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SYNTHETIC VARIATIONS OF THE PROGESTERONE ANTAGONIST RU 38 486

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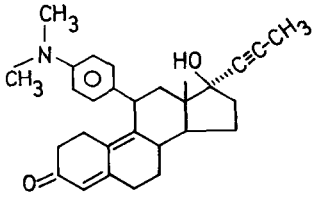
Summary: Irradiation of 17-keto-estranes bearing an 11-aryl substituent offers a preparatively useful access to pharmacologically interesting steroids with inverted configuration at C-13.

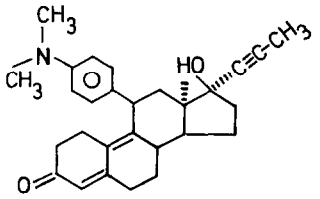
11ß-(4-Dimethylaminophenyl)-17ß-hydroxy-17α-(1-propinyl)-4,9-estradien-3-one (Ru 38 486) has turned out to be the first competitive progesterone antagonist[1]. A second, equally remarkable property of this compound is its strong anti-glucocorticoid activity. Possible applications of Ru 38 486 include human fertility regulation and treatment of corticoid induced side effects such as Cushing's syndrome[2].

First clinical studies[3] indicated that it might be desirable to increase the anti-progestational potency of Ru 38 486 and to get rid of the anti-glucocorticoid component. The hitherto unknown pharmacological profile and our lack of information concerning the progesterone receptor[4] demanded an empirical structure-activity study, part of which is summarized in this report.

Among the multitude of conceivable structural alterations we chose to invert C-13 stereochemistry, a process which should ultimately lead to gonane derivative 1. This idea was inspired by a previous observation that the C-13 epimers of norethisterone showed comparable affinities for the progesterone receptor[5].



Ru 38 486

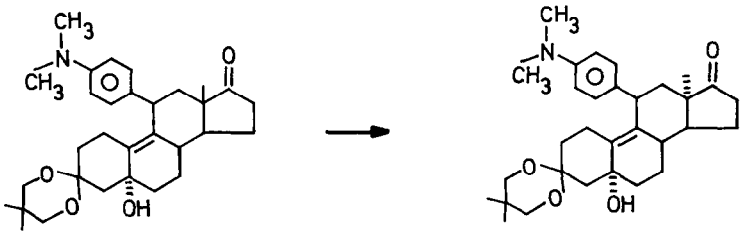


1

An obvious synthetic approach to compound 1, namely applying Teutsch's synthetic strategy[6] to 13-epi estrone methyl ether turned out to be

wearisome because it was difficult to prepare large quantities of 13-epi estrone methyl ether by the known methods[7,8]. Furthermore, the conformational diversity of 13-episteroids from the natural series offered serious problems to synthesize compounds of type 1 by mere analogy to the Roussel-Uclaf sequence[6].

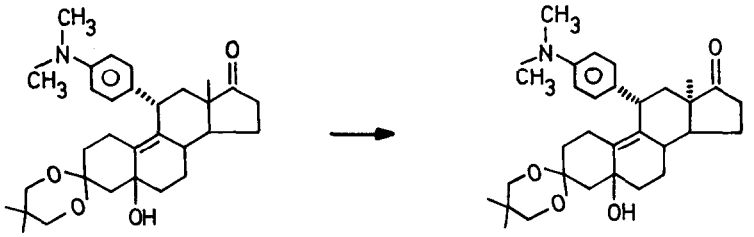
We, therefore, had to look for an alternative method to get access to 13-episteroids of type 1. The intermediate 2 of Teutsch's synthetic scheme proved to be a suitable starting material. Irradiation of 2 proceeded smoothly with formation of its epimer 3 isolated in a 62% yield. The ease and the yield of this transformation[9] are in marked contrast to the difficulties normally encountered in photochemical epimerizations of 17-ketosteroids[10].



2 3

It may seem plausible at first sight that the epimerization of 2 versus 3 should constitute a thermodynamically favorable process, as the 1,3-diaxial relationship between 11ß-aryl substituent and 13ß-methyl group is replaced by a less hindered arrangement of these substituents.

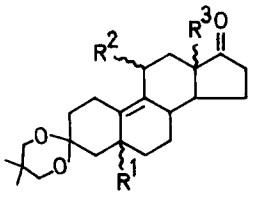
The following experiment, however, shows that this hypothesis cannot account for the observed result. Irradiation of the 11α-aryl substituted compound 4[11] proceeds equally well to give the epimer 5 in an isolated yield of 67%.



4 5

In this case the photochemical process creates a 1,3-diaxial relationship between 11α-aryl substituent and 13α-methyl group. Although molecular models show that compound 5 could exist in a conformation which would avoid such an interaction, the ^1H nmr spectrum of 5 leaves no doubt about a 1,3-diaxial arrangement (large upfield shift of C-13 methyl signal). A further conclusion based on the nmr spectrum and molecular models is, that ring C of epimer 5 must adopt a boat-like conformation.

Characteristic chemical shifts:



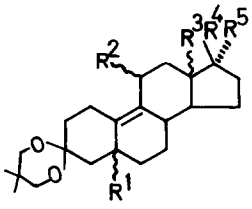
I

comp.	R^1	R^2	R^3	^{1}H nmr($CDCl_3$) $\delta_{C\text{-}13\text{-}CH_3}$(s)	$\delta_{H\text{-}11}$(m)
I a	α-OH	ß-aryl	ß-CH_3	0.51	4.23
I b	α-OH	ß-aryl	α-CH_3	1.10	3.74
I c	ß-OH	α-aryl	ß-CH_3	0.98	3.78
I d	ß-OH	α-aryl	α-CH_3	0.47	3.96

aryl = 4-dimethylaminophenyl

Thus the basis was laid for the synthesis of several epimers of Ru 38 486. The question that remained to be investigated was site-specificity of nucleophilic attack upon ketones 3 and 5. Sodium borohydride reduction of ketone 3 produced a mixture of C-17-epimeric alcohols with a slight predominance of ß-side attack (α-OH/ß-OH = 6:4). Ketone 5 gave a similar result on reduction with sodium borohydride or diisobutyl aluminum hydride.
ß-Selectivity was more pronounced in the case of nucleophilic attack by propinyl lithium: epimer 3 produced an 85/15 mixture of isomers in favor of the 17ß-alkinyl compound and ketone 5 was almost exclusively attacked from the ß-face of the molecule (95/5).

Solvent-induced shifts (assignment of C-17 configuration)



II

comp.	R^1	R^2	R^3	R^4	R^5	$\delta_{C\text{-}13\text{-}CH_3}$ ($CHCl_3$)	$\delta_{C\text{-}13\text{-}CH_3}$ (pyridine)
II a	α-OH	ß-aryl	α-CH_3	ß-OH	α-H	1.04	1.16
II b	α-OH	ß-aryl	α-CH_3	α-OH	ß-H	0.99	1.26
II c	ß-OH	α-aryl	α-CH_3	ß-OH	α-H	0.22	0.44
II d	ß-OH	α-aryl	α-CH_3	α-OH	ß-H	0.24	0.63
II e	α-OH	ß-aryl	α-CH_3	ß-OH	α-C≡C-CH_3	1.14	1.36
II f	α-OH	ß-aryl	α-CH_3	ß-C≡C-CH_3	α-OH	1.10	1.44

Acid hydrolysis of intermediate II e under the conditions described by Teutsch et al.[6] produced the target compound 1 which was tested for anti-progestational and anti-glucocorticoid activities. The rather interesting biological results obtained for compound 1 and several related derivatives will be the subject of a forthcoming publication.

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References and notes:

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9. In a typical experiment a solution of 2 in dioxane (4 g, 600 ml) is irradiated in a quartz immersion apparatus for 23 min at 25°C (Hg-high pressure lamp, Philips HPK 125) using the full spectrum of the lamp. Evaporation of the solvent followed by chromatography on neutral alumina with hexane/ethyl acetate yields 3 (2,48 g).
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