ESTERIFICATION OF ACID CHLORIDES WITH THALLIUM AND POTASSIUM SALTS OF 19-NORETHISTERONE: FORMATION OF 17-ENOL ESTERS

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ABSTRACT

During the esterification of acid chlorides with thallium and potassium salts of 19-norethisterone, 17-enol esters were isolated. The enol esters are formed *via* the intermediate, 4-estrene-3,17-dione.

INTRODUCTION

Esters of hindered acids with 19-norethisterone (NET) (17-ethinyl-17β-hydroxy-4-estren-3-one) are potentially useful as long-acting contraceptive agents in the female (1). Hence several methods of esterification of carboxylic acids with NET(I) have been developed (1-3). An obvious synthetic approach would involve the reaction of a metal salt of NET (such as II and III) with an acid chloride. We have investigated the possibility of employing both the thallium and potassium salts of NET with acid chlorides. The results are reported in this paper.

RESULTS AND DISCUSSION

The esterification of ketopinic acid (7,7-dimethyl-2-oxo-bicyclo(2,2,1)heptan-1-carboxylic acid) with NET was attempted by condensing the derived acid chlorides with the thallium salt of NET. Since very little reaction occurred at room temperature, the reaction mixture was refluxed in benzene. TLC monitoring of the reaction mixture indicated the formation of two products with very close TLC R_f values. Separation by PTLC gave the ester, 19-norethisterone-17-ketopinate (IV). The other reaction product was identified as 4-estrene-3,17-dione (V). The ratio of IV:V was found to be 1:2. In another experiment involving N,N-dibutylcarbamoyl chloride, the thallium salt of NET (II) gave three products: N,N-dibutylcarbamate of NET(VI), 4-estrene-3,17-dione (V), and N,N-dibutylcarbamate of 17-hydroxy-4,16-estradien-3-one (VII). These products were obtained in the ratio 2:2:1. The identity of the enone, V, was confirmed by the synthesis of an authentic sample prepared according to the procedure by Vitali *et al*(4). The formation of the enol-carbamate (VII) is possibly *via* the enone intermediate, V. This was confirmed when the enol-ester, VIII, was obtained during treatment of the potassium salt of NET (III) with acetyl chloride. In the latter experiment the intermediate enone (V) was not isolated. The enol-esters were characterised using their

^{1}H n.m.r., i.r. and m.s. data. The enol-acetate (VIII) was shown to be different to 19-norethisterone-17-acetate (IX) which was prepared by coupling NET(I) directly with acetic acid using benzenesulphonyl chloride as the coupling agent (3) which avoids the formation of the undesirable enone intermediate (V) in the esterification of acids with NET. Scheme I outlines the reactions carried out.

EXPERIMENTAL

Microanalyses were performed at Imperial College, London and Butterworth Laboratories, Inc., Teddington, Middlesex, England. Melting points were determined on Kofler hot-stage and Buchi apparatus and are uncorrected. Infra-red spectra were recorded on a Pye Unicam SP-1000 or a Perkin-Elmer 257 grating spectrophotometer. Ultra-violet spectra were recorded on a Varian EM 360 or T 60 spectrometer. Mass spectra were obtained from the Department of Chemistry, University of Chicago or using AEI MS-9 spectrometer at Imperial College, London. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Preparative thin layer chromatographic (PTLC) separations were performed using MERCK silica gel plates of 0.5 mm thickness.

Esterification of ketopinic acid with NET

NET(0.45 g) in dry benzene (30 ml) was refluxed with TIOEt(0.1 ml) for 1 hr. Ketopinic acid chloride (from 0.7 g of acid and 1.4 ml $SOCl_2$) in dry benzene (5 ml) was added to the above hot solution dropwise with stirring. The mixture was refluxed for a further 5 min, cooled and the precipitated thallous chloride was filtered off. The benzene layer was washed with water, and was dried over anh. $MgSO_4$. Evaporation of the benzene gave an oily residue which on trituration with ether gave a white solid which was purified by PTLC on silica gel to give IV, (0.16 g, 24%), m.p. 247-9°, $[\alpha]_D$ = + 27.0°($CHCl_3$); ν_{max} (KBr) 3280, 2940-2840, 1745, 1720, 1650, 1610, 1320, 1220, 1095, 960 and 900 cm^{-1}; δ ($CDCl_3$) 5.85(1H,s, =CH), 2.6 (1H,s, =CH), 1.2(3H,s,-CH_3),1.1(3H,s, CH_3), 0.95(3H,s,CH_3), 2.5-1.0(CH_2). Calcd. for $C_{30}H_{38}O_4$ C, 77.93% H, 8.23%. Found C, 77.88%; H, 8.47%.

The ether soluble fraction in the above experiment was concentrated and was separated by PTLC on silica gel to give V(0.20 g, 48%), m.p. 160-2°; ν_{max} 1740, 1675 cm^{-1}; δ (CCl_4) 5.75(1H,s, =CH), 0.9(3H,s, CH_3), 2.6-1.0(CH_2).

Reaction of N,N-dibutylcarbamoyl chloride with thallium salt of NET

When the preparation of N,N-dibutylcarbamate of NET (VI) was carried out in the usual way as described (1) earlier, the reaction proceeded very slowly. Prolonged heating gave a mixture of VI, V and VII. The three products were separated by repeated dry-column chromatography on silica gel with hexane-benzene(30:7). VI, oil, $[\alpha]_D$, + 22°($CHCl_3$); λ_{max}^{EtOH} 244 nm(log ε 4.07); ν_{max} 3325, 1715, 1680, 1620, 1470 cm^{-1}; δ 5.75(1H,s, =CH), 3.2(4H,m, -N-CH_2-), 2.58(1H,s, -C=CH), 0.95(6H,t,CH_3), 0.9(3H,s,CH_3). Calcd. for $C_{29}H_{43}O_3N$(453.67,M^+), C, 76.78%; H, 9.55%; N, 3.09%. Found C, 76.82%; H, 10.09%; N, 3.02%. The N,N-dibutylcarbamate of 19-NET (VI), was synthesised by another unequivocal way (5) and was found to be identical with (VI). V, was found to be identical with an authentic sample prepared according to Vitali et al(4).

VII, oil, ν_{max} 3040, 1750, 1715 cm^{-1}. There was no signal at 3325 cm^{-1}(-C=CH); δ 5.78(1H,s, =CH), 5.45(1H, br.d,=CH), 3.25(4H, br.t, -NCH_2-), 1.0(6H,t, -CH_3), 0.95(3H,s, CH_3). MS: m/z 427(M^+),384 , 284, 241, 156, 128, 100, 43.

Reaction of acetyl chloride with NET in the presence of potassium hydride and 18-crown-6-ether

To a stirred suspension of potassium hydride (20%, 1.15 g) in dry THF (2.5 ml) under N_2, a solution of NET (0.72 g) and 18-crown-6-ether (0.07 g) in dry THF (7.5 ml) was added dropwise and the mixture heated to reflux for 3h and allowed to cool to room temperature. Acetyl chloride (0.30 g) in dry benzene (1.5 ml) was added to the mixture and stirred for 24 h. Excess potassium hydride was quenched with g. HOAc. Water was added and the product extracted with benzene, washed with aqueous $NaHCO_3$, water , dried ($MgSO_4$) and evaporated in vacuo. The solid thus obtained on chromatography gave the ester VIII, which on recrystallisation from chloroform-methanol afforded colourless needles (0.55 g, 72.5%), m.p. 154°C, $[\alpha]_D$ = -79.4° ($CHCl_3$); ν_{max} (KBr) 1750, 1730, 1670, and 1640 cm^{-1}. Signal at 3325 cm^{-1} due to -C=CH was found to be absent.

δ (CCl_4) 5.60(1H,s, =CH), 5.37(1H, br.d, =CH), 2.07(3H,s, $OCOCH_3$), 0.95(3H,s, CH_3). MS: m/z 314(M^+), 272(100%), 257, 174, 149, 122, 57, 43, 41. Calcd. for $C_{20}H_{26}O_3$ C, 76.43%, H, 8.28%. Found C, 76.5%; H, 8.6%.

Esterification of acetic acid with NET

Benzenesulphonyl chloride (0.475 g) was added to acetic acid (0.162 g) in dry pyridine (1 ml). After 1 h, NET (200 mg) in pyridine (1 ml) was added to the reaction mixture. The reaction mixture was left standing for 2 days with occasional shaking and was poured onto ice-water. The mixture was extracted with chloroform. The chloroform layer was washed with HCl, water, Na_2CO_3 solution and then with water. The chloroform layer was dried (anh. $MgSO_4$) and solvent was removed to give 0.28 g of the product. PTLC separation gave 19-norethisterone-17-acetate (IX), (0.18 g, 79%) as an oil. Crystallisation using CH_2Cl_2-hexane afforded crystals, m.p. 159-161°C, lit (6) mp 161-162°C. δ ($CDCl_3$) 5.85(1H,s, =CH), 2.6(1H,s, =CH), 2.07(3H,s, $OCOCH_3$), 0.95(3H,s, CH_3).

2,4-dinitrophenylhydrazone of IX had m.p. 134-136°

2,4-dinitrophenylhydrazone of VIII had m.p. 142-144°

Each 2,4-dinitrophenylhydrazone depressed the m.p. of the other indicating that the two were not identical.

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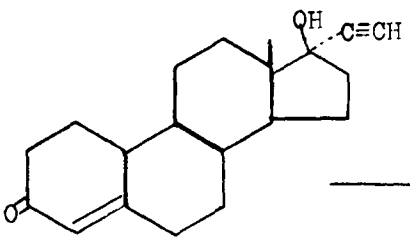

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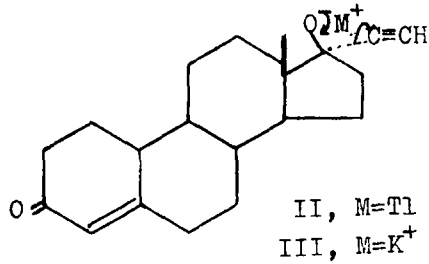
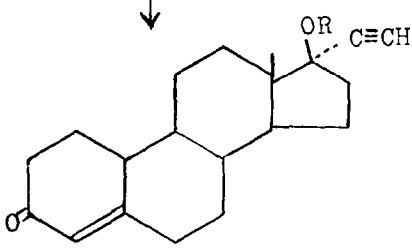
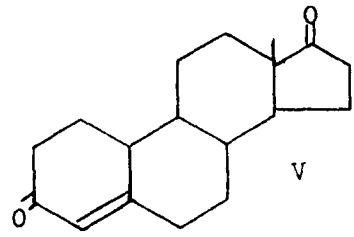
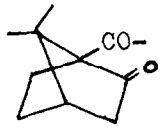


II, M=Tl
III, M=K+



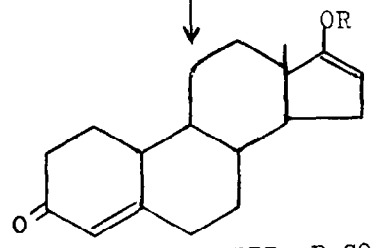


V

IV, R= 

VI, R=CON(C_4H_9)$_2$

IX, R=$COCH_3$



VIII, R=$COCH_3$

VII, R=CON(C_4H_9)2

SCHEME I

SYNTHESIS OF 3-METHOXY-5,6-SECOESTRA-1,3,5(10),8,14-PENTAEN-17-ONE

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ABSTRACT

A facile synthesis of 3-methoxy-5,6-secoestra-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 → AD → ACD → 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 1-(p-methoxyphenyl)-3-buten-1-ol (5) (prepared from p-anisaldehyde and allylmagnesium bromide) in methylene chloride furnished the ketone 1 in 75% yield. Addition of

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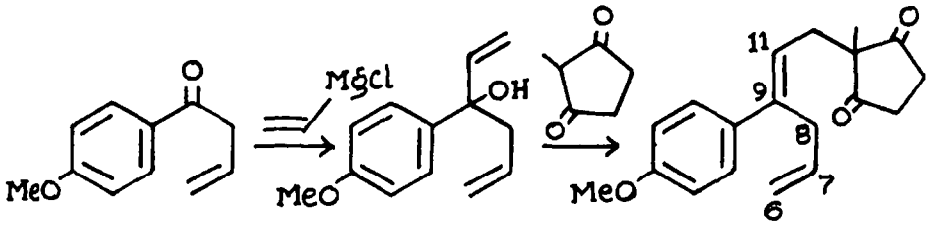
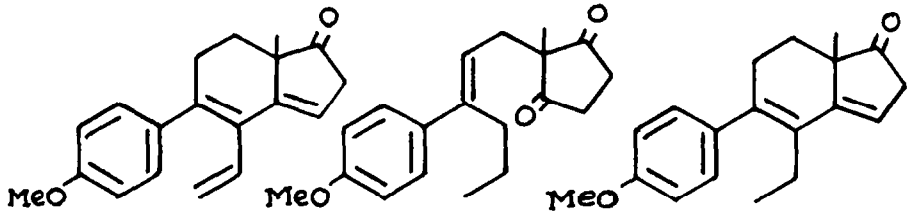
vinylmagnesium chloride to the ketone yielded the vinyl carbinol 2 in 73% yield. The structure of the carbinol was confirmed by IR, NMR and mass spectral data. The Torgov reaction (6) of the vinyl carbinol 2 with 2-methylcyclopentane-1,3-dione using Triton-B as catalyst was unsuccessful. Attempted preparation of the isothiouronium salt of the carbinol 2 following the procedure of Kuo et 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 δ. It has been reported (7) that 6-methoxy-1-vinyl-1-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 4 being isolated.



1 2 3



4 5 6

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

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_6 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)-3-buten-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 ($CHCl_3$) :

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

The ketone 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 ($MgSO_4$). Removal of solvent and chromatography over silica gel (benzene - ethyl acetate 9:1) yielded a colourless oil (15 g, 73%). IR ($CHCl_3$) : 3560 (OH) and 1635 cm^{-1} (C=C); NMR (CCl_4/TMS) δ 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, 6H, olefinic), 6.84-7.46 (AB quartet, 4H, aromatic) : MS : m/e 204 (M^+).

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

3-Methoxy-5,6,8,14-disecoestra-1,3,5(10),6,9(11)-pentaen-17-one 3 :

To a stirred solution of the carbinol 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 3 as a yellow oil (6.3 g, 60%). UV ($CHCl_3$) : λ_{max} 261 nm; IR($CHCl_3$) : 1720 (C=O) and 1630 cm^{-1} (C=C); NMR ($CDCl_3$/TMS)

δ 1.17 (s, 3H, CH_3), 2.53 (d, 2H, J = 8 Hz, allylic methylene), 2.76 (s, 4H, methylenes of cyclopentane ring), 3.21 (d, 2H, J = 6 Hz, biallylic methylene), 3.83 (s, 3H, OCH_3), 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^+).

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found : C, 76.22; H, 7.36%

3-Methoxy-5,6,8,14-disecoestra-1,3,5(10),9(11)tetraen-17-one 5 :

A solution of compound 3 (0.5 g, 1.7 m mol) in ethanol (20 ml) was hydrogenated at 15 psi pressure of H_2 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 5 (0.4 g, 80%). UV (EtOH) : λ_{max} 252 nm (ϵ = 21,370); IR ($CHCl_3$) : 1770, 1730 (C=O), 1615 cm^{-1} (C=C); NMR (CCl_4/TMS) δ 0.84 - 1.53 (m, 8H, angular CH_3 and CH_2-CH_3), 2.20 - 2.74 (m, 8H, C_8, C_{12}, C_{15} and C_{16} methylenes), 3.87 (s, 3H, OCH_3), 5.36 (t, 1H, J = 8 Hz, olefinic), 6.80 - 7.30 (AB quartet, 4H, aromatic); MS : m/e 300 (M^+).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found : C, 76.10; H, 8.08%.

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

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 (ϵ = 25,980); IR ($CHCl_3$) : 1740 cm^{-1} (C=O); NMR (CCl_4/TMS) δ 0.97 (t, 3H, J = 8 Hz, CH_3), 1.15 (s, 3H, C_{13}-CH_3), 1.43 - 3.16 (m, 8H, methylenes), 3.81 (s, 3H, OCH_3), 5.81 (t, 1H, J = 2 Hz, vinylic), 6.79 - 7.12 (AB quartet, 4H, aromatic).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found : C, 80.72; H, 7.62%.

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