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STEREOSELECTIVITY IN THE METHYLATION OF THE ENOLATE OF DIETHYL 3-t-BUTYLGLUTARATE

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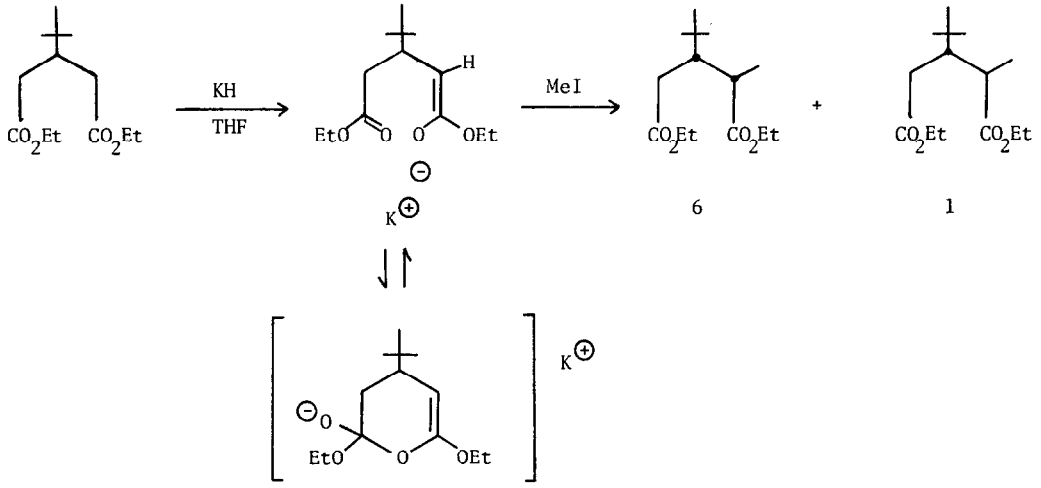
In recent years considerable research has been done on ketone enolates because of the immense synthetic utility of these intermediates. Considerably less work has been done on the enolates of esters. A notable exception is the isolation of the stable litho t-butyl acetate and the alkylations of this compound by Rathke and co-workers.[1] In connection with another problem we desired a sample of diethyl 2-methyl-3-t-butylglutarate, and since diethyl 3-t-butylglutarate was readily available from 4-t-butylcyclohexanone,[2] it seemed reasonable simply to methylate this material to arrive at the desired product.

Diethyl 3-t-butylglutarate was treated with a 1.05 mol equivalent of KH in THF at room temperature. The KH was consumed in approximately 30 min resulting in a slightly yellow clear solution of the enolate. Methyl iodide (2 eq) in THF was added quickly. Immediately a white precipitate formed. The reaction mixture was allowed to stir for 1 hr, diluting with hexane, and worked up to give a 95% yield of a 8:85:7 mixture of the starting material, the monoalkylated product, and the dialkylated product, respectively (bp 110 a .2 Torr (air bath)). A sample of the monoalkylated product was separated by preparative glpc (6' x 3/8", 10% SE-30 on Chrom A).[3,4] A ^{13}C NMR spectrum of this material showed it to be a 6:1 mixture of two monoalkylated products (i.e., erythro- and threo-). The stereochemistry was established by reducing the crude mixture of diesters to a mixture of diols with LAH in ether. The diol mixture was converted to a mixture of ditosylates with p-toluenesulfonyl chloride in pyridine. The ditosylate mixture was cyclized in 90% yield to a mixture of thianes by $Na_2S \cdot 9H_2O$ in refluxing EtOH/H_2O. Glpc analysis showed a 8:85:7 mixture of thianes. The mono-methyl major product was isolated from this mixture by a combination of fractional recrystallization of the $HgCl_2$ complexes and preparative glpc.[3,4] The ^{13}C NMR spectrum of this compound displayed signals at 14.02 (q), 23.18 (t), 28.33 (q), 29.91 (d), 30.02 (t), 39.80 (t), and 50.38 (d) in the ratio of 1:1:3:1:1:1:1:1, resepctively. By comparing the ^{13}C shifts of this compound with those of known thianes[5]

it is possible to assign to this compound the cis-stereochemistry on the basis of the upfield shift of the 5-methylene group and the 3-methyl group. This clearly establishes that the predominant mono-methylation product from the methylation of diethyl 3-t-butylglutarate is the erythro-diethyl 2-methyl-3-t-butylglutarate. Inspection of possible models for the intermediate enolate suggests that to explain the stereoselectivity of the methylation and the stability of the enolate, a plausible intermediate is the cyclic anion depicted below. The stereoselectivity of the reaction could then be explained by analogy to the reactions of 3-t-butylcyclohexene where the t-butyl group blocks one face of the double bond.[6]



Further work in this area is continuing.

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