SYNTHESIS OF 3-METHOXY-5,6-SECOESTRA-1,3,5(10),8,14-PENTAEN-17-ONE S.Jayaraman¹, N.Raju and K.Rajagopalan* Department of Organic Chemistry University of Madras, Guindy Campus Madras-600 025, India.

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ABSTRACT

A facile synthesis of 3-methoxy-5,6-seccestra-1,3,5(10),8,14-pentaen-17-one from the readily available p-anisaldehyde is reported.

In recent years there has been a tremendous spurt in the design and execution of total synthesis of steroids (2,3). We report in this communication results obtained with our new synthetic approach to steroids involving an $A + D \rightarrow AD \rightarrow ACD \rightarrow ABCD$ route. The strategy of coupling A and D rings and further elaboration to the tetracyclic system in the present study involves two key reactions : i) the Torgov reaction and ii) an electrocyclic ring closure towards the formation of ring B.

Pyridinium dichromate oxidation (4) of the known l-(p-methoxyphenyl)-3-buten-l-ol (5) (prepared from p-anisaldehyde and allylmagnesium bromide) in methylene chloride furnished the ketone <u>1</u> in 75% yield. Addition of

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vinylmagnesium chloride to the ketone yielded the vinyl carbinol 2 in 73% yield. The structure of the carbinol was confirmed by IR, NMR and mass spectral data. The Torgov reaction (6) of the vinyl carbinol 2 with 2-methylcyclopentane-1,3-dione using Triton-B as catalyst was unsuccessful. Attempted preparation of the isothiouronium salt of the carbinol $\underline{2}$ following the procedure of Kuo \underline{et} \underline{al} (7) also did not succeed. However, refluxing the carbinol 2 and the 1,3-diketone in an acetic acid - xylene mixture resulted in a smooth condensation to furnish the diketone 3 in 60% yield. The success of the Torgov reaction was distinctly shown by the product having NMR signals for the angular methyl and biallylic methylene protons. Based on NMR (8) an 'E' configuration has been assigned for the product. However, a small amount (10%) of 'Z' isomer was also present, as revealed by an angular methyl signal at $1.02 \circ$. It has been reported (7) that 6-methoxy-l-vinyl-l-tetralol undergoes both condensation and cyclodehydration leading to a tetracyclic system. In the present study, the reaction was found to stop at the condensation stage with no trace of cyclodehydration product $\underline{4}$ being isolated.

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Attempted acid catalysed cyclodehydration of diketone <u>3</u> under a variety of conditions led to a mixture of products. This could be explained on the basis of the fact that the triene <u>4</u> - the cyclodehydration product of diketone <u>3</u> - is perhaps sensitive to acids. Alternatively, the isomerisation of the <u>9,11</u>-double bond to the 8,9position in diketone <u>3</u> will generate a phenylbutadiene moiety which could also be sensitive to acids.

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Selective hydrogenation of diketone 3 resulted in the formation of compound 5 in 80% yield (9,10). The structure of the reduced product 5 was attested by the disappearance of olefinic protons at C_{f} and C_{7} in the NMR spectrum. Cyclodehydration of compound 5 using p-toluenesulfonic acid in refluxing benzene furnished compound 6 as an oil in 35% yield. The spectral data clearly indicated the cyclised structure for the product. (This constitutes yet another method of synthesis of the already reported (10)title compound). The complications encountered during the attempts at cyclisation of compound 3 could very well be attributed to the presence of an extra double bond between $C_{6}-C_{7}$ which probably confers greater acidity to the C_{8} methylene protons. This assumption is amply borne out by the successful cyclisation of the reduced product 5.

EXPERIMENTAL

1-(p-Methoxyphenyl)-3-buten-1-ol was prepared according to the literature (5).

1-(p-Methoxyphenyl)-3-buten-1-one 1:

Pyridinium dichromate (75 g, 0.2 mol) was added in portions to a stirred solution of 1-(p-methoxyphenyl)-3buten-1-ol (17.8 g, 0.1 mol) in dry dichloromethane (500 ml). After stirring for 24 hr, the reaction mixture was filtered through celite and the filtrate was washed successively with saturated sodium bisulfite solution, saturated copper sulfate solution and then with water. Drying and solvent removal gave a viscous liquid (13.2 g, 75%). IR (CHCl₃) :

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1690 (C=O), and 1620 cm $^{-1}$ (C=C).

The ketone $\underline{1}$ (homogeneous on TLC) turned dark brown on storage and hence was used as such in the next step without further purification.

3-(p-Methoxyphenyl)-1,5-hexadien-3-ol 2 :

A solution of ketone 1 (17.6 g, 0.1 mol) in THF (50 ml) was added dropwise under nitrogen for 1 hr to a stirred and cooled (-70°) solution of vinylmagnesium chloride prepared from magnesium (10.56 g, 0.44 g atom) and vinyl chloride (28 g, 0.44 mol) in THF (100 ml). The reaction mixture was stirred in an ice-salt bath for 2 hr and then refluxed over a steam bath for 2 hr. After having been left over-night at room temperature, the Grignard complex was decomposed with saturated ammonium chloride solution (50 ml). The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with water and dried (MgSOA). Removal of solvent and chromatography over silica gel (benzene - ethyl acetate 9:1) yielded a colourless oil (15 g, 73%). IR (CHCl₃) : 3560 (OH) and 1635 cm⁻¹ (C=C); NMR (CCl4/TMS) 0 2.23 (broad singlet, 1H, OH), 2.69 (d, 2H, J = 7 Hz, $-CH_2$), $3.79 (s, 3H, OCH_3)$, 5.03-6.36 (m, M)6H, olefinic), 6.84-7.46 (AB quartet, 4H, aromatic) : MS : m/e 204 (M⁺).

<u>Anal</u>. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found : C, 76.08; H, 7.92%.

<u>3-Methoxy-5,6,8,14-diseccestra-1,3,5(10),6,9(11)-pentaen-</u> <u>17-one</u> <u>3</u>:

To a stirred solution of the carbinol $\underline{2}$ (7.2 g, 0.035 mol) in xylene (40 ml) was added 2-methylcyclopentane-1,3-dione (5 g, 0.045 mol) and acetic acid (25 ml). The mixture was refluxed for 7 hr and the solvent was removed under vacuum. To the residue, benzene (100 ml) was added; the benzene phase was washed successively with water, saturated sodium bicarbonate solution and finally with water. Drying and solvent removal yielded a viscous red-brown liquid which was purified by chromatography over silica gel. Elution with benzene yielded the diketone $\underline{3}$ as a yellow oil (6.3 g, 60%). UV (CHCl₃) : λ_{max} 261 nm; IR(CHCl₃): 1720 (C=0) and 1630 cm⁻¹ (C=C); NMR (CDCl₃/TMS) O 1.17 (s, 3H, CH₃), 2.53 (d, 2H, J = 8 Hz, allylic methylene), 2.76 ($\frac{3}{5}$, 4H, methylenes of cyclopentane ring), 3.21 (d, 2H, J = 6 Hz, biallylic methylene), 3.83 (s, 3H, OCH₃), 4.93 - 5.18 (m, 2H, terminal methylene), 5.48 - 6.03 (m, 2H, olefinic), 6.83 - 7.36 (AB quartet, 4H, aromatic); MS : m/e 298 (M⁺).

<u>Anal</u>. Calcd. for C₁₉H_{22O3} : C, 76.48; H, 7.43. Found : C, 76.22; H, 7.36%

<u>3-Methoxy-5,6,8,14-diseccestra-1,3,5(10),9(11)tetraen-17one 5</u>:

A solution of compound $\underline{3}$ (0.5 g, 1.7 m mol) in ethanol (20 ml) was hydrogenated at 15 psi pressure of H₂ for 15 min in the presence of 10% Pd-C (0.1 g). The product was filtered through celite and the solvent was removed under reduced pressure. The pale yellow liquid obtained was purified by preparative TLC to furnish compound $\underline{5}$ (0.4 g, 80%). UV (EtOH) : λ_{max} 252 nm ($\underline{C} =$ 21,370); IR (CHCl₃) : 1770, 1730 (C=O), 1615 cm⁻¹ (C=C); NMR (CCl₄/TMS) $\underline{0}$ 0.84 - 1.53 (m, 8H, angular CH₃ and CH₂-CH₃), 2.20 - 2.74 (m, 8H, C₈, Cl₂, Cl₅ and Cl₆ methylenes), 3.87 (s, 3H, OCH₃), 5.36 (t, 1H, J = 8 Hz, olefinic), 6.80 - 7.30 (AB quartet, 4H, aromatic); MS : m/e 300 (M⁺).

Anal. Calcd. for C H O : C, 75.97; H, 8.05. Found : C, 76.10; H, 8.08%.

<u>3-Methoxy-5,6-secoestra-1,3,5(10),8,14-pentaen-17-one 6</u>:

To a solution of compound 5 (0.3 g, 1 m mol) in benzene (30 ml) was added p-toluenesulfonic acid (0.17 g, 1 m mol) and refluxed over a steambath for 2 hr. The reaction mixture was diluted with benzene (100 ml). The benzene phase was washed successively with water, saturated sodium bicarbonate solution and finally with water. Drying and solvent removal gave a red-brown liquid. This was purified by preparative TLC (petroleum ether - benzene 1:3) to yield compound 6 as a viscous liquid (0.1 g, 35%) UV (EtOH) : λ_{max} 266 nm (C = 25,980); IR (CHCl₃) : 1740 cm⁻¹ (C=0); NMR (CCl₄/TMS) \bigcirc 0.97 (t, 3H, J = 8 Hz, CH₃), 1.15 (s, 3H, Cl₃-CH₃), 1.43 - 3.16 (m, 8H, methylenes), 3.81 (s, 3H, OCH₃), 5.81 (t, 1H, J = 2 Hz, vinylic), 6.79 -7.12 (AB quartet, 4H, aromatic). <u>Anal</u>. Calcd. for C₁₉^H₂₂^O₂ : C, 80.82; H, 7.85. Found : C, 80.72; H, 7.62%.

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