JOJ Sciences
ISSN: 2641-8290

Juniper Publishers
key to the Researchers

Mini Review
Volume 3 Issue 5- June 2024
DOI: 10.19080/JOJS.2024.03.555623

JOJ scin

An Unusual Inversion of Configuration of 3 β -Hydroxy to 3 α -Hydroxy-5 β -Estran-17-Ethylene Ketal

Ohad Ilovich and Joseph Deutsch*§

The Institute of Drugs Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

Submission: June 21, 2024 ; **Published:** June 27, 2024

***Corresponding author:** Joseph Deutsch, The Institute of Drugs Research, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, E-mails: josephd@ekmd.huji.ac.il

§Affiliated with the David R. Bloom Center for Pharmacy and Alex Grass Center for Drug Design.

Abstract

NaH a compact reagent can induce an inversion of configuration when it is boiled with a 3 β -hydroxy-5 β -estrane derivative in toluene. The inversion of steroidal hydroxyl group from β to α configuration depended on the duration of the reflux with NaH in toluene. Three hours reflux of the 3 β -hydroxy-5 β -estrane-17-ethylene ketal, resulted in a complete inversion of the hydroxyl group from β to α configuration. The benzyloxy derivative was synthesized to produce a crystalline 3 α -benzyloxy-5 β -estrane-17-one suitable for the X-ray diffraction measurement which further, strongly supported the inversion of configuration, and the assumption that the change was induced by NaH and toluene.

Keywords: Unusual inversion; Dimethyl aminopyridine; Hydroxyl group; Crystals; White solid powder; Reduced Pressure

Introduction

Inversion of steroidal hydroxyl groups from β to α configuration was the subject of many reports [1-4]. The most common chemical reaction involved in hydroxyl inversions is the SN2 Walden [1] inversion involving reactions as tosylation, saponification, and reesterification [3]. In the Mitsunobu reaction [2], the inversion of the hydroxyl group was implemented by reaction with diethyl azodicarboxylate and triphenyl phosphine followed by an esterification process [3,4]. Recently an inversion of hydroxyl configuration was shown to take place when 3β-colestanyl mesytilate was boiled with cesium carboxylate in toluene in presence of trace amount of dimethyl aminopyridine (DMAP)[5]. The mechanism involved in these processes, involves the formation of an intermediate by reaction of the hydroxyl with a bulky reagent - producing a good leaving group. When the bulky group, is removed (usually via a SN2 mechanism) the new group is attached from the opposite direction to the leaving group.

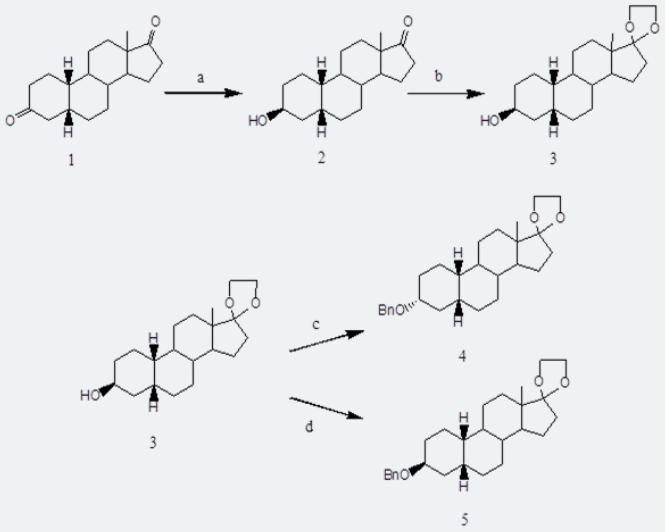
Results and Discussion

We found that NaH, a compact reagent could induce a similar inversion of configuration when it is boiled with a 3β-hydroxy-5β-estrane derivative in toluene. In an attempt to synthesize 3β-benzyloxy-5β-estrane [9], by direct benzylation of the 3β hydroxyl group in presence of NaH in dry toluene we received, a mixture of 3α-OBn and 3β-OBn isomers. Their ratio depended on the duration of the reflux with NaH in toluene before the addition of the benzylation reagent. Three hours of reflux of the 3β-hydroxy-5β-estrane-17-ethylene ketal, with NaH in toluene resulted in a complete inversion of the hydroxyl group from β to α configuration.

The synthesis of 2 was implemented by a modification of published procedures [6,7]. The reaction used a stereo- and site-selective reduction of the 3-keto group with K-selectride that gave the 3β-hydroxy-5β-estran-17-one (2).

Before benzyloxylation [9], the 17-keto group was protected as ethylene ketal and then submitted to benzylation in presence of NaH in toluene (Scheme 1). Boiling of 3 with NaH in toluene for at least 3 hours before addition of benzyl bromide produced the inversion of configuration of the 3β-hydroxy and gave the 3α-benzyloxy isomer (4). Stopping the reaction before addition of benzyl

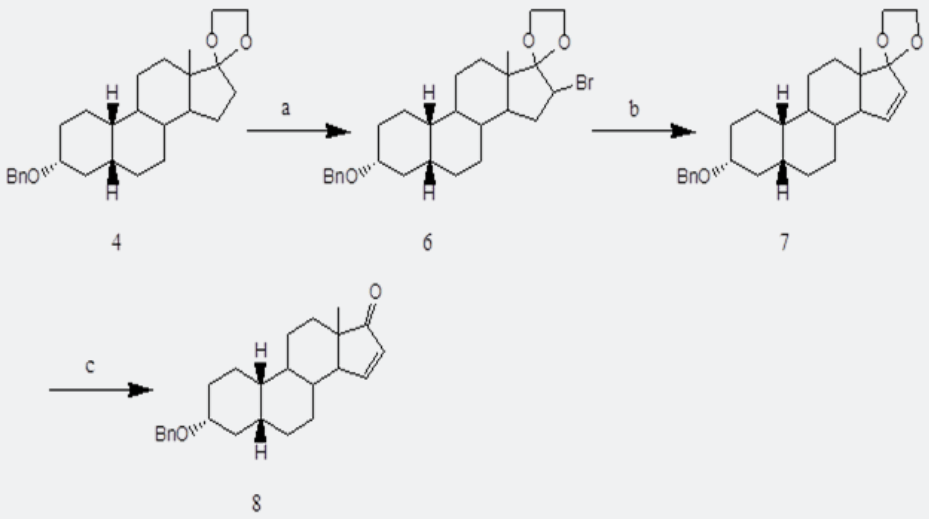
bromide, by addition of water produced 99% of the 3α-hydroxy derivative. Addition of benzyl bromide together with the NaH gave only partial inversion of the 3β position, giving a mixture of both 3α and 3β-benzyloxy isomers.



Scheme 1: Reagents (a) K-selectride/THF/-70°C. (b) ethylene glycol/PPTS/benzene. (c) BnBr/NaH/toluene. (d) BnBr/NaH/THF.

The change in configuration was monitored by NMR measurement of the chemical shift at 3.38 ppm for 3αCHOBn and 3αCHOH protons at 3.61 ppm. Replacing the toluene solvent with THF afforded absolute preservation of the 3β configuration, resulting only in the 3β-benzyloxy isomer (5) with a chemical shift of 3.66 ppm for 3βCHOBn, proton and 4.11 ppm for 3βCHOH, proton. The conservation of spatial configuration was independent of the duration of reflux of the steroid in the presence of NaH before the addition of benzyl bromide.

Further, in order to obtain crystals, suitable to X-ray crystallography measurements, 4 was submitted to bromination, debromination, and hydrolysis of the ethylene ketal protecting group that produced a crystalline product (8) (Scheme 2). X-ray diffraction measurement of compound 8 (Figure 1) strongly supported the 3α configuration, and the assumption that a change in the configuration of the hydroxyl group was induced by NaH.



Scheme 2: Reagents (a) PTAP/THF/10°C. (b) K t-BuO/benzene/DMSO. (c) PPTS/acetone/water.

How to cite this article: Joseph Deutsch. An Unusual Inversion of Configuration of 3 β -Hydroxy to 3 α -Hydroxy-5 β -Estran-17-Ethylene Ketal. JOJ scin. 2024; 3(5): 555623. DOI:10.19080/JOJS.2024.03.555623

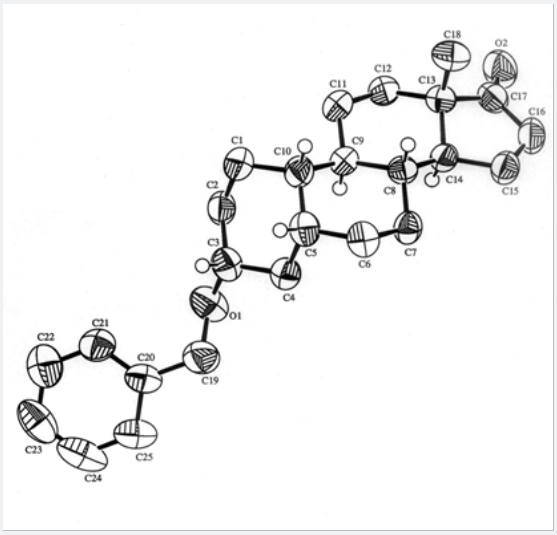


Figure 1: X ray crystal structure of compound 8. Most of the hydrogen atoms were omitted for clarity. The bezyloxy group is trans to the C5 and C10 hydrogens.

The preservation of spatial configuration in a polar solvent (e.g THF) and total inversion in a less-polar solvent (e.g. toluene) suggest that, charge stabilization plays a role in the mechanism. A more polar solvent can donate electrons and stabilize the $M^+...O^-$ interaction and thus sustain the less stable β configuration. In a less polar solvent, the $M^+...O^-$ interaction is not stabilized, enabling the loss of the C3-hydrogen, giving a sp^2 intermediate that upon return of the hydrogen inverts the hydroxyl to the stable α configuration.

Experimental

Materials and Methods

Solvents were purchased from Biolab (Jerusalem, Israel), Aldrich Chemical Co. (Milwaukee, WI), and Frutarom (Haifa, Israel). Chemical reagents RhCl3.H2O, Aliquat 336, Pd $(OH)_2$/10%C, n-butyllithium, pyridinium tribromide, ethylene glycol, and potassium tert-butoxide were purchased from Aldrich Chemical Co. Estrane-4-ene-3,17-dione was purchased from Taizhou Xingye Chemical Co., Ltd, Shanghai 201507, P.R. China. Electron impact mass spectra were obtained using a Thermo Quest Trace MS (San Jose, CA) mass spectrometer. The 1H NMR (300 MHz) measurements were performed using a Varian VXR-300S (Palo Alto, CA) spectrometer in $CDCl_3$. Crystallographic structure analysis was done on an ENRAF-NONIUS CAD-4 computer-controlled difractometer, and all crystallographic computing was done on a VAX9000 computer at the Hebrew University of Jerusalem

3β-Hydroxy-5β-estran-17-one (2)

K-Selectride (22 mL, 22 mmol, 1.0 M solution in THF) was added, under nitrogen, to a solution of 5β-Estrane-3,17-dione (1) (4 g, 14.58 mmol) in freshly distilled dry THF (125 mL) at -70°C. After 6 hours the reaction was stopped by addition of 10% NaOH (60 mL) and 30% H_2O_2 (60 mL). The reaction mixture was allowed to warm up to room temperature and the stirring continued for 30 additional minutes. The mixture was extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Solvent removal gave compound 2 (3.74 g, 93%) as white solid powder.

MS: m/z (M^+.) 276. IR 3472, 1725 cm^{-1}.

^{1}H NMR: δ=4.15 (m, 1H, 3-CHOH), 0.85 (s, 3H, CH_3).

3β-Hydroxy-5β-estran-17-one ethylene ketal (3)

Compound 2 (10 g, 36.2 mmol) was dissolved in dry benzene (75 ml) mixed with ethylene glycol (25 ml, 360 mmol) and pyridinium p-toluenesulfonate (1 g, 3.9 mmol) and refluxed using a Dean-stark separator overnight till no starting material was detected by TLC. The cold solution was diluted with EtOAc (100 ml), washed twice with brine, dried over Na_2SO_4. Solvent removal followed by flash-chromatography on silica gel with EtOAc: Hexane 3:7 gave compound 3 (11.0 g, 94%) as a white solid.

MS: m/z (M^+.) 320. IR 3343, 1733 cm^{-1}.

^{1}H NMR: δ=4.11(m, 1H, CHOH), 3.81(m, 4H, OCH_2CH_2O), 0.87(s, 3H, CH_3[18]).

3α-Benzyloxy-5β-estran-17-one ethylene ketal (4)

A solution of compound 3 (6.0 g, 18.7 mmol) in dry toluene (80 ml) was boiled in a system fitted with a Dean Stark separator.

How to cite this article: Joseph Deutsch. An Unusual Inversion of Configuration of 3 β -Hydroxy to 3 α -Hydroxy-5 β -Estran-17-Ethylene Ketal. JOJ scin. 2024; 3(5): 555623. DOI:10.19080/JOJS.2024.03.555623

After 90 min, the solution was cooled and NaH powder (1.5 g, 60 mmol) was added and boiled for three hours. Benzyl bromide (3.2 g, 18.7 mmol) was added slowly through a syringe under nitrogen and boiled for additional 6 hours. After cooling, the toluene solution was poured slowly in ice. The organic phase was separated, washed with water and the toluene evaporated under reduced pressure. The oily product was dissolved in hexane, washed with water, and dried on Na_2SO_4. Solvent removal gave an oily product. Flash-chromatography on silica gel with diethyl ether: hexane (1:9) gave compound 4 (6.2 g, 80%) as a white solid.

MS: m/z (M^+.) 410.

^{1}H NMR: δ=7.35(m, 5H, Ph), 4.50 (s, 2H, CH_2Ph), 3.89(m, 4H, OCH_2CH_2O), 3.38(m,1H, H-C(3)), 0.83(s, 3H, CH_3[18]).

3β-Benzyloxy-5β-estran-17-one ethylene ketal (5)

To a solution of compound 3 (6.0 g, 18.7 mmol) in freshly distilled dry THF (125 mL), NaH powder (1.5 g, 60 mmol) and benzyl bromide (3.2 g, 18.7 mmol) were added and the reaction boiled for 6 hours. After cooling, the THF solution was poured slowly in ice. The THF was evaporated and the aqueous phase extracted with diethyl ether. The organic phase was separated, washed with water and the diethyl ether evaporated under reduced pressure.

MS: m/z (M^+.) 410.

^{1}H NMR: δ=7.35(m, 5H, Ph), 4.48(s, 2H, CH_2Ph), 3.89(m, 4H, OCH_2CH_2O), 3.66(m, H-C(3). 0.85(s, 3H, CH_3[18]).

3α-Benzyloxy-5β-estran-16-bromo-17-one ethylene ketal (6)

To a stirred solution of compound 4 (9 g, 21.9 mmol) in THF (45 mL), phenyltrimethylammonium tribromide (9 g, 25.2 mmol) was added slowly. After 20 h at 4°C the mixture was poured into a cold solution of 5% $NaHCO_3$ (30 mL) and 10 % $Na_2S_2O_3$ (30 mL). The organic phase was extracted with hexane washed twice with brine, dried over Na_2SO_4 and the solvent removed under reduced pressure to give 9 g (84%) the title compound as oil. The crude oil was subjected to dehydrobromination without additional purification.

MS: m/z (M^+.) 488, 490.

3α-Benzyloxy-5β-estr-15-en-17-one ethylene ketal (7)

Compound 6 (12 g, 24.4 mmol), dried by distillation with dry benzene, was dissolved in dry benzene (50 mL) and dry DMSO (30 mL) and potassium t-butoxide (12.0 g) was slowly added. The mixture was stirred and heated to 60°C under nitrogen. After 2 h, the product was cooled and diethyl ether (50 mL) was added. The mixture was filtered through silica gel, and washed with brine. Solvent removal gave compound 7 (5.6 g, 55%) an oily compound. The protecting group was removed without additional purification.

MS: m/z (M^+.) 408.

^{1}H NMR: δ= 7.34(m, 5H, Ph), 6.19 (d, 1H, H-C[16]) 5.68 (d x d, 1H, H-C[15]), 4.59(m, 2H CH_2Ph), 3.93 (m, 4H, OCH_2CH_2O), 3.74 (m, 1H, H-C[3]) 0.93 (s, 3H, CH_3[18']).

3α-Benzyloxy-5β-estr-15-en-17-one (8)

To a solution of compound 7 (5.6 g, 13.4 mmol) in acetone: water 10:2 (120 mL), pyridinium p-toluenesulfonate (1 g, 4 mmol) was added. The mixture was stirred overnight and the deprotection monitored by TLC. The acetone was removed under reduced pressure and the product extracted by hexane. The hexane solution was washed with brine, dried over Na_2SO_4. Solvent removal and triturating with diethyl ether gave compound 8 (4.0 g, 82%), as a yellow solid. Crystallization from diethyl ether gave mp 92-94°C.

MS: m/z (M^+.) 364. IR 1707 cm^{-1}.

^{1}H NMR: δ=7.52(d, 1H, H-C[16]), 7.34(m, 5H, Ph), 6.02(d x d, 1H, H-C[15]), 4.56(m, 2H CH2Ph), 3.40 (m, 1H, H-C[3]) 1.06(s, 3H, CH_3[18']).

$C_{25}H_32O_2$ (MW 364), Cal. C 82.42%, H 8.79%; Found C 82.10%, H 8.80%.

References

1. Shoppee CW, Coll JCJ (1970) Steroids and Walden inversion. Part LXVII. Substitution reactions of the 19-nor-5α-cholestan-2-ols. J Chem Soc Sec C: Organic 8: 1121-1123.
2. Ahn C, Correia R, DeShong PJ (2002) Mechanistic study of the Mitsunobu reaction. J Org Chem 67(6): 1751.
3. Bose KA, Lal B, Hoffman AW, Manhas SM (1973) Steroids. IX. Facile inversion of unhindered sterol configuration Tetrahedron Lett 14(18): 1619-1622.
4. Mitsunobu O (1981) The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. Synthesis 1(1): 1-28.
5. Hawryluk AN, Snider BBJ (2000) Alcohol inversion using cesium carboxylates and DMAP in toluene. J Org Chem 65(24): 8379.
6. Han M, Convey DF (1996) An Improved Synthesis of 18-Nor-17-ketosteroids and Application of the Method for the Preparation of (3beta,5beta,13alpha)- and (3beta,5beta,13beta)-3-Hydroxygonan-17-one. J Org Chem 61(21): 7614-7616.
7. Di-Capua S, Jang HG, Barasch D, Halperin G, Deutsch J (1997) Mass spectral determination of the configuration of 17β-tetrahydropyranyloxy-19-norandrostan-3β-ol. Int J Mass Spectrom 167/168: 79-85.
8. Yamato T, Haraguchi M, Nishikawa J, Ide SJ (1998) Synthesis, conformational studies and inclusion properties of O-benzylated calixarene analogues of trihydroxy[3.3.3]metacyclophanes. J Chem Soc Perkin Trans 1: 609-614.

How to cite this article: Joseph Deutsch. An Unusual Inversion of Configuration of 3 β -Hydroxy to 3 α -Hydroxy-5 β -Estran-17-Ethylene Ketal. JOJ scin. 2024; 3(5): 555623. DOI:10.19080/JOJS.2024.03.555623

9. Deutsch J, Jang H.G, Mansur N, Ilovitch O, Sopolianski U, et al (2006). 4-(3'alpha15'beta-dihydroxy-5'beta-estran-17'beta-yl)furan-2-methyl alcohol: an anti-digoxin agent with a novel mechanism of action. J Med Chem 49: 600-606.

DOI: 10.19080/JOJS.2024.03.555623

How to cite this article: Joseph Deutsch. An Unusual Inversion of Configuration of 3 β -Hydroxy to 3 α -Hydroxy-5 β -Estran-17-Ethylene Ketal. JOJ scin. 2024; 3(5): 555623. DOI:10.19080/JOJS.2024.03.555623