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THE SYNTHESIS OF SPIRO[5,6]-3-OXAUNDECAN-7-ONE

OBSERVATION OF A SPECIFIC OXYGEN-DIRECTING EFFECT

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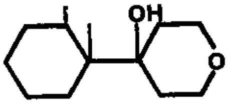
Abstract The title compound was prepared by pinacol rearrangement, where a remote oxygenheteroatom gave specific orientation to the course of rearrangement.

As a consequence of our studies on factors controlling the course of pinacol rearrangement[2],we have developed a working hypothesis that suggests that the stability of the initially-formed carbonium ion controls the course of the reaction. A unique opportunity to test this idea within the framework of heterocyclic systems seemed most appropriate because (1) very little has been reported concerning the pinacol rearrangement of heterocyclic molecules, and (2) a wealth of solvolytic data are available to allow for judgements on carbonium ion formation. Specifically, we were intrigued by the synthetic and mechanistic opportunities offered by the study of the rearrangement of **1**. Structural studies have demonstrated that the tetrahydropyranyl ring is very similar to the cyclohexane ring[3]; thus, we viewed the structural differences in the two rings would be minimal. Also, solvolytic studies have demonstrated a rate-retarding "dipole effect"[4] for 2 relative to 3, presumeably via **4.**



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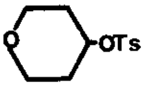

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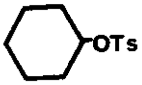

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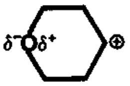

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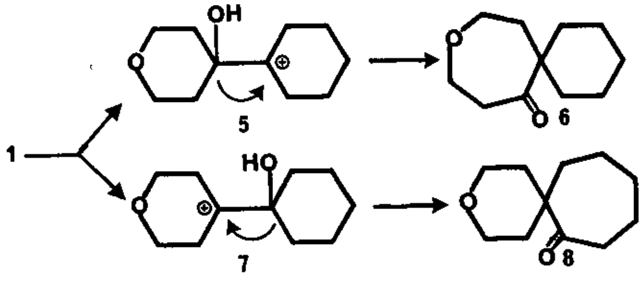
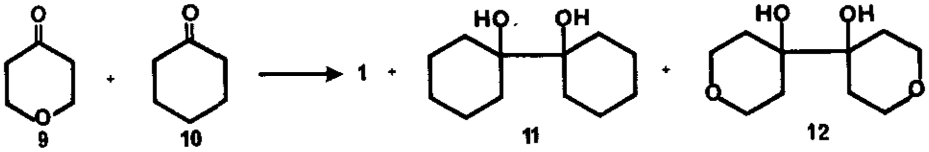
With these background ideas, the course of rearrangement for 1 could be predicted by comparing the relative predicted carbonium ion stabilities (**Eq.** 1). The "dipole effect" would predict 5 to be more stable than 7; thus, also predicting the formation of **6.**



1

Preparation of 1 was accomplished by the titanium-mediated reductive coupling of cyclohexanone and tetrahydropyran-4-one (**Eq.2**)^5. In this synthesis we utilized a 4-fold excess of cyclohexanone to favor formation of the mixed coupling product. Clearly, the ratios of the coupling products do not reflect the expected "statistically-driven" ratios; an observation further buttressed by our ability to prepare **12** in only 9% yield when we attempted the self-coupling of **9**. It is likely that a dipole effect is playing a role in reducing the ability of **9** to form an anion-radical or ketyl intermediate.



2

Rearrangement of 1 in concentrated sulfuric acid at 0° C gave a <u>single</u> spiranone product in 91% yield. Proton and ^{13}C NMR spectroscopic methods unambiguously fixed the structure of the product as **8** rather than the expected **6**. Details of the assignments are presented below (**Figure 1**).

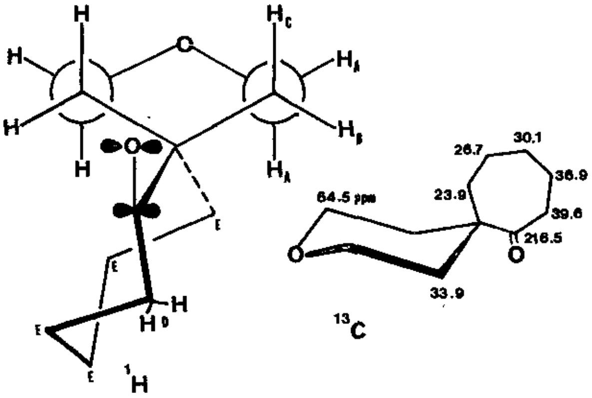
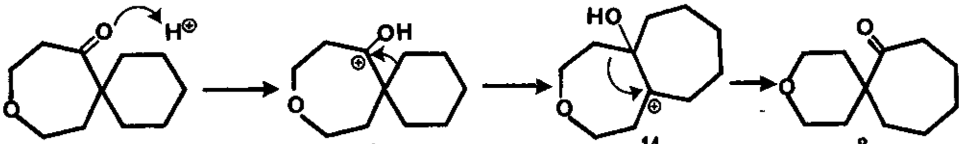


Figure 1. NMR assignments for the rearrangement product

Four distinct proton regions were observed in the proton NMR spectrum (250 MHz). A doublet of triplets (4H, centered at 3.69 ppm) was assigned to H_A , and is most likely unresolved overlapping signals from the two non-equivalent**A** protons; a triplet (2H, 2.52 ppm) was assigned to H_D; a multiplet (2 H, 1.91-2.00 ppm) was assigned to H_B, and a large complex proton envelope (10 H, 1.39-1.76 ppm) was assigned to H_C and the remaining protons. The H_C protons are shielded to ca. 1.49 ppm, most likely an anisotropic shift due to the ether oxygen. Irradiation of the protons centered at 3.69

ppm caused a collapse of the 1.91-2.00 ppm multiplet to distinct doublets centered at 1.99 and 1.93 ppm, as well as simplification of the 1.44-1.49 ppm portion of the spectrum. The reverse decoupling experiments gave the expected, complimentary results. The carbon spectrum gave the most convincing evidence for the structure. A combination of broad-band and off-resonance carbon NMR spectra gave the results summarized in **Figure 1.** Particularly important was the observation of the doubling in intensity of the 64.5 and 33.9 ppm signals, demonstrating the symmetrical carbon pattern around the oxygen portion of the spiranone.

The formation of the "unexpected product" and our hypothesis about the importance of the carbonium ion stabilities can be reconciled by consideration of the mechanism described by **Equation** 3.



6 13 14 8

3

Examination of Dreiding models shows that for **5** there exists a proper orientation for a destabilizing dipole effect between the oxygen and carbonyl carbon. This destabilization is attenuated in the acid conditions of the rearrangement, where a formal positive charge is placed on the carbonyl carbon. Furthermore, the unfavorable 1,4 -relationship of the heteroatom to charged carbon (see original structural relationships for the "dipole effect" in 4) associated with 7 is also found in **13.** From **6** to **14** the dipole effect presents itself and can only be relieved by conversion to **8.** Thus, under the conditions of sulfuric acid, 0°C, and 2 h (our suggested conditions for all reactions that are to have any "standard conditions"[2]) the powerful directing effect of a remote oxygen is made manifest in specific product formation. It should be noted at this juncture that even after 5 min, the **only** spiranone observed is **8**, further supporting the concept of a heteroatom dipole effect controlling the reaction. This observation, the first example of a documented influence of a heteroatom controlling pinacol rearrangement, opens a new and exciting frontier for research.

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Experimental

Preparation of 4-tetrahydropyranylcyclohexane-1,1'-diol (1): Cyclohexanone (3.37 g, 34.4 mmol) and tetrahydropyran-4-one (1.0 g, 8.6 mmol) were added to a suspension of reduced titanium in THF according to the procedure of Corey[5]. The white, crystalline diol was purified by column chromatography (silica gel, methanol:hexane::1.5:1), m.p. 148-148.5° C.

Calculated for $C_{11}H_{20}O_3$: C,65.97; H,10.07

Found for $C_{11}H_{20}O_3$: C,65.70; H, 9.84

Pinacol rearrangement of 1: The diol (180 mg, 0.9 mmol) was added to 20 mL of concentrated (Baker, 96.3%) sulfuric acid. The reaction mixture was stirred and maintained at 0° C by an external ice-water bath. After 2 hr, the acidic reaction mixture was poured onto excess crushed ice and the organic materials were removed by extraction with ether. The organic extracts were washed with saturated bicarbonate, brine and then water. After drying over anhydrous $MgSO_4$, the extracts were reduced in volume, and the pure product (91% of the reaction mixture) was isolated by GLC (20% SE-30).

References and Notes

1. Visiting professor of chemistry, Montana State University, 1979-1980. Current address: Simpson College, Indianola, Iowa 50125.

2. For the previous paper in this series, see B.P. Mundy, R. Srinivasa, R.D. Otzenberger, and A.R. DeBernardis, **Tetrahedron Lett.** 1979, 2673.

3.a. By the R-value technique[3b],the dihedral angle (torsional angle) of cyclohexane and tetrahydropyran differ by only 2° .

b. J.B. Lambert, **Acc. Chem. Res.** 1974, 4,87.

4. D.S. Tarbell and J.R. Hazen, **J. Am. Chem. Soc.** 1969, 91, 7657.

5. E.J. Corey, R.L. Danheiser and S. Chandrasekaran, **J. Org. Chem.** 1976, 41, 260.

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