Brief Communications

η^4-*endo*-(17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione)-(η^5-cyclopentadienyl)rhodium(I)

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η^4-*endo*-(17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione)(η^5-cyclopentadienyl)rhodium(I) was synthesized by successive treatment of 17α,21-dihydroxypregna-1,4-diene-3,11,20-trione with $[(C_2H_4)_2RhCl]_2$ and CpTl in a yield of 54%. ^1H NMR studies demonstrated that coordination of the organometallic moiety occurs from the side opposite to the 19-CH_3 group. Upon coordination, ring *A* of the prednisone ligand is fixed to adopt a boat conformation, and the basicity of the 3-CO group increases substantially.

Key words: steroids, prednisone, rhodium complexes, NMR spectroscopy, coordination-induced shift.

17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione (**1**) (synonyms: Δ^1-dehydrocortisone, Δ^1-cortisone, and prednisone), which was first prepared by a microbiological method[1,2] and then was synthesized chemically,[3,4] is a well-known commercial glucocorticoid (adrenocorticosteroid) with a broad spectrum of action.[5] Due to the presence of a π-diene system of bonds, a saturated unit with geminal substitution (C(10)), and an *exo*-unsaturated group (C(3)=O) in ring *A*, the compound under study can be assigned to the *para*-semiquinoid class, whose organometallic chemistry is being extensively studied by us (see, for example, Refs. 6—8), including reactions of model 4,4-disubstituted 2,5-cyclohexadienones with rhodium derivatives.[9,10] In this work, we carried out successive conversions of prednisone **1** under the action of $[(C_2H_4)_2RhCl]_2$ (Ref. 11), CpTl (Ref. 12), and CF_3COOH, which allowed us to reveal (by ^1H NMR spectroscopy) the characteristic and very clear picture of the effect of the transition metal coordination to the π-diene on the change in the magnetic shielding of the regioindicator group (the system of three vinyl protons of the ring) and stereoindicator group (19-Me) (Fig. 1).

Coordination of the monovalent metallofragment RhCl to ring *A* to form unstable product **2** (we did not isolate **2** in the individual form) leads to the expected upfield shift of the vinylic protons ($\Delta\delta$ = 2—3; *cf.* Refs. 10 and 11), which appears to be accompanied by a substantial broadening of these signals (this can be reasonably accounted for by the possibility of reversible decomposition of complex **2** that was formed by an excess of the coordinating solvent, deuteriomethanol). The replacement of the chlorine atom at the Rh atom by the Cp group to form stable product **3**, which was isolated in the individual form, leads to the upfield shift of C(1)—H ($\Delta\delta$ = 0.6) and to the downfield shifts of both vinylic protons: C(2)—H ($\Delta\delta$ = −0.3) and C(4)—H ($\Delta\delta$ = −0.4). Finally, protonation of the 3-CO group of complex **3** with 1 equiv. of CF_3COOH yielded a representative of mixed cationic 3-hydroxycyclohexadienyl Rh^{III} complexes (**4**).

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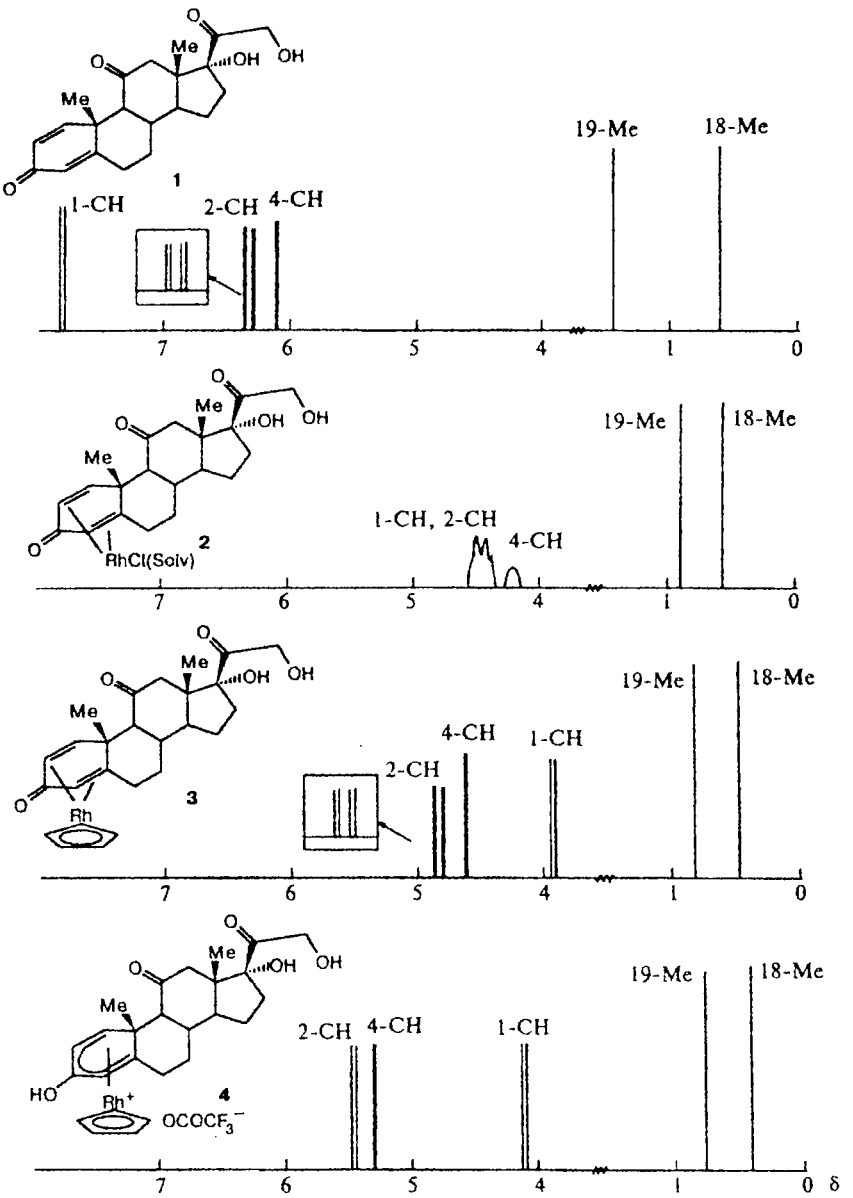

Fig. 1. Scheme of changes in the chemical shifts of the signals for the characteristic protons in the ^{1}H NMR spectra as a result of a series of conversions **1** → **2** → **3** → **4** (Bruker AMX 400, 400 MHz, methanol-d_4, 24 °C).

In all the cases under study, coordination of the metal atom occurs stereospecifically, namely, exclusively from the side of the prednisone molecule that is opposite to the 19-Me group. This is unambiguously shown by the pronounced upfield shift of this group (see Fig. 1) as a consequence of its orientation in the negative segment of the shielding cone of the double bonds of the diene ring, which adopts a boat conformation upon coordination (*cf.* Refs. 9 and 10).

Therefore, the results of this work extend in principle the scope of organometallic chemistry of semiquinoid systems to include ligands of the semiquinoid type that are promising in biological and biomedical aspects.

Experimental

17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione (1). ^{1}H NMR (CD_3OD), δ: 0.64 (s, 3 H, 18-Me); 1.45 (s, 3 H, 19-Me); 1.23—2.93 (overlapping multiplets, 8 H, 6-CH_2, 7-CH_2, 15-CH_2, 16-CH_2); 2.08 (d, 1 H, 12-CH, ^2J = 12.3 Hz); 2.11—2.73 (overlapping multiplets, 3 H, 8-CH, 9-CH, 14-CH); 2.94 (d, 1 H, 12-CH); 4.22 (d, 1 H, 21-CH,

^2J = 19.5 Hz); 4.59 (d, 1 H, 21-CH); 6.08 (br.s, 1 H, 4-CH); 6.18 (dd, 1 H, 2-CH, ^3J = 10.24 Hz, ^5J = 1.99 Hz); 7.78 (d, 1 H, 1-CH, ^3J = 10.24 Hz).

Reaction of 17α,21-dihydroxypregna-1,4-diene-3,11,20-trione (1) with $[(C_2H_4)_2RhCl]_2$. The complex $[(C_2H_4)_2RhCl]_2$ (0.017 g, 0.044 mmol) was added with stirring to a solution of prednisone **1** (0.02 g, 0.056 mmol) in methanol-d_4 (2 mL). A weak flow of argon was passed through the reaction mixture at 20 °C for 2 h. Then the mixture was concentrated to 0.5 mL and filtered. The Rh^I complex (**2**) was identified in the filtrate. ^1H NMR (methanol-d_4), δ: 0.62 (s, 3 H, 18-Me); 0.95 (s, 3 H, 19-Me); 1.23—2.90 (overlapping multiplets, 11 H, 6-CH_2, 7-CH_2, 15-CH_2, 16-CH_2, 8-CH, 9-CH, 14-CH); 2.23 (d, 1 H, 12-CH, ^2J = 14.0 Hz); 3.19 (d, 1 H, 12-CH); 4.23 (very br.s, 1 H, 4-CH); 4.30 (d, 1 H, 21-CH, ^2J = 19.5 Hz); 4.44 (br.m, 2 H, 1-CH, 2-CH); 4.66 (d, 1 H, 21-CH). The solution also contained prednisone **1**.

η⁴-*endo*-(17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione)(η⁵-cyclopentadienyl)rhodium(I) (3). A mixture of prednisone **1** (0.108 g, 0.3 mmol) and $[(C_2H_4)_2RhCl]_2$ (0.059 g, 0.3 mmol) in methanol (12 mL) was vigorously stirred for 1 h. Then the solvent was evaporated. The residue was dissolved in THF (5 mL), and CpTl (0.08 g, 0.3 mmol) was added. The color of the solution changed from red to pale-brown. The reaction mixture was stirred for 1 h, the solvent was evaporated, and the residue was extracted with MeOH (3×5 mL). When the extract was concentrated, pale-yellow crystals were precipitated. The crystals were separated by decantation and washed with cold MeOH. After evaporation of the solvent, the residue was recrystallized from a MeOH—Pr^iOH mixture to yield an additional amount of **3**. The total yield of **3** was 0.086 g (54.4%). The yellow crystals are readily soluble in MeOH and poorly soluble in Pr^iOH and $CHCl_3$. Found (%): C, 58.52; H, 6.43. $4[C_{26}H_{31}O_5Rh] \cdot CH_3OH$. Calculated (%): C, 58.76; H, 6.07. IR (KBr), ν/cm^{-1}: 1585 (C=O), 1720 (C=O). ^1H NMR (methanol-d_4), δ: 0.45 (s, 3 H, 18-Me); 0.70 (s, 3 H, 19-Me); 1.18—1.96 (overlapping multiplets, 8 H, 6-CH_2, 7-CH_2, 15-CH_2, 16-CH_2); 2.04 (d, 1 H, 12-CH, ^2J = 14.1 Hz); 2.08—2.66 (overlapping multiplets, 2 H, 8-CH, 14-CH); 2.77 (d, 1 H, 9-CH, ^3J = 11.1 Hz); 2.94 (d, 1 H, 12-CH); 3.87 (d, 1 H, 1-CH, ^3J = 6.9 Hz); 4.17 (d, 1 H, 21-CH, ^2J = 19.5 Hz); 4.53 (d, 1 H, 21-CH); 4.64 (br.s, 1 H, 4-CH); 4.76 (dd, 1 H, 2-CH, ^3J = 6.9 Hz, ^5J = 1.2 Hz); 5.45 (s, 5 H, Cp).

Protonation of complex 3 with trifluoroacetic acid. An 0.2 *M* solution (0.1 mL, 0.02 mmol) of CF_3COOH in methanol-d_4 was added to a solution of complex **3** (0.011 g, 0.02 mmol) in methanol-d_4 placed in an NMR tube. ^1H NMR (methanol-d_4), δ: 0.44 (s, 3 H, 18-Me); 0.69 (s, 3 H, 19-Me); 1.31—1.95 (overlapping multiplets, 8 H, 6-CH_2, 7-CH_2, 15-CH_2, 16-CH_2); 2.05 (d, 1 H, 12-CH, ^2J = 14.0 Hz); 2.16—2.59 (multiplets, 2 H, 8-CH, 14-CH); 2.63 (d, 1 H, 9-CH, ^3J = 11.0 Hz); 2.97 (d, 1 H, 12-CH); 4.15 (d, 1 H, 1-CH, ^3J = 6.9 Hz); 4.19 (d, 1 H, 21-CH, ^2J = 19.4 Hz); 4.55 (d, 1 H, 21-CH); 5.35 (br.s, 1 H, 4-CH); 5.44 (d, 1 H, 2-CH, ^3J = 6.9 Hz); 5.71 (s, 5 H, Cp). The spectrum remained unchanged upon storage of the tube at −20 °C for 6 days.

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