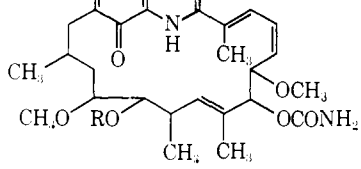
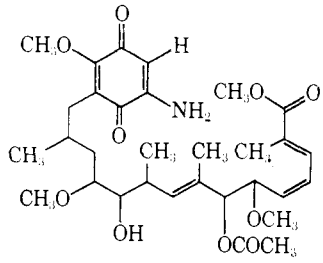
consumed by the dienamide (2 mol), the isolated olefin (1 mol), and the quinone (1 mol) groups. The dienamide group is assigned from the ultraviolet spectrum (λ_{max} 257 nm, ϵ 16,900)[14] and the nmr spectral properties discussed below; the isolated olefin is assigned from the nmr spectra.

The juxtaposition of the three unsaturated groups is established as in **b** by the nmr data shown for geldanamycin acetate (**3**, $C_{31}H_{42}N_2O_{10}$),[8,9] obtained on acetic anhydride–pyridine acetylation of **1** (see Chart I). Solid lines indicate proximate protons located by spin decoupling, dotted lines those assumed to be proximate but not established by decoupling. Chemical shifts in parentheses may be interchanged; those underlined are for exchangeable protons. These nmr data are substantiated by those for the methanolysis product **4** ($C_{30}H_{44}N_2O_{10}$),[8,9] the product obtained by treating geldanamycin with potassium carbonate in refluxing methanol–chloroform (1:1). Alternative structures derived from other junctures of the units $\mathbf{b}_1$, $\mathbf{b}_2$, and $\mathbf{b}_3$ would not fit the chemical shift and coupling data. Detailed arguments will be presented in the full paper.



1, R = H

3, R = $COCH_3$



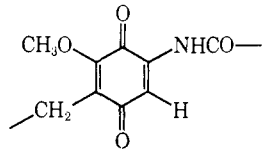
4

The sum of the molecular formulas of units **a** ($C_7H_4O_3$) and **b** ($C_{24}H_{38}N_2O_7$) is $C_{31}H_{42}N_2O_{10}$, the molecular formula of **3**. Thus, the complete structure of **3** (and **1**) is assigned by joining the ends of the unit **b** to two positions of the benzoquinone unit **a**.

The juxtaposition of substituents on the benzoquinone nucleus can be assigned as shown in **1**. Of the six theoretically possible arrangements of **a** and **b**, those in which the benzylic methylene group and aromatic proton are adjacent are eliminated by the lack of coupling between those two groups in the nmr spectrum of **3** (and **4**, *vide infra*). Positive evidence in favor of an arrangement with the amide group and aromatic hydrogen on adjacent positions is provided by the nmr spectrum of **4**. The aromatic proton of **4** is found at δ 5.51, 1.66-ppm upfield from its position in **1**, and is accompanied by an Ar–NH_2 singlet at δ 5.33. The upfield shift would be best explained by an attachment of the amide adjacent to the aromatic proton as in formula **1**.

(14) D. Peters, *J. Chem. Soc.*, 1832 (1960).

The aromatic chromophore of **4** gives maxima at 307 and 485 nm (ϵ 12,700 and 1245, respectively), and the methyl dienoate chromophore occurs at 265 nm (ϵ_{max} 23,000)[15] [*vs.* λ_{max} 257 (ϵ_{max} 16,900),[15] 305 (19,000), 400 nm (991) for **1**]. While the alternative arrangement **c** of substituents on the quinone can only be eliminated



c

by the synthesis of model chromophores,[16] the close similarity between the aromatic chromophore maxima of **4** and those reported for 2-methoxy-5-dimethylaminobenzoquinone [λ_{max} 218 (ϵ_{max} 18,500), 305 (13,900), 490 nm (3900)][17] argues forcefully for structure **1** for geldanamycin.[16]

Acknowledgment. This work was supported in part by Public Health Service Grants AI 01278 and AI 04769 from the National Institute of Allergy and Infectious Diseases. We thank Mr. R. J. Wnuk for high-resolution mass spectra and Mr. S. A. Mizsak for assistance with the nmr spectra.

(15) Methyl sorbate has λ_{max} 258 nm (ϵ 25,700) *vs.* λ_{max} 254 nm (ϵ 26,900) for sorbamide.[14]

(16) Recently completed syntheses of model chromophores (both for 1 and **c**) strengthen the argument in favor of 1 [C. D. Tipton, M. W. McMillan, and K. L. Rinehart, Jr., to be submitted].

(17) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Amer. Chem. Soc.*, 84, 3185 (1962).

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A New Endocyclic Enamine Synthesis

Sir:

In recent years the concept of using cyclic enamines[1] as versatile synthetic intermediates has played a prominent role in the design of numerous alkaloid syntheses.[2] Several recent examples where such methodology has been utilized successfully are illustrated in the synthesis of minovine,[3] mesembrine,[4] and cepharamine.[5] As an outgrowth of our work which has been focused on the synthesis of cepharamine and other related hausbanan alkaloids,[5b] we have had the

(1) K. Blaha and O. Cervinka, *Advan. Heterocycl. Chem.*, 6, 147 (1966).

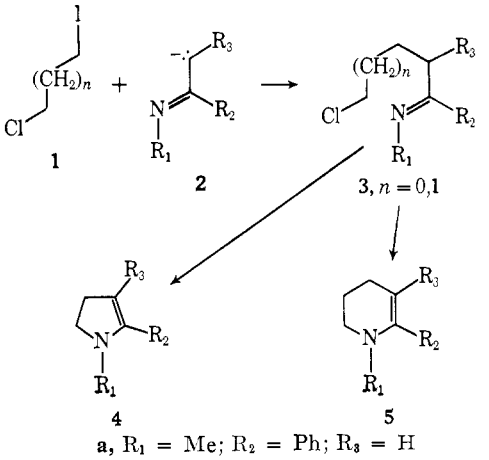
(2) E. Wenkert, *Accounts Chem. Res.*, 1, 78 (1968).

(3) F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).

(4) (a) S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); (b) R. V. Stevens and M. P. Wentland, *ibid.*, **90**, 5580 (1968); (c) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

(5) (a) A formal total synthesis of cepharamine has recently been completed: S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron*, in press. (b) The synthesis of the hasubanan alkaloid skeleton has been reported: D. A. Evans, *Tetrahedron Lett.*, 1573 (1969); D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970).

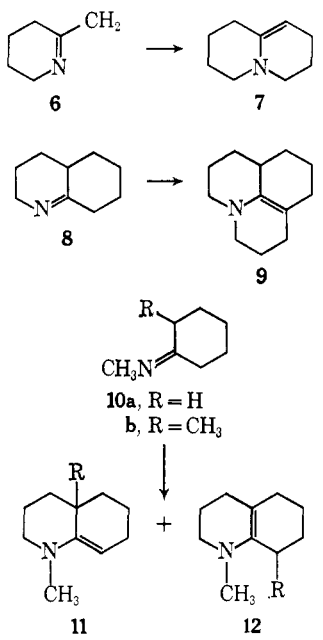
occasion to test the feasibility of the general ring extension concept illustrated below.



a, R_1 = Me; R_2 = Ph; R_3 = H

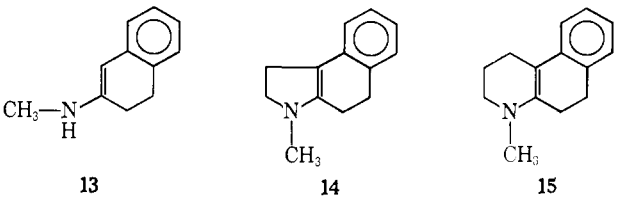
We wish to report on the success of this approach as a general method for the synthesis of a variety of cyclic enamines from structurally diverse imine anions.[6,7] The following experimental conditions have been found to be generally applicable to the synthesis of Δ^2-tetrahydropyridine derivatives.[8]

To a cooled (−30°) solution of lithium diisopropylamide[9] (15.5 mmol) in 1:1 tetrahydrofuran (THF)–hexane, 20 ml, was added imine **2a**[8,10] (15.5 mmol) *via* syringe. After 15 min the reaction was cooled to −50° and 1-chloro-3-iodopropane (16.0 mmol) was added in one lot. The resulting solution was then heated at reflux for 3 hr to effect final ring closure.[11] Evaporative distillation (50° (0.01 mm)) afforded 2.27 g (85%) of **5a** whose purity by glc was >99%.



(6) G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, 7, 7 (1968).
(7) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, 85, 2178 (1963).
(8) Satisfactory spectra and elemental analyses have been obtained for all new compounds reported herein.
(9) Prepared by the addition of *n*-butyllithium in hexane to a cooled ($t \leq 0°$) solution of amine in THF.
(10) The *N*-methylimines were prepared in excellent yields by the method of Weingarten: H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, 32, 3246 (1967).
(11) If the heating step is eliminated, the uncyclized imine **3a** may be isolated.

In an effort to test the effect of structure on the position of proton removal from unsymmetrical imines, we have applied our annelation sequence to the compounds illustrated above. Surprisingly, although 2-methyl-Δ^1-tetrahydropyridine (**6**) and $\Delta^{1(9)}$-octahydroquinoline (**8**) could both be transformed cleanly into the cyclic bases **7** and **9** in excellent yields, the methylimine of 2-methylcyclohexanone (**10b**) afforded an equal mixture of **11b** and **12b**.[12] This result contrasts with the report that the magnesium salt of the cyclohexylimine of 2-methylcyclohexanone can be alkylated in good yield with methyl iodide to give the 2,6-dimethyl derivative.[7] Whether these differing results are a consequence of the different bases which were used or the different nitrogen substituents (methyl *vs.* cyclohexyl) which were employed is not presently known.



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The only attempt at the synthesis of a Δ^2-pyrroline derivative is represented by the transformation of enamine **13** into the tetrahydrobenz[*e*]indole **14**.[5b] In this case **13** was treated with 2 equiv of isopropylmagnesium chloride in THF followed by 1-bromo-2-chloroethane. The second equivalent of base was required here due to the fact that the intermolecular alkylation step proceeded at a rate which was comparable to the rate of intramolecular ring closure. The resulting iminium salt then served as a proton source to quench starting imine anion. This inconvenience only appears to be a problem in the synthesis of Δ^2-pyrroline derivatives. No difficulty was experienced in the synthesis of **15** using either of the methods described above.

The simplicity and versatility of this annelation concept should be of considerable value in the syntheses of nitrogen-containing ring systems, and, as illustrated in Table I, the yields of this process appear to be generally good.

Table I. Bisalkylation of Imines

Imine	Product	Yield, %[a,b]
2a[c,d]	**5a**[e]	84
6[f]	**7**[g]	84
8[h]	**9**[g]	78.5
10a[d]	**12a**[g]	86
10b[c,d]	**11b** + **12b**[i]	*96*[i]
13[c,d,k]	**14**[k]	100[i]
13	**15**[c,d,l]	83

[a] Consistent spectral data and correct melting points of perchlorate salts were obtained. [b] Yields of distilled product given except where noted. [c] See ref 8. [d] See ref 10. [e] R. Lukes and O. Grossman, *Collect. Czech. Chem. Commun.*, **8**, 533 (1936). [f] M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.*, 2445 (1965). [g] N. J. Leonard, C. K. Steinhardt, and C. Lee, *J. Org. Chem.*, **27**, 4027 (1962). [h] L. A. Cohen and B. Witkop, *J. Amer. Chem. Soc.*, **77**, 6595 (1955). [i] A 1:1 product ratio was obtained. [j] Crude yield ≥95% by glc. [k] See ref 5b. [l] N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Amer. Chem. Soc.*, **80**, 6633 (1958).

(12) Under our described conditions for anion formation it appears that little, if any, anion equilibration occurs.

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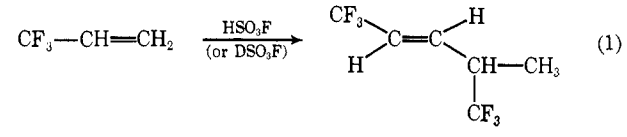
Solvolysis in Strong Acid Media. Solvolytic Dimerization of 3,3,3-Trifluoropropene

Sir:

This investigation had its origin in a study of the solvolytic behavior of $CF_3CH_2CH_2OTs$ and $CF_3CH(OTs)CH_3$ in strong acid media. Our intent was to find systems in which solvolysis of sufficiently destabilized secondary alkyl systems would proceed with hydrogen participation to yield primary alkyl derivatives. Solvolysis of CH_3CH_2OTs in HSO_3F occurs with apparent rate-limiting hydrogen participation,[1] and electrophilic addition of hydrogen halides to $CF_3CH{=}CH_2$ yields the anti-Markovnikov addition products.[2] Assuming these observations indicate both the feasibility of observing such a rearrangement and a molecular structure in which the normal carbonium ion stabilities have been inverted,[3] we anticipated that $CF_3CH_2CH_2OTs$ would solvolyze slowly in powerful ionizing solvents of low nucleophilicity to yield unrearranged product, while the secondary isomer, $CF_3CH(OTs)CH_3$, might solvolyze more rapidly with rearrangement to a primary alkyl derivative.

Our expectations were not completely realized. While observed rates of solvolysis are in accord with prediction, we found that neither $CF_3CH(OTs)CH_3$ nor $CF_3CH_2CH_2OTs$ solvolyze with detectable rearrangement (nmr) in solvent systems that include H_2SO_4, HSO_3Cl, HSO_3F, and HSO_3F–SbF_5.

Supporting investigations of the behavior of $CF_3CH{=}CH_2$ in HSO_3F revealed an apparent paradox. We do not observe addition of fluorosulfuric acid to 3,3,3-trifluoropropene. Rather, in freshly distilled HSO_3F solvent, $CF_3CH{=}CH_2$ undergoes dimerization to yield *trans*-1,1,1,5,5,5-hexafluoro-4-methyl-2 pentene (**1**) *without* incorporation of solvent protons, eq 1.



(1)

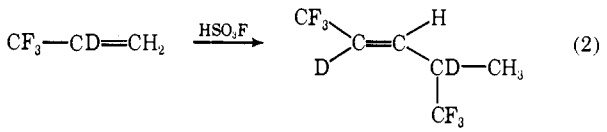
1

Dimerization proceeds cleanly as judged by the developing product nmr spectrum (*vide infra*); integration of nmr spectra of reaction mixtures yielded kinetic data demonstrating clear second-order dependence on alkene In freshly distilled HSO_3F containing 3 *M* alkene, observed rate constants are 1.5×10^{-4} l. mol^{-1} sec^{-1} at 30°. Rates of dimerization fall off dramatically upon addition of KSO_3F: 4.6×10^{-6} l. mol^{-1} sec^{-1} (0.43 *M* KSO_3F), 1.5×10^{-6} l. mol^{-1} sec^{-1} (0.85 *M* KSO_3F).[4]

The dimer **1** could be isolated in good yield (75–80%) by carefully quenching the reaction mixture in aqueous methanol at −40° followed by centrifugation of the dense organic layer and normal work-up; bp 64°; $d^{25}{}_4$ 1.298. (*Anal.* Calcd: C, 37.2; H, 2.95; mol ion, 192. Found: C, 37.5; H, 3.15; mol ion, 192.) Structural characterization follows from the observed spectral properties.[5] The nmr spectrum of the vinyl proton region is noteworthy; the two high-field lines of the AB quartet are each split into quartets by vicinal fluorines, and the two low-field lines are each split into doublets of quartets by vicinal proton and stereospecific four-bond fluorine coupling [7]

Reaction of $CF_3CH{=}CH_2$ with DSO_3F gave nmr spectra identical with that found by reaction of alkene with HSO_3F. After 90% conversion, nmr spectra of solvent, reactant, and product regions showed no evidence of significant hydrogen exchange. Mass spectral analysis of product isolated at this degree of conversion showed that 96.4% of dimer contained no deuterium.[8]

Reaction of $CF_3CD{=}CH_2$[9] with HSO_3F afforded dimer labeled with deuterium at C-2 and C-4, eq 2. Thus the nmr spectrum shows only two bands, a broad singlet (3 H) at δ 1.3 and a very broad band at 6.4 (1 H); the mass spectrum shows the molecular ion at *m/e* 194 (>96% *1-d*$_2$) with a fragmentation pattern consistent with the structure shown, eq 2.



(2)

In summary, $CF_3CH{=}CH_2$ dimerizes stereospecifically in HSO_3F to yield an apparent Markovnikov addition product. Dimerization rates show marked acid catalysis; however, this catalysis does not involve transfer of solvent protons to olefinic carbon of reactant. Dimer must form from precursor by mi-

(1) P. C. Myhre and E. Evans, *J. Amer. Chem. Soc.*, 91, 5641 (1969).
(2) A. L. Henne and S. Kaye, *ibid.*, 72, 3369 (1950).
(3) H. Bodot and J. Jullien, *Bull. Soc. Chim. Fr.*, 1488 (1962).

(4) Rates in HSO_3F also fall off rapidly with the "age" of the acid indicating a marked decelerating effect of trace amounts of water.

(5) Spectral properties were: ^{1}H nmr ($\delta_{CCl_4}^{TMS}$) 1.26 (doublet, 3 H, $J_{H,H}$ = 7 Hz, 4-CH_3); 2.95 (broad octet, 1 H, $J_{H,H-F}$ = 8 Hz, H_4); 5.80 (doublet of quartets, 1 H, J_{H_2,H_3} = 17.5 Hz, J_{H_2,CF_3} = 6.3 Hz); 6.42 (doublet of doublets of quartets, 1 H, J_{H_3,H_4} = 6.7 Hz, J_{H_3,CF_3} = 2.2 Hz). ^{19}F nmr at 94.5 MHz showed two bands of equal intensity separated by 7.4 ppm; the signal at high field was a simple doublet ($J_{F,H}$ = 8 Hz), and the signal at low field is a doublet of triplets (J_{F,H_2} = 6 Hz, J_{F,H_3} = 2 Hz).[6] Mass spectral characteristics (70 V) are: *m/e* 192 (28%, mol ion), 173 (22%, M − F), 123 (100% M − CF_3), 103 (24%, M − (CF_3,HF)), 95 (71%, M − CH_3CHCF_3); ir (CCl_4) 1680 (m), 1455 (m), 1370–1100 (s multiple bands), 1010 (m), 961 (m) cm^{-1}.

(6) We are grateful to Professor Kenneth Servis for examination of the ^{19}F nmr spectrum.

(7) A. A. Bothner-By, S. Castellano, and H. Günther, *J. Amer. Chem. Soc.*, 87, 2439 (1965).

(8) We attribute the small amount of deuterium incorporation to a slow protonation–deprotonation or addition–elimination reaction.

$$\mathbf{1} + HA \rightleftharpoons \text{ion (or adduct)} \rightleftharpoons CF_3CH_2CH{=}C(CF_3)CH_3 + HA$$

Evidence for this reaction includes (1) the observation of slow changes in the nmr spectrum of 1 (*ca.* 20% conversion in 7 days) with the development of a singlet at δ 1.85, a multiplet at ~3, and a triplet at 4.8, and (2) observation of similar spectral changes of 1 in D_2SO_4 and, in addition, the slow change of the methyl doublet of 1 (δ 1.26) to a broad singlet.

(9) $CF_3CD{=}CH_2$ was prepared by the sequence:

$$CF_3COCH_3 \xrightarrow{LiAlD_4} CF_3CD(OH)CH_3 \longrightarrow CF_3CD(OAc)CH_3 \xrightarrow{600°} CF_3CD{=}CH_2$$