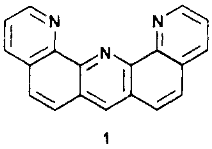
764 *J. Org. Chem.* **1986**, *51*, 764-765

Communications

Construction of a Soluble Heptacyclic Terpyridine

Summary: A new synthesis of the quino[8,7-*b*][1,10]-phenanthroline nucleus is reported, allowing the introduction of solubilizing substituents and saturated terminal rings.

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 tetrahydrodibenzo 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.



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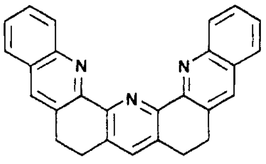

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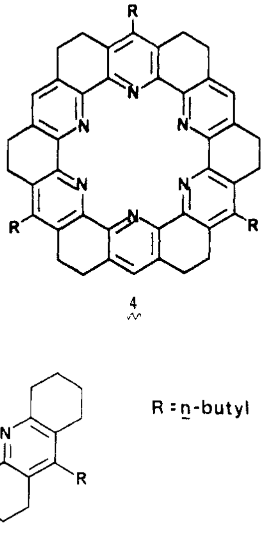

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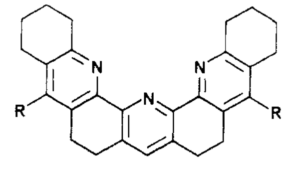

3

R = n-butyl

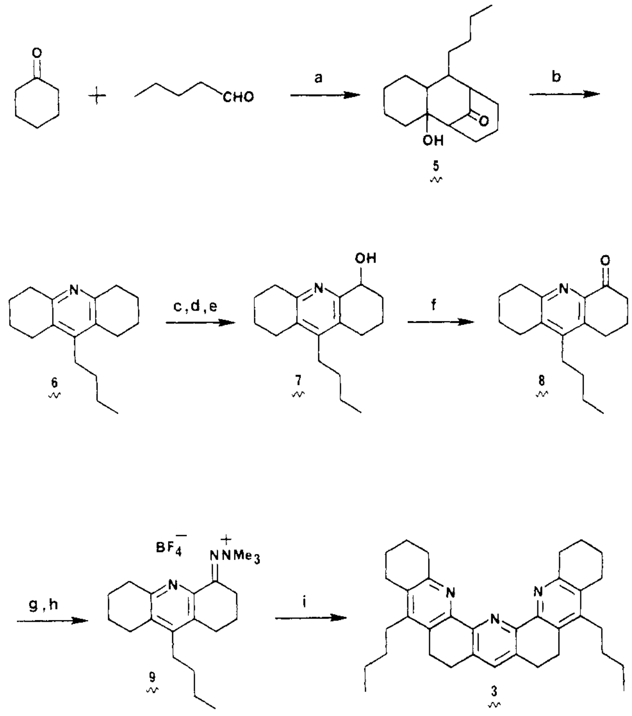

Figure 1. Synthesis of 5,11-di-*n*-butyl-1,2,3,4,6,7,9,10,12,13,14,15-dodecahydroacridino[4,3-*b*]benzo[*j*][1,10]-phenanthroline: (a) KOH, ethanol, 70 °C, 7 h (49%); (b) $NH_2OH\cdot HCl$, $NaOAc\cdot 3H_2O$, HOAc, distill, 185 °C, 12 h (32%); (c) MCPBA, CH_2Cl_2, room temperature, 1 h; (d) Ac_2O, 110 °C, 70 min; (e) 3 M HCl, 100 °C, 1 h (69% from **6**); (f) CrO_3, HOAc, H_2O, H_2SO_4, room temperature, 2 h (92%); (g) Me_2NNH_2, cyclohexane, EtOH, $TsOH\cdot H_2O$, room temperature, 16 h/C_6H_6, reflux, 15 min; (h) Me_3OBF_4, CH_2Cl_2, room temperature, 30 min; (i) 210 °C, N_2, 5 min (23% from **8**).

We are interested both in complexation properties of rigidified terpyridines, such as **3**, and in synthetic approaches to hexaazakekulene[5] 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*-butyloctahydroacridine **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-CH_2 position, which may be effected by ozonolysis of a benzylidene derivative.[10] Unfortunately, condensation of **6** with benzaldehyde in acetic anhydride results in a

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(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.

(7) Tilichenko, M. N. *Uch. Zap. Sarat. Gos. Univ.* **1962**, *75*, 60-65; *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.

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mixture of starting material and monobenzylidine and dibenzylidine derivatives. An alternative four-step sequence employing Boekelheide rearrangement of an acetylated *N*-oxide[11] 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 acid[12] gave ketone **8**[8] in 63% yield overall from **6**.

Conversion of **8** to hepatcyclic 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 **3**[14] 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., CH_2Cl_2, $CHCl_3$, 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; $NH_2OH{\cdot}HCl$, 5470-11-1; Me_2NNH_2, 57-14-7; cyclohexanone, 108-94-1; valeraldehyde, 110-62-3.

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[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, $CDCl_3$, δ relative to Me_4Si) 7.36 (s, 1 H, Ar H), 3.8 (br s, 3 H, H_2O), 3.0–3.2 (m, 4 H, α-$PyCH_2$), 2.92 (s, 8 H, $ArCH_2CH_2Ar$), 2.5–2.9 (m, 8 H, Ar CH_2), 1.7–1.9 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.25–1.5 (m, 8 H, $CH_2CH_2CH_2CH_3$), 0.97 (t, 6 H, CH_3); IR (KBr) 3350 (br), 2940 (s), 2850 (ms), 1650 (sh), 1550 (m), 1430 (m), 1390 (m), 1240 (m), cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 245 (22 000), 297 (10 000), 306 (14 000), 346 (24 000), nm; MS (70 eV), *m/e* (relative intensity) 505 (M^+, 100). Anal. Calcd for $C_{35}H_{46}N_3O_{1.5}$: 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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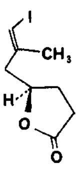
Received October 17, 1985

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 (+)-lophotoxin[1] 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)-catalyzed[4] 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 alkyne[5] 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, carbometalation[5] 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.



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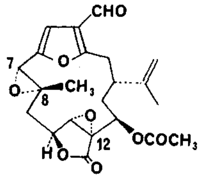
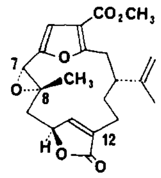


(+) - Lophotoxin



(+) - Pukalide

The conceptual simplicity of the carbometalation–iodination[5] 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). Carbometalation[5] 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 Pummerer[10] reaction of **7**

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[6] Lombardo, L. *Tetrahedron Lett.* **1984**, 227–228.

[7] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.

[8] Propargylmagnesium bromide was prepared from propargyl bromide and magnesium in the presence of catalytic mercuric chloride: Sondheimer, F.; Amiel, Y.; Gaoni, Y. *J. Am. Chem. Soc.* **1962**, *84*, 270–274.

[9] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

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