

CD spectra of pharmaceuticals substances - Steroids (2)

In this report, the gestagen (corpus luteum hormones: progesterone) female hormones were examined.

1. Progesterone

Progesterone is used by intramuscular injection for functional uterine bleeding from endometrium during the proliferative phase, as well as for menstrual problems.¹⁾ It is mainly secreted in the corpus luteum and placenta. Its concentration in blood plasma for a normal woman is less than 1 ng/ml during the follicular phase, 8 ng/ml during the luteal phase and 160 ng/ml during pregnancy (36th week).²⁾ Progesterone functions to prepare for the implantation of a fertilized egg, as well as to maintain pregnancy.¹⁾

Figure 1 shows the CD/UV spectra of progesterone. In both of the spectra, there are overlapped absorptions of the two bands, the R-band assigned to the α , β -unsaturated ketone (enone) at 350 to 300 nm and the R-band assigned to the saturated ketone of the 17 β -acetyl group. For wavelengths less than 270 nm, the K-band of enone is observed. The observed CD of the enone, negative for the R-band and positive for the K-band, shows a good correspondence with the results for testosterone. The positive CD, observed for the 17 β -acetyl group, is discussed below in the investigation of pregnanolone.

2. Pregnanolone

Pregnanolone is not described in the Japanese Pharmacopoeia. Pregnanolone is one of the metabolites from progesterone. Figure 2 shows the CD/UV spectra of pregnanolone, where the absorption can be assigned to the R-band of the saturated ketone in the 17 β -acetyl group. The 17 β -acetyl group, as a result of its hindered rotation affected by the steric hindrance of the adjacent 18 β -methyl group, has two rotational isomers or conformers, A and B shown below. The conformer A is dominant in a solution at or under room temperature.^{4,5)} The octant projection chart in the vicinity of the D-ring in the conformer A, shown below, supports a positive, strong Cotton effect.

3. Norethisterone

Norethisterone is used orally for conditions such as menstrual problems, and ovarian and corpus luteum insufficiency.¹⁾ Figure 3 shows the CD/UV spectra of norethisterone, which are similar to those of testosterone.

4. Chlormadinone acetate

Chlormadinone acetate is a corpus luteum hormone agonist and is used orally for problems such as prostatic cancer.¹⁾ Its strong action as a corpus luteum hormone agonist is known to be 32.4 times and 38.5 times more effective than progesterone by subcutaneous injection, and norethindrone by oral dosage, respectively.¹⁾

Figure 4 shows the CD/UV spectra of chlormadinone acetate, where the effect of the $\Delta^{4,6}$ -dien-3-one (linear dienone) chromophore is dominant and its R-band and K-band are observed around 350 nm and for wavelengths less than 310 nm, respectively. The UV absorption of the 17 β -acetyl group, existing around 290 nm, is concealed by the strong K-band, and the positive CD also overlaps with the K-band, having a positive value at 296 nm, and a negative value at 270 nm. The Cotton effect of the R-band for the $\Delta^{4,6}$ -dien-3-one in 10 β -substituted steroids is known to be generally positive, as shown in the figure and thus opposite to the case of the Δ^4 -en-3-one.⁶⁾

References

- 1) The Manual of Japanese Pharmacopoeia, 12th Edition, Hirokawa Shoten, 1991.
- 2) The Dictionary of Biochemistry, Tokyo Kagaku Dojin, 1st Edition, 1984.

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- 1] Two rotational isomers, A and B, in the 17 β -acetyl group
- 2] The octant projection chart of the conformer A in the vicinity of the C and D rings, (+) octant.
- 3] Sample: SIGMA P0130
- 4] Measurement apparatus
CD: J-720 Circular Dichroism Spectrophotometer
UV: Ubest V-550 Ultraviolet and Visible Light Spectrophotometer
- 5] Figure 1. The CD/UV and IR spectra of progesterone
- 6] The structure of progesterone
- 7] IR spectrum (KBr tablet method)
- 8] Measurement apparatus: FT/IR-300
- 9] Figure 2. The CD/UV and IR spectra of pregnanolone
- 10] The structure of pregnanolone
- 11] Figure 3. The CD/UV and IR spectra of norethisterone.
- 12] The structure of norethisterone.
- 13] The CD/UV and IR spectra of chlormadinone acetate
- 14] The structure of chlormadinone acetate

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