; N, 5.67%; *M*, 247.0997).

1-*Methyl*-3-*phenacylquinolinium Iodide*.—3-Phenacylquinoline (1.5 g) was quaternised with methyl iodide (8.6 g) at reflux in ethyl acetate (15 ml) for 5 h. The resulting solid was filtered off and recrystallised from ethanol to give the *iodide* (2.21 g), m.p. 203—204 °C; $\lambda_{max.}$ 239, 310sh, and 320 nm (log ε 5.71, 4.87, and 4.93); $\lambda_{max.}$ (EtOH–NaOH) 277sh, 294, 386, and 530 nm (log ε 5.09, 5.15, 5.48, and 4.99); $\nu_{max.}$ 1 680s cm^{-1}; τ (CD_3OD) 0.56 (1 H, br s, 2-H), 0.89 (1 H, br s, 4-H), 5.05 (2 H, s, CH_2), and 5.26 (3 H, s, N^+CH_3) (Found: C, 55.1; H, 4.1; I, 32.1; N, 3.55. $C_{18}H_{16}INO$ requires C, 55.5; H, 4.1; I, 32.65; N, 3.6%).

4-(2-*Methylaminobenzyl*)-6-*phenylpyridazine* (15a).—1-Methyl-3-phenacylquinolinium iodide (220 mg) was treated with hydrazine hydrate (2.2 g) in diethylene glycol (12 ml) at 110 °C for 20 min. The mixture was cooled, diluted with water, and extracted with ether and the basic material then extracted into dilute hydrochloric acid; the aqueous layer was basified and extracted with ether to give a solid, which was extracted with hot hexane and crystallised from hexane–ethyl acetate to give the *pyridazine* (15a) (85 mg), m.p. 141 °C, $\lambda_{max.}$ 246 and 288sh nm (log ε 4.5 and 3.76); $\lambda_{max.}$ (EtOH–HCl) 254 nm (log ε 4.27); $\nu_{max.}$ 3 440w cm^{-1}; τ 1.04 (1 H, d, *J* 2 Hz, 3-H), 6.1 (2 H, s, CH_2), 7.18 (3 H, s, NCH_3), and 6.52 (1 H, br s, NH); *m/e* 275 (M^+, 47%), 232 (100), 230 (23), 217 (15), 157 (16), 144 (17), 130 (27), 120 (22), 115 (22), 103 (15), 102 (16), 91 (37), 77 (34), 65 (21), 58 (11), and 43 (17) (Found: C, 78.2; H, 6.2; N, 15.2%; *M*, by mass spectrometry, 275.1426. $C_{18}H_{17}N_3$ requires C, 78.55; H, 6.2; N, 15.3%; *M*, 275.1422).

6-*Methyl*-3-*phenacylquinoline* (13b).—3,6-Dimethylquinoline [4] (0.98 g) was deprotonated with lithium di-isopropylamide, prepared from di-isopropylamine (0.63 g) in THF (2 ml) and n-butyl-lithium 1.8M in hexane (3.6 ml) with subsequent addition of HMPA (1.13 g), for 30 min at 0 °C. Methyl benzoate (0.85 g) in THF (3 ml) was then added all at once and the whole left at room temperature for 3 h. The product was extracted into dilute hydrochloric acid which, after thorough washing with ethyl acetate was basified and extracted with ether to give an oil which was distilled at 140 °C and 0.5 mmHg. The *phenacylquinoline* (13b) (0.76 g) was crystallised from the distillate using hexane, m.p. 67—68 °C; $\lambda_{max.}$ 236, 247sh, 282, 307, and 321 nm (log ε 4.44, 4.08, 3.46, 3.30, and 3.33); $\lambda_{max.}$ (EtOH–HCl) 243, 314sh, and 322 nm (log ε 4.59, 3.95, and 4.0); $\lambda_{max.}$ (EtOH–NaOH) 236, 248, 285, 321, 360, and 419 nm (log ε 4.29, 4.06, 3.63, 3.46, 3.63, and 3.59); τ 1.22 (1 H, br s, 2-H), 5.56 (2 H, s, CH_2), and 7.48 (3 H, s, CH_3); $\nu_{max.}$ ($CHCl_3$) 1 681s cm^{-1}; *m/e* 261 (M^+, 68%), 156 (30), 129 (18), 128 (40), 105 (37), and 77 (100) (Found: *M*, by mass spectrometry, 261.1148. $C_{18}H_{15}N$ requires *M*, 261.1153).

1,6-*Dimethyl*-3-*phenacylquinolinium Iodide*.—6-Methyl-3-phenacylquinoline (300 mg) was quaternised with methyl iodide (1.6 g) in refluxing ethyl acetate (10 ml) for 4 h. The resulting salt was filtered off and crystallised from ethanol to give 1,6-*dimethyl*-3-*phenacylquinolinium iodide* (405 mg), m.p. 214—216 °C; $\lambda_{max.}$ 243, 315sh, and 325 nm (log ε 5.74, 4.86, and 4.94); $\lambda_{max.}$ (EtOH–NaOH) 279sh, 296, 333, and 531 nm (log ε 5.00, 5.09, 5.46, and 4.82); $\nu_{max.}$ 1 682s cm^{-1} (Found: C, 56.2; H, 4.4; I, 31.2; N, 3.5. $C_{19}H_{18}INO$ requires C, 56.57; H, 4.5; I, 31.5; N, 3.5%).

4-(3-*Methyl*-6-*methylaminobenzyl*)-6-*phenylpyridazine* (15b).—1,6-Dimethyl-3-phenacylquinolinium iodide (120 mg) was treated with hydrazine hydrate (1.2 g) in diethylene glycol (6 ml) at 110 °C for 10 min and then at reflux for 10 min. After cooling and dilution the mixture was extracted with ether. The ether layer was extracted with aqueous hydrochloric acid and the acidic layer basified and re-extracted with ether to give a residue which was extracted with hexane to give a material which was crystallised from hexane–ethyl acetate to give the *pyridazine* (15b) (42 mg), m.p. 131—132 °C; $\lambda_{max.}$ 247 and 289sh nm (log ε 4.45 and 3.66); $\lambda_{max.}$ (EtOH–HCl) 258 nm (log ε 4.27); $\nu_{max.}$ 3 440w cm^{-1}; τ 1.02 (1 H, d, *J* 2 Hz, 3-H), 6.13 (2 H, s, CH_2), 6.75 (1 H, br s, NH), 7.21 (3 H, s, NCH_3), and 7.75 (3 H, s, CH_3); *m/e* 289 (M^+, 72%), 246 (100), 231 (22), 158 (17), 157 (14), 144 (19), 134 (16), 115 (14), 91 (20), 76 (13), and 58 (34) (Found: *M*, 289.1569. $C_{19}H_{19}N_3$ requires *M*, 189.1568).

3-*Benzoyl*-1-*methylpyridinium Methiodide* (16a).—3-Benzoylpyridine (2 g) was quaternised with methyl iodide (15 g) in refluxing ethyl acetate (20 ml) for 2 h. The salt was filtered off and recrystallised from ethanol to give the *iodide* (16a) (3.21 g), m.p. 148—149 °C; τ(D_2O) 0.58 (1 H, s, 2-H), 0.74 (1 H, d, *J* 8 Hz, 6-H), 1.56 (1 H, t, *J* 8 Hz, 5-H), and 5.37 (3 H, s, N^+CH_3) (Found: C, 47.7; H, 3.7; I, 39.1; N, 4.2. $C_{13}H_{12}INO$ requires C, 48.0; H, 3.7; I, 39.1; N, 4.3%).

3-*Phenyl*-4-*propylpyrazole* (18).—3-Benzoyl-4-propylpyridinium iodide (500 mg) was treated with hydrazine hydrate (3.5 g) in diethylene glycol (15 ml) at reflux for 1 h. After cooling the mixture was treated with potassium hydroxide (powdered, 1.2 g) and then the whole refluxed for 2 h. After cooling and dilution with water, extraction with ether gave an oil (98 mg) which was immediately hydrogenated over Pd–C (10%, 98 mg) in ethanol (4 ml) at atmospheric pressure for 3 h. The catalyst was removed and the filtrate evaporated to give a solid (78 mg) which was crystallised from hexane to give the *pyrazole* (18), m.p. 85—88 °C; $\lambda_{max.}$ 247 and 269sh nm (log ε 4.14 and 3.81); $\lambda_{max.}$ (EtOH–

HCl) 251 and 271sh nm (log ε 4.26 and 3.87); $\nu_{max.}$ 3 445m cm^{-1}; τ 0.2 (1 H, br s, NH), 7.2 (2 H, t, *J* 8 Hz, pyrazolyl-CH_2), 8.4 (2 H, sextet, *J* 8 Hz, CH_2Me), and 9.08 (3 H, t, *J* 8 Hz, CH_3CH_2); *m/e* 186 (M^+, 41%), 157 (100), 130 (20), and 77 (23) (Found: *M*, by mass spectrometry, 186.1160. $C_{12}H_{14}N_2$ requires *M*, 186.1156).

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