A General and Practicable Synthesis of Polycyclic Heteroaromatic Compounds. Part 2.[1] Reaction of Quinone-methides of Pyridones, Pyrimidines, Coumarin, and Benzene with Aromatic Amines in a Novel Synthesis of Polycyclic Heteroaromatic Compounds

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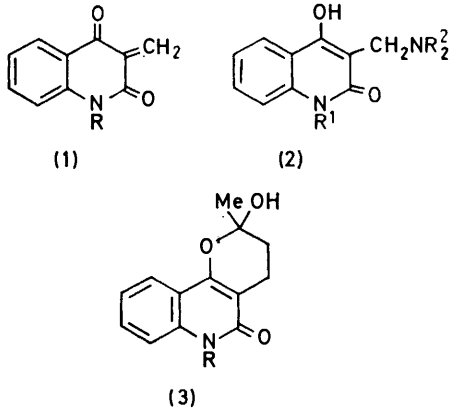
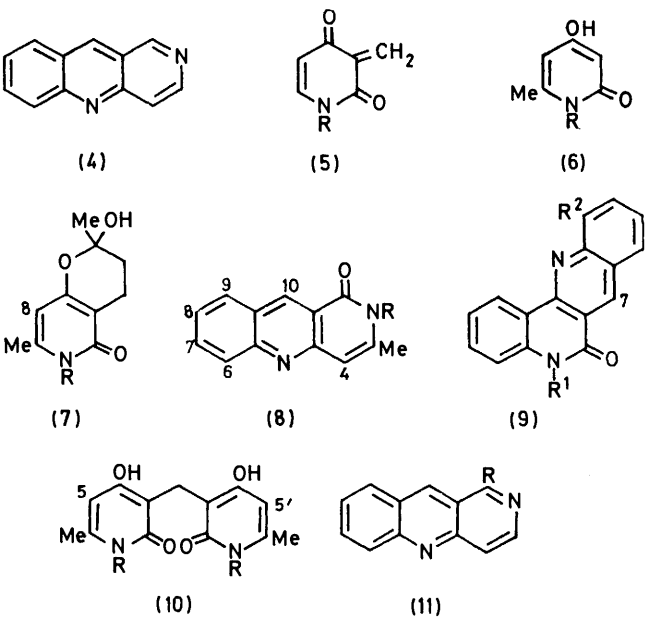
The synthesis of polycyclic heteroaromatic compounds using the reaction of a quinone-methide, generated *in situ*, with an aromatic amine has been successfully extended using quinone-methides of coumarin and of pyridones. Preliminary studies with the benzenoid quinone-methide (33) have so far proved to give only low yields of the expected acridines. Generation of ' quinone-methides ' in which the carbonyl is part of an amide group did not lead to polycyclic heteroaromatic compounds.

In the preceding paper we described a general synthesis of polycyclic heteroaromatic compounds by treating quinolone-enones (1), generated *in situ*, with aromatic amines.[1] The enones (1) may be regarded as quinone-methides and the regiospecificity of the synthesis with respect to the ' enone ' component is the *opposite* of that found in the Skraup synthesis [2] where aromatic amines react with ' normal ' enones to form heterocyclic products. A new and potentially very useful heterocyclic synthesis is, therefore, now available. The quinone-methides (1) were generated *in situ* either by pyrolysis of the Mannich bases (2) or by a thermal *retro*-Diels–Alder reaction of the hemiacetals (3). Yields were very much better from the *retro*-Diels–Alder approach and the hemiacetals (3) could readily be prepared in one step from the parent 4-hydroxy-2-quinolones.[1] A large variety of amines could be used in the reaction, making the synthesis very flexible. Very electron-deficient amines, however, did not give useful yields. The regiospecificity of the reaction with respect to the aromatic amine component was the same as in the Skraup synthesis.[1]



It was of considerable interest to investigate the potential of the synthesis with other quinone-methides. The pyridoquinolone ring system (4) is of some interest [3] and deazariboflavin analogues have chemotherapeutic properties.[4-6] Use of the quinone-methide (5) in our synthesis would afford very ready entry to the ring system (4) among others, and we elected to study the potential of a pyridone-quinone-methide in our synthesis. The substituted pyridones (6; R = H) and (6; R = Me) were easily synthesized from dehydroacetic acid,[7,8] and these were readily converted into the hemiacetals (7; R = H) and (7; R = Me) in 83 and 88% yields respectively using 1-(*NN*-diethylamino)-butan-3-one, methyl iodide, and potassium hydroxide.

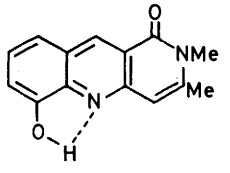
The hemiacetals (7; R = H) and (7; R = Me) reacted with aniline to afford products in 48 and 47% yields respectively. These had analytical and spectral data which were in accord with the expected structures (8; R = H) and (8; R = Me). The similarity of the chemical shift of the low-field singlet assigned to 10-H in compound (8) to that of the low-field singlet assigned [1] to 7-H in the tetracyclic analogues (9) was particularly significant. A bathochromic shift of 43 nm, observed in the u.v. spectrum of the tricyclic compound (8; R = Me) on addition of acid, was comparable to a bathochromic acid shift of 59 nm [9] in the u.v. spectrum of the



corresponding tetracyclic compound (9; R^1 = Me, R^2 = H). The reactions yielded by-products in addition to the desired tricyclic compounds (8). These were shown to be the 3,3′-methylenebis-4-hydroxy-6-methyl-2-pyridones (10; R = H) and (10; R = Me) by comparison with authentic compounds prepared by reaction of the relevant pyridone (6) with formaldehyde.

If the assignment of the structure (8) was correct, it was evident that our synthesis could be extended to the preparation of compounds other than those which could be prepared from the quinone-methide (1). Further support for the structural assignment was obtained by conversion of compound (8; R = H) into the unstable chloride (11; R = Cl) which was then reduced to the fully aromatic compound (11; R = H) in low yield using hydrogen and Raney nickel. The m.p. and u.v. spectrum of this compound were similar to those reported in the literature.[10]

When the quinolone-quinone-methides (1) had been generated in the presence of *o*-anisidine, the tetracyclic compounds (9; R^1 = H, R^2 = OMe) and (9; R^1 = Me, R^2 = OMe) had been obtained in good yield.[1] The hemiacetal (7; R = Me) was therefore heated to 250 °C with *o*-anisidine in diphenyl ether when a 25% yield of a compound having analytical and spectroscopic data consistent with the structure (12) was obtained. A bathochromic shift of 10 nm in the u.v. spectrum on addition of base compared well with the 10 nm base shift for 8-hydroxyquinoline. It was evident that thermal demethylation had occurred in the reaction, presumably by the process illustrated in formula (13). This side-reaction was eliminated by performing the reaction at 180 °C when the expected product (13) was obtained in 6% yield. When the reaction was performed



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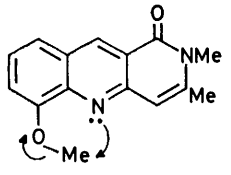

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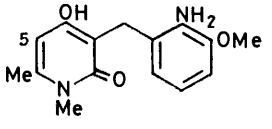

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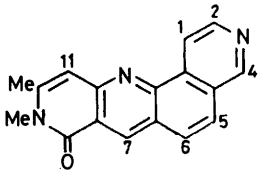
at 150 °C then a 19% yield of a compound which had a ^{1}H n.m.r. spectrum in keeping with the structure (14) was obtained. This type of compound had been suggested [1] as an intermediate in our synthesis and indeed a small yield of the tricyclic phenol (12) was obtained when compound (14) was heated to 250 °C in diphenyl ether.

The pyranopyridone (7; R = Me) reacted with 5-aminoisoquinolone to give a 58% yield of a product having analytical and spectral properties consistent with structure (15). Reaction with 5-aminoindazole gave but one of the two possible products (16) and (17) in 46% yield. The ^{1}H n.m.r. spectrum with three one-proton singlets and two one-proton doublets defined this unambiguously as the angular isomer (16). Reaction with 5-aminoindole also proved regiospecific, the product $C_{16}H_{13}N_3O$, obtained in 53% yield, having a ^{1}H n.m.r. spectrum with four one-proton singlets and two one-proton doublets. The product was therefore the linear isomer (18) rather than the alternative compound (19).



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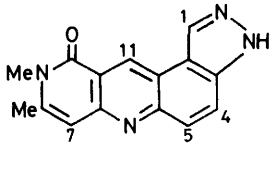

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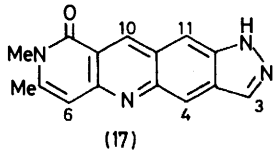

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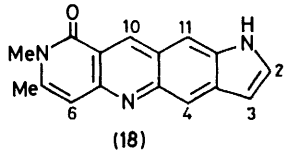

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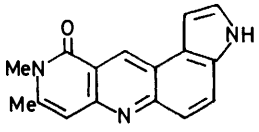

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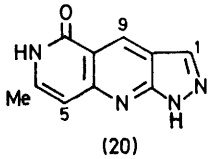

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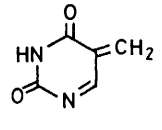
The regiospecificities of the reactions with 5-aminoindazole and 5-aminoindole with respect to the aromatic amine were identical to those found for the quinolone-quinone-methides (1) [1] and were in keeping with the pattern found in the Skraup synthesis [11] if 5-aminoindole is considered to be an aniline substituted in the *meta*-position with an electron-donating group and 5-aminoindazole is considered to be an aniline substituted in the *meta*-position with an electron-withdrawing group.

Extension of the synthesis to non-benzenoid amines was achieved by treating the pyranopyridone (7; R = H) with 3-aminopyrazole when a 56% yield of the expected tricyclic product (20) was obtained.

In view of the importance of riboflavin analogues in medicine,[4-6] it was of interest to examine the potential of the 'uracil-quinone-methide' (21) in the synthesis. Since both of the carbonyl groups in this compound would be amides, investigation of the synthetic potential of this quinone-methide would be of considerable theoretical interest. The Mannich bases (22; X = NMe_2) and (22; X = $\overline{-NCH_2CH_2OCH_2CH_2}$) were therefore prepared by reaction of uracil with formaldehyde and either dimethylamine or morpholine. The ^{1}H n.m.r. spectra of these compounds exhibited but one aromatic singlet and so the structures (22) suggested by Burckhalter [12] were preferred to the alternative *N*-substituted structures of Bombardieri.[13] The Mannich base (22;

X = NMe_2) was found to revert to uracil on prolonged standing while the Mannich base (22; X = $-NCH_2CH_2OCH_2CH_2$) proved to be more stable.

When the Mannich base (22, X = $-NCH_2CH_2OCH_2CH_2$) was treated with aniline in diphenyl ether at 250 °C, a compound $C_{11}H_{11}N_3O_2$, was obtained in 89% yield. This had spectra in keeping with the structure (22; X = NHPh) and was identical to an authentic sample prepared by the method of Santi.[14] Reaction of the Mannich base (22; X = NMe_2) with aniline again gave the adduct (22; X = NHPh) together with some uracil. Since compounds of the type (22; X = NHPh) had been suggested [1] as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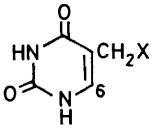
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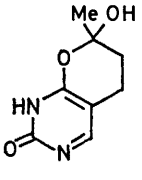
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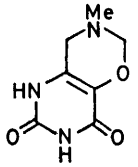
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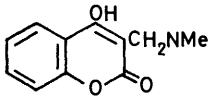
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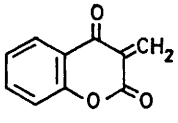
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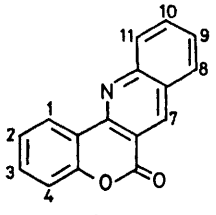
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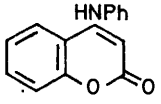
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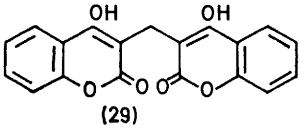
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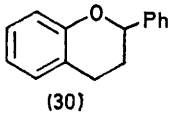
intermediates in our synthesis, it was of interest to have isolated this compound. Presumably the decreased reactivity of the amide carbonyl group in the quinone-methide (21) had prevented the reaction from proceeding further. When the adduct (22; X = NHPh) was subjected to prolonged heating, the only product obtained was uracil.

An attempt was now made to prepare the hemiacetal (23) with a view to generating the quinone-methide (21) *in situ* by a *retro*-Diels–Alder reaction. When uracil reacted with 1-(*NN*-diethylamino)butan-3-one, methyl iodide, and potassium hydroxide, however, the ^1H n.m.r. spectrum of the product, $C_8H_{10}N_2O_3$, indicated that *N*-alkylation had occurred. In a final attempt to incorporate a pyrimidine ring in our synthesis the adduct (24) of isobarbituric acid was prepared by the method of O'Brien.[15] No tricyclic heteroaromatic compounds were observed when this compound was heated in the presence of aniline.

Since 3-(*NN*-dimethylamino)methyl-4-hydroxycoumarin (25) was known [16] to be stable it was decided to use this to generate the quinone-methide (26) in the presence of aniline. This reaction led to a 47% yield of a product with spectral properties in keeping with the tetracyclic structure (27). The entire ^1H n.m.r. spectrum of this compound paralleled that of the nitrogen analogue (9; R^1 = Me, R^2 = H) very closely. The same product was obtained in 43% yield together with the known [17,18] anilide (28) when 3,3′-methylenebis-4-hydroxycoumarin (29) [18] was heated at 250 °C in diphenyl ether with aniline.

Although the synthesis had obviously proved very effective using quinone-methides of quinolones, pyridones, and coumarins, it had not been tested with benzenoid quinone-methides. For this reason, flavan (30) was prepared from flavanone (31) by the method of Philbin.[19] The yield proved to be low by this method and we found it more convenient to reduce flavanone to a mixture of the diols (32) followed by dehydration and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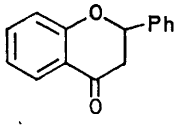
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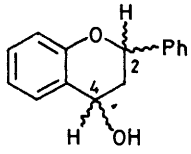
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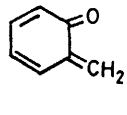
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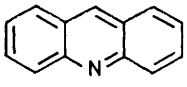
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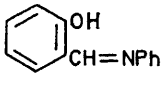
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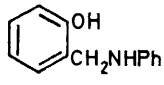
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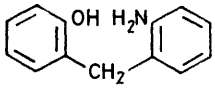
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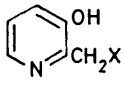
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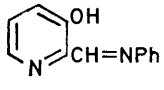
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reduction. Flavan (30) should undergo *retro*-Diels–Alder reaction to yield the quinone-methide (33) and so it was heated in the presence of aniline. A 4% yield of acridine (34) was obtained in this reaction together with the Schiff's base (35) [20,21] and the Mannich base (36).[20,22] A fourth product, $C_{13}H_{13}NO$, had spectral characteristics in keeping with structure (37) and this could be converted to a diacetate. On reaction with polyphosphoric acid this amine gave acridine (34) in 12% yield. The Mannich base (36) and the amine (37) are postulated [1] intermediates in our synthesis. When the Mannich base

(36) was pyrolysed both acridine (34) and the amine (37) were obtained. Pyrolysis of the amine (37) gave acridine (34) in 12% yield. Thus although yields are low when the synthesis is applied to a benzenoid quinone-methide, the by-products and their reactions support the suggested mechanism [1] for the synthesis. Pyrolysis of the commercially available Mannich base (38; X = NMe_2) in the presence of aniline in an attempt to extend the synthesis to a pyridine quinone-methide gave no polycyclic products. The production of the Mannich base (38; X = NHPh) and the imine (39) was observed in this reaction.

EXPERIMENTAL

General details were as for Part 1.[1]

3,4-Dihydro-2-hydroxy-2,7-dimethyl-2H-pyrano[3,2-c]-*pyridin-5(6H)-one* (7; R = H).—Methyl iodide (5.7 g, 40 mmol) was added to a solution of 1-(*NN*-diethylamino)-butan-3-one [23] (5.7 g, 40 mmol) in redistilled dry ethanol (20 cm^3). This solution was added dropwise over 30 min to a solution of 4-hydroxy-6-methyl-2-pyridone [7] (2.4 g, 19 mmol) and potassium hydroxide (2.2 g, 39 mmol) in dry ethanol (50 cm^3) with stirring at room temperature under nitrogen. The reaction was heated to reflux for 30 min and distilled water (20 cm^3) was added. The ethanol was removed *in vacuo* and the mixture was made neutral to litmus by addition of 3N-hydrochloric acid. The solution was extracted with chloroform and the extracts were dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a solid which crystallised from acetone as white *needles* (3.1 g, 83%), m.p. 148 °C (Found: C, 61.9; H, 6.5; N, 6.9. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%); *m/e* 195 (M^+); $\nu_{max.}$ (Nujol) 3 250 (NH and OH) and 1 630 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 213 and 285 nm (log ε 4.77 and 4.35); $\lambda_{max.}$ (OH^-) 220 and 280 nm (log ε 4.89 and 4.37); $\lambda_{max.}$ (H^+) 209, 234, and 269 nm (log ε 4.66, 4.16, and 4.35); τ(CF_3CO_2H) 3.75 (1 H, s, 8-H), 7.50 (4 H, br s, CH_2), 7.97 (3 H, s, Me), and 8.17 (3 H, s, Me).

3,4-Dihydro-2-hydroxy-2,6,7-trimethyl-2H-pyrano[3,2-c]-*pyridin-5(6H)-one* (7; R = Me) was prepared by the above method using 4-hydroxy-1,6-dimethyl-2-pyridone [8] (2.46 g, 18 mmol). The product solidified on trituration with diethyl ether and cyclohexane to yield a white powder which crystallised from ethyl acetate as *needles* (3.26 g, 88%), m.p. 148 °C (Found: C, 62.9; H, 7.4; N, 6.5%; M^+, 209.105 810. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%; *M*, 209.105 185); $\nu_{max.}$ (Nujol) 1 625 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 215 and 290 nm (log ε 4.70 and 4.22); $\lambda_{max.}$ (OH^-) 220 and 282 nm (log ε 4.78 and 4.25); $\lambda_{max.}$ (H^+) 211, 237, and 274 nm (log ε 4.65, 4.07, and 4.16); τ($CDCl_3$) 4.05 (1 H, s, 8-H), 6.53 (3 H, s, NMe), 7.22 (4 H, m, CH_2), and 7.72 and 7.83 (2 × 3 H, 2 s, CMe).

Reaction of the Hemiacetal (7; R = H) *with Aniline.*—The hemiacetal (7; R = H) (46 mg, 0.24 mmol) was heated at 190 °C with distilled aniline (7 cm^3) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield an orange solid which was triturated with diethyl ether and acetone. The residue was further washed with methanol and sublimed *in vacuo* to yield *3,3'-methylenebis-4-hydroxy-6-methyl-2-pyridone* (10; R = H) (5 mg, 15%), identical (i.r. spectrum) with an authentic sample prepared as described below. The ether–acetone soluble material crystallised from benzene as yellow needles (24 mg, 48%) of *3-methylbenzo*[b]-[1,6]*naphthyridin-1(2H)-one* (8; R = H), m.p. 240 °C (Found: C, 73.9; H, 4.9; N, 13.0. $C_{13}H_{10}N_2O$ requires C, 74.3; H, 4.8; N, 13.3%); *m/e* 210 (M^+); $\nu_{max.}$ (Nujol) 1 660 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 208, 234, 246, 252, 265sh, 274, 295, 318sh, and 390 nm (log ε 4.25, 4.58, 4.54, 4.50, 4.32, 4.42, 4.19, 3.83, and 3.74); $\lambda_{max.}$ (H^+) 230 and 252sh, 258, 272sh, 284, 311, 352, and 425 nm (log ε 4.45, 4.34, 4.40, 4.10, 4.31, 4.04, 3.47, and 3.96); τ([$^2H_6$]DMSO) 0.81 (1 H, s, 10-H), 1.79 and 1.95 (2 × 1 H, 2 d, *J* 8 Hz, 6- and 9-H), 2.10 and 2.40 (2 × 1 H, 2 t, *J* 8 Hz, 7- and 8-H), 3.47 (1 H, s, 4-H), and 7.70 (3 H, s, Me).

Reaction of the Hemiacetal (7; R = Me) *with Aniline.*—The hemiacetal (7; R = Me) (102 mg, 0.5 mmol) was heated at 190 °C with distilled aniline (10 cm^3) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a yellow solid which was triturated with hot light petroleum (b.p. 60—80 °C). The residue was washed with methanol and crystallised from methanol as needles (13 mg, 18%) of *3,3'-methylenebis-4-hydroxy-1,6-dimethyl-2-pyridone* (10; R = Me), m.p. 285 °C, identical (i.r. spectrum) with an authentic sample prepared as described below. Yellow crystals (51 mg, 47%), obtained from the light petroleum filtrate, were *2,3-dimethylbenzo*[b][1,6]-*naphthyridin-1(2H)-one* (8; R = Me), m.p. 140—141 °C (Found: C, 74.7; H, 5.4; N, 12.4. $C_{14}H_{12}N_2O$ requires C, 75.0; H, 5.4; N, 12.5%); *m/e* 224 (M^+); $\nu_{max.}$ (Nujol) 1 660 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 208, 244, 277, 300sh, 320sh, and 390 nm (log ε 4.60, 4.83, 4.66, 4.35, 4.05, and 3.93); $\lambda_{max.}$ (H^+) 208sh, 229, 258, 285, 315, 352, and 433 nm (log ε 4.54, 4.66, 4.62, 4.61, 4.18, 3.77, and 4.13); τ($CDCl_3$; 220 MHz) 0.72 (1 H, s, 10-H), 1.88 and 1.99 (2 × 1 H, 2 d, *J* 8 Hz, 6- and 9-H), 2.16 and 2.46 (2 × 1 H, 2 t, *J* 8 Hz, 7- and 8-H), 3.25 (1 H, s, 4-H), 6.36 (3 H, s, NMe), and 7.48 (3 H, s, CMe).

3,3'-Methylenebis-4-hydroxy-6-methyl-2-pyridone (10; R = H).—4-Hydroxy-6-methyl-2-pyridone [7] (6; R = H) (103 mg, 0.8 mmol) was dissolved in distilled water (60 cm^3) and 40% aqueous formaldehyde (3 cm^3, 40 mmol) added. The mixture was heated to reflux for 5 min and allowed to cool. The precipitate was filtered off, washed with cold ethanol, and crystallised from ethanol as white needles (96 mg, 89%), m.p. >330 °C (Found: C, 59.6; H, 5.6; N, 10.7. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.4; N, 10.7%); *m/e* 262 (M^+); $\nu_{max.}$ (Nujol) 1 640 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 210 and 290 nm (log ε 4.44 and 4.03); $\lambda_{max.}$ (OH^-) 216 and 284 nm (log ε 4.67 and 4.03); $\lambda_{max.}$ (H^+) 210, 226, and 285 nm (log ε 4.42, 4.13, and 4.02); τ(CF_3CO_2H) 3.87 (2 H, br s, 5- and 5'-H), 6.57 (2 H, br s, CH_2), and 8.0 (6 H, s, 2 × CMe).

3,3'-Methylenebis-4-hydroxy-1,6-dimethyl-2-pyridone (10; R = Me).—4-Hydroxy-1,6-dimethyl-2-pyridone [8] (6; R = Me) (403 mg, 2.9 mmol) was dissolved in distilled water (40 cm^3) and 40% aqueous formaldehyde (2 cm^3, 27 mmol). The mixture was heated to reflux for 5 min and allowed to cool. The precipitate was filtered off, washed with ethanol, and crystallised from methanol as white needles (386 mg, 92%), m.p. 285 °C, *m/e* 290 (M^+); $\nu_{max.}$ (Nujol) 1 650 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 217 and 293 nm (log ε 4.64 and 4.55); $\lambda_{max.}$ (OH^-) 220, 226, and 292 nm (log ε 4.70, 4.71, and 4.43); $\lambda_{max.}$ (H^+) 216 and 288 nm (log ε 4.64 and 4.52); τ([$^2H_6$]-DMSO) 3.98 (2 H, s, 5- and 5'-H), 6.51 (2 H, s, CH_2), 6.60 (6 H, s, NMe), and 7.71 (6 H, s, CMe).

3-Methylbenzo[b][1,6]*naphthyridine* (11; R = H).—The naphthyridone (8; R = H) (10 mg, 0.05 mmol) was heated at 90 °C in phosphorus oxychloride (2 cm^3) for 30 min and then at 120 °C for 30 min. The solvent was removed *in*

vacuo to yield a glass which had no carbonyl absorption in its i.r. spectrum. The glassy chloride (11; R = Cl) was added to a slurry of freshly prepared Raney nickel in dioxan [24] (20 cm³) and stirred under hydrogen for 15 h at room temperature and pressure. The mixture was filtered through Celite which was then washed well with methanol. Removal of the solvents *in vacuo* gave a product which was purified by preparative t.l.c. (SiO_2; CH_2Cl_3–MeOH, 9 : 1). The minor component crystallised from ethyl acetate as needles (2 mg), m.p. 138—139 °C (lit.,[10] 139.5—140 °C) (Found: M^+, 194.084 413. Calc. for $C_{13}H_{10}N_2$: *M*, 194.084 394); $\lambda_{max.}$ (MeOH) 252, 322sh, 329sh, 338sh, and 345 nm (log ε 4.99, 3.73, 3.89, 3.89, and 4.04) [lit.,[10] $\lambda_{max.}$ (unspecified solvent) 252 (high intensity) and 345 nm (low intensity)].

Reaction of the Hemiacetal (7; R = Me) *with* o-*Anisidine*.—(a) *At* 250 °C. The hemiacetal (7; R = Me) (56 mg, 0.3 mmol) was heated at 250 °C with distilled *o*-anisidine (5 cm³) and diphenyl ether (7 cm³) for 15 h under nitrogen. The solvents were removed *in vacuo* to yield an oil which was triturated with diethyl ether–light petroleum (b.p. 60—80 °C). The residue (11 mg, 28%) proved to be 3,3′-methylenebis-4-hydroxy-1,6-dimethyl-2-pyridone (10; R = Me), identical (i.r. spectrum) with an authentic sample. The soluble portion from the trituration was crystallised from ethanol as needles (16 mg, 25%) of 6-*hydroxy*-2,3-*dimethylbenzo*[b][1,6]*naphthyridin*-1(2H)-*one* (12), m.p. 230—231 °C (Found: C, 69.8; H, 5.0; N, 11.5%; M^+, 240.089 687. $C_{14}H_{12}N_2O_2$ requires C, 70.0; H, 5.0; N, 11.7%; *M*, 240.089 872); $\nu_{max.}$ (Nujol) 1 655 cm⁻¹ (amide); $\lambda_{max.}$ (MeOH) 209, 264, 280sh, 306sh, and 318 nm (log ε 4.29, 4.55, 4.12, 4.06, and 4.14); $\lambda_{max.}$ (OH^-) 216, 268, 317sh, and 328 nm (log ε 4.29, 4.11, 3.92, and 3.99); $\lambda_{max.}$ (H^+) 210, 273, 289sh, 331, 400, and 450 nm (log ε 4.01, 4.16, 3.83, 3.87, 3.53, and 3.38); τ($CDCl_3$) 0.80 (1 H, s, 10-H), 2.54—2.84 (3 H, m, ArH), 3.34 (1 H, s, 4-H), 6.40 (3 H, s, NMe), and 7.51 (3 H, s, CMe).

(b) *At* 180 °C. The hemiacetal (7; R = Me) (62 mg, 0.3 mmol) was heated at 180 °C with distilled *o*-anisidine (5 cm³) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a solid which was triturated with methanol. The residue was 3,3′-methylenebis-4-hydroxy-1,6-dimethyl-2-pyridone (10; R = Me) (9 mg, 21%), identical (i.r. spectrum) with an authentic sample. The methanol-soluble material was purified by preparative t.l.c. (SiO_2; $CHCl_3$–MeOH, 9 : 1) to yield a solid which crystallised from ethanol (4 mg, 6%). The product was 6-*methoxy*-2,3-*dimethylbenzo*[b][1,6]*naphthyridin*-1(2H)-*one* (13), m.p. 220—221 °C, *m/e* 254 (M^+); $\nu_{max.}$ (Nujol) 1 655 cm⁻¹ (amide); $\lambda_{max.}$ (MeOH) 212, 260, 278, 300sh, 310, and 400 nm (log ε 4.50, 4.77, 4.38, 4.45, 4.52, and 4.01); $\lambda_{max.}$ (H^+) 208, 268, 287sh, 325, 390, and 440 nm (log ε 4.21, 4.35, 3.95, 4.09, 3.77, and 3.68); τ($CDCl_3$) 0.80 (1 H, s, 10-H), 2.43—2.7 (3 H, m, ArH), 3.27 (1 H, s, 4-H), 5.83 (3 H, s, OMe), 6.33 (3 H, s, NMe), and 7.47 (3 H, s, C-Me).

(c) *at* 150 °C.—The hemiacetal (7; R = Me) (24 mg, 0.1 mmol) was heated at 150 °C with distilled *o*-anisidine (7 cm³) for 12 h under nitrogen. The solvent was removed *in vacuo* to yield a brown solid which was purified by preparative t.l.c. (SiO_2; $CHCl_3$–MeOH 9 : 1). One fraction was solid and crystallised from methanol as needles (6 mg, 19%) to which the *structure* (14) could tentatively be assigned, m.p. 226 °C (Found: M^+, 274.132 362. $C_{15}H_{18}N_2O_3$ requires *M*, 274.131 74); $\nu_{max.}$ (Nujol) 1 640 cm⁻¹ (amide); $\lambda_{max.}$ (MeOH) 216 and 294 nm (log ε 4.43 and 4.03); $\lambda_{max.}$ (H^+) 213 and 274 nm (log ε 4.44 and 3.94); τ([$^2H_6$]DMSO) 3.24 (1 H, br s, ArH), 3.50 (2 H, m, ArH), 4.16 (1 H, s, 5-H), 6.31 (3 H, s, OMe), 6.56 (2 H, s, CH_2), 6.68 (3 H, s, NMe), and 7.76 (3 H, s, CMe).

Pyrolysis of the Amine (14).—The amine (14) (4 mg, 0.015 mmol) was heated in diphenyl ether (5 cm³) at reflux for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown solid which was purified by preparative t.l.c. (SiO_2; $CHCl_3$–MeOH, 9 : 1). A small amount (1 mg) of 6-hydroxy-2,3-dimethylbenzo[*b*][1,6]naphthyridin-1(2*H*)-one (12) was obtained, identical (i.r. spectrum) with the sample above.

Reaction of the Hemiacetal (7, R = Me) *with* 5-*Aminoisoquinoline*.—The hemiacetal (7; R = Me) (209 mg, 1 mmol) and 5-aminoisoquinoline (144 mg, 1 mmol) were heated at 200 °C in diphenyl ether (20 cm³) for 24 h under nitrogen. After cooling, a dark green solid was filtered off, washed with diethyl ether, and sublimed at 240 °C and 0.5 mmHg as yellow crystals (160 mg, 58%) of 9,10-*dimethylisoquinolino*[5,6-b][1,6]*naphthyridin*-8(9H)-*one* (15), m.p. 230 °C (decomp.) (Found: C, 74.1; H, 4.75; N, 15.4. $C_{17}H_{13}N_3O$ requires C, 74.2; H, 4.8; N, 15.3%), *m/e* 275 (M^+), $\nu_{max.}$ (KBr) 1 645 cm⁻¹ (amide); $\lambda_{max.}$ (MeOH) 213, 243, 255, 269, 276, 323, 338, and 404 nm (log ε 3.80, 3.80, 3.81, 3.91, 3.92, 3.50, 3.52, and 3.04); $\lambda_{max.}$ (H^+) 261, 279sh, 287, 348, and 430 nm (log ε 3.78, 3.78, 3.82, 3.46, and 2.92); τ($CDCl_3$) 0.70 (1 H, br, 4-H), 0.83 (1 H, s, 7-H), 0.93 (1 H, d, *J* 6 Hz, ArH), 1.11 (1 H, m), 2.11 and 2.23 (2 × 1 H, 2 d, *J* 8 Hz, ArH), 3.16 (1 H, s, 11-H), 6.39 (3 H, s, NMe), and 7.49 (3 H, s, CMe).

Reaction of the Hemiacetal (7; R = Me) *with* 5-*Aminoindazole*.—The hemiacetal (7; R = Me) (209 mg, 1 mmol) and 5-aminoindazole (133 mg, 1 mmol) were heated at reflux in diphenyl ether (25 cm³) for 20 h under nitrogen. After a further 24 h at room temperature crystals separated out. These were filtered, washed with diethyl ether, and sublimed at 260 °C and 0.5 mmHg to give yellow crystals (121 mg, 46%) of 8,9-*dimethylindazolo*[5,4-b][1,6]*naphthyridin*-10(9H)-*one* (16), m.p. 250 °C (decomp.) (Found: C, 68.3; H, 4.6; N, 21.2. $C_{15}H_{12}N_4O$ requires C, 68.2; H, 4.6; N, 21.2%); *m/e* 264 (M^+); $\nu_{max.}$ (KBr) 1 635 cm⁻¹ (amide); $\lambda_{max.}$ (MeOH) 223, 236, 289, 300sh, 320sh, and 396 nm (log ε 3.90, 3.92, 3.88, 3.81, 3.42, and 2.99); $\lambda_{max.}$ (H^+) 223, 245, 256sh, 315, and 440 nm (log ε 3.85, 3.86, 3.75, 3.70, and 2.86); τ([$^2H_6$]DMSO–CF_3CO_2H) 0.17 and 0.97 (2 × 1 H, 2 s, 1- and 11-H), 1.62 and 2.13 (2 × 1 H, 2 d, *J* 9 Hz, 4- and 5-H), 3.33 (1 H, s, 7-H), 6.46 (3 H, s, NMe), and 7.42 (3 H, s, CMe).

Reaction of the Hemiacetal (7; R = Me) *with* 5-*Aminoindole*.—The hemiacetal (7; R = Me) (105 mg, 0.5 mmol) and 5-aminoindole (66 mg, 0.5 mmol) were heated to reflux in diphenyl ether (20 cm³) for 16 h under nitrogen. After a further 24 h at room temperature, a brown solid was obtained which sublimed at 250 °C and 0.5 mmHg as yellow crystals (70 mg, 53%) of 7,8-*dimethylindolo*[5,6-b][1,6]-*naphthyridin*-9(8H)-*one* (18), m.p. 190—195 °C decomp.) (Found: C, 72.5; H, 5.0; N, 15.6. $C_{16}H_{13}N_3O$ requires C, 72.9; H, 5.0; N, 15.9%); *m/e* 263 (M^+); $\nu_{max.}$ (KBr) 1 640 cm⁻¹ (amide); $\lambda_{max.}$ (MeOH) 234, 253, 262sh, 293, 311, and 388 nm (log ε 3.86, 3.82, 3.72, 3.97, 3.89, and 3.35); $\lambda_{max.}$ (H^+) 230, 244sh, 261sh, 273, 312, 328, and 438 nm (log ε 3.96, 3.81, 3.64, 3.74, 3.86 3.79, and 3.61); τ([$^2H_6$]-DMSO) 0.51 (1 H, s, 10-H), 1.91 and 2.24 (2 × 1 H, 2 d, *J* 8 Hz, 2- and 3-H), 2.38, 2.61, and 3.20 (3 × 1 H, 3 s, 4-, 6- and 11-H), 6.40 (3 H, s, NMe), and 7.45 (3 H, s, CMe).

Reaction of the Hemiacetal (7; R = H) *with* 3-*Aminopyrazole*.—The hemiacetal (7; R = H) (26 mg, 0.13 mmol) was heated to 250 °C with 3-aminopyrazole (13 mg, 1.6 mmol) in diphenyl ether (5 cm^3) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a pale yellow solid which was triturated with methanol and filtered to remove the bispyridone (10; R = H). The methanol-soluble material was crystallised from ethanol as yellow crystals (15 mg, 56%) of 6-*methyl*-3H-*pyrazolo*[5,4-b][1,6]-*naphthyridin*-8(7H)-*one* (20), m.p. 200 °C (Found: M^+, 200.069 768. $C_{10}H_8N_4O$ requires M, 200.069 807); $\nu_{max.}$ (Nujol) 1 610br cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 220, 226, 278, 287, 310, and 344 nm (log ε 4.60, 4.61, 4.23, 4.25, 4.15, and 4.13); $\lambda_{max.}$ (H^+) 220, 264, 296, 312, and 390 nm (log ε 4.57, 4.21, 4.06, 4.02, and 4.11); τ([$^2H_6$]DMSO) 1.08, 1.74, and 3.65 (3 × 1 H, 3 s, 1-, 5-, and 9-H), 6.2 (br, NH, exchangeable in D_2O), and 7.78 (3 H, s, NMe).

5-(NN-*Dimethylaminomethyl*)*uracil* (22; X = NMe_2).—Anhydrous dimethylamine (4 cm^3) was added to 35% aqueous formaldehyde (2.7 cm^3) in distilled water (40 cm^3) at 0 °C. The mixture was left at 0 °C for 20 min and uracil (3.4 g) was added. The reaction was left at room temperature for 50 h when the solvents were removed *in vacuo* to yield a solid (3.93 g, 77%), m.p. 203—206 °C (decomp.) (Found: C, 49.7; H, 6.4; N, 24.8. $C_7H_{11}N_3O_2$ requires C, 49.7; H, 6.5; N, 24.9%); $\nu_{max.}$ 1 740 and 1 675 cm^{-1}; $\lambda_{max.}$ (MeOH) 210 and 262 nm; $\lambda_{max.}$ (OH^-) 215 and 291 nm; τ(D_2O) 2.50 (1 H, s, 6-H), 6.15 (2 H, s, CH_2N), and 7.25 (6 H, s, NMe).

Reaction of 5-N-*Morpholinomethyluracil* (22; X = $-\overline{NCH_2CH_2OCH_2CH_2}$) *with Aniline*.—The Mannich base (22; X = $-\overline{NCH_2CH_2OCH_2CH_2}$) [12,13] (160 mg, 0.76 mmol) was heated at 250 °C with distilled aniline (6 cm^3) in diphenyl ether (5 cm^3) for 15 h. Initially the solid dissolved and finally a yellow precipitate was obtained. The solvents were removed *in vacuo* to yield the *Mannich base* (22; X = NHPh) on washing with methanol (146 mg, 89%). The spectra were consistent with the proposed structure and were identical with those of an authentic sample prepared by the method of Santi.[14]

Reaction of 5-(NN-*Dimethylaminomethyl*)*uracil* (22; X = NMe_2) *with Aniline*.—The Mannich base (22; X = NMe_2) (158 mg, 0.9 mmol) was treated as above to yield the adduct (22; X = NHPh) (120 mg, 59%) as the product which was insoluble in hot ethanol, and uracil (22 mg, 21%) as the product which was soluble in hot ethanol.

Reaction of Uracil with 1-(NN-*Diethylamino*)*butan*-3-*one*.—Methyl iodide (5.7 g, 40 mmol) was added to a solution of 1-(*NN*-diethylamino)butan-3-one [23] (5.7 g, 40 mmol) in absolute ethanol (20 cm^3). The solution was added dropwise over 30 min to a solution of uracil (2.4 g, 21 mmol) and potassium hydroxide (2.2 g, 40 mmol) in dry ethanol (50 cm^3) with stirring at room temperature. The reaction was heated to reflux for 30 min and distilled water was then added until the precipitate dissolved. The ethanol was removed *in vacuo* and the solution was made neutral to litmus with 3N-hydrochloric acid. The mixture was extracted with chloroform and the extracts were dried (Na_2SO_4). The solvent was removed *in vacuo* to yield an oil which was triturated with acetone and crystallised from ethanol as white crystals (2.8 g, 72%) of the N-*substituted adduct*, m.p. 125—127 °C (Found: C, 52.9; H, 5.5; N, 15.5. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.5; N, 15.4%), *m/e* 182 (M^+); $\nu_{max.}$ (Nujol), 1 720, 1 690, and 1 650 cm^{-1}; $\lambda_{max.}$ (MeOH) 211 and 266 nm; τ($CDCl_3$) 2.47 (1 H, d, *J* 8 Hz, 6-H), 4.25 (1 H, d, *J* 8 Hz, 5-H), 5.94 (2 H, t, *J* 5 Hz, CH_2N), 6.97 (2 H, t, *J* 5 Hz, CH_2), and 7.72 (3 H, s, COMe).

Reaction of 3-(NN-*Dimethylamino*)*methyl*-4-*hydroxycoumarin* (25) *with Aniline*.—The Mannich base (25) [16] (72 mg, 0.3 mmol) was heated at 250 °C with distilled aniline (3 cm^3) in diphenyl ether (5 cm^3) for 15 h under nitrogen. The solvents were removed *in vacuo* and the resultant gum was triturated with and crystallised from methanol as yellow needles (38 mg, 47%) of [1]*benzopyrano*[4,3-b]-*quinolin*-6-*one* (27), m.p. 225 °C; *m/e* 247 (M^+); $\nu_{max.}$ (Nujol) 1 740 cm^{-1} (lactone); $\lambda_{max.}$ (MeOH) 228, 265sh, 273, 302sh, 340, 355, and 370 nm (log ε 4.20, 4.38, 4.54, 3.69, 3.39, 3.43, and 3.35); $\lambda_{max.}$ (H^+) 218, 248, 266sh, 275, 360, and 370 nm (log ε 4.48, 4.49, 4.45, 4.52, 3.87, and 3.87); τ($CDCl_3$) 0.83 (1 H, s, 7-H), 1.27 (1 H, d, *J* 8 Hz, 1-H), 1.81, 2.18, and 2.78 (3 × 1 H, 3 d, *J* 8 Hz, 4-, 8-, and 11-H), and 2.07, 2.44, 2.52, and 2.63 (4 × 1 H, 4 t, *J* 8 Hz, 2-, 3-, 9-, and 10-H).

Reaction of 3,3'-*Methylenebis*-4-*hydroxycoumarin* (29) *with Aniline*.—The biscoumarin (29) [18] (86 mg, 0.26 mmol) was heated at 250 °C with distilled aniline (3 cm^3) and diphenyl ether (5 cm^3) for 15 h under nitrogen. The solvents were removed *in vacuo* to yield a solid which was triturated with hot methanol. The first crystals from the methanol solution proved to be the *tetracyclic compound* (27) (27 mg, 43%), identical with the sample prepared above. The second compound to precipitate from the methanol solution was further purified by preparative t.l.c. (25 mg, 21%) and proved to be 4-*N*-anilinocoumarin (28), m.p. 270 °C (lit.,[17] 259—260 °C) with the expected spectral properties.

Flavan (30).—Flavanone (31) (1 g, 4.5 mmol) was dissolved in cold absolute ethanol (50 cm^3), and solid sodium borohydride (excess) was added in portions. The mixture was stirred at room temperature for 15 h and water was added. The precipitate was filtered off and appeared to be a mixture of 4α- and 4β-flavanol (32), m.p. 120—128 °C (lit.,[25] 4α-isomer m.p. 118 °C, 4β-isomer 148 °C) (Found: C, 79.7; H, 6.1. Calc. for $C_{15}H_{14}O_2$: C, 79.65; H, 6.2%), *m/e* 226 (M^+); $\nu_{max.}$ (Nujol) 3 300 cm^{-1} (OH); $\lambda_{max.}$ (MeOH) 218, 224sh, 278, and 285 nm; τ($CDCl_3$) 2.47—3.20 (9 H, m, ArH), 4.86 (1 H, dd, *J* 10 and 2 Hz, 2-H), 4.90 (1 H, m, 4-H), and 7.35—8.35 (2 H, m, CH_2). The mixture of flavanols (32) (106 mg, 0.47 mmol) and toluene-*p*-sulphonic acid (4 mg) were dissolved in dry benzene (50 cm^3) and heated to reflux for 3 h under a Soxhlet containing calcium hydride. The solvent was removed to yield an oil which was triturated with methanol and crystallised from ethanol–water (40 mg, 41%), m.p. 65 °C (flav-2-ene, lit.,[26] 50—51, lit.,[27] 54—55 °C; flav-3-ene, lit.,[26] b.p. 100—102 °C at 0.2 mmHg) (Found: C, 86.5; H, 6.05. Calc. for $C_{15}H_{12}O$: C, 86.5; H, 5.8%); *m/e* 208 (M^+); $\nu_{max.}$ (Nujol) 1 580 cm^{-1}; $\lambda_{max.}$ (MeOH) 214 and 255 nm; The flavene (21 mg, 0.1 mmol) was dissolved in dry ethanol (20 cm^3) with 10% palladium–charcoal and stirred under hydrogen for 18 h. The mixture was filtered through Celite and the solvent was removed *in vacuo*. The product was purified by preparative t.l.c. and crystallised from methanol (9 mg, 43%), m.p. 44 °C (lit.,[19] 44—45 °C).

Reaction of Flavan (30) *with Aniline*.—Flavan (30) (48 mg, 0.2 mmol) was heated to 260 °C with distilled aniline (3 cm^3) in diphenyl ether (5 cm^3) for 15 h under nitrogen. The solvents were removed *in vacuo*. At 40 °C, a gum collected at the top of the reaction flask. This was tritu-

rated with methanol and crystallised from ethanol–water as yellow crystals (3 mg, 7%) of *N*-(2-hydroxybenzylidene)-aniline (35), m.p. 51 °C (lit.,[21] 50.5 °C), undepressed on admixture with an authentic sample. The residual oil after removal of the solvents was purified by preparative *t.l.c.* (SiO_2; $CHCl_3$). The most polar compound crystallised from methanol as plates (5 mg, 11%) of N-(2-*hydroxybenzyl*)-*aniline* (36), m.p. 110—111 °C (lit.,[22] m.p. 108 °C), identical (spectra) with an authentic sample. A second compound crystallised from ethanol–water as yellow plates (2 mg, 4%) of *acridine* (34), m.p. 111 °C, identical in all respects with an authentic sample. The final compound from preparative t.l.c. crystallised from cyclohexane as a white solid (4 mg, 8%) assigned as 2-(2-*aminobenzyl*)*phenol* (37), m.p. 140 °C (Found: C, 78.3; H, 6.4; N, 6.7. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.5; N, 7.0%); *m/e* 199 (M^+), 106, and 93; $\nu_{max.}$ (Nujol) 3 380 and 3 300 cm^{-1} (NH and OH); $\lambda_{max.}$ (MeOH) 220, 228, and 283 nm (log ε 4.58, 4.70, and 4.38); $\lambda_{max.}$ (OH^-) 220, 230, and 294 nm (log ε 4.60, 4.78, and 4.51); $\lambda_{max.}$ (H^+) 220, 225, 276, and 280sh nm (log ε 4.55, 4.55, 4.29, and 4.25); τ($CDCl_3$) 2.79—3.40 (8 H, m, ArH), 5.7 (3 H, br, NH, OH), and 6.19 (2 H, s, CH_2).

Acetylation of the Amine (37).—The amine (37) (21 mg, 0.1 mmol) was dissolved in dry pyridine (2 cm^3) with acetic anhydride (2 cm^3) and the mixture was stirred overnight at room temperature under nitrogen. The solvents were removed *in vacuo* and the resultant gum was triturated with cyclohexane and crystallised from cyclohexane (22 mg, 74%) as the *diacetate*, m.p. 110—112 °C (Found: C, 71.7; H, 5.9; N, 4.9. $C_{17}H_{17}NO_3$ requires C, 72.1; H, 6.0; N, 4.95%); *m/e* 283 (M^+); $\nu_{max.}$ (Nujol) 3 280 (NH), 1 740br (ester), and 1 650 cm^{-1} (amide); $\lambda_{max.}$ (MeOH) 219 and 224 nm; $\lambda_{max.}$ (OH^-) 220, 235, and 300 nm; $\lambda_{max.}$ (H^+) 220, 225, 246sh, 275, and 283sh nm; τ($CDCl_3$) 2.17 (1 H, br s, NH or OH exchangeable with D_2O), 2.80—3.36 (9 H, m, ArH and NH), 6.21 (2 H, s, CH_2), and 7.75 and 8.13 (2 × 3 H, 2 s, COMe).

Reaction of the Amine (37) *with Polyphosphoric Acid.*—The amine (37) (31 mg, 0.15 mmol) was suspended in polyphosphoric acid (5 g; s.g. 2.2) and heated at 95 °C for 30 min. The temperature was raised to 120 °C for 15 min and the mixture was cooled and diluted with water. The solution was extracted with chloroform and the extracts were dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a brown solid which was purified by preparative t.l.c. to give acridine (34), (2 mg, 7%), m.p. 110 °C, identical with an authentic sample.

Pyrolysis of N-(2-*Hydroxybenzyl*)*aniline* (36).—The Mannich base (36) (38 mg, 0.2 mmol) was heated to 260 °C in diphenyl ether (5 cm^3) for 15 h under nitrogen. The solvent was removed *in vacuo* to give an oil which solidified on trituration with cyclohexane. The solid crystallised from cyclohexane (15 mg, 40%) and was shown to be the amine (37) by comparison with an authentic sample. The remaining oil was triturated with methanol–water to yield a yellow solid which was further purified by preparative t.l.c. This proved to be acridine (34) (2 mg, 5%), identical with an authentic sample.

Pyrolysis of the Amine (37).—The amine (37) (29 mg, 0.15 mmol) was heated at 260 °C in diphenyl ether (5 cm^3) under nitrogen for 15 h. The solvent was removed *in vacuo* and the residue was purified by preparative t.l.c. to give acridine (34) (3 mg, 12%), identical with an authentic sample.

Reaction of 2-(NN-*Dimethylaminomethyl*)-3-*hydroxypyridine* (38; X = NMe_2) *with Aniline.*—The Mannich base (38; X = NMe_2) (126 mg, 0.8 mmol) was heated to 250 °C with aniline (5 cm^3) in diphenyl ether (4 cm^3) for 15 h under nitrogen. The solvents were removed *in vacuo* to yield a glass which was purified by preparative t.l.c. (SiO_2; $CHCl_3$). One product proved to be 3-hydroxypyridine (23 mg, 30%). A second compound crystallised from methanol (32 mg, 20%) as 2-(N-*anilinomethyl*)-3-*hydroxypyridine* (38; X = NHPh), m.p. 140—142 °C (Found: M^+, 200.094 4. $C_{12}H_{12}N_2O$ requires *M*, 200.094 96); $\nu_{max.}$ ($CHCl_3$) 3 600 and 3 450 cm^{-1}; $\lambda_{max.}$ (MeOH) 207, 236, and 290 nm; $\lambda_{max.}$ (OH^-) 212, 246, and 306 nm; τ($CDCl_3$) 1.92 (1 H, m, ArH), 2.7—3.3 (7 H, m, ArH), and 5.4 (2 H, s, CH_2). A third compound crystallised from benzene–light petroleum (b.p. 60—80 °C) (16 mg, 10%) as 3-*hydroxy*-2-*pyridylmethyleneaniline* (39), m.p. 62—63 °C, *m/e* 198 (M^+); $\lambda_{max.}$ (MeOH) 220 and 345 nm; $\lambda_{max.}$ (OH^-) 226, 262sh, and 386 nm; $\lambda_{max.}$ (H^+) 228 and 292 nm; τ($CDCl_3$) 1.18 (1 H, s, CH=N), 1.78 (1 H, m, ArH), and 2.58—3.20 (7 H, m, ArH).

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