

Communications to the Editor

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**Synthesis of 12 α and 12 β -Carboxyestradiol Derivatives *via* the
Thermal Elimination of β -Ketosulfoxide**

The unsaturated keto ester (3) prepared from the β -ketosulfoxide (2) by the mild thermal elimination was condensed with 2-methylcyclopentane-1,3-dione to give the trione (4), which was converted into the novel title compounds (14) and (15).

Keywords— β -ketosulfoxide; estra-1,3,5(10),8,14-pentaene; estra-1,3,5(10),8-tetraene; steroid synthesis; thermal elimination; Michael condensation; epimerisation; stereoselective reduction; 12-methoxycarbonyl estradiol

Although there have been many reports on the synthesis of nuclear substituted steroids in order to seek for potential hormonal activities,^{1,2)} no report has appeared on the introduction of a carboxyl group at C-12 position of estrogens since that is a complicated problem in the synthesis by conventional methods. Recently, radioimmunoassays have been developed for estimation of estrogenic hormones in biological fluids, and it was attempted to produce highly specific antibodies for individual estrogens.^{3,4)} Aromatic steroids having a functional group at C ring are expected to be utilized for preparation of the specific antibodies by coupling to a carrier protein without any disturbance in the functional groups in A and D rings of estrogens. In the course of our investigation on the application of β -ketosulfoxide for the aromatic steroid synthesis,^{5,6)} we report here the synthesis of 12 α and 12 β -methoxycarbonyl-estradiol 3,17-diacetates in good yields.

The thermal elimination of the β -ketosulfoxide (2) in refluxing dioxane for 15 min afforded the unsaturated keto ester (3) [88%; NMR (CDCl₃) δ : 6.60 (d, J =7.7 Hz), 6.88 (d, J =7.3 Hz)], which must be a key intermediate in the Smith type steroid synthesis.⁷⁾ Then 3 was readily converted into the trione (4) [88%, mp 123—123.5°C; NMR (CDCl₃) δ : 0.98 (s, Me), 2.80 (s, cyclic methylene), 3.55 (s, COOMe), 3.77 (s, OMe), 3.83 (t, CHCOOMe)] by the Michael condensation with 2-methylcyclopentane-1,3-dione. Cyclization of 4 in the presence of methanesulfonic acid in dichloromethane at 0° gave the desired 12 β -methoxycarbonyl steroidal pentaene (5) [90%, mp 139—140.5°C; NMR (CDCl₃) δ : 1.30 (s, 18-Me), 3.80 (s, 12-COOMe), 3.82 (s, 3-OMe), 5.93 (dd, 15-H)]. The 12 α -isomer of 5 was also isolated as a by-product from the reaction mixture and its configuration was proved by the lactonization of 12 α -carboxyl and 17 α -hydroxyl groups after reduction of the 17-ketone with NaBH₄. Catalytic hydrogenation of 5 over 10% Pd/C in benzene afforded the 14 α -tetraene (7) [80%, UV (EtOH) 280 nm; MS m/z : 340 (M⁺), 224] and a small amount of the 14 β -isomer (2%). To avoid the formation of the undesirable 14 β -isomer, the 17 β -hydroxy compound (6) prepared from 5 by the reduction with NaBH₄, was hydrogenated under the above conditions to give the 14 α -tetraene-17 β -ol (8) [IR (Nujol) cm⁻¹: 3480, 1730; NMR (CDCl₃) δ : 1.00 (s, 18-Me), 3.74 (s, 12-COOMe, 3-OMe), 4.05 (m, 17-H)] in quantitative yield. Hydrolysis of 8 in refluxing 2 N KOH-MeOH afforded the 12 β -carboxy-tetraene-17 α -ol (11) [IR (Nujol) cm⁻¹: 3300, 1705; NMR (pyridine-*d*₅) δ : 1.05 (s, 18-Me), 3.68 (s, 3-OMe), 4.33 (dd, 17-H)], while 7 prepared from 8 by the oxidation with CrO₃ quantitatively, was hydrolyzed under the same conditions to give the 12 α -carboxy-tetraene (9) [90%, mp 187—189 °C; NMR (CDCl₃) δ : 0.90 (s, 18-Me), 3.80 (s, 3-OMe)]. The epimerization at C-12 can be explained in terms of that an enolate anion was formed from the equatorial 7 and protonated to give the axial 12 α -ester, then it was hydrolyzed to 9 from the following facts: the 12 α and 12 β -carboxy-tetraenes (9, 10) were not interconvertible under the above conditions, and 7 was epimerized by heating in KOMe-MeOH to the 12 α -ester (mp 109—112°C).

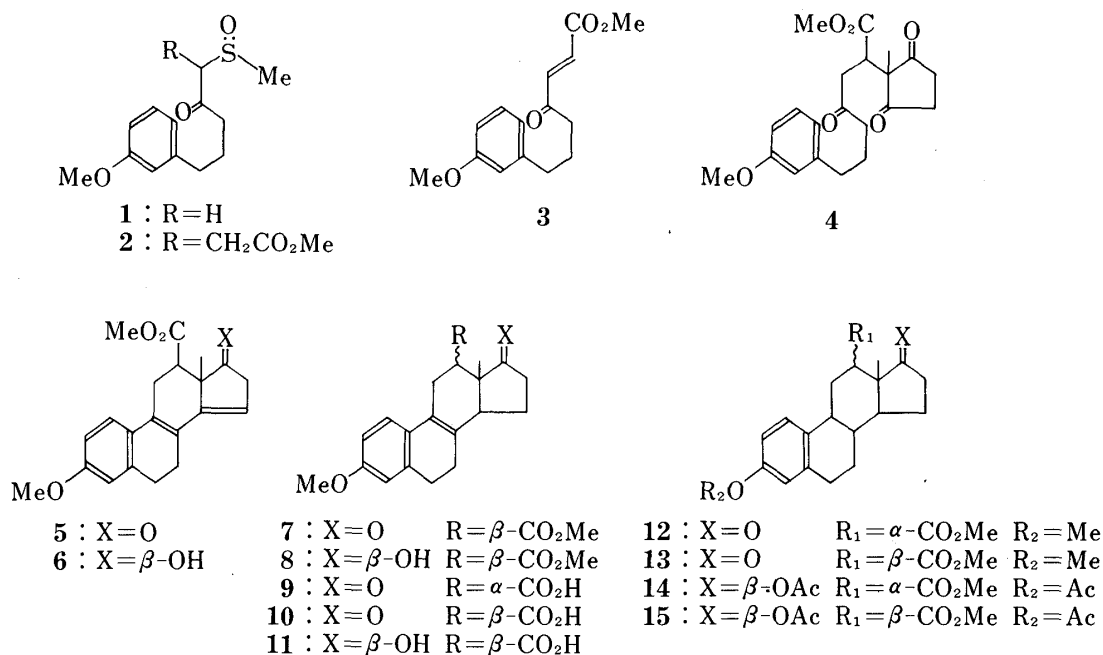


Chart 1

Subsequently, **9** was reduced with sodium in liquid ammonia, followed by esterification with diazomethane, and oxidation with CrO₃ to give 12α-methoxycarbonyl estrone methyl ether (**12**) [mp 173—174.5°C; IR (Nujol) cm⁻¹: 1740, 1735; NMR (CDCl₃) δ: 1.05 (s, 18-Me), 3.71 (s, 12-COOMe), 3.75 (s, 3-OMe); MS *m/z*: 342 (M⁺), 282 (M⁺—HCOOMe)]. Similarly, **10** and **11** gave 12β-methoxycarbonyl estrone methyl ether (**13**) [mp 155—156°C; IR (Nujol) cm⁻¹: 1735, 1720; NMR (CDCl₃) δ: 1.13 (s, 18-Me), 3.80 (s, 12-COOMe, 3-OMe); MS *m/z*: 342 (M⁺), 282 (M⁺—HCOOMe)]. The structure of **12** and **13** were defined by the conversion into estrone methyl ether through decarboxylation of their *tert*-butyl peresters, respectively.⁸⁾

Finally, the compounds **12** and **13** were reduced with NaBH₄ and demethylated with trimethylsilyl iodide to give estradiol derivatives,⁹⁾ which were purified after acetylation and methylation to afford 12α-methoxycarbonyl estradiol 3,17-diacetate (**14**) [mp 194—195.5°C; IR (Nujol) cm⁻¹: 1760, 1730 (sh), 1720; NMR (CDCl₃) δ: 1.02 (s, 18-Me), 2.01 (s, 17-OCOMe), 2.23 (s, 3-OCOMe), 3.65 (s, 12-COOMe), 4.81 (dd, 17-H); MS *m/z*: 414, 382, 352, 312] and 12β-methoxycarbonyl estradiol 3,17-diacetate (**15**) [mp 162.5—163.5°C; IR (Nujol) cm⁻¹: 1760, 1735, 1720; NMR (CDCl₃) δ: 0.93 (s, 18-Me), 1.99 (s, 17-OCOMe), 2.24 (s, 3-OCOMe), 3.62 (s, 12-COOMe), 4.88 (dd, 17-H); MS *m/z*: 414 (M⁺), 372].

These compounds were converted into the new haptens conjugated with bovine serum albumin for the immunoassay of estradiol, and details of the investigations will be reported in another paper.

References and Notes

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Interconvertible *cis* and *trans* Rotational Isomers of 1,8-Di(1-naphthyl)naphthalene

New stable *cis* and *trans* rotational isomers of 1,8-di(1-naphthyl)naphthalene were prepared by the Kharash-type Grignard cross-coupling of 1-naphthylmagnesium iodide and 1,8-diiodonaphthalene in the presence of *N,N'*-bis(1-methyl-3-oxobutylidene)ethylenediaminatonicel(II). Thermoanalytical and proton magnetic resonance spectral studies indicated that both rotamers are stable in the solid state as well as in a solution, but are interconvertible at temperatures above their melting points. A convenient method, obtaining pure *trans* rotamer from the equilibrium mixture of both rotamers, is also presented.

Keywords—Ni-complex-catalyzed cross-coupling; 1,8-diarylnaphthalene; rotational isomer; interconversion; DSC; NMR

Concerning the geometry of *peri*-aryl naphthalenes, it has already been known that phenyl rings in 1,8-diphenylnaphthalene are constrained to the conformation in which both benzene rings are approximately parallel to one another and perpendicular to the plane of naphthalene ring.¹⁾ This would lead to the expectation that 1,8-diphenylnaphthalenes having *o*- or *m*-substituent on each phenyl ring should exist as stable *cis* and *trans* isomers due to restricted rotation around the phenyl-naphthylene bonds. However, the attempts, proceeded by House and Bashe, to separate *cis* and *trans* isomer pair of compounds such as 1,8-bis(3-chlorophenyl)naphthalene or 1,8-bis(3-carbomethoxyphenyl)naphthalene were unsuccessful,²⁾ presumably owing to the low energy barrier which was not enough for their separation.³⁾ Recently, Clough and Roberts resolved *cis* and *trans* isomers of 1,8-di(*o*-tolyl)naphthalene, which were stable in the crystalline state, but had a half-life in solution of about only 1 day at room temperature.⁴⁾

We have found that 1,8-di(1-naphthyl)naphthalene could be resolved to *cis* and *trans* rotamers which were stable in solid state as well as in solution, but were interconvertible at temperatures above their melting points.

1,8-Di(1-naphthyl)naphthalene (**1**) was prepared using Kharash-type Grignard cross-coupling reaction⁵⁾ analogously to the preparation of 1,8-di(*o*-tolyl)naphthalene,^{4,5b)} but under modified reaction conditions in the presence of different catalyst. Thus 1-naphthylmagnesium iodide (8 fold excess) was directly coupled with 1,8-diiodonaphthalene in an ether-benzene mixture under refluxing in the presence of *N,N'*-bis(1-methyl-3-oxobutylidene)-ethylenediaminatonicel(II) as a catalyst.⁶⁾ Two isomers **1a** and **1b** were isolated from