Allenes. Part 49.[1] 4-Amino-2-(1-hydroxyalkyl)quinolines from Phenylhydroxylamine and Allenic Nitriles

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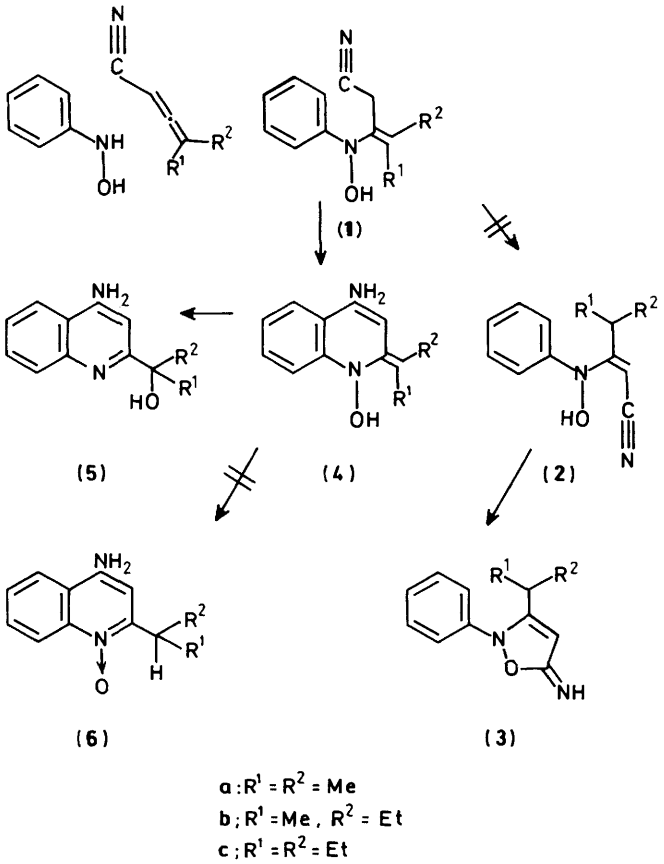
Allenic nitriles, when heated with phenylhydroxylamine in ethanol for 24 h, form the intermediate 2-alkylidene-4-amino-1,2-dihydro-1-hydroxyquinolines (**4**) which rearrange spontaneously by a 1,3-hydroxy shift to 4-amino-2-(1-hydroxyalkyl)quinolines. The 1-hydroxyquinoline intermediate (**4**) does *not* isomerise to 2-alkyl-4-aminoquinoline 1-oxide by a 1,4-proton shift as shown by an independent synthesis of the latter. Phenylpropynenitrile with phenylhydroxylamine gave 8% of 4-amino-2-(2-hydroxyphenyl)quinoline (**15**).

Isoxazoles are readily formed from hydroxylamine and allenic and acetylenic nitriles.[2] However, the reaction between phenylhydroxylamine and allenic nitriles does *not* give a 2,5-dihydro-2-phenylisoxazole (**3**) *via* the conjugated adduct (**2**), but rather the unconjugated adduct (**1**) ring closes *ortho* to the nitrogen on the benzene ring to form a 2-alkylidene-4-amino-1,2-dihydro-1-hydroxyquinoline (**4**).†

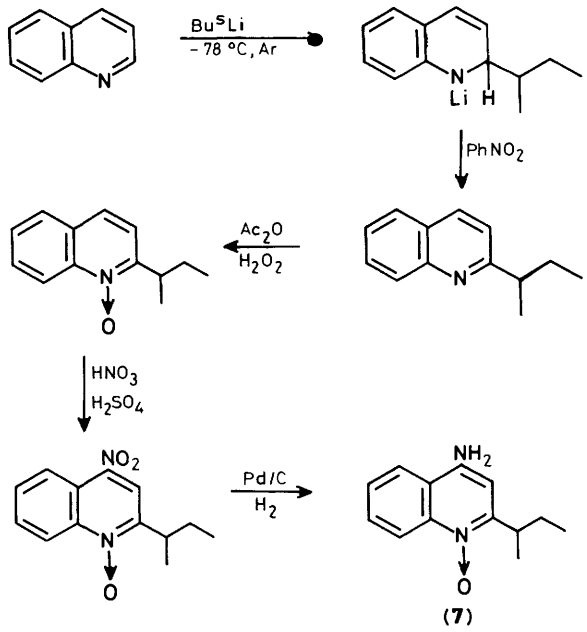
Here electrophilic ring closure of the unconjugated adduct (**1**) is evidently considerably faster than a proton shift to the conjugated adduct (**2**) (Scheme 1).‡ 4-Amino-1-hydroxyquinolines (**4**) are unstable even under the neutral conditions of the reaction and rearrange by a 1,3-hydroxy shift to give 4-amino-2-(1-hydroxyalkyl)quinolines (**5**).§

We have shown that the alternative 1,4-proton shift to 4-amino-2-alkylquinoline 1-oxide (**6**) does not occur by synthesizing 4-amino-2-s-butylquinoline 1-oxide (**7**) (Scheme 2) with very different spectroscopic properties from the



a: $R^1 = R^2 = Me$
b; $R^1 = Me$, $R^2 = Et$
c; $R^1 = R^2 = Et$

Scheme 1.



Scheme 2.

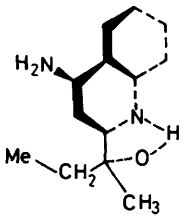
† 6-Membered 2-alkylidene-1-hydroxyheterocycles have not been reported in the literature, only a few examples of 1-hydroxy-2-pyridones and -quinolin-2-ones are known.[3,4]

‡ The 3,3-sigmatropic rearrangement of the unconjugated phenylhydrazine adduct was shown to have approximately the same activation energy as the 1,3-proton shift to the conjugated adduct.[5]

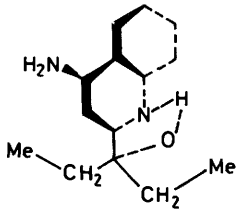
§ Phenylhydroxylamines are well known to rearrange under acid conditions to *C*-hydroxyanilines by a 1,5-hydroxy shift through a nitrenium ion intermediate.[6] 1,3-Hydroxy shifts of phenylhydroxylamines have not been reported in the literature; since our conditions are mildly basic either a concerted or an intimate ion-pair mechanism is suggested.

corresponding product from the reaction of 4-methylhexa-2,3-dienenitrile with phenylhydroxylamine.

4-Amino-2-(1-hydroxyalkyl)quinolines show a sharp i.r. band near 3 450 cm^{-1} for hydrogen bonded hydroxy and bands at 3 350 and 3 200 for the amino group and characteristic twin maxima in the u.v. region near 297 and 315 nm. The ^1H n.m.r. spectra always show a 1 H singlet at δ 4.7 for the shielded 3-H, a 2 H broad singlet at *ca.* δ 5.3 for NH_2, a 4 H complex resolving at high field to two doublets and two triplets in the range δ 6.7—7.3 for 5-,8-ArH and 6-,7-ArH, and a 1 H very broad singlet at *ca.* δ 10.3 for the hydrogen bonded OH. The isopropyl side chain shows a 6 H singlet at δ 1.33 for the two equivalent methyls, the s-butyl side chain, a shielded 3 H triplet at 0.555 [see (**8**)], a 3 H singlet at δ 1.333 and two distorted quintets for the two non-equivalent diastereotopic protons of the CH_2 at δ 1.646 and 1.838; the 3-pentyl side chain similarly shows a shielded 6 H triplet at δ 0.56 for the two methyls shielded by the ring current (**9**), and a 4 H quartet at δ 1.65.



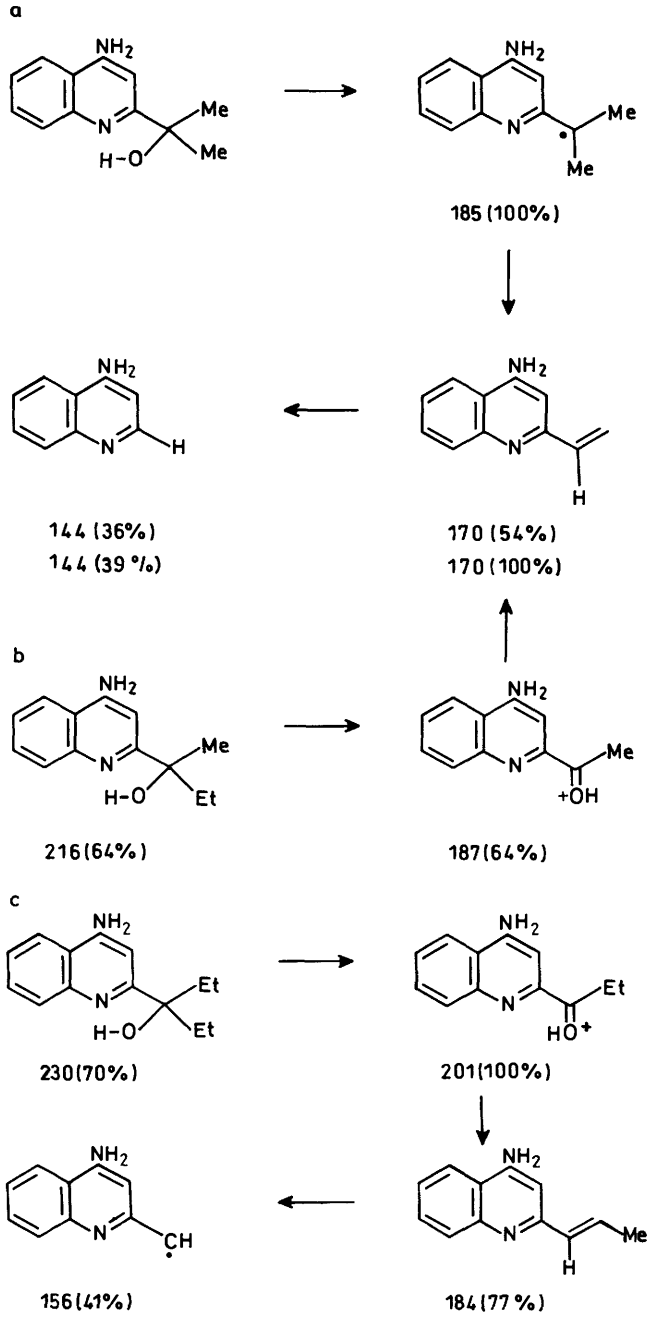
(**8**)



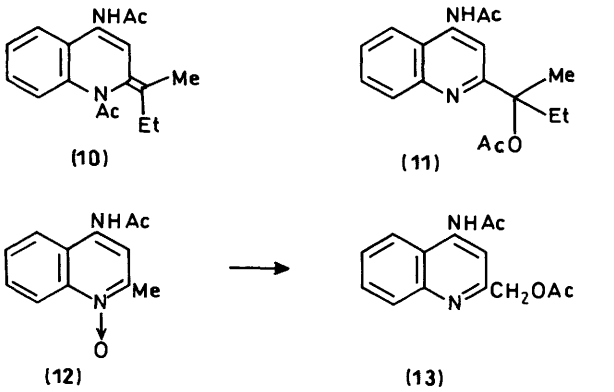
(**9**)

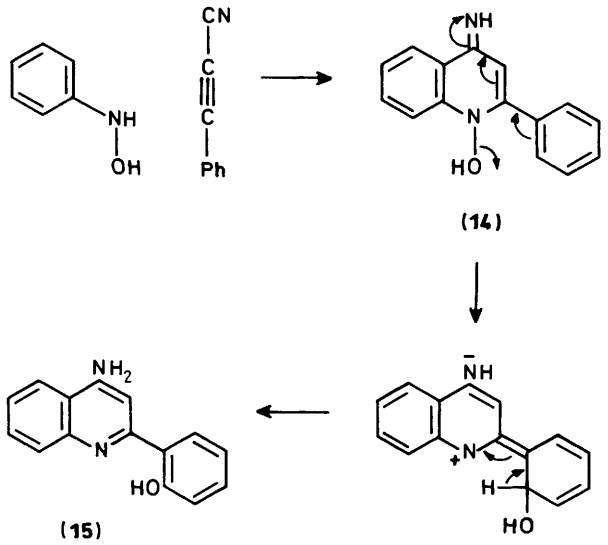
The ^{13}C n.m.r. spectrum confirms the 2-(1-hydroxyalkyl) side chain with a quaternary carbon at δ 51.218 p.p.m. The mass spectra show molecular ions (64—83%); a principal fission pattern for a three-carbon chain shows first loss of ethyl followed by hydroxy (see Scheme 3, b and c) whereas a two-carbon chain first loses OH• and then Me• (see Scheme 3a). Detailed analysis of the mass spectra show that they do *not* fit alternative structures (**3**), (**4**), or (**6**).

4-Amino-2-(1-hydroxyalkyl)quinolines (**5**) are stable to acid and base. Treatment with 2.5% alcoholic hydrochloric acid or 4% alcoholic sulphuric acid for 24 h and work-up with carbonate gave a product with a u.v. spectrum identical with that of the starting material. Acetylation with acetic anhydride gave the diacetamide (**10**) in 15% yield as well as other acetylated products none of which correspond to (**11**). It is interesting to note that acetylation of the isomeric quinoline *N*-oxide (**7**) gave a mixture of acetylated products from which the diacetyl compound (**11**) was isolated (29%) by p.l.c. A model experiment, starting with *N*-acetyl-4-aminoquinaldine *N*-oxide (**12**), gave 4-acetamido-2-acetoxymethylquinoline (**13**) in 45% yield by a Katritzky mechanism[11] and (**11**) is assumed to form from (**7**) by a similar mechanism. However the acetamidoacetate (**11**) could not be hydrolysed to (**5b**). Phenylpropynenitrile and phenylhydroxylamine for 20 h under reflux in ethanol gave, after repeated chromatography, 8% of a stable product, 4-amino-2-(2-hydroxyphenyl)quinoline (**15**), this structure being proposed on the basis of the following spectroscopic evidence (Scheme 4). Strongly hydrogen bonded, broad hydroxy absorption centred at $\nu_{max.}$ 3 200 cm^{-1} and NH_2 absorption at 3 360 and 3 450 cm^{-1}; $\lambda_{max.}$ at 211, 242, and 300 nm; δ_H for chelated OH at 11 p.p.m. and a mass spectrum which gave the molecular ion (M^+, 236, 100%) as the base peak, a strong $M-1$ peak at 235 (33%) and $M-16$ (2270, 76%). These results are consistent with the phenolic 4-amino-2-(2-hydroxyphenyl)quinoline structure (**15**) but not the 4-amino-2-phenyl-*N*-hydroxy-1,2-dihydroquinoline structure (**14**). Other chromatography fractions consisted of decomposition products of the starting materials.



Scheme 3.





Scheme 4.

Experimental

I.r. spectra were determined with Perkin-Elmer 257 and 735 B spectrometers, u.v. spectra for ethanolic solutions with Perkin-Elmer 137, Beckman 25 and Cary 219 spectrometers, and ^1H n.m.r. spectra with Perkin-Elmer R12B and JEOL 60 instruments in deuteriochloroform unless otherwise stated. Highfield ^1H and ^{13}C spectra were determined with a Bruker 250 instrument. Preparation thin layer chromatography (p.l.c.) was carried out on SiO_2 (Merck PF 254 + 366). Allenic nitriles were prepared as previously reported.[7] Phenylhydroxylamine was freshly prepared by the standard method.[8]

4-*Amino*-2-(1-*hydroxy*-1-*isopropyl*)*quinoline*.—4-Methylpenta-2,3-dienenitrile (2.79 g, 0.03 mol) in ethanol (95%; 25 ml) and phenylhydroxylamine (3.27 g, 0.03 mol) in ethanol (95%; 25 ml) were heated under reflux for 48 h and solvent was evaporated from the reaction mixture and the residue chromatographed [neutral alumina (activity 2; 300 g), elution with ethyl acetate] to give the *title compound* (5.25 g, 86%), m.p. 165 °C (Found: C, 71.55; H, 7.1; N, 14.0. $C_{12}H_{14}N_2O$ requires C, 71.29; H, 6.93; N, 13.86%); $\nu_{max.}$ 3 390 and 3 200 (NH_2) and 3 400 cm^{-1} (br, OH); $\lambda_{max.}$ 298 (22 300) and 316 nm (22 800); δ 1.33 (6 H, s, CMe_2), 4.77, 5.3 (2 H, br s, NH_2, exchanges D_2O), 6.6—7.4 (4 H, m, aromatic 4-H), and 10.25 (1 H, br s, OH, exchanges D_2O); *m/z* 202 (M^+, 83), 185 (100), 170 (54), 157 (47), 144 (36), and 115 (29).

4-*Amino*-2-(1-*hydroxy*-1-*methylpropyl*)*quinoline*.—Similarly, 4-methylhexa-2,3-diene (4.28 g, 0.04 mol) and phenylhydroxylamine (4.36, 0.04 mol) when heated under reflux in ethanol (95%; 50 ml) for 48 h gave the *title compound* (7.34 g, 85%), m.p. 158 °C (Found: C, 72.1; H, 7.3; N, 13.0. $C_{13}H_{16}N_2O$ requires C, 72.22; H, 7.41; N, 12.96%); $\nu_{max.}$ 3 460 (OH) and 3 325 and 3 180 cm^{-1} (NH_2); $\lambda_{max.}$ 298 (21 700) and 316 nm (23 500); δ_H 0.555 (3 H, t, CH_2CH_2), 1.333 (3 H, s, CH_3C), 1.646 and 1.838 (2 H, 2 × quin, $HCHCH_3$), 4.708 (1 H, s, =CN-3), 5.196 (2 H, br s, NH_2), 6.6—7.3 (4 H, 2 × t + 2 × d, aromatic 4-H), and 10.282 (1 H, br s, OH); δ_C 8.79 ($MeCH_2$), 27.40 (*Me*C), 34.71 (CH_2), 51.22 (*C*MeEtOH), 81.36 (NH_2C=*C*H), 108.79 (=CH), 120.68 (=CH), 122.24 (=CH), 127.80 (=CH), 135.01 (C), 144.00 (C), 168.80 (C), and 172.19 (C); M^+, 216 (64), 199 (42), 187 (64), 170 (100), and 144 (27).

4-*Amino*-2-(1-*hydroxy*-1-*ethylpropyl*)*quinoline*.—Similarly, 4-ethylhexa-2,3-dienenitrile (3.63 g, 0.03 mol) and phenylhydroxylamine (3.27 g, 0.03 mol) when heated under reflux in ethanol (95%; 50 ml) for 48 h gave the *title compound* (5.73 g, 83%), m.p. 140 °C (Found: C, 73.15; H, 7.85; N, 12.25. $C_{14}H_{18}N_2O$ requires C, 73.04; H, 7.83; N, 12.17%); $\nu_{max.}$ 3 400 (OH) and 3 360 and 3 180 cm^{-1} (NH_2); $\lambda_{max.}$ 297 (22 600) and 318 nm (25 000); δ 0.52 [6 H, t, $(CH_3CH_2)_2$], 1.62 [4 H, q, $(CH_3CH_2)_2$], 4.58 (1 H, s, =CH), 5.30 (2 H, br s, NH_2), 6.7—7.2 (4 H, m, aromatic 4-H), and 10.29 (1 H, br s, OH); 230 (M^+, 70), 213 (38), 201 (100), 184 (77), and 156 (41).

4-*Amino*-2-(2-*hydroxyphenyl*)*quinoline*.—3-Phenylpropynenitrile (3.81 g, 0.03 mol) and phenylhydroxylamine (3.27 g, 0.03 mol) when heated under reflux in ethanol (150 ml; 95%) for 60 h gave, on evaporation of solvent, a brown oil (6.9 g). Repeated chromatography of this followed by recrystallisation of the product gave the *title compound* (0.57 g, 8%), m.p. 118 °C (Found: C, 76.3; H, 5.1; N, 11.95. $C_{15}H_{12}N_2O$ requires C, 76.27; H, 5.08; N, 11.86); $\nu_{max.}$ 3 450 and 3 340 (NH_2) and 3 200 cm^{-1} (OH); $\lambda_{max.}$ 210 (31 500), 243 (22 000), and 301 nm (13 600); δ($CDCl_3$ + [$^2H_6$]DMSO) 3.30 (1 H, s, CH), 6.25 (2 H, br s, NH_2), 7.0—8.1 (9 H, m, aromatic 9-H), 11.41 (1 H, br s, OH); 236 (M^+, 100), 235 (33), 220 (76), 191 (15), 165 (22), and 149 (23).

2-(1-*Methylpropyl*)*quinoline* N-*Oxide*.—2-(1-Methylpropyl)-quinoline (6.23 g, 34 mmol; b.p. 105—108 °C at 1.0 mmHg, prepared by a modified literature method[9]), glacial acetic acid (30 ml), and hydrogen peroxide (30 wt% in water; 7.5 ml), were heated under reflux for 6.5 h. The mixture was then evaporated, neutralised with aqueous sodium hydroxide (10%) and extracted with chloroform. Work-up of the extract followed by p.l.c. gave 2-(1-methylpropyl)quinoline *N*-oxide (3.2 g, 46%) and starting material (2.7 g, 44%) (Found: C, 75.35; H, 7.45; N, 7.15. $C_{13}H_{15}NO\cdot\frac{1}{3}H_2O$ requires C, 75.36; H, 7.57; N, 6.76%); $\lambda_{max.}$ 232 (37 500), 238 (41 800), 318 (8 000), and 330 (7 200); δ 0.9 (3 H, t, CH_3CH_2), 1.33 (3 H, d, CH_3CH), 1.6 (2 H, m, CH_3CH_3CH), 3.96 (1 H, sextet, CH_2CHCH_3), 7.1—7.9 (5 H, m, ArH), and 8.8 (1 H, dd, 8-H); 201 (M^+, 29) and 184 (100).

2-(1-*Methylpropyl*)-4-*nitroquinoline* N-*Oxide*.—2-(1-Methylpropyl)quinoline *N*-oxide (0.52 g, 2.5 mmol) in ice–salt was treated with concentrated sulphuric acid (*d* 1.84; 1.5 ml added dropwise) and then heated to 65 °C when concentrated nitric acid (*d* 1.42; 9.3 ml) was added slowly with constant shaking (30 min). Shaking was continued for 1.5 h after which the mixture was poured into ice–water and extracted with chloroform; work-up of the extract followed by p.l.c. gave the *title compound* (0.21 g, 34%), m.p. 56—57 °C (Found: C, 63.25; H, 5.95; N, 11.0; O, 19.2. $C_{13}H_{14}N_2O_3$ requires C, 63.4; H, 5.69; N, 113.8; O, 19.49%); $\lambda_{max.}$ 257 (21 000) and 380 (10 800); δ 7.6—7.8 (2 H, m, 6-H, 7-H), 8.10 (1 H, s, 3-H), 8.5—8.8 (2 H, 5-H, 8-H); 246 (M^+, 14), 229 (33), 218 (19), 204 (27), 202 (32), 183 (32), 170 (63), and 157 (100).

4-*Amino*-2-(1-*methylpropyl*)*quinoline* N-*Oxide*.—The above nitroquinoline *N*-oxide (0.185 g, 0.75 mmol) in ethanol (40 ml) with Pd/C (10; 0.069 g) was allowed to adsorb hydrogen (50 ml, 2.2 mmol) for 1 h. Work-up of the mixture gave the *title compound* (0.10 g, 62%), m.p. 190—192 °C (Found: C, 72.9; H, 7.0; N, 13.15. $C_{13}H_{16}N_2O$ requires C, 72.22; H, 7.41; N, 12.96); $\nu_{max.}$ 3 280 and 3 140 cm^{-1} (NH_2); $\lambda_{max.}$ 218 (38 500), 244 (18 000), 257 (18 000), 262 (18 000), 350 (11 000), and 366 (10 200); δ 0.89 (3 H, t, CH_3CH_2), 1.23 (3 H, d, CH_3CH), 1.3—2.0 (2 H, overlapping quintets $HCHCH_3$), 3.89 (1 H, sextet, CH_3CHCH_2), 6.32 (2 H, s, NH_2, exchanges D_2O), 6.48 (1 H, s, 3-H), 7.33 (1 H, t, 7-H), 7.62 (1 H, t, 6-H), 8.02 (1 H, dd, 8-H, *J* 8 and 10 Hz), and 8.66 (1 H, dd, 8-H, *J* 8 and 10 Hz); 216 (M^+, 9.4), 199 (30), 183 (13), 171 (32), 143 (14.8), 116 (28), 56 (55), 54 (49), and 42 (100).

4-*Acetamido*-1-*acetyl*-2-(1-*methylpropylidene*)-1,2-*dihydroquinoline* (**10**).—4-Amino-2-(1-hydroxy-1-methylpropyl)-quinoline (0.216 g, 1 mmol) with acetic anhydride (2.4 ml) at 100 °C for 45 min gave a mixture of acetates (0.29 g, oil). P.l.c. (EtOAc–C_6H_{14}; 4:1) gave the title compound (0.045 g, 15%), m.p. 212—215 °C; $\nu_{max.}$ 3 400 (NH) and 1 660 (CO); $\lambda_{max.}$ 234 (14 900), 254 (10 000), 274 (7 200), and 283 (7 500); δ_H 1.26 (6 H, s, 2 × CH_3CO), 1.5 (3 H, 2 × t, CH_3CH_2, *E* and *Z*), 1.89—1.99 (2 H, 2 × 9, CH_2, *E* and *Z*), 2.24 (3 H, 2 × s, CH_3C=C, *E* and *Z*), 5.77 (1 H, s, =CH-3), and 7.26—7.68 (SH, m, ArH and NH); δ_C 8.7 (CH_3), 27.3 ($3H_3$), 29.7 (CH_2), 30.3 (CH_3), 35.0 (CH_2), 83 (CH), 99 (CH), 114 (CH), 123 (CH), 126 (CH), and 129 (CH); 284 (M^+, 68), 268 (46), 239 (24), 200 (49), 171 (53), 115 (22), 85 (41), 71 (63), 57 (100), 43 (69), and 41 (28).

4-*Acetamido*-2-(1-*acetyl*-1-*methylpropyl*)*quinoline* (**11**).—4-Amino-2-(1-methylpropyl)quinoline *N*-oxide (0.05 g, 0.23 mmol) in acetic anhydride (1 ml) under reflux for 45 min gave a mixture of acetyl compounds (0.044 g, 64%) which on p.l.c. gave the title compound (0.02 g, 29%); $\nu_{max.}$ 3 250 (NH), 1 720 and 1 660 cm^{-1} (CO); $\lambda_{max.}$ 232 (38 900) and 295 (8 700), and 320 (6 200); δ 1.18 (3 H, t, CH_3CH_2, 1.26 (3 H, s, CH_3C), 2.09—2.17 (1 H, quin., HCHMe), 2.11 (3 H, s, MeCO), 2.19 (3 H, s, MeCONH), 2.76 (1 H, quin., HCHMe), 5.63 (1 H, s, NH_2C=CH), and 7.26—8.38 (5 H, m, N*H* + H-4); 241 (M^+ − $MeCO_2$, 11), 240 (33), 197 (42), 182 (87), 181 (64), 127 (10), 58 (19), 57 (100), 56 (19), 55 (43), and 43 (98).

4-*Acetamido*-2-*methylquinoline* N-*Oxide*.—A cooled solution (0—5 °C) of *m*-chloroperbenzoic acid (1.09 g, 6.3 mmol) in chloroform (15 ml), was added slowly with stirring to an ice-cold solution of 4-acetamido-2-methylquinoline (1.0 g, 5 mmol) [m.p. 162—164 °C, lit.,[10] m.p. 162—164 °C] in chloroform (10 ml). The mixture was allowed to warm to room temperature and evaporated after 3 h to yield, after chromatography, recovered starting material (0.5 g, 50%) and the *title compound* (0.33 g, 28%), m.p. 122 °C (after recrystallisation from acetone) (Found: C, 61.55; H, 5.85; N, 11.9. $C_{12}H_{12}N_2O_2 \cdot H_2O$ requires C, 61.54; H, 5.98; N, 11.97%); $\nu_{max.}$ 3 600—2 900 (H_2O), 3 250 (NH), and 1 700 cm^{-1} (CO); $\lambda_{max.}$ 229 (35 000), 244 (30 000), and 344 nm (12 000); δ 2.3 (3 H, s, CH_3C=), 2.63 (3 H, s, CH_3CO), 7—8.7 (5 H, m, ArH), and 10.13 (1 H, br s, NH).

4-*Acetamido*-2-*acetoxymethylenequinoline*.—4-Acetamido-2-methylquinoline *N*-oxide hydrate (0.22 g, 0.94 mmol) and acetic anhydride (4.32 g, 42 mmol) refluxed for 45 min gave, after p.l.c. (EtOAc–C_6H_{14}, 4:1), the *title compound* (0.11 g, 45.4%), m.p. 134—135 °C (Found: C, 65.2; H, 5.7; N, 10.9; O, 18.2. $C_{14}H_{14}N_2O_3$ requires C, 65.12; H, 5.43; N, 10.85; O, 18.6%); $\nu_{max.}$ 3 340 (NH), 1 720, and 1 690 cm^{-1} (CO); $\lambda_{max.}$ 258 (57 000), 297 (10 400), and 318 (6 500); δ_H 2.16 (3 H, s, CH_3CO), 2.25 (3 H, s, CH_3CON), 5.27 (2 H, s, CH_2O), 7.2—8.13 (5 H, m, ArH), and 8.33 (1 H, s, NH; δ_C 20.89 (CH_3CON), 67.49 (CH_2O), 109.08 (C-2), 119.39 (CH-3), 119.56 (CH-8), 126.31 (CH-7), 129.69 (CH-6), 130.04 (CH-5), 141.35 (CH-4), 148.30 (C-9), 156.94 (C-10), 169.35 (COO), and 171.15 (CON). Recovered starting material (0.09 g, 41%).

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