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THE AUTOXIDATION OF 2-(2-AMINOPHENYL)-3-METHYLINDOLE

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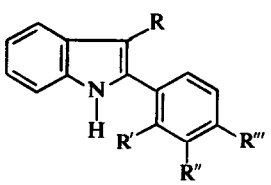
Abstract—Fischer indolisation of 2-aminophenyl ethyl ketone phenylhydrazone using glacial acetic acid saturated with hydrogen chloride as catalyst affords 3-methylindolo(1′:2′-3:4)2-methylquinazoline and 2-(2-aminophenyl)-3-methylindole. The latter compound is autoxidised to 2-(2-aminophenyl)-3-hydroxy-3-methyl-3H-indole, a reaction which is shown to be dependent upon the presence of the primary amino group at the 2-position of the 2-phenyl substituent and which is much slower than the corresponding autoxidation of 2-(2-hydroxyphenyl)-3-methylindole to 3-hydroxy-2-(2-hydroxyphenyl)-3-methyl-3H-indole previously[1] reported. Nitration of isopropyl phenyl ketone occurs preferentially at the *ortho*- rather than the *meta*- positions of the benzene nucleus.

We recently reported[1] that 2-(2-hydroxyphenyl)-3-methylindole **1** (R=Me, R′=OH, R″=R‴=H) undergoes oxidation, upon boiling its solution in light petroleum exposed to the atmosphere, to afford 3-hydroxy-2-(2-hydroxyphenyl)-3-methyl-3H-indole **2** (R=OH, X=O). Since both 2-(4-hydroxyphenyl)-3-methylindole **1** (R=Me, R′=R″=H, R‴=OH) and 2-(2-methoxyphenyl)-3-methylindole **1** (R=Me, R′=OMe, R″=R‴=H) remain



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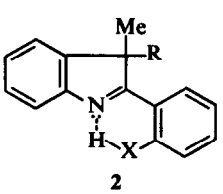

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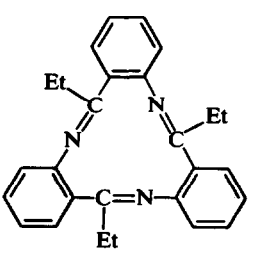
unchanged under these conditions it was suggested[1] that the above autoxidation occurs via formation of the 3H-indole **2** (R=H, X=O), which is in equilibrium with 2-(2-hydroxyphenyl)-3-methylindole **1** (R=Me, R′=OH, R″=R‴=H) and whose formation in this equilibrium is made possible by its stabilisation by intramolecular H-bonding as shown. Alternatively, the autoxidation may proceed directly via formation of the 3-hydroperoxide **2** (R=OOH, X=O), similar stabilisation of this or the final product by intramolecular H-bonding being the deciding factor responsible for the autoxidation. We have now investigated the possibility of the similar autoxidation of 2-(2-aminophenyl)-3-methylindole **1** (R=Me, R′=NH_2, R″=R‴=H).

Ethyl 2-nitrophenyl ketone[2] was reduced to 2-aminophenyl ethyl ketone by hydrogenation in the presence of 10% Pt-C at room temperature and atmospheric pressure (using a Pd-C catalyst, the same hydrogenation requires[2] an elevated temperature and pressure). Heating this product with phenylhydrazine afforded only compound **3**. The required phenylhydrazone was therefore prepared by reacting equimolar quantities of the ketone and phenylhydrazine in boiling ethanolic solution in the presence of glacial acetic acid. This was then subjected to Fischer indolisation,[3] using glacial acetic acid saturated with hydrogen chloride as the catalyst, to afford 2-(2-aminophenyl)-3-methylindole **1** (R=Me, R′=NH_2, R″=R‴=H) along with 3′-methylindolo(1′:2′-3:4)2-methylquinazoline **4** (R=R′=Me). The structure of this latter product was verified by examination of its PMR spectral properties and by the close similarity of its UV spectrum to that of indolo(1′:2′-3:4) quinazoline **4** (R=R′=H), prepared[4] by reaction of 2-(2-aminophenyl)indole **1** (R=R″=R‴=H, R′=NH_2) with formic acid. Since the monoacetyl derivative of 2-(2-aminophenyl)indole **1** (R=R″=R‴=H, R′=NH.CO.Me) has been converted[4] into indolo(1′:2′-3:4)2-methylquinazoline **4** (R=Me, R′=H) by heating it in glacial acetic acid containing hydrogen chloride, it appears that in the present studies compound **4** (R=R′=CH_3) is produced by similar cyclisation of 2-(2-acetylaminophenyl)-3-methylindole **1** (R=Me, R′=NH.CO.Me, R″=R‴=H)



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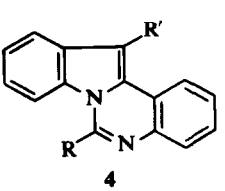

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which is formed by N-acetylation of the initial indolic reaction product. The presence of this intermediate in the *total reaction product was indicated* by a significant peak at $m/e = 264$ in the mass spectrum of this product. The formation of this by-product was averted by indolising the phenylhydrazone using the non-catalytic thermal technique[3] by boiling under reflux its solution in monoethylene glycol.

Boiling under reflux for nine weeks a solution of 2-(2-aminophenyl)-3-methylindole in light petroleum exposed to the atmosphere afforded a small yield of 2-(2-aminophenyl)-3-hydroxy-3-methyl-3H-indole **2** (R=OH, X=NH). The structure of this autoxidation product was supported by its IR and mass spectra and by the close similarity of its UV spectrum with that of 2-(2-aminophenyl)-3,3-dimethyl-3H-indole **2**(R=Me, X=NH). Attempts to prepare this latter compound by 3-methylation (with MeI) of the Grignard derivative of 2-(2-aminophenyl)-3-methylindole **1** (R=Me, R′=NH_2, R″=R‴=H) failed, the reaction mixture undergoing extensive decomposition. It was therefore prepared by the following route. Friedel-Crafts acylation of benzene with 2-methylpropanoyl chloride afforded isopropyl phenyl ketone which upon nitration afforded a mixture of isopropyl 2- and 3-nitrophenyl ketones. This was catalytically hydrogenated to afford a mixture of 2- and 3-aminophenyl isopropyl ketones, from which the two isomers could be separated by steam-distillation. The structures of these isomers were confirmed by their behaviour upon steam-distillation (the *ortho*-isomer is steam-volatile (cf Ref 3)), the C=O stretching frequency in their IR spectra (the *ortho*-isomer has the lowest stretching frequency) and their UV spectra, these *spectral data being compared with* those of 2- and 3-aminophenyl ethyl ketones which were prepared as described in the literature.[2]

It is interesting to note that the yield of the *ortho*-amino isomer was much greater than the yield of the *meta*-amino isomer, reflecting the preferential *ortho*- rather than *meta*- nitration of isopropyl phenyl ketone, contrary to what would have been expected (see, for *e.g.*, Ref 2).

2-Aminophenyl isopropyl ketone was then converted into its phenylhydrazone which was indolised using glacial acetic acid saturated with hydrogen chloride to give the required product.

2-(2-Benzylidenoaminophenyl)-3-methylindole **1** (R=Me, R′=PhCH=N, R″=R‴=H), prepared by reacting **1** (R=Me, R′=NH_2, R″=R‴=H) with benzaldehyde, and 2-(3- and 4-aminophenyl)-3-methylindoles **1** (R=Me, R′=R‴=H, R″=NH_2) and **1** (R=Me, R′=R″=H, R‴=NH_2), respectively, prepared by Fischer indolisation of the phenylhydrazones of 3-[2] and 4-aminophenyl ethyl ketones respectively, all remained unchanged when their solutions in light petroleum were boiled under reflux for 9 weeks exposed to the atmosphere. The autoxidation of compound **1** (R=Me, R′=NH_2, R″=R‴=H) to **2** (R=OH, X=NH) is therefore *dependent upon the presence of the 2-amino group* on the indolic 2-phenyl substituent. This, by analogy with the probable function of the phenolic OH group in the similar autoxidation[1] of 2-(2-hydroxyphenyl)-3-methylindole **1** (R=Me, R′=OH, R″=R‴=H) to 3-hydroxy-2(2-hydroxyphenyl)-3-methyl-3H-indole **2** (R=OH, X=O), probably stabilises, by intramolecular H-bonding as shown in **2**, the possible autoxidation intermediate products **2** (R=H and OOH, X=NH) or the final autoxidation product. In connection with this it has been reported[6] that the H-bond formed between the p-electrons of a tertiary N atom and the H atom of an OH group is more stable than the H-bond formed between this electron pair and one of the H atoms of a primary amino group, observations which possibly account for the comparative ease of autoxidation of 2-(2-hydroxyphenyl)-3-methylindole **1** (R=Me, R′=OH, R″=R‴=H)[1] relative to that of the amino analogue **1** (R=Me, R′=NH_2, R″=R‴=H) described above.

EXPERIMENTAL

M.ps were determined on a Kofler hot stage apparatus and are uncorrected. UV spectra were recorded in 95% EtOH with a Perkin–Elmer model 137 spectrophotometer, IR spectra were recorded (solids as mulls in Nujol, oils as *liquid films*) with a *Perkin–Elmer model 237* spectrophotometer, PMR spectra were recorded in $CDCl_3$ with a Varian HA-100 spectrophotometer with TMS as internal standard and mass spectra were recorded with AEI MS-12 (low resolution) and MS-9 (high resolution) spectrometers. Solns were dried over $MgSO_4$ and evaporations were carried out under reduced pressure (water-pump) on a Buchi rotary evaporator. Solid analytical samples were dried over P_2O_5 at 80°/0·1 mm for 4 hr immediately prior to analysis.

2-Aminophenyl ethyl ketone. A soln of ethyl 2-nitrophenyl ketone[2] (18·0 g) in benzene (60 ml) was shaken under an atmosphere of H_2 at room temp and atmospheric pressure in the presence of 10% Pt-C. After the theoretical volume of H_2 had been absorbed, the catalyst was removed by filtration, the filtrate dried, and the benzene evaporated to afford *2-aminophenyl ethyl ketone* as a pale-yellow oil (14·1 g; 93%) b.p. 142–146°/15 mm. The UV and IR spectra were identical with those of a sample prepared by the literature method.[2] UV λ_{max} 227, 256–257, 364–368, λ_{min} 209 nm ($\log \epsilon = 4{\cdot}43, 3{\cdot}87, 3{\cdot}73, 4{\cdot}06$, *respectively*). *IR 3435, 3320 (both ± 10) cm*$^{-1}$ (N—H), 1640 cm^{-1} (C=O).

2-(2-Aminophenyl)-3-methylindole **1** (R=Me, R′=NH_2, R″=R‴=H). A mixture of 2-aminophenyl ethyl ketone (3·0 g) and phenylhydrazine (2·2 g) was heated (oil bath) at 110–120° for 1½ hr, during which time white crystals of **3** were formed. After trituration with ether this product was collected and recrystallised from EtOH–ether to afford cream-coloured prisms (1·9 g; 73%) m.p. 215–217°. ($M^+ = 393{\cdot}223175$; $C_{27}H_{27}N_3$ requires: 393·220487).

Method 1. A soln of 2-aminophenyl ethyl ketone (7·5 g) and phenylhydrazine (5·4 g) in a mixture of EtOH (15 ml) and glacial AcOH (1·0 ml) was boiled under reflux

for 8 hr, the EtOH then evaporated and the residual *phenylhydrazone* dried *in vacuo* overnight. It was then dissolved in glacial AcOH saturated with HCl (96 ml), the soln was boiled under reflux for ½ hr, cooled and poured onto crushed ice. Basification of the resulting soln with Na_2CO_3 liberated an oil which was extracted into ether (4 × 100 ml). The combined ethereal extracts were washed with water (100 ml), dried, and the solvent evaporated to afford a dark-brown oil which was subjected to column chromatography on silica gel. Initial elution with a light petroleum (30–40°)-ether (9:1 v/v) mixture afforded, after evaporation of the solvent from the eluates and recrystallisation of the yellow crystalline residue from light petroleum (40–60°), 2-(2-*aminophenyl*)-3-*methylindole* as pale-yellow needles (3·1 g, 28%) m.p. 89–90°. (Found: C, 81·2; H, 6·4; N, 12·4; $C_{15}H_{14}N_2$ requires; C, 81·1; H, 6·3; N, 12·6%), ($M^+ = 222$). UV λ_{max} 229, 302, λ_{infl} 245 nm (log ϵ = 4·83, 4·24, 4·39, respectively); IR 3440, 3400, 3370, 3350, 3290 (all ± 10) cm^{-1} (N—H). PMR singlet 7·76 (3H), multiplet between 3·70–2·00 τ (8H).

Continued elution with a light petroleum (40–60°)-ether (7:3 v/v) mixture afforded, after evaporation of the solvent from the eluates, a yellow oil which crystallised from acetone to afford 3′-*methylindolo*(1′:2′-3:4)2-*methylquinazoline* **4** (R=R′=Me) as yellow prisms (1·2 g, 10%) m.p. 152–153° (Found: C, 83·3; H, 5·8; N, 11·5; $C_{17}H_{14}N_2$ requires: C, 82·9; H, 5·7; N, 11·4%); ($M^+ = 246$). UV λ_{max} 238, 271, 280, 295, 343, 359, λ_{infl} 261, 324 nm (log ϵ = 4·14, 4·51, 4·63, 3·79, 3·90, 3·91, 4·25, 3·67, respectively) [*cf* indolo(1′:2′-3:4)quinazoline **4** (R=R′=H),[4] UV λ_{max} 234, 240, 276, 285, 294, 335, 352, λ_{infl} 322 nm (log ϵ = 4·33, 4·35, 4·69, 4·72, 4·30, 3·99, 3·97, 3·85, respectively)]. PMR singlets 7·50 (3H, 7·17 (3H), multiplet between 2·85–1·90 τ (8H).

Method 2. 2-Aminophenyl ethyl ketone phenylhydrazone (5·0 g), prepared as described in method 1, was dissolved in monoethylene glycol (40 ml) and the soln was boiled under reflux for 18 hr. After cooling, the mixture was poured onto crushed ice and the liberated oil was extracted into ether (3 × 75 ml). The combined ethereal extracts were dried and the ether evaporated to afford a dark-brown oil from which *the indole* was extracted using boiling light petroleum (40–60°) (200 ml). Evaporation of the light petroleum from the extract gave buff-coloured crystals which upon recrystallisation from light petroleum (40–60°) afforded pale-yellow needles (1·1 g, 23%) m.p. 89–90°, whose UV and IR spectra were identical with those of the indolic product obtained using method 1.

2-(2-*Aminophenyl*)-3-*hydroxy*-3-*methyl*-3H-*indole* **2** (R=OH, X=NH). A soln of 2-(2-aminophenyl)-3-methylindole (500 mg) in light petroleum (60–80°) (20 ml) was boiled under reflux for 9 weeks exposed to the atmosphere. The dark-brown oil (521 mg) obtained after evaporation of the solvent was subjected to column chromatography on silica gel using a mixture of light petroleum (40–60°)-ether (9:1 v/v) as eluting solvent. The initial eluates (440 ml) afforded, upon evaporation of the solvent, starting material which was identified by m.p., UV and IR comparisons. Subsequent eluates (80 ml), upon evaporation of the solvent, afforded 2-(2-*aminophenyl*)-3-*hydroxy*-3-*methyl*-3H-*indole* as a pale-yellow oil (12 mg, 2%), further purification of which for spectral analysis was effected by preparative TLC [R_f = 0·82 on silica gel sheets using a benzene-ether (3:1 v/v) mixture as solvent and UV light and iodine vapour as developer]. (M^+ = 238·109634; $C_{15}H_{14}N_2O$ requires: 238·110607, $M^+ - OH$ = 221·107591; $C_{15}H_{13}N_2$ requires: 221·107868); UV λ_{max} 232, 300, 391, λ_{infl} 323 nm (log ϵ = 4·07, 3·56, 3·47, 3·40, respectively).

2-(2-*Benzylidenoaminophenyl*)-3-*methylindole* **1** (R=Me, R′=PhCH=N, R″=R‴=H). A soln of 2-(2-aminophenyl)-3-methylindole (220 mg) and freshly-redistilled benzaldehyde (102 mg) in EtOH (3 ml) was boiled under reflux for 2 hr. Evaporation of the EtOH gave a solid residue which was recrystallised from cyclohexane to give white prisms (251 mg, 81%) m.p. 143–144°. (Found: C, 85·1; H, 5·8; N, 9·0; $C_{22}H_{18}N_2$ requires: C, 85·0; H, 5·8; N, 9·0%), (M^+ = 310).

A soln of this compound in light petroleum (60–80°) remained unchanged when treated as described in the above autoxidation.

2-(3-*Aminophenyl*)-3-*methylindole* **1** (R=Me, R′=R‴=H, R″=NH_2). A mixture of 3-aminophenyl ethyl ketone[2] [UV λ_{max} 231, 349–352, λ_{infl} 205, 260 nm (log ϵ = 4·38, 3·27, 3·99, 3·92, respectively). IR 3455, 3363, 3230 (all ± 10) cm^{-1} (N—H). 1679 cm^{-1} (C=O)] (3·0 g) and phenylhydrazine (2·2 g) was converted into the phenylhydrazone and then idolised by method 2 described above, except that the reaction time for the indolisation was increased to 29 hr. The total reaction product, a dark-brown oil (3·2 g), was dissolved in dry ether (20 ml) and this soln was saturated with HCl. The crystalline ppt was recrystallised from MeOH-ether to afford 2-(3-*aminophenyl*)-3-*methylindole hydrochloride monohydrate* as light-brown prisms (1·1 g, 20%) m.p. 180–184°. (Found: C, 65·2, 65·6; H, 5·8, 5·9; N, 10·1, 10·1; $C_{15}H_{15}ClN_2.H_2O$ requires: C, 65·1; H, 6·1; N, 10·1%).

The free base was obtained by basifying a soln of the hydrochloride (0·50 g) in warm water (10 ml) with ammonium hydroxide (d = 0·880). The liberated oil was extracted into ether (3 × 25 ml) and the ether was evaporated from the combined dried ethereal extracts to afford *the indole* as a light-brown oil b.p. 170–180° (bath temp)/15 mm (Found: C, 81·0; H, 6·5; N, 12·1; $C_{15}H_{14}N_2$ requires: C, 81·1; H, 6·3; N, 12·6%); (M^+ = 222). IR 3405, 3370 (both ± 10) cm^{-1} (N—H).

2-(4-*Aminophenyl*)-3-*methylindole* **1** (R=Me, R′=R″=H, R‴=NH_2). A soln of 4-aminophenyl ethyl ketone (3·0 g) and phenylhydrazine (2·2 g) in monoethylene glycol (40 ml) was boiled under reflux for 14 hr, after which time ammonia-evolution had ceased. After cooling, the mixture was poured into water (400 ml) and the liberated oil, which rapidly solidified, was extracted into ether (2 × 150 ml). The combined ethereal extracts were washed with water (150 ml), dried, and the ether evaporated to afford a solid residue which upon recrystallisation from ether gave pale-tan coloured prisms (4·1 g, 93%) m.p. 165–167°. (Found: C, 81·3; H, 6·4; $C_{15}H_{14}N_2$ requires: C, 81·1; H, 6·3%); IR 3310, 3390 (both ± 10) cm^{-1} (N—H).

Both this indole and its 3-amino isomer prepared above remained unchanged when treated as described in the above autoxidation.

2- *and* 3-*Aminophenyl isopropyl ketones.* 2-Methylpropanoic acid (88 g) was added dropwise to warm redistilled thionyl chloride (150 g) over a period of ½ hr. After addition was complete the mixture was heated on a steam-bath for ½ hr and then fractionally distilled, 2-*methylpropanoyl chloride* (100·5 g, 94%) being collected between 92–93°.

To a suspension of finely-powdered anhyd $AlCl_3$ (70 g) in dry benzene (135 ml) was added dropwise 2-methylpropanoyl chloride (53·3 g) over a period of 2 hr, the mixture being warmed to initiate the reaction and being kept well-stirred during the addition. After boiling under

reflux for ½ hr, the mixture was cooled and poured carefully into stirred ice-water. The water-immiscible layer was washed with 10% NaOHaq (3 × 100 ml) and then with water (3 × 100 ml), dried and the benzene removed to afford a brown oil which was fractionally distilled, *phenyl isopropyl ketone* (40·5 g, 55%) being collected between 101–103°/15 mm.

To cooled (0–5°) fuming HNO_3 (d 1·5) (450 ml) was added phenyl isopropyl ketone (74 g) dropwise and with stirring such that the temp of the mixture was maintained below 10°. After addition was complete, stirring was continued a further 10 min and the mixture was then poured onto crushed ice. Neutralisation with Na_2CO_3 liberated an oil which was extracted into benzene (5 × 100 ml), the combined benzene extracts being washed with water (100 ml), with 10% NaOHaq until the washings were almost colourless and finally with water (2 × 100 ml) and the solvent removed to afford a mixture of *2- and 3-nitrophenyl isopropyl ketones* (72 g, 75%).

A soln of this mixture (40 g) in benzene (120 ml) was shaken under an atmosphere of H_2 at room temp and atmospheric pressure in the presence of 10% Pd-C until the theoretical volume of H_2 had been absorbed. The catalyst was removed by filtration, the water layer separated from the filtrate and the benzene distilled from the organic layer to afford a mixture of 2- *and* 3-*aminophenyl isopropyl ketones* (32·3 g). Steam-distillation of this mixture (30 g) (*cf* Ref. 5), followed by extraction of the distillate with ether (3 × 200 ml) and drying and removal of the solvent from the combined ethereal extracts afforded *2-aminophenyl isopropyl ketone* as a pale-yellow oil (20·3 g, 59%) which was used as described below without further purification. An analytical specimen was prepared by distillation, b.p. 40–50° (bath temp)/15 mm (Found: C, 74·2; H, 8·0; $C_{10}H_{13}NO$ requires: C, 73·6; H, 8·0%); ($M^+ = 163$). UV λ_{max} 227–228, 257–258, 367–368, λ_{infl} 210 nm (log ϵ = 4·47, 3·89, 3·71, 4·08, respectively); IR 3460, 3335, (both ± 10) cm^{-1} (N—H), 1640 cm^{-1} (C=O).

The residue remaining from the steam distillation was extracted with benzene (4 × 100 ml). After drying, the volume of the combined extracts was reduced to about 100 ml and the soln then saturated with HCl, when *3-aminophenyl isopropyl ketone hydrochloride* precipitated out. Recrystallisation from acetone-light petroleum (40–60°) afforded cream-coloured prisms (6·1 g, 18%) m.p. 151–153°. (Found: C, 59·9; H, 7·1; N, 6·7; $C_{10}H_{14}ClNO$ requires: C, 60·1; H, 7·0; N, 7·0%).

The free base was prepared by basifying a soln of the hydrochloride (5·0 g) in warm water (30 ml) with ammonium hydroxide (d = 0·880). The liberated oil was extracted into benzene (3 × 25 ml), the combined extracts were dried and the solvent was removed to afford *3-aminophenyl isopropyl ketone* (4·1 g, 84%) as a pale-yellow oil which was used as described below without further purification. An analytical specimen was prepared by distillation, b.p. 135–145° (bath temp)/15 mm (Found: C, 73·9; H, 8·5; $C_{10}H_{13}NO$ requires: C, 73·6; H, 8·0%); ($M^+ = 163$); UV λ_{max} 231, 333–336, λ_{infl} 208, 261 nm (log ϵ = 4·45, 3·39, 4·03, 3·91, respectively); IR 3450, 3360, 3223 (all ± 10) cm^{-1} (N—H), 1678 cm^{-1} (C=O).

2-(2-Aminophenyl)-3,3-dimethyl-3H-indole 2 (R=Me, X=NH). 2-Aminophenyl isopropyl ketone (3·3 g) and phenylhydrazine (2·2 g) were converted into the phenylhydrazone which was indolised by the method described in method 1 above. The total reaction product, a dark-brown oil (2·8 g), was subjected to column chromatography on silica gel using a petroleum ether (40–60°)-ether (9:1 v/v) mixture as eluting solvent. Evaporation of the solvent from the initial eluates afforded a pale-yellow oil (1·2 g) which crystallised on standing. Recrystallisation from light petroleum (40–60°) gave the 3H-*indole* as pale-yellow prisms (0·75 g, 20%) m.p. 116–117°. (Found: C, 81·2; H, 7·0; N, 11·2; $C_{16}H_{16}N_2$ requires: C, 81·3; H, 6·8; N, 11·8%); ($M^+ = 236$); UV λ_{max} 238, 294, 306, 321, 383, λ_{infl} 246 and 264 nm (log ϵ = 4·36, 4·09, 4·07, 3·85, 4·06, 4·30, 4·01, respectively); IR 3440, 3230 (both ± 10) cm^{-1} (N—H); PMR singlet 8·42 (6H), multiplet between 3·45–2·21 τ (8H).

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