Synthesis of Asymmetrically Substituted Aminohalogenobenzimidazoles

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2-Fluoroacetanilide (**1**) upon treatment with HNO_3–H_2SO_4 at −5 to 0 °C gave 6-fluoro-4-nitroacetanilide (**3**) whereas at −20 to −10 °C the product was 6-fluoro-3,4-dinitroacetanilide (**5**). Although the formation of compound (**5**) could be accounted for by a conventional nitration mechanism, the fact that (**3**) could not be nitrated to give (**5**) and that (**5**) was formed at a lower temperature than was (**3**) suggested that the reaction might proceed *via* an *ipso* δ intermediate (**2**). Deacetylation of (**5**) followed by reduction and condensation with formic acid in the presence of HCl gave 6(5)-fluoro-5(6)-formylaminobenzimidazole (**11**), 5(6)-amino-6(5)-fluorobenzimidazole (**12**) and 5-amino-4-chloro-6-fluorobenzimidazole (**13**). Reduction of (**5**) with tin followed by condensation with acetic acid gave 5(6)-amino-6(5)-fluoro-2-methylbenzimidazole (**14**). Concomitant reduction and cyclisation of 6-chloro-2,4-dinitroaniline with formic acid and HCl gave a mixture of 7(4)-chloro-5(6)-formylaminobenzimidazole (**15**) and 5-amino-4,7-dichlorobenzimidazole (**16**).

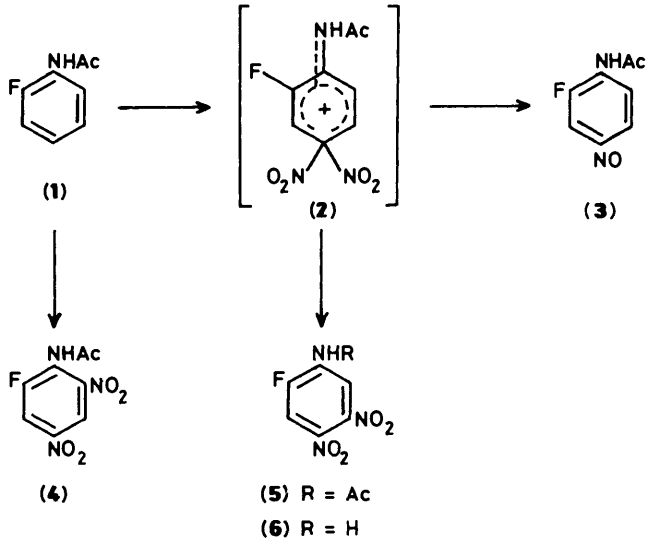
Various benzimidazole derivatives have been used in the chemotherapy of viral diseases,[1] the most interesting being 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole which inhibits RNA synthesis,[2,3] influenza virus, vaccinia virus,[4] and adenovirus.[5] Benzimidazoles designed as guanine analogues have been shown to inhibit various guanine-sensitive test systems[6] and thus inhibit virus multiplication.

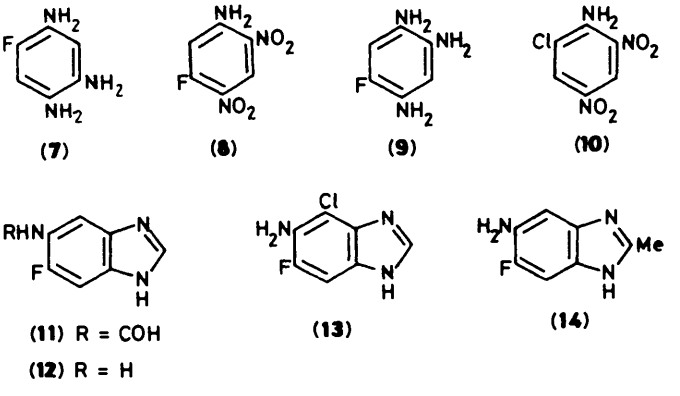
As part of a programme designed to elucidate structure–activity relationships amongst asymmetrically substituted aminohalogenobenzimidazoles, and nucleosides derived from them, we report here the syntheses of a series of substituted benzimidazoles.

Acetylation of 2-fluoroaniline with acetic anhydride–pyridine gave 2-fluoroacetanilide (**1**) in quantitative yield. Nitration of compound (**1**) with fuming nitric acid–concentrated sulphuric acid at −20 to −10 °C gave the dinitro compound (**5**). On the other hand, when the reaction was carried out between −5 and 0 °C, only the mononitro derivative (**3**) was obtained. No further nitration of compound (**3**) to the dinitro compound (**5**) was observed and extended reaction times gave only decomposition to coloured compounds.

The formation of 6-fluoro-3,4-dinitroacetanilide (**5**) rather than 6-fluoro-2,4-dinitroacetanilide (**4**) is at first sight rather surprising. However, careful consideration of the activating/deactivating effects of $NHCOCH_3$, F, and NO_2 reveals that compound (**5**) should be the expected product, consistent with the fact that nitration of 1,2-difluorobenzene gives 1,2-difluoro-4,5-dinitrobenzene.[7] However, the inability to nitrate compound (**3**) to give (**5**), and the fact that dinitration of compound (**1**) takes place under milder conditions than the mononitration, suggests that the nitration might take place *via* an *ipso* mechanism.[9–11] According to this, nitration occurs first at the position *para* to the acetamido group, and then the second nitro group enters at the *ipso* position to give the *ipso* σ complex (**2**). This intermediate, which is relatively stable at < −10 °C slowly rearranges and gives compound (**5**), whereas at higher temperatures the nitro group is lost to give (**3**). This kind of intermediate has been reported for the nitration of other aromatic compounds.[9,10]

Compound (**5**) was deacetylated with boiling 2M-hydrochloric acid to give 6-fluoro-3,4-dinitroaniline (**6**). Attempts to reduce this compound (**6**) to the triamino derivative (**7**) by a number of reagents such as tin(II) chloride,[12] catalytic hydrogenation, sodium dithionite,[13] and hydrazine hydrate with palladium on charcoal,[14] were unsuccessful owing to the instability of compound (**7**), which decomposed before it could be used in the cyclisation to the required benzimidazole. Subsequently, reduction and simultaneous closure of the imidazole ring was carried out by the Phillips procedure[15] using tin, and hydrochloric acid with formic acid as the condensing agent, under a nitrogen or argon atmosphere. Under these conditions compound (**6**) gave 6(5)-fluoro-5(6)-formylaminobenzimidazole (**11**) and 5(6)-amino-6(5)-fluorobenzimidazole (**12**) and, unexpectedly, 5-





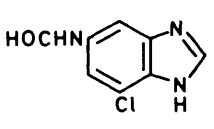
amino-4-chloro-6-fluorobenzimidazole (**13**), in 20, 46, and 13% yields respectively. Compound (**13**) was not produced when either benzimidazole (**11**) or (**12**) was treated with tin and hydrochloric acid and formic acid under the Phillips conditions.[15] Thus, it seems that the entry of the chlorine atom in the benzimidazole ring takes place before the ring closure takes place. A similar reaction of compound (**6**) with acetic acid as the condensation reagent gave only 5-amino-6-fluoro-2-methylbenzimidazole (**14**) in 39% yield. The formation of compound (**13**) is unexplained, therefore; it is difficult to envisage electrophilic substitution of compound (**5**) by chlorine under the conditions of the reaction, and nucleophilic attack by chloride also appears unlikely.

Compound (**11**) was obtained as the only product (63% yield) when commercially available 5-fluoro-2,4-dinitroaniline (**8**) was reduced by catalytic hydrogenation in the presence of palladium on charcoal in formic acid, and then cyclised with formic acid. Attempts to obtain the 2-methylbenzimidazole derivative (**14**) by a similar procedure failed; the use of acetic acid in the catalytic hydrogenation led to the decomposition of the presumed intermediate triamine (**9**).

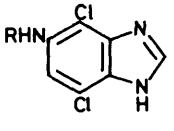
The assignment of structures to the benzimidazoles (**11**)—(**14**) was based upon analyses of hydrogen–fluorine coupling constants in the n.m.r. spectra (see Experimental section). The signals appearing at 7.48 p.p.m. in the spectrum of (**11**), at 7.20 p.p.m. for (**12**), at 7.32 p.p.m. for (**13**), and at 7.12 p.p.m. for (**14**), with H–F coupling constants of 11, 12, 10, and 12 Hz respectively, were assigned to the 7-H proton in the *ortho* position to the fluorine atom. The signals with an H–F coupling constant of 8 Hz which appeared at 8.32, 6.82, and 6.82 p.p.m. in compounds (**11**), (**12**), and (**14**), respectively, were assigned to 4-H. These H–F coupling constants are consistent with those corresponding to *ortho* and *meta* coupling constant values respectively.[16,17] The presence of chlorine in compound (**13**) was deduced from its mass spectrum, and the position of the chlorine atom was assigned as 4 by comparison of the n.m.r. spectrum of compound (**13**) with that of (**12**), the former showing the disappearance of the signal at δ 6.82 p.p.m. corresponding to 4-H in (**12**).

Reduction of compound (**8**) with tin and hydrochloric acid in the presence of formic acid gave a mixture of compounds (**11**), (**12**), and (**13**) in yields of 11, 46, and 5% respectively. A similar reaction of compound (**8**), but with acetic acid instead of formic acid, gave the product (**14**) in 68% yield. These reactions confirmed the structures of compounds (**11**)—(**14**) and of the dinitro compound (**5**).

Other halogeno-substituted benzimidazoles were obtained by a similar synthetic route to that described above. Thus, when 6-chloro-2,4-dinitroaniline (**10**) was treated with tin and hydrochloric acid as reducing agent and formic acid as condensing agent, 7(4)-chloro-5(6)-formylaminobenzimidazole (**15**) and 5-amino-4,7-dichlorobenzimidazole (**16**) were obtained



(**15**)



(**16**) R = H

(**17**) R = Ac

in yields of 20 and 23% respectively. As in the case of the synthesis of the fluorobenzimidazoles already mentioned, a compound with an extra chlorine atom, namely (**16**), was isolated. However, catalytic hydrogenation of compound (**10**) in the presence of formic acid and subsequent condensation with formic acid gave compound (**15**) as the only isolatable reaction product, in 19% yield. Acetylation of compound (**16**) gave the acetyl derivative (**17**) in 67% yield.

The structures of the chlorobenzimidazole derivatives (**15**)—(**17**) were established from their mass and n.m.r. spectra (see Experimental section). The signals appearing in the ^{1}H n.m.r. spectra at δ 7.51, 6.86, and 7.52 p.p.m. in compounds (**15**), (**16**), and (**17**), respectively, were assigned to 6-H. The disappearance of this signal in compound (**17**) indicated that the second chlorine group was located at position 4 of the benzimidazole ring.

The compounds described above have been tested for activity against herpes simplex virus types 1 and 2, vaccinia virus, vesicular stomatis virus, coxsackie virus B-4, and polio virus-1, but none showed any activity. Further tests of these compounds in other biological systems are in progress.

Experimental

Melting points were measured on an electrothermal m.p. apparatus or a Kofler block, and are uncorrected. N.m.r. spectra were measured at 100 MHz on a Varian XL100 spectrometer with $(CD_3)_2SO$ as solvent, mass spectra were obtained on a Kratos MS 80 RF mass spectrometer, and u.v. absorption spectra were recorded on a Perkin-Elmer 552 spectrophotometer. Analytical t.l.c. was carried out on silica gel 60 F_{254} (Merck), preparative layer chromatography on silica gel PF_{254} (Merck), and column chromatography on Kieselgel 60, 70-230 mesh ASTM type 7734 (Merck).

6-*Fluoro*-4-*nitroacetanilide* (**3**).—To a mixture of fuming nitric acid (8.2 g) and concentrated sulphuric acid (24.5 g), stirred at −5 to 0 °C, 2-fluoroacetanilide (3.0 g) was added in portions over a period of 2 h. After being stirred for a further 6 h while the temperature was gradually raised to room temperature, the mixture was poured onto ice and allowed to stand at *ca.* 0 °C for 1 h. The resulting solid was then filtered off and washed successively with water, aqueous sodium hydrogen carbonate, and water to give the product (1.65 g, 43%) as a solid, m.p. 200—201 °C (from ethanol) (lit.,[18] m.p. 203—204 °C); δ 2.20 (3 H, s, $NCOCH_3$), 8.02—8.26 (2 H, m, 3-H, 5-H), 8.46 (1 H, dd, $J_{F,H}$ 8 Hz, 2-H, and 10.40 (1 H, br s, NH); *m/z* 198 (M^+, 9%), 182(3), 156(75), 140(15), 126(20), 110(27), 98(3), 90(11), 83(17), 63(9), and 43(100).

6-*Fluoro*-3,4-*dinitroacetanilide* (**5**).—To a mixture of fuming nitric acid (13.5 g) and concentrated sulphuric acid (40.9 g) stirred at −20 to −10 °C, 2-fluoroacetanilide (5.0 g) was added in portions over a period of 3 h. The temperature was allowed to rise slowly to 0 °C and the mixture stirred at this temperature for 6 h. A work-up procedure similar to that described above afforded the *product* (**5**) (4.65 g, 59%) as yellow needles, m.p. 170—172 °C (from aqueous ethanol) (Found: C, 39.7; H, 2.3; N, 17.5. $C_8H_6FN_3O_5$ requires C, 39.51; H, 2.47; N, 17.28%); $\lambda_{max.}$(ethanol) 302 (ε 7 600) and 239 nm (13 600); δ 2.20 (3 H, s, $NCOCH_3$), 8.28 (1 H, d, $J_{F,H}$ 11 Hz, 5-H), 8.87 (1 H, d, $J_{F,H}$ 7 Hz, 2-H), and 10.5 (1 H, br s, NH).

6-*Fluoro*-3,4-*dinitroaniline* (**6**).—Compound (**5**) (2.0 g) was added to 2M-hydrochloric acid (10 ml) and the mixture boiled under reflux for 4 h. After cooling the reaction mixture was neutralised with aqueous sodium hydrogen carbonate and cooled to 0 °C. The resulting solid was filtered off and crystallised from water to give the *product* (1.31 g, 83%) as needles, m.p. 135 °C (decomp.) (Found: C, 35.7; H, 2.0; N, 20.6. $C_6H_4FN_3O_4$ requires C, 35.82; H, 1.99; N, 20.89%); $\lambda_{max.}$(ethanol) 372 (ε 9 800) and 243 nm (7 100); δ 7.13 (1 H, d, $J_{F,H}$ 8 Hz, 2-H), 7.22 (2 H, br s, NH_2), and 7.96 (1 H, d, $J_{F,H}$ 12 Hz, 5-H).

6(5)-*Fluoro*-5(6)-*formylaminobenzimidazole* (**11**), 5(6)-*Amino*-6(5)-*fluorobenzimidazole* (**12**), *and* 5-*Amino*-4-*chloro*-6-*fluorobenzimidazole* (**13**).—(*a*) To the dinitro derivative (**6**) (2.0 g) in a mixture of concentrated hydrochloric acid (40 ml) and formic acid (2.5 ml) at 70 °C under nitrogen, tin (6.21 g) was added in the form of strips over a period of 1.5 h. The temperature was raised to 110 °C and the reaction mixture boiled under reflux for 2 h while adding formic acid (5 ml). After cooling, propan-2-ol (50 ml) was added and the solution adjusted to pH 8—9 with aqueous ammonia. The precipitate of tin compounds was filtered off through Celite and the filtrate evaporated to dryness to give a dark solid which was purified by column chromatography using ethyl acetate–ethanol (5:1) as the eluant. From the faster-moving fractions, 5-*amino*-4-*chloro*-6-*fluorobenzimidazole* (**13**) (0.24 g, 13%) was isolated as white needles by sublimation *in vacuo*, m.p. 218 °C (decomp.) (Found: C, 45.3; H, 3.0; N, 22.3. $C_7H_5ClFN_3$ requires C, 45.28; H, 2.69; N, 22.64%); $\lambda_{max.}$(0.1M-NaOH) 293 (ε 3 150) and 268 nm (3 080); $\lambda_{max.}$(0.1M-HCl) 298 (ε 2 990) and 248 nm (2 620); δ 4.94 (2 H, s, NH_2), 7.32 (1 H, d, $J_{F,H}$ 11 Hz, 7-H), and 8.02 (1 H, s, 2-H); *m/z* 187 (M^+ + 2, 30%), 185 (M^+, 100), 152(3), 150(10), 123(19), 96(11), 76(5), 52(8), and 44(37).

The slower-moving fractions yielded a mixture of compounds (**11**) and (**12**) that was separated by column chromatography, using ethyl acetate–ethanol–acetic acid (4:0.8:1) as the eluant. From the resulting faster-moving fractions, 6(5)-*fluoro*-5(6)-*formylaminobenzimidazole* (**11**) (0.36 g, 20%) was isolated as an amorphous solid, m.p. >220 °C (Found: M^+ 179.0492. $C_8H_6FN_3O$ requires *M*, 179.0495); $\lambda_{max.}$(0.1M-NaOH) 277 (ε 9 613) and 269 nm (10 130); $\lambda_{max.}$(0.1M-HCl) 285 (ε 5 540) and 283 nm (5 490); λ_{sh} 240 nm; δ 7.48 (1 H, d, $J_{F,H}$ 11 Hz, 7-H), 8.22 (1 H, s, 2-H), 8.32 (1 H, d, $J_{F,H}$ 8 Hz, 4-H), 8.36 (1 H, s, HCON), 10.08 (1 H, br s, NH), and 12.4 (1 H, br s, NH); *m/z* 179 (M^+, 70%), 123(30), 104(7), 97(29), 76(12), 70(14), and 52(14). The slower-moving fractions afforded 5(6)-*amino*-6(5)-*fluorobenzimidazole* (**12**) (0.69 g, 46%) m.p. >220 °C upon crystallisation from ethyl acetate–hexane (Found: M^+ 151.0549. $C_7H_6FN_3$ requires *M*, 151.0546); $\lambda_{max.}$(0.1M-NaOH) 296 (ε 6 170) and 249 nm (3 100); $\lambda_{max.}$(0.1M-HCl) 299 (ε 1 240), 277 (4 590), 272 (4 550), and 239 nm (3 530); δ 5.75—6.6 (3 H, br, 5-NH_2, 1-NH), 6.86 (1 H, d, $J_{F,H}$ 8 Hz, 4-H), 7.20 (1 H, d, $J_{F,H}$ 12 Hz, 7-H), and 7.92 (1 H, s, 2-H); *m/z* 152 (m^+ + 1, 10%), 151 (M^+, 100), 150(12), 124(11), 123(8), 104(5), 97(21), 75(10), 70(12), and 62(4).

(*b*) This procedure was similar to method (*a*) except that 5-fluoro-2,4-dinitroaniline (**8**) was used as the starting material and the reaction was carried out under argon. On work-up, the yields of the products isolated were: (**11**) (0.20 g, 11%), (**12**) (0.7 g, 46%), and (**13**) (0.1 g, 5.5%).

(*c*) The dinitro derivative (**8**) (2.5 g) was hydrogenated in a mixture of methanol (150 ml) and formic acid with palladium–charcoal catalyst at *ca.* 20 °C at 3 atm. for 22 h. The catalyst was filtered off and the filtrate evaporated to dryness. To the residue was added formic acid (15 ml) and the solution boiled for 8 h. The solvent was removed by evaporation and the residue purified by column chromatography using ethyl acetate–ethanol (5:1) as the eluant. Collection of the appropriate fractions gave compound (**11**) (1.39 g, 63%), identical with that prepared by methods (*a*) and (*b*).

5(6)-*Amino*-6(5)-*fluoro*-2-*methylbenzimidazole* (**14**).—(*a*) To a mixture of concentrated hydrochloric acid (30 ml) and acetic acid (2 ml), was added compound (**5**) (2.0 g) and the mixture heated to 70 °C under nitrogen. Then tin (4.92 g) in the form of strips was added in portions over a period of 1.5 h, and the mixture then boiled under reflux for 2 h, cooled, diluted with water (20 ml) and propan-2-ol (62 ml), and adjusted to pH 9 with aqueous ammonia. Insoluble tin compounds were filtered off through Celite and the filtrate evaporated to dryness to give a dark solid. This was purified by column chromatography using ethyl acetate–methanol (10:1) as the eluant and finally by preparative t.l.c. using ethyl acetate–methanol (8:1) as the eluant. The *product* (**14**) was obtained as a white solid (0.51 g, 39%), m.p. 155—157 °C upon crystallisation from ethyl acetate–hexane (Found: M^+, 165.0707. $C_8H_8FN_3$ requires *M*, 165.0702); $\lambda_{max.}$(0.1M-NaOH) 295 (ε 5 560) and 246 nm (3 280); $\lambda_{max.}$(0.1M-HCl) 294 (ε 700), 278 (4 960), 274 (5 140), 270 (4 830), and 233 nm (3 310); δ 2.42 (3 H, s, CH_3), 4.42—5.12 (3 H, br, NH_2, NH), 6.82 (1 H, d, $J_{F,H}$ 8 Hz, 4-H), and 7.12 (1 H, d, $J_{F,H}$ 12 Hz, 7-H); *m/z* 165 (M^+, 100%), 164(80), 137(5), 123(8), 110(2), 97(16), 82(10), 70(8), and 60(40).

(*b*) This procedure was similar to method (*a*) except that compound (**8**) (2.0 g) was used as the starting material and the reaction mixture was heated under reflux for 3 h. On work-up the residue was purified by column chromatography using ethyl acetate–ethanol (5:1) as the eluant to give compound (**14**) (0.92 g, 68%), identical with that prepared by method (*a*).

7(4)-*Chloro*-5(6)-*formylaminobenzimidazole* (**15**) *and* 5-*Amino*-4,7-*dichlorobenzimidazole* (**16**).—(*a*) To a mixture of concentrated hydrochloric acid (92 ml) and formic acid (6 ml) was added 6-chloro-2,4-dinitroaniline (**10**) (5.0 g) and the mixture heated to 70 °C under argon. Tin (14.3 g) in the form of strips was added in portions over a period of 1.5 h and the mixture was then boiled under reflux for 6 h while adding formic acid (15 ml). On work-up as previously described, a dark solid was obtained. This was purified by column chromatography using ethyl acetate–methanol (10:1) as the eluant. From the faster-moving fractions 5-*amino*-4,7-*dichlorobenzimidazole* (**16**) (1.08 g, 23.5%), m.p. >265 °C was obtained (Found: C, 41.9; H, 2.5; N, 30.1. $C_7H_5Cl_2N_3$ requires C, 41.58; H, 2.47; N, 29.79%); $\lambda_{max.}$(0.1M-NaOH) 301 (ε 2 273) and 270 nm (3 520); $\lambda_{max.}$(0.1M-HCl) 309 (ε 1 050) and 252 nm (3 530); δ 5.32 (2 H, br s, NH_2), 6.86 (1 H, s, 6-H), and 8.05 (1 H, s, 2-H); *m/z* 205 (M^+ + 4, 7%), 203 (M^+ + 2, 44), 201 (M^+, 100), 166(10), 139(19), 112(9), 103(18), 87(7), and 76(9).

The slower-moving fractions afforded 7(4)-*chloro*-5(6)-*formylaminobenzimidazole* (**15**) (0.89 g, 20%) as an amorphous solid, m.p. >220 °C (Found: C, 49.4; H, 3.0; N, 21.3. $C_8H_6ClN_3O$ requires C, 49.10; H, 3.06; N, 21.48%); δ 7.51 (1 H, d, 6-H), 8.00 (1 H, d, *J* 2 Hz, 4-H), 8.30 (1 H, s, 2-H), 8.36 (1 H, d, *J* 2 Hz, HCON, collapses to s on D_2O shake), and 10.39 (1 H, br s, NH); *m/z* 195 (M^+ − 1, 25%), 193(72), 179(9), 177(26), 169(34), 167(100), 130(38), 103(22), 88(11), and 76(20).

(*b*) The dinitro compound (**10**) (1.0 g) was hydrogenated in a mixture of methanol (150 ml) and formic acid (7 ml) with palladium-on-charcoal catalyst at 3 atm. at *ca.* 20 °C for 23 h. Following removal of the catalyst and the solvent, the residue thus obtained was dissolved in formic acid (20 ml) and the solution boiled under reflux for 5 h. Removal of the solvent and column chromatography of the residue using ethyl acetate–ethanol (5:1) as the eluant gave compound (**15**) (0.13 g, 15%), identical with that obtained in (*a*).

5-*Acetylamino*-4,7-*dichlorobenzimidazole* (**17**).—Compound (**16**) (0.64 g) and dimethylaminopyridine (0.05 g) was dissolved in dimethylformamide (10 ml) and acetic anhydride (20 ml) and the solution allowed to stand at *ca.* 20 °C for 2 days. The solvent was removed by evaporation and the residue crystallised from ethanol–ethyl acetate to give the *product* (**17**) (0.52 g, 67%) (Found: C, 44.6; H, 3.0; N, 17.5. $C_9H_7Cl_2N_3O$ requires C, 44.26; H, 2.86; N, 17.21%); $\lambda_{max.}$(0.1M-NaOH) 283 (ε 7 590) and 278 nm (8 150); $\lambda_{max.}$(0.1M-HCl) 261 nm (8 970); δ 2.08 (3 H, s, $NCOCH_3$), 7.52 (1 H, s, 6-H), 8.38 (1 H, s, 2-H), and 9.64 (1 H, br s, NH); *m/z* 247 (M^+ + 4, 3%), 245 (M^+ + 2,

12), 243 (M^+, 35), 210(27), 208(52), 205(15), 203(66), 201(100), 172(11), 166(12), 139(10), and 103(9).

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