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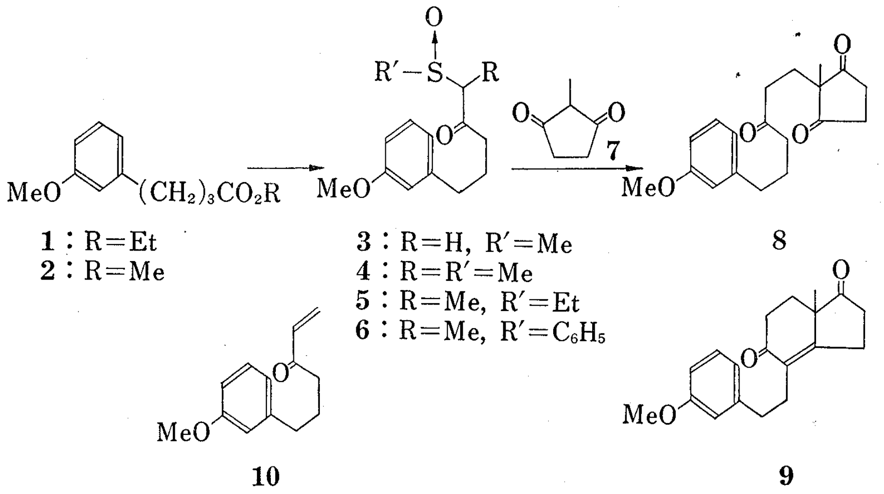
An Application of Reactions of β-Ketosulfoxides to Estrone Synthesis

Thermal elimination of β-ketosulfoxides prepared from esters of *m*-methoxyphenylbutyric acid and sulfoxides in the presence of methylcyclopentanedione gave easily a trione and a dione, key intermediates in the Smith's synthesis of estrone.

Although there are so many reports on the synthesis of estrone, seeking for more practical methods is still very important because of invaluable physiological properties of estrogens. Recently several reports on thermal elimination of β-ketosulfoxides to αβ-unsaturated ketones and its synthetic applications were published.[1] We are also investigating on various reactions of β-ketosulfoxides, in which a novel synthesis of condensed aromatics and heterocycles, such as naphthalenes, indoles, benzothiophenes, and carbazoles, has already reported.[2] As an extension of our studies, we wish to report here an application for the synthesis of estrone, *viz.*, a convenient and short-step synthesis of a trione (**8**) and a dione (**9**) which are known to be key intermediates in the Smith's method, one of the most efficient and stereospecific syntheses of estrone.[3]

A β-ketosulfoxide (**3**) [Mass Spectrum *m/e*: 254 (M^+, 16%), 177 (24%), 134 (100%). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1705, 1040.] prepared from ethyl *m*-methoxyphenylbutyrate (**1**) and dimethyl sulfoxide[4] in 95% yield was treated with methyl iodide in tetrahydrofuran at room temperature in the presence of potassium hydride or sodium hydride to give **4** in 82% yield. Its mass spectrum has no molecular ion, but a peak due to M^+-CH_3SOH at *m/e* 204 (4%), and the base peak appears at *m/e* 134 (100%). Thermal elimination of β-ketosulfoxides gives αβ-unsaturated ketones, *i.e.*, on heating **4** gave **10** which condensed with methylcyclopentanedione (**7**) to yield **8**, whereas more conveniently **4** and **7** (1.3 eq.) in diglyme was heated under reflux for 4.5 hr



1 : R=Et
2 : R=Me

3 : R=H, R'=Me
4 : R=R'=Me
5 : R=Me, R'=Et
6 : R=Me, R'=C_6H_5

8

9

10

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to give **8** [Mass Spectrum *m/e*: 316 (M^+, 6%), 134 (100%), 121 (14%). IR ν_{max}^{neat} cm^{-1}: 1760, 1720.] in 70% yield through a series of the elimination and Michael addition. In refluxing toluene, xylene and dimethylformamide, the formation of **8** was sluggish.

In order to dispense with the methylation step, **2** was condensed at —10° with an anion prepared from diethyl sulfoxide and lithium diisopropylamide in tetrahydrofuran to give **5** in 98% yield [Mass Spectrum *m/e*: 204 (M^+—EtSOH, 5%), 134 (100%), 121 (9%). IR ν_{max}^{neat} cm^{-1}: 1700, 1041.]. In analogy with **4**, **5** was heated with **7** to give **8**, though the yield (41%) was unsatisfactory because of a concomitant elimination in the unfavorable direction.

Compound **6** [Mass Spectrum *m/e* 218 ($C_6H_5SSC_6H_5$, 7%), 204 (M^+—C_6H_5SOH, 7%), 134 (100%), 121 (9%). IR ν_{max}^{neat} cm^{-1}: 1700, 1040.] was prepared from **2** with ethyl phenyl sulfoxide and lithium diisopropylamide in 90% yield, and on heating with **7** under the conditions described above gave interestingly an acid-catalyzed cyclization product (**9**) (35%) [Mass Spectrum *m/e*: 298 (M^+, 32%), 164 (98%), 134 (100%), 121 (88%). IR ν_{max}^{neat} cm^{-1}: 1740, 1660.]. Benzenesulphenic acid, though unstable, produced as the elimination of **6** proceeded probably acted as a catalyst.

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