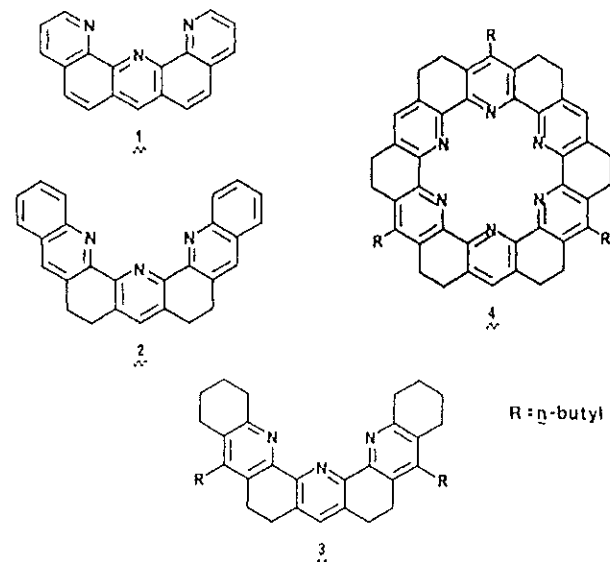


ings.

Sir: The useful complexation properties of 2,2'-bipyridine and 2,2':6',2''-terpyridine have stimulated interest in higher polypyridine homologues.¹ Despite the utility of 1,10-phenanthroline as a ligand,² synthetic difficulties have limited access to higher homologues in the pyridine/1,10-phenanthroline series. Synthesis of the next member, quino[8,7-*b*][1,10]phenanthroline (1), was reported by Case, using the double Skraup condensation of 4,5-diaminoacridine.³ Recently, Thummel achieved the synthesis of a tetrahydrido derivative (2) by Friedlander condensation of 2,3,7,8-tetrahydro-4,5(1*H*,6*H*)-acridinedione with *o*-aminobenzaldehyde.⁴ We have now synthesized the di-*n*-butyldodecahydro analogue 3, employing a new method for construction of the quino[8,7-*b*][1,10]phenanthroline nucleus.



We are interested both in complexation properties of rigidified terpyridines, such as 3, and in synthetic approaches to hexaazakekulene⁵ derivatives, such as 4. Since flexible side chains are known to enhance the solubilities of some rigidly planar molecules,⁶ our synthetic strategy incorporated *n*-butyl substituents. The 9-*n*-butylocta-

(1) E.g., quinquepyridine: Constable, E. C.; Lewis, J.; Schroder, M. *Polyhedron* 1982, 1, 311-312. Sexipyridine: Newkome, G. R.; Lee, H.-W. *J. Am. Chem. Soc.* 1983, 105, 5956-5957. Toner, J. L. *Tetrahedron Lett.* 1983, 24, 2707-2710.

(2) McBryde, W. A., Ed. "A Critical Review of Equilibrium Data for Proton and Metal Complexes of 1,10-Phenanthroline, 2,2'-Bipyridyl and Related Compounds"; Pergamon Press: Oxford, 1978. Sliwa, W. *Heterocycles* 1979, 12, 1207-1237.

(3) Koft, E.; Case, F. H. *J. Org. Chem.* 1962, 27, 865-868.

(4) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* 1985, 50, 2407-2412.

(5) For studies on the carbocyclic parent system, kekulene, see: Diederick, F.; Staab, H. A. *Angew. Chem., Int. Ed. Engl.* 1978, 17, 372-375.

(6) E.g.: Piechocki, C.; Simon, J.; Skoulios, A.; Guillon, D.; Weber, P. *J. Am. Chem. Soc.* 1982, 104, 5245-5247.

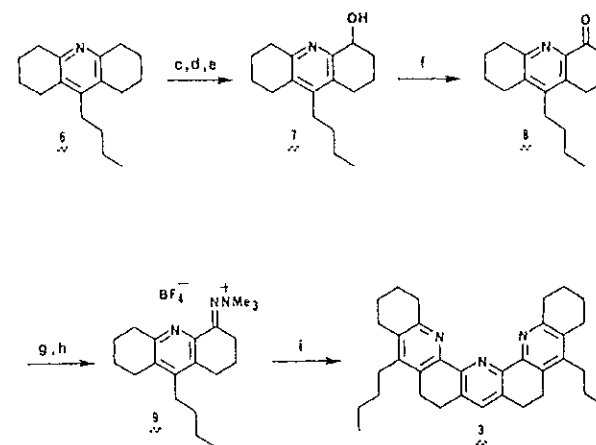


Figure 1. Synthesis of 5,11-di-*n*-butyl-1,2,3,4,6,7,9,10,12,13,14,15-dodecahydroacridino[4,3-*b*]benzo[7][1,10]-phenanthroline: (a) KOH, ethanol, 70 °C, 7 h (49%); (b) NH₂O·H·HCl, NaOAc·3H₂O, HOAc, distill, 185 °C, 12 h (32%); (c) MCPBA, CH₂Cl₂, room temperature, 1 h; (d) Ac₂O, 110 °C, 70 min; (e) 3 M HCl, 100 °C, 1 h (69% from 6); (f) CrO₃, HOAc, H₂O, H₂SO₄, room temperature, 2 h (92%); (g) Me₂NNH₂, cyclohexane, EtOH, TsOH·H₂O, room temperature, 16 h/C₆H₆, reflux, 15 min; (h) Me₂OBF₄, CH₂Cl₂, room temperature, 30 min; (i) 210 °C, N₂, 5 min (23% from 8).

hydroacridine 6 was therefore chosen as a key intermediate. Our synthesis (Figure 1) commenced with the aldol condensation of cyclohexanone with valeraldehyde, using conditions previously described for reaction of cyclohexanone with other aldehydes.⁷ The initial aldol product apparently dehydrates, the resulting enone undergoing Michael addition to afford a 1,5-diketone, which is isolated as crystalline ketol 5.⁸ Conversion to 9-*n*-butyl-1,2,3,4,5,6,7,8-octahydroacridine (6)⁸ is achieved directly by reaction of 5 with hydroxylamine hydrochloride and acetic acid.⁹ Although the overall yield of 6 from valeraldehyde is low (16%), the preparation of 6 on a 100-g scale may be conducted easily and inexpensively.

The transformation of 6 into 9-*n*-butyl-2,3,5,6,7,8-hexahydro-4(1*H*)-acridinone (8) involves oxidation at an α -CH₂ position, which may be effected by ozonolysis of a benzylidene derivative.¹⁰ Unfortunately, condensation of 6 with benzaldehyde in acetic anhydride results in a

(7) Tilichenko, M. N. *Uch. Zap. Sarat. Gos. Univ.* 1962, 75, 60-66; *Chem. Abstr.* 1964, 60, 419a.

(8) Microanalytical data and ¹H NMR, IR, and mass spectra were consistent with the proposed structure.

(9) As suggested by a reviewer, this transformation may be conducted by using ammonium acetate in refluxing acetic acid (cf. ref 4). This method gives 6 in somewhat better yield but involves an additional purification step.

(10) Lodde, N.; Reimann, E. *Arch. Pharm.* 1979, 312, 940-950.

mixture of starting material and monobenzylidene and dibenzylidene derivatives. An alternative four-step sequence employing Boekelheide rearrangement of an acetylated *N*-oxide¹¹ proved more convenient (Figure 1). Thus, the *N*-oxide of 6 was treated with hot, deoxygenated acetic anhydride, hydrolyzing the resulting acetate in situ to afford 7.⁸ Oxidation of this alcohol with chromic acid in aqueous acetic acid¹² gave ketone 8 in 63% yield overall from 6.

Conversion of 8 to heptacyclic terpyridine 3 requires symmetrical coupling of a ketone with the introduction of a carbon at C-4 of the new pyridine ring. Thummel used the reaction of an enamine with formaldehyde, followed by aromatization of the resulting diketone, to prepare a tetrahydro derivative of 1.⁴ Newkome and Fishel have reported an unusual pyridine synthesis, in which C-4 is introduced by methyl migration in the pyrolysis of trimethylhydrazonium salts of aromatic ketones.¹³ We have found that this remarkable reaction may be applied to hexahydro-4-acridinones (Figure 1). Thus, 8 is converted first to the dimethylhydrazone and then to the trimethylhydrazonium salt 9 by alkylation with trimethyloxonium tetrafluoroborate. Pyrolysis of the crude salt at 210 °C under a stream of nitrogen, followed by recrystallization from ethanol, gave the heptacyclic terpyridine 3¹⁴ in 23% yield overall from 8. The product was obtained as the sesquihydrate in the form of straw-colored needles (mp 220–221 °C), which were soluble in many organic solvents (e.g., CH₂Cl₂, CHCl₃, pyridine, 2-propanol, DMF, and acetic acid) and slightly soluble in others (e.g., benzene, acetonitrile, ether, THF, and ethanol).

Heptacyclic terpyridine 3 differs from 2 in the presence of flexible substituents and saturated terminal rings. These features make 3 particularly suitable as a precursor to hexaazakekulene derivatives, such as 4. Oxidative functionalization of 3 and methods for pyridine synthesis by unsymmetrical coupling of two ketones are currently under investigation.

Acknowledgment. This research was supported by the National Institutes of Health (PHS Grant GM32937), and the National Science Foundation is acknowledged for providing funds toward the purchase of a Nicolet NT-300 NMR spectrometer (Grant 8114412).

Registry No. 3, 99922-89-1; 5, 24133-22-0; 6, 99922-90-4; 7, 99922-91-5; 8, 99922-92-6; 9, 99922-94-8; NH₂OH·HCl, 5470-11-1; Me₂NNH₂, 57-14-7; cyclohexanone, 108-94-1; valeraldehyde, 110-62-3.

(11) Review: Traynelis, V. J. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Interscience: New York, 1969; Vol. 2, pp 1-42. See also: Cohen, T.; Deets, G. L. *J. Am. Chem. Soc.* 1972, 94, 932-938.

(12) Yanagida, A. J.; Gansser, C. *J. Heterocycl. Chem.* 1978, 15, 249-251.

(13) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* 1972, 37, 1329-1336.

(14) ¹H NMR (80 MHz, CDCl₃, δ relative to Me₄Si) 7.36 (s, 1 H, Ar H), 3.8 (br s, 3 H, H₂O), 3.0-3.2 (m, 4 H, α-PyCH₂), 2.92 (s, 8 H, ArCH₂CH₂Ar), 2.5-2.9 (m, 8 H, Ar CH₂), 1.7-1.9 (m, 8 H, CH₂CH₂CH₂CH₂), 1.25-1.5 (m, 8 H, CH₂CH₂CH₂CH₂), 0.97 (t, 6 H, CH₃); IR (KBr) 3350 (br), 2940 (s), 2850 (ms), 1650 (sh), 1550 (ms), 1430 (m), 1390 (m), 1240 (m), cm⁻¹; UV (95% EtOH) λ_{max} (ε) 245 (22000), 297 (10000), 306 (14000), 346 (24000), nm; MS (70 eV), *m/e* (relative intensity) 505 (M⁺, 100). Anal. Calcd for C₃₃H₄₆N₂O_{1.5}: C, 78.90; H, 8.70; N, 7.89. Found: C, 78.73; H, 8.68; N, 7.65.

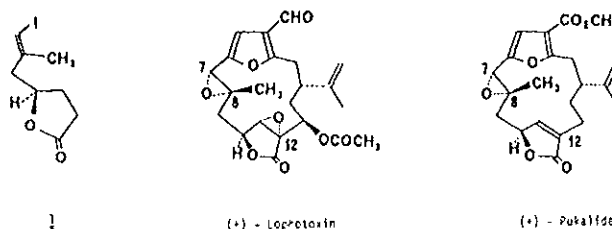
(15) Note added in proof: An alternate approach to unsubstituted hexaazakekulene derivatives has appeared recently: Ransohoff, J. E. B.; Staab, H. A. *Tetrahedron Lett.* 1985, 26, 6179-6182.

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Synthesis of a Lophotoxin Intermediate

Summary: The carbometalation of an optically active homopropargyl alcohol is the key step in preparing the C-7,C-12 fragment of the marine neuromuscular agent (+)-lophotoxin.

Sir: During the course of our synthetic study of the related marine furanocembranoids (+)-lophotoxin¹ and (+)-pukalide,² we wished to prepare lactone 1. The vinyl iodide



provides the functionality that is needed to form the C-6,C-7 bond of the natural products either through palladium(0)³ or rhodium(I)-catalyzed⁴ coupling to a furyl nucleophile. Control of the geometry of the trisubstituted alkene is crucial to the success of this approach. The zirconocene dichloride mediated addition of trimethylaluminum to an alkyne⁵ appeared to offer a convenient solution to this problem. This reaction has been reported to be successful with unprotected homopropargyl alcohols;⁵ therefore the reaction with racemic alcohol 2 was examined (Scheme I). The preparation of 2 from 1,4-butanediol was straightforward; however, the yield of the following synthetic step, carbometalation⁶ followed by quenching with iodine, was disappointing (35% isolated yield of 3a). Silyl ether 4 was prepared and was subjected to the same reaction conditions. The yield was again unacceptably low (20% isolated yield of 3b). In neither reaction was there any evidence of unreacted starting material.

The conceptual simplicity of the carbometalation-iodination⁶ sequence suggested that this approach to the C-7,C-12 fragment be pursued. Since homopropargyl alcohols have been shown to be good substrates for this reaction it was reasonable to assume that the remote oxygen was responsible for the poor yields of 3a and 3b. Accordingly 7-(phenylthio)hept-1-yn-4-ol (5) and 7-chlorohept-1-yn-4-ol (6) were prepared (Scheme II). Carbometalation⁶ of 5 and 6 followed by iodination produced vinyl iodides 7 (70-80% yield) and 8 (76-82% yield), respectively. The vastly improved yields for the reactions of 5 and 6 suggested that the earlier results with 2 and 4 were a consequence of bidentate chelation of aluminum by both oxygen atoms.

The introduction of the second oxygen atom could be accomplished either through a Pummerer¹⁰ reaction of 7

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(2) Missakian, M. G.; Burreson, B. J.; Scheuer, P. J. *Tetrahedron* 1976, 31, 2513-2515.

(3) Negishi, E.-i.; Luo, F.-T.; Frisbee, R.; Matsushita, H. *Heterocycles* 1982, 18, 117-122.

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(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* 1972, 94,