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A Novel Base Catalyzed Bis Cyclization

S. Danishefsky and B. H. Migdalof

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

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Recently we prepared the enetrione, I, and demonstrated that intermolecular additions of nucleophiles to the double bond triggers a series of intramolecular condensations leading to products of relevance to steroids.[1] We now report an interesting isomerization of I, occasioned by its treatment with potassium t-butoxide/t-butyl alcohol at room temperature for one week. The high melting (172-174°) product thus obtained in 72% yield is assigned the homobrendanedione[2] structure, II on the basis of the data which follow.

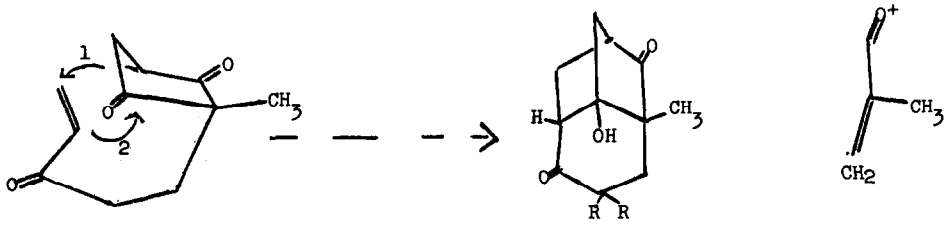
Its infrared [$\lambda_{max}^{CHCl_3}$ 2.90, 5.73, 5.88μ] spectrum points to the presence of hydroxyl, cyclopentanone and cyclohexanone groupings. While its nmr spectrum ($CDCl_3$) awaits full analysis, the gross features [τ 6.49-1H-singlet (OH disappears on shaking with D_2O), 7.3-8.5-10H-multiplet, 8.89-3H-singlet (C-$\underset{\sim}{CH_3}$)] is also consistent. Its mass spectrum exhibits a parent peak at m/e 194 and a base peak at m/e 69. The latter could well arise from the fragment indicated.

Reaction of the isomer with NaOD-D_2O-dioxane followed by shaking with H_2O (to remove oxygen bound deuterium) affords a dideutero product, III m/e 196 (parent), 69 (base peak). The nmr spectrum of the dideutero product exhibits a reduction in the τ 7.3-8.5 multiplet to eight protons.

The most attractive interpretation of the genesis of II involves formation of an enolate of the five membered ring followed by intramolecular Michael addition[3,4] to the double bond (arrow 1) and intramolecular aldol addition of the anion so produced with the other cyclic carbonyl function (arrow 2)in the manner indicated.[5] While this interpretation has the virtue of simplicity, several other courses might be considered. One of these involves the sequence (i) conjugate addition by t-butoxide (ii) aldol condensation between the anion so generated with a proximate ketone (iii) β-elimination of t-butoxide and (iv) intramolecular conjugate addition. It should, however, be recognized that step (iv) gives rise to an anion at the bridgehead adjacent to the six membered ketone. The deuterium exchange experiment on II, conducted under considerably more forcing conditions than those of its formation, suggests that this anion is not readily accessible. Still another formal alternative involves the first two steps postulate above,

followed by a ring closure involving intramolecular displacement (SN_2) of t-butoxide by the enolate. While esthetically unactractive, this variant is less readily dismissed in rigorous terms.

Studies involving the mechanism and generality of this interesting base catalyzed bis cyclization, as well as the conversion of compound II to related sesquiterpenes, are in progress.



I II R=H III R=D m/e = 69

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References

1. S. Danishefsky and B. H. Migdalof, J. Am. Chem. Soc., 91, 2806 (1969).

2. For the synthesis of brendanone see: A. Nickson, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. Di Giorgio, ibid, 87, 1615 (1965).

3. The well known santonin-santonic acid transformation[4a] and the total synthesis of longifolene[4b] contain intramolecular Michael reactions on bicyclic systems resulting in the formation of homo and bishomo "brexane"[2] systems respectively.

4. (a) R. B. Woodward, F. Brutschy and H. Baer, J. Am. Chem. Soc., 70, 4216 (1948).
(b) E. J. Corey, M. Ohno, R. B. Mitra and P. A. Vatakancherry, ibid, 86, 478 (1964).

5. The degree of concertedness of the Michael and aldol steps is not specified and is currently under investigation.