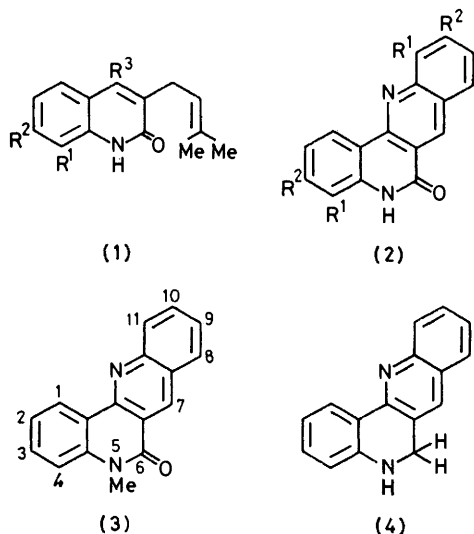


## A General and Practicable Synthesis of Polycyclic Heteroaromatic Compounds. Part 1. Use of a Putative Quinolone-quinone-methide in the Synthesis of Polycyclic Heteroaromatic Compounds<sup>1</sup>

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A general and straightforward new synthesis of polycyclic heteroaromatic compounds has been developed. In the synthesis a putative quinolone-quinone-methide is generated in the presence of an aniline. The ensuing reaction results in a polycyclic heteroaromatic product. In the most useful approach, a hemiacetal (25) is prepared in one step from the parent quinolone and this is heated in the presence of an aromatic amine to produce the polycyclic heteroaromatic compound in good yield. The regioselectivity of the reaction is the opposite to that expected in the Skraup synthesis with respect to the quinone-methide component. With respect to the aniline component, however, regioselectivity is the same as in the Skraup synthesis.

We have isolated an alkaloid from the root of *Dictamnus albus* L<sup>2</sup> which was proved by synthesis<sup>2</sup> to be 4,7,8-trimethoxy-3-(3-methylbut-2-enyl)-2-quinolone (1; R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = OMe). In this synthesis, use was made of the 'standard' method of preparing 3-(3,3-dimethylallyl)-4-hydroxy-2-quinolones (1; R<sup>3</sup> = OH) by condensation of substituted anilines with diethyl 2-(3-methylbut-2-enyl)malonate, a method which had been used to prepare the quinolones (1; R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = OH)<sup>3</sup> and (1; R<sup>1</sup> = OMe, R<sup>2</sup> = H, R<sup>3</sup> = OH).<sup>4</sup>



On preparing the quinolone (1; R<sup>1</sup> = R<sup>2</sup> = OMe, R<sup>3</sup> = OH) by reaction of 2,3-dimethoxyaniline with diethyl 2-(3-methylbut-2-enyl)malonate, a by-product was obtained which proved to be the tetracyclic compound (2; R<sup>1</sup> = R<sup>2</sup> = OMe).<sup>5</sup> Reinvestigation<sup>5</sup> of the syntheses using aniline<sup>3</sup> and *o*-anisidine<sup>4</sup> showed that the tetracyclic products (2; R<sup>1</sup> = R<sup>2</sup> = H) and (2; R<sup>1</sup> = OMe, R<sup>2</sup> = H) were obtained in the reactions.<sup>5</sup> *N*-Methylation of the unsubstituted compound (2; R<sup>1</sup> = R<sup>2</sup> = H) gave the product (3) which could also be prepared from the known<sup>6</sup> dihydrodibenzonaphthyridine (4) by oxidative methylation.<sup>5</sup> Since compound (4) had been prepared in an unambiguous manner by

the Pfizinger synthesis, the structures of the tetracyclic by-products were proven.

Although the yields of the tetracyclic compounds (2) in these reactions were low, in principle it appeared that we had a novel and potentially useful method of synthesising polycyclic heteroaromatic compounds. It was evident, however, that if we were to develop the method into a useful synthetic tool, the yields of the heteroaromatic products would have to be improved. With the aim of improving the method, consideration was given to the possible mechanisms by which the tetracyclic compounds (2) were formed from the reaction of the substituted aniline with 2-(3-methylbut-2-enyl)malonate. Preliminary work on the mechanism indicated<sup>5</sup> that the first steps in the sequence were formation of the 4-hydroxy-2-quinolone (1; R<sup>3</sup> = OH) followed by Markownikoff addition of the 4-hydroxy-group to the olefinic bond to yield the tricyclic compound (5; R = H).

A possible sequel is shown in Scheme 1. *Retro*-Diels-Alder reaction would yield the enone-amide (6). This might be thought of as a quinone methide inasmuch as a quinolone may be considered to have aromatic character. Subsequent 1,4-addition of aniline might be expected,<sup>7</sup> yielding either the Mannich base (7) by addition of the aniline at nitrogen or the *ortho*-substituted product (8) by direct attack of the *ortho*-carbon. The Mannich base (7) might rearrange to the isomer (8).<sup>8</sup> Cyclisation and oxidation would then yield the tetracyclic amide (2). Alternatively, reaction of a second mole of aniline with the Mannich base (7) might yield the adduct (9) which could cyclise as shown.

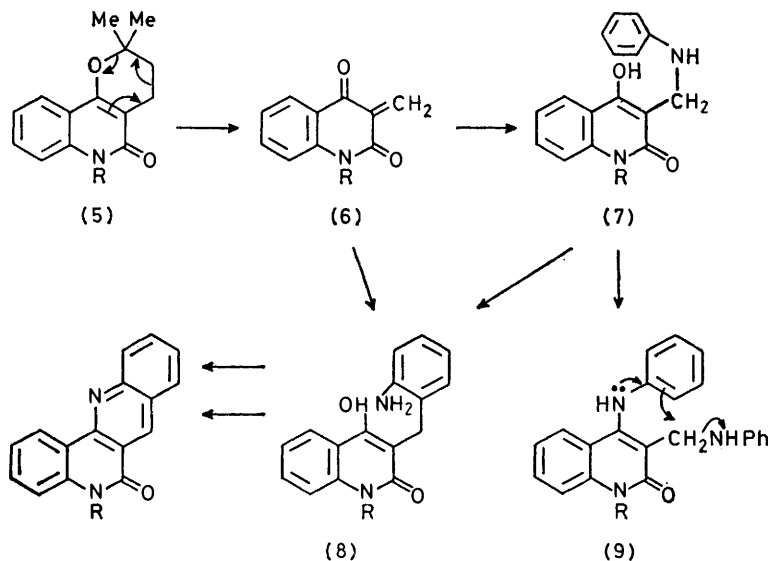
A route not involving a *retro*-Diels-Alder reaction is shown in Scheme 2 where Michael addition of aniline followed by elimination would yield the alcohol (11). A vinylogous *retro*-Prins process, as illustrated in (11), should yield a 'triene' (12). Electrocyclic ring-closure and oxidation would then yield the tetracyclic amide (2).

Acting on the assumption that the reaction followed the route outlined in Scheme 1, it seemed that the synthesis might be improved if a more direct route to

the quinone-methide (6) could be found. Pyrolysis of the Mannich base (13) might be expected<sup>7</sup> to yield the quinone-methide (6; R = H), and so we prepared the Mannich base (13; R = H) by reaction of 4-hydroxy-2-quinolone with formaldehyde and dimethylamine.

major product being the bisquinolone (14; R<sup>1</sup> = Me, R<sup>2</sup> = H).

When the Mannich base (13; R = H) was heated in refluxing aniline, a 36% yield of dibenzo[*b,h*][1,6]-naphthyridin-6(5*H*)-one (2; R<sup>1</sup> = R<sup>2</sup> = H) was

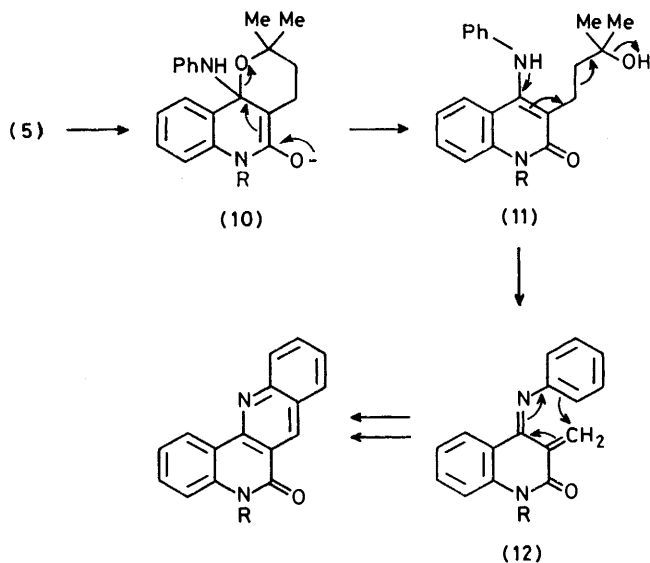


SCHEME 1

The compound decomposed on attempted purification, yielding 3,3'-methylenebis-4-hydroxy-2-quinolone (14; R<sup>1</sup> = R<sup>2</sup> = H), identical with an authentic sample.<sup>5</sup> The mass spectrum of the Mannich base (13; R = H)

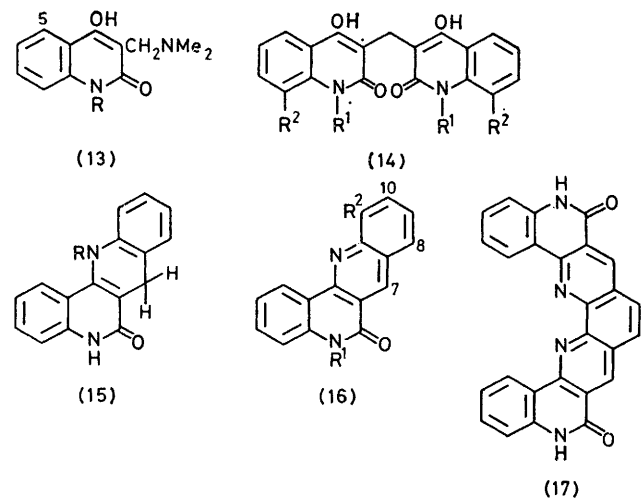
obtained. This compound was identical in all respects with an authentic sample.<sup>5</sup> The major by-product (27%) was 3,3'-methylenebis-4-hydroxy-2-quinolone (14; R<sup>1</sup> = R<sup>2</sup> = H). A small amount of an unstable compound was also obtained. This had a similar u.v. spectrum to the reduced dibenzonaphthyridone (15; R = Me), prepared as described below, and hence was concluded to be compound (15; R = H), expected in the penultimate step of the Scheme.

The Mannich base (13; R = H) was now treated in



SCHEME 2

showed no parent ion, the ion of highest mass corresponding to the quinone-methide (6; R = H). The <sup>1</sup>H n.m.r. spectrum, however, was consistent with the structure. An effort was made to prepare the *N*-methyl-Mannich base (13; R = Me) from 4-hydroxy-1-methyl-2-quinolone. The reaction, however, failed, the



turn with *o*-phenylenediamine in diphenyl ether and with *o*-anisidine at reflux when the expected tetracyclic products (16; R<sup>1</sup> = H, R<sup>2</sup> = NH<sub>2</sub>) and (16; R<sup>1</sup> = H,

$R^2 = \text{OMe}$ ) were obtained in 29 and 26% yields respectively. There was no evidence that the diamine had reacted with two moles of the quinone-methide to yield the polycyclic molecule (17) in the former reaction. The amine (16;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) could be acetylated to yield the acetamide (16;  $R^1 = \text{H}$ ,  $R^2 = \text{NHAc}$ ). The bisquinolone (14;  $R^1 = R^2 = \text{H}$ ) was the major by-product in both reactions and the structures of the tetracyclic compounds were implied from the analytical and spectroscopic data. Particularly compelling was a comparison of the chemical shifts of 7- and 1-H in the  $^1\text{H}$  n.m.r. spectra of the series of compounds (Table 1). Compounds (2;  $R^1 = R^2 = \text{H}$ ) and (16;  $R^1 = \text{H}$ ,  $R^2 = \text{OMe}$ ) both showed a bathochromic shift in the

n.m.r., u.v., and mass spectra indicated that these were the tetracyclic compounds (18) and (19) respectively. The  $^1\text{H}$  n.m.r. spectrum of the product from the reaction with 3-aminopyridine excluded the alternative structure (20) which should have two low field singlets for 7- and 11-H in the n.m.r. spectrum. In fact only one singlet [7-H in (19)] was observed and this was at a lower-than-average chemical shift (Table 1). Deshielding of the 7-H proton seems to be characteristic of all the compounds in the series with a *peri* substituent at C-8 (Table 1). Deshielding of protons by a *peri* aza-function has been observed in other heteroaromatic compounds.<sup>9</sup>

The reaction with 3-aminopyridine appears to have been regiospecific even allowing for the very low yield.

TABLE 1

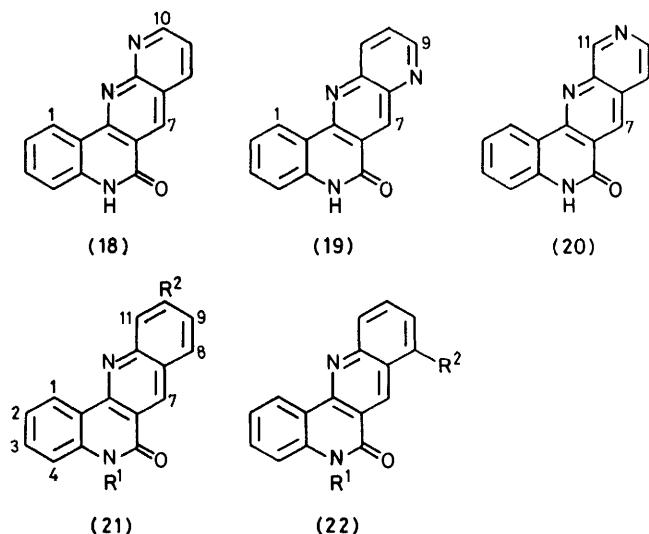
Compound	$^1\text{H}$ N.m.r. spectral assignments of the polycyclic heteroaromatic compounds in $[\text{}^2\text{H}_6]\text{DMSO}$						
	(2; $R^1 = R^2 = \text{H}$ )	(16; $R^1 = \text{H}$ , $R^2 = \text{NH}_2$ )	(16; $R^1 = \text{H}$ , $R^2 = \text{MeO}$ )	(21; $R^1 = \text{H}$ , $R^2 = \text{NH}_2$ )	(21; $R^1 = \text{H}$ , $R^2 = \text{NHAc}$ )	(21; $R^1 = \text{H}$ , $R^2 = \text{OMe}$ )	
Chemical Shift ( $\tau$ )	0.72	0.94	0.74	1.10	0.80	0.78	
1-H	1.25	1.02	1.20	1.30	1.21	1.22	
Compound	(21; $R^1 = \text{Me}$ , $R^2 = \text{OMe}$ )	(22; $R^1 = \text{H}$ , $R^2 = \text{NH}_2$ )	(22; $R^1 = \text{H}$ , $R^2 = \text{OMe}$ )	(22; $R^1 = \text{Me}$ , $R^2 = \text{OMe}$ )	(18)	(19)	(32)
Chemical Shift ( $\tau$ )	0.72	0.45	0.57	0.53	1.18	0.57	0.45
1-H	1.04	1.26	1.22	1.04	1.16	1.21	1.02

u.v. on addition of acid. This shift was characteristic of most compounds in the series except for the amino-substituted compounds (16;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) and (16;  $R^1 = \text{H}$ ,  $R^2 = \text{NHAc}$ ).

Reaction of the Mannich base (13;  $R = \text{H}$ ) with aniline and with anilines substituted with an electron-donating group had evidently given the desired tetracyclic compounds in moderate yield. It was therefore of

The regiospecificity is the same as in the Skraup synthesis with respect to the aniline component when anilines substituted in the *meta*-position with an electron-withdrawing group are used.<sup>10</sup> The regiospecificity with respect to the 'quinone-methide' constituent is of course the reverse of that found in the Skraup synthesis in all the reactions studied.

Having observed regiospecificity in the reaction with 3-aminopyridine, it was of interest to examine the reaction of the Mannich base (13;  $R = \text{H}$ ) with anilines *meta*-substituted with an electron-donating substituent. The Mannich base (13;  $R = \text{H}$ ) was therefore treated with *meta*-phenylenediamine in refluxing diphenyl ether to afford a product in 20% yield. This analysed as  $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}$  and ran as one compound on a variety of t.l.c. systems. It was evident from the  $^1\text{H}$  n.m.r. spectrum, however, that the product was a mixture of two isomers, there being two singlets for 7-H at  $\tau$  0.45 and 1.1 as well as two superimposed *ortho*-coupled doublets for 1-H. The lower of the 7-H singlets was assigned to compound (22;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) since the *peri* effect of the 8-amino-group would be expected<sup>11</sup> to deshield the 7-H proton. Integration of the two 7-H singlets indicated that the ratio of the 10-amine (21;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) to the 8-amine (22;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) was 2 : 1. Attempts to separate the isomers failed but acetylation of the mixture followed by sublimation did give an apparently pure sample of the acetamide (21;  $R^1 = \text{H}$ ,  $R^2 = \text{NHAc}$ ), there being singlets at  $\tau$  0.80 for 7-H and 1.29 for 11-H in the  $^1\text{H}$  n.m.r. spectrum run in  $[\text{}^2\text{H}_6]\text{DMSO}$ . The remainder of the spectrum was consistent with this assignment. The fact that the predominant isomer in the reaction was the 10-amine (21;  $R^1 = \text{H}$ ,  $R^2 = \text{NH}_2$ ) meant that the regiospecificity of the reaction with respect to the

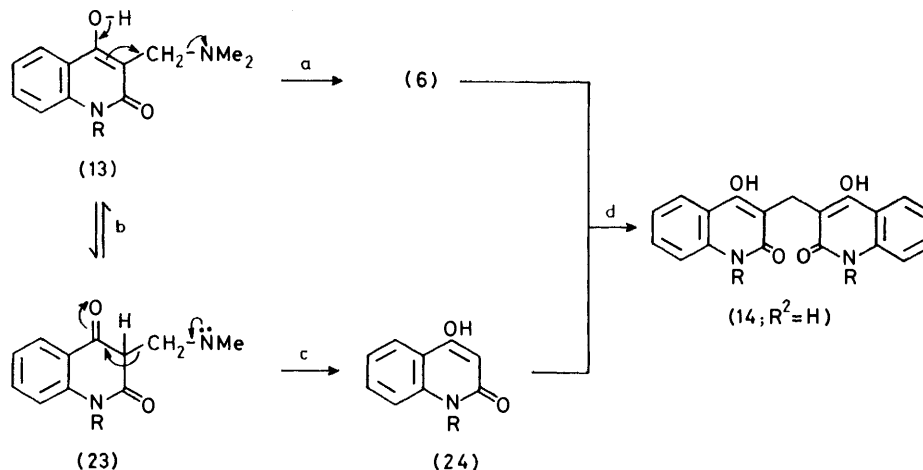


interest to examine the potential of anilines substituted with electron-withdrawing groups in the reaction. The Mannich base (13;  $R = \text{H}$ ) was therefore treated in turn with 2- and 3-aminopyridine. The major product from both reactions was 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = \text{H}$ ). A small yield of a second compound was obtained in each case and  $^1\text{H}$

aniline component was the same as the Skraup synthesis when anilines substituted in the *meta*-position with electron-donating substituents were used.<sup>10</sup>

Use of the Mannich base (13; R = H) as a precursor for the proposed quinone-methide synthon had improved the original synthesis<sup>5</sup> but yields were still only of the order of 30% (see Table 2). The major by-product in

din-6(5*H*)-one (2; R<sup>1</sup> = R<sup>2</sup> = H) and a 71% yield of 11-aminodibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (16; R<sup>1</sup> = H, R<sup>2</sup> = NH<sub>2</sub>). Thus generation of the quinone-methide by a *retro*-Diels-Alder reaction had proved to lead to a viable synthesis. The usefulness of the method was however limited by the fact that synthesis of dihydroflindersine (5; R = H)<sup>12</sup> was a multistep process.



SCHEME 3

each of the reactions studied proved to be the bisquinolone (14; R<sup>1</sup> = R<sup>2</sup> = H) and the most likely explanation for the formation of this compound is outlined in Scheme 3. Tautomerism to the keto form (23), followed by a *retro*-Mannich reaction would convert the Mannich base (13; R = H) to the quinolone (24). This nucleophile might then react with the quinone-methide (6; R = H) to form the bisquinolone (14; R<sup>1</sup> = R<sup>2</sup> = H). We were able to generate two of the quinone-methides (6) from the bisquinolones (14;

This last problem was overcome by synthesis of the hemiacetals (25; R = H) and (25; R = Me) in one step by reaction of the corresponding 4-hydroxy-2-quinolones with 1-*N,N*-diethylaminobutan-3-one, methyl iodide, and KOH. Reaction of these hemiacetals separately with aniline gave dibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (2; R<sup>1</sup> = R<sup>2</sup> = H) in 76% yield and 5-methyldibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (3) in 80% yield. Acetone was trapped as its 2,4-dinitrophenylhydrazone in one of these experiments. Reaction

TABLE 2

Polycyclic heteroaromatic compounds from the Mannich base (13; R = H)

Product	(2; R <sup>1</sup> = R <sup>2</sup> = H)	(16; R <sup>1</sup> = H, R <sup>2</sup> = NH <sub>2</sub> )	(16; R <sup>1</sup> = H, R <sup>2</sup> = OMe)	(18)	(19)
Yield (%)	36	29	26	5	1

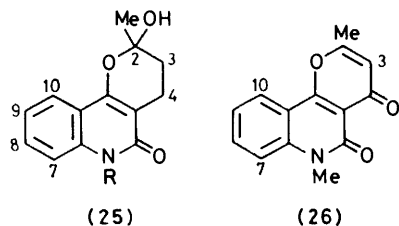
R<sup>1</sup> = Me, R<sup>2</sup> = H) and (14; R<sup>1</sup> = H, R<sup>2</sup> = OMe) by the reverse of reaction d in Scheme 3, and by trapping these with an aniline we were able to prepare the tetracyclic compounds (3) and (2; R<sup>1</sup> = OMe, R<sup>2</sup> = H) respectively.

If the major drawback to the use of the Mannich base (13; R = H) in this synthesis were the tendency for the *retro*-Mannich reaction to lead to bisquinolones (14) as in Scheme 3, then the synthesis might be improved if this process could be obviated. It seemed to us that use of the tricyclic compounds (5) as the precursors for the quinone-methides (6) might solve this problem. The tricyclic compound (5; R = H) had been prepared by a lengthy synthesis<sup>12</sup> and by reduction of a naturally occurring alkaloid and hence was available. Reaction of dihydroflindersine<sup>12</sup> (5; R = H) with aniline and with *o*-phenylenediamine in refluxing diphenyl ether gave respectively a 77% yield of dibenzo[*b,h*][1,6]naphthyri-

of the hemiacetals (25; R = H) and (25; R = Me) separately with *ortho*-anisidine gave the dibenzonaphthyridines (16; R<sup>1</sup> = H, R<sup>2</sup> = OMe) and (16; R<sup>1</sup> = Me, R<sup>2</sup> = OMe) in 64 and 60% yields respectively, and reaction of (25; R = H) with *o*-phenylenediamine gave the product (16; R<sup>1</sup> = H, R<sup>2</sup> = NH<sub>2</sub>) in 66% yield.

An acceptable synthetic method had now been obtained and it was of interest to examine the potential of electron-deficient aromatic amines in the synthesis. The hemiacetal (25; R = Me) was therefore treated in turn with 2-aminopyridine, 3-aminopyridine, and *o*-nitroaniline in refluxing diphenyl ether. No tetracyclic product was obtained in any of these reactions, the major product being the bisquinolone (14; R<sup>1</sup> = Me, R<sup>2</sup> = H). The bisquinolone was *not* observed in the corresponding reactions with the electron-rich anilines and it is significant that it was *not* obtained on reaction of dihydroflindersine (5; R = H) with 2-aminopyridine.

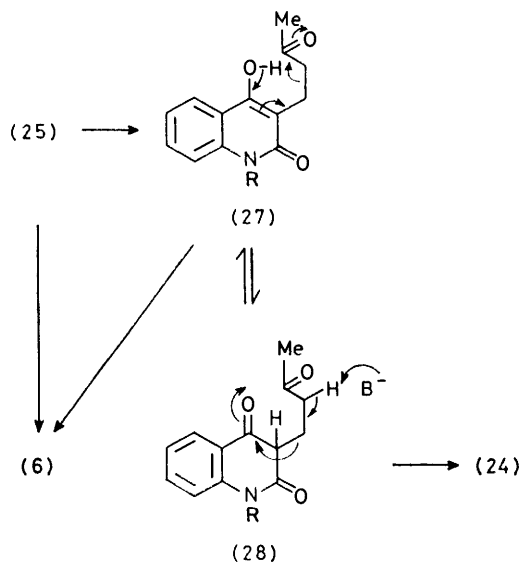
The reaction of the hemiacetal (25; R = Me) with *o*-nitroaniline gave, in addition to the bisquinolone (14; R<sup>1</sup> = Me, R<sup>2</sup> = H), a 17% yield of a compound with molecular formula and spectroscopic data consistent with structure (26). This had evidently arisen from dehydration and allylic oxidation. The formation of the



bisquinolones (14; R<sup>1</sup> = Me, R<sup>2</sup> = H) from the hemiacetal (25; R = Me) can be rationalised as in Scheme 4 where the less nucleophilic amine would act as a base with the diketone valence isomer (28) of the hemiacetal (25). The subsequent *retro*-Michael reaction would yield the quinolone (24) which would react with the quinone-methide (6) to yield the bisquinolone (14).

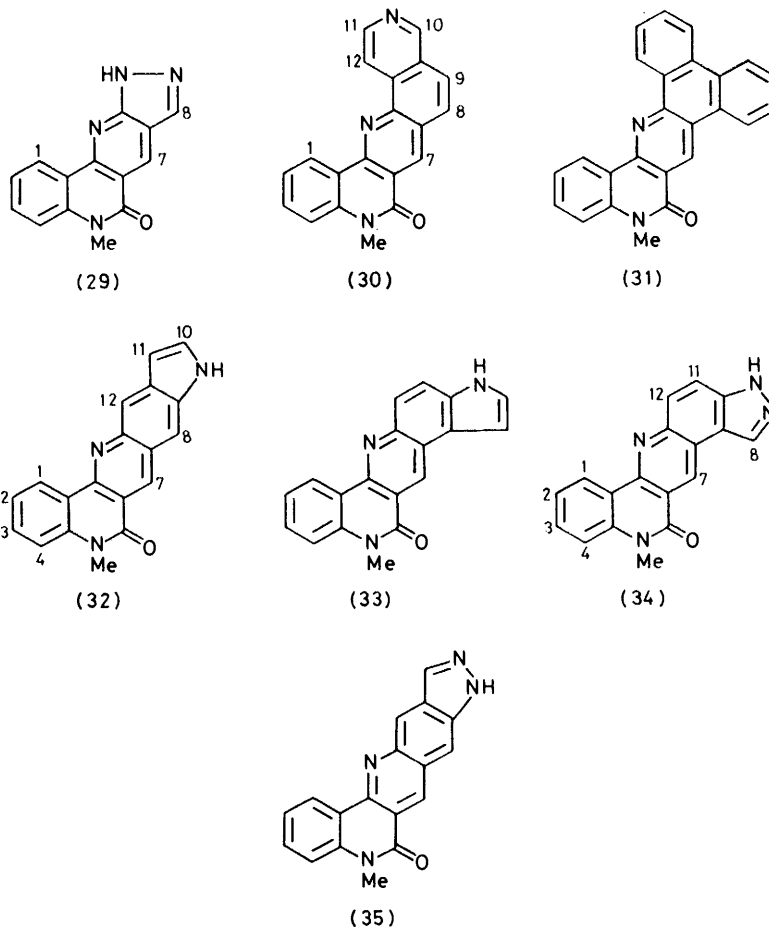
The regiospecificity of the synthesis using the hemiacetals (25) was investigated by separately treating the hemiacetals (25; R = H) and (25; R = Me) with *m*-anisidine. In each case the product was a mixture of the

isomers (21; R<sup>2</sup> = OMe) and (22, R<sup>2</sup> = OMe). The isomer with the 7-H proton to lower field in each case



SCHEME 4

was assigned the 8-methoxy-structure (22; R<sup>2</sup> = OMe) on the basis of the *peri* effect.<sup>11</sup> Integration showed the ratio of the 10-methoxy- to the 8-methoxy-derivative to



be 2.5:1 when  $R^1 = H$  and 1.7:1 when  $R^1 = Me$ . The regioselectivity of the reaction with respect to the aniline component was again as in the Skraup reaction for anilines substituted in the *meta*-position with electron-donating groups.<sup>10</sup>

In an effort to extend the synthesis further, the hemiacetal (25;  $R = Me$ ) was treated with 3-aminopyrazole, 5-aminoisoquinoline, and 9-aminophenanthrene when the polycyclic heteroaromatic compounds (29), (30), and (31) were obtained in 84, 46, and 29% yields respectively. When 5-aminoindole and 5-aminoindazole were used in the reaction, in each case only one of the two possible products was obtained. The reaction with

## 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.  $^1H$  N.m.r. spectra were recorded on Varian T60, EM360, and HA100 and Perkin-Elmer R32 instruments, and 220 MHz spectra were obtained from P.C.M.U., Harwell. Mass spectra were recorded on AEI MS9 and MS30 and Hitachi RMU-6 machines. Merck Kieselgel GF<sub>254</sub> type 60 was used (0.75 mm layers) for preparative t.l.c.

3-*NN*-Dimethylaminomethyl-4-hydroxy-2-quinolone (13;  $R = H$ ).—Cold 40% v/v formaldehyde-water (1 g, 13 mmol) was added to a cooled solution of anhydrous dime-

TABLE 3  
Polycyclic heteroaromatic compounds from the hemiacetals (25)

Product (2; $R^1 = R^2 = H$ ) Yield (%)	(3)	(16; $R^1 = H$ , $R^2 = NH_2$ )	(16; $R^1 = H$ , $R^2 = OMe$ )	(16; $R^1 = Me$ , $R^2 = OMe$ )	(21 + 22; $R^1 = H$ , $R^2 = OMe$ )	(21 + 22; $R^1 = Me$ , $R^2 = OMe$ )	(29)	(30)	(31)	(32)	(34)
		76	80	66	64	60	48	56	84	46	29

5-aminoindole gave a product,  $C_{19}H_{13}N_3O$ , in 73% yield. The  $^1H$  n.m.r. spectrum had three one-proton singlets and so the product was evidently the compound (32) rather than the alternative (33). The product,  $C_{18}H_{12}N_4O$ , obtained in 71% yield from the reaction with 5-aminoindazole had a  $^1H$  n.m.r. spectrum consisting of two one-proton singlets, four one-proton doublets, and two one-proton triplets. Thus the compound was evidently the pentacyclic heteroaromatic compound (34) rather than the alternative formulation (35).

The regioselectivity of the reactions with 5-aminoindole and 5-aminoindazole was again in keeping with expectations<sup>10</sup> from the Skraup synthesis, 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.

Since in any mechanism for the synthesis the penultimate stage must be a dihydro-compound such as (15) and since the compound (15;  $R = H$ ) had been isolated in one reaction, it was of interest to study the reaction of the hemiacetals (25) with *N*-methylaniline. Reaction of the hemiacetal (25;  $R = H$ ) with *N*-methylaniline gave a product,  $C_{17}H_{14}N_2O$ , in 36% yield. The  $^1H$  n.m.r. spectrum lacked the usual 7-H low-field singlet and a two-proton singlet was present at  $\tau$  6.22. On attempted crystallisation, oxidative demethylation occurred to yield the known aromatic compound (2;  $R^1 = R^2 = H$ ). The product was therefore the dihydro-compound (15;  $R = Me$ ) and its u.v. spectrum was very similar to that of the unstable compound (15;  $R = H$ ) isolated earlier.

The 'hemiacetal method' had now afforded a straightforward and general synthesis of a large variety of polycyclic heteroaromatic compounds in reasonably good yield (Table 3). The regioselectivity of the synthesis is the reverse of that found in the Skraup synthesis with respect to the 'enone component' and is the same as that found in the Skraup synthesis with respect to the aniline component.

thylamine (1 g, 22 mmol) in absolute ethanol (10  $cm^3$ ). The solution was left at  $-5^\circ C$  for 1 h and a suspension of 4-hydroxy-2-quinolone (1.61 g, 10 mmol) in absolute ethanol (50  $cm^3$ ) at  $-5^\circ C$  was added. The reaction mixture was left at  $-5^\circ C$  for 40 h when all of the solid had dissolved. The solvents were removed *in vacuo* at room temperature to yield the Mannich base as a pale yellow solid (1.75 g, 80%), m.p.  $>330^\circ C$ ;  $m/e$  173 ( $M^+ - MeNH_2$ );  $\nu_{max}$  (Nujol) 1655  $cm^{-1}$  (amide);  $\lambda_{max}$  (MeOH) 232, 275, 285, and 325 nm;  $\lambda_{max}$  (OH<sup>-</sup>) 236 and 309 nm;  $\tau$ (NaOD- $D_2O$ ) 2.01 (1 H, d,  $J$  7.5 Hz, 5-H), 2.40–2.90 (3 H, m, ArH), 6.37 (2 H, s,  $CH_2$ ), and 7.68 (3 H, s, NMe). Attempts to purify this compound further led to 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ), identical in all respects with an authentic sample.<sup>5</sup>

*Reaction of the Mannich Base (13;  $R = H$ ) with Aniline.*—The Mannich base (13;  $R = H$ ) (1 g, 4.6 mmol) was heated to  $180^\circ C$  in freshly distilled aniline (10  $cm^3$ ) for 15 h under nitrogen. The solvents were removed *in vacuo* to yield a solid which was dissolved in hot glacial acetic acid and the solution filtered. The insoluble material was 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ) (210 mg, 27%), m.p.  $>330^\circ C$ , identical (i.r.) with an authentic sample<sup>5</sup>. The solvent was removed from the acetic acid solution *in vacuo* and the residue triturated with methanol. The solid residue was purified by sublimation at  $300^\circ C$  *in vacuo*. The product (406 mg, 36%) was dibenzo[*b,h*]-[1,6]naphthyridin-6(5*H*)-one (2;  $R^1 = R^2 = H$ ), m.p. 326–328  $^\circ C$  (lit.,<sup>5</sup> 329–330  $^\circ C$ ), identical ( $^1H$  n.m.r., i.r., and u.v. spectra) with an authentic sample.<sup>5</sup> When chloroform was added to the methanol used in trituration, a very small amount of a compound,  $\lambda_{max}$  (MeOH) 233, 258, 334, and 354 nm, was obtained. This quickly oxidised to the dibenzonaphthyridone (2;  $R^1 = R^2 = H$ ) and was concluded to be 7,12-dihydrodibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (15;  $R = H$ ).

*Reaction of the Mannich Base (13;  $R = H$ ) with *o*-Phenylenediamine.*—The Mannich base (13;  $R = H$ ) (1 g, 4.6 mmol) and *o*-phenylenediamine (1.5 g, 13.8 mmol) were heated to  $250^\circ C$  in diphenyl ether (10  $cm^3$ ) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown solid which was dissolved in hot dimethyl sulphoxide and the solution filtered. The insoluble material was 3,3'-

methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ) (92 mg, 12%) identical (i.r. spectrum) with an authentic sample.<sup>5</sup> The solvent was removed from the dimethyl sulphoxide solution and the residue was sublimed at 300 °C *in vacuo* to afford 11-aminodibenzo[b,h][1,6]naphthyridin-6(5H)-one (16;  $R^1 = H$ ,  $R^2 = NH_2$ ) (345 mg, 29%), m.p. >330 °C (Found: C, 73.4; H, 4.7; N, 15.8.  $C_{16}H_{11}N_3O$  requires C, 73.6; H, 4.2; N, 16.1%);  $m/e$  261 ( $M^+$ );  $\nu_{max.}$  (Nujol) 3 400, 3 300 (NH), and 1 660  $cm^{-1}$  (amide);  $\lambda_{max.}$  (MeOH) 222, 294, 336sh, and 386 nm (log  $\epsilon$  4.68, 4.58, 3.81, and 3.54);  $\lambda_{max.}$  ( $H^+$ ) 230, 252, 277, 293, and 370 nm (log  $\epsilon$  4.45, 4.21, 4.54, 4.26, and 3.42);  $\tau$ ( $[^2H_6]$ DMSO) 0.94 (1 H, s, 7-H), 1.02 (1 H, dd,  $J$  8 and 2 Hz, 1-H), and 2.4—3.04 (6 H, m, ArH).

11-Acetylamino-dibenzo[b,h][1,6]naphthyridin-6(5H)-one (16,  $R^1 = H$ ,  $R^2 = NHAc$ ).—11-Aminodibenzo[b,h][1,6]naphthyridin-6(5H)-one (16;  $R^1 = H$ ,  $R^2 = NH_2$ ) (7 mg, 0.027 mmol) was added to dry pyridine (5  $cm^3$ ) and acetic anhydride (3  $cm^3$ ) and the reaction was stirred overnight at room temperature. The solvents were removed *in vacuo* to yield a yellow powder, pure by t.l.c. (6 mg, 73%), which was taken to be 11-acetylamino-dibenzo[b,h][1,6]naphthyridin-6(5H)-one (16;  $R^1 = H$ ,  $R^2 = NHAc$ ); m.p. >330 °C;  $m/e$  303 ( $M^+$ );  $\nu_{max.}$  (Nujol) 3 400, 3 300 (NH), and 1 650  $cm^{-1}$  (amide);  $\lambda_{max.}$  (MeOH) 222, 294, 336sh, and 386 nm;  $\lambda_{max.}$  ( $H^+$ ) 230, 252, 277, 293, 338, and 370 nm;  $\tau$ ( $[^2H_6]$ -DMSO, CAT on aromatics only) 0.74 (1 H, s, 7-H), 0.92 (1 H, d,  $J$  8 Hz, 1-H), 1.25 (1 H, d,  $J$  8 Hz, 10-H), and 2.0—2.7 (5 H, m, ArH).

Reaction of the Mannich Base (13;  $R = H$ ) with *o*-Anisidine.—The Mannich base (13;  $R = H$ ) (221 mg, 1 mmol) was heated to reflux in *o*-anisidine (6  $cm^3$ ) for 15 h under nitrogen. The excess of solvent was removed *in vacuo* to yield a brown solid which was dissolved in glacial acetic acid and the solution filtered. The insoluble material was 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ) (17 mg, 10%), identical (i.r. spectrum) with an authentic sample.<sup>5</sup> The solvent was removed *in vacuo* from the acetic acid-soluble material and the residue was triturated with diethyl ether-ethanol to yield a yellow powder which sublimed at 300 °C *in vacuo* as yellow needles (72 mg, 26%) of 11-methoxydibenzo[b,h][1,6]naphthyridin-6(5H)-one (16;  $R^1 = H$ ,  $R^2 = OMe$ ); m.p. 313 °C (Found: C, 73.8; H, 4.4; N, 9.95.  $C_{17}H_{12}N_2O_2$  requires C, 73.9; H, 4.4; N, 10.1%);  $m/e$  276 ( $M^+$ );  $\nu_{max.}$  (Nujol) 3 400 (NH) and 1 670  $cm^{-1}$  (amide);  $\lambda_{max.}$  (MeOH) 220, 286, 355, 374, and 394sh nm (log  $\epsilon$  4.70, 4.82, 3.79, 3.77, and 3.58);  $\lambda_{max.}$  ( $H^+$ ) 218, 286, 310, 352, 373, 398sh, and 430 nm (log  $\epsilon$  4.58, 4.64, 4.27, 3.68, 3.65, 3.54, and 3.15);  $\tau$ ( $[^2H_6]$ DMSO) 0.74 (1 H, s, 7-H), 1.20 (1 H, dd,  $J$  7.5 and 1 Hz, 1-H), 2.11—2.72 (5 H, m, ArH), and 5.91 (3 H, s, OMe).

Reaction of the Mannich Base (13;  $R = H$ ) with 2-Aminopyridine.—The Mannich base (13;  $R = H$ ) (400 mg, 1.8 mmol) and 2-aminopyridine (200 mg, 2.1 mmol) were heated to 220 °C in diphenyl ether (10  $cm^3$ ) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown powder which was dissolved in glacial acetic acid and the solution filtered. The insoluble material was 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ) (140 mg, 46%), identical (i.r. spectrum) with an authentic sample.<sup>5</sup> The solvent was removed from the acetic acid solution *in vacuo*, and the residue was sublimed at 200 °C *in vacuo* to yield benzo[h]pyrido[2,3-b][1,6]naphthyridin-6(5H)-one (18) (21 mg, 5%), m.p. 300 °C (decomp.) (Found:  $M^+$ , 247.074 825.  $C_{15}H_9N_3O$  requires  $M$ , 247.074 557);  $\nu_{max.}$

(Nujol) 1 660  $cm^{-1}$  (amide);  $\lambda_{max.}$  (MeOH) 226, 254, and 370 nm (log  $\epsilon$  4.04, 3.89, and 3.82);  $\lambda_{max.}$  ( $OH^-$ ) 284, 324, and 356 nm (log  $\epsilon$  3.67, 3.60, and 3.62);  $\lambda_{max.}$  ( $H^+$ ) 227, 315, and 367 nm (log  $\epsilon$  3.97, 3.53, and 3.44);  $\tau$ ( $[^2H_6]$ DMSO) 1.18 (1 H, s, 7-H), 1.16 (1 H, d,  $J$  8 Hz, 1-H), 1.53 (1 H, d, 10-H), and 1.93—2.9 (m, ArH).

Reaction of the Mannich Base (13;  $R = H$ ) with 3-Aminopyridine.—The Mannich base (13;  $R = H$ ) (400 mg, 1.8 mmol) and 3-aminopyridine (200 mg, 2.1 mmol) were heated to 250 °C in diphenyl ether (10  $cm^3$ ) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown powder which was dissolved in glacial acetic acid and the solution filtered. The insoluble material was 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ) (173 mg, 56%), identical (i.r. spectrum) with an authentic sample.<sup>5</sup> The solvent was removed *in vacuo* from the acetic acid solution to yield benzo[h]pyrido[3,2-b][1,6]naphthyridin-6(5H)-one (19) (4 mg, 1%); m.p. 305 °C (decomp.) (Found:  $M^+$ , 247.073 610.  $C_{15}H_9N_3O$  requires  $M$ , 247.074 557);  $\nu_{max.}$  (Nujol) 1 650  $cm^{-1}$  (amide);  $\tau$ ( $[^2H_6]$ -DMSO) 0.57 (1 H, s, 7-H), 0.72 (1 H, m, 9-H), 1.21 (1 H, d,  $J$  8 Hz, 1-H), and 2.1—2.7 (m, ArH).

Reaction of the Mannich Base (13;  $R = H$ ) with *m*-Phenylenediamine.—The Mannich base (13;  $R = H$ ) (406 mg, 1.9 mmol) and *m*-phenylenediamine (300 mg, 2.8 mmol) were heated at 250 °C in diphenyl ether (10  $cm^3$ ) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a dark brown solid which was dissolved in hot dimethyl sulphoxide and the solution filtered. The insoluble material was 3,3'-methylenebis-4-hydroxy-2-quinolone (14;  $R^1 = R^2 = H$ ) (37 mg, 12%), identical (i.r. spectrum) with an authentic sample.<sup>5</sup> The solvent was removed *in vacuo* from the dimethyl sulphoxide solution to yield an orange solid which was sublimed *in vacuo*. The product (96 mg, 20%) was a mixture of 8-amino- and 10-amino-dibenzo[b,h][1,6]naphthyridin-6(5H)-one (22 and 21;  $R^1 = H$ ,  $R^2 = NH_2$ ) (Found: C, 73.4; H, 4.3; N, 16.0.  $C_{16}H_{11}N_3O$  requires C, 73.6; H, 4.2; N, 16.1%);  $m/e$  261 ( $M^+$ );  $\lambda_{max.}$  (MeOH) 224, 285, 329sh, and 399 nm;  $\lambda_{max.}$  ( $H^+$ ) 226, 258sh, 281sh, 295, 318sh, and 452 nm;  $\tau$ ( $[^2H_6]$ DMSO) 0.45 and 1.10 [1 H, 2 s, 7-H in (22) and (21)], 1.26 and 1.30 [1 H, 2 d,  $J$  7 Hz, 1-H in (21) and (22)], 2.06 (1 H, d,  $J$  8 Hz), and 2.4—2.9 (m, ArH). The ratio of the 10-amino (21;  $R^1 = H$ ,  $R^2 = NH_2$ ) to the 8-amino (22;  $R^1 = H$ ,  $R^2 = NH_2$ ) was 2 : 1 by integration.

Acetylation of 8- and 10-Aminodibenzo[b,h][1,6]naphthyridin-6(5H)-one (22 and 21;  $R^1 = H$ ,  $R^2 = NH_2$ ).—The mixture of amines from above (23 mg, 0.09 mmol) was dissolved with acetic anhydride (3  $cm^3$ ) in dry pyridine (3  $cm^3$ ) and stirred overnight at room temperature. The solvents were removed *in vacuo* to afford a yellow powder which was purified by sublimation to yield yellow needles (3 mg, 11%), m.p. >330 °C;  $m/e$  303 ( $M^+$ );  $\tau$ ( $[^2H_6]$ DMSO) 0.80 (1 H, s, 7-H), 1.21 (1 H, d,  $J$  8 Hz, 1-H), 1.29 [1 H, s, 11-H in (21)], 1.75, 2.25, and 2.58 (3  $\times$  1 H, 3 d,  $J$  8 Hz, 8-, 9-, and 4-H), 2.43 and 2.64 (2  $\times$  1 H, 2 t,  $J$  8 Hz, 2- and 3-H).

Reaction of 3,3'-Methylenebis-4-hydroxy-1-methyl-2-quinolone (14;  $R^1 = Me$ ,  $R^2 = H$ ) with Aniline.—The bis-quinolone (14;  $R^1 = Me$ ,  $R^2 = H$ )<sup>5</sup> (93 mg, 0.26 mmol) was heated to 250 °C with freshly distilled aniline (4 g, 43 mmol) in diphenyl ether (5  $cm^3$ ) for 15 h under nitrogen. The solvents were removed *in vacuo* to yield a yellow solid which was dissolved in glacial acetic acid and the solution filtered. The solvent was removed *in vacuo* from the

filtrate and the residue recrystallised from acetone as yellow needles (20 mg, 30%), m.p. 223—224 °C (lit.,<sup>5</sup> 218 °C), identical (i.r. and u.v. spectra and mixed m.p.) with an authentic sample of 5-methyldibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (3).<sup>5</sup>

*Reaction of 3,3'-Methylenebis-4-hydroxy-8-methoxy-2-quinolone (14; R<sup>1</sup> = H, R<sup>2</sup> = OMe) with o-Anisidine.*—The bisquinolone (14; R<sup>1</sup> = H, R<sup>2</sup> = OMe)<sup>5</sup> (80 mg, 0.2 mmol) was heated to 200 °C in freshly distilled *o*-anisidine (3 g) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown solid which was triturated with methanol. The insoluble material was filtered off and sublimed at 250 °C *in vacuo* to yield yellow needles (20 mg, 32%) of 4,11-dimethoxydibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (2; R<sup>1</sup> = OMe, R<sup>2</sup> = H), m.p. 275—276 °C (lit.,<sup>5</sup> 271—273 °C), identical (i.r., <sup>1</sup>H n.m.r., and u.v. spectra) with an authentic sample.

*Reaction of Dihydroflindersine (5; R = H) with Aniline.*—Dihydroflindersine (5; R = H)<sup>12</sup> (28 mg, 0.12 mmol) was suspended in freshly distilled aniline (5 g) and heated at reflux for 15 h under nitrogen. The aniline was removed *in vacuo* to yield a yellow solid which sublimed at 250 °C *in vacuo* as yellow needles (23 mg, 77%) of dibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (2; R<sup>1</sup> = R<sup>2</sup> = H), m.p. 328—330 °C (lit.,<sup>5</sup> 329—330 °C), identical (i.r., u.v., and n.m.r. spectra, and mixed m.p.) with an authentic sample.

*Reaction of Dihydroflindersine (5; R = H) with o-Phenylenediamine.*—Dihydroflindersine (5; R = H)<sup>12</sup> (123 mg, 0.53 mmol) and *o*-phenylenediamine (80 mg, 0.74 mmol) were heated to 250 °C in diphenyl ether (10 cm<sup>3</sup>) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield an orange solid which was purified by sublimation *in vacuo*. The product (99 mg, 71%), m.p. >330 °C had i.r., u.v., and <sup>1</sup>H n.m.r. spectra identical with those of an authentic sample of 11-aminodibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (16; R<sup>1</sup> = H, R<sup>2</sup> = NH<sub>2</sub>) prepared as above.

*3,4-Dihydro-2-hydroxy-2-methyl-2H-pyrano[3,2-*c*]quinolin-5(6*H*)-one (25; R = H).*—Methyl iodide (5.7 g, 40 mmol) was added to a solution of 1-(diethylamino)butan-3-one<sup>13</sup> (5.7 g, 40 mmol) in redistilled dry ethanol (20 cm<sup>3</sup>). This solution was added dropwise over 30 min to a solution of 4-hydroxy-2-quinolone (3.2 g, 20 mmol) and potassium hydroxide (2.2 g, 39 mmol) in dry redistilled ethanol (50 cm<sup>3</sup>) with stirring at room temperature under nitrogen. The reaction was heated under reflux for 30 min when a precipitate appeared. Water (30 cm<sup>3</sup>) was added whereupon the precipitate dissolved. Cold 3*N*-hydrochloric acid was added dropwise until the solution was neutral to litmus. The precipitate was filtered, washed with water, and recrystallised from acetone as white needles (3.35 g, 73%), m.p. 190—191 °C (Found: C, 67.5; H, 5.8; N, 6.2. C<sub>13</sub>H<sub>13</sub>NO<sub>3</sub> requires C, 67.5; H, 5.7; N, 6.1%), *m/e* 231 (*M*<sup>+</sup>);  $\nu_{\max}$  (Nujol) 3 200br (OH) and 1 640 cm<sup>-1</sup> (amide);  $\lambda_{\max}$  (MeOH) 225, 260, 273, 283, 314, and 324 nm (log  $\epsilon$  4.66, 3.90, 3.90, 3.93, 4.10, and 3.85);  $\lambda_{\max}$  (OH<sup>-</sup>) 226, 250sh, and 310 nm (log  $\epsilon$  4.56, 4.20, and 4.16);  $\tau$ (CF<sub>3</sub>CO<sub>2</sub>H) 1.64 (1 H, d, *J* 8 Hz, 10-H), 2.0—2.42 (3 H, m, ArH), 6.87 (4 H, br s, CH<sub>2</sub>CH<sub>2</sub>), and 7.64 (3 H, s, Me).

*3,4-Dihydro-2-hydroxy-2,6-dimethyl-2H-pyrano[3,2-*c*]quinolin-5(6*H*)-one (25; R = Me)* was made using the method above with 4-hydroxy-1-methyl-2-quinolone (3.2 g). The product (25; R = Me) was obtained as white needles from acetone (3.1 g, 69%); m.p. 80—81 °C (Found: C, 68.3; H, 6.35; N, 5.6. C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub> requires C, 68.6; H, 6.1; N, 5.7%); *m/e* 245 (*M*<sup>+</sup>);  $\nu_{\max}$  (Nujol) 3 480 (OH) and

1 640 cm<sup>-1</sup> (amide);  $\lambda_{\max}$  (MeOH) 226, 262sh, 276, 287, 317, and 330sh nm (log  $\epsilon$  4.70, 3.92, 3.89, 3.93, 4.05, and 3.91);  $\lambda_{\max}$  (OH<sup>-</sup>) 218, 256sh, and 312 nm (log  $\epsilon$  4.84, 4.29 and 4.29);  $\tau$ (CDCl<sub>3</sub>) 0.45 (1 H, s, OH, exchangeable in D<sub>2</sub>O), 1.89 (1 H, d, *J* 8 Hz, 10-H), 2.36—2.84 (3 H, m, ArH), 6.32 (3 H, s, NMe), 7.08 (4 H, m, CH<sub>2</sub>CH<sub>2</sub>), and 7.82 (3 H, s, CMe).

*Reaction of the Hemiacetal (25; R = H) with Aniline.*—The apparatus was washed well and kept free of acetone. The reaction mixture was flushed with nitrogen and the effluent passed through a trap containing 2,4-dinitrophenylhydrazine solution.<sup>14</sup> The hemiacetal (25; R = H) (48 mg, 0.2 mmol) was dissolved in freshly distilled aniline (7 g) and flushed with nitrogen for 4 h. No precipitate appeared in the trap. The mixture was heated at 180 °C for 15 h under nitrogen to afford crystals of acetone 2,4-dinitrophenylhydrazone, m.p. 126—127 °C (lit.,<sup>15</sup> 128 °C), identical (i.r. spectrum) with an authentic sample. The solvent was removed *in vacuo* from the reaction mixture to yield a yellow solid which was washed well with methanol, dried *in vacuo*, and purified by sublimation. The product (39 mg, 76%) was identical (i.r., u.v., and <sup>1</sup>H n.m.r. spectra, and mixed m.p.) with an authentic sample of dibenzo[*b,h*]-[1,6]naphthyridin-6(5*H*)-one (2; R<sup>1</sup> = R<sup>2</sup> = H).

*Reaction of the Hemiacetal (25; R = Me) with Aniline.*—The hemiacetal (25; R = Me) (228 mg, 0.9 mmol) was heated to reflux in aniline (7 g) for 15 h under nitrogen. The solvent was removed *in vacuo* to give a solid which was recrystallised from methanol as yellow needles (193 mg, 80%) of 5-methyldibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (3), m.p. 223—224 °C (lit.,<sup>5</sup> 224—225 °C), identical (i.r., u.v. and <sup>1</sup>H n.m.r. spectra) with an authentic sample.

*Reaction of the Hemiacetal (25; R = H) with o-Anisidine.*—The hemiacetal (25; R = H) (115 mg, 0.5 mmol) was heated to reflux in freshly distilled *o*-anisidine (6 g) for 15 h under nitrogen. The solvent was removed *in vacuo* to give an orange powder which sublimed at 200 °C *in vacuo* as yellow needles (88 mg, 64%) of 11-methoxydibenzo[*b,h*]-[1,6]naphthyridin-6(5*H*)-one (16; R<sup>1</sup> = H, R<sup>2</sup> = OMe), m.p. 312—314 °C, identical (i.r., u.v., and n.m.r. spectra) with an authentic sample.

*Reaction of the Hemiacetal (25; R = Me) with o-Anisidine.*—The hemiacetal (25; R = Me) (303 mg, 1.2 mmol) was heated to reflux in freshly distilled *o*-anisidine (6 g) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a solid which crystallised from acetone as yellow needles (216 mg, 60%) of 11-methoxy-5-methyldibenzo[*b,h*]-[1,6]naphthyridin-6(5*H*)-one (16; R<sup>1</sup> = Me, R<sup>2</sup> = OMe), m.p. 250—252 °C (Found: C, 74.4; H, 4.8; N, 9.5. C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> requires C, 74.5; H, 4.9; N, 9.65%); *m/e* 290 (*M*<sup>+</sup>);  $\nu_{\max}$  (Nujol) 1 655 cm<sup>-1</sup> (amide);  $\lambda_{\max}$  (MeOH) 220, 287, 358, 370, and 398sh nm (log  $\epsilon$  4.57, 4.67, 3.67, 3.59, and 3.33);  $\lambda_{\max}$  (H<sup>+</sup>) 222, 288, 356, 376, 398, and 436 nm (log  $\epsilon$  4.53, 4.63, 3.61, 3.57, 3.37, and 2.76);  $\tau$ (CDCl<sub>3</sub>) 0.68 (1 H, s, 7-H), 0.83 (1 H, dd, *J* 8 and 1 Hz, 1-H), 2.28—2.86 (m, ArH), 5.83 (3 H, s, OMe), and 6.17 (3 H, s, NMe).

*Reaction of the Hemiacetal (25; R = H) with o-Phenylenediamine.*—The hemiacetal (25; R = H) (368 mg, 1.6 mmol) and *o*-phenylenediamine (202 mg, 1.9 mmol) were heated at 250 °C in diphenyl ether (10 cm<sup>3</sup>) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a solid which sublimed *in vacuo* as orange needles (276 mg, 66%) of 11-aminodibenzo[*b,h*][1,6]naphthyridin-6(5*H*)-one (16; R<sup>1</sup> = H, R<sup>2</sup> = NH<sub>2</sub>), identical in all respects with an authentic sample prepared as above.



*Reaction of the Hemiacetal (25; R = Me) with o-Nitroaniline.*—The hemiacetal (25; R = Me) (42 mg, 0.2 mmol) and *o*-nitroaniline (25 mg, 0.2 mmol) were heated to reflux in diphenyl ether (5 cm<sup>3</sup>). The solvent was removed *in vacuo* to yield an oil which on trituration with methanol-diethyl ether gave a brown solid. This sublimed as white needles (24 mg, 77%) of 3,3'-methylenebis-4-hydroxy-1-methyl-2-quinoline (14; R<sup>1</sup> = Me, R<sup>2</sup> = H), m.p. 300–302 °C (lit.,<sup>5</sup> 300–302 °C), identical (i.r. spectrum) with an authentic sample. Preparative t.l.c. of the soluble portion after trituration (SiO<sub>2</sub>; CHCl<sub>3</sub>-MeOH, 9 : 1) gave 2,6-dimethyl-4H-pyrano[3,2-c]quinoline-4,5(6H)-dione (26) (R<sub>F</sub> 0.6) which crystallised from methanol as white needles (7 mg, 17%), m.p. 232 °C (Found: C, 69.3; H, 4.5; N, 6.0%; M<sup>+</sup>, 241.076 227. C<sub>14</sub>H<sub>11</sub>NO<sub>3</sub> requires C, 69.7; H, 4.6; N, 5.8%; M, 241.073 887); ν<sub>max.</sub> (Nujol) 1 670 cm<sup>-1</sup> (C=O); λ<sub>max.</sub> (MeOH) 220, 242sh, 262, 280sh, 308, and 340 nm; τ(CDCl<sub>3</sub>) 1.88 (1 H, d, J 8 Hz, 10-H), 2.29 (1 H, s, 3-H), 2.38–2.8 (3 H, m, ArH), 6.24 (3 H, s, NMe), and 7.42 (3 H, s, CMe).

*Reaction of the Hemiacetal (25; R = H) with m-Anisidine.*—The hemiacetal (25; R = H) (86 mg, 0.4 mmol) was heated to reflux in freshly distilled *m*-anisidine (7 g) for 15 h under nitrogen. The solvent was removed *in vacuo* and the residual solid was washed with diethyl ether and sublimed at 290 °C *in vacuo* to yield yellow needles (49 mg, 48%) of a mixture of 8- and 10-methoxydibenzo[b,h][1,6]naphthyridin-6(5H)-one (22 and 21; R<sup>1</sup> = H, R<sup>2</sup> = OMe), m.p. 312 °C (Found: C, 73.6; H, 4.6; N, 10.2. C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> requires C, 73.9; H, 4.4; N, 10.1%; m/e 276 (M<sup>+</sup>); λ<sub>max.</sub> (MeOH) 220, 276, 288sh, 322, 348, and 365 nm; λ<sub>max.</sub> (H<sup>+</sup>) 228, 279sh, 284, 306, and 404 nm; τ([<sup>2</sup>H<sub>6</sub>]DMSO) 0.57 [s, 7-H in (22)], 0.78 [s, 7-H in (21)], 1.22 (1 H, d, J 8 Hz, 1-H), 1.80 (1 H, d, J 8 Hz, ArH), 2.06–2.90 (m, ArH), and 5.91 and 5.97 (3 H, 2 s, OMe). The ratio (21; R<sup>1</sup> = H, R<sup>2</sup> = OMe): (22; R<sup>1</sup> = H, R<sup>2</sup> = OMe) was 2.5 : 1 (by integration of n.m.r. signals).

*Reaction of the Hemiacetal (25; R = Me) with m-Anisidine.*—The hemiacetal (25; R = Me) (54 mg, 0.2 mmol) was heated to reflux in freshly distilled *m*-anisidine (9 g) for 15 h under nitrogen. The solvent was removed *in vacuo* and the residue was triturated with diethyl ether to give a yellow solid. This was purified by preparative t.l.c. (SiO<sub>2</sub>; CHCl<sub>3</sub>-MeOH, 9 : 1) and the fraction of R<sub>F</sub> 0.5 was sublimed at 180 °C *in vacuo* yielding as yellow needles (36 mg, 56%) a mixture of 8- and 10-methoxy-5-methylidibenzo[b,h][1,6]naphthyridin-6(5H)-one (22 and 21; R<sup>1</sup> = Me, R<sup>2</sup> = OMe), m.p. 209–211 °C (Found: C, 74.7; H, 4.8; N, 9.45. C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> requires C, 74.5; H, 4.9; N, 9.7%; m/e 290 (M<sup>+</sup>); λ<sub>max.</sub> (MeOH) 220, 280, 288sh, 322, 349, and 366 nm; λ<sub>max.</sub> (H<sup>+</sup>) 228, 269sh, 287, 307, 348, and 401 nm; τ([<sup>2</sup>H<sub>6</sub>]DMSO) 0.53 [s, 7-H in (22)], 0.72 [s, 7-H in (21)], 1.04 (1 H, d, J 8 Hz, 1-H), 1.76 [d, J 8 Hz, 8-H or 9-H in (21)], 2.05–2.86 (m, ArH), 5.90 and 5.97 (3 H, 2 s, OMe), and 6.25 (3 H, s, NMe). The ratio (21; R<sup>1</sup> = Me, R<sup>2</sup> = OMe): (22; R<sup>1</sup> = Me, R<sup>2</sup> = OMe) was 1.7 : 1 (by integration).

*Reaction of the Hemiacetal (25; R = Me) with 3-Aminopyrazole.*—The hemiacetal (25; R = Me) (36 mg, 0.15 mmol) and 3-aminopyrazole (28 mg, 0.34 mmol) were heated to reflux in diphenyl ether (5 cm<sup>3</sup>) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a yellow solid which sublimed at 270 °C *in vacuo* as yellow needles (31 mg, 84%) of 5-methylbenzo[h]pyrazolo[5,4-b][1,6]naphthyridin-6(5H)-one (29), m.p. 322 °C (Found: C, 67.3; H, 4.2; N,

22.7. C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O requires C, 67.2; H, 4.0; N, 22.4%); m/e 250 (M<sup>+</sup>); ν<sub>max.</sub> (Nujol) 1 640 cm<sup>-1</sup> (amide); λ<sub>max.</sub> (MeOH) 229, 251, 277, and 323 nm (log ε 4.49, 4.25, 4.11, and 3.81); λ<sub>max.</sub> (H<sup>+</sup>) 222sh, 228, 252, 276, 326, and 350sh nm (log ε 4.57, 4.67, 4.56, 4.49, 4.11, and 3.93); τ(CF<sub>3</sub>CO<sub>2</sub>H) 0.79 (1 H, s, 7-H), 1.25 (1 H, d, J 8 Hz, 1-H), 1.88 (1 H, t, ArH), 1.96 (1 H, s, 8-H), 2.1–2.34 (2 H, m, ArH), and 6.0 (3 H, s, NMe).

*Reaction of the Hemiacetal (25; R = Me) with 5-Aminoisoquinoline.*—The hemiacetal (25; R = Me) (39 mg, 0.16 mmol) and 5-aminoisoquinoline (30 mg, 0.2 mmol) were heated to 250 °C in diphenyl ether (6 cm<sup>3</sup>) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a solid which was purified by preparative t.l.c. (SiO<sub>2</sub>; CHCl<sub>3</sub>-MeOH 9 : 1). The most polar compound (3 mg, 10%) was 3,3'-methylenebis-4-hydroxy-1-methyl-2-quinolone (14; R<sup>1</sup> = Me, R<sup>2</sup> = H), m.p. 300–302 °C (lit.,<sup>5</sup> 300–302 °C), identical (i.r. spectrum) with an authentic sample.<sup>5</sup> A compound with R<sub>F</sub> 0.5 crystallised from ethanol as pale yellow needles (23 mg, 46%) of 5-methylbenzo[h]isoquinolino[5,6-b][1,6]naphthyridin-6(5H)-one (30), m.p. 305 °C (Found: C, 77.3; H, 4.4; N, 13.45. C<sub>20</sub>H<sub>13</sub>N<sub>3</sub>O requires C, 77.2; H, 4.2; N, 13.5%); m/e 311 (M<sup>+</sup>); ν<sub>max.</sub> (Nujol) 1 650 cm<sup>-1</sup> (amide); λ<sub>max.</sub> (MeOH) 228, 260, 270, 287, 295sh, 379, and 399 nm (log ε 4.70, 4.80, 4.80, 4.79, 4.77, 3.67, and 3.66); λ<sub>max.</sub> (H<sup>+</sup>) 230, 278, 335sh, 400, and 415 nm (log ε 4.67, 4.85, 4.07, 3.19, and 3.19); τ(CDCl<sub>3</sub>) 0.73 (1 H, s, 7-H), 0.78 (1 H, s, 10-H), 0.85 (1 H, d, J 8 Hz, 12-H), 1.13 (1 H, d, J 9 Hz, 1-H), 2.15–2.67 (m, ArH), and 6.20 (3 H, s, NMe). A third product, R<sub>F</sub> 0.6, crystallised from methanol as white needles (3 mg, 8%), m.p. 232 °C, and had identical spectra to the compound which had been assumed to be 2,6-dimethyl-4H-pyrano[3,2-c]quinoline-4,5(6H)-dione (26).

*Reaction of the Hemiacetal (25; R = Me) with 9-Amino-phenanthrene.*—The hemiacetal (25; R = Me) (48 mg, 0.2 mmol) and 9-aminophenanthrene (40 mg, 0.2 mmol) were heated to 250 °C in diphenyl ether (10 cm<sup>3</sup>) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a yellow powder which was purified by preparative t.l.c. (SiO<sub>2</sub>; CHCl<sub>3</sub>-MeOH, 9 : 1). The more polar compound crystallised from methanol as white needles (5 mg, 14%) of 3,3'-methylenebis-4-hydroxy-1-methyl-2-quinolone (14; R<sup>1</sup> = Me, R<sup>2</sup> = H), m.p. 299–300 °C (lit.,<sup>5</sup> 300–302 °C); identical (i.r. spectrum) with an authentic sample.<sup>5</sup> A second compound was recrystallised from ethanol as yellow needles (20 mg, 29%) of 5-methylbenzo[h]phenanthro[9,10-b][1,6]naphthyridin-6(5H)-one (31), m.p. >330 °C (Found: C, 82.8; H, 4.6; N, 7.8. C<sub>22</sub>H<sub>16</sub>N<sub>2</sub>O requires C, 83.3; H, 4.5; N, 7.8%); m/e 360 (M<sup>+</sup>); ν<sub>max.</sub> (Nujol) 1 652 cm<sup>-1</sup> (amide); λ<sub>max.</sub> (MeOH) 240, 266, 273, 305, 348, 365, and 382 nm (log ε 3.99, 4.05, 4.06, 3.86, 3.36, 3.26, and 3.11); λ<sub>max.</sub> (H<sup>+</sup>) 232, 265, 273, 304, 365, and 382 nm (log ε 4.13, 4.04, 4.04, 3.83, 3.26, and 3.07); τ(CF<sub>3</sub>CO<sub>2</sub>H) 0.94–1.26 (5 H, m, ArH), 1.82–2.28 (8 H, m, ArH), and 5.91 (3 H, s, NMe).

*Reaction of the Hemiacetal (25; R = Me) with 5-Aminoindole.*—The hemiacetal (25; R = Me) (42 mg, 0.17 mmol) and 5-aminoindole (22 mg, 0.17 mmol) were heated at 250 °C in diphenyl ether (5 cm<sup>3</sup>) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown solid which was purified by sublimation at 340 °C *in vacuo*. The resultant yellow powder (37 mg, 73%) was 5-methylbenzo[h]indolo[5,6-b][1,6]naphthyridin-6(5H)-one (32), m.p. >330 °C (Found: C, 76.3; H, 4.5; N, 13.8. C<sub>19</sub>H<sub>13</sub>N<sub>3</sub>O

requires C, 76.25; H, 4.4; N, 14.05%);  $m/e$  299 ( $M^+$ );  $\nu_{\max.}$  (Nujol) 1640  $\text{cm}^{-1}$ ;  $\lambda_{\max.}$  (MeOH) 230, 302, and 380 nm ( $\log \epsilon$  4.65, 4.69, and 4.04);  $\lambda_{\max.}$  ( $\text{H}^+$ ) 230, 300, 330, and 425 nm ( $\log \epsilon$  4.84, 4.67, 4.75, and 4.34);  $\tau$  ( $[\text{H}_6]$ -DMSO; 220 MHz) 0.45 (1 H, s, 7-H), 1.02 (1 H, d,  $J$  8 Hz, 1-H), 1.92, 2.13, and 2.38 ( $3 \times 1$  H, 3 d,  $J$  8 Hz, 4-, 10- and 11-H); 2.36 and 2.55 ( $2 \times 1$  H, 2 t,  $J$  8 Hz, 2- and 3-H), 2.40 and 2.63 ( $2 \times 1$  H, 2 s, 8- and 12-H), and 6.21 (3 H, s, NMe).

**Reaction of the Hemiacetal (25; R = Me) with 5-Aminoindazole.**—The hemiacetal (25; R = Me) (38 mg, 0.16 mmol) and 5-aminoindazole (20 mg, 0.15 mmol) were heated to reflux in diphenyl ether (5  $\text{cm}^3$ ) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a brown solid which sublimed at 380 °C *in vacuo* as yellow needles (33 mg, 71%) of 5-methylbenzo[h]indazolo[5,4-b][1,6]naphthyridin-6(5H)-one (34), m.p. >330 °C (Found: C, 71.65; H, 4.17; N, 18.75%.  $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}$  requires C, 72.0; H, 4.0; N, 18.7%);  $m/e$  300 ( $M^+$ );  $\nu_{\max.}$  (Nujol) 1630  $\text{cm}^{-1}$  (amide);  $\lambda_{\max.}$  (MeOH) 226, 246sh, 283, 312sh, 368, and 384sh nm ( $\log \epsilon$  4.46, 4.26, 4.59, 4.12, 3.73, and 3.62);  $\lambda_{\max.}$  ( $\text{H}^+$ ) 230, 254sh, 297, 322sh, 388, and 412 nm ( $\log \epsilon$  4.62, 4.35, 4.51, 4.35, 4.06, and 4.05);  $\tau$  ( $[\text{H}_6]$ -DMSO; 220 MHz) 0.40 (1 H, s, 7-H), 1.06 (1 H, s, 8-H), 1.08 (1 H, d,  $J$  8 Hz, 1-H), 1.88, 2.02, and 2.39 ( $3 \times 1$  H, 3 d,  $J$  8 Hz, 4-, 11-, and 12-H), 2.31 and 2.58 ( $2 \times 1$  H, 2 t,  $J$  8 Hz, 2- and 3-H), and 6.24 (3 H, s, NMe).

**Reaction of the Hemiacetal (25; R = H) with N-Methylaniline.**—The hemiacetal (25; R = H) (111 mg, 0.48 mmol) was heated to 190 °C in redistilled N-methylaniline [containing <0.45% aniline (g.l.c.)] (7  $\text{cm}^3$ ) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a red powder which sublimed *in vacuo* as white crystals (45 mg, 36%) of 12-methyl-7,12-dihydrodibenzo[b,h][1,6]naphthyridin-6(5H)-one (15; R = Me), m.p. 250 °C (Found:

$M^+$ , 262.109 153.  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$  requires  $M$ , 262.110 67);  $\nu_{\max.}$  (Nujol) 1640  $\text{cm}^{-1}$  (amide);  $\lambda_{\max.}$  (MeOH) 233, 258, 334, and 356sh nm ( $\log \epsilon$  4.78, 4.50, 4.17, and 4.06);  $\tau$  ( $[\text{H}_6]$ -DMSO) 2.09 (1 H, d,  $J$  8 Hz, 1-H), 2.52–3.03 (7 H, m, ArH), 6.22 (2 H, s,  $\text{CH}_2$ ), and 6.36 (3 H, s, NMe).

We thank Dr. R. Galt, I.C.I. Pharmaceuticals Division for helpful discussions, Mr. and Mrs. A. G. Olney for the microanalyses, and Mr. A. Greenway for the mass spectra. One of us (J. L. A.) thanks the S.R.C. for a studentship.

[9/803 Received, 23rd May, 1979]

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