Regioselective Angular Annelation. Stereochemical Control Determined by the Sequence of Introduction of Reactants

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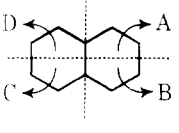
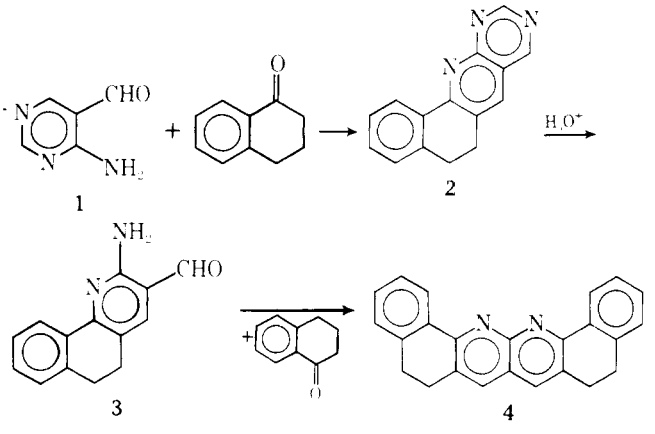
The possibility of regioselective angular fusion is demonstrated in the annelation of two benzo[*b*]-1,8-naphthyridine units on a 1,8-naphthyridine nucleus, leading to three isomeric octacyclic compounds each composed of three 1,8-naphthyridine moieties. These polycyclic systems differ only in their direction of angular ring fusion. Two isomers (**12** and **17**) are the result of two distinct modes of syn fusion, whereas the third (**15**) derives its zig-zag shape from anti annelation of the two benzo[*b*]-1,8-naphthyridine moieties. The key synthetic element resides in the unique dual potential of fused pyrimidines to generate coreactive *o*-amino aldehyde and ketone functionalities, which themselves are used in the elaboration of the starting fused pyrimidines. Each of the isomeric octacyclic compounds (**12**, **15**, and **17**) is obtained from identical starting materials in the same relative proportions: 2 mol of 1,3-cyclohexanedione, 1 mol of 4-aminopyrimidine-5-carboxaldehyde, and 2 mol of 2-aminonicotinaldehyde. The stereochemical outcome of the ring fusions is solely determined by the sequence of introduction of these reactants.

Fusion of carbocyclic or heterocyclic six-membered ring structures into polycyclic systems can lead to products derived from linear or angular annelation. This type of isomerism is well documented in carbocyclic ("acene" and "phene" series of hydrocarbons[1]) and heterocyclic fused systems containing three or more participating ring structures. However, despite the wide-spread use of these terms to describe the shape of fused systems, a uniquely defined orientation of nonlinear ring assemblies cannot be conveyed in these simple terms. Indeed, simple geometric considerations indicate that angular fusion on a bicyclic system can in principle proceed in four different directions (A–D) and can result therefore in isomeric phene



structures when applied to appropriately designed substrates. This type of isomerism is revealed most clearly when twofold angular annelation involving each of the participating rings is considered. Ring growth in the A and D or B and C quadrants can be regarded as syn annelation, whereas fusion in the A and C or B and D quadrants corresponds to anti annelation. Furthermore, syn annelation in the AD direction may be differentiated from the syn fusion in the BC direction; anti-annelation in the AC and BD direction may similarly result in isomeric products. Such differentiation in angular annelation directions and stereochemical control over the different modes of ring fusion has not yet been reported. This paper describes the regioselective synthesis of three isomeric octacyclic ring systems each composed of three 1,8-naphthyridine moieties and derived from identical starting materials. These isomeric structures differ only in their direction of angular annelation and reveal the possibility of anti and syn fusions in the 1,8-naphthyridine system.

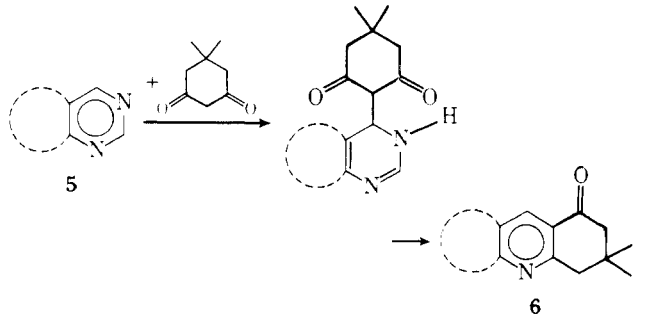
In a recent communication we reported on a new annelation sequence for polycondensed 1,8-naphthyridines.[2] This synthetic method relies on the base-catalyzed Friedländer condensation of cyclic ketones with 4-aminopyrimidine-5-carboxaldehyde (**1**), followed by acid-catalyzed ring opening of the resulting pyrido[2,3-*d*]pyrimidine moiety. This sequence leads to the formation of a new *o*-amino aldehyde functionality which can then be used in a second Friedländer condensation with formation of symmetrical or nonsymmetrical fused 1,8-naphthyridines. This sequence is illustrated by the facile, high-yield conversion of α-tetralone into 5,6,9,10-tetrahydro-1-phenanthridino[2,3-*b*]-1-phenanthridine (**4**). The



1 2 3 4

pyrimidine moiety of the fused pyrido[2,3-*d*]pyrimidine **2** is thus employed as a latent 5,6-fused 2-aminonicotinaldehyde or from a different viewpoint (conversion of **1** into **3**) the pyrimidine nucleus of **1** is used as a latent 5,6-fused pyridine ring, enriched with the ketonic residue while retaining its *o*-aminoaldehyde functionality.

Pyrimidines fused through their 4,5 positions to other aromatic ring systems are susceptible to nucleophilic attack.[3] Of particular interest is their reaction with 5,5-dimethyl-1,3-cyclohexanedione (dimedone), since the primary addition product is readily transformed into a fused ketone containing an additional six-membered ring. Once again, the pyrimidine moiety of the condensed system **5** serves as a latent pyridine



5 6

ring, fused now with a carbocyclic ring containing a ketone group in the 3 position of the pyridine ring system **6**. Fused pyrimidines can thus be directed to yield the *o*-aminoaldehyde (**2** → **3**) and ketone (**5** → **6**) functional groups. This capability to generate co-reactive functional groups from a single substrate, itself obtained from the same functionalities, forms the basis of our stereoselective angular annelation sequence.

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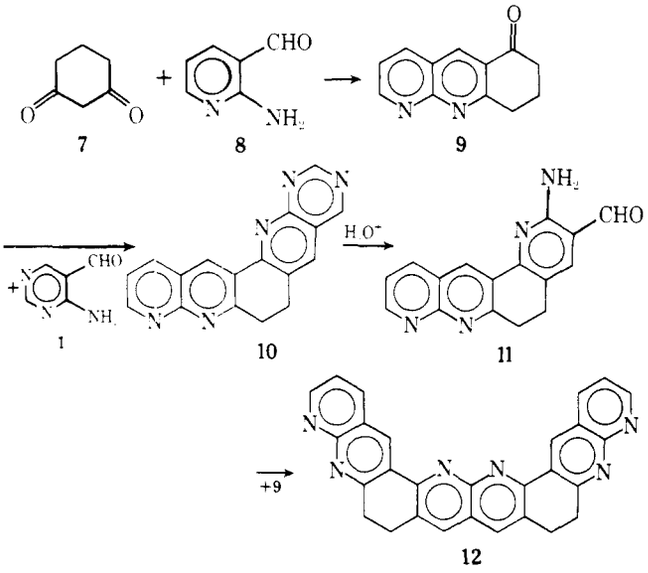
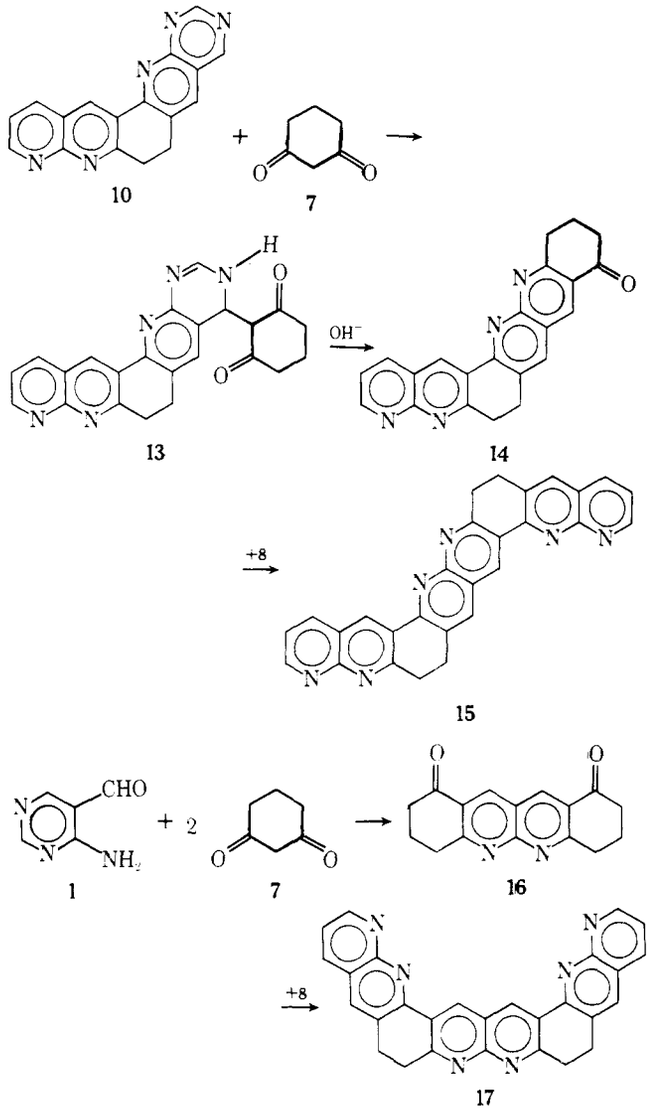
The use of dimedone in the reaction with fused pyrimidines results in the incorporation of a geminal dimethyl group in the β position of the annelated ketone **6**. This structural feature is undesirable since it can interfere sterically during condensation reactions of such ketones and *o*-aminoaldehydes. Utilization of 1,3-cyclohexanedione **7** eliminates this potential difficulty. Furthermore, it was found in this laboratory that **7** could be condensed with *o*-aminoaldehydes[4,5] and would thus provide a useful addition to the sequences outlined earlier.



The reaction of 1,3-cyclohexanedione (**7**) and 2-aminonicotinaldehyde (**8**) in a 1:1 molar ratio gives 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**9**).[4] Although **9** should also be available from pyrido[2,3-*d*]pyrimidine and **7**, this sequence was not followed since the former is not readily obtained, whereas **8** is available from nicotinamide.[6] Condensation of **9** with **1** under carefully controlled conditions (see Experimental Section) gave 6,7-dihydropyrimido[4,5-*b*]-pyrido[2′,3′-*j*]-1,7-phenanthroline (**10**) in 60% yield. Hydrolysis in a large volume of 0.01 N HCl resulted in the formation of the fused *o*-aminoaldehyde: 2-amino-5,6-dihydropyrido[2,3-*j*]-1,7-phenanthroline-3-carboxaldehyde (**11**) in excellent yield. Friedländer condensation of **11** with **9** gave octacyclic 6,7,10,11-tetrahydropyrido[2′,3′-8,9]-1,7-phenanthrolino[2,3-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (**12**) in 90% yield.

Reaction of the fused pyrimidine **10** with 1,3-cyclohexanedione on the other hand resulted in the formation of the addition product **13** in quantitative yield. Treatment of **13** with 1 N NaOH gave annelated ketone 10-oxo-6,7,10,11,12,13-hexahydropyrido[2,3-*j*]quinolino[2,3-*b*]-1,7-phenanthroline (**14**) in 95% yield. Friedländer condensation of **14** with 2-aminonicotinaldehyde gave octacyclic 6,7,16,17-tetrahydropyrido[2′,3′-2,3]-1,7-phenanthrolino-[8,9-*b*]pyrido[2,3-*j*]-1,7-phenanthroline **15** in 90% yield.

Another route to fused 1,8-naphthyridines may be found in the reaction of 1,3-cyclohexanedione and 4-aminopyrimidine-5-carboxaldehyde. Of particular interest is the formation of 1,10-dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b*,*g*]-1,8-naphthyridine (**16**) from **7** and **1** in a 2:1 molar ratio.[5] This tetracyclic ketone contains the necessary structural features for angular annelation via Friedländer condensation with 2-aminonicotinaldehyde. Base-catalyzed condensation of **16** and excess **8** gave 6,7,10,11-tetrahydropyrido[2′,3′-2,3]-1,7-phenanthrolino[8,9-*j*]pyrido[2,3-*b*]-1,7-phenanthroline (**17**), although in very low yield (ca 5%). Numerous attempts to alter the outcome of this reaction were not successful. The low yield

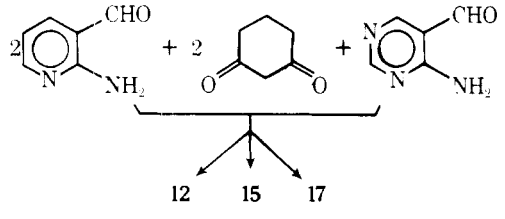


of **17** can be attributed to the instability of **16** in the basic reaction mixture. Indeed, addition of catalytic amounts of methanolic potassium hydroxide to an alcoholic solution of **16** resulted in the fast disappearance of the diketone. The exact nature of the reaction product could not yet be ascertained. Condensation of **16** and **8** in polyphosphoric acid was unsuccessful.

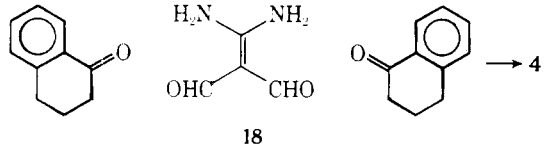
The NMR spectra of **12**, **15**, and **17** confirm their proposed structures. The different magnetic environment on the "bay" side of aromatic angular systems[7] provides us with a basis for the interpretation of the spectra. Furthermore, the deshielding of protons by neighboring nitrogen pairs permits the characterization of the various bays present in the isomeric compounds. The architecture of the bays in **12** and **17** is geometrically the same but differing in topology. The former contains one pair of nitrogen atoms, whereas the latter is characterized by two sets of nitrogen pairs. Bay protons under the influence of two such pairs (H_{18} and H_{19} in **17**) absorb at δ 9.64; protons in close proximity to one pair are found at δ 9.60 (H_{17} and H_{20} in **12**). A comparison between H_1 and H_{20} in **12** (δ 8.43 and 9.60, respectively) illustrates the effect of the location along the bay side of these angular systems. Similar protons on the outside of the bay are found at δ 8.22 (H_4 and H_{13} in **17**) and 8.12 (H_8 and H_9 in **12**). The geometry of the bays in **15** is clearly different from that of **12** and **17**. The absence of symmetry gives rise to a more complex spectrum. The striking feature in the spectrum of **15** is a set of two singlets at δ 9.58 and 9.53. A comparison with similar values in **12** and **17** suggests that these absorptions correspond to bay-side protons

under the direct influence of nitrogen atoms, i.e., H_{10} and H_{19}. This difference in chemical shift is surprising since the two bays in **15** have nearly identical topologies. An assignment for the individual absorptions may be arrived at in the following way. Superposition of the first quadrants of **15** and **17** reveals an upfield shift of the bay proton H_{19} from δ 9.64 in **17** to δ 9.58 in **15**. Superposition of the third quadrant of **15** and the fourth quadrant of **12** shows an upfield shift for the bay proton H_{17} of **12** from δ 9.60 to δ 9.53 for the superimposable proton H_{10} of **15**. Both superpositions result in nearly identical upfield shifts for the respective protons. These differences in chemical shift are the result of the different geometries of the bays of **12** or **17** and the zig-zag shaped **15**. It should be noted that the reverse mode of superpositions is not possible.

Inspection of the three octacyclic systems **12, 15,** and **17** (Figure 1) clearly reveals them as isomeric compounds. The relative position of the nitrogen atoms in each consecutive pair of 1,8-naphthyridine units is the same in all of them and is a reflection of the carbonyl groups in 1,3-cyclohexanedione, which ultimately dictate the position of the 1,8-naphthyridine units. If the direct linkage of one 1,8-naphthyridine moiety to the next is denoted as either α or β, then isomer **12** can be described as composed of $\beta,\alpha,\alpha,\beta$ linkages, isomer **17** as a $\alpha,\beta,\beta,\alpha$ chain, and **15** as a $\alpha,\beta,\alpha,\beta$ sequence. The alternative sequence for the latter, namely $\beta,\alpha,\beta,\alpha$, gives rise to **15′**, identical with **15**.[9] The three isomeric polycyclic systems **12, 15,** and **17** differ therefore in their direction of angular ring fusion: **12** and **17** represent a syn fusion, whereas the zig-zag shaped **15** can be described as an anti fused system. Thus, the octacyclic fused systems represent products of a regioselective angular annelation of two benzo[*b*]-1,8-naphthyridine units on a central 1,3-naphthyridine system or, from a different viewpoint, of two 1,8-naphthyridine units on a central dibenzo[*b,g*]-1,8-naphthyridine unit. Inspection of the synthetic sequences employed for the elaboration of **12, 15,** and **17** reveals that they are obtained from identical starting materials in the same relative proportions. It should be stressed that they are not obtained as a mixture of isomeric products. On the contrary, only one specific isomer is obtained in each sequence. The order of introduction of the reagents determines in an absolute way the stereochemical outcome of the successive ring annelations.



The condensation–hydrolysis–condensation sequence based on the Friedländer condensation of 4-aminopyrimidine-5-carboxaldehyde (**1**) provides us with a synthon for the unknown diaminomethylenemalonaldehyde (**18**) in its reactions



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with ketones. This is seen most clearly in the synthesis of **4** from **1** and 2 mol of α-tetralone. Using this synthon, an antithetic dissection of the octacyclic compounds **12, 15, 15′,** and **17** reveals the source of their isomerism. The two 1,3-cyclohexanedione molecules employed in their synthesis emerge in four possible combinations with diaminomethylenemalonaldehyde. The remaining ketone groups are further combined with 2-aminonicotinaldehyde. The formation of **17**

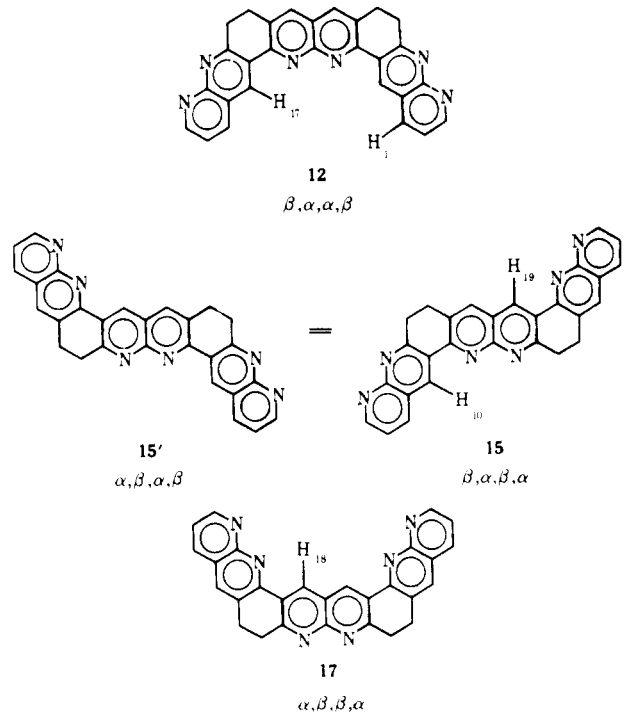
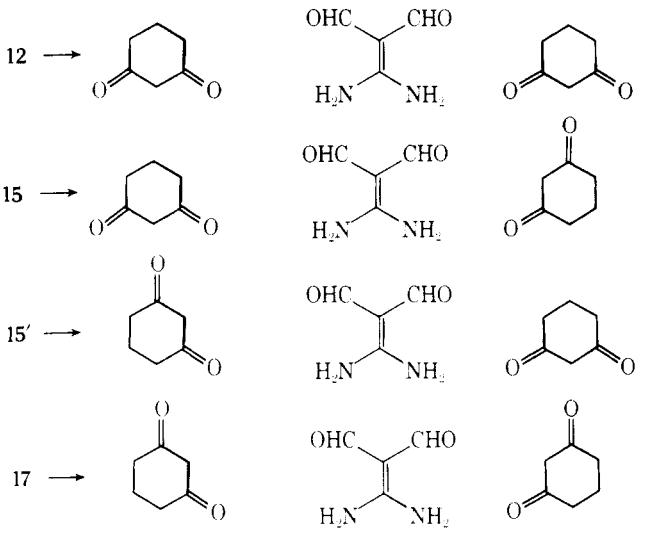
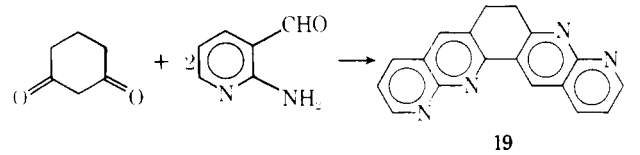


Figure 1. Polycyclic systems (ref 8).



is seen as the expected product, because it involves reaction with the doubly activated methylene group of 1,3-cyclohexanedione. The formation of **12** and **15** (**15′**), on the other hand, necessitates reaction at the far less reactive, singly activated methylene group of the 1,3-dione.

Further insight into the structural realtionships of these polycondensed 1,8-naphthyridines may be gained by focusing our attention on a different combination of the reactants. The reaction of 1,3-cyclohexanedione and 2 mol of 2-aminonicotinaldehyde (**8**) results in the formation of the pentacyclic 6,7-dihydrodipyrido[2,3-*b*:2,3-*j*]-1,7-phenanthroline (**19**).[4] A comparison with **12, 15,** and **17** indicates that **19** is an inte-



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gral structural part of all the isomeric octacyclic compounds. The remaining reactants, namely 1,3-cyclohexanedione and

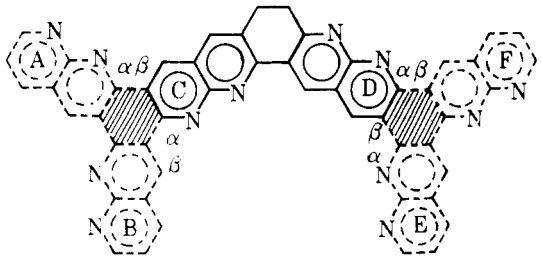

Figure 2. Polycyclic systems (ref 10).

4-aminopyrimidine-5-carboxaldehyde, are responsible therefore for the annelation of a three-ring fragment onto **19**. Fusion of this unit may take place on the terminal ring D of the pentacyclic system (CD) in two distinct ways: $\alpha\beta$ or $\beta\alpha$ (once again the relative position of the 1,8-naphthyridine units must reflect the positions of the carbonyl groups in 1,3-cyclohexanedione). In this fashion only two octacyclic isomers, i.e., CE (**17**) and CF (**15** or **15'**) can be generated (Figure 2). It is necessary, therefore, to perform similar fusions on the other terminal ring of the pentacyclic unit (ring C). This analysis generates the remaining isomers BD (**12**) and AD (**15** or **15'**). Although **19** is not capable of isomerism, fusion of an identical fragment on either end ring can thus generate isomeric annelated products.

Experimental Section

General. NMR spectra were recorded with a Varian A-60 and/or Varian XL-100 FT spectrometer using Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU6E instrument; infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. All melting points are uncorrected. Microanalyses were done by Instranal Laboratory, Inc., Rensselaer, N.Y.

5,6-Dihydropyrimido[4,5-*b*]-1-phenanthridine (2). To a refluxing solution of 0.492 g (4 mmol) of 4-aminopyrimidine-5-carboxaldehyde (**1**) and 0.6 g (4.1 mmol) of α-tetralone in 25 mL of ethanol was added 4 drops of methanolic KOH (15%). The solution was refluxed for 24 h. The product crystallized upon cooling (0.79 g, 85%) and was decolorized with carbon in ethanol: mp 223.5–224 °C; IR (Nujol) 1615, 1595, 1580, 1535, 1425, 1390, 1335, 1315, 1300, 1270, 1250, 1230, 1205, 1175, 1160, 1075, 1030, 1015, 980, 945, 935, 915, 900, 890, 820, 780, 735, 730, and 715 cm^{-1}; NMR ($CDCl_3$) δ 9.48 (s, 1, H-10), 9.35 (s, 1, H-8), 8.73 (m, 1, H-1), 8.01 (s, 1, H-7), 7.36 (m, 3, H-2, H-3, and H-4), 3.10 (s, 4, H-5 and H-6); mass spectrum M^+ at *m/e* 233.

Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.04; H, 4.67; N, 18.06

2-Amino-5,6-dihydro-1-phenanthridine-3-carboxaldehyde (3). A solution of 1.0 g of **2** in 1 L of 0.01 N HCl was refluxed for 3 h, cooled, and neutralized (NH_4OH). The yellow precipitate was recrystallized (EtOH) to yield 0.87 g (90%) of **3**: mp 130.5–131 °C; IR (Nujol) 3420, 3260, 3160, 2720, 1660, 1610, 1590, 1570, 1525, 1420, 1350, 1290, 1265, 1230, 1180, 1165, 1150, 1000, 960, 910, 890, 805, 790, 760, 750, 735, 710, and 700 cm^{-1}; NMR ($CDCl_3$) δ 9.75 (s, 1, CHO), 8.25 (m, 1, H-10), 7.50 (s, 1, H-4), 7.38–7.13 (m, 3, H-7, H-8, and H-9), 6.7 (broad singlet, 2, NH_2), 2.83 (s, 4, H-5 and H-6); mass spectrum M^+ at *m/e* 224.

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.94; H, 5.30; N, 12.33.

5,6,9,10-Tetrahydro-1-phenanthridino[2,3-*b*]-1-phenanthridine (4). To a refluxing solution of 0.5 g (2.2 mmol) of **3** and 0.35 g (2.4 mmol) of α-tetralone in 50 mL of ethanol was added 4 drops of methanolic KOH (15%). The mixture was refluxed for 24 h. The precipitate was collected and recrystallized (EtOH) to yield 0.665 g (90%) of **4**: mp 225–256 °C; IR (Nujol) 1615, 1590, 1575, 1525, 1450, 1420, 1410, 1350, 1330, 1300, 1280, 1250, 1165, 1150, 1100, 1025, 1010, 980, 960, 925, 885, 875, 815, 785, 775, 740, 730, 700, and 690 cm^{-1}; NMR ($CDCl_3$) δ 8.80 (m, 2, H-1 and H-14), 7.77 (s, 2, H-7 and H-8), 7.48–7.25 (m, 6, remaining aromatic protons), 3.01 (s, 8, H-5, H-6, H-9, and H-10); mass spectrum M^+ at *m/e* 334.

Anal. Calcd for $C_{24}H_{18}N_2$: C, 86.20; H, 5.43; N, 8.38. Found: C, 86.08; H, 5.49; N, 8.36.

6,7-Dihydropyrimido[4,5-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (10). To a vigorously refluxing solution of 1.0 g (5 mmol) of 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**9**) and 0.62 g (5 mmol) of **1** in 50 mL of ethanol was added 5 drops of methanolic KOH (15%). Reflux was continued for 24 h. The precipitate was collected to give 0.875 g (61%) of **10**, recrystallized from 2-ethoxyethanol, mp >300 °C dec. An analytical sample was prepared by percolation through a small column of alumina in $CHCl_3$: IR (Nujol) 1590, 1560, 1530, 1330, 1280, 1235, 1220, 1190, 1150, 1000, 940, 915, 820, 810, 800 and 790 cm^{-1}; NMR ($CDCl_3$) δ 9.58 (s, 1, H-2), 9.54 (s, 1, H-13), 9.46 (s, 1, H-4), 9.17 (dd, 1, H-10, $J_{H10-H11}$ = 4 Hz, $J_{H10-H12}$ = 2 Hz), 8.38 (dd, 1, H-12, $J_{H11-H12}$ = 8 Hz), 8.22 (s, 1, H-5), 7.54 (dd, 1, H-11), 3.66–3.30 (m, 4, H-6 and H-7); mass spectrum M^+ at *m/e* 285.

Anal. Calcd for $C_{17}H_{11}N_5$: C, 71.57; H, 3.89; N, 24.55. Found: C, 71.46; H, 3.95; N, 24.44.

2-Amino-5,6-dihydropyrido[2,3-*j*]-1,7-phenanthroline-3-carboxaldehyde (11). A mixture of 1 g of **10** in 1500 mL of 0.1 N HCl was refluxed for 3 h, cooled, and neutralized (NH_4OH). The yellow precipitate was recrystallized from pyridine and ethanol to yield 0.8 g (83%) of **11** (decomposition without melting): IR (Nujol) 3400, 3220, 3150, 2700, 1650, 1615, 1585, 1525, 1275, 1245, 1170, 960, 905, 790, 770, 750, and 735 cm^{-1}; NMR ($CDCl_3$) δ 9.91 (s, 1, HCO), 9.10 (dd, 1, H-9, J_{H9-H10} = 4 Hz, J_{H9-H11} = 2 Hz), 9.01 (s, 1, H-12), 8.28 (dd, 1, H-11, $J_{H10-H11}$ = 8 Hz), 7.73 (s, 1, H-4), 7.47 (dd, 1, H-10), 6.70 (broad, s, 2, NH_2), 3.58–3.26 (m, 2, H-6), 3.20–2.96 (m, 2, H-5); mass spectrum M^+ at *m/e* 276.

Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.51; H, 4.30; N, 20.16.

6,7,10,11-Tetrahydropyrido[2',3'-8,9]-1,7-phenanthrolino-[2,3-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (12). To a refluxing mixture of 0.64 g (2.3 mmol) of **11** and 0.475 g (2.4 mmol) of **9** in 40 mL of ethanol was added 5 drops of methanolic KOH (15%). Reflux was continued for 24 h. The precipitate was recrystallized from 1-propanol to give 0.9 g (90%) of **12**: yellow needles; mp >500 °C; IR (Nujol) 1590, 1540, 1470, 1225, 1175–1150, 990, 905, 805, and 790 cm^{-1}; NMR ($CDCl_3$) δ 9.60 (s, 2, H-17 and H-20), 9.16 (dd, 2, H-3 and H-14, J_{H2-H3} = 4 Hz, J_{H1-H3} = 2 Hz), 8.43 (dd, 2, H-1 and H-16, J_{H1-H2} = 8 Hz), 8.12 (s, 2, H-8 and H-9), 7.55 (dd, 2, H-2 and H-15), 3.70–3.24 (m, 8, H-6, H-7, H-10, and H-11).

Anal. Calcd for $C_{28}H_{18}N_6$: C, 76.69; H, 4.14; N, 19.17. Found: C, 76.39; H, 4.14; N, 19.04.

4-(2',6'-Dioxocyclohexyl)-3,4,6,7-tetrahydropyrimido[4,5-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (13). To a refluxing solution of 2.0 g of **10** in 1 L of methanol was added 1.0 g of 1,3-cyclohexanedione (**7**). The solution was put aside at room temperature for 24 h. The precipitate was collected to give **13** in quantitative yield: IR (Nujol) 3350 (broad), 1660, 1610, 1600, 1550, 1450 (broad), 1325, 1230, 1175, 1000, 915, 870, 790, and 770 cm^{-1}. The product could not be purified without decomposition and was used therefore in the next step as received.

10-Oxo-6,7,10,11,12,13-hexahydropyrido[2,3-*j*]quinolino-[2,3-*b*]-1,7-phenanthroline (14). A mixture of 0.5 g of **13** was heated in 250 mL of 1 N NaOH at 80 °C until a complete solution was obtained (15 min). The solution was cooled, neutralized (HCl), and thoroughly extracted with chloroform. The combined extracts were evaporated to dryness under reduced pressure, to give 0.425 g (96%) of **14**, recrystallized from 1-propanol (decomposition without melting): IR (Nujol) 1690, 1610, 1550, 1535, 1470, 1250, 1225, 1175, 1150, 980, 950, 940, 910, 810, and 795 cm^{-1}; NMR ($CDCl_3$) δ 9.55 (s, 1, H-16), 9.14 (dd, 1, H-3, J_{H2-H3} = 4 Hz, J_{H1-H3} = 2 Hz), 8.80 (s, 1, H-9), 8.33 (dd, 1, H-1, J_{H1-H2} = 8 Hz), 8.16 (s, 1, H-8), 7.51 (dd, 1, H-2), 3.64–3.24 (m, 6, H-6, H-7, and H-13), 2.84 (t, 2, H-11, $J_{H11-H12}$ = 6 Hz), 2.34 (m, 2, H-12); mass spectrum M^+ at *m/e* 352.

Anal. Calcd for $C_{22}H_{16}N_4O$: C, 74.98; H, 4.58; N, 15.90. Found: C, 73.54; H, 4.76; N, 15.60.

6,7,16,17-Tetrahydropyrido[2',3'-2,3]-1,7-phenanthrolino-[8,9-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (15). To a refluxing mixture of 2.0 g (6 mmol) of **14** and 2.0 g of 2-aminonicotinaldehyde in 100 mL of ethanol were added 20 drops of methanolic KOH (15%). The mixture was refluxed for 48 h and the precipitate collected and recrystallized from chloroform to give 2.3 g (88%) of **15**: yellow needles; mp > 500 °C; IR (Nujol) 1590, 1550, 1480, 1285, 1240, 1160, 1145, 985, 975, 935, 890, 800, 745, and 725 cm^{-1}; NMR ($CDCl_3$) δ 9.58 (s, 1, H-19), 9.53 (s, 1, H-10), 9.13 and 9.14 (two sets of dd, 2, H-2 and H-13, J_{H2-H3} = 4 Hz, J_{H2-H4} = 2 Hz), 8.35 (dd, 1, H-11, $J_{H11-H12}$ = 8 Hz), 8.22 (s, 1, H-18), 8.19 (dd, 1, H-4), 8.11 (s, 1, H-5), 7.56 and 7.55 (two sets of dd, 2, H-3 and H-12), 3.80–3.30 (m, 8, H-6, H-7, H-16, and H-17).

Anal. Calcd for $C_{28}H_{18}N_6$: C, 76.69; H, 4.14; N, 19.17. Found: C, 76.45; H, 4.10; N, 18.98.

6,7,10,11-Tetrahydropyrido[2',3'-2,3]-1,7-phenanthrolino-[8,9-*j*]pyrido[2,3-*b*]-1,7-phenanthroline (17). To a refluxing solution of 0.250 g (0.9 mmol) of 1,10-dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b,g*]-1,8-naphthyridine (**16**) and 0.5 g of 2-aminoicotinaldehyde in 50 mL of 1-propanol were added 3 drops of methanolic KOH (15%). After refluxing for 48 h another drop of methanolic KOH

was added. Reflux was continued for 24 h. The precipitate was filtered, the filtrate evaporated to dryness on a rotary evaporator, and the residue washed with ether followed with methanol. The combined precipitates were treated with 50 mL of chloroform, and the filtrate passed through a column of alumina. The fluorescent fraction was collected, the chloroform evaporated, and the residue crystallized from xylene: mp >500 °C; IR (Nujol) 1600, 1550, 1480, 1280, 1235, 1220, 1150, 955, 940, 910, 805, and 790 cm^{-1}; NMR ($CDCl_3$) δ 9.64 (s, 2, H-18 and H-19), 9.16 (dd, 2, H-2 and H-15, J_{H2-H3} = 4 Hz, H_{H2-H4} = 2 Hz), 8.22 (dd, 2, H-4 and H-12, J_{H3-H4} = 8 Hz), 8.10 (s, 2, H-5 and H-12), 7.50 (dd, 2, H-3 and H-14), 3.80–3.26 (m, 8, H-6, H-7, H-10, and H-11).

Anal. Calcd for $C_{28}H_{18}N_6$: C, 76.69; H, 4.14; N, 19.17. Found: C, 75.37; H, 4.07; N, 18.99

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Registry No.—**1**, 16357-83-8; **2**, 56685-47-3; **3**, 56644-58-7; **4**, 56644-59-8; **7**, 504-02-9; **8**, 7521-41-7; **9**, 56488-08-5; **10**, 68475-25-2; **11**, 68475-26-3; **12**, 68475-27-4; **13**, 68475-28-5; **14**, 68475-29-6; **15**, 68475-30-9; **16**, 57694-96-9; **17**, 68475-31-0; α-tetralone, 529-34-0.

References and Notes

(1) E. Clar, "Polycyclic Hydrocarbons", Vol. 1, Academic Press, New York, 1964.
(2) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **40**, 2566 (1975).
(3) A. Albert and H. Mizuno, *J. Chem. Soc., Perkin Trans.* **1**, 1615 (1973); A. Albert and W. Pendergast, *ibid.*, 1620 (1973), and references cited therein.
(4) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **40**, 3407 (1975).
(5) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **41**, 1058 (1976).
(6) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **39**, 720 (1974).
(7) K. D. Bartle and D. W. Jones, *Adv. Org. Chem.*, **8**, 317 (1972).
(8) To facilitate comparison of the polycyclic systems represented in Figure 1, the central 1,8-naphthyridine unit is kept constant. This results in the correct orientation for **15** and **17**, but not for **12** and **15'**, according to IUPAC rule A-22. [A. D. McNaught, *Adv. Heterocycl. Chem.*, **20**, 175 (1976).]
(9) Although **15** is identical with **15'**, two IUPAC names may be derived, namely 6,7,16,17-tetrahydropyrido[2',3'-2,3]1,7-phenanthrolino[8,9-*b*]pyrido-[2,3-*j*]-1,7-phenanthroline and 6,7,16,17-tetrahydropyrido[2',3'-8,9]-1,7-phenanthrolino[2,3-*j*]pyrido[2,3-*b*]-1,7-phenanthroline.
(10) The shaded rings in Figure 2 do not represent branching points for the polycyclic system. They indicate the position for the ring common in the two different modes of ring annelation.

Study of the Pictet–Spengler Reaction in Aprotic Media: Synthesis of the β-Galactosidase Inhibitor, Pyridindolol[1c]

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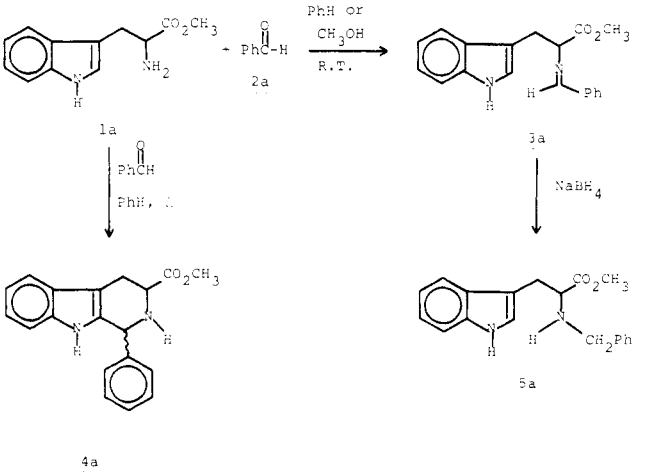
Factors which influence the Pictet–Spengler reaction in nonacidic, aprotic media have been studied. The condensation has been shown to work well with aldehydes when tryptophan methyl ester derivatives and N_b-benzyltryptamines were employed as substrates. The optimum conditions were realized when the N_b-benzyl derivatives were stirred with aldehydes in refluxing toluene. The factors (electrophilic character of the intermediate imine) which determine the ease of cyclization have been examined, as well as the effect of temperature on the condensation. The synthesis of many tetrahydro-β-carbolines, **6a–6i, 7a,** and **7b,** heretofore difficult to prepare, have been accomplished in good yield in the aprotic medium. This methodology has permitted the synthesis of the antibiotic pyridindolol (**16**).

In the course of work directed toward the construction of potential antihypertensive agents,[1a] the need arose for a preparation of N_b-benzyltryptophan methyl ester. This ester can be prepared by stirring tryptophan methyl ester (**1a**) and benzaldehyde (**2a**) in benzene at room temperature, followed by reduction of the resulting imine (**3a**) with sodium borohydride, similar to the work of Yoneda.[2] To improve the conversion of ester (**1a**) to imine (**3a**), the aldehyde (**2a**) and amine were heated in refluxing benzene, while a Dean-Stark trap was employed to remove water which formed in the reaction (Scheme I). Although the imine (**3a**) was initially observed, after prolonged heating the products of this sequence, isolated in 95% yield,[1b] were the cis and trans isomers of 1-phenyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline (**4a**).[3]

The result in the aprotic solvent was surprising, for generally the Pictet–Spengler reaction is carried out in a protic solvent with acid catalysts.[4–7] Reports in the literature are well-documented which indicate that furfural and tryptamine yielded only imine[8] when heated in refluxing benzene, while similar findings have been observed by Jackson and Smith[9] with tryptamine (**1f**) and benzaldehyde (**2a**). Both bases would not cyclize to tetrahydro-β-carbolines unless hydrochloric acid was added to the solution.[8,9] Presumably, the Pictet–Spengler reaction in the tryptophan methyl ester (**1a**) case had occurred without the aid of acid catalysis; therefore, it was decided to make a detailed study of this observation.

A variety of tryptophan methyl ester (**1**) derivatives have been employed in this condensation; some of these are outlined in Table I. Excellent yields of tetrahydro-β-carbolines (**4a–e**) were obtained with N_b-benzyltryptophan methyl ester

Scheme I



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