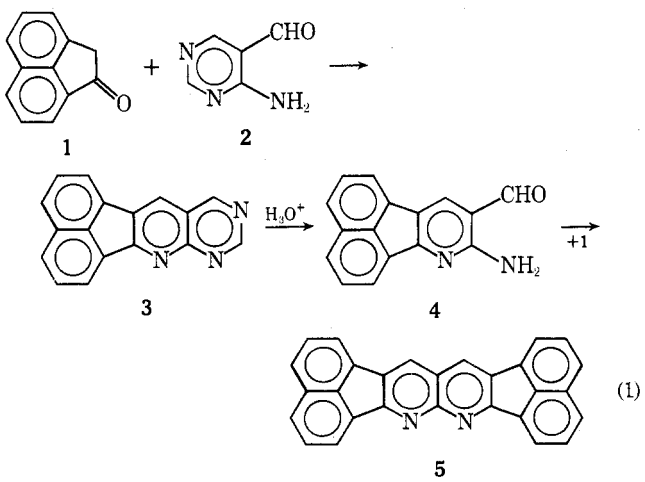
A New Annelation Sequence. Polycondensed 1,8-Naphthyridines

Summary: Friedländer condensations of compounds containing the ortho aminoaldehyde functional groups—readily obtained from aromatic cyclic ketones and 4-aminopyrimidine-5-carboxaldehyde—with aromatic ketones leads to symmetrically and nonsymmetrically fused 1,8-naphthyridines with equal ease.

Sir: The object of the research which is outlined herein has been the development of a general synthetic method for the introduction of the 1,8-naphthyridine heterocyclic ring system into fused polycyclic frameworks of different architecture. The remarkable properties and stability of "black orlon"—itself composed of a linearly annelated sequence of partially oxygenated 1,8-naphthyridine units[1]—made synthesis of such systems desirable.

Incorporation of this heterocyclic system into larger units has met with limited success even in the case of simple benzo-fused systems.[2] The reported obstacles[3] of converting oxo or amino functional groups into the unsubstituted heterocyclic unit made the one-step construction of the unsubstituted 1,8-naphthyridine moiety imperative. The Friedländer condensation of compounds containing the ortho aminoaldehyde functional groups offers such opportunity. This report describes a facile annelation sequence leading to fused 1,8-naphthyridines starting from readily accessible aromatic keto methylenes.

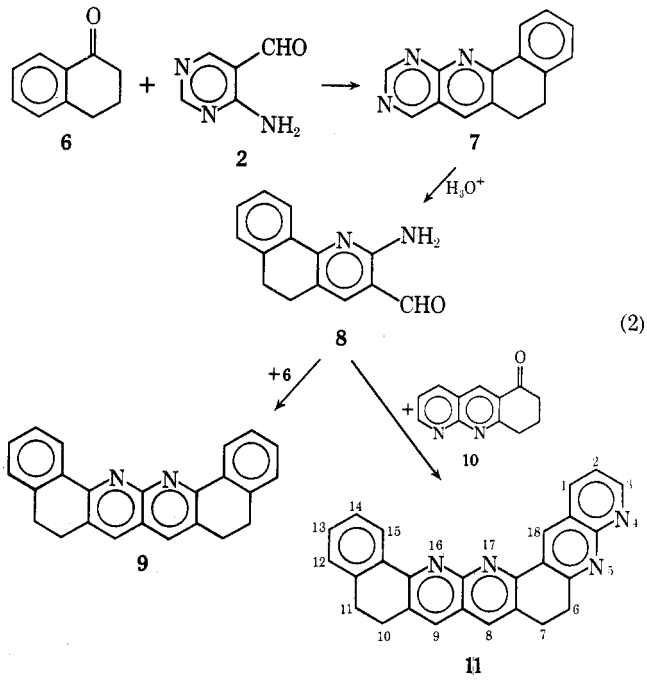
The synthetic strategy relies on our earlier observation[4] that pyrido[2,3-*d*]pyrimidines can be used as latent 2-aminonicotinaldehydes by acid-catalyzed hydrolysis of their pyrimidine moiety. It became thus necessary to first assemble fused polycyclic systems containing a terminal pyrimidine moiety. This was achieved by Friedländer condensation of 4-aminopyrimidine-5-carboxaldehyde (**2**) and aromatic cyclic keto methylenes as illustrated in eq 1.



(1)

To a refluxing ethanolic solution of acenaphthenone and **2** were added a few drops of methanolic KOH (20%); a precipitate was formed within a few minutes. The reaction mixture was further refluxed for 12 hr to give acenaphtho[1′,2′:5,6]pyrido[2,3-*d*]pyrimidine (**3**) in 95% yield, mp 269–270°.[5] Covalent hydration[6] of **3** followed by irreversible ring opening of the pyrimidine moiety, carried out by heating in 2 *N* HCl for 4 hr, provided 8-aminoacenaphtho[1,2-*b*]pyridine-9-carboxaldehyde (**4**) in 95% yield, mp 215–217.[5] This newly formed ortho aminoaldehyde was readily recondensed with starting acenaphthenone to form diacenaphtho[1,2-*b*:1′,2′-*g*]-1,8-naphthyridine (**5**) in quantitative yield, mp 422 (bright yellow needles from pyridine).[5]

A similar sequence of Friedländer condensations was followed in the synthesis of the hexacyclic 1-phenanthridino-[2,3-*b*]-1-phenanthridine (**9**) using α-tetralone in the consecutive cyclizations as outlined in eq 2.



(2)

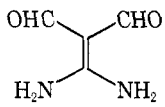
Friedländer condensation of **2** with the less reactive α-tetralone resulted in the formation of 5,6-dihydropyrimido[4,5-*b*]-1-phenanthridine in 85% yield, mp 223.5–224°.[5] Hydrolytic cleavage of this heterocyclic system was best carried out in dilute hydrochloric acid (0.01 *N*) to generate the highly fluorescent 2-amino-5,6-dihydro-1-phenanthridine-3-carboxaldehyde (**8**) in 90% yield, mp 130.5–131°.[5] Reutilization of α-tetralone in the second Friedländer condensation gave **9** in 90% yield, mp 255–256°.[5]

The isolation of compounds containing the ortho aminoaldehyde functional group in this annelation sequence allows for the synthesis of nonsymmetrical, fused 1,8-naphthyridines as exemplified by the facile synthesis of the heptacyclic 6,7,10,11-tetrahydro(1-phenanthridino)[2,3-*b*]pyrido[2,3-*j*]-1,7-phenanthroline (**11**) from α-tetralone and 6-oxo-6,7,8,9-tetrahydrobenzo[*b*]-1,8-naphthyridine (**10**).[7] To a refluxing solution of **8** and **10** in ethanol were added a few drops of methanolic KOH (20%). A precipitate formed slowly. The mixture was refluxed for 48 hr to yield **11** in 85% yield, mp 329° dec.[5]

The key step in this annelation sequence leading to polycondensed 1,8-naphthyridines is the use of cyclic keto methylenes for the introduction of the pyrido[2,3-*d*]pyrimidine moiety in a polycondensed framework (Friedländer condensations of 4-aminopyrimidine-5-carboxaldehyde represent a new and facile entry into such systems) and

reuse of the same functionality in a second ring formation reaction. This two-step sequence can therefore be directed with equal ease to the synthesis of symmetric and nonsymmetric polycondensed 1,8-naphthyridines depending on whether or not the same ketone is supplied in the second condensation. The general availability of cyclic keto methylenes ensures a successful application of this new sequence for a multitude of polycondensed systems.

Finally, it is interesting to note that this sequence formally represents a double Friedländer condensation of aromatic keto methylenes with the unknown diaminomethylene malonaldehyde.



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Supplementary Material Available. Experimental details and full analytical and spectroscopic data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2566.

References and Notes

(1) C. G. Overberger and J. A. Moore, *Adv. Polym. Sci.*, **7**, 125–127 (1970), and references cited therein.
(2) C. V. Wilson, "Chemistry of Heterocyclic Compounds", Vol. 12, Arnold Weissberger, Ed., Interscience, New York, N.Y., 1958, pp 91–99.
(3) J. V. Crawford and E. R. Webster, "Chemistry of Heterocyclic Compounds", Vol. 2, Arnold Weissberger, Ed., Interscience, New York, 1951, pp 117–119.
(4) G. Evens and P. Caluwe, *J. Org. Chem.*, **40**, 1438 (1975).
(5) See paragraph at the end of paper regarding supplementary material.
(6) For a review on covalent hydration, see A. Albert and W. L. F. Armarego, *Adv. Heterocycl. Chem.*, **4**, 1 (1965).
(7) T. G. Majewicz and P. Caluwe, unpublished work.

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Neighboring Group Assistance in Azabicyclic Derivatives. Tremendous Rate Accelerations in 2-Aza-6-halobicyclo[2.2.2]- and 6-Aza-4-halobicyclo[3.2.1]octanes

Summary: The incorporation of a nitrogen atom into the 2 position of bicyclo[2.2.2]octane and the 6 position of bicyclo[3.2.1]octane results in exceptional solvolytic rate enhancements (up to 10^9) of halo substituents located 1,3 from the nitrogen compared to similar carbon–carbon σ bond participation and 1,3-nitrogen participation in alicyclic compounds.

Sir: Although considerable effort has been devoted to investigations of participation and skeletal rearrangements in carbobicyclic structures,[1] relatively limited attention has been accorded analogous systems containing heteroatoms[2–4] in spite of the well-established ability of several atoms to offer neighboring group assistance in solvolytic and related reactions.

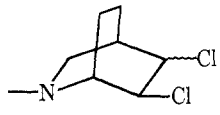
Table I
Rates of Solvolysis of Azabicyclic and Related Compounds in 80% Aqueous Ethanol

Compd	Temp, °C	k, min^{-1}	Rel rate
1	0	8.53	4×10^8
2	75	4.48×10^{-6}	1[a]
3	0	6.22×10^{-5}	2.4×10^3
4	85	2.5×10^{-3}	2.8×10^{2a}
5	0	>42	1.7×10^9
6	0	>42	1.7×10^9

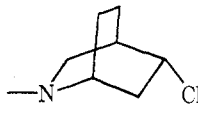
[a] Corrected to 0°.

We wish to report that the incorporation of a nitrogen into the 2 position of bicyclo[2.2.2]octane and the 6 position of bicyclo[3.2.1]octane results in exceptional solvolytic rate enhancement of halo substituents located cross-ring and exo compared to similar carbon–carbon σ bond participation in these systems and even analogous 1,3-nitrogen participation in alicyclic compounds. Table I presents rate data for a variety of compounds chosen to compare various participation possibilities in bicyclic derivatives (**1**, **2**, **4–6**) and the open-chain equivalent (**3**). As evident, the ability of nitrogen to enhance the solvolysis of a 6-*exo*-chloro group is phenomenal, the rate being over *10^8 as fast as a 5-chloro substituent and ca. ~10^5 as fast as N,N-dimethylamino-2-chloroethane (**3**)*! The effect on a 6-bromo substituent is equally dramatic. Both the bicyclo[2.2.2] and the bicyclo[3.2.1] compounds **5** and **6** were solvolyzed so rapidly (half-lives <1 sec at 0°) that accurate rate data could not be obtained. Nevertheless, a lower limit estimate of ~10^9–10^{10} compared with **2** illustrates that nitrogen possesses super assisting ability in these systems.

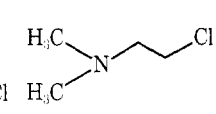
Compounds **5** and **6** (and to a lesser extent **1**) were so reactive in the free amine state that they could be isolated only as the HBr salts **5a** and **6a**.[5] Treatment of either **5a** or



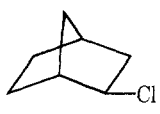
1 **1a** HCl salt



2 **2a** HCl salt



3 **3a** HCl salt



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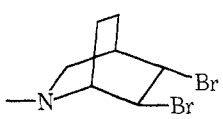
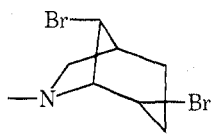


5 **5a** HBr salt



6 **6a** HBr salt

6a with ethanolic ethoxide or hydroxide in aqueous *tert*-butyl alcohol initially gave the *exo*-4-hydroxy derivative **7a** with the latter reagent or the corresponding ethyl ether **7b** with the former. The hydroxy compounds **7a** was converted to the tricyclic ether **8** upon longer reaction time. Reduction of either **7a** or **8** with lithium triethylborohydride ("Super-hydride")[7] afforded 4-*exo*-hydroxyl-2-methyl-2-azabicyclo[3.2.1]octane (**9**).[8] Evidently, release of the free amine by base results in rapid formation of the cyclic aziridinium ion which is opened by base to the more stable bicyclo[3.2.1] derivative **7a**. Further reaction with base furnishes the ether **8** by internal cyclization.