Synthesis of Benzonaphthyridines

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A large number of benzonaphthyridines have been synthesized from *o*-aminoformylquinolines substituted on the pyridine ring by use of the Friedlander cyclization.

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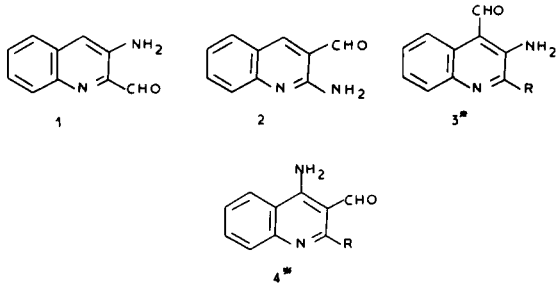
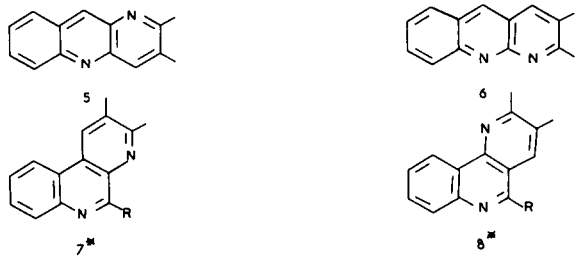
In an earlier report (1) we described the synthesis of *o*-aminoformylquinolines substituted on the pyridine ring. These compounds allowed us to prepare a large number of benzonaphthyridines by use of the Friedlander synthesis.

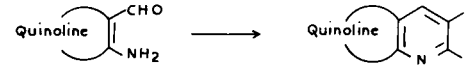


In this series three benzo[*f*][1,7]naphthyridines have been already synthesized using the Borsch modification of the Friedlander method (2) (3).

As part of studies on nitrogen-containing heterocyclic compounds we described, in a brief report, the synthesis of some benzo[*f*][1,7]naphthyridines (**7**) and benzo[*b*][1,6]-naphthyridines (**8**) (4). We now report the details of a general synthesis of benzo[*b*][1,5]naphthyridines (**5**), benzo-[*b*][1,8]naphthyridines (**6**), benzo[*f*][1,7]naphthyridines (**7**) and benzo[*h*][1,6]naphthyridines (**8**) (10).

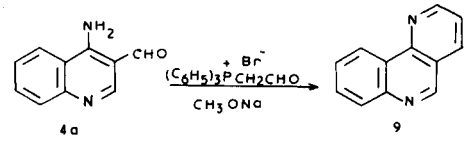


Formation of cyclic structures from *o*-aminoaldehydes is a method of choice for the elaboration of polycondensed materials composed with fused rings and those heteroannelation with *o*-aminoaldehydes have been reviewed recently (5). The Friedlander synthesis, which consists in the reaction of *o*-aminoaldehydes with ketones and aldehydes to provide quinolines, is an important example of heteroannelation. We have used this method to prepare benzonaphthyridine ring systems from *o*-aminoformylquinolines.



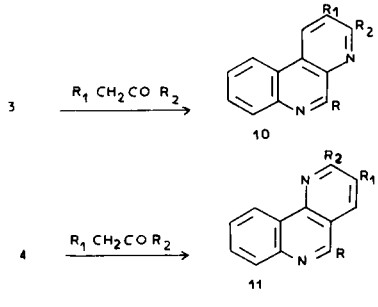
Condensations are generally carried out with basic catalysis (potassium hydroxide, sodium alkoxide, piperidine) in alcoholic solvents. Reactions are controlled by use of vapor chromatography.

An attempt to synthetise unsubstituted heterocycles was made using the Wittig reaction as the first step of a Friedlander cyclisation.



This method has allowed us to prepare little amounts of benzo[*h*][1,6]naphthyridine (**9**) but unfortunately failed for benzo[*f*][1,7]naphthyridine (**7**). The heterocycle **9** has been already prepared from 4-aminoquinoline using other methods with better yields (6) (7).

Friedlander condensation of aminoaldehyde **3** and **4** with ketones and aldehydes R_1-CH_2-CO-R_2 leads to 2, 3, 2,3, 3,5 and 2,3,5-substituted benzo[*f*][1,7]naphthyridines (**10**) and benzo[*h*][1,6]naphthyridines (**11**).



10 and **11**; R, R_1, R_2 = H, H, CH_3; CH_3, H, CH_3; H, CH_3, H; CH_3, CH_3, H; H, CH_3, CH_3; CH_3, CH_3, CH_3.

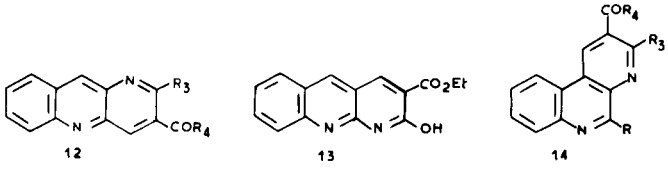
Some benzo[*f*][1,7]naphthyridines have already been prepared using 3-aminoquinoline as starting material. Paudler and Kress (8) reinvestigated these cyclizations which could potentially afford either the linear benzo[*b*]-

[1,5]naphthyridines (**5**) or the angular heterocycle **7**. An nmr study has allowed the authors to propose the condensation products as possessing the angular structure **7**.

This structure assignment is confirmed by the unambiguous Friedlander synthesis of compound **10** (R, R_1, R_2 = H, H, CH_3). This compound was prepared by Paudler and Kress using the Conrad Limpach condensation, mp 101°; nmr (deuteriochloroform/tetramethylsilane): δ ppm 8.48 (H-1), 7.38 (H-2), 9.37 (H-5), 7.57 (H-8, H-9), 8.2 (H-7, H-10), 2.53 (H, CH_3). This compound was prepared from **3a** using the Friedlander method, mp 100°; nmr (deuteriochloroform/tetramethylsilane): δ ppm 8.53 (H-1), 7.43 (H-2), 9.32 (H-5), 7.6 (H-8, H-9), 8.2 (H-7, H-10), 2.67 (H, CH_3), J_{1-2} = 8.5 Hz.

It could be also noted that the condensation of aminoaldehydes **3** and **4** with the unsymmetrical methyl ethyl ketone may lead to two different products. It results in the formation of only 2,3-dimethylbenzonaphthyridines. A small amount of 2-ethyl-5-methylbenzo[*f*][1,7]naphthyridine have been observed but could not be isolated. It is conceivable that small amounts of 2-ethylderivative isomers were also formed in other cases, but remained undetected in the reaction mixture.

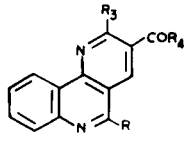
Reactions of compounds **1, 2, 3** and **4** with ketones of type R_3-CO-CH_2-CO-R_4 afford various substituted benzonaphthyridines **12, 13, 14** and **15**.



12 R_3,R_4 : CH_3,CH_3 ; CH_3,OEt.

14 15 R : H, CH_3

R_3,R_4 : CH_3,CH_3 ; CH_3,OEt.



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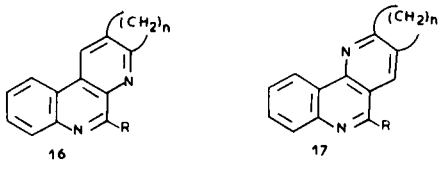
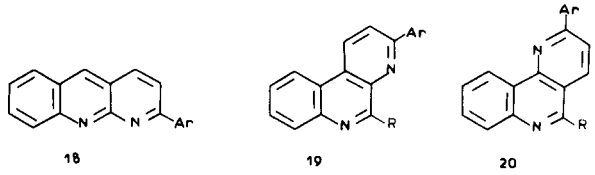
The base catalyzed reactions of aminoaldehydes **3** and **4** with cyclic ketones provides easy and direct access to several fused heterocyclic systems.



16 and 17 n = 3, 4

It can be noted that Baumgarten, *et al.*, have synthesized a similar compound namely, 5,7-diaza-8,9,10,11-tetrahydro-10-methylbenzo[*a*]anthracene using the Borsche synthesis (2) (3).

The reactions with aromatic ketones may also be carried out successfully. Acetyl aromatic ketones are readily transformed into 2-arylbenzonaphthyridines **18, 19, 20**.



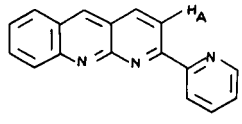
18, Ar = phenyl, pyridyl-2

19, phenyl F = 157°; F (lit) = 156/158.5° (3) pyridyl-2, thienyl-2

20, phenyl, pyridyl-2, thienyl-2

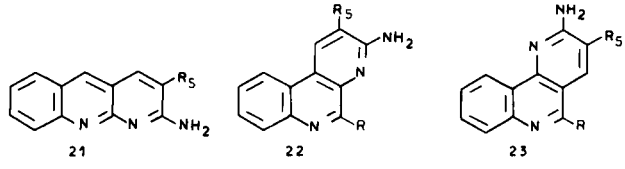
A comparison of nmr spectra of (2-pyridyl)benzonaphthyridine with those of phenylbenzonaphthyridine showed preferential conformations for the former.

A deshielding of H_A (nearly 0.4 ppm) is observed in spectra of pyridyl benzonaphthyridines in comparison with phenylbenzonaphthyridines. Thus, the nmr spectra strongly suggests a planar or near planar preferential conformation where H_A is near the pyridyl *N*-heterocyclic nitrogen atom as shown below in the example:



Such conformations can be readily explained by an electrostatic repulsion between the pyridinic and the naphthyridinic nitrogen atoms.

Condensations carried out with R_5CH_2CN as reagent lead to the aminobenzonaphthiridines **21, 22** and **23**.

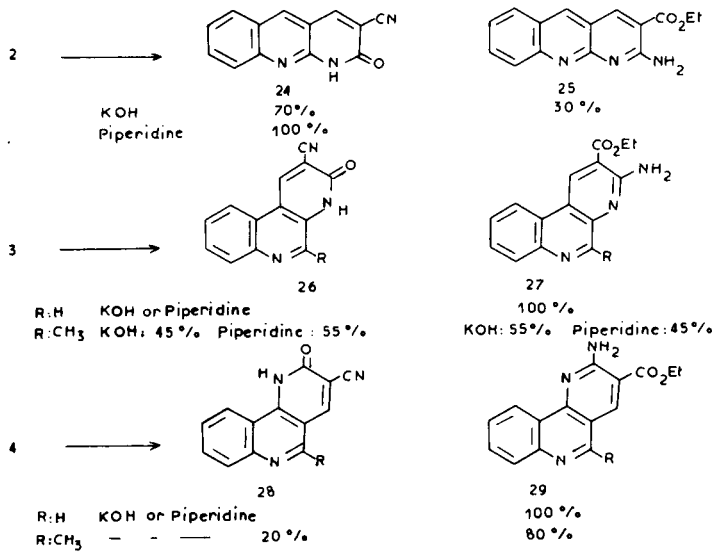


22

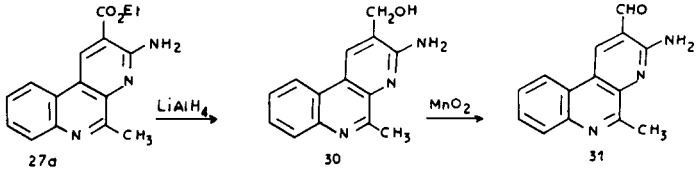
23

R_5 = H, CN; CH_3, CN; H, $CONH_2$; CH_3, $CONH_2$

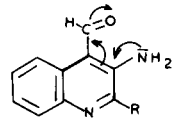
Ethyl cyanoacetate (R_5 = CO_2Et) can be readily condensed with aminoaldehydes **2, 3** and **4** with formation of functionalized benzonaphthyridines. The ring closure involved the ester or the nitrile group as evidenced by the formation of cyanonaphthyridone **24, 26, 28** or aminocarboxylate compounds **25, 27, 29**.



Compounds **27b** allowed us to prepare an aminoaldehyde **31** of the benzonaphthyridine series.



We have synthesized a number of benzonaphthyridines which show potential pharmaceutical properties. The method used, appeared general. It should be noted that syntheses are easier in the angular series **7** and **8** than in the linear series **5** and **6**. This probably results from a relative stability of compounds **3** and **4** compared with those of compounds **1** and **2**. When substituted in the 3 and 4 positions, the CHO and NH_2 groups are well conjugated.



When substituted in the 2 and 3 position CHO and NH_2 groups are less conjugated and more reactive. Thus compounds **1** and **2** can afford side products (*i.e.*, polymers) in the condensation reactions.

EXPERIMENTAL

Benzo[*h*][1,6]naphthyridine (**9**).

A solution of 5.0 g of triphenyl phosphonium bromide acetyldehyde in 40 ml of ethyl alcohol was added to a solution of sodium ethoxide prepared from 0.3 g of sodium and 10 ml of ethyl alcohol. The solution was heated under reflux for 15 minutes. After addition of 1.72 g (0.01 mole) of 4-amino-3-formylquinoline the solution was boiled. After reaction, the solution was concentrated *in vacuo* and the residue steam distil-

Table 1

No. R, R_1, R_2	Mp°	Yield %	Analyses %	NMR Spectra (deuteriochloroform/tetramethylsilane) δ ppm
10 H, H, CH_3	100	30	Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.5; H, 5.2; N, 14.4.	8.53 (d, H-1), 7.43 (d, H-2), 9.32 (s, H-5), 8.20 (m, H-7, H-10), 7.60 (m, H-3, H-9), 2.67 (s, CH_3).
10 CH_3, H, CH_3	115	40	Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.8; H, 5.8; N, 13.3.	8.57 (d, H-1), 7.46 (d, H-2), 8.20 (m, H-7, H-10), 7.63 (m, H-8, H-9), 2.76 and 3.12 (2 s, CH_3).
11 H, H, CH_3	106	50	Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.4; H, 5.2; N, 14.5.	7.31 (d, H-3); 8.03 (d, H-4), 9.13 (s, H-5), 8.16 (m, H-7); 7.71 (m, H-8, H-9), 9.10 (m, H-10), 2.78 (s, CH_3).
11 CH_3, H, CH_3	106	50	Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.4; H, 5.7; N, 13.3.	7.27 (d, H-3), 8.16 (d, H-4), 8.05 (m, H-7), 7.66 (m, H-8, H-9), 9.03 (m, H-10), 2.77 and 2.90 (2 s, CH_3).

Table 2

No. R, R_1, R_2	Mp°	Yield %	Analyses %	NMR Spectra (deuteriochloroform/tetramethylsilane) δ ppm
10 H, CH_3, H	110	20	Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.5; H, 5.2; N, 14.3.	8.50 (d, H-1), 8.82 (d, H-3), 9.42 (s, H-5), 8.18 (m, H-7), 8.42 (m, H-10), 7.70 (m, H-8, H-9), 2.58 (s, CH_3).
10 CH_3, CH_3, H	128	30	Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.6; H, 5.7; N, 13.4.	8.46 (d, H-1), 8.76 (d, H-3), 8.10 (m, H-7), 8.35 (m, H-10), 7.60 (m, H-8, H-9), 2.55 and 3.09 (2 s, CH_3).
11 H, CH_3, H	146 148	40	Calcd. for $C_{13}H_{10}N_2$: C, 80.4; H, 5.2; N, 14.4. Found: C, 80.4; H, 5.1; N, 14.3.	8.95 (d, H-2), 8.01 (d, H-4), 9.18 (s, H-5), 8.20 (m, H-7), 9.08 (m, H-10), 7.74 (m, H-8, H-9), 2.55 (s, CH_3).
11 CH_3, CH_3, H	165	40	Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.6; H, 5.8; N, 13.3.	8.88 (d, H-2), 8.07 (d, H-4), 8.06 (m, H-7), 8.98 (m, H-10), 7.67 (m, H-8, H-9), 2.52 and 2.94 (2 s, CH_3).

led. The aqueous layer was saturated wtih sodium chloride and extracted with chloroform. The organic layer was concentratd *in vacuo* and benzo[*h*][1,6]naphthyridine (**9**) was purified by sublimation, yield 2%, mp 96° [95-96° (6) (7)]; nmr (deuteriochloroform): δ 9.14 (q, H-2), 7.50 (q, H-3), 8.29 (q, H-4), 9.26 (s, H-5), 8.19 (m, H-7), 7.77 (m, H-8, H-9), 9.14 (m, H-10).

Anal. Calcd. for $C_{12}H_8N_2$: C, 80.0; H, 4.5; N, 15.5. Found: C, 80.0; H, 4.5; N, 15.5.

Friedlander Reactions of Aminoformylquinolines (**3**, R = H, CH_3 and **4**, R = H, CH_3) With Acetone.

A solution of 0.005 mole of aminoformylquinoline and 0.1 g of potassium hydroxide in acetone was refluxed. After the reaction, the solution was concentrated *in vacuo*. Benzonaphthyridines were extracted with petroleum ether in continous and recrystallized from petroleum ether.

Reactions of **3** and **4** With Propionic Aldehyde.

A solution of 0.3 g of propionic aldehyde (0.0052 mole) of 0.005 mole of the aminoformylquinoline (**3**, R = H, CH_3 and **4**, R = H, CH_3) and of 0.5 ml of potassium hydroxide (10% in ethyl alcohol) or sodium ethylate (in ethyl alcohol) in 30 ml of ethyl alcohol was boiled. Removal of the solvent after reaction afforded a raw product which was then extracted several times with petroleum ether. The residue was recrystallized from petroleum ether or sublimated.

Condensations With Methyl Ethyl Ketone.

A mixture prepared from 0.005 mole of aminoformylquinoline, (**3**, R = H, CH_3 and **4**, R = H, CH_3), 50 ml of methyl ethyl ketone and 0.5 ml of potassium hydroxide (10% in ethyl alcohol) or sodium ethylate (in ethyl alcohol) was heated under reflux. The solvent was evaporated after reaction and the residue analyzed by nmr. The mixture was extracted in continous with petroleum ether.

Condensation of **1** with Acetylacetone.

Benzo[*b*][1,5]naphthyridine (**12**).

A mixture of 3-amino-2-hydroxymethylquinoline (0.4 g) and 3.2 g of freshly prepared manganous oxide in 10 ml of dry tetrahydrofuran was stirred for ½ hour at 20°. After filtration, the solvent was evaporated (temperature <20°) to give a crude product which contains 3-aminoquinoline-2-carboxaldehyde (**1**).

To a solution of the crude aminoaldehyde obtained in the first step, in 5 ml of ethyl alcohol was added 120 mg of acetyl acetone and a few drops of priperidine. The solution was allowed to stand 24 hours in the dark and the crystals formed were filtered.

Benzo[*f*][1,7]naphthyridine (**14**) and Benzo[*h*][1,6]naphthyridine (**15**).

A solution of 0.55 g of acetyl acetone (0.0055 mole) of 0.005 mole of aminoformylquinoline (**3**, R = H, CH_3, **4**, R = H, CH_3), and 0.5 ml of potassium hydroxide (10% in ethyl alcohol) or sodium ethylate (in ethyl alcohol) in 20 ml of ethyl alcohol was boiled. After reaction, the solvent was evaporated and the residue extracted in continous with petroleum ether. The crude product was purified by recrystallisation or sublimation.

Reactions With Ethyl Acetoacetate.

Benzo[*f*][1,7]naphthyridine (**14**) and Benzo[*h*][1,6]naphthyridine (**15**).

To a solution of 0.005 mole of aminoformylquinoline (**3**, R = H, CH_3, **4**, R = H, CH_3), in 20 ml of ethyl alcohol was added 720 mg of ethyl acetoacetate and a few drops of piperidine. The solution was boiled and, after reaction, the mixture was allowed to stand 24 hours. The precipitate was collected, washed with ether and dried.

Benzo[*b*][1,5]naphthyridine (**12**).

To a solution of 3-aminoquinoline-2-carboxaldehyde (**1**) prepared as described above, in 5 ml of ethyl alcohol was added 180 mg of ethyl acetoacetate and a few drops of piperidine. The mixture was allowed to stand two days in the dark. Crystals were collected and dried.

1-Oxo-1,2-dihydrobenzo[*b*][1,8]naphthyridine (**13**).

A solution of 0.005 mole of 2-amino-3-formylquinoline (**2**), 0.9 g of ethyl malonate and a few drops of piperidine was heated on a steam bath. After reaction, the mixture was allowed to stand 24 hours at 0°. The precipitate was collected, washed with ether, dried, and recrystallized from ethyl alcohol; nmr (dimethyl sulfoxide/hexamethyldisiloxane): δ ppm 8.46 and 8.76 (2 s, H-4, H-5), 7.5 and 7.8 (2 m, H-7, H-8 and H-6, H-9), 1.27 (t, CH_3), 4.27 (q, CH_2).

Reaction of **3** and **4** With Cyclic Ketones.

To a solution of 0.005 mole of aminoformylquinoline (**3**, R = H, CH_3, **4**, R = H, CH_3), in 30 ml of ethyl alcohol was added 0.0055 mole of cyclopentanone or cyclohexanone and 0.5 ml of potassium hydroxide (10% in ethyl alcohol). The solution was boiled and the solvent removed after eaction. The residue was extracted in continous with petroleum ether.

Condensations with Aromatic Ketones.

A solution of 0.005 mole of aminoformylquinoline (**2**, **3**, R = H, CH_3, **4**, R = H, CH_3), of 0.0055 mole of aryl ketone and of 0.5 ml of potassium hydroxide (10% in ethyl alcohol) in ethyl alcohol was boiled. After reaction, the solution is allowed to stand 24 hours. The mixture was evaporated under reduced pressure and the residue extracted with petroleum ether.

Condensation of **3** and **4** With Malononitrile and With Cyanacetamide.

A solution of 0.0055 mole of aminoformylquinoline (**3**, R = H, CH_3, **4**, R = H, CH_3), of 0.0055 mole of malononitrile (or cyanamide) and a few drops of piperidine in 30 ml of ethyl alcohol was boiled. The precipitate which appeared was filtered and washed with ethyl alcohol.

Table 3

No. R, R_1, R_2	Mp°	Yield %	Analyses %	NMR Spectra (deuteriochloroform/tetramethylsilane) δ ppm
10 H, CH_3, CH_3	156	50	Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.8; H, 5.8; N , 13.2	8.47 (s, H-1), 9.37 (s, H-5), 7.68 (m, H-8, H-9), 8.25 (m, H-7, H-10), 2.46 and 2.66 (2 s, CH_3).
10 CH_3, CH_3, CH_3	155	60	Calcd. for $C_{15}H_{14}N_2$: C, 81.0; H, 6.3; N, 12.6. Found: C, 81.1; H, 6.3; N, 12.5.	8.39 (s, H-1), 8.11 (m, H-7), 8.33 (m, H-10), 7.66 (m, H-8, H-9), 2.47, 2.68 and 3.10 (3 s, CH_3).
11 H, CH_3, CH_3	154	56	Calcd. for $C_{14}H_{12}N_2$: C, 80.7; H, 5.8; N, 13.5. Found: C, 80.6; H, 5.7; N, 13.2.	7.80 (s, H-4), 9.08 (s, H-5), 8.15 (m, H-7), 9.08 (m, H-10), 7.75 (m, H-8, H-9), 2.39 and 2.71 (2 s, CH_3).
11 CH_3, CH_3, CH_3	168	40	Calcd. for $C_{15}H_{14}N_2$: C, 81.0; H, 6.3; N, 12.6. Found: C, 81.0; H, 6.5; N, 12.4.	7.78 (s, H-4), 8.01 (m, H-7), 8.96 (m, H-10), 7.67 (m, H-8, H-9), 2.29, 2.64 and 2.83 (3 s, CH_3).

Table 4

No. R_3, R_4	Mp°	Yield %	Analyses %	NMR Spectra (δ ppm) (a) dimethylsulfoxide/hexamethyldisiloxane (b) deuteriochloroform/tetramethylsilane
12 CH_3, CH_3	173	74		8.73 and 8.70 (s, H-4, H-10), 7.80 (m, H-6, H-7, H-8, H-9), 2.47 and 2.90 (2 s, CH_3) (a).
14 CH_3, CH_3 (R = H)	151	30	Calcd. for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.1; N, 11.9. Found: C, 76.0; H, 5.1; N, 11.5.	9.02 (s, H-1), 9.45 (s, H-5), 8.33 (m, H-7, H-10), 7.77 (m, H-8, H-9), 2.78 and 2.93 (2 s, CH_3) (b).
14 CH_3, CH_3 (R = CH_3)	150	60	Calcd. for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2. Found: C, 76.8; H, 5.5; N, 11.0	8.80 (s, H-1), 8.04 (m, H-7), 7.67 (m, H-8, H-9), 8.24 (m, H-10), 2.72, 2.86 and 3.02 (3 s, CH_3) (b).
15 CH_3, CH_3 (R = H)	156	45	Calcd. for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.1; N, 11.9. Found: C, 76.2; H, 5.1; N, 11.8.	8.46 (s, H-4), 9.18 (s, H-5), 8.12 (m, H-7), 7.75 (m, H-8, H-9), 9.08 (m, H-10), 2.73 and 2.98 (2 s, CH_3) (b).
15 CH_3, CH_3 R = CH_3)	150	52	Calcd. for $C_{16}H_{14}N_2O$: C, 76.8; H, 5.6; N, 11.2. Found: C, 76.7; H, 5.5; N, 11.0.	8.46 (s, H-4), 8.03 (m, H-7), 7.70 (m, H-8, H-9), 8.98 (m, H-10), 2.78, 2.93 and 2.97 (3 s, CH_3) (b).

Table 5

No. R_3, R_4	Mp°	Yield %	Analyses %	NMR Spectra (deuteriochloroform/tetramethylsilane) δ ppm
12 CH_3, OEt	110	70	Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.0; H, 5.2; N, 10.3	8.82 and 9.00 (2 s, H-4, H-10), 7.75 (m, H-6, H-7, H-8, H-9), 4.45 (q, CH_2), 1.45 (t, CH_3), 3.02 (s, CH_3).
14 CH_3, OEt (R = H)	124	60	Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.0; H, 5.3; N, 10.2.	9.24 (s, H-1), 9.42 (s, H-5), 8.19 (m, H-7), 7.75 (m, H-8, H-9), 8.43 (m, H-10), 4.50 (q, CH_2), 1.48 (t, CH_3), 3.01 (s, CH_3).
14 CH_3, OEt (R = CH_3)	145	62	Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.8; H, 5.8; N, 10.0. Found: C, 73.0; H, 5.6; N, 10.0.	9.12 (s, H-1), 8.04 (m, H-7), 7.67 (m, H-8, H-9), 8.31 (m, H-10), 4.52 (q, CH_2), 1.58 (s, CH_3), 3.08 and 3.17 (2 s, CH_3).
15 CH_3 OEt (R = H)	146	40	Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 72.1; H, 5.2; N, 10.4.	8.78 (s, H-4), 9.24 (s, H-5), 8.18 (m, H-7), 7.81 (m, H-8, H-9), 9.15 (m, H-10), 4.47 (q, CH_2), 1.46 (t, CH_3), 3.1 (s, CH_3).
15 CH_3, OEt (R = CH_3)	171	35	Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.8; H, 5.8; N, 10.0. Found: C, 72.7; H, 5.7; N, 10.0.	8.91 (s, H-4), 8.04 (m, H-7), 7.72 (m, H-8, H-9), 9.08 (m, H-10), 4.47 (q, CH_2), 1.46 (t, CH_3), 3.01 and 3.08 (2 s, CH_3).

Table 6

No. R, n	Mp°	Yield %	Analyses %	NMR Spectra (dimethyl sulfoxide/hexamethyldisiloxane) δ ppm
16 H, 3	100	75	Calcd. for $C_{15}H_{12}N_2$: C, 81.8; H, 5.5; N, 12.7. Found: C, 81.8; H, 5.2; N, 12.5.	8.82 (s, H-1), 9.23 (s, H-5), 8.12 (m, H-7), 7.73 (m, H-8, H-9), 8.67 (m, H-10), 3.07 and 2.13 [2 m, (4H-2H), CH_2].
16 CH_3, 3	140	75	Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 82.2; H, 6.0; N, 11.4.	8.73 (s, H-1), 7.97 (m, H-7), 7.65 (m, H-8, H-9), 8.54 (m, H-10), 3.0 and 2.1 [2 m, (4H-2H) CH_2].
17 H, 3	143	60	Calcd. for $C_{15}H_{12}N_2$: C, 81.8; H, 5.5; N, 12.7. Found: C, 81.7; H, 5.4; N, 12.6.	8.15 (s, H-4), 9.22 (s, H-5), 8.05 (m, H-7), 7.73 (m, H-8, H-9), 8.93 (m, H-10), 3.02 and 2.1 [2 m, (4H-2H), CH_2].
17 CH_3, 3	168	50	Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 82.3; H, 6.2; N, 12.0.	8.17 (s, H-4), 7.90 (m, H-7), 7.73 (m, H-8, H-9), 8.85 (m, H-10), 2.97 and 2.1 [2 m, (4H-2H), CH_2], 2.81 (s, CH_3).
16 H, 4	112	50	Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 81.9; H, 6.0; N, 11.9.	8.70 (s, H-1), 9.20 (s, H-5), 8.05 (m, H-7), 7.22 (m, H-8, H-9), 8.6 (m, H-10), 2.98 and 1.85 [2 m, (4H-4H), CH_2].
16 CH_3, 4	151	75	Calcd. for $C_{17}H_{16}N_2$: C, 82.2; H, 6.5; N, 11.3. Found: C, 82.5; H, 6.3; N, 11.1.	8.55 (s, H-1), 7.97 (m, H-7), 7.63 (m, H-8, H-9), 8.47 (m, H-10), 3.0 and 1.87 [2 m, (4H-4H), CH_2], 2.9 (s, CH_3).
17 H, 4	170	50	Calcd. for $C_{16}H_{14}N_2$: C, 82.0; H, 6.0; N, 12.0. Found: C, 82.2; H, 6.1; N, 12.1.	8.14 (s, H-4), 9.23 (s, H-5), 8.1 (m, H-7), 7.69 (m, H-8, H-9), 8.97 (m, H-10), 3.0 and 1.9 [2 m, (4H-4H), CH_2].
17 CH_3, 4	170	50	Calcd. for $C_{17}H_{16}N_2$: C, 82.2; H, 6.5; N, 11.3. Found: C, 82.3; H, 6.6; N, 12.0.	8.17 (s, H-4), 8.02 (m, H-7), 7.75 (m, H-8, H-9), 8.93 (m, H-10), 2.97 and 1.9 [2 m, (4H-4H), CH_2], 2.85 (s, CH_3).

Table 7

No. Ar	Mp°	Yield %	Analyses %	H_A	NMR Spectra (δ ppm) (a) dimethylsulfoxide/hexamethyldisiloxane (b) deuteriochloroform/tetramethylsilane
18 Ar = phenyl	219	60	Calcd. for $C_{16}H_{12}N_2$: C, 84.4; H, 4.7; N, 10.9. Found: C, 84.5; H, 5.0; N, 11.0.	7.86	7.86 (d, H-3), 8.62 (s, H-5), 8.33, 7.9 and 7.53 [3 m, (4H-2H-4H), other aromatic protons] (b).
18 Ar = pyridyl-2	201	60	Calcd. for $C_{17}H_{11}N_3$: C, 79.4; H, 4.3; N, 16.3. Found: C, 79.8; H, 4.2; N, 16.2.	8.29	8.29 (d, H-3), 8.64 (d, H-4), 8.65 (s, H-5), 8.95 (m, H'-6), 8.65 (m, H'-3), 7.83 and 7.45 [2 m, (3H-3H) other aromatic protons] (b).
19 R = H Ar = phenyl	157	75	Calcd. for $C_{18}H_{12}N_2$: C, 84.4; H, 4.7; N, 10.9. Found: C, 84.1; H, 4.5; N, 11.0.	8.38	9.17 (d, H-1), 8.38 (d, H-2), 9.4 (s, H-5), 8.2 (m, H-7, H'-2, H'-6), 7.75 (m, H-8, H-9), 8.7 (m, H-10), 7.53 (m, H'-3, H'-4, H'-5) (a)
19 R = CH_3 Ar = phenyl	140	70	Calcd. for $C_{19}H_{14}N_2$: C, 84.4; H, 5.2; N, 10.4. Found: C, 84.3; H, 5.3; N, 10.4.	8.25	9.0 (d, H-1), 8.25 (d, H-2), 7.98 (m, H-7), 7.63 (m, H-8, H-9, H'-3, H'-4, H'-5), 8.58 (m, H-10), 8.2 (m, H'-2, H'-6), 3.0 (s, CH_3) (a).
19 R = H Ar = pyridyl-2	200	55	Calcd. for $C_{17}H_{11}N_3$: C, 79.4; H, 4.3; N, 16.3. Found: C, 79.3; H, 4.2; N, 16.2.	8.74	9.18 (d, H-1), 8.74 (d, H-2), 9.36 (s, H-5), 7.9 (m, H-7, H-8, H-9, H'-4), 8.6 (m, H-10, H'-3, H'-6), 7.45 (m, H'-5) (a).
19 R = CH_3 Ar = pyridyl-2	172	70	Calcd. for $C_{18}H_{13}N_3$: C, 79.7; H, 4.8; N, 15.5. Found: C, 79.9; H, 4.6; N, 15.6.	8.68	9.17 (d, H-1), 8.68 (d, H-2), 7.85 (m, H-7, H-8, H-9, H'-4), 8.6 (m, H-10, H'-3, H'-6), 7.45 (m, H'-5), 3.03 (s, CH_3) (a).
20 R = H Ar = phenyl	141	65	Calcd. for $C_{18}H_{12}N_2$: C, 84.4; H, 4.7; N, 10.9. Found: C, 84.2; H, 4.6; N, 10.9.	8.33	8.33 (d, H-3), 8.66 (d, H-4), 9.4 (s, H-5), 8.08 (m, H-7), 7.83 (m, H-8, H-9), 9.17 (m, H-10), 8.37 (m, H'-2, H'-6), 7.6 (m, H'-3, H'-4, H'-5) (a).
20 R = CH_3 Ar = phenyl	163	60	Calcd. for $C_{19}H_{14}N_2$: C, 84.4; H, 5.2; N, 10.4. Found: C, 84.4; H, 5.2; N, 10.2.	8.17	8.17 (d, H-3), 8.55 (d, H-4), 7.7 (m, H-8, H-9), 9.06 (m, H-10), 8.33 (m, H'-2, H'-6), 7.55 (m, H'-3, H'-4, H'-5), 2.9 (s, CH_3) (a).
20 R = H Ar = pyridyl-2	170	70	Calcd. for $C_{17}H_{11}N_3$: C, 79.4; H, 4.3; N, 16.3. Found: C, 79.2; H, 4.2; N, 16.2	8.72	8.72 (1 s, H-3, H-4), 9.42 (s, H-5), 8.02 (m, H-7, H-8, H-9, H'-4), 9.18 (m, H-10), 8.78 (m, H'-3, H'-6), 7.55 (m, H'-5) (a).
20 R = CH_3 Ar = pyridyl-2	194	80	Calcd. for $C_{18}H_{13}N_3$: C, 79.7; H, 4.8; N, 15.5. Found: C, 79.8; H, 4.8; N, 15.3.	8.68	8.68 (1 s, H-3, H-4), 7.83 (m, H-7, H-8, H-9, H'-4, H'-5), 9.12 (m, H-10), 8.75 (m, H'-3, H'-6), 2.94 (s, CH_3) (a).
19			Calcd. for $C_{16}H_{10}N_2S$: C, 73.3; H, 3.8; N, 10.7.		9.05 (d, H-1), 8.27 (d, H-2), 9.25 (s, H-5), 8.02

R = H Ar = thienyl-2	169	40	Found: C, 73.0; H, 3.6; N, 10.8.	(m, H-7), 7.71 (m, H-8, H-9), 8.62 (m, H-10), 7.94 (q, H'-3), 7.18 (9, H'-4), 7.78 (q, H'-5) (a).
19 R = CH_3 Ar = thienyl-2	164	65	Calcd. for $C_{17}H_{12}N_2S$: C, 73.9; H, 4.4; N, 10.1. Found: C, 74.0; H, 4.2; N, 10.0.	9.07 (d, H-1), 8.30 (d, H-2), 7.95 (m, H-7), 7.71 (m, H-8, H-9), 8.61 (m, H-10), 7.98 (q, H'-3), 7.22 (q, H'-4), 7.72 (q, H'-5), 2.97 (s, CH_3), (a).
20 R = H Ar = thienyl-2	135	65	Calcd. for $C_{16}H_{10}N_2S$: C, 73.3; H, 3.8; N, 10.7. Found: C, 73.1; H, 3.7; N, 10.5.	8.20 (d, H-3), 8.55 (d, H-4), 9.62 (s, H-5), 8.03 (m, H-7), 7.8 (m, H-8, H-9), 9.0 (m, H-10), 8.05 (q, H'-3), 7.23 (q, H'-4), 7.8 (q, H'-5) (a).
20 R = CH_3 Ar = thienyl-2	156	40	Calcd. for $C_{17}H_{12}N_2S$: C, 73.9; H, 4.4; N, 10.1. Found: C, 73.7; H, 4.2; N, 10.0.	8.15 (d, H-3), 8.55 (d, H-4), 7.78 (m, H-7, H-8, H-9), 8.92 (m, H-10), 8.02 (q, H'-3), 7.23 (q, H'-4), 7.79 (q, H'-5), 2.9 (s, CH_3) (a).

Table 8

No. R_5	Mp°	Yield %	Analyses %	NMR Spectra (dimethylsulfoxide/hexamethyldisiloxane) δ ppm
22 H, CN	>300	95	Calcd. for $C_{13}H_8N_4$: C, 70.9; H, 3.7; N, 25.4. Found: C, 70.6; H, 3.7; N, 25.1.	9.5 (s, H-1), 9.05 (s, H-5), 8.03 (m, H-5), 8.03 (m, H-7), 7.7 (m, H-8, H-9), 8.63 (m, H-10), 7.33 (s, NH_2).
22 CH_3, CN	>300	90	Calcd. for $C_{14}H_{10}N_4$: C, 71.8; H, 4.3; N, 23.9. Found: C, 71.5; H, 4.1; N, 23.5.	9.38 (s, H-1), 7.02 (m, H-7), 7.6 (m, H-8, H-9), 8.48 (m, H-10), 7.28 (s, NH_2), 2.82 (s, CH_3).
23 H, CN	>300	95	Calcd. for $C_{13}H_8N_4$: C, 70.9; H, 3.7; N, 25.4. Found: C, 70.6; H, 3.6; N, 25.0.	8.75 (s, H-4), 9.02 (s, H-5), 7.8 (m, H-7, H-8, H-9), 8.83 (m, H-10), 7.43 (s, NH_2).
23 CH_3, CN	>300	90	Calcd. for $C_{14}H_{10}N_4$: C, 71.8; H, 4.3; N, 23.9. Found: C, 71.8; H, 4.5; N, 24.0.	8.67 (s, H-4), 7.66 (m, H-7, H-8, H-9), 8.57 (m, H-10), 2.9 (s, CH_3) (dimethyl sulfoxide + trifluoroacetic acid).
22 H, $CONH_2$	>280	90	Calcd. for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.7; H, 4.1; N, 23.3.	9.31 (s, H-1), 9.02 (s, H-5), 8.03 (m, H-7), 7.67 (m, H-8, H-9), 8.53 (m, H-10).
22 CH_3, $CONH_2$	>280	90	Calcd. for $C_{14}H_{12}N_4O$: C, 66.7; H, 4.8; N, 22.2. Found: C, 66.9; H, 4.8; N, 22.0.	9.30 (s, H-1), 7.91 (m, H-7), 7.5 (m, H-8, H-9), 8.53 (m, H-10), 2.86 (s, CH_3).
23 H, $CONH_2$	>280	95	Calcd. for $C_{13}H_{10}N_4O$: C, 65.5; H, 4.2; N, 23.5. Found: C, 65.4; H, 4.2; N, 23.1.	8.73 (s, H-4), 9.00 (s, H-5), 8.0 (m, NH_2, H-7, H-8, H-9), 8.79 (m, H-10).
23 CH_3, $CONH_2$	>280	85	Calcd. for $C_{14}H_{12}N_4O$: C, 66.7; H, 4.8; N, 22.2. Found: C, 66.5; H, 4.7; N, 22.0.	8.78 (s, H-4), 7.9 (m, NH_2, H-7, H-8, H-9), 8.75 (m, H-10), 2.87 (s, CH_3).

Table 9

No. R, R_1, R_2	Mp°	Analyses %	NMR Spectra (dimethyl sulfoxide/hexamethyldisiloxane) δ ppm
24	>260	Calcd. for $C_{13}H_7N_3O$: C, 70.6; H, 3.2; N, 19.0. Found: C, 70.2; H, 3.0; N, 18.5.	8.83 (s, H-4 or H-5), 8.87 (s, H-5 or H-4), 8.08, 7.88 and 7.57 (m, H-6, H-7, H-8, H-9), 12.63 (OH, NH).
25	—	—	8.92 (s, H-4 or H-5), 8.87 (s, H-5 or H-4), 7.75 (m, H-6, H-7, H-8, H-9), 1.35 (t, CH_3), 4.35 (q, CH_2).
26a	>280	Calcd. for $C_{13}H_7N_3O$: C, 70.6; H, 3.2; N, 19.0. Found: C, 70.3; H, 3.4; N, 18.6.	—
27a	185	Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.3; H, 4.8; N, 15.5.	9.24 (s, H-1), 8.97 (s, H-5), 7.95 (m, H-7), 7.6 (m, H-8, H-9), 8.43 (m, H-10), 7.60 (s, NH_2), 4.4 (q, CH_2), 1.41 (t, CH_3).
26b	>300	Calcd. for $C_{14}H_9N_3O$: C, 71.5; H, 3.9; N, 17.9. Found: C, 71.2; H, 3.7; N, 17.8.	9.48 (s, H-1), 7.87 (m, H-7), 7.54 (m, H-8, H-9), 8.31 (m, H-10), 2.76 (s, CH_3).
27b	180	Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.3; H, 5.4; N, 14.9. Found: C, 68.5; H, 5.4; N, 15.2.	9.15 (s, H-1), 7.87 (m, H-7), 7.53 (m, H-8, H-9), 8.31 (m, H-10), 7.4 (s, NH_2), 4.4 (q, CH_2), 1.42 (t, CH_3), 2.81 (s, CH_3).
29a	242-243	Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.4; H, 4.8; N, 15.6.	8.84 (s, H-4), 9.08 (s, H-5), 7.75 (m, H-7, H-8, H-9, NH_2), 8.73 (m, H-10), 4.38 (q, CH_2), 1.4 (t, CH_3).
29b	257	Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.3; H, 5.4; N, 14.9. Found: C, 68.4; H, 5.3; N, 15.0.	8.84 (s, H-4), 7.66 (m, H-7, H-8, H-9, NH_2), 8.79 (m, H-10), 4.38 (q, CH_2), 1.35 (t, CH_3), 2.81 (s, CH_3).
28b	>300	Calcd. for $C_{14}H_9N_3O$: C, 71.5; H, 3.9; N, 17.9. Found: C, 71.1; H, 3.7; N, 17.7.	

Condensation of **2, 3, 4** With Ethyl Cyanoacetate.

A solution of 0.005 mole of aminoformylquinoline (**2, 3**, R = H, CH_3, **4**, R = H, CH_3), of 0.63 g of ethyl cyanoacetate and of a few drops of piperidine or 0.5 ml of potassium hydroxide (10% in ethyl alcohol) in 30 ml of ethyl alcohol was refluxed. After reaction, the solvent was evaporated and the residue analyzed by nmr or ir analysis. When a mixture of two compounds was obtained they were separated by extraction using the difference of solubility in petroleum ether or in ethyl alcohol.

3-Amino-2-hydroxymethyl-5-methylbenzo[*b*][1,7]naphthyridine (**30**).

To a solution of 1.0 g of **27a** in 100 ml of tetrahydrofuran, was added slowly 0.4 g of lithium aluminium hydride at a temperature lower than 10°. Stirring was continued for 1 hour and a solution of 100 ml of tetrahydrofuran and 1 ml of water was added. Then the precipitate was filtered and washed with tetrahydrofuran. The solvent was removed and 340 mg, yield, 80%, of **30** was obtained, mp 235°; nmr (dimethyl sulfoxide/hexamethyldisiloxane): δ ppm 8.71 (s, H-1), 7.92 (m, H-7), 7.59 (m, H-8, H-9), 8.44 (m, H-10), 6.48 (s, NH_2), 4.63 (s, CH_2), 2.9 (s, CH_3).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.3; H, 5.5; N, 17.6. Found: C, 70.0; H, 5.4; N, 17.4.

3-Amino-2-formyl-5-methylbenzo[*7f*][1,7]naphthyridine (**31**).

To a solution of 1.0 g of **30** in 100 ml of anhydrous tetrahydrofuran was added 4.0 g of freshly prepared manganous oxide. The mixture was stirred for 1 hour at room temperature. The mixture was then filtered and the solvent was evaporated at temperature lower than 40°. Compound **31** was recrystallized in ethyl alcohol, yield, 50%, mp 180°; nmr (dimethyl sulfoxide/hexamethyldisiloxane): δ ppm 9.40 (s, H-1), 8.47 (m, H-7,H-10), 7.76 (m, H-8, H-9), 10.15 (s, CHO), 7.67 (s, NH_2), 2.82 (s, CH_3).

Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.9; H, 4.7; N, 17.7. Found: C, 70.6; H, 4.5; N, 17.6.

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