

A NOVEL TRANSFORMATION IN THE QUADRONE SERIES

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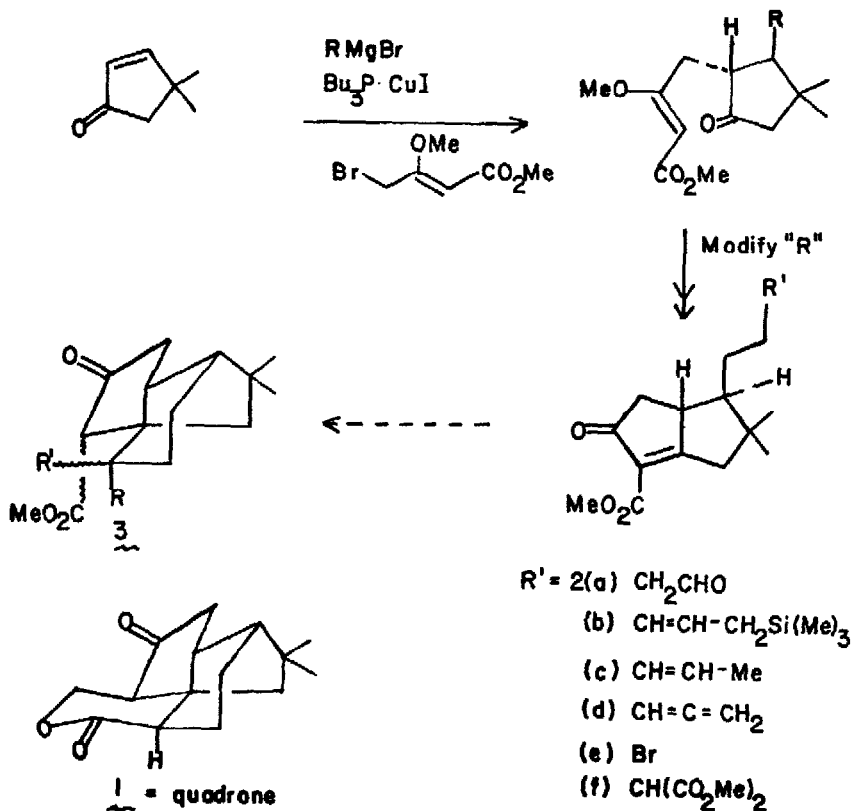
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Summary: A remarkable reaction of the substituted bicyclo [3,3,0] oct-3-ene-2-one (2_e) with the sodium enolate of malonic ester is described.

During our total synthesis² of the tumor inhibitor quadrone (1)^{3a,b} we had occasion to prepare compounds of the type 2_e, by the general sequence shown, with the hope that cyclization to systems such as 3 could be achieved.



The difficulties associated with the closure of a propano bridge on the exo (i.e. convex) face of a bicyclo [3,3,0] octanone system are suggested by our inability to achieve the cyclization of any of the compounds $2a-d$ to systems of the type 3 by well precedented reaction types^{4,5,6,7}. Below, we relate a particularly surprising occurrence with compound $2e$.

Reaction of $2e$ with dimethyl sodiomalonate in THF under reflux was examined. Depending on the reaction conditions, there were obtained varying ratios of oily $2f$ and a crystalline (mp 153-155°) isomer thereof. The maximum yield of this "isomer" was 70%. Its infrared and nmr spectra were in no way inconsistent with its formulation as the long desired 3 (R=R'=CO₂Me).

Doubts about the wisdom of this formulation soon arose. Thus, reaction of $2f$ with bases under a variety of conditions failed to produce the "isomer" or any other material corresponding to 3 . Compound 4 (R=H, mp 91-92°), the other possible precursor to 3 (R=R'=CO₂Me), was independently synthesized in 86% yield by a Mukaiyama reaction⁸ of $2f$ with 5 . Its structure and stereochemistry are fully supported by its crystal structure⁹ (see figure 1). Given the mildness of the conditions of the Mukaiyama reaction ($2f+5$, TiCl₄, -78°, CH₂Cl₂), the stereochemistry of $2e$ is also thus corroborated.

Under a variety of conditions,¹⁰ reaction of 4 (R=H) with bases led to its instantaneous conversion to $2e$. No indication of the alleged 3 could be had from any of these experiments. Hence, both mechanistically reasonable routes to the alleged 3 had been excluded.

The dilemma¹¹ was solved by X-ray crystallographic analysis wherein it was found that the isomer was in fact compound 6 ¹² (see figure 2) rather than 3 .

It is recognized that in going from $2e$ to 6 there is required a change of stereochemistry for the bromoethyl side chain from the exo to the endo configuration prior to its cyclization. The scheme $2e(\text{exo}) \rightarrow 2e(\text{anion}) \rightarrow 2e(\text{endo})$ rationalizes this de facto epimerization. Taken in isolation, the exo→endo transformation would undoubtedly be endothermic. Apparently this unfavorable equilibrium is "driven" by Michael addition of malonate to the endo isomer, followed by creation of a stable endo propano bridged system 6 via intramolecular alkylation of the resultant β-keto-ester enolate. The inherent strain of the exo bridge apparently mitigates against its formation by, what would have been, a much simpler pathway from $2e$ or $2f$.

Several other interesting transformations were observed pursuant to our synthesis of quadrone. These will be disclosed in due course.

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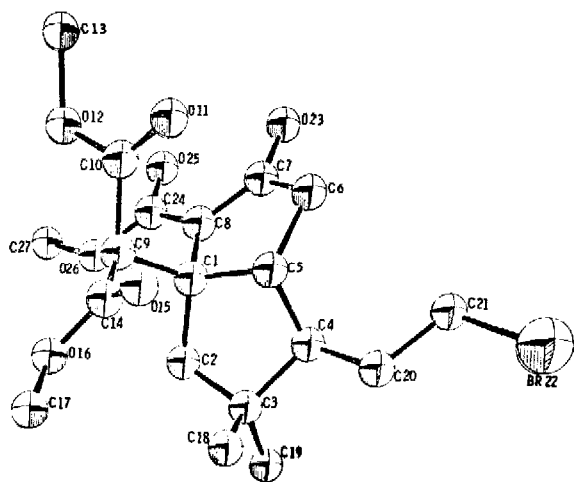
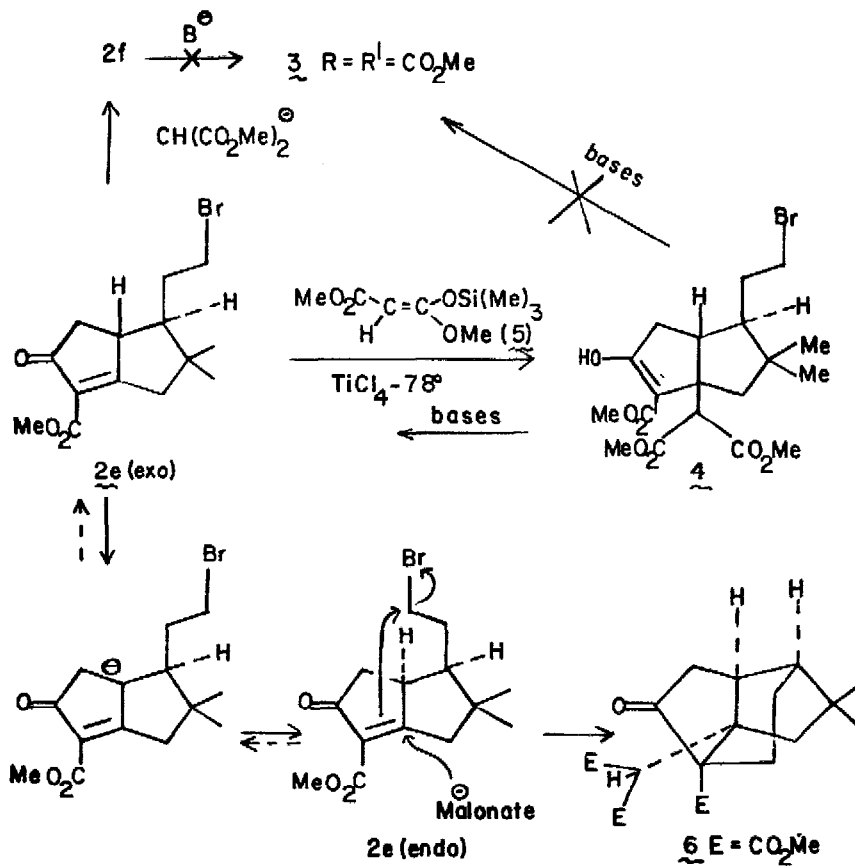


fig. 1⁹ Computer generated drawing of compound 4

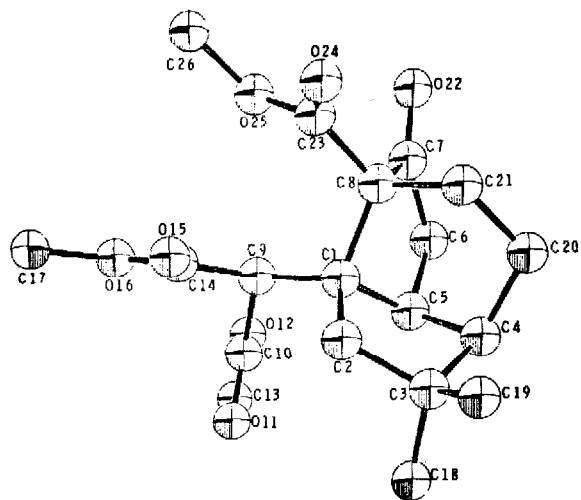


fig. 2¹² Computer generated drawing of compound 6

References:

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2. S. Danishefsky, K. Vaughan, R. C. Gadwood, and K. Tsuzuki; *J. Amer. Chem. Soc.*, in press.
3. (a.) R. L. Ranieri and G. J. Calton; *Tetrahedron Lett.* 499 (1978).
(b.) G. J. Calton, R. L. Ranieri, and M. A. Espenshade; *J. Antibiot.* 31, 38 (1978).
4. None of the desired type 3 ring systems could be found by (i) treating 2a with a variety of acids and bases (including secondary amines), (ii) reaction of 2b with titanium tetrachloride⁵, (iii) thermolysis of 2c⁶, or (iv) photolysis of 2d⁷.
5. cf. Hosomi, A., Sakurai, H.; *J. Am. Chem. Soc.* 1977, 99, 1673.
6. cf. Oppolzer, W., Snieckus, V.; *Angew. Chem. Int. Ed. Engl.* 1978, 17, 476.
7. cf. Wiesner, K., Musil, V., Wiesner, K. J.; *Tetrahedron Lett.* 1968, 5643.
8. Saigo, K., Osaki, M., Mukaiyama, T.; *Chem. Lett.* 1976, 163
9. Crystals of 4 (C₁₉H₂₇BrO₇) formed with symmetry P $\bar{1}$ and $\alpha = 11.023(2)\text{\AA}$, $b = 12.550(3)$, $c = 8.569(2)$, $\alpha = 102.47(2)^\circ$, $\beta = 105.85(2)$, and $\gamma = 104.70(2)$. 2922 reflections were measured with $2\theta \leq 114^\circ$ using CuK α radiation and a four-circle diffractometer. Of these unique reflections, 2642 (94%) were observed ($I \geq 3\sigma I$) and corrected for background, Lorentz and polarization effects. The structure was solved with standard direct methods and structural refinement was accomplished with full-matrix least-squares by minimizing $\sum w (|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$. The final unweighted residual index was .063 using anisotropic temperature parameters for the non-hydrogen atoms and fixed isotropic temperature parameters for the hydrogens.
10. Parenthetically, we note that the corresponding enol ether, of 4 mp 128-130°, also failed to cyclize under a variety of basic conditions.
11. In practice, the structure of compound 6 was also surmised by a series of chemical manipulations. These will be described in a full paper.
12. Crystals of 6 (C₁₉H₂₆O₇) grew from methylene chloride/heptane mixtures as clear prisms of symmetry P2₁2₁2₁ with $\alpha = 8.215(1)\text{\AA}$, $b = 14.803(2)$ and $c = 15.157(2)$. 1374 unique reflections were considered observed out of the 1448 measured with CuK α radiation. Standard direct methods and Fourier difference techniques gave initial coordinates for all the atoms. Full-matrix least-squares refinements using anisotropic temperature factors for the non-hydrogen atoms and fixed isotropic temperature parameters for the hydrogens gave an unweighted R factor of .038.

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