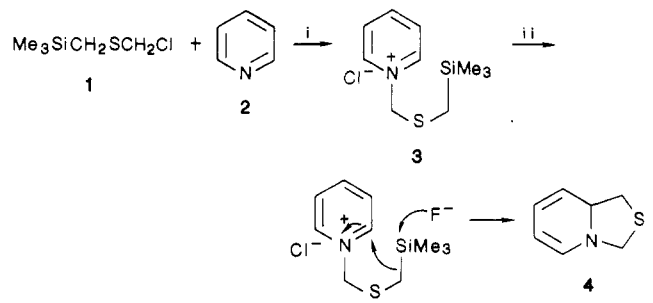
Scheme I[a,3]



[a] Reagents: i, 60 °C, 1 h; ii, CsF, CH_3CN, room temperature.

rative thin layer chromatography on silica gel gave the pure 1,3-thiazolidine (**4**).

Acknowledgment. We thank Torey Silicone Co., Ltd., for a gift of chlorotrimethylsilane. The work was supported in part by the Ministry of Education, Science and Culture (Grants-in-Aid for Scientific Research), the Research Foundation for Pharmaceutical Sciences, the Houan-sha, the Takeda Science Foundation, the Yamada Science Foundation, and the Mitsubishi Foundation.

Supplementary Material Available: Experimental and ^1H NMR, IR, UV, and MS spectral data of **1**, **3**, and **4** (5 pages). Ordering information is given on any current masthead page.

(1) (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117. (b) Hosomi, A.; Matsuyama, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1986**, 1073.

(2) For simplicity, the substituents on the heteroaromatic ring including benzo-fused derivatives are omitted.

(3) Although an equilibrium between **3** and **1** + **2** and a [3 + 2] cycloaddition of the parent thiocarbonyl ylide derived from **1** and CsF with heteroaromatics may be possible as the actual mechanism, an experiment using **3** and CsF in the presence of excess methyl acrylate did not give any trace of 3-(methoxycarbonyl)tetrahydrothiophene which was expectedly formed by the cycloaddition, if thiocarbonyl ylide was present in this reaction media.[2b] This strongly suggests that the reaction proceeds via the direct desilylation of **3** followed by the intramolecular cyclization.

(4) For the nonstabilized 1,3-dipolar reagents by the desilylation method, see: (a) Aono, M.; Hyodo, C.; Terao, Y.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4039. (b) Imai, N.; Tokiwa, H.; Aono, M.; Terao, Y.; Akahori, Y.; Achiwa, K. *Heterocycles* **1986**, *24*, 2423. (c) Terao, Y.; Tanaka, N.; Imai, N.; Achiwa, K. *Tetrahedron Lett.* **1985**, *26*, 3011. (d) Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Chem. Lett.* **1984**, 801. (e) Padwa, A.; Chen, Y.-Y. *Tetrahedron Lett.* **1983**, *24*, 3447. (f) Turro, N. J.; Cha, Y.; Gould, I. R.; Padwa, A.; Gasdaska, J. R.; Tomas, M. *J. Org. Chem.* **1985**, *50*, 4415. (g) Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235. (h) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941 and references cited therein.

(5) Although α-silyl-substituted onium salts have been readily desilylated by fluoride ion to give the corresponding ylide, the desilylation at the remote site such as **3** is unprecedented.[4h]

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On the Remarkable Stability of Derivatives of Leucomitomycin F. Novel Mitomycin Analogues

Summary: The leuco form of mitomycin F reacts with silica gel in the presence of oxygen to afford 9-epimitomycin B. A notable stability is manifested by hydroquinoid forms (leucomitomycin) bearing a 9,10-exocyclic methylene group.

Sir: Recently, leucomitomycins and leucoaziridinomitosenes have been characterized for the first time.[1,2] Access to these labile systems has allowed us to probe, in a more critical way than had heretofore been possible, the nature of the reductive activation of mitomycins and the chemical characteristics of activation cascade intermediates. Recent results[2] have suggested a key role for the mitomycin semiquinone **1** in the critical ejection of the C_{9a} heterofunction en route to leucoaziridinomitosenes, aziridinomitosenes, and apomitosenes. In our past studies, the intermediate oxidation state was reached by one-electron reduction of the quinone.[2] In the chemistry described below a species such as **1** is approached by one-electron oxidation of a leucomitomycin. We also provide evidence for the remarkable inherent stability of leucomitomycin derivatives bearing an exocyclic (9,10-) methylene group.

Reduction (H_2–Pd/C–pyridine) of mitomycin F (**2**),[3] followed by filtration of the catalyst under strictly anaerobic conditions, generated a solution of leuco compound **3** (Scheme I). After removal of the solvent in vacuo, a solution of **3** in triethylamine/chloroform or diisopropylamine/chloroform was administered to a silica gel prep plate in the presence of oxygen (air). Elution and isolation of the products yielded aziridinomitosene **4** (40–50%), starting mitomycin **2** (30–40%), and a new blue-purple material in 20–30% yield. That this compound was, in fact, 9-epimitomycin B (**5**) was rigorously established by an X-ray crystallographic determination (see ORTEP drawing,[4] Scheme II).

Activation of mitomycins usually leads to ejection of the C_{9a} heterofunction accompanied by loss of the C_9 proton, the result being the formation of mitosene compounds. In the formation of 9-epimitomycin B, these processes have been uncoupled from each other.[5] Control experiments were performed in order to assess the parameters of the reaction. The stability of a solution of leucomitomycin **3** and triethylamine in degassed $CDCl_3$ was determined by high-field NMR analysis. No decomposition of the leucomitomycin was evident. We were thus confident that ejection of the angular substituent was not occuring before the solution was exposed to silica gel and air. In another control experiment, access to oxygen was minimized during exposure to the silica gel.[6] The course of this reaction was very different. The bulk of the material was converted to intractable material, and only traces of **6** and disproportionation product **7** were obtained. No aziridinomitosene **3**, starting mitomycin **2**, or epimitomycin B **5** were formed. Furthermore, the starting mitomycin **2** is not converted to **5** via silica gel chromatography. *We conclude that the active species undergoing conversion of C_{9a} methoxy to C_{9a} hydroxy is intermediate in oxidation level between **3** and **2** (cf. semiquinone **1**).*

With the C_{9a} hydroxy compounds now available, it was of interest to determine whether 9-epimitomycin B (**5**)

(1) Danishefsky, S.; Ciufolini, M. *J. Am. Chem. Soc.* **1984**, *106*, 6424.

(2) Danishefsky, S. J.; Egbertson, M. *J. Am. Chem. Soc.* **1986**, *108*, 4648.

(3) Mitomycin F (*N*-methylmitomycin A) was prepared from mitomycin C by the method of Remers: Cheng, L.; Remers, W. A. *J. Med. Chem.* **1977**, *20*, 767.

(4) A summary of the X-ray analysis including fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors is provided in the supplementary material.

(5) For a previous example of such a decoupling, see: Hornemann, U.; Ho, Y.; Mackey, J. K., Jr.; Srivastava, S. C. *J. Am. Chem. Soc.* **1976**, *98*, 7069. It is not improbable that the apparent displacement is occuring during the reoxidation process.

(6) The silica gel plates were placed in a glovebag filled with nitrogen and preeluted in degassed solvent. They were then allowed to dry while still in the glovebag. The leuco compound was applied to the plates and then eluted with the same degassed solvent.

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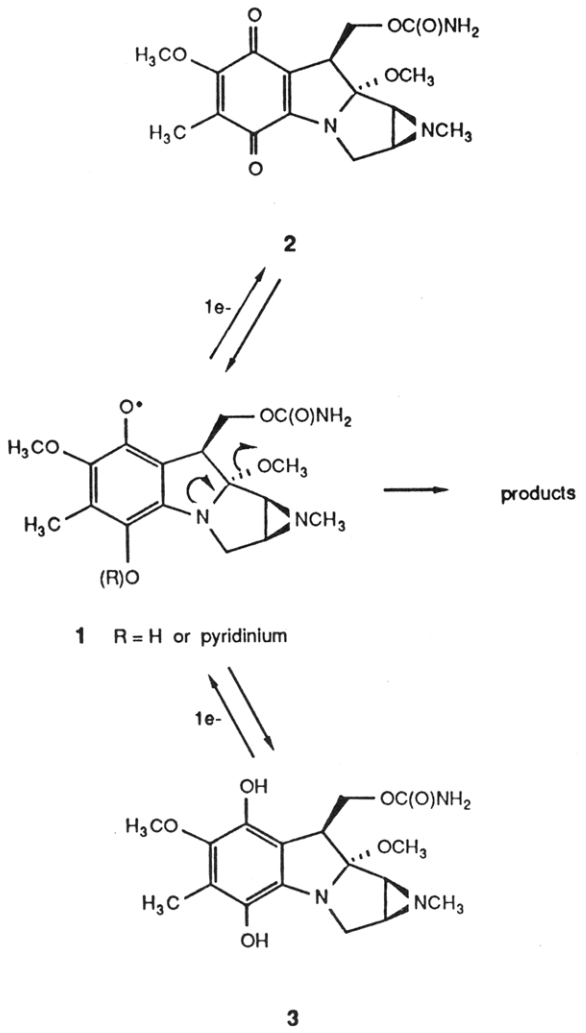
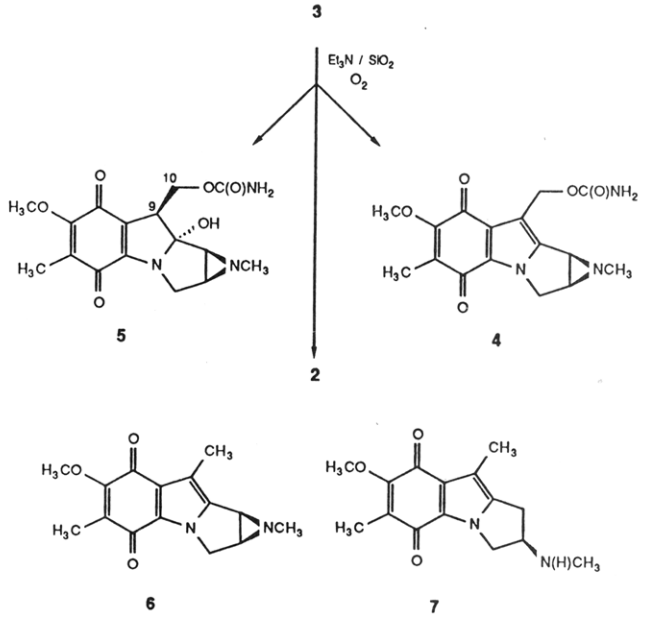
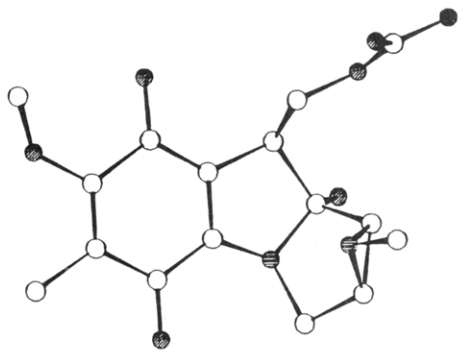
Scheme I



Scheme II





ORTEP of compound **5**

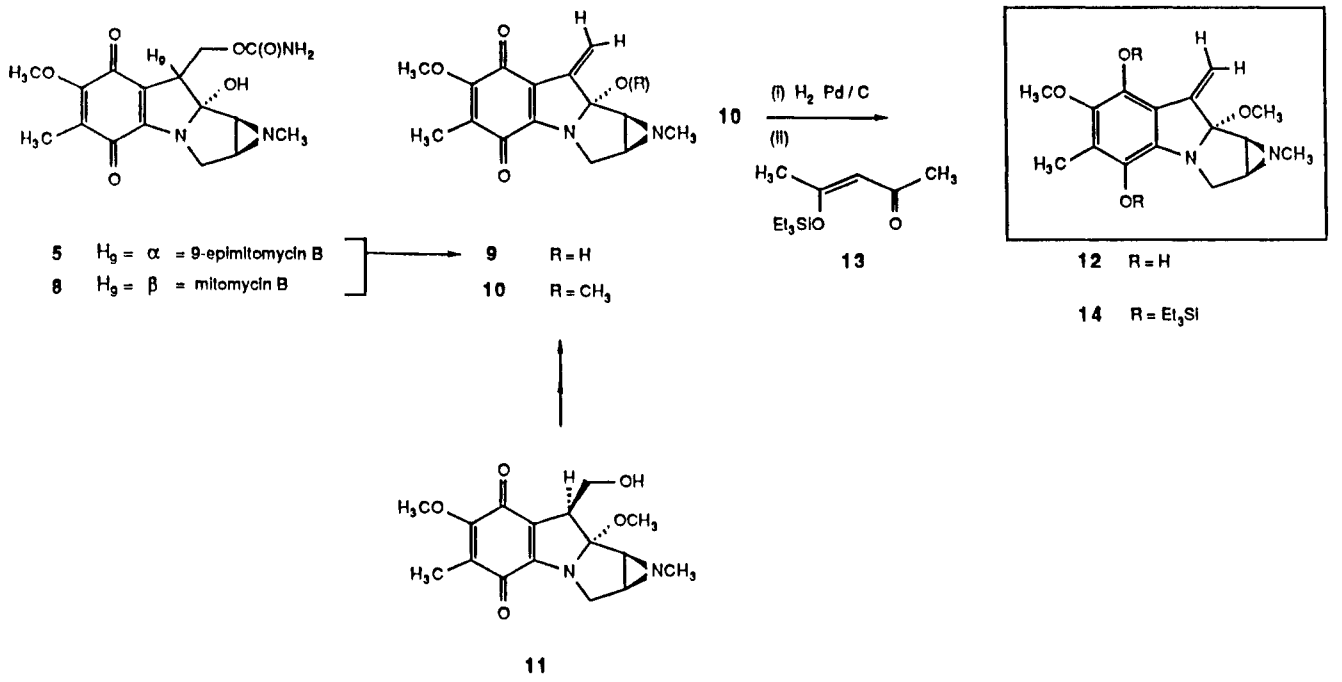
could be converted to the naturally occurring 10-de(carbamoyloxy)-9-dehydro compound **9** (Scheme III).[7] Such a transformation had indeed been reported with mitomycin B itself, using sodium hydride.[8] With a small sample of **8** available to us we examined the reaction and could achieve a 30% yield (at 80% conversion) of **9**. However, with the 9-epi compound **5**, only traces of **9** could be generated in this fashion.[9] A more efficient route to the 10-de(carbamoyloxy)-9-dehydro series was achieved via descarbamoylmitomycin F (**11**).[10] Treatment of compound **11** with methanesulfonyl chloride followed by DBU provided a 76% yield of **10**.[11]

With a sound route to at least one member of the very interesting exocyclic methylene series in hand, we could probe the feasibility of generating the corresponding leuco compounds. In the event, catalytic reduction of **10** as described for **2**[1,2] did generate **12** as a solution in pyridine-d_5. Thus, reduction of the quinone had preceeded reduction of the terminal methylene group. Compound **12** was protected as its bis(triethylsilyl) derivative through the action of excess **13**.[12] There was thus obtained a ~95% yield of the protected leuco compound **14**. Desilylation followed by oxidation cleanly converts **14** back to **10** in ca. 60% yield.

When obtained in homogeneous form, compound **14** *is remarkably stable and shows no tendency toward what might have been expected to be a facile allylic isomerization to the corresponding indole series.* The stability of this compound serves to support the growing perception that mitomycin compounds containing an even number of electrons are not the maximally reactive species. New

(7) Urakawa, C.; Tsuchiya, H.; Nakano, K. *J. Antibiot.* **1981**, *34*, 243.
(8) Urakawa, C.; Tsuchiya, H.; Nakano, K.; Nakamura, N. *J. Antibiot.* **1981**, *34*, 1152.
(9) The variations between **5** and **8** in the quality of the elimination reactions leading to **9** may reflect differences in formation of the C_{9a} ketone[8] by ring–chain tautomerism. Alternatively they may be the result of differences in the elimination reaction per se.
(10) Compound **11** was prepared from decarbamoyl porfiromycin by hydrolysis and methylation (see supplementary material). Decarbamoyl porfiromycin was prepared from mitomycin C by the method of Kinoshita from mitomycin C: *J. Med. Chem.* **1971** *14*, 103, 109.
(11) A similar transformation has been reported in the patent literature: Kyowa Hakko Kogyo Co., Ltd. Japanese Patent 80 120 587, 1980. Kasai, M.; Kono, M.; Shirahata, K.; Urakawa, C.; Tsuchiya, H.; Nakano, K.; Takahashi, I.; Mineura, K. Eur. Patent 8 021, 1980.
(12) Cf.: Mitscher, C. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, *1303*.

Scheme III



explorations in the synthesis of mitomycins analogues which build upon these findings are planned.

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Supplementary Material Available: Experimental data for compounds 4–7, 10–12, and 14 and a summary of the X-ray analysis of 5 including fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors (11 pages). Ordering information is given on any current masthead page.

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