METHODS OF SYNTHESIS AND TECHNOLOGY OF DRUG MANUFACTURE

HOMOGENEOUS CATALYTIC HYDROGENATION OF Δ^1-DOUBLE BONDS IN STEROIDAL DIENONES

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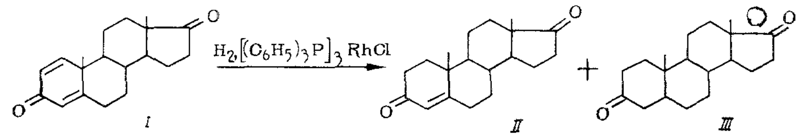
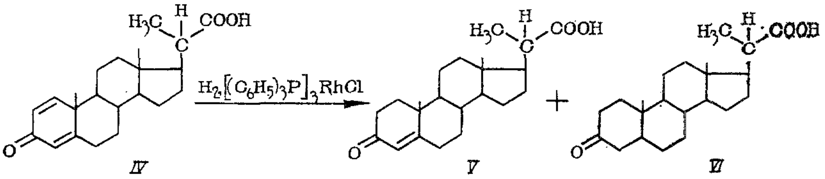
Tris-(triphenylphosphine)rhodium chloride has been used in recent years for the selective reduction of the Δ^1-double bond in steroidal dienones. Unhindered conjugated 1,2-double bonds of Δ^1-3-ketosteroids and β,β-disubstituted ketones are readily reduced and in high yield in the presence of this catalyst. Under the same conditions Δ^4-3-keto- and Δ^5-7-ketosteroids do not participate in the reaction. Steroidal $\Delta^{1,4}$- and $\Delta^{4,6}$-dienones are reduced to Δ^4-3-ketones in 75-85% yield. For this the reduction time was 72 h. Saturated ketones are formed as side products of the reaction [1-4]. In a study of the reduction of androsta-1,4-diene-3,17-dione (I) and 3-keto-bis-norchola-1,4-dienoic acid (IV) with the aid of the rhodium catalyst it was discovered that the activity of the tris-(triphenylphosphine)rhodium chloride catalyst used was an important feature determining the rate and selectivity of the reduction of 1,2-double bonds. In view of the capability of the catalyst to form complexes with oxygen of the air and carbon monoxide leading to its deactivation, which is described in the literature [5, 6], we prepared the catalyst by a known method [5] strictly in an inert gas atmosphere (argon). This permitted a significant reduction in the hydrogenation time from 72 h [1] to 2-8 h. It was then noted that the process went more selectively: fewer side products (III, VI) of the reaction were formed. So when reducing (I), the reaction was stopped after 2 h and when reducing (IV), after 8 h. The process went practically to completion in the time indicated since, according to data of thin layer chromatography (TLC) in the system cyclohexane–acetone–benzene (9:4:1): only 0.5% (I) remained in the first case and less than 5% (IV) in the second. The IR and PMR spectra of the obtained compounds (II and V) indicated the selectivity of reduction of the 1,2-double bond under the conditions proposed by us.





EXPERIMENTAL

Solution of rhodium trichloride trihydrate and triphenylphosphine in ethanol, the preparation of the catalyst, and its isolation were conducted in an atmosphere of argon. Triphenylphosphine was first recrystallized from ethyl alcohol to remove oxide. Agitation during hydrogenation was carried out with the aid of a magnetic stirrer. Specific rotation was determined in chloroform (c 0.7) on an EAPU-01 instrument. Extinction coefficients were determined on an SF-4 spectrophotometer. IR spectra of compounds (II, V) were taken in Nujol mulls on a Perkin-Elmer 457 spectrophotometer. PMR spectra were obtained on a Varian XL-100A instrument with tetramethylsilane as standard. TLC was carried out on Silufol UV-254 plates in the system cyclohexane–acetone–benzene (9:4:1). Visualization was in UV light by spraying the plates with a 10% solution of phosphomolybdic acid in alcohol with subsequent heating at 70-80°C for 1-2 min. The following Rf values were obtained: (I) 0.43; (II) 0.57; (III) 0.6; (IV) 0.25; (V) 0.31; (VI) 0.4; triphenylphosphine 0.96; triphenylphosphine oxide 0.14.

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Preparation of tris-(Triphenylphosphine)rhodium Chloride. A solution of triphenylphosphine (2.4 g) in hot 95% ethanol (70 ml) was added with stirring to a solution of rhodium trichloride trihydrate (0.4 g) in 95% ethanol (14 ml) heated to 40-50°C. The reaction mixture was boiled for 2 h. The precipitate of tris-(triphenylphosphine)rhodium chloride was then filtered off from the hot solution on a glass filter, washed with small portions (twice with 6 ml) of ethanol and of ether, and dried in a water-jet pump vacuum. The yield of tris-(triphenylphosphine)rhodium chloride was 1.13 g (88.4% calculated on rhodium). Found, %: C 69.89; H 4.9; Cl 4.11. $C_{54}H_{45}ClP_3Rh$. Calculated, %: C 70.1; H 4.9; Cl 3.8.

Preparation of Androst-4-ene-3,17-dione (II). To dry benzene (105 ml), previously saturated with hydrogen by stirring, was added tris-(triphenylphosphine)rhodium chloride (1.61 g). The vessel, in which the catalyst was suspended, was rinsed with dry benzene (17.5 ml) which was poured into the reaction mixture and the obtained suspension of catalyst in benzene was once again saturated with hydrogen for 5-10 min. After 20-30 min the solid had completely dissolved and the solution acquired an orange color. Then (I) (0.35 g) in dry benzene (17.5 ml) was added to the solution. The mixture was saturated with hydrogen and the resulting dark-red solution was stirred in a hydrogen atmosphere at a temperature of about 20°C at atmospheric pressure for 2 h.

After checking by TLC (traces of I) the benzene solution was filtered through a layer (18 cm) of aluminum oxide (120 g) of activity grade 2, which was washed first with benzene (to eliminate catalyst and its conversion products triphenylphosphine and the oxide), and then with a mixture of benzene—ether (1:1) to elute (II). The benzene—ether mixture was distilled in vacuum (bath temperature 30-40°C). After recrystallization of crude (II) (0.36 g) from a sevenfold quantity of acetone, compound (II) (0.2 g; 57.1%) of mp 170.5-172°C, $[\alpha]_D^{20} = +203°$ was obtained. The material gave no depression of melting point when mixed with an authentic sample of androst-4-ene-3,17-dione. UV spectrum, λ_{max}, nm (log E) (in alcohol); 242 (4.20). IR spectrum ν_D: 1730 (CO); 1660 (CO=C=C); 1615 (C=C) cm^{-1}. A further quantity of (II) (0.05 g; 14.2%) of mp 169-170.5°C was obtained from the mother liquor. UV spectrum, λ_{max}, nm (log E) (in alcohol) 242 (4.20). IR spectrum, ν 1730 (CO): 1660 (CO=C=C), 1615 (C=C) cm^{-1}.

Literature data [7]: analytically pure sample, mp 173-174°C. UV spectrum, λ_{max}, nm (log E) (in alcohol): 242 (4.25).

Preparation of 3-Keto-bis-norchol-4-enoic Acid (IV). The interaction of (IV) (0.1 g) with tris-(triphenylphosphine)rhodium chloride in benzene solution in an atmosphere of hydrogen at room temperature was conducted under conditions analogous to those described for (II) for 6-8 h. After checking by TLC (IV ∿ 5%, traces of VI) the benzene solution with the precipitate was extracted 8 times with portions (15 ml) of 2% aqueous sodium hydroxide solution. The alkaline solution of the sodium salt of (V) was saturated with sodium chloride, acidified with hydrochloric acid to pH 1.0, and extracted with butyl acetate. The combined butyl acetate extracts were washed with saturated sodium chloride solution and the solvent distilled off in vacuum (bath temperature 50-60°C). Compound (V) (0.06 g: 64.5%) of mp 264-265°C (from ether) was obtained. IR spectrum, ν: 1715 (CO); 1650 (CO=C=C); 1610 (C=C) cm^{-1}. PMR spectrum, ppm (in deuterochloroform): 0.74 (singlet, 18-CH_3); 1.21 (doublet, 21-CH_3); 1.24 (singlet, 19-CH_3); 5.73 (singlet, 4-H).

Literature data [8]: mp 260-265°C, $[\alpha]_D^{24} = +60°$ (chloroform).

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