A General and Practicable Synthesis of Polycyclic Heteroaromatic Compounds. Part 3.[1,2] Extension of the Synthesis to 'Quinone Methides' of Naphthalene, Phenanthrene, and Benzene

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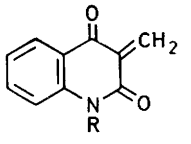
The general synthesis of polycyclic heteroaromatic compounds by generation of a quinone methide in the presence of an aromatic amine has been successfully extended to naphthalene and phenanthrene 'quinone methides'. Whereas yields had been highest when the putative quinone methides of less aromatic compounds were generated by a *retro*-Diels–Alder process, this method was inappropriate for the 'quinone methides' of more aromatic compounds. Good yields were obtained for the naphthalene and phenanthrene series when the 'quinone methides' were generated by pyrolysis of a Mannich base. Attempts to extend the synthesis of benzenoid quinone methides gave low yields of the polycyclic heteroaromatic product.

We have recently developed a successful general synthesis of polycyclic heteroaromatic compounds using reactions in which a putative quinone methide is generated in the presence of an aromatic amine.[1,2] A large variety of amines has been used and, so far, reasonable yields have been obtained using 'quinone methides' of compounds of relatively low aromaticity such as the quinolone, pyridone, and coumarin derivatives (1), (2), and (3) respectively. When an attempt was made [2] to extend the synthesis to the quinone methide (4) of a fully aromatic compound, however, very low yields were obtained.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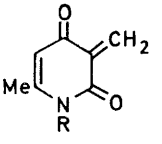
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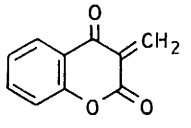
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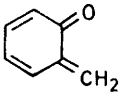
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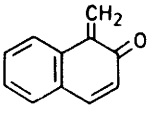
Since a rationale for our synthesis is that a quinone methide reacts with an aromatic amine, it is of interest to compare the synthesis with the Skraup synthesis [3] where the 'quinone methide' component is replaced by an enone. The two syntheses have entirely opposite regiospecificities with respect to the enone component and so it would seem that, if we accept the intermediacy of a quinone methide in our own synthesis, then the aromatic character of the parent system must be important in directing the course of the reaction. A further synthesis with identical regiospecificity to our own is that of Ullmann and Fedvadjian [4] where a phenol and an aniline react with formaldehyde to yield a heteroaromatic product. Buu-Hoi [5] has exploited this synthesis for the preparation of polycyclic heteroaromatic compounds albeit in variable yields, and it would be feasible to postulate quinone methides as intermediates in these reactions. A synthesis of acridines using α-hydroxymethylphenols [6] has also the regiospecificity observed in our synthesis and again we might postulate a quinone methide intermediate in this reaction.

It was evident that our synthesis had so far been applicable only to 'quinone methides' of compounds of comparatively low aromaticity and that there was a need to extend it to more aromatic compounds. It seemed to us that more success might be obtained with the naphthalene quinone methide (5) than had been obtained with its benzenoid counterpart (4) [2] and, since the synthesis had been most successful [1,2] when the 'quinone methide' was generated by a *retro*-Diels–Alder process, the hemiacetal (6; R = H) was our first synthetic objective. When β-naphthol was treated with (*NN*-diethylamino)butan-3-one, methyl iodide, and potassium hydroxide in ethanol, however, a compound was obtained which had analytical and spectral data in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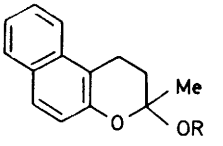
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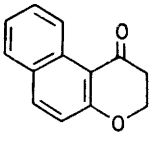
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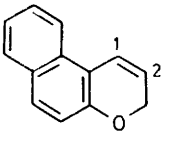
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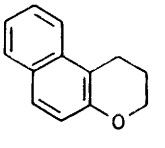
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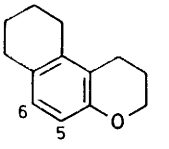
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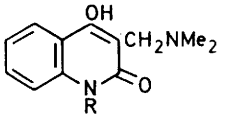
keeping with its being the ethyl acetal (6; R = Et). This was pyrolysed in the presence of *o*-anisidine but no polycyclic heteroaromatic product was obtained. The chromanone (7) [7] seemed like a further useful starting point for the *retro*-Diels–Alder approach and this was reduced to the alcohol which was then dehydrated to yield the chromen (8). Hydrogenation at room temperature and pressure using 10% palladium–charcoal as catalyst yielded not the expected product (9) but a compound (10) in which further reduction of the less substituted aromatic ring had occurred in addition to reduction of the double bond. Selective reduction of the double bond could be achieved by reducing the chromen (8) with di-imide when the product (9) was obtained. Pyrolysis of this in the presence of *o*-anisidine again failed to give any useful product.

It seemed that our attempts to use the *retro*-Diels–Alder approach to extend the synthesis to naphthalene quinone methides had been unsuccessful. In the synthesis using the ' quinolone quinone methide (1),' an



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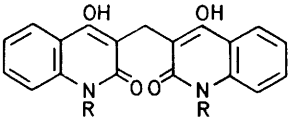

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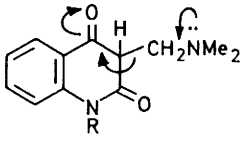

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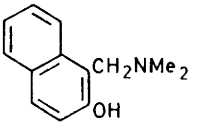

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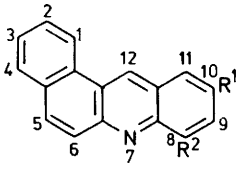

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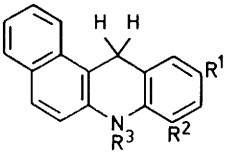
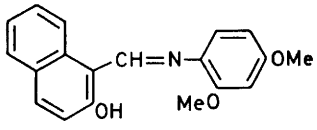


(16)

alternative approach had been to pyrolyse the Mannich base (11) in the presence of an aromatic amine.[1] Yields had been much lower using this method due to the formation of the by-product (12) by a mechanism involving the *retro*-Mannich reaction outlined in structure (13). Since this involved the keto-form (13) it could be reasoned that the side-reaction would be less important if the more aromatic β-naphthol derivative (14) were used in the synthesis. The Mannich base (14) [8] was therefore prepared and heated in refluxing diphenyl ether in the presence of aniline. A mixture of two compounds was obtained and these were separated by preparative t.l.c. The first compound, obtained in 25% yield, was benz[*a*]acridine (15; $R^1 = R^2 = H$) which had a melting point and a u.v. spectrum identical with those previously reported.[9] Other spectral data were in keeping with this assignment. The second product, obtained in 36% yield, had a ^1H n.m.r. spectrum in which the singlet at τ 0.60 for 12-H in benz[*a*]acridine (15; $R^1 = R^2 = H$) was missing and a singlet integrating for two protons at τ 5.6 was evident. This was evidently 7,12-dihydrobenz[*a*]acridine (16; $R^1 = R^2 = R^3 = H$) and oxidation with potassium dichromate gave benz[*a*]acridine (15; $R^1 = R^2 = H$) in 65% yield. Reaction of the Mannich base (14) with *N*-methylaniline gave a product, $C_{18}H_{15}N$, with spectral characteristics in keeping with its being 7,12-dihydro-7-methylbenz[*a*]acridine (16; $R^1 = R^2 = H$, $R^3 = Me$). The ^1H n.m.r. and u.v. spectra were very similar to those of the product from the reaction with aniline, which had been assigned the structure (16; $R^1 = R^2 = R^3 = H$).

Reaction of the Mannich base (14) with *o*-phenylenediamine gave the fully aromatic benzacridine (15; $R^1 = H$, $R^2 = NH_2$) in 43% yield whereas reaction with *o*-anisidine gave the dihydrobenzacridine (16; $R^1 = R^3 = H$, $R^2 = OMe$) in 66% yield. This latter compound could be oxidised with dichromate to yield 8-methoxybenz[*a*]acridine (15; $R^1 = H$, $R^2 = OMe$). Reaction of the Mannich base (14) with 2,4-dimethoxyaniline gave the benzacridine (15; $R^1 = R^2 = OMe$) in 41% yield together with a 16% yield of the imine (17). The imine (17) could be prepared independently by



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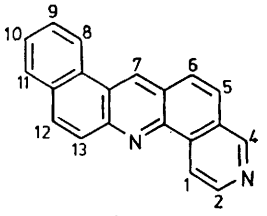
reaction of 2-hydroxy-1-naphthaldehyde with 2,4-dimethoxyaniline. Reaction of the Mannich base (14) with *p*-toluidine resulted in the dihydrobenzacridine (16; $R^1 = Me$, $R^2 = R^3 = H$) in 74% yield. This was oxidised to the benzacridine (15; $R^1 = Me$, $R^2 = H$) on leaving in acetic anhydride and pyridine at room temperature.

It is evident that the ' Mannich route ' has enabled the synthesis to be extended to naphthalene quinone methides and that there were no problems associated with the *retro*-Mannich reaction such as had been present when the Mannich bases of less aromatic compounds had been used. In spite of attempts to keep the reaction conditions constant, some reactions have led to benzacridines while others have given dihydrobenzacridines. In view of the ease of oxidation of the latter compounds, however, this is not a drawback to the general synthesis.

Extension of the synthesis to ring systems other than the benz[*a*]acridine system was achieved by treating the Mannich base (14) with 5-aminoisoquinoline when a product, $C_{20}H_{12}N_2$, was obtained in 68% yield. This compound had spectral properties in keeping with its formulation as the pentacyclic heteroaromatic compound (18). Reaction of the Mannich base (14) with 5-aminoindole gave a 40% yield of a compound,

$C_{19}H_{12}N_2$, which had a ^1H n.m.r. spectrum consisting of three one-proton singlets, six one-proton doublets, and two one-proton triplets in addition to an NH proton which exchanged on addition of D_2O. This compound evidently had the ' linear ' structure (19) rather than the alternative angular structure (20). A 24% yield of 1-methyl-2-naphthol was also obtained in this reaction, presumably being formed by reduction of the quinone methide (5) by the dihydro-derivative (21) which would be involved in the reaction. When the reaction was repeated using apparently the same conditions, a 67% yield of the pentacyclic compound (19) was obtained and no 1-methyl-2-naphthol was observed.



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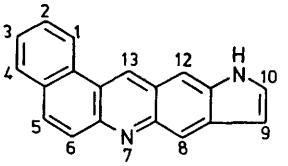

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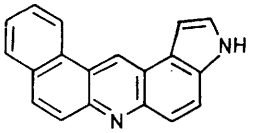

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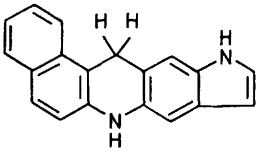

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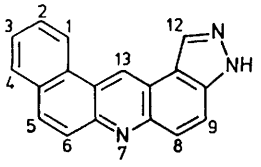

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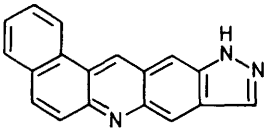

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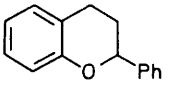
Reaction of the Mannich base (14) with 5-aminoindazole gave a single product, $C_{18}N_{11}N_3$, in 61% yield. This had a ^1H n.m.r. spectrum consisting of two one-proton singlets, six one-proton doublets, and two one-proton triplets. The angular structure (22) was therefore more appropriate than the ' linear ' structure (23). It is evident from the reactions with 5-aminoindole and 5-aminoindazole that the regiospecificity of the synthesis with respect to the amine component is the same as had been found in the syntheses using the quinone methides of less aromatic compounds.[1,2] It was also the same as had been found [10] in the Skraup synthesis if 5-aminoindole is regarded as an aromatic amine *meta*-substituted with an electron-donating substituent and 5-aminoindazole is regarded as an aromatic amine *meta*-substituted with an electron-withdrawing substituent.

Having successfully applied the ' Mannich route ' to the synthesis based on the putative naphthoquinone methide (5), it was of interest to see if we might now be successful in applying the synthesis to ' benzoquinone methide ' (4). In previous attempts using the ' *retro*-Diels–Alder approach,' pyrolysis of the flavan (24) in the presence of aniline had led to very low yields of acridine (25).[2] The *comparative* success of the *retro*-Diels–Alder reaction here may be due to the phenyl group which would conjugate with the ' ene ' produced in the reaction.



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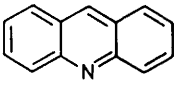

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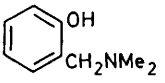

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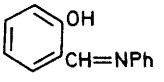
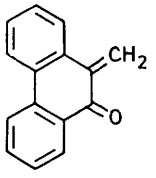


(27)

Such conjugation is not possible when the naphthalene derivatives (6; R = Et) or (9) are used. It was interesting in this context to note that when the benzenoid derivative (10) was pyrolysed in the presence of aniline, no substituted acridine was obtained in the product. In view of the results in the naphthalene series, it was hoped that use of the Mannich base (26) [11] in our synthesis would yield acridines in good yield, but when this base was pyrolysed in the presence of aniline, only 7% of acridine was obtained together with 28% of the imine (27). This latter compound was identical in all respects with an authentic sample prepared from salicylaldehyde and aniline. It seemed therefore that yields in the benzene series could not be made comparable to those in the naphthalene series.

The trend in yields observed for ' quinone methides ' of more aromatic compounds seemed to suggest some correlation with the aromaticity of the parent system, and so it was hoped that the synthesis might readily be applied to the phenanthrene derivative (28). When the crude unstable Mannich base (29) was prepared [12] and pyrolysed in the presence of aniline, a 62% yield of a compound was obtained with spectra in keeping with the



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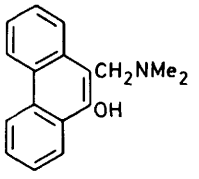

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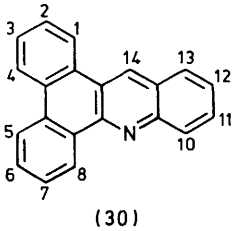

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pentacyclic structure (30). The melting point [13] and u.v. spectrum [14] reported for this compound were in keeping with our findings.

EXPERIMENTAL

M.p.s were determined on a Kofler block. I.r. spectra were recorded on Perkin-Elmer 237 or 257 machines and u.v. spectra on Unicam SP800 and SP1800 spectrophotometers. ^{1}H N.m.r. spectra were recorded on Varian T60 and EM360 and Perkin-Elmer R32 instruments, and 220 MHz spectra were obtained from P.C.M.U., Harwell. Mass spectra were recorded on Hitachi RMU-6 or A.E.I. MS30 instruments. Merck Kieselgel GF_{254} type 60 was used in 0.75 mm layers for preparative t.l.c.

*3-Ethoxy-2,3-dihydro-3-methyl-*1H*-naphtho*[2,1-b]*pyran* (6; R = Et).—Methyl iodide (5.78 g, 0.04 mol) was added to a solution of 1-(*NN*-diethylamino)butan-3-one [15] (5.72 g, 0.04 mol) in distilled dry ethanol (120 cm^3). This solution was added dropwise over 30 min to a solution of β-naphthol (2.88 g, 0.02 mol) and potassium hydroxide (2.24 g, 0.04 mol) in dry ethanol (50 cm^3) with stirring at room temperature under nitrogen. The reaction was heated at reflux for 30 min when a precipitate formed. Water (20 cm^3) was added to dissolve the precipitate and the solvent was removed *in vacuo* to leave a small volume. Cold 3N-hydrochloric acid was added until the mixture was neutral and the solution was extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a gum which crystallised from ethanol as colourless *needles* (2.35 g, 49%), m.p. 80—81 °C (Found: C, 79.3; H, 7.5. $C_{16}H_{18}O_2$ requires C, 79.3; H, 7.5%); *m/e* 242 (M^+); $\nu_{max.}$ ($CHCl_3$) 1 620 and 1 590 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 231, 258(sh), 267, 278, 289, 305(sh), 319, and 332 nm (log ε 4.92, 3.46, 3.65, 3.74, 3.61, 2.99, 3.27, and 3.38); τ ($CDCl_3$) 2.01—2.93 (6 H, m, aromatic), 6.43 (2 H, m, CH_2O), 6.92 (2 H, m, CH_2), 7.63—8.32 (2 H, m, CH_2), 8.32 (3 H, s, CMe), and 9.01 (3 H, t, *J* 6 Hz, CH_2CH_3).

*2,3-Dihydro-1-hydroxy-*1H*-naphtho*[2,1-b]*pyran*.—A solution of chromanone (7) [7] (1.98 g, 0.01 mol) in dry methanol (20 cm^3) was added to a suspension of sodium borohydride (380 mg, 0.01 mol) in dry methanol (50 cm^3) over 1 h at 0 °C. The reaction was stirred at 0 °C for 2 h and at room temperature for 24 h. Water (10 cm^3) was added and the volume of the solution was reduced *in vacuo*. Water (100 cm^3) was added and the solution was neutralised with 1N-hydrochloric acid and extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The product crystallised from diethyl ether (1.78 g, 89%), m.p. 107—108 °C (lit.,[16] 109 °C) (Found: C, 78.2; H, 5.9. Calc. for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0%); *m/e* 200 (M^+); $\nu_{max.}$ ($CHCl_3$) 3 400 cm^{-1} (OH); τ ($CDCl_3$) 1.96—3.12 (6 H, m, aromatic), 4.88 (1 H, br t, *CH*OH), 5.78 (2 H, t, *J* 8 Hz, CH_2O), 7.68 (1 H, br s, OH, exchangeable in D_2O), and 7.88—8.15 (2 H, m, CH_2).

3H-Naphtho[2,1-b]*pyran* (8).—The above alcohol (1 g, 5 mmol) and toluene-*p*-sulphonic acid (2 crystals) were heated to reflux in dry benzene (50 cm^3) under a Soxhlet apparatus containing calcium hydride for 24 h. The solvent was removed *in vacuo* and the residue was dissolved in chloroform. The solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue crystallised from diethyl ether–ethanol (780 mg, 86%), m.p. 32—33 °C (lit.,[16] 41 °C) (Found: C, 85.7; H, 5.5. Calc. for $C_{13}H_{10}O$: C, 85.7; H, 5.5%); *m/e* 182 (M^+); $\nu_{max.}$ (KBr) 1 625 and 1 582 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 242, 262, 290(sh), 302, 315, and 347 nm (log ε 4.51, 3.29, 3.24, 3.42, 3.46, and 3.35); τ ($CDCl_3$) 1.90—2.84 (7 H, m, aromatic + olefinic), 3.98 (1 H, dt, *J* 9 and 3 Hz, 2-H), and 5.02 (2 H, m, CH_2O).

Catalytic Reduction of 3H-*Naphtho*[2,1-b]*pyran* (8).—10% Palladium–charcoal (35 mg) was added to a solution of the naphthopyran (8) (68 mg, 0.37 mmol) in methanol (25 cm^3). The mixture was stirred under hydrogen at room temperature and atmospheric pressure until uptake of hydrogen had ceased. The mixture was filtered through Celite and the residue was washed with methanol The solvent was removed from the combined methanolic solutions *in vacuo* to yield a liquid which was purified by preparative t.l.c. (SiO_2–$CHCl_3$) (62 mg, 88%) as *2,3,7,8,9,10-hexahydro-*1H*-naphtho*[2,1-b]*pyran* (10) (Found: *m/e*, 188.120 136. $C_{13}H_{16}O$ requires *M*, 188.120 109); $\nu_{max.}$ ($CHCl_3$) 1 660 and 1 590 cm^{-1}; τ ($CDCl_3$) 3.11 and 3.37 (2 × 1 H, AB, *J* 9 Hz, 5- and 6-H), 5.88 (2 H, t, *J* 6 Hz, CH_2O), and 7.14—8.30 (12 H, m).

Di-imide Reduction of 3H-*Naphtho*[2,1-b]*pyran* (8).—Potassium azodicarboxylate [17] (481 mg) was added to an ice-cooled solution of 3*H*-naphtho[2,1-*b*]pyran (8) (100 mg, 0.55 mmol) in dry methanol (20 cm^3). Acetic acid (149 mg) in dry methanol (10 cm^3) was added to the suspension over 30 min and the mixture was stirred at 0 °C for 1 h and at room temperature for 3 days. The solvents were removed *in vacuo* at room temperature and the resultant solid was extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran (9) as an oil which crystallised on standing in the refrigerator (68 mg, 68%), m.p. 33—34 °C (lit.,[16] 39 °C) (Found: C, 84.6; H, 6.4. Calc. for $C_{13}H_{12}O$: C, 84.75; H, 6.6%); *m/e* 184 (M^+); $\nu_{max.}$ ($CDCl_3$) 1 618 and 1 590 cm^{-1}; λ (MeOH) 233, 257(sh), 268, 278, 289, 308(sh), 321, and 335 nm (log ε 4.54, 3.30 3.46, 3.54, 3.42, 2.90, 3.13, and 3.22); τ ($CDCl_3$) (2.18—3.06 (6 H, m, aromatic), 5.78 (2 H, t, *J* 6 Hz, CH_2O), 6.98 (2 H, t, *J* 6 Hz, $ArCH_2$), and 7.68—8.10 (2 H, m, CH_2).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with Aniline*.—The Mannich base (14) [8] (1 g, 5 mmol) was heated to 198 °C with distilled aniline (9 cm^3) in diphenyl ether (10 cm^3) for 4 h under nitrogen. The solvent was removed *in vacuo* to yield a yellow gum which was purified by preparative t.l.c. (SiO_2; EtOAc–hexane, 4 : 6 v/v). The slower moving component (286 mg, 25%) was benz[*a*]-acridine (15; $R^1 = R^2 = H$), m.p. 130—131 °C (lit.,[9] 131 °C); *m/e* 229 (M^+); $\nu_{max.}$ (KBr) 1 628, 1 610, and 1 580 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 225, 237, 278, 284(sh), 323(sh), 333(sh), 348, 366, and 385 nm (log ε 4.43, 4.38, 4.66, 4.56, 3.43, 3.57, 3.69, 3.82, and 3.85); $\lambda_{max.}$ (H^+) 235, 250, 258, 283(sh), 287, 293, 390, and 401 (log ε 4.36, 4.31, 4.33, 4.39, 4.43, 4.44, 3.97, and 4.06); τ ($CDCl_3$) 0.60 (1 H, s, 12-H), 1.22 (1 H, br d, *J* 9 Hz, aromatic), and 1.61—2.35 (9 H, m, aromatic). The faster moving component was 7,12-dihydrobenz[*a*]acridine (16; $R^1 = R^2 = R^3 = H$) (422 mg, 36%), *m/e* 231 (M^+), $\lambda_{max.}$ (MeOH) 220, 264, 275, 313, and 370 nm; $\lambda_{max.}$ (H^+) 220, 258, 271, 292, 315, and 380 nm; τ ($CDCl_3$) 2.21—3.3 (10 H, m, aromatic), 4.03 (1 H, br s, NH exchangeable in D_2O), and 5.06 (2 H, s, CH_2).

Oxidation of 7,12-*Dihydrobenz*[a]*acridine* (16; $R^1 = R^2 = R^3 = H$).—The dihydrobenzacridine (16; $R^1 = R^2 = R^3 = H$) (231 mg, 1 mmol) was added to a refluxing mixture of sulphuric acid (1 cm^3; *d* 1.19) and water (20 cm^3). The solution was stirred until homogeneous and a hot solution of potassium dichromate (106 mg) in water (1.3 cm^3) was

added. The mixture was heated at reflux for a further 10 min and a hot solution of potassium dichromate (265 mg) in water (2 cm³) was added. Reflux was continued for 5 min and the mixture was cooled and filtered. The solid was suspended in hot water (7 cm³) and ammonia (2 cm³; *d* 0.88) was added. The mixture was heated to reflux and cooled to room temperature. The precipitate was dissolved in dilute HCl and the product was precipitated with ammonia, dried, and recrystallised from ethanol (149 mg, 65%). The product was identical in all respects with an authentic sample of benz[*a*]acridine.

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* N-*Methylaniline*.—The Mannich base (14) (500 mg, 2.5 mmol) was heated at 200 °C with distilled *N*-methylaniline (1.05 g) in diphenyl ether (10 cm³) for 16 h under nitrogen. The solvents were removed *in vacuo* to yield a gum which was crystallised from ethanol (452 mg, 74%) as 7-*methyl*-7,12-*dihydrobenz*[a]*acridine* (16; $R^1 = R^2 = H$, R^3 = Me), m.p. 122—123 °C (Found: C, 87.6; H, 6.3; N, 5.9. $C_{18}H_{15}N$ requires C, 88.1; H, 6.2; N, 5.7%); *m/e* 245 (M^+); $\nu_{max.}$ (KBr) 1 620, 1 595, and 1 580 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 267(sh), 275, 296, 312, and 366 nm (log ε 4.04, 4.07, 3.65, 3.69, and 3.12); $\lambda_{max.}$ (H^+) 267(sh), 275, 295, 310, and 366 nm (log ε 4.02, 4.05, 3.75, 3.64, and 3.11); τ ($CDCl_3$) 2.04—3.21 (10 H, m, aromatic), 5.73 (2 H, s, CH_2), and 6.62 (3 H, s, NMe).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* o-*Phenylenediamine*.—The Mannich base (14) (201 mg, 1 mmol) and *o*-phenylenediamine (108 mg, 1 mmol) were heated to reflux in diphenyl ether (20 cm³) under nitrogen for 16 h. The solvent was removed *in vacuo* to yield a black gum. Crystallisation from ethanol gave 8-*amino*-*benz*[a]*acridine* (15; $R^1 = H$, $R^2 = NH_2$) as yellow needles (120 mg, 49%), m.p. 170—171 °C (Found: C, 83.45; H, 5.0; N, 11.3. $C_{17}H_{12}N_2$ requires C, 83.6; H, 4.95; N, 11.5%); *m/e* 244 (M^+), $\nu_{max.}$ (KBr) 3 400 (OH) and 1 610 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 231, 278(sh), 290, and 303 nm (log ε 4.48, 4.31, 4.39, and 4.31); $\lambda_{max.}$ (H^+) 226, 233, 277, 287, 297(sh), 332, 368, 387, and 408 nm (log ε 4.45, 4.46, 4.40, 4.44, 4.07, 3.93, 3.51, 3.63, and 3.89); τ ($CDCl_3$) 0.74 (1 H, s, 12-H), 1.33 (1 H, br d, *J* 9 Hz, aromatic), 2.08—3.12 (8 H, m, aromatic), and 5.0 (2 H, br s, NH exchangeable in D_2O).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* o-*Anisidine*.—The Mannich base (14) (500 mg, 2.5 mmol) and distilled *o*-anisidine (930 mg) were heated to reflux in diphenyl ether (20 cm³) for 16 h under nitrogen. The solvents were removed *in vacuo* to yield a gum which crystallised from ethanol as yellow needles (430 mg, 66%) of 7,12-*dihydro*-8-*methoxybenz*[a]*acridine* (16; $R^1 = R^3 =$ H, R^2 = OMe), m.p. 135—136 °C (Found: C, 82.8; H, 5.9; N, 5.5. $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4%); *m/e* 261 (M^+); $\nu_{max.}$ (KBr) 3 415 (NH), 1 620, 1 608, and 1 580 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 221, 267, 278, 325, and 366 nm (log ε 4.39, 4.03, 4.04, 3.71, and 3.21); $\lambda_{max.}$ (H^+) 222, 235(sh), 249(sh), 268(sh), 282, 294, 308, 330(sh), and 380 nm (log ε 4.29, 4.05, 3.85, 3.97, 4.03, 4.14, 3.78, 3.51, and 3.25); τ ($CDCl_3$) 2.21—3.48 (10 H, m, aromatic and NH), 5.57 (2 H, s, CH_2), and 6.16 (3 H, s, OMe).

Oxidation of 7,12-*Dihydro*-8-*methoxybenz*[a]*acridine* (16; $R^1 = R^3 = H$, R^2 = OMe).—The dihydrobenzacridine (16; $R^1 = R^3 = H$, R^2 = OMe) (250 mg, 1 mmol) was stirred in boiling water (18.5 cm³) containing sulphuric acid (0.9 ml, *d* 1.19) until homogeneous and a solution of potassium dichromate (110 mg) in boiling water (1.3 cm³) was added in two equal portions 5 min apart. The mixture was heated to reflux for a further 10 min and a solution of potassium dichromate (223 mg) in boiling water (2.3 cm³) was added. The mixture was heated to reflux for a further 5 min, cooled, and filtered. The precipitate was suspended in hot water (6 cm³), treated with ammonia (1.5 cm³; *d* 0.88), heated to reflux, and cooled. The precipitate was washed well with water and dissolved in hot dilute hydrochloric acid. The solution was filtered, precipitated with ammonia (0.88), and recrystallised from ethanol (212 mg, 86%) as 8-*methoxybenz*[a]*acridine* (15; $R^1 = H$, R^2 = OMe), m.p. 182—183 °C (Found: C, 82.8; H, 5.1; N, 5.3. $C_{18}H_{13}NO$ requires C, 83.4; H, 5.1; N, 5.4%); *m/e* 259 (M^+); $\nu_{max.}$ (KBr) 1 610 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 230, 244(sh), 285, 348(sh), 366, and 384 nm (log ε 4.55, 4.19, 4.74, 3.51, 3.64, and 3.60); $\lambda_{max.}$ (H^+), 230, 236, 247(sh), 294, 308, 384(sh), and 401 nm (log ε 4.48, 4.45, 4.14, 4.68, 4.20, 3.76, and 3.91); τ ($CDCl_3$) 0.66 (1 H, s, 12-H), 1.31 (1 H, d, *J* 9 Hz, aromatic), 1.78—2.99 (8 H, m, aromatic), and 5.88 (3 H, s, OMe).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* 2,4-*Dimethoxyaniline*.—The Mannich base (14) (201 mg, 1 mmol) and 2,4-dimethoxyaniline (141 mg, 1 mmol) were heated to 200 °C in diphenyl ether (10 cm³) under nitrogen. The solvent was removed *in vacuo* and the resultant gum was purified by preparative t.l.c. (SiO_2; $CHCl_3$). The faster moving compound was crystallised from ethanol as needles (118 mg, 41%) of 8,10-*dimethoxybenz*[a]*acridine* (15; $R^1 = R^2$ = OMe), m.p. 129—131 °C (Found: C, 78.7; H, 5.3; N, 4.9. $C_{19}H_{15}NO_2$ requires C, 78.9; H, 5.2; N, 4.8%); *m/e* 289 (M^+); $\nu_{max.}$ (KBr) 1 620 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 218, 226, 248(sh), 278(sh), 287, 295(sh), 330, 344, 362, 382, and 402 nm (log ε 4.26, 4.41, 4.06, 4.46, 4.60, 4.52, 3.34, 3.39, 3.40, 3.57, and 3.61); $\lambda_{max.}$ (H^+) 231, 266, 301, 384, and 400 nm (log ε 4.51, 3.89, 4.56, 3.52, and 3.61); τ ($CDCl_3$) 0.85 (1 H, s, 12-H), 1.35 (1 H, br d, *J* 9 Hz, aromatic), 1.85—3.30 (7 H, m, aromatic), and 5.94 and 6.08 (2 × 3 H, 2 × s, OMe). The slower moving compound was crystallised from ethanol as yellow needles (48 mg, 16%) of 1-(2,4-*dimethoxyphenyliminomethyl*)-2-*naphthol* (17), m.p. 130—132 °C; *m/e* 307 (M^+); $\nu_{max.}$ (KBr) 3 400 (br, OH), and 1 610 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 234, 245(sh), 265(sh), 275(sh), 300(sh), 331, 345, 360(sh), 454, and 474 nm (log ε 4.31, 4.27, 3.98, 3.83, 3.58, 3.72, 3.71, 3.68, 4.17, and 4.14); τ ($CDCl_3$) 0.75 (1 H, s, C*H*=N), 1.82—3.21 (9 H, m, aromatic), and 5.99 and 6.10 (2 × 3 H, 2 × s, OMe). These spectra were identical to those of an authentic sample prepared by the method of Derieg and Sternbach [18] in 96% yield, m.p. 131—132 °C (Found: C, 74.1; H, 5.75; N, 4.5. $C_{19}H_{17}NO_3$ requires C, 74.3; H, 5.6; N, 4.6%).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* p-*Toluidine*.—The Mannich base (14) (201 mg, 1 mmol) and *p*-toluidine (107 mg, 1 mmol) were heated to 200 °C in diphenyl ether (10 cm³) for 10 h under nitrogen. The solvent was removed *in vacuo* to yield a gum which crystallised from ethanol as yellow needles (180 mg, 74%) of 7,12-*dihydro*-10-*methylbenz*[a]*acridine* (16; R^1 = Me, $R^2 = R^3 =$ H); m.p. 129—131 °C (Found: C, 88.0; H, 6.3; N, 5.75. $C_{18}H_{15}N$ requires C, 88.1; H, 6.2; N, 5.7%); *m/e* 245 (M^+); $\nu_{max.}$ (KBr) 3 390 (NH), 1 620, and 1 608 cm⁻¹ (aromatic); $\lambda_{max.}$ (MeOH) 222, 267, 278, 313, and 374 nm (log ε 4.34, 3.97, 4.00, 3.71, and 3.16); $\lambda_{max.}$ (H^+), 222, 253(sh), 263, 280, 294, 315, and 384 nm (log ε 4.28, 3.87, 3.97, 3.99, 3.98, 3.57, and 3.26); τ ($CDCl_3$) 2.02—2.32 (9 H, m, aromatic), 3.87

(1 H, s, NH, exchangeable with D_2O), 5.44 (2 H, s, CH_2), and 7.56 (3 H, s, CMe).

10-*Methylbenz*[a]*acridine* (15; R^1 = Me, R^2 = H).—The dihydrobenz[*a*]acridine (16; R^1 = Me, R^2 = R^3 = H) (110 mg, 0.45 mmol) was dissolved in dry pyridine (5 cm^3) with acetic anhydride (3 cm^3) and the reaction was stirred overnight at room temperature. The solvents were removed *in vacuo* to yield a gum which crystallised from ethanol as yellow crystals (95 mg, 86%) of 10-*methylbenz*[a]*acridine* (15; R^1 = Me, R^2 = H), m.p. 153—155 °C (Found: C, 88.6; H, 5.4; N, 5.7. $C_{18}H_{13}N$ requires C, 88.9; H, 5.4; N, 5.8%); *m/e* 243 (M^+); $\nu_{max.}$ (KBr) 1 620 and 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 225, 238, 269(sh), 278, 287, 348, 367, and 387 nm (log ε 4.44, 4.23, 4.40, 4.59, 4.58, 3.55, 3.72, and 3.77); $\lambda_{max.}$ (H^+) 228, 236(sh), 254, 262, 286, 295, and 401 nm (log ε 4.38, 4.29, 4.16, 4.22, 4.40, 4.55, and 3.89); τ ($CDCl_3$) 0.82 (1 H, s, 12-H), 1.38 (1 H, br d, *J* 9 Hz, aromatic), 1.83—2.47 (8 H, m, aromatic), and 7.46 (3 H, s, CMe).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* 5-*Aminoisoquinoline*.—The Mannich base (14) (402 mg, 2 mmol) and 5-aminoisoquinoline (288 mg, 2 mmol) were heated to reflux in diphenyl ether (25 cm^3) for 24 h under nitrogen. The mixture was cooled and left at room temperature for 24 h when crystals precipitated from the solution. These were filtered off, washed with diethyl ether, and dried. Sublimation at 260 °C and 0.5 mmHg gave yellow crystals (378 mg, 68%) of *naphtho*[2,1-b][1,8]*phenanthroline* (18), m.p. 298—300 °C (Found: C, 85.7; H, 4.35; N, 10.0. $C_{20}H_{12}N_2$ requires C, 85.7; H, 4.3; N, 9.9%), *m/e* 280 (M^+), $\nu_{max.}$ (KBr) 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 218, 245, 251, 258, 264, 290, 317, 332, 359, 378, and 399 nm (log ε 4.57, 4.34, 4.32, 4.32, 4.31, 4.86, 5.13, 5.14, 4.45, 4.80, and 4.92); $\lambda_{max.}$ (H^+) 217, 230, 251, 257, 263(sh), 275, 304, 340, 398, and 420 nm (log ε 4.62, 4.41, 4.54, 4.57, 4.46, 4.28, 4.76, 4.17, 3.57, and 3.59); τ [CF_3CO_2H–$(CD_3)_2SO$; 220 MHz] −0.68 and −0.04 (2 × 1 H, 2 × s, 4- and 7-H), 0.02 (1 H, d, *J* 7 Hz, 2-H, collapsed to s on irradiation at τ + 0.75), 0.75 (1 H, d, *J* 7 Hz, 1-H); 0.82, 1.1, 1.18, 1.3, 1.46, and 1.66 (6 H, 6 × d, aromatic), and 1.79 and 1.88 (2 × 1 H, 2 × t, aromatic).

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* 5-*Aminoindole*.—(*a*) The Mannich base (14) (201 mg, 1 mmol) and 5-aminoindole (132 mg, 1 mmol) were heated to reflux in diphenyl ether (20 cm^3) for 16 h under nitrogen. The solvent was removed *in vacuo* to yield a gum which was purified by preparative t.l.c. (SiO_2; $CHCl_3$–EtOAc, 9 : 1 v/v). The slower moving compound proved to be 1-methyl-2-naphthol (38 mg, 24%), m.p. 108—110 °C (lit.,[19] 110 °C); *m/e* 158 (M^+); τ ($CDCl_3$) 1.98—2.03 (6 H, m, aromatic) and 7.42 (3 H, s, CMe). The faster moving component was recrystallised from ethanol (108 mg, 40%) as *benzo*[f]*indolo*-[6,5-b]*quinoline* (19), m.p. 200 °C (decomp.) (Found: C, 85.0; H, 4.6; N, 10.4. $C_{19}H_{12}N_2$ requires C, 85.05; H, 4.5; N, 10.4%); *m/e* 268 (M^+); $\nu_{max.}$ (KBr) 3 100 (NH), 1 610, and 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 226, 240, 253, 262, 294, 312(sh), 358(sh), 376, and 397 nm (log ε 4.39, 4.11, 4.11, 4.11, 4.36, 4.23, 3.42, 3.69, and 3.77); $\lambda_{max.}$ (H^+) 248(sh), 306, and 415 nm (log ε 4.02, 4.28, and 3.67); τ [$(CD_3)_2SO$; 220 MHz] −1.79 (1 H, s, NH, exchangeable in D_2O), −0.16 (1 H, s, 13-H), 0.77, 1.97, 1.99, 2.01, 2.04, and 2.18 (6 H, 6 × d, 1-, 4-, 5-, 6-, 9-, and 10-H), 2.21 and 2.29 (2 H, 2 × t, 2- and 3-H), and 2.45 (2 H, br s, 8- and 12-H).

(*b*) When the reaction was repeated, heating to reflux for 24 h, and the cooled solution was left at room temperature overnight a solid could be filtered off and sublimed at 260 °C and 0.5 mmHg (180 mg, 67%), m.p. 200 °C (decomp.). This was spectroscopically identical to the pentacyclic compound (19) obtained in the previous reaction and there appeared to be no 1-methyl-2-naphthol present.

Reaction of 1-(NN-*Dimethylaminomethyl*)-2-*naphthol* (14) *with* 5-*Aminoindazole*.—The Mannich base (14) (201 mg, 1 mmol) and 5-aminoindazole (133 mg, 1 mmol) were heated to reflux in diphenyl ether (20 cm^3) under nitrogen for 16 h. The solvent was removed *in vacuo* to yield a gum which sublimed at 220 °C and 6 mmHg as yellow needles (163 mg, 61%) of *benzo*[f]*indazolo*[4,5-b]*quinoline* (22), m.p. 300 °C (Found: C, 80.6; H, 4.2; N, 15.5. $C_{18}H_{11}N_3$ requires C, 80.3; H, 4.1; N, 15.6%); *m/e* 269 (M^+); $\nu_{max.}$ (KBr) 3 420 (NH), 1 615, and 1 600 cm^{-1} (aromatic); $\lambda_{max.}$ (MeOH) 220, 257(sh), 285, 290(sh), 353, 372, and 392 nm (log ε 3.62, 3.35, 3.74, 3.72, 3.75, 2.87, and 2.98); $\lambda_{max.}$ (H^+) 228, 273(sh), 295, 398(sh), and 420 nm (log ε 3.70, 3.19, 3.68, 3.08, and 3.17); τ [$(CD_3)_2SO$; 220 MHz] −0.26 and 0.98 (2 × 1 H, 2 × s, 12- and 13-H), 0.80, 1.88, 1.92, 1.95, and 1.98 (6 H, 5 × d, *J* 8 Hz, 1-, 4-, 5-, 6-, 8-, and 9-H), and 2.15 and 2.24 (2 × 1 H, 2 × t, *J* 8 Hz, 3- and 4-H).

Reaction of 2-(NN-*Dimethylaminomethyl*)*phenol* (26) *with Aniline*.—The Mannich base (26) [11] (154 mg, 1 mmol) and aniline (94 mg, 1 mmol) were heated to 200 °C in diphenyl ether (5 cm^3) under nitrogen for 48 h. The solvents were removed *in vacuo* to yield a gum which was purified by preparative t.l.c. (SiO_2; $CHCl_3$). The slower moving product was acridine (25) which recrystallised from ethanol as plates, (13 mg, 7%), m.p. 110 °C, identical in all respects with an authentic sample. The faster moving product was the imine (27) (50 mg, 25%), m.p. 48—49 °C (lit.,[20] 50.5 °C), identical in all respects with a sample prepared from salicyladehyde and aniline by the method of Derieg and Sternbach.[18]

Reaction of 10-(NN-*Dimethylaminomethyl*)-9-*phenanthrol* (29) *with Aniline*.—The crude Mannich base (29) [12] (125 mg, 0.5 mmol) and aniline (50 mg, 0.5 mmol) were heated to 200 °C in diphenyl ether (5 cm^3) for 24 h under nitrogen. The solvent was removed *in vacuo* to yield a gum which was purified by preparative t.l.c. (SiO_2; $CHCl_3$) and crystallisation from ethanol as needles (87 mg, 62%) of dibenz[*a*,*c*]-acridine (30), m.p. 202—204 °C (lit.,[13] 204 °C), *m/e* 279 (M^+); $\lambda_{max.}$ (MeOH) 251(sh), 257, 272, 281, 305, 324, 340, 357, and 375 nm (log ε 3.75, 3.78, 3.81, 3.92, 4.29, 3.96, 4.08, 4.27, and 4.32); $\lambda_{max.}$ (H^+) 248(sh), 256, 264, 280, 290, 304, 318, and 398 nm (log ε 3.72, 3.84, 3.69, 3.51, 3.49, 4.41, 4.48, and 4.43); τ ($CDCl_3$) 0.51 (1 H, m, 8-H), 0.81 (1 H, s, 14-H), and 1.35—2.47 (11 H, m, aromatic).

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