APPROACH TO SYNTHESIS OF PREDNISOLONE FROM 9α-HYDROXY ANDROSTENEDIONE

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Received 25 August 2013

Abstract

In this report we showed an efficient approach to synthesis of prednisolone from 9α-hydroxy androst-4-ene-3,17-dione via 16α,17α-epoxy-pregn-4,9(11)-diene-21-ol-3,20-dione. Structure of obtained products has been studied by spectral methods such as IR, MS, NMR.

Keywords: 9α-hydroxy androst-4-ene-3,17-dione,16α,17α-epoxy- pregn-4,9(11)-diene-21-ol-3,20-dione.

1. INTRODUCTION

Bioconversion of phytosterols mixture, which is recovered from a waste by-products of paper, sugar and soybeans industries, provides an inexpensive source of 17-ketosteroid such as androst-4-ene-3,17-dione (AD), androsta-1,4-diene-3,17-dione (ADD) and 9α-hydroxy androst-4-ene-3,17-dione (9α-OH AD) [1, 2]. The latter [3] and its Δ^9-analogue [4, 5] are considered at present to be the most attractive intermediates for synthesis of commercially important corticoids [6-9] such as betamethasone and triamcinolone, etc.

Phytosterols may be isolated from different inexpensive sources, mostly tall-oil in paper industry [10] or filter cake in sugar cane industry [11]. Another very important source of phytosterols is soybean, which constitutes a highly remarkable food additive in Asia and all over the World. Soybean oil has lately gained good acceptance in cuisine everywhere [12]. Paper and sugar cane as well as soybean industries are currently developing in Viet Nam. In fact, soybean is one of the most important agricultural products. According to recent reports hundreds of thousand (~ a million in the near future) tons of soybean oil per a year are being produced**.** On the other hand, this country must import all steroidal drugs, so that it would be highly profitable to use by-products from these industries as raw materials and developing the technology necessary for synthesizing steroidal drugs. Soybean phytosterols in Vietnam can be extracted and purified from by-product of soybean oil production by a very efficient procedure, which renders a very good yield [13, 14].

Vietnamese soybean phytosterols are bioconverted to AD, ADD [15], and 9α-OH AD in very good yields [16-18]. According to report [14], the AD and 9α-OH AD technologies are very efficient and high practically.

To seek the most efficient and practical scheme for synthesis of corticoids such as betamethasone etc, we now described the conversion of 9α-hydroxy androst-4-ene-3,17-dione into 16α,17α-epoxy-pregn-4,9(11)-diene-21-ol-3,20-dione via androsta-4,9-diene-3,17-dione (Δ^9-AD).

It is known that acetylene and cyanohydrins methods, at present are most efficient and practical for preparation of pregnanes from androsta-4-ene-3,17-dione.

Acetylene synthesis is consisting of the stereo- and regioselective condensation of 17-cetostroids with acetylenide of alkali metals to obtain 17α-ethynyl-17β-hydroxy steroids correspondingly [19, 20].

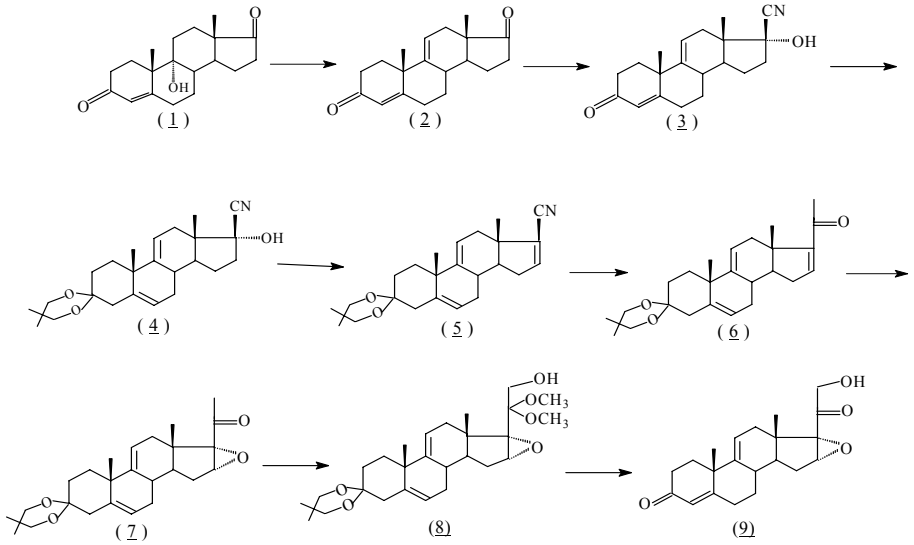
Cyanohydrins synthesis, in recent years is more interested [21-24].

α-Hydroxylation of a carbonyl function is a key procedure in the synthesis of corticoids from their 17β-acetyl precursors which has been performed in various ways [25]. However when faced with the problem of transformation of 16α,17α-disubstituted 17β-acetylsteroids into their 21-hydroxy derivatives, it was found that many of the existing synthetic methods for α-hydroxylation were not successful.

A new synthesis of α-hydroxyketone dimethyl acetals from aryl methyl ketones using iodosobenzene or its diacetate as the hydroxylating agent has been described [26]. This method has also been used for the conversion of pregnenolone into 3β,21-dihydroxy-20-oxopregn-5-ene [27]. Also, it was reported the applicability of the diacetoxyphenyliodine method to the synthesis of 21-hydroxy-20-oxosteroids fused to sensitive heterocycles in the 16α,17α-position from the corresponding 17β-acetyl steroids of 3β-hydroxy-Δ^5 series via the α-hydroxyketone dimethyl acetals [28]. Further applications of the method to the synthesis of steroidal α-hydroxyketone dimethyl acetals have hitherto not been described so that the method can not, at present, be considered as a generally useful procedure for converting the 17β-acetyl group of the 17β-acetyl steroids of 3-keto-Δ^4 series into the corticoid side chain.

We now report the development of this method for converting 17β-acetyl group of the 16α,17α-epoxy-17β-acetyl steroid of 3-keto-Δ^4 series into corticoid correspondingly. We have found that, in this case, protection of 3-keto-Δ^4 group is required

The reaction steps in this conversion are summarized in scheme 1.



Scheme 1: Transformation of 9α-OH AD into 16α,17α-epoxy-pregn-4,9(11)-diene-21-ol-3,20-dione

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

All reagents, solvents, adsorbents were purchased from Aldrich Co. (USA) and Merck clevenot Co. (France). Solvents were purified, distilled prior was used.

Melting points were determined on Boetius apparatus.

IR spectra were recorded on FTIR-IMPACT-410 with KBr pellets.

NMR spectra were recorded on Bruker AM 500 spectrometer in $CDCl_3$ with TMS as internal reference.

Analytical thin-layer chromatography was performed using Merck 60 GF_{254}.

Androst-4,9(11)-dien-3,17-dione (Δ^9-AD) (2) [29]. Compound (**2**) has been synthesized as described in [29]. Yield: 93 %; Mp. 201-203 ^oC. IR spectrum (KBr, cm^{-1}): absorption at 1732 and 1659 (C=O); 1616 and 1449 (C=C). ^{1}H-NMR spectrum ($CDCl_3$, 500MHz, ppm): 5.76 (br s, 4-H); 5.57 (br t, 11-H); 1.36 (s, 19-CH_3); 0.88 (s, 18-CH_3).

17α-hydroxy-17β-cyano-androst-4,9(11)-dien-3-one (Compound 3). Acetic acid (3.6 ml) was added over a period of 30 min at room temperature to a stirred mixture of Δ^9-AD (11.2 g) and potassium cyanide (10.0 g) in methanol (80.0 ml). The mixture was stirred at room temperature. The starting material was completely dissolved within 1.5 hours and product began to crystallize after reaction for 2.5 hours. The mixture was kept overnight at room temperature and then acetic acid (6.0 ml) was added. After dilution with water, the precipitated product was collected by filtration, washed with water and dried to give crude (**3**) (11.0 g, 89.7 %). Recrystallization from ethanol afforded the analytically pure sample melting at 182-183 ^oC. IR (KBr, cm^{-1}): 3236 (γO-H); 1645 (C=O); 1528 and 1452 (C=C). MS spectrum ($CHCl_3$): 313 [M^+]; 284 [M-HCN]$^+$. ^{1}H-NMR spectrum ($CDCl_3$, 500 MHz,

ppm): 5.76 (br s, 4-H); 5.57 (br t, 11-H); 2.97 (s, O-H); 1.34 (s, 19-CH_3); 0.93 (s, 18-CH_3).

17α-hydroxy-3,3-(2,2-dimethyl propylene dioxy)-17β-cyano-androst-5,9(11)-dien (4)

40.2 g of 17α-hydroxy-17β-cyano-androst-4,9(11)-dien-3-one (**3**) and 155 ml of dichlomethane were mixed together under nitrogene gas atmosphere and then 63 g of neopentyl glycol, 40 ml of triethylorthoformiat were added. The mixture was cooled at 0-5 ^oC and then 4 g of p-toluene sulfonic acid was introduced. After 8 hours added 4 ml triethylamine and 320 ml of water. The crystals were separated, washed with water. The filtered liquid was extracted with $CHCl_3$. The extract was washed with water and then dried. The residue remaining after removal of solvent in vacuo was poured into a mixture of 12 ml of hexane and 12 ml heptane. The crystals were separated, washed with water and dried. To obtained 42 g (81.9 %) of the total product melting at 213-215 ^oC (acetone). IR spectrum (KBr, cm^{-1}): absorption at 3423 (O-H); 1673 and 1641 (C=C); 1105 (C-H ketal). ^{1}H-NMR spectrum ($CDCl_3$, 500MHz, ppm): 5.54 (d, 11-H); 5.42 (d, 6-H); 3.55 (dd) and 3.45 (q) (CH_2-O-ketals); 1.19 (s, 19-CH_3); 0.99 (s, 18-CH_3); 0.93 (s, ketals-CH_3).

3,3-(2,2-dimethyl propylene dioxy)-17-cyano-androst-5,9(11),16(17)-trien(5)

56 g of 17α-hydroxy-3,3-(2,2-dimethyl propylene dioxy)-17β-cyano-androst-5,9(11)-dien (**4**) and 400 ml of anhydrous pyridine were mixed together under nitrogen gas atmosphere and then 50 ml of phosphorus oxychloride were added. The reaction medium was stirred for 2 hours in an oil bath at 40 ^oC and about 5 hours at 45 ^oC. The mixture was poured into a mixture of 80 g of ice, 2 ml of concentrated hydrochloric acid and 80 ml of water. The mixture was stirred at room temperature, and the crystals were washed with water, and then dried. Recrystallization of the crude product from acetone gave 44.5 g (83 %) of the expected product melting at 224-225 ^oC. IR spectrum (KBr, cm^{-1}): absorption at 2210 (C≡N); 1669, 1587 and 1461 (C=C); 1101 (C-H ketals). ^{1}H-NMR spectrum ($CDCl_3$, 500 MHz, ppm): 6.64 (t, 16-H); 5.53 (d, 11-H); 5.43 (d, 6-H); 3.54 (dd) and 3.44 (q) (CH_2-O -ketals); 1.21 (s, 19-CH_3); 0.98 (s, 18-CH_3); 0.92 and 0.90 (s, ketals-CH_3).

3,3-(2,2-dimethyl propylene dioxy)-pregn-5,9(11),16(17)-trien-20-one (6)

30 g of 3,3-(2,2-dimethyl propylene dioxy)-17-cyano-androst-5,9(11),16(17)-trien (**5**) and 81 ml toluene were mixed together under nitrogene gas atmosphere and then 8 ml of a 3 M solution of methylmagnesium bromide in diethylether were introduced. The reaction medium was taken to 60-65 ^oC for 3 hours 30 minutes and then cooled using an ice-methanol bath. 105 ml tetrahydrofuran and then a mixture of 24 g of ice, 8 ml of water and 40 ml of acetic acid were added. The mixture was concentrated under reduced pressure and then poured into 300 ml of water. The crystals were separated, washed with water and dried. Recrystallization of the crude product from acetone gave 24.8 g (79 %) of the expected product melting at 198-200 ^oC. IR spectrum (KBr, cm^{-1}): absorption at 1665 (C=O); 1591 and 1433 (C=C); 1099 (C-H ketals). ^{1}H-NMR spectrum ($CDCl_3$, 500 MHz, ppm): 6.72 (t, 16-H); 5.52 (d, 11-H); 5.43 (d, 6-H); 3.54 (dd) and 3.44 (q) (2 groups of CH_2-O -ketals); 2.27 (s, CH_3CO); 1.21 (s, 19-CH_3); 0.99 (s, 18-CH_3); 0.91 and 0.87 (s, 2 groups of CH_3-ketals).

3,3-(2,2-dimethyl propylene dioxy)-16α,17α-epoxy-pregn-5,9(11)-dien-20-one (7)

23.5 g of 3,3-(2,2-dimethyl propylene dioxy)-pregn-5,9(11),16(17)-trien-20-one (**6**), 200 ml of tetra hydrofuran (THF), 100 ml of methanol (MeOH), 20 ml of concentrated sodium hydroxide in MeOH and 20 ml of hydrogen peroxide H_2O_2 60 % were mixed together under the N_2 gas. The reaction medium was heated at 40-45 ^oC for 24 hours. The solvent was evaporated under reduced pressure, then a mixture of water and ice were added, the crystals were separated, washed with water, and dried to obtain 22.78 g (**7**) (93.2 %), melting at 212-215 ^oC (recrystallization of the crude product from acetone). IR spectrum (KBr, cm^{-1}): absorption at 1701 (γC=O); 1667; 1468 (γC=C); 1101 (γC-O ketal). ^{1}H-NMR spectrum ($CDCl_3$, 500 MHz, ppm): 5.49 (t, H-11); 5.41 (d, H-6); 3.75 (s, H-16); 3.54 (dd) và 3.44 (q) (CH_2-O ketal); 2.04 (s, CH_3-21); 1.25 (s, CH_3-19); 0.92 (s, CH_3-18); 0.99 (s, 2 CH_3-ketal).

20,20-dimethoxy 3,3-(2,2-dimethyl propylene dioxy)-16α,17α-epoxy-pregn-5,9(11)-diene (8)

16.5 g of 3,3-(2,2-dimethyl propylene dioxy)-16α,17α-epoxy-pregn-5,9(11)-dien-20-one (**7**), 300 ml a 4 N solution potassium hydroxide in methanol, 15 g phenyliodosodiacetate. The reaction medium was stirred at 18-25 ^oC, after 4 hours 15 g $PhI(OAc)_2$ was added. After 24 hours, solvent was removed in vacuo at a maximum temprature of 25 ^oC over a 30 minutes period. The residue is diluted with water (200 ml) and extracted with $CHCl_3$ (4x100 ml). The extract was washed with water and dried, then

removal of solvent in vacuo. After that, a) The product was purified by chromatography on silica eluting with a *n*-hexane:acetone mixture (10:1), to gave 9.5 g (**8**), (50 %), melting at 151-152 (recrystallization of the crude product from EtOAc). IR spectrum (KBr, cm^{-1}): absorption at 3511 (γO-H); 1622, 1461 (γC=C); 1091 (γC-O ketal). ^{1}H-NMR spectrum ($CDCl_3$, 500 MHz, ppm): 5.46 (br d, H-11); 5.41 (m, H-6); 3.71 (m, CH_2OH-21); 3.52 (s, H-16); 3.54 (dd) và 3.44 (q) (2 groups of CH_2-O ketal); 3.29 và 3.27 (s, 2 groups of OCH_3-20); 1.19 (s, CH_3-19); 0.98 (s, 2 groups of CH_3-ketal); 0.92 (s, CH_3-18); b) The crude product (**8**) was directly converted to (**9**) as follows.

16α,17α-epoxy–pregn-4,9(11)-dien-21-ol-3,20-dione (9)

All crude product (**8**) received above, was dissolved in 150 ml of acetone containing 2 g of p-toluen sulfonic acid. The reaction medium was stirred at 18-25 ^{o}C for 4 hours. Acetone is then removed in vacuo, 100 ml of water/ice were added. After separation, the crystal were washed with water and then dried. The product was purified by chromatography on silica eluting with a *n*-hexane:acetone mixture (10:4), to gave 6.85 g (**9**), (50 %, calculated on (**7**), melting at 196-200 ^{o}C (recrystallization of the crude product from $CHCl_3$). IR spectrum (KBr, cm^{-1}): 3360 (γO-H); 1707; 1665 (γC=O); 1448 (γC=C). ^{1}H-NMR spectrum ($CDCl_3$, 500MHz, ppm): 5.74 (br s, H-4); 5.54 (d, H-11); 4.21 (dd, J = 20, CH_2-21); 3.77 (s, H-16); 2.95 (br s, O-H); 1.25 (s, CH_3-19); 1.11 (s, CH_3-18).

3. CONCLUSIONS

1. 16α,17α-epoxy-pregn-4,9(11)-diene-21-ol-3,20-dione has been synthesized in good yield from 9α-hydroxy androstenedione via its Δ^9-analogue

2. Structure of all obtained products is examined by physical methods: IR, ^{1}H-NMR.

Acknowledgements: *The author L. D. Huy gratefully acknowledges support from the Ministry of Science and Technology (project: DTDL.2011-G/49).*

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