The ^1H NMR spectrum of the thermolysis products was superimposable on the spectrum of olefin **3**. GC analysis (conditions A and B) revealed that **4**, **5**, and **1** were also present but in a combined yield of <10%. Subjecting authentic olefins **3–5** to the thermolysis conditions showed that they do not interconvert.

The only circumstance under which any product besides **3** was formed in substantial yield was when unpurified solvents were used in thermolyses. For example, thermolysis in reagent benzene from a freshly opened bottle yielded ca. 20% of **4**. Repeating the experiment after purifying the benzene as described above resulted in <5% yield of **4**.

Photolysis of PMDE. Precisely measured quantities of PMDE stock solutions were irradiated in two sealed Pyrex cells in a Rayonet reactor at room temperature. One cell was removed after 0.5 h and the other was left in the reactor until the diazo color had bleached (2 h).

The percent conversion in the partially photolyzed samples was determined by observing the reduction in absorbance at 516 nm. This value agreed, to within 1%, with the value determined by quenching excess PMDE with DEAD[41] and quantifying the total yield of **3–5** by GC (conditions A and B).

Similarly, GC analysis of the completely photolyzed solutions established that **3–5** accounted for 99% of PMDE converted. No other products were detected. The ratio **3**:(**4** + **5**) was found to be invariant; only the relative amounts of **4** and **5** varied since **4** is efficiently photoisomerized to **5**.

Acknowledgment. We thank J. Carter Cook and Dr. Richard Milberg for their assistance with the mass spectrometric analyses. This work was supported by the National Science Foundation. GBS is a Dreyfus Teacher-Scholar.

Registry No. 1, 5350-76-5; **1** (formamide), 92345-71-6; **1** (amine), 92345-72-7; **2**, 92345-67-0; **3**, 1667-02-3; **4**, 17024-58-7; **5**, 20488-50-0; **6**, 92345-73-8; **6** radical cation, 92345-86-3; (*Z*)-**7**, 92365-81-6; (*E*)-**7**, 92345-78-3; **8**, 92345-79-4; **9**, 92345-70-5; (*E*)-**10**, 92345-81-8; (*Z*)-**10**, 92345-82-9; (*E*)-**11**, 92345-83-0; (*Z*)-**11**, 92345-84-1; PMDE, 92345-68-1; PME, 92345-69-2; Ag_2O, 20667-12-3; $Cu(ClO_4)_2$, 13770-18-8; mesitylacetonitrile, 34688-71-6; (2,4,6-trimethylbenzyl)triphenylphosphonium chloride, 54757-04-9; 4-methylbenzophenone, 134-84-9; mesitylene, 108-67-8; 4-mesitoylbenzophenone, 92345-74-9; (2,4,6-trimethylbenzylidene)triphenylphosphine, 92345-75-0; (*E*)-1-mesitoyl-4-(1-phenyl-2-mesitylethenyl)benzene, 92345-76-1; (*Z*)-1-mesityl-4-(1-phenyl-2-mesitylethenyl)benzene, 92365-82-7; 1-mesitylhydroxymethyl-4-(1-phenyl-2-mesitylethenyl)benzene, 92345-77-2; 4,4′-dibenzoylbibenzyl, 47658-53-7; α-bromo-4,4′-dibenzoylbibenzyl, 92345-80-7; Red Transient (12), 92345-87-4; bromobenzene, 108-86-1; 2,4,6-trimethylbenzyl chloride, 1585-16-6; 4-benzoylbenzoic acid, 611-95-0; 4-benzoylbenzoyl chloride, 39148-58-8; 4,4′-dibenzoylstilbene, 53178-88-4; 4-benzoylbenzaldehyde, 20912-50-9; tris(*p*-bromophenyl)aminium hexachloroantimonate, 40927-19-3; $PMDE^{+\cdot}$, 92345-85-2.

The Stabilized Iminium Ylide–Olefin [3 + 2] Cycloaddition Reaction. Total Synthesis of *Sceletium* Alkaloid A_4

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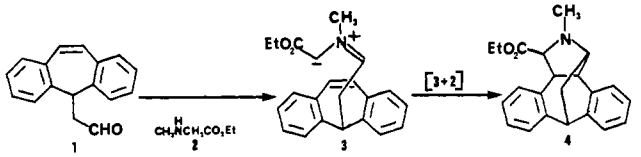
Abstract: A new method for performing an intramolecular [3 + 2] cycloaddition generating two carbon–carbon bonds utilizing a stabilized iminium ylide (**3**) has been developed. In practice, an olefin aldehyde is condensed with a secondary amino acid ester, generating **3** in situ which undergoes a [3 + 2] cycloaddition. Effectively, a proline is annulated to an internal olefin. Application of this method to the total synthesis of *Sceletium* alkaloid A_4 is discussed.

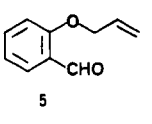
We recently reported that the reaction of the aldehyde **1** and sarcosine ethyl ester (**2**) afforded the cycloadduct **4** under dehydrating conditions.[1] This transformation presumably proceeds



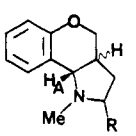
via the stabilized iminium ylide **3** which underwent an intramolecular [3 + 2] cycloaddition. *This reaction mode is predicted to be very powerful since it simultaneously constructs two carbon–carbon bonds, forms complex ring systems with stereocontrol, and effectively annulates a proline moiety to an internal olefin.*[2]

In order to further exemplify this chemistry, we examined the reaction of a number of olefin aldehydes with secondary amino acid esters and applied these results to the total synthesis of a naturally occurring substance, *Sceletium* alkaloid A_4.

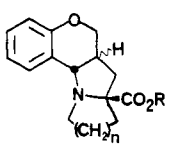
O-Allylsalicylaldehyde (**5**)[3] was treated with **2**, proline methyl ester (**6**), and pipecoline ethyl ester (**7**) to afford the polycyclic adducts **8**, **9**, and **10**, respectively, in corresponding yields of 97%,



5



8 R = CO_2Et
15 R = CO_2H
16 R = H



9 n = 1 R = Me
10 n = 2 R = Et

98%, and 99%, In practice, the reaction is carried out by reacting the olefinic aldehyde with the amino acid ester in refluxing toluene and driving off water by means of a Dean–Stark trap.[4] The amino acid ester hydrochloride may also be used if 1 equiv of diiso-

(1) Confalone, P. N.; Huie, E. M. *J. Org. Chem.* **1983**, *48*, 2994.

(2) Other examples of related reactions: (a) Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 135. (b) Livinghouse, T.; Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 210. (c) Grigg, R.; Gunaratne, H. Q. N. *Tetrahedron Lett.* **1983**, *24*, 4457. (d) Texier, F.; Carrie, R. *Bull. Soc. Chim. Fr.* **1974**, 310. (e) Huisgen, R.; Schees, W.; Sziemies, G.; Huber, H. *Tetrahedron Lett.* **1966**, 397. (f) Achiwa, K.; Sekiya, M. *Heterocycles* **1983**, *20*, 167. (g) Padwa, A.; Hoffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, *24*, 4304. (h) Tsuge, O.; Ueno, K.; Ueda, I. *Heterocycles* **1981**, *16*, 1503. (i) Grigg, R.; Aly, M. F. Sridhasan, V.; Thianpatanagul, S. *J. Chem. Soc. Chem. Commun.* **1984**, 180, 182.

(3) For a typical procedure, see: *Org. Synth.* **1955**, *3*, 418.

(4) Removal of water was not essential but improved the yields by preventing ester hydrolysis. Reactions were faster and gave higher yields at high concentrations (1 M) of both substrates.

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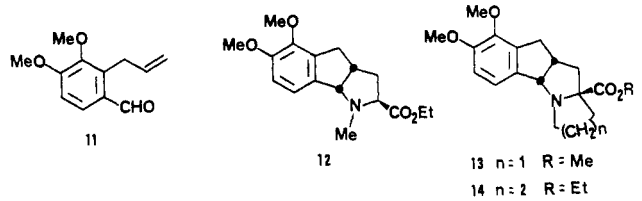
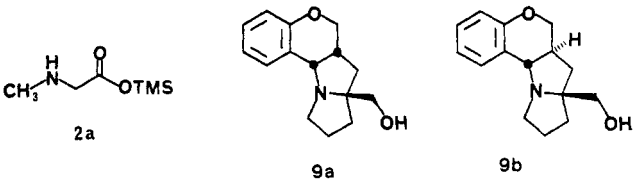
propylethylamine is added to the reaction mixture.[5] Cyclization to generate 5,5-bicyclic systems was demonstrated by the reaction of 3,4-dimethoxy-2-allylbenzaldehyde (**11**)[6] with **2**, **6**, and **7** to afford the cycloadducts **12**, **13**, and **14** in yields of 89%, 93%, and



99%, respectively. For eventual application to natural products synthesis, however, both the stereochemical outcome of these reactions as well as the deletion of the usually unwanted ester functionality had to be addressed.

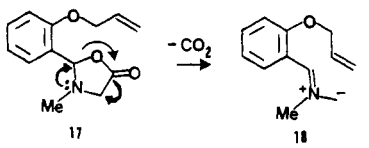
The stereochemistry at the ring juncture in compounds **8** and **10** was easily assigned by NMR after chromatographic separation of isomers. The isomers of pyrrolidine **9** were inseparable; however, after reduction to the corresponding alcohols **9a** and **9b**, fractional



crystallization provided pure samples of each isomer. The benzylic methine proton (H_A in **8**) exhibited a doublet with a coupling of 5–7 Hz for the cis-fused compounds and 10–12 Hz, a typical diaxial coupling, for the trans-fused adducts. In all three cases, the cis-ring fusion predominated with cis/trans ratios of 10.0 (in **8**), 2.5 (in **9**), and 11.5 (in **10**).[7] As expected for the 5,5-ring systems, only cis ring-fusion isomers of compounds **12–14** were obtained. The stereochemistry of the ester appendage could not be determined spectroscopicaly, but was assigned as shown on the basis of steric considerations present in the dipolar intermediates.[8]

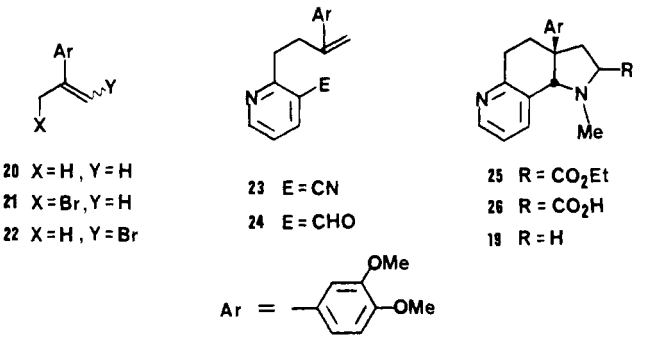
The removal of the ester functionality was accomplished by using the method of Rapoport.[9] Accordingly, the tricyclic amino ester **8** was saponified quantitatively to the amino acid **15** and treated with phosphorus oxychloride at 100 °C for 15 min. The resulting iminium chloride was hydrolytically reduced in situ with sodium cyanoborohydride. The final decarbethoxylated product **16** was obtained in 54% overall yield from the aldehyde **4**.[10]

In related studies, it was discovered that the decarboxylated pyrrolidine **16** could be obtained *directly* from **5** in 61% yield by refluxing a dry solution of **5** with 3 equiv of sarcosine trimethylsilyl ester (**2a**) for 20 h. This result presumably involves decarboxylation of the cyclic intermediate **17** to the *unstabilized* zwitterion **18** which cycloadds[11] to the internal olefin. Further investigation



of this decarboxylative cycloaddition, which eliminates the Rapoport sequence from this chemistry, is under way.

Recently, some effort has been directed toward the synthesis of alkaloids using various types of iminium ylide based dipoles.[12] Thus, we decided to demonstrate the utility of this stabilized iminium ylide–olefin cycloaddition reaction by a total synthesis of the *Sceletium* alkaloid A_4[13] (**19**), a member of the Aizoaceae family, first isolated by Popelak and Lettenbauer[14] and later characterized by Jeffs in 1971.[15] The allylic bromide **21** was prepared from 3,4-dimethoxyacetophenone via a Wittig condensation of methylenetriphenylphosphorane in THF to yield the olefin **20** in 90% yield, followed by bromination with *N*-bromosuccin-



imide to give a 2/1 mixture of the allylic bromide **21** and the corresponding vinylic bromide **22** in 57% yield. Deprotonation of the methyl group of 3-cyano-2-methylpyridine[16] occurred rapidly at −78 °C with lithium hexamethyldisilazane in 10% HMPA/THF. Alkylation of this carbanion at −78 °C using 1.5 equiv of allyl bromide **21** afforded the cyano olefin **23** in 72% yield. Reduction of **23** with diisobutylaluminum hydride at 0 °C provided the desired aldehyde **24** in 64% yield.

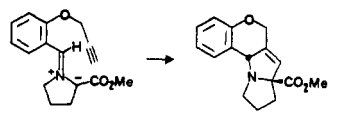
The 1,1-disubstituted olefin present in **24** leads to a quaternary carbon in the cycloadduct. This steric compression accounted for failure to achieve cycloaddition under our standard conditions. However, heating **24** and 3 equiv of **2** in xylene with molecular sieves in a sealed tube at 180 °C for 7 h afforded a 40% yield of the tricyclic adduct **25**. The amino acid **26** was obtained by saponification of **25** with 1 N NaOH in THF/methanol. Treatment of **26** in phenyl dichlorophosphate at 100 °C for 20 min followed by quenching with water, addition of methanol, adjusting the pH to 1, and reducing the sodium cyanoborohydride gave (±)-*Sceletium* alkaloid A_4 (**19**) in 87% yield. This compound exhibited identical spectroscopic properties (IR, NMR, UV, MS) and TLC behavior in numerous solvent systems with an authentic sample previously synthesized by Stevens.[17] Our specimen melted at 126–127.5 °C, exhibiting polymorphism with respect to published vlaues of 152–154 °C. This five-step synthesis of *Sceletium* alkaloid A_4 is the shortest to date and the most convergent. We are presently further elaborating the scope and limitations of the

(5) The yields in the reactions of hydrochloride salts were usually 10–25% lower, however.

(6) Caesar, F.; Mondon, A. *Chem. Ber.* **1968**, *101*, 990.

(7) For NMR data in model systems, see: ref 2 h and Brokatzky-Geiger, J.; Eberbach, W. *Chem. Ber.* **1983**, *116*, 2383.

(8) For example, *O*-propargylsalicylaldehyde was condensed with **6** to give a *single* dihydropyrrolidine B. The intermediate dipole presumably exists in the conformation as shown in A where the bulky aromatic ring and ester are anti. This cycloaddition of A leads to the product B where the benzylic proton and the esters are cis as shown.



(9) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448.

(10) Interestingly, none of the trans isomer corresponding to **16** was found. Presumably, equilibration of ring fusion isomers occurs during the decarboxylation sequence.

(11) Eschenmoser, A. *Chem. Soc. Rev.* **1976**, *5*, 377–8. Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069. Reference 2 i.

(12) Kraus, G. A.; Nagy, J. O. *Tetrahedron Lett.* **1983**, *24*, 3427. Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554. Vedejs, E.; Marttinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993.

(13) Stevens, R. V.; Lesko, P. M.; Lapalme, R. *J. Org. Chem.* **1975**, *40*, 3495. Forbes, C. P.; Wenteler, G. L. *J. Chem. Soc., Perkin Trans. 1* **1981**, 29.

(14) Popelak, A.; Lettenbauer, G. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. IX, p 467.

(15) Jeffs, P. W.; Luhan, P. A.; McPhail, A. T.; Martin, N. H. *J. Chem. Soc. D* **1971**, 1466.

(16) This compound was prepared as reported: *Chem. Abstr.* **1966**, *64*, 9694d.

(17) We thank the late Prof. R. V. Stevens for providing us with a synthetic sample of (±)-*Sceletium* alkaloid A_4.

intramolecular iminium ylide–olefin [3 + 2] cycloaddition reaction. Additional applications to the total synthesis of alkaloids and related substances are also in progress and will be reported in due course.

Experimental Section

General Method for the Preparation of [3 + 2] Cycloadducts. A 0.1–1.0 M solution of the olefin aldehyde (1.0 equiv) and the secondary acid ester (1.1–1.5 equiv) in toluene was refluxed into a Dean–Stark trap until the olefin aldehyde was consumed by TLC (usually less than 1 day). The reactions proceeded faster, and the yields were better at higher concentrations in both substrates. The toluene was removed in vacuo and the residue was chromatographed on silica gel with a mixture of hexanes/ethyl acetate to obtain the pure cycloadduct.

Pyrrolidine 8 (cis fused): clear oil; NMR ($CDCl_3$, 360 MHz) δ 7.18 (m, 2 H), 7.00 (m, 2 H), 4.21 (q, 2 H, J = 7.4 Hz), 4.02 (d, 1 H, J = 7.0 Hz), 3.98 (dd, 1 H, J = 10.9, 5.0 Hz), 3.90 (dd, 1 H, J = 10.9, 8.5 Hz), 3.73 (dd, 1 H, J = 8.4, 3.6 Hz), 2.67 (m, 1 H), 2.47 (s, 3 H), 2.20 (ddd, 1 H, J = 14, 9.5, 3.6 Hz), 1.98 (ddd, 1 H, J = 14, 8.4, 4.7 Hz), 1.32 (t, 3 H, J = 7.4 Hz).

Pyrrolidine 8 (trans fused): clear oil; NMR ($CDCl_3$, 360 MHz) δ 7.35 (m, 1 H), 7.12 (m, 1 H), 6.86 (m, 2 H), 4.53 (dd, 1 H, J = 10.2, 4.2 Hz), 4.21 (m, 2 H), 4.13 (dd, 1 H, J = 11.0, 10.2 Hz), 3.92 (dd, 1 H, J = 8.4, 6.8 Hz), 3.87 (d, 1 H, J = 11.0 Hz), 2.58 (s, 3 H), 2.28 (m, 2 H), 1.72 (m, 1 H), 1.31 (t, 3 H, J = 7.4 Hz).

Cycloaddition Leading to 9. After chromatography, a 98% yield of two isomers was obtained: clear oil; high resolution mass spectrum, obsd 273.1367, $C_{16}H_{19}NO_3$ requires 273.1365. These isomers could not be separated on TLC. Upon reduction of the mixture with 1 equiv of LAH in THF at room temperature and working up with $Na_2SO_4 \cdot 10H_2O$, an 81% yield of a solid was obtained The two resulting amino alcohols could be fractionally crystallized from EtOAc/hexane. **9a**: white needles, mp 111–112 °C; NMR ($CDCl_3$, 360 MHz) δ 7.40 (m, 1 H), 7.18 (m, 1 H), 6.93 (m, 2 H), 4.25 (d, 1 H, J = 7.4 Hz), 4.21 (dd, 1 H, J = 11.4, 5.8 Hz), 3.58 (t, 1 H, J = 11.4 Hz), 3.42 (m, 2 H), 3.11 (br, 1 H), 2.55–2.85 (m, 3 H), 2.18 (m, 2 H), 1.65–1.8 (m, 3 H), 1.46 (dd, 1 H, J = 14, 4.0 Hz). **9b**: white cubes, mp 183.5–184.5 °C; NMR ($CDCl_3$, 360 MHz) δ 7.37 (m, 1 H), 7.12 (m, 1 H), 6.85 (m, 2 H), 4.53 (dd, 1 H, J = 10.4, 4.2 Hz), 4.06 (dd, 1 H, J = 11.2, 10.4 Hz), 3.80 (d, 1 H, J = 11.8 Hz), 3.47 (br, 2 H), 3.17 (m, 1 H), 2.3–2.45 (m, 2 H), 2.07 (m, 1 H), 1.5–1.8 (m, 5 H).

Cycloaddition Leading to 10. A solution of **5** (8.84 g, 54.6 mmol) and **7** (12.9 g, 81.9 mmol) in 150 mL of toluene was refluxed into a Dean–Stark trap for 18 h. About 1 mL of water was in the trap. Evaporation of the solvent and column chromatography on silica gel using 10% EtOAc/hexane as eluent gave 14.78 g of the cis isomer of **10** and 1.55 g of the trans isomer of **10**. The total yield was 99%, and the ratio of isomers was 9.5/1.0 = cis/trans. For **10** (cis fused): clear oil; NMR ($CDCl_3$, 360 MHz) δ 6.87–7.20 (m, 4 H), 4.14–4.24 (m, 2 H), 4.16 (d, 1 H, J = 7.2 Hz), 3.89 (dd, 1 H, J = 11.2, 5.0 Hz), 3.84 (dd, 1 H, J = 11.2, 7.8 Hz), 2.99 (m, 2 H), 2.25–2.4 (m, 3 H), 1.5–1.65 (m, 3 H), 1.29 (t, 3 H, J = 7.2 Hz), 1.15–1.3 (m, 3 H); high-resolution mass spectrum, obsd 301.1670, $c_{18}H_{23}NO_3$ requires 301.1678.

For **10** (trans fused): light yellow oil; NMR ($CDCl_3$, 360 MHz) δ 6.8–7.1 (m, 4 H), 4.43 (dd, 1 H, J = 9.6, 4.8 Hz), 4.15–4.25 (m, 2 H), 4.07 (dd, 1 H, J = 11.8, 9.6 Hz), 4.06 (d, 1 H, J = 10.8 Hz), 3.23 (m, 1 H), 3.12 (m, 1 H), 2.2–2.45 (m, 2 H), 2.03 (dd, 1 H, J = 13.8, 10.0 Hz), 1.90 (dd, 1 H, J = 13.8, 9.4 Hz), 1.6–1.75 (m, 3 H), 1.4–1.55 (m, 1 H), 1.27 (m, 4 H).

Pyrrolidine 12: clear oil; IR (neat) 2970, 2940, 2910, 1730, 1610, 1490, 1270, 1180, 1080 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 7.03 (d, 1 H, J = 8.4 Hz), 6.78 (d, 1 H, J = 8.4 Hz), 4.55 (d, 1 H, J = 7.8 Hz), 4.19 (q, 2 H, J = 7.2 Hz), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.56 (dd, 1 H, J = 7.2, 4.8 Hz), 3.15–3.35 (m, 2 H), 2.68 (dd, 1 H, J = 17, 3.8 Hz), 2.59 (s, 3 H), 2.28 (m, 1 H), 1.97 (m, 1 H), 1.28 (t, 3 H, J = 7.2 Hz); high-resolution mass spectrum, obsd 305.1621, $C_{17}H_{23}NO_4$ requires 305.1627.

Pyrrolidine 13: clear oil; IR (neat) 2950, 2870, 2835, 1730, 1605, 1490, 1275, 1220, 1080 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 7.03 (d, 1 H, J = 8.2 Hz), 6.80 (d, 1 H, J = 8.2 Hz), 4.91 (d, 1 H, J = 7.8 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.18 (m, 2 H), 2.89 (m, 1 H), 2.63 (m, 2 H), 2.45 (m, 1 H), 2.25 (m, 1 H), 1.75–2.0 (m, 3 H), 1.55 (dd, 1 H, J = 13.2, 8.2 Hz); high-resolution mass spectrum ($M^+ - H_2$), obsd 315.1462, $C_{18}H_{21}NO_4$ requires 315.1470.

Pyrrolidine 14: white clusters of tiny plates, mp 111.5–112.5 (EtOAc/hexane); NMR ($CDCl_3$, 360 MHz) δ 7.04 (d, 1 H, J = 8.2 Hz), 6.77 (d, 1 H, J = 8.2 Hz), 4.58 (d, 1 H, J = 8.0 Hz), 4.18 (m, 2 H), 3.83 (s, ,3 H), 3.82 (s, 3 H), 3.05–3.25 (m, 3 H), 2.95 (m, 1 H), 2.75 (dd, 1 H, J = 17, 3.8 Hz), 2.44 (dd, 1 H, J = 12.2, 8.8 Hz), 2.30 (m, 1 H), 1.4–1.7 (m, 5 H), 1.1–1.5 (m, 6 H).

Decarboxylative Cycloaddition of 2a and 5. A solution of **5** (207 mg, 1.28 mmol) and **2a** (1.0 mL) in 6 mL of dry toluene was refluxed under N_2 for 24 h. After cooling, 5 mL of water was added, and the mixture was stirred 5 min. The reaction was partitioned between saturated $NaHCO_3/CH_2Cl_2$, dried (Na_2SO_4), and evaporated. A yellow oil (199 mg) was obtained. Column chromatography on silica gel using a gradient of 0–2% $MeOH/CH_2Cl_2$ as eluent afforded 148 mg (61%) of pure **16** (cis fusion only) as a yellow oil: mp (HCl salt from 2-propanol/ether) 200.5–201.5 °C; NMR ($CDCl_3$, 360 MHz) δ 7.16 (m, 2 H), 6.87 (m, 2 H), 4.00 (dd, 1 H, J = 11, 5.4 Hz), 3.88 (t, 1 H, J = 11 Hz, 3.57 (dt, 1 H, J = 2.1, 9.0 Hz), 2.89 (d, 1 H, J = 5.6 Hz), 2.43 (s, 3 H), 2.38 (m, 1 H), 2.28 (q, 1 H, J = 9.0 Hz), 2.02 (m, 1 H), 143 (m, 1 H); mass spectrum, m/z 189, 188, 145, 131.

Anal. Calcd for $C_{12}H_{16}NOCl$: C, 63.85; H, 7.16; N, 6.21; Cl, 15.71. Found: C, 63.75; H, 7.15; N, 5.95; Cl, 15.92.

Preparation of 16 via the Method of Rapoport. A mixture of 5 (2.00 g, 12.3 mmol), sarcosine ethyl ester HCl (2.66 g, 17.3 mmol), and diisopropylethylamine (3.7 mL, 21 mmol) in 63 mL of toluene was refluxed for 26 h. partitioned between saturated $NaHCO_3/Ch_2Cl_2$, dried (Na_2SO_4), and evaporated. To the crude, red oil was added 50 mL of MeOH and 25.0 mL of 1.0 N NaOH. After stirring 2 h, 25.0 mL of 1.0 N HCl was added. The solvent was removed in vacuo. The product was extracted several times with hot EtOAc. Evaporation of EtOAc gave a yellow solid. To the dried solid was added 10 mL of phosphorus oxychloride, and the slurry was heated in an oil bath at 103 °C with swirling for 10 min (bubbling ceased). After cooling in ice, 25 mL of water was added slowly. Partitioned between 3 M NaOH/ether, dried ($MgSO_4$), and evaporated the solvent. To the oil was added 25 mL of MeOH followed by 0.38 g of sodium borohydride. The solution was stirred for 30 min, then partitioned between water/CH_2Cl_2. After drying (Na_2SO_4), the solvent was evaported leaving 1.27 g of a yellow oil. Column chromatography on silica gel as before gave 1.04 g (45% overall) of **16** as a yellow oil. The spectral data agreed with **16** prepared by the decarboxylative cycloaddition, and again only the cis isomer was obtained.

3,4-Dimethoxy-α-methylstyrene: white needles; mp 33–34 °C (Et_2O/petroleum ether); NMR ($CDCl_3$, 90 MHz) δ 6.9 (m, 3 H), 5.27 (s, 1 H), 4.99 (m, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 2.24 (br s, 3 H).

Bromide 21: clear oil; NMR (CCl_4, 90 MHz) δ 6.6–7.0 (m, 3 H), 5.38 (s, 1 H), 5.33 (s, 1 H), 3.80 (s, 6 H), 2.15 (s, 2 H).

Pyridine 23: clear oil; IR (neat) 3080, 3000, 2960, 2230, 1605, 1580, 1565, 1515, 1255, 1145, 1025 cm^{-1}; NMR ($CDCl_3$, 80 MHz) δ 8.72 (dd, 1 H, J = 4.5, 1.5 Hz), 7.87 (m, 1 H), 6.7–7.3 (m, 4 H), 5.28 (br, 1 H), 5.10 (br, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 2.8–3.4 (m, 4 H); UV (MeOH) λ_{max}258 (ϵ 12500); high-resolution mass spectru, obsd 294.1355, $C_{18}H_{18}N_2O_2$ requires 294.1368.

Pyridine 24: clear oil; IR (neat) 3080, 3000, 2950, 1700, 1600, 1585, 1565, 1515, 1255 cm^{-1}; UV (EtOH) λ_{max} 260 (ϵ 13000), 290 nm (ϵ 6160); high-resolution mass spectrum, obsd 297.1360, $C_{18}H_{19}NO_3$ requires 297.1365.

Pyrrolidine 25: clear oil; IR (neat) 3060, 3050, 2975, 1730, 1605, 1585, 1575, 1520, 1255, 1180 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 8.47 (dd, 1 H, J = 4.8, 1.8 Hz), 7.58 (dd, 1 H, J = 8.0, 1.8 Hz), 7.15 (dd, 1 H, J = 8.0, 4.8 Hz), 5.80–6.70 (m, 3 H), 4.34 (s, 1 H), 4.15 (q, 2 H, J = 7.2 Hz), 3.97 (dd, 1 H, J = 8.8, 5.2 Hz), 3.80 (s, 3 H), 3.72 (s, 3 H), 2.90 (m, 1 H), 2.50–2.60 (m, 3 H), 2.37 (s, 3 H), 2.32 (dd, 1 H, J = 13.2, 5.4 Hz), 1.96 (m, 1 H), 1.26 (t, 3 H, J = 7.2 Hz); high-resolution mass spectrum, obsd 396.2006, $C_{23}H_{28}N_2O_4$ requires 396.2049.

(±)-*Sceletium* Alkaloid A_4 (19). A solution of 129 mg (0.326 mmol) of pyrrolidine **25** in 3 mL of 33% THF/EtOH was stirred with 1.00 mL of 1.00 N NaOH at room temperature for 1 h. After adding 1.00 mL of 1.00 N HCl, the solvent was removed in vacuo. The residue was heated with 20 mL of EtOAc and filtered. Evaporation gave 124 mg (100%) of an amorphous solid: high resolution mass spectrum, obsd 368.1733, $C_{21}H_{24}N_2O_4$ requires 368.1735. About 1 mL of phenyl dichlorophosphate was added to this solid, and the mixture was heated to 105 °C for 30 min with swirling. After cooling, 5 mL of water was added, followed by 10 mL of MeOH. The pH was adjusted to 2 with 3 M NaOH. Sodium cyanoborohydride (100 mg) was added, and the mixture was stirred at room temperature for 2 h. The solution was partitioned between CH_2Cl_2/saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated to give 188 mg of a yellow oil. Column chromatography on silica gel using a gradient of 100/0/0 to 90/9/1 CH_2Cl_2/MeOH/concentrated NH_4OH gave 99 mg of **19** as a solid. Recrystallization from EtOAc/hexane gave small white plates of **19**: mp 126–127.5 °C; TLC is identical with a known sample: R_f is 0.46 (CH_2Cl_2/MeOH/concentrated NH_4OH, 90/9/1) on silica gel and 0.34 (EtOAc/hexane 1:1) on alumina.

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Registry No. 2, 13200-60-7; **2a**, 5269-39-6; **5**, 28752-82-1; (±)-**6**, 52183-82-1; (±)-**7**, 35677-84-0; **8**, 92345-88-5; (±)-*cis*-**9**, 92346-01-5; (±)-*trans*-**9**, 92419-26-6; (±)-**9a**, 92469-48-2; (±)-**9b**, 92345-89-6; (±)-*cis*-**10**, 92345-94-3; (±)-*trans*-**10**, 92419-25-5; **11**, 92345-90-9; (±)-**12**, 92345-91-0; (±)-**13**, 92345-92-1; (±)-**14**, 92345-93-2; (±)-**16**, 92345-95-4; (±)-**16**·HCl, 92345-96-5; (±)-**19**, 56782-26-4; **21**, 92345-97-6; **22**, 92346-00-4; **23**, 92345-98-7; **24**, 92345-99-8; **25**, 92365-83-8; 3,4-dimethoxy-α-methylstyrene, 30405-75-5; 3,4-dimethoxyacetophenone, 1131-62-0.

Nucleophilic Reactions in Solutions of Nonmicellized Hydrophobic Ammonium Ions

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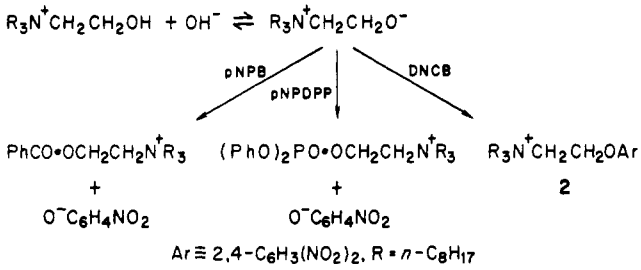
Abstract: Rate constants of reactions of *p*-nitrophenyl diphenyl phosphate, 2,4-dinitrochlorobenzene, and *p*-nitrophenyl benzoate with (2-hydroxyethyl)-tri-*n*-octylammonium bromide or mesylate in aqueous solvents at high pH can be treated quantitatively in terms of binding of reactants to nonmicellar aggregates and second-order rate constants of reaction in aggregates. These rate constants are very similar to those in cationic micelles, but micelles are the more effective at binding substrate. The apparent acid dissociation constant of the hydroxyl group is also larger in the micellar system.

Salts of tri-*n*-octylalkylammonium ions (**1a-c**) increase the extent of deprotonation of hydrophobic weak acids and speed reactions of hydrophobic nucleophilic anions and of amphiphilic nucleophiles.[2,3] The rate enhancements involve the bringing together of reactants in an association complex which includes the ammonium ion or an aggregate of it, and for dephosphorylation by benzimidazolide ion second-order rate constants are similar in the aggregate and in solutions of micellized cetyltrimethylammonium bromide (CTABr).[3] The effects of these ions are similar to those of a variety of other amphiphiles which form so-called "organized assemblies", for example, many reactions are speeded by micellized surfactants, microemulsions, and vesicles.[4-7] The colloidal particles in these assemblies are relatively large and contain large numbers of monomeric amphiphiles.

$(n\text{-}C_8H_{17})_3N^+R\ X^-$
1a, R = Me; X = Cl
1b, R = Et; X = Br
1c, R = Et; X = OMs
1d, R = CH_2CH_2OH; X = Br
1e, R = CH_2CH_2OH; X = OMs

Salts of **1** are surface active, but unlike surfactants they do not have a critical micelle concentration (cmc), although they are believed to aggregate.[2a,b] In some kinetic systems, but not all, the reagent has been a functionalized surfactant, which could promote formation of micelle-like species. The rate enhancements are sometimes larger than those found with comicelles of a functional and an inert surfactant, e.g., cetyltrimethylammonium bromide, and **1a** (X = Cl) has been considered to be a "better catalyst" than micellized surfactants.[2] But for such a statement to be significant it is necessary to isolate the sources of rate enhancements and to decide the extent to which size of the assembly is important.

Scheme I



Rate constants in nonfunctional and functional aqueous micelles and microemulsions can be treated quantitatively in terms of reactant concentrations and rate constants in the micelles or droplets which are treated as a pseudophase.[6,7-10] Dephosphorylation by areneimidazolide ions in solutions of **1b,c** appears to be governed by the same factors which govern micellar rate enhancements,[3,11] and the aim of the present work was to apply a similar treatment to reactions in functionalized hydrophobic ammonium ions (**1d,e**). It was necessary to demonstrate nucleophilic attack by the functional group and to estimate the relative importance of substrate binding and reactivity of bound substrate.

We used two substrates of very different hydrophobicities,[6] 2,4-dinitrochlorobenzene (DNCB) and *p*-nitrophenyl diphenyl phosphate (pNPDPP), in order to obtain information regarding the importance of substrate binding. A major problem in the study of rate enhancements by nonmicellizing, hydrophobic ammonium

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