Hacettepe Bulletin of Natural Sciences and Engineering
1975 / Volume 4 / pp. 77 – 84

Total Syntheses of Some 7-Methyl Substituted Estrogens

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Introduction

Within the last ten years many of the steroidal hormones have been totally synthesized.[1-13] A French firm, Roussel, has even started to manufacture most of the steroidal hormones, used in chemical therapy, by total synthesis.[1,2] So far nothing has been reported about the total syntheses of 7-methyl substituted steroids. While studying the effect of the 7-methyl group on a certain biological activity[14-16] several 7-methyl substituted steroids have been prepared by partial synthesis[15,16] with rather poor yields. For this purpose first of all a double bond must be introduced to the steroid molecule at 5-C. The resulting unsaturated molecule should then be oxidized to a 7-keto-Δ^5 steroid. Finally the unsaturated ketone, thus obtained, when reacted with methyl magnesium iodide leads to a 7-oxo methylene steroid which could be hydrogenated with palladium oxide in glacial acetic acid-acetic anhydride mixture. For the oxidation of the Δ^5 steroids to the 7-keto-Δ^5 steroids t-butyl chromate or alternatively chromic oxide in pyridine is used. The first method suffers from a low yield as well as the extreme care necessary in working with large amounts of t-butyl chromate. The second method results in an even lower yield. One other method for the preparation of 7-keto-Δ^5 steroids involves a three step sequence reported by Lenhard and Bernstein.[16] This method involves allylic bromination (C-7) of Δ^5 with N-bromo succinimide followed by reaction of the bromo compound with neutral alumina to produce the 7-OH steroid which can then be oxidized with chromium trioxide in pyridine to 7-keto-Δ^5 steroid.

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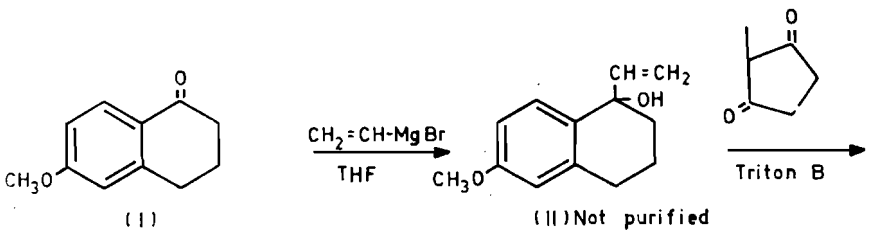
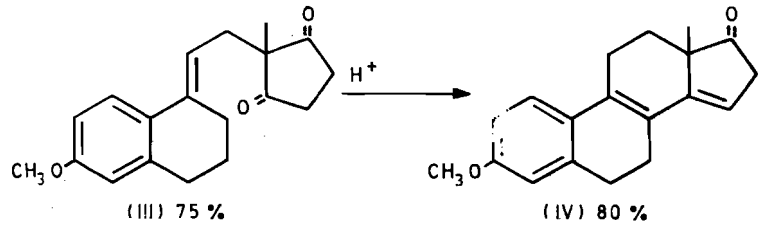
In the work of Torgov[5, 6] for the total synthesis of d,l-8, 14-bis-dehydroestrone methyl ether (IV) (see Scheme I) triton B catalyzed condensation of crude 1,2,3,4-tetrahydro-6-methoxy-1-vinyl-1-naphthol (II) with 2-methylcyclopentane-1,3-dione afforded 2-(6-methoxy-1,2,3,4-tetrahydronaphthylidene ethyl)-2-methylcyclopentane-1, 3-dione (III) which on cyclization with p-toluenesulphonic acid in refluxing benzene, afforded d,l-8, 14-bisdehydroestrone methyl ether (IV).

SCHEME I

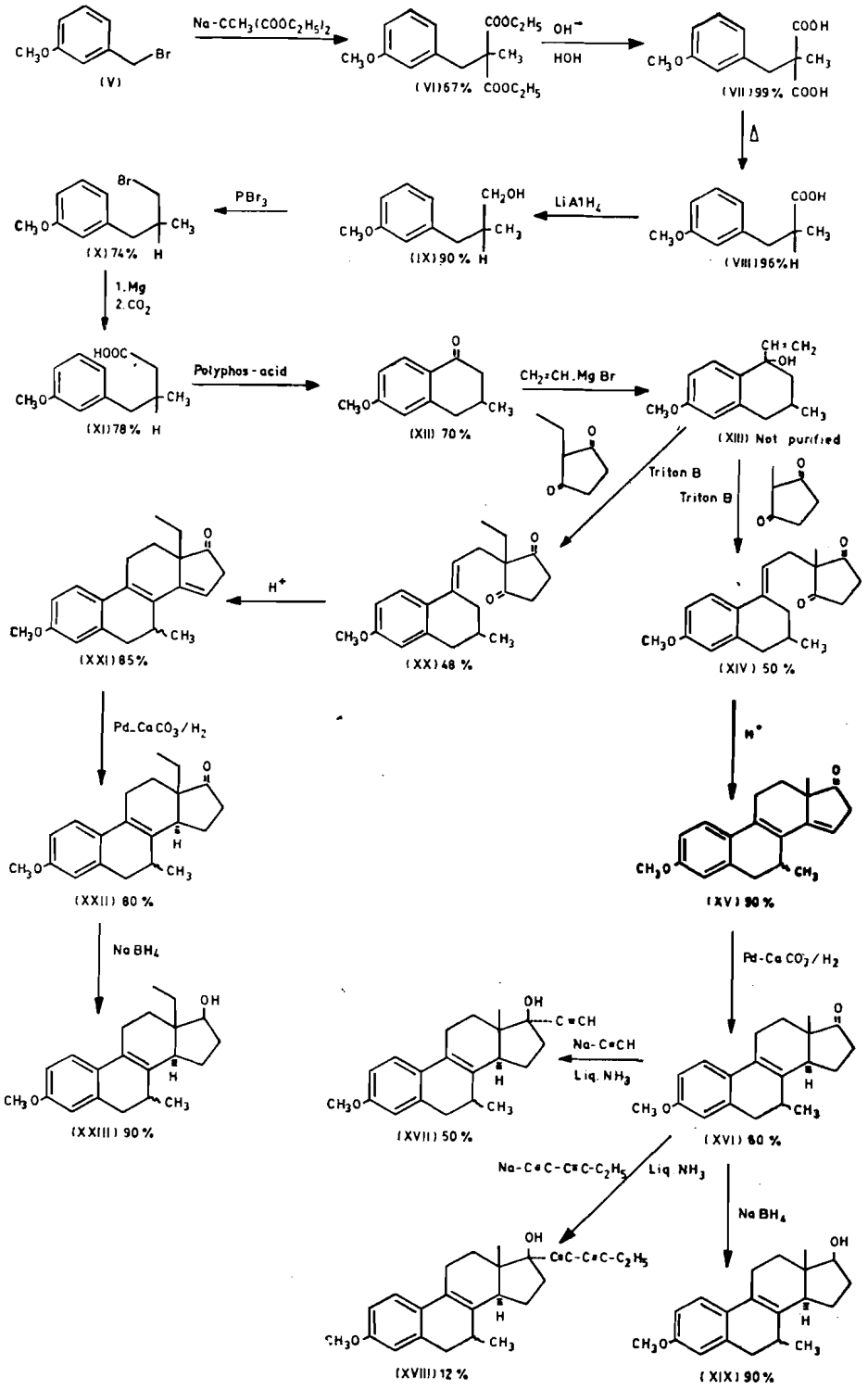




Method

In the present work (see Scheme II) subsititution of the tetralone (I) by a CH_3 at C-3 could, according to the Scheme I, yield methyl substituted derivatives of II, III and IV (XIII, XIV, XV) and XX, XXI which could be converted to some other additional 7-methyl substituted estrogens. Since 3-methyl-6-methoxy tetralone (XII) is not a known compound 7-methyl estrogens described in this paper were totally synthesized from o-methoxybenzyl bromide (see Scheme II).

SCHEME II


Na-CCH3(COOC2H5)2
OH⁻
HOH
(V)
(VI) 67%
(VII) 99%
Δ
PBr3
LiAlH4
(X) 74%
(IX) 90%
(VIII) 96%
1. Mg
2. CO2
Polyphos-acid
(XI) 78%
(XII) 70%
CH2=CH.Mg Br
(XIII) Not purified
Triton B
Triton B
H+
(XXI) 85%
(XX) 48%
(XIV) 50%
Pd-CaCO3/H2
H+
(XXII) 80%
(XV) 90%
NaBH4
Pd-CaCO3/H2
(XXIII) 90%
Na-C≡CH
Liq. NH3
(XVII) 50%
(XVI) 60%
Na-C≡C-C≡C-C2H5
Liq. NH3
NaBH4
(XVIII) 12%
(XIX) 90%

Results

Several 7-methyl substituted estrogenic steroids have been totally synthesized from o-methoxybenzyl bromide.

Experimental

Methyl-o-methoxybenzyl-diethylmalonate (VI). To a freshly prepared solution of sodium ethoxide, prepared from sodium (20 gr., 0.87 atom gram) in super dry ethanol (500 cc.), methyl-diethyl-malonate (151 gr., 0.8 mole gram) was added with stirring. This was followed by the addition of o-methoxybenzyl bromide (174 gr., 0.86 mole gram). The reaction mixture was refluxed (2 hours). Most of the solvent was distilled off and the residue was poured onto crushed ice. The mixture was extracted with ether (3X). The extracts were washed (water) and dried ($MgSO_4$). The solvent was removed and the residue distilled under reduced pressure to give methyl-o-methoxybenzyl-diethylmalonate (VI, 170 gr. 67 %), b.p 138-142°/0.3 mm.; $n_D^{28°}$ 1.4902; (Found: C, 65.20 %; H, 7.60 %. $C_{16}H_{22}O_5$ requires: C, 65.30 %; H, 7.54 %).

Methyl-o-methoxybenzyl-malonic acid (VII). To a refluxed solution of potassium hydroxide (280 gr., 5 mole gram) in water (290 cc.) methyl-o-methoxybenzyl-diethylmalonate (VI, 295 gr., 1 mole gram) was added (30 minutes). The mixture was refluxed for an additional 2 hours period, cooled and acidified with conc. hydrcchloric acid. The precipitate was collected, washed (water) and dried ($MgSO_4$). Yield: 232 gr. (almost quantitative); m.p 146-147°; (Found: C, 60.45 %; H, 5.90 %. $C_{12}H_{14}O_5$ requires: C, 60.50 %; H, 5.93 %).

α-Methyl-α-o-methoxybenzylacetic acid (VIII). Methyl-o-methoxybenzyl-malonic acid (VII, 77.6 gr., 0.4 mole gram) was heated at 200° for 2 hours and finally distilled to yield α-methyl-α-o-methoxybenzylacetic acid (VIII, 61 gr., 96 %), b.p 140-144°/1 mm.; $n_D^{23°}$ 1.5218; (Found: C, 67.90 %; H, 7.25 %; $C_{11}H_{14}O_3$ requires: C, 68.03 %; H, 7.27 %).

2-Methyl-3-o-methoxyphenylpropan-1-ol (IX). A solution of α-methyl-α-o-methoxybenzylacetic acid (VIII, 255 gr., 1.30 mole gram) in sodium dried ether (250 cc.) was added (60 minutis) to a susppension of lithium aluminium hydride (70 gr., 1.84 mole gram) in dry ether (500 cc.). The reaction mixture was refluxed for 1 hour and then cooled (0°). Excess of the hydride was carefully decomposed with water (150 cc.). This was followed by the addition of 20 % sulphuric acid (500 cc.). The mixture was extracted with ether. Ethereal layers were washed (water) and dried ($MgSO_4$). Evaporation of the solvent

and distillation of the residue yielded 2-methyl-3-o-methoxpyhenylpropan-1-ol (IX, 188 gr., 90 %), b.p 116°/1 mm.; $n_D^{24°}$ 1.5225; (Found: C, 73.35 %; H,8.90 %; $C_{11}H_{16}O_2$ requires: C, 73.39 %; H, 8.95 %).

1-Bromo-2-methyl-3-o-methoxyphenylpropane (X). Phosporous tribromide (180 gr., 0.66 mole gram) was added (45 minutes) to a solution of 2-methyl-3-o-methoxyphenylpropan-1-ol (IX, 180 gr., 1 mole gram) in sodium dried benzene (300 cc.) at 0°. The reaction mixture was then stirred (30 minutes) at room temperature and finally refluxed (4 hours). The mixture was cooled and poured onto crushed ice. Benzene layer was separated, washed first with aqueous bicarbonate solution, then with water and dried ($MgSO_4$). The solvent was removed and the residue distilled to yield 1-bromo-2-methyl-3-o-methoxyphenylpropane (X, 180 gr., 74 %), b.p 104°/0.4 mm.; $n_D^{24°}$1.5405; (Found: C, 54.20 %; H, 6.35 %; $C_{11}H_{15}OBr$ requires: C, 54.34 %; H, 6.25 %).

β-Methyl-γ-o-methoxyphenylbutyric acid (XI). A Grignard reagent was prepared from magnesium (12.2 gr., 0.5 atom gram) and 1-bromo-2-methyl-3-o-methoxyphenylpropane (X, 122 gr., 0.5 mole gram) using a total 260 cc. of dry tetrahydro furane. This reagent was poured onto an excess of solid carbon dioxide and left to stand overnight. The mixture was then diluted with water (300 cc.), acidified (conc. hydrochloric acid) and extracted with ether (3X). Ethereal layers were washed with 30 % aqueous sodium hydroxide solution and the aqueous layers were acidified (conc. hydrochloric acid). Acidic layers were extracted with ether (3X). Ethereal layers were dried ($MgSO_4$) and the solvent removed. The residue was distilled to yield β-methyl-γ-o-methoxyphenylbutyric acid (XI, 81 gr., 78 %), b.p 152°/0.5 mm.; $n_D^{24°}$ 1.5198; (Found: C, 69,15 %; H, 7.80 %; $C_{12}H_{16}O_3$ requires: C, 69.22 %; H, 7.75 %).

3-Methyl-6-methoxy-α-tetralone (XII). A. mixture of polyposphoric acid (125 cc.) and β-methyl-γ-o-methoxyphenylbutyric acid (XI, 42 gr., 0.2 mole gram) was heated (100°) with vigorous shaking (45 minutes). The mixture was poured onto crushed ice, scratched and warmed until the red coloured gum turned to a colourless precipitate. The precipitate was collected, washed (water) and crystallised (petrol ether 40-60°) to yield 3-methyl-6-methoxy-α-tetralone (XII, 26 gr., 70 %), m.p 71-72°; (Found: C, 75.70 %; H, 7.50 %; $C_{12}H_{14}O_2$ requires: C, 75.76 %; H, 7.43 %).

2-(3-Methyl-6-methoxy-1, 2, 3-4-tetrahydronaphthylidene-ethyl)-2-methylcyclopentane-1, 3-dione (XIV) and 2-(3-methyl-6-methoxy-1, 2, 3, 4-tetrahydronaphthylideneethyl)-2-ethylcyclopentane-

1,3-dione (XX). A Grignard reagent was prepared from magnesium (24.4 gr., 1 mole gram) and vinyl bromide (108 gr., 1 mole gram) using a total amount of 400 cc. of dry tetrahydro furane as solvent. This reagent was reacted with 57 gr. (0.3 mole gram) of 3-methyl-6-methoxy-α-tetralone dissolved in 100 cc. of tetrahydro furane and 400 cc. of ether. The crude vinyl carbinol thus obtained was dissolved in 500 cc. of xylene and 110 cc. of tertiary butyl alcohol, and 33 gr (0.3 mole gram) of 2-methylcyclopentane -1,3-dione or 37.8 gr. (0.3 mole gram) 2-ethylcyclopentane-1,3-dione was added. After stirring (15 minutes) at room temperature 10 cc. of 40 % solution of triton B in methanol was added and the mixture stirred and heated at the reflux temperature for 2 hours. After cooling ether (1000 cc.) was added and the mixture stirred with cooling for 4-5 minutes. The mixture was filtered and the filtrate was washed (3X) with 5 % potassium hydroxide solution and with water (3X). The filtrate was then dried ($MgSO_4$) and concentrated in vacuo. The residues were crystallised (petrol ether 40-60°) to yield: a- 2-(3-methyl-6-methoxy-1,2,3,4-tetrahydronaphthylideneethyl)-2-methylcyclopentane-1,3-dione (XIV, 48 gr., 50 %); (Found: C, 76.85 %; H, 7.70 %; $C_{20}H_{24}O_3$ requires: C, 76.90 %; H,7.75 %), b- 2-(3-methyl-6-methoxy-1, 2, 3, 4-tetrahydronaphthylideneethyl)-2-ethylcyclopentane-1, 3-dione (XX, 55 gr., 48 %), m.p 81°; (Found: C, 77.60 %; H, 8.00 %; $C_{21}H_{26}O_3$ requires: C, 77.27 %;H, 8.03 %).

d,1-8,14-Bisdehydro-7ξ-methyloestronemethylether (XV) and d,1-8,14-bisdehydro-7ξ, 18-dimethyloestronemethylether (XXI). A solution of XIV (20 gr., 0,07 mole gram) or of XX (50 gr., 0.16 mole gram) in methanol (500 cc.) containing 2N HCl (10 cc.) was heated (100°) for 2 hours. The reaction mixtures were diltuted with water (2000 cc.) and extracted (ether, 3X). The ethereal layers were washed (water) and dried ($MgSO_4$). Organic solvents were removed and the residues crystallised to yield: a- d,1-8,14-bisdehydro-7ξ -methyloestronemethylether (XV, 17 gr., 90 %), m.p 151-152°; (Found: C, 81.50 %; H, 7.60 %; $C_{20}H_{22}O_2$ requires: C, 81.60 %; H, 7.54 %), b- d,1-8,14-bisdehydro -7ξ, 18-dimethyloestronemethylether (XXI, 40 gr., 85%), m.p 105°; (Found: C, 81.65 %; H, 7.90 %; $C_{21}H_{24}O_2$ requires: C, 81.78 %; H, 7.85 %).

d,1-8-Dehydro-7ξ-methyloestronemethylether (XVI) and d,1-8-dehydro-7 ξ-18-dimethyloestronemethylether (XXII). Hydrogenations of XV (15 gr., 0.05 mole gram) and of XXI (15 gr., 0.05 mole gram) in analar benzene (150 cc.) in the presence of prereduced pallladium on calcium carbonate catalyst (5 %, 5 gr.) yielded by spontaneous crystallisation (methanol) from the filtrated, concentrated

reaction products: a- d,l -8-dehydro-7ξ- methyloestronemethylether (XVI, 12 gr., 80 %), m.p 95-97°; (Found: C, 81.00 %; H, 8.20 %; $C_{20}H_{24}O_2$ requires: C, 81.05 %; H, 8.17 %), b- d,l -8-dehydro-7ξ, 18-dimethyloestronemethylether (XXII, 12 gr., 80 %), m.p 100°; (Found: C, 81.20 %; H, 10.30 %; $C_{21}H_{26}O_2$ requires: C, 81.26 %; H, 10.30 %),.

d, 1-3-Methoxy-7 ξ-methylestra-1,3,5 (10), 8-tetraen-17β-o 1 (XIX) and d,1-3-methoxy-7 ξ-18-dimethylestra-1,3,5 (10), 8-tetraen-17β-o 1 (XXIII). Reduction of compounds XVI (2.9 gr., 0.01 mole gram) and XXII (3.1 gr., 0.01 mole gram) by sodium borohydride (1.5 gr., 0.04 mole gram) in methanol yielded: a- XIX (2.6 gr., 90 %), m.p 131.5°; (Found: C, 45 %; H, 8.80 %; $C_{20}H_{26}O_2$ requires: C, 80.50 %; H,8. 78 %), b- XXIII (2.7 gr., 90 %), m.p 129°; (Found: C, 80.50 %; H, 9.00 %; $C_{21}H_{28}O_2$ requires: C, 80.73 %; H, 9.04 %).

d,1-17α-Ethynyl-3-methoxy-7ξ-methylestra-1,3,5 (10), 8-tetraen-17 β-ol (XVII) and d,l-17α-(1,3-hexadiynyl)-3-methoxy-7ξ, 18-dimethylestra-1,3,5 (10), 8-tetraen-17 β-o 1 (XVIII). Compounds XVII and XVIII were prepared from XVI and appropriate sodium acetylides in liquid ammonia. Crystallisation (methanol) of the crude reaction products yielded: â- XVII (a gum, 50 %); (Found: C, 81.85, %; H, 8.20 %; $C_{22}H_{26}O_2$ requires: C, 81.95 %; H, 8.13 %) b- XVIII (12 %), m.p 120-122°; (Found: C, 83,15 %; H, 8.20 %; $C_{26}H_{30}O_2$ requires: C, 83.40 %; H, 8.09 %).

Summary

Introduction of a 7-CH_3 group to the steroid skeleton is a tedious method involving several steps and suffering from low yields. Although within the last ten years many of the steroidal compounds have been totally synthesized[1-13] so for nothing has been reported about the total syntheses of 7-methyl substituted steroids. In the present work total syntheses of some 7-methyl steroids, starting with o-methoxybenzyl bromide, are described.

Manuscript Received in January, 1975

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