Biological Activity and Chemical Structure

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EXTRACT

The basic activity, i.e. the progestational activity, shows a distinct relationship to the chemical structure of the compounds so far studied. The introduction of a double binding in δ', δ', δ'X, δ'Y, and the 19nor-δ' configuration in pregnane, increases the potency of the parent compound. About equally potent are the δ' and δ'X derivatives. The acetylation of the parent compound increases the progestational activity considerably. The most potent acetates are the ones of the δ', δ', δ'Y, and 19 nor-δ' steroids. Slightly less influenced is the activity in the δ'X-compound.

The introduction of methyl-group in the 17α-hydroxy-progesterone-17α-acetate in 6α-position increases the progestational potency of the parent compound 3 times on subcutaneous and 10 times on oral administration.

The potency is increased in about the same order by introduction of 6α-F group. The 2α-methyl and 16α-methyl derivatives are less active as the parent compound. A 6α-Cl group does not influence the basic activity. An additional 4-OH function does not influence the basic potency on subcutaneous administration but increases the oral activity about 5 times.

In the 17α-hydroxy δ'-progesterone-17α acetate the introduction of a 6α-Cl group increases the basic potency, a 6α-methyl group does not change the subcutaneous, but reduces the oral potency. A 16α-methyl group reduces the potency in both routes of administration.

In the 17α-hydroxy-δ'-progesterone-17α-acetate the most favorable increase of the potency is achieved by the introduction of 6-Cl group, the corresponding 6-methyl compound is less active on subcutaneous and equally active on oral administration. The 6,16α-dimethyl derivative is equally active subcutaneously and 10 times more active orally when contrasted to the parent compound.

In the studied androstane derivatives it was show that the introduction of a 17α-ethinyl group increases the progestational activity of testosterone on subcutaneous administration. The practically inactive testosterone on oral administration becomes active. The 6α-21-dimethyl derivative of ethinyltestosterone is the most potent compound in this group of weak progestational steroids.

Due to the fact that they are androstane derivatives an androgenic side-effect can be expected.

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In the other large group of 17α-alkyl-19-nor-testosterone derivatives, the progestational potency is influenced in all the cases when contrasted to the activity of 19-nortestosterone. The most potent compounds in this line are represented by the 17α-ethyl and 17α-ethinyl-17β-acetate. The 17α-ethinyl-Δ4 (10) derivative is a weakly active compound which does not induce a complete progestational transformation of the rabbits endometrium.

The corresponding 3-deoxo-compounds of 17α-ethyl, 17α-ethinyl and 17α-allyl-19-nortestosterone are less active as the 3-keto-steroids on subcutaneous and on oral administration, only the 17α-ethyl derivative retains the potency on oral administration when contrasted to the parent compound.

The basic activity of progesterone is increased about 3 times on subcutaneous administration in the retro Δ4-progesterone, the oral potency is more as 10× progesterone, which is practically inactive on this route of administration.

A relationship between the pregnancy maintaining effect and chemical structure cannot be established, since only few compounds have been studied in this sense. However, in this type of study a species difference is evident. There is no parallelism between the progestational activity assayed in the Clauberg test and the maintenance of pregnancy in spayed animals.

It has been shown that compounds so far studied will maintain pregnancy in spayed rats without oestrogens, when they exert a pituitary inhibiting effect. The exception is represented by the 17α-ethinyl-19-nor-testosterone and its 17β-acetate. They will maintain pregnancy in the spayed rat for a short period of time only, it may be explained by the oestrogenic side effect of these compounds, which does not seem to be adequate in the sense of the progestagen:oestrogen ratio.

In some of the steroids described, a virilizing effect upon the female fetus has been reported in experiments, especially in the derivatives of androstane and 17α-alkyl-19-nor-testosterone. There is only one compound, the 6α-methyl-17α-hydroxyprogesterone-17α-acetate deriving from the 17α-hydroxy-progesterone line which has virilizing properties in the rat. At the present time experimental studies are carried out which should help to clear this rather strange and diverse behaviour. According to clinical studies a virilization of a female newborn has never been reported or observed.

In 898 cases with assumed 52% female babies studied in USA, no signs of virilization were observed. In Italy in 207 cases with 49% female babies the results are similar. In Denmark, figures cannot be given, the survey revealed no signs of virilization in female babies whose mothers have been treated with 80mg/d the first, 40mg/d the second and 20mg/d the third week when submitted to the hospital for threatening abortion. At the moment, according to our knowledge the transformation of the experimental data to men are doubtful; at least have to be restricted. As far as the fertility control is concerned two models are used for experimental work, one is the rabbit. We do not
believe that the rabbit is suitable for this type of work since the ovulation is always induced.

A model more adequate to the physiology of a rhythmic ovulation is represented by the rat. In one of the most recent papers on this subject, a lack of the correlation between the inhibition of gonadotrophins in the parabiotic rat and the inhibition of the ovulation was found in the rabbit. According to our experience there is always a correlation between these two parameters in the rat, although we would not like to exclude exceptions. These discrepancies may be explained in two ways, the one possibility is: the mode of action of the inhibition of ovulation is not yet established, some compounds may act directly on the ovary, others via the hypothalamic-hypophyseal axis and the rest both ways. The other explanation may be, that the response of an animal ovulating on stimulation only, may be diverse from the one in spontaneous and rhythmic ovulating species.

However in the rat, in our experience one may differentiate between inactive or poorly active pregnane-derivatives and the highly active steroids deriving from 17α-alkyl-19-nor-testosterone. For the first group has to be mentioned one exception, the 6α-methyl-17α-hydroxyprogesterone-17α-acetate, whose activity is in the same range of the 17α-alkyl-19-nor-testosterone derivatives. The 17α-ethinyl compound and its 17β-acetate are very potent inhibitors of ovulation, less active is the 17α-ethinyl-β (10) compound and the 17α-ethinyl-3-deoxo derivatives. All four of them exhibit an estrogenic activity which certainly enhances the inhibition of ovulation. The disadvantage of the two ethinyl-19-nor-compounds may be the androgenic side effect.

Concluding our presentation one may state, that the relationship between the chemical structure and biological activity was established for the progestational and ovulation inhibiting potency. The maintenance of pregnancy, due to species specificity and due to the rather complex condition, shows no signs of relationship at the present time.