SYNTHESIS OF ANTIPROGESTATIONAL STEROIDS

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Summary—The discovery of the first competitive progesterone antagonist RU 38 486 has initiated an intense search for more potent and more selective anti-progestins. Among several hundreds of compounds under preliminary investigation, biological characterization is most advanced for derivatives RU 38 486, ZK 98 734 and ZK 98 299. These compounds do not only differ in relative potency, but are clearly distinguished by their different behaviour in various animal models. Emphasis is laid on the synthetic problems associated with chemical operations in a sterically crowded environment as represented by structures RU 38 486 and ZK 98 299.

Steroid chemistry continues to be a source of new compounds and new pharmacological principles. The recent discovery of the first competitive progesterone antagonist RU 38 486 by the Roussel–Uclaf group has to be considered another milestone in steroid history[1]. (Fig. 1) For many years efforts have been made to find anti-progestins, or, more precisely, compounds that antagonize the effects of progesterone at the receptor level. As progesterone is an essential hormone in the establishment and maintenance of pregnancy, the effect of an anti-progestin must necessarily be termination of pregnancy. Some of the potential applications are obvious: inhibition of nidation (morning after pill), induction of menstruation (once a month pill) and interruption in later stages of pregnancy (abortion). Apart from these obvious applications, an anti-progestin might serve to facilitate the process of birth, since several compounds have been shown to enhance softening and ripening of the cervix when given towards the end of pregnancy. Pretreatment with an anti-progestin might, therefore, become a useful technique to prevent delivery by Caesarean section in those cases, where the onset of labour and cervix dilatation do not occur in a synchronous fashion. Another field of application lies in the treatment of hormone dependent tumours, however

an account of results and mechanism would be untimely at this stage of investigations[2].

Undoubtedly, the most prominent structural feature of Ru 38 486 is a dimethylamino-phenyl group in the 11β-position of a 19-nor-steroid. Without this substituent the molecule would be expected to act as a rather good agonist. Consequently, a large variety of compounds were synthesized containing 11β-aryl residues. (Fig. 2) At present, three compounds of this series are under closer investigation: RU 38 486, ZK 98 734 and ZK 98 299[3].

ZK 98 734 represents a minor variation of the lead compound RU 38 486 having a Z-configurated 17α-(3-hydroxy-1-propenyl)-group instead of a 17α-(1-propinyl)-side chain. The biological profiles, however, reveal major differences: As RU 38 486 does not only act as a progesterone antagonist but also effectively antagonizes the effects of cortisol, our interest was focussed on compounds with a better dissociation between anti-progestational and anti-glucocorticoid activities. In this respect, ZK 98 734 was a large step towards reduction of antigluco-corticoid properties combined with a slightly increased antiprogestin effect in comparison with RU 38 486.

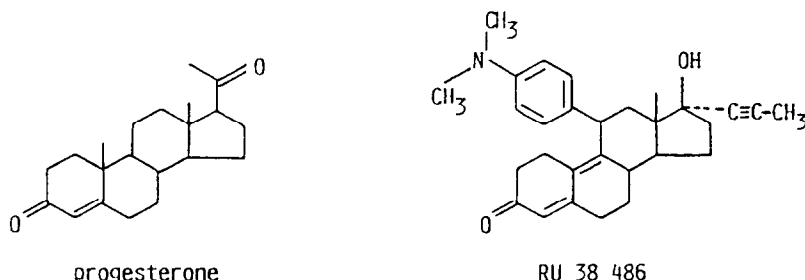ZK 98 299, though seeming a closely related structure in a two-dimensional picture, incorporates
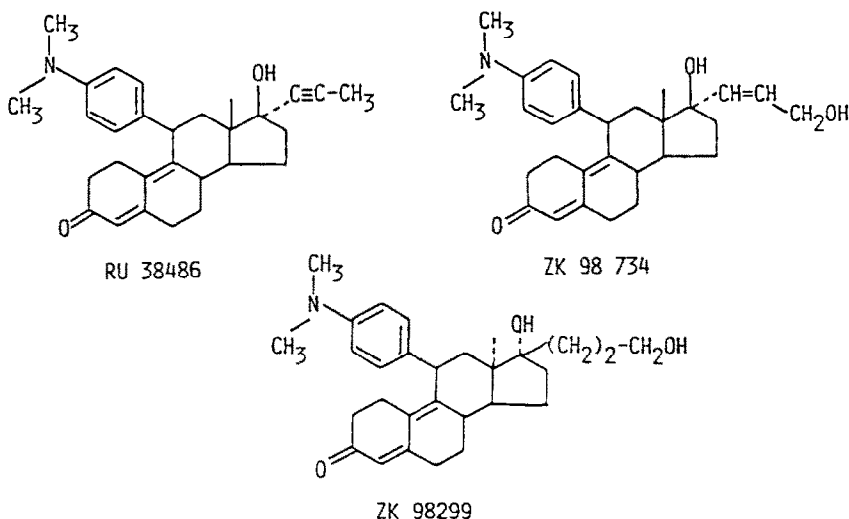

Fig. 1

RU 38486

ZK 98 734

ZK 98299

Fig. 2

two major deviations from the aforementioned compounds: configurational inversion at C-13 and C-17 makes ZK 98 299 distinctly different in molecular shape as exemplified by the X-ray structures of 11β-(4-fluorophenyl)-substituted derivatives 1 and 2 [4]. (Fig. 3)

The X-ray structure of compound I (natural estrane series) almost perfectly corresponds to the shape predicted by molecular models and spectroscopic data. The 11β-phenyl residue is fixed in an axial position exerting a strong shielding effect upon the angular C-13-methyl group the ^{1}H-nmr signal of which is shifted upfield by approx 0.4 ppm compared with the 11-unsubstituted analogue.

Of course, after inversion at C-13 the molecular shape is drastically changed in the region of rings C and D, as demonstrated by the X-ray structure of compound 2. (Fig. 4) Ring C changes its conformation into a distorted boat form and rings A and B consequently adopt conformations no longer superimposable with respect to compound 1. However, the orientation of the 11β-phenyl ring is not drastically altered as can be seen from a superposition of both structures. (Fig. 5)

The oxygen functions at C-17, generally assumed to participate in drug–receptor interaction, clearly point to opposite directions; both differently located OH-groups may, however, be linked by hydrogen bonding to a common imaginary point at the receptor, as shown in the Fig. 6. (Fig. 6)
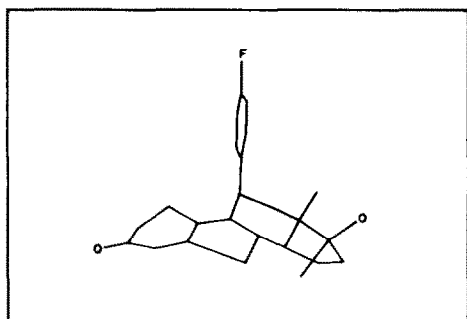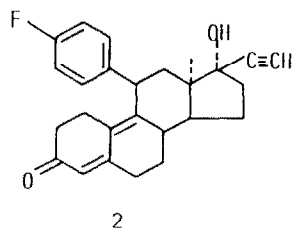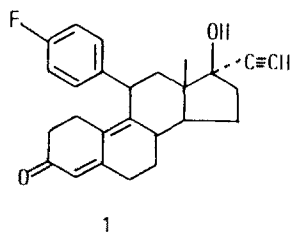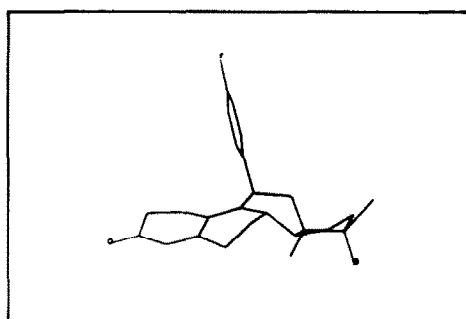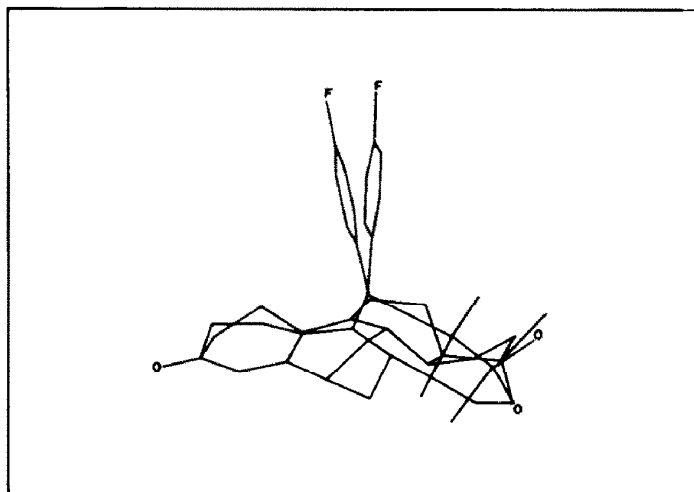

1

2

Fig. 3

Fig. 4

Fig. 5

The biological characterization of ZK 98 299 reveals similarities and surprising differences with respect to RU 38 486 and ZK 98 734: Anti-progestational and anti-glucocorticoid activities are comparable to Zk 98 734, although there are minor species differences.

Given in combination with prostaglandins or oxytocin ZK 98 299 exerts the strongest synergistic effects of all compounds hitherto synthesized in this series.

As another unique aspect, ZK 98 299 has the most potent effect on the cervix, at least in comparative studies with a guinea pig model.

The general and efficient strategy developed by Teutsch et al.[5] for the synthesis of 11β-substituted

estra-4,9-dienes was adopted in part to prepare ZK 98 299. (Fig. 7)

Starting material is the Birch reduction product of estradiol methyl ether, appropriate hydrolysis leads to the deconjugate enone 4 which by a bromination-dehydrobromation sequence is transformed to dienone 5. Ketalization of 5 proceeds with a double bond shift to form 5(10), 9(11)-diene 6, which is submitted to epoxidation to form 5α,10α-epoxide 7. Now the molecule is prepared for introduction of the 11β-substituent which is conveniently achieved by a copper(I)-catalyzed Grignard reaction.

After Oppenauer oxidation intermediate 9 (Fig. 8) is photolyzed with the full spectrum of a mercury high pressure lamp in dioxane and by Norrish-type I
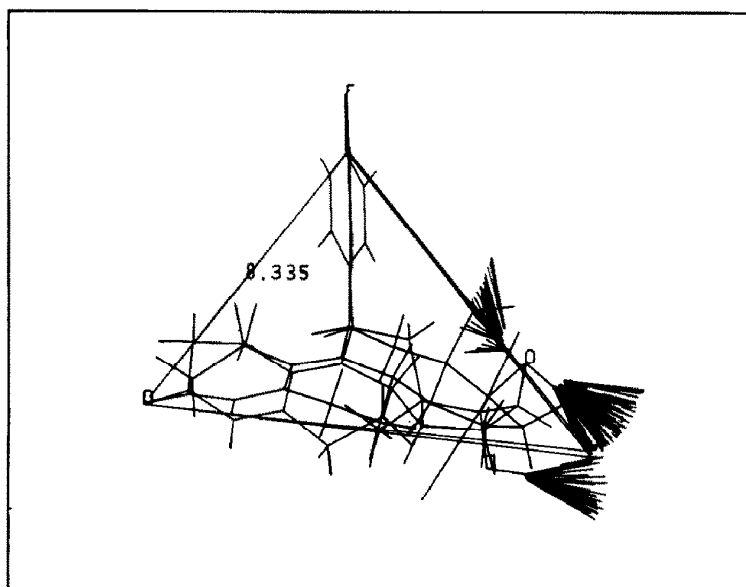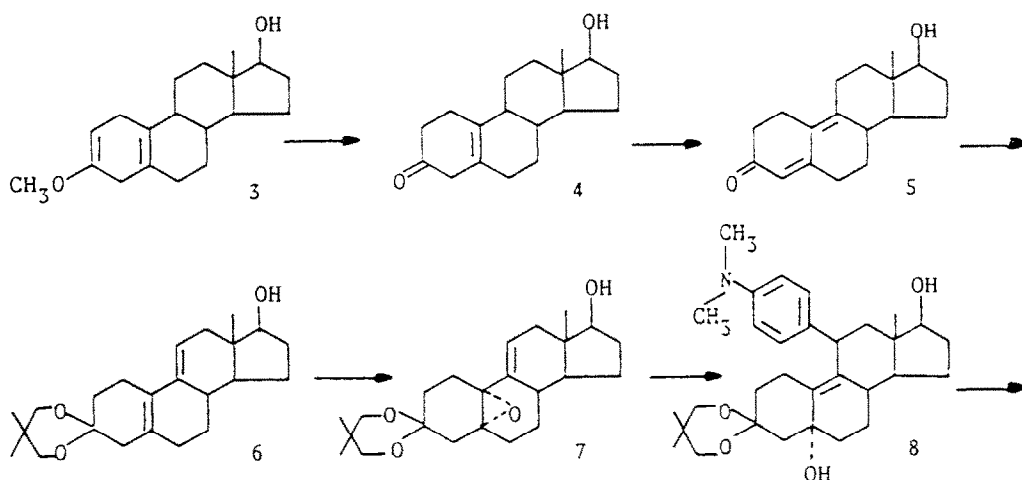

Fig. 6

Fig. 7

cleavage and recombination 13α-methyl gonane 10 is obtained in a good yield. The side chain at C-17 is constructed by adding the lithio derivative of pro-pargylic-THP-ether. In contrast to the natural estrane series, nucleophilic attack at C-17 is not perfectly stereoselective giving both isomers with predominant formation of 17β-adduct 11. Subsequent hydrogenation followed by acid-catalyzed deprotection-dehydration leads to the target compound ZK 98 299.

In this synthetic scheme, there are three remarkable steps which deserve more detailed comment.

Epoxidation of diene 6 (Fig. 9) was the first synthetic problem without a satisfying solution. Oxidative attack upon intermediate 6 had to be carried out regioselectively and stereoselectively. The solution presented by Teutsch et al.[6] (H₂O₂, hexachloro(fluoro)acetone) proved to be perfectly regioselective, however stereoselectivity was not as

good since a mixture of 5α,10α-epoxide 7a (65%) and the corresponding 5β,10β-isomer 7b (35%) was formed.

Among the multitude of existing epoxidation procedures only one system could be detected to give a better result. Taking Fe(II)-phthalocyanine, a cheap and readily accessible pigment, as catalyst in combination with iodosyl benzene as oxygen source we considerable promoted formation of 5α,10α-epoxide 14a [7]. A free hydroxy group at C-17 must be protected by ether formation or should be oxidized.

The second remarkable step in the Roussel-synthesis is the introduction of the 11β-substituent [7–15]. (Fig. 10) Although conjugate opening of an unsaturated epoxide by copper(II)-modified Grignard reagents or cuprates is not an unusual procedure, but it came as a surprise that a large number of bulky groups obviously ignore the unfavorable
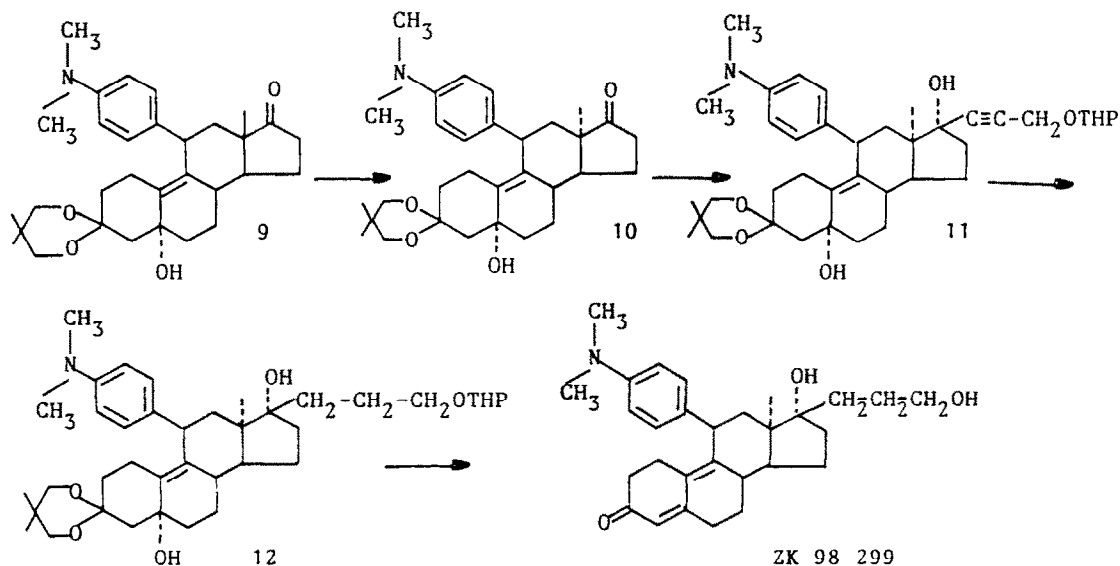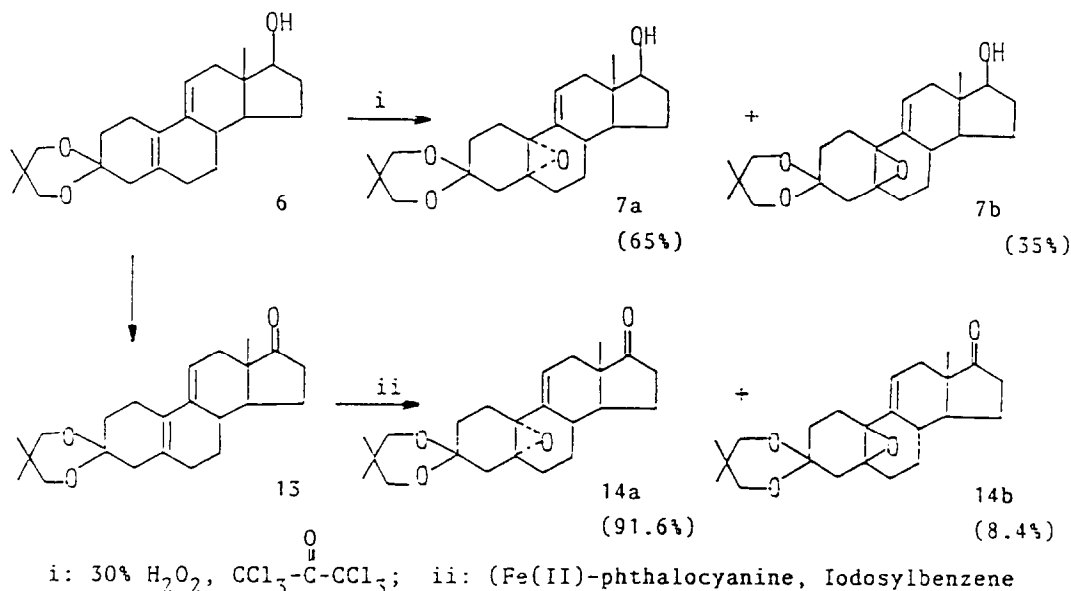

Fig. 8

i: 30% H_2O_2, $CCl_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}CCl_3$;   ii: (Fe(II)-phthalocyanine, Iodosylbenzene

Fig. 9

steric situation of position C-11β which is in a 1,3-diaxial relationship with the angular methyl group at C-13. A number of other approaches conceivable for the introduction of an 11β-substituent met with failure, due to steric hindrance (Fig. 11)

As a third remarkable step in the synthesis of ZK 98 299, photochemical inversion at C-13 [8] deserves a more detailed consideration. In marked contrast to previously examined 17-ketosteroids compound 9 is readily transformed to its C-13 epimer 10 in an isolated yield of 62%. The reaction can be run in high concentration with a short period of irradiation (25–35 min). Therefore, performance on a technical scale does not create a major problem.

At first sight, it may seem plausible that the conversion of 9 to 10 should constitute a thermodynamically favorable process, since the 1,3-diaxial relationship between 11β-aryl substituent and 13β-methyl group is replaced by a less hindered arrangement of these residues.

The following experiment, however, shows that this assumption cannot account for the observed result: Irradiation of the 11α-aryl substituted compound 16 proceeds equally well to give epimer 17 in an isolated yield of 67%.

In the case of product 17 the photochemical

process creates a 1,3-diaxial relationship between 11α-aryl group and 13α-methyl substituent. Although molecular models show that compound 17 could exist in a conformation which would avoid such an interaction, the ^{1}H-nmr spectrum of 17 leaves no doubt about a 1,3-diaxial arrangement.

Thus it became questionable whether the good results of photochemical epimerization in this series could be ascribed to steric or electronic effects exercised by the 11-substituent.

These doubts were confirmed by a series of further experiments: Irradiation of 11β-vinyl substituted ketone 18 proceeded with formation of the C-13 epimer 19 in a comparable yield (56%). Therefore, it appears improbable that intramolecular sensitization mediated by the 11-phenyl residue should be an important factor.

Of course, these results raise the question whether a substituent at C-11 plays any role at all for the outcome of photochemistry in this series.

We consequently synthesized the 11-unsubstituted analogues 20 and 22 (Fig. 12) and found them smoothly transformed to their C-13 epimers 21 and 23, although this transformation required a longer period of irradiation (60–75 min) than in the aforementioned cases (25–35 min).

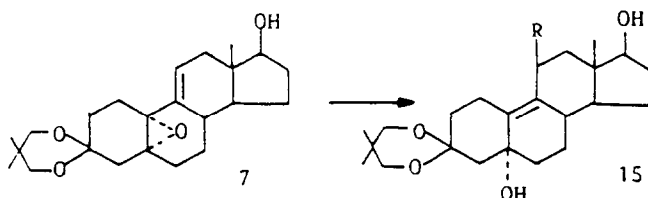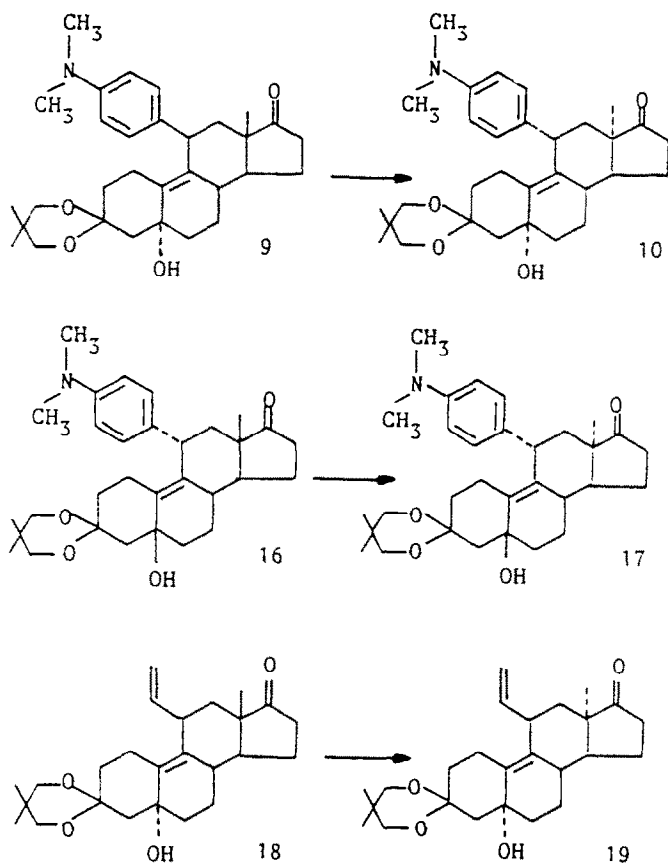*In vitro* (liver tissue) and *in vivo* (rat) investigations

Fig. 10

Fig. 11

had shown that RU 38 486, ZK 98 734 and ZK 98 299 were readily metabolized by oxidative dealkylation of the N,N-dimethylaniline moiety (Fig. 13).

The facile attack at the dimethylamino group is also reflected in microbiological reactions of RU 38 486 as well, since hydroxylation at skeleton positions is always accompanied by dealkylation at nitrogen. Generally, it may be concluded that the large variety of microorganisms known to effect steroid hydroxy-

lation, is reduced to quite a few species that can functionalize 11β-aryl substituted estradienes. An extensive screening programme gave the results shown in Fig. 14.

The few remarks about metabolism and microbial conversion are meant to illustrate that a 11β-(dimethylamino)-phenyl group may create problems for further chemical modification and pharmacodynamics. Consequently, the search for new
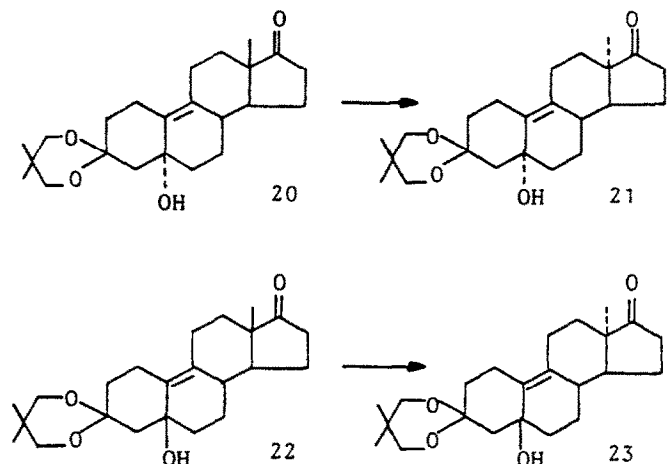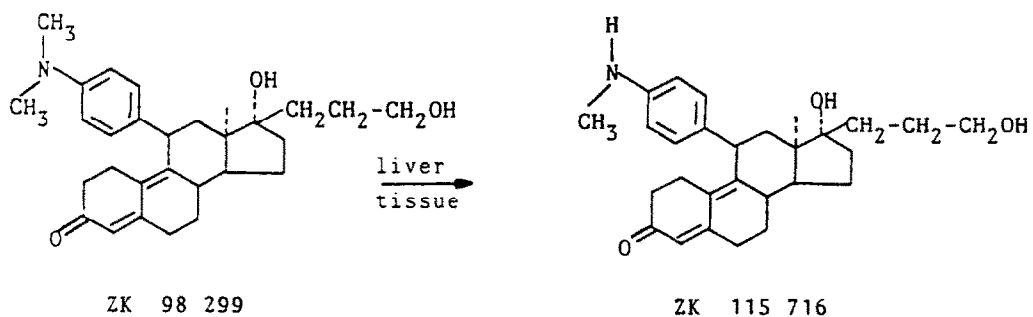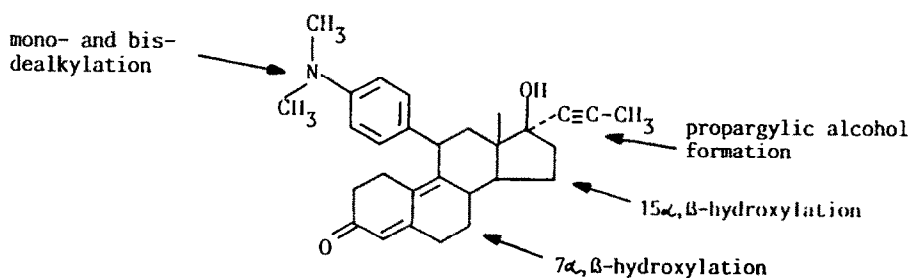

Fig. 12

ZK 98 299   ZK   115 716

Fig. 13

mono- and bis-
dealkylation

propargylic alcohol
formation

15α,ß-hydroxylation

7α,ß-hydroxylation

Fig. 14

ZK 112 993

Fig. 15

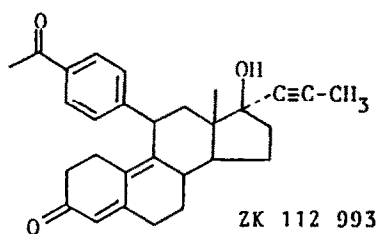
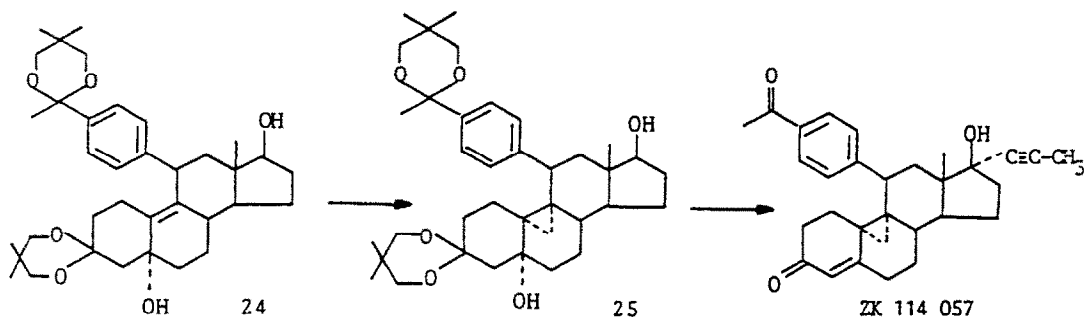24   25   ZK 114 057

Fig. 16

compounds cannot be abandoned at this stage. The remarkable discovery that a large variety of 11β-aryl substituted estradienes show high affinity for the progesterone receptor must not lead to the conclusion that all of them act as anti-progestins *in vivo*. Actually, a rather limited number of those compounds which display high binding affinities will antagonize the effects of progesterone in the pregnant animal.

Therefore, it came as a surprise that among a multitude of modifications the acetyl substituted derivative Zk 112 993 (Fig. 15) brought an increase in anti-progestational activity by a factor of 10–15 with respect to RU 38 486 in the rat model.

Of course, chemical, microbiological and metabolic processes are completely different from the dimethylaniline-substituted analogues. The 9α,10α-methylene derivative Zk 114 057 (Fig. 16) which, due to nitrogen basicity, was inaccessible in the RU 38 486 series, is conveniently prepared by the following route:

Simmons-Smith-methylenation of precursor **24** cleanly proceeds with formation of 9,10-methylene derivative **25** which is transformed in the usual fashion to give ZK 114 057, a compound similar in activity to ZK 112 993.

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