

Dihydro-1,3-oxazines. XIV (1). A Versatile Synthesis of  
Pyrrolo[2,1-c][1,3,4H]oxazines and a New approach to Pyrroles

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Sir:

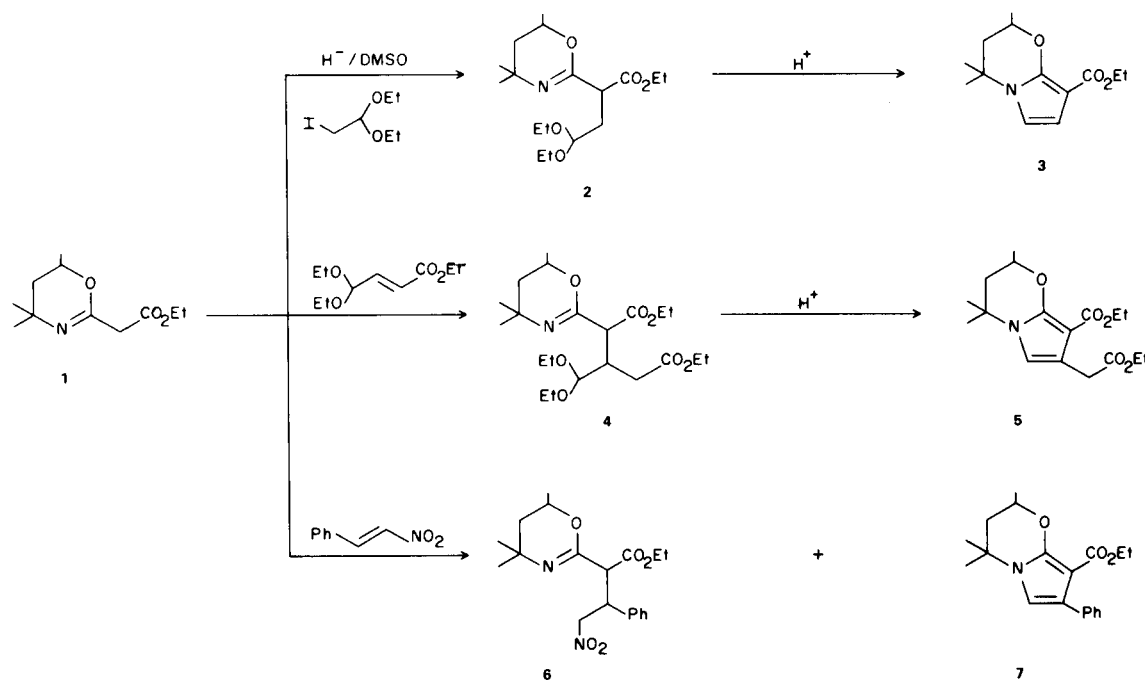
In view of the recent interest in fused pyrroles such as those found in mitomycin C and anthramycin (2), we wish to report some preliminary experiments utilizing the versatile dihydro-1,3-oxazine system (1) which led not only to fused pyrrolooxazines (3, 5, 7) but also to monocyclic pyrroles (9).

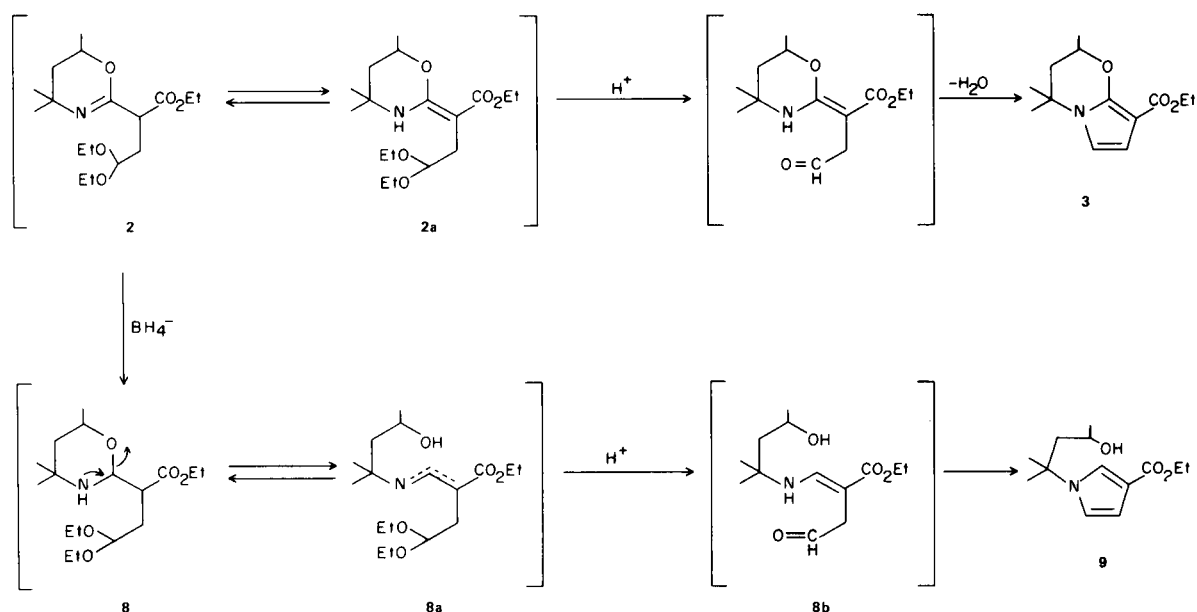
The sequence demonstrated herein employs the readily available ester oxazine (1) (3) which may be elaborated by alkylation of its sodium salt or by Michael addition to electrophilic olefins. Thus, treatment of 1 with 1.0 equivalent of sodium hydride in DMSO (25°) followed by addition of bromo- or iodoacetaldehyde diethyl acetal (4) produced, after 16 hours, the oxazine 2 in 78% yield [b.p. 90-95° (0.05 mm); 1640, 1675 cm<sup>-1</sup>, m/e 329]. Elaboration of 1 via Michael addition was demonstrated by heating (sealed tube) in absolute ethanol containing 10% sodium ethoxide and the  $\gamma$ -diethoxycrotonic ester (5) at

145° for 45 hours. In this fashion, 4 was obtained in 62% yield [b.p. 125-140° (0.06 mm) 1740, 1670 cm<sup>-1</sup>, m/e 415].

When 2 or 4 were dissolved in wet toluene containing a trace of trifluoroacetic acid and the solution heated to reflux (water and ethanol removed azeotropically) for 2-6 hours, the pyrrolo oxazines 3 [98%, m.p. 82-83° (petroleum ether); 1675, 1550 cm<sup>-1</sup>, m/e 237] and 5 [78%, m.p. 94-94.5°, 1740, 1675, 1550 cm<sup>-1</sup>; m/e 323] were obtained.

An unexpected result was experienced during the course of addition of 1 to  $\beta$ -nitrostyrene (anhydrous *t*-butyl alcohol, reflux for 20 hours). Along with the Michael adduct 6 [68%, b.p. 120-150° (0.06 mm), 1740, 1600, 1555 cm<sup>-1</sup>; m/e 362] there was also formed the pyrrolo-oxazine 7 [30%, m.p. 136-137°, 1700, 1545 cm<sup>-1</sup>; m/e 313]. Experiments are planned to determine the origin





of **7** since it does not appear at this time that it is derived from **6**, *via* a Nef reaction.

The formation of the pyrrolooxazines may be formulated as proceeding through the tautomeric forms (**6**) of **2** which after hydrolytic cleavage of the acetal moiety (**2b**) undergoes a facile cyclodehydration to **3** (or **5**).

An interesting extension to this sequence was realized when the dihydro-1,3-oxazine (**2**), was reduced with sodium borohydride (**7**) (pH 4-5,  $-40^{\circ}$ , THF-ethanol) to the tetrahydro derivative **8** [95%, m.p.  $54-55^{\circ}$  (pentane); 3230,  $1735\text{ cm}^{-1}$ ;  $m/e$  331]. Heating the latter in toluene (2 hours) containing a catalytic amount of trifluoroacetic acid produced the monocyclic pyrrole **9** [83%,  $135-145^{\circ}$  (0.02 mm); 3350, 1705, 1695,  $1540\text{ cm}^{-1}$ ,  $m/e$  239]. Thus, the tautomerism of the tetrahydrooxazine with its open chain form (**8a**) results in cyclization with the newly generated carbonyl group (**8b**) producing the *N*-alkyl pyrrole. We are planning to examine efficient means for removing the alkyl group in **9** and if this should prove successful, we shall have in hand coupled with the intro-

duction of substituents in **2**, **4**, and **6**, an entry into polysubstituted pyrroles (**8**).

#### REFERENCES

- (1) For previous papers in this series, see A. I. Meyers, E. M. Smith and A. J. Jurjevich, *J. Am. Chem. Soc.*, **93**, 2314 (1971).
- (2) M. Artico, G. C. Porretta, and G. DeMartino, *J. Heterocyclic Chem.*, **8**, 283 (1971).
- (3) Commercially available from Columbia Organic Chemicals, Columbia, South Carolina.
- (4) Prepared by reaction of bromoacetaldehyde diethyl acetal (Aldrich) with 2.0 equivalents of sodium iodide in acetone (refluxed for one week).
- (5) F. Farina, M. Lora-Tomayo and M. V. Martin, *An. Real Soc. Espan. Fis. Quim., Ser. B.*, **60**, 715 (1964); *Chem. Abstr.*, **63**, 4213C (1965).
- (6) The two forms **2** and **2a** are clearly discernible from both infrared and nmr spectra.
- (7) A. I. Meyers, H. W. Adickes, J. R. Politzer, and W. N. Beverung, *J. Am. Chem. Soc.*, **91**, 765 (1969).
- (8) All new compounds described herein gave satisfactory elemental analysis.