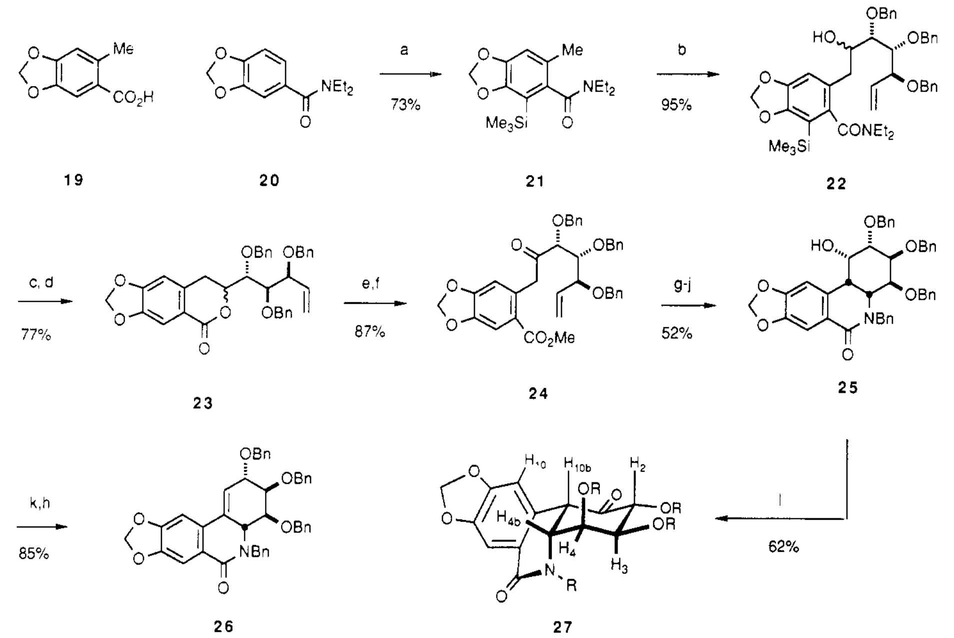
Scheme III[a]



[a] Reagents: (a) s-BuLi, Me_3SiCl, THF, TMEDA, −78 °C; s-BuLi, THF, TMEDA, MeI; (b) s-BuLi, THF, −78 °C, 7; (c) Bu_4NF, THF, 0 → 25 °C; (d) CSA, PhH, 90 °C; (e) LiOH, THF–MeOH, then CH_2N_2, Et_2O; (f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (g) O_3, MeOH, −78 °C, then Me_2S; (h) DBU, THF; (i) $PhCh_2NH_2$, PPTs; (j) $NaCNBH_3$, MeOH–10% aqueous HCl; (k) $MeP(OPh_3)I$, HMPA, 100 °C; (l) $(nPr)_4NRuO_4$, NMO, CH_2Cl_2.

a sample prepared from authentic (+)-**2**.[19] Finally, NOE studies of the derived ketone **27** have confirmed the spatial proximity of the methine proton at C_{10b} to those at C_2, C_{4b}, and C_{10}, an observation uniquely consistent with cis fusion of the C ring and equatorial disposition of the C_2 benzyloxy substituent.

The sequence described above constitutes a highly efficient, asymmetric route to the phenanthridone systems of pancratistatin and structurally related alkaloids of biological interest and provides a viable preparative entry to C-ring analogues of pancratistatin and the narciclasines from which specific structure–activity relationships can be elucidated. Our scheme effectively defines four of the six stereogenic centers of the pancratistatin C ring and presents several options for final elaboration of the desired trans-fused phenanthridone system. Interestingly, preliminary attempts to directly establish a trans-fused phenanthridone by epimerization of ketones **18** and **27** have revealed an unexpected kinetic preference for deprotonation of both substrates at the undesired C_2 position. The nature of the protecting groups used to mask the C-ring hydroxyl substituents may profoundly effect the regiochemistry of deprotonation for these intermediates; efforts to define an alternative strategy for elaboration of the requisite trans-fused phenanthridones and to extend our scheme to the synthesis of pancratistatin are in progress.

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Supplementary Material Available: Experimental procedures for the preparation of all new compounds and full characterization data (14 pages). Ordering information is given on any current masthead page.

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(19) An authentic sample of **26** was prepared by treatment of (+)-lycoricidine (**2**), kindly provided by Professor G. Pettit, with sodium hydride and excess benzyl bromide in DMF.

Effects on Anions and Radicals of α-Quaternary Ammonium Substituents

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Summary: α-Pyridinium groups increase the acidities of acetophenone, acetonitrile, and ethyl acetate much more than do α-Me_3N^+ groups; they decrease the BDEs of the acidic C–H bonds, whereas α-Me_3N^+ groups increase them.

The $\sigma_\alpha^\bullet$ scale of Wayner and Arnold indicates that meta substituents in benzylic radicals are generally destabilizing.[1] Similarly, in our laboratory, recent estimates of the homolytic bond dissociation energies (BDEs) in DMSO of the O–H bonds in phenols has led to the conclusion that all meta substituents possess an inherent bond strengthening (i.e., radical destabilizing) factor, and that the bond-strengthening effects of para electron-withdrawing

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(1) Wayner, D. D. M.; Arnold, D. R. *Can. J. Chem.* **1984**, *62*, 1164–1168.

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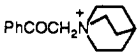
Table I. Acidities and Homolytic Bond Dissociation Energies of the Acidic C–H Bonds in Quaternary Ammonium Salts in DMSO Solution

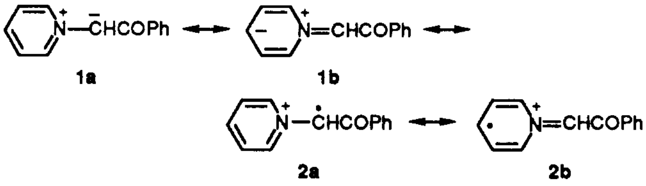
compound	pK_{HA}[a]	ΔpK_{HA}[g]	$E_{ox}(A^-)$[h]	BDE[i]	ΔBDE
$PhCOCH_3$	24.7[b]	(0.0)	0.143 (60)	93.0	(0.0)
$PhCOCH_2{}^+NMe_3\ Br^-$	14.6[c]	10.3	0.871 (60)	96.1	−3.1
$PhCOCH_2{}^+NMe_3\ Cl^-$	14.6[d]	10.3	0.903 (82)	96.8	−3.8
$PhCOCH_2{}^+NMe_3\ NO_3{}^-$	14.6[d]	10.3	0.897 (110)	96.7	−3.7
	14.6	10.3	0.857 (80)	95.8	−2.8
$PhCOCH_2{}^+NC_5H_5\ Br^-$	10.7	14.2	0.714 (80)	87.1	5.9
CH_3CN	31.3[b]	(0.0)		93.0	(0.0)
$Me_3{}^+NCH_2CN$	20.6[c]	10.9	0.479 (65)	95.3	−2.3
$C_5H_5{}^+NCH_2CN$	16.5[e]	15.0	0.390 (sh)	87.6	5.4
CH_3CO_2Et	28–29[f]	(0.0)		~95[j]	
$Me_3{}^+NCH_2CO_2Et$	20.0	9.2	0.609 (76)	97.4	−2.4
$C_5H_5{}^+NCH_2CO_2Et$	14.10	15.1	0.638 (100)	90.0	5.0

[a] Average of equilibrium measurements made against two indicators in the present study, unless otherwise indicated. [b] Reference 5. [c] Reference 6. [d] Assumed to be the same as for the bromide salt. [e] Average of two one-point titrations. [f] Estimated by extrapolation. [g] Relative to the parent (statistically corrected). [h] Measured by cyclic voltammetry (in eV) with a Ag/AgI reference electrode in DMSO relative to the ferrocene–ferrocenium couple under the conditions previously reported (ref 7); referenced to the standard hydrogen electrode by adding −0.125.[7] Wave widths are given in parentheses; sh = shoulder. [i] Estimated by using the equation: $BDE = 1.37pK_{HA} + 23.06E_{ox}(A^-) + 56$.[8] Estimates for the parent acids are ±3 kcal/mol, those for their derivatives are ±1 kcal/mol. [j] Estimated by adding the ΔBDE of 11 for $PhCH_2COCH_3$ vs CH_3COCH_3 to the BDE of 84 estimated for $PhCH_2CO_2Et$ by our method.

substituents are larger than those of their meta counterparts.[2] (Since radicals are electron deficient it is reasonable for electron withdrawal to cause destabilization.) According to this view groups like α-CN, α-COPh, or α-CO_2Et therefore play a dual role toward radicals, i.e., destabilizing by virtue of their group electronegativities and stabilizing by virtue of their abilities to delocalize an odd electron. Quaternary ammonium groups such as Me_3N^+ are among the strongest electron-withdrawing groups known by virtue of their positive charge and are unique in possessing little or no ability to delocalize an adjacent negative charge or odd electron. The observation that the α-Me_3N^+ groups in $PhCOCH_2NMe_3{}^+$ and 9-Me_3N^+ FlH strengthen the acidic C–H bonds by 4 and 5 kcal/mol, respectively.[3,4] supports the conclusion that electrostatic effects do indeed lead to the destabilization of radicals.

In this paper pyridinium groups are shown to produce much larger acidifying effects when substituted for an α-hydrogen atom in acetophenone, acetonitrile, or ethyl acetate than do Me_3N^+ groups. Also, the pyridinium groups in these compounds have been found to weaken the acidic C–H bonds substantially, whereas the Me_3N^+ groups have the opposite effect. These differences are attributed to the ability of the pyridinium group to stabilize a negative charge or odd electron on an adjacent atom by delocalization, as well as by an electrostatic effect, whereas the Me_3N^+ group acts solely by an electrostatic effect. In this respect the pyridinium group resembles conventional electron-attracting groups such as CN, COPh, SO_2Ph, and CO_2Et. The experimental evidence upon which these statements are based is summarized in Table I.

The first six entries in Table I are for acetophenone and acetophenone derivatives in which quaternary ammonium substituents have been substituted for an α-hydrogen atom. The three entries with α-Me_3N^+ substituents and Br^-, Cl^-, and $NO_3{}^-$ counterions demonstrate that the homolytic bond dissociation energies for the α-C–H bonds are independent of the nature of the counterion. They indicate that α-Me_3N^+ and α-quinuclidinium substituents cause decreases in pK_{HA} of 10.3 units (statistically corrected) and *increases* in the BDEs of the acidic C–H bonds of 3 ± 1 kcal/mol. The α-pyridinium group causes a larger increase in acidity (14.2 pK_{HA} units) than α-Me_3N^+, and a *decrease* in the BDE of 5.9 kcal/mol. The acidity increase is comparable in size to, or greater than, those caused in acetophenone by the presence of the strong α-electron-withdrawing groups CN, SO_2Ph, or COPh (14.7, 13.5, and 11.5 pK_{HA} units, respectively). The large effect of the α-pyridinium group can be accounted for in terms of its large field/inductive effect, coupled with its ability to delocalize the negative charge in the ylide (**1a** ↔ **1b**). The decrease in the BDE for the acidic C–H bond in the α-pyridinium salt can similarly be rationalized in terms of the ability of the pyridinium group to delocalize the odd electron in the cation radical (**2a** ↔ **2b**), which overshadows its radical destabilizing electrostatic effect.



Similar effects were observed for substituting α-Me_3N^+ and α-pyridinium functions into acetonitrile and ethyl acetate (Table I). We conclude that the enhanced acidifying effect of α-pyridinium type functions and their unique ability among α-quaternary ammonium cations to stabilize radicals is a general phenomenon. This conclusion supports the view that most electron-withdrawing groups play a dual role of destabilizing adjacent radicals by field/induction and stabilizing them by delocalization of the odd electron.

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