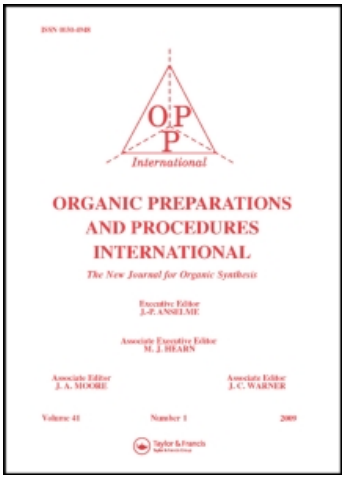

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A CONVENIENT "HYDROGEN TRANSFER" HYDROGENATION OF TESTOSTERONE

Dimitris M. Spyriounis[a]; George Ikonomidis[a]; Vassilis J. Demopoulos[a]
[a] Division of Pharamamutical Chemistry, Department of Pharmacy, University of Tessaloniki, Thessaloniki, GREECE

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EXPERIMENTAL SECTION

The mp. was determined on a Boetius micro hotstage and is uncorrected. The micro analysis was made on an elemental analyzer Heraeus CHN-O-RAPID. Isatin oxime was prepared according to the literature.[4b]

2-Isocyanatobenzonitrile (2).- To a stirred suspension of isatin oxime (1) (16.2 g, 0.10 mol) in warm dry benzene (200 ml) was rapidly (5 min) added a solution of phosphorus pentachloride (20.9 g, 0.10 mol) in warm dry benzene (250 ml). After refluxing for 2 hrs, the mixture became nearly clear. The solution was filtered and the filtrate was evaporated and the oily pale orange residue extracted with boiling ligroin (bp 50-80°) (2 x 125 ml). On cooling the extract, 13.7 g of crude product separated and, after recrystallisation from ligroin, 13.0 g (90%) of 2-isocyanatobenzonitrile was obtained as colorless needles, mp. 61-62°, lit.[4b] mp. 61°.

Anal. Calcd. for $C_8H_4N_2O$: C, 66.64; H, 2.80; N, 19.45. Found: C, 66.41; H, 2.86; N, 19.45

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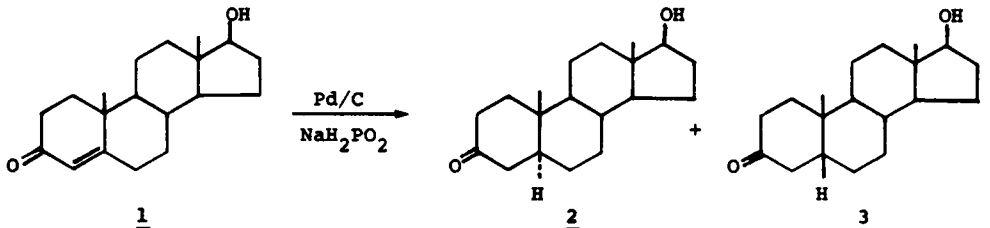
A CONVENIENT "HYDROGEN TRANSFER" HYDROGENATION OF TESTOSTERONE

Submitted by (06/27/88) Dimitris M. Spyriounis*, George Ikonomidis and Vassilis J. Demopoulos

Division of Pharamaceutical Chemistry, Department of Pharmacy
University of Tessaloniki, Thessaloniki, GREECE 540 06

17β-hydroxy-5α-androstane-3-one (2) and 17β-hydroxy-5β-androstane-3-one (3) are the prominent metabolites of testosterone (1) and are under active pharmacological investigation.[1] Thus, any easy access to these compounds would be of interest. The catalytic hydrogenation of 3-oxo-4-ene steriods, like that of testosterone, usually requires large excesses of Pd catalyst and gives mainly the 5β-epimer.[2] Recently, it has been reported that sodium hypophosphite and 10%

Pd/C is a mild, selective and economical system for the hydrogenation of a variety of functionalities.[3] The present communication describes the use of the above mentioned type of hydrogen transfer hydrogenation of testosterone.



1 2 3

In contrast to previously reported catalytic hydrogenations of testosterone and related steroids,[2b,4b,5] the present method requires no special apparatus or precautions and uses very small quantities (5% w/w) of catalyst; in addition, acceptable selectivity can be realized by judicious selection of solvent (runs 1 and 5). Our results differ from the previously reported predominant formation of the 5β-epimer under the classical hydrogenation conditions.[2b]

Table. "Hydrogen Transfer" Hydrogenation of Testosterone

Solvent	mps (°C) 2[b]	mps (°C) 3[c]	Yields[a] (%) 2	Yields[a] (%) 3	Reaction time (hrs)
1. Pottassium hydroxide in 2-propanol (0.09 N)	180-181	139-141	60	24	2.20
2. Acetonitrile	182-183	138-140	50	32	2.40
3. Tetrahydrofuran	180-182	138-140	40	40	0.45
4. Ethanol	182-183	139-141	35	46	2.00
5. Acetic acid	182-183	139-140	21	60	1.45

a) Recrystallized from acetone-petroleum ether. b) lit.[4a] (178°); lit.[4b] (179-180°). c) lit.[4] (139-140°); lit.[5a] (142-144°); lit.[5b] (142-142.5°). d) IR, NMR and optical rotation are identical with commercially available samples.

EXPERIMENTAL SECTION

General Procedure.- To a solution of testosterone (1) (500 mg, 1.73 mmol) dissolved in the appropriate solvent (3.5 ml) containing 10% Pd/C (25 mg), was added a solution of sodium hypophosphite monohydrate (367 mg, 3.46 mmol) dissolved in water (1.75 ml); the reaction mixture was heated with stirring at 90° for the specified amount of time [Table]. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was flash chromatographed[6] on silica gel with petroleum ether-ethyl acetate-cyclohexane (16:2:1) as the eluent. The separation process was monitored by TLC on silica gel with cyclohexane-ethyl acetate (1:1) as the developing solvent. The TLC plates were sprayed with freshly prepared

"anisaldehyde-sulfuric acid" reagent[7] and heated gently for 1-2 min at 75-80°. The 5α-epimer eluted first and gave a yellow spot on TLC. This separated well from the 5β-epimer which eluted next and gave an orange spot. They further recrystallized from acetone-petroleum ether to afford pure products.

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TEREPHTHALOHYDROXIMOYL CHLORIDE

Submitted by (08/08/88)

Ibrahim Karatas and Celal Tuzun*†

Department of Chemistry, Faculty of Arts and Sciences
Selcuk University, 42049 Konya, TURKEY

and

† Department of Chemistry, Faculty of Science
Ankara University, 06100 Ankara, TURKEY

Terephthalohydroximoyl chloride, which is used as bactericide and mould killer in the textile industry,[1] has been synthesized by several workers, [2-7] in yields between 48-78% with