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INFLUENCE OF BULKY 11ß-SUBSTITUENTS ON REACTIVITY OF ESTRENE DERIVATIVES

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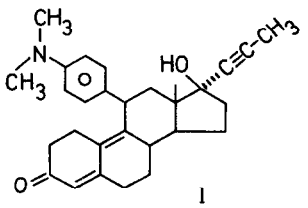
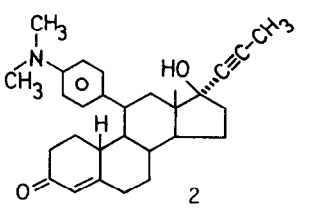
Summary: Steric constraint exercised by 11ß-aryl substituents prevents transformation of 5(10)-estrene derivatives to their 4-estrene analogues.

11ß-Aryl substituted estradiene derivatives which were recently made accessible by Teutsch et al.[1] have been shown to be competitive progesterone antagonists and may, therefore, mark a new course in fertility regulation.[2] 11ß-(4-Dimethylaminophenyl)-17ß-hydroxy-17α-(1-propinyl)-4,9-estradien-3-one 1 is the first anti-progesterone to be under clinical investigation. Obviously, introduction of an 11ß-aryl rest brings about the change from progestogenic[3] to anti-progestational activity.

In order to interact with the progesterone receptor, a Δ^4-3-oxo-element is an essential feature for a steroid molecule whereas the enlargement of the chromophore by an additional 9(10)-double bond has no important influence on receptor affinity. We, therefore, attempted to eliminate the 9(10)-double bond of 1, thus producing compound 2 which might be expected to display pharmacological properties similar to 1.



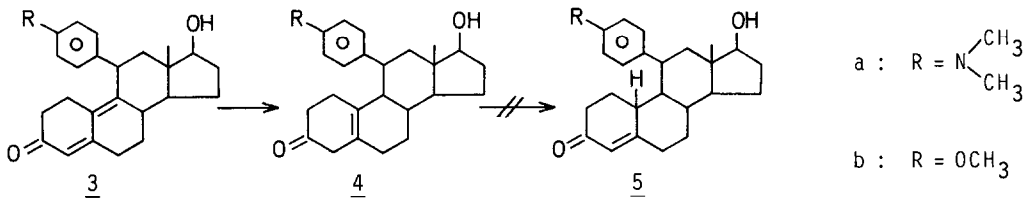
1



2

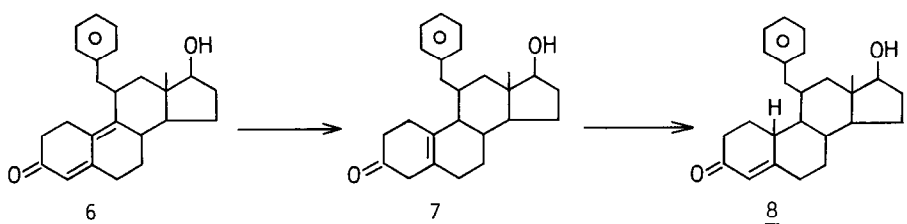
Model compounds 3a,b were synthesized according to the elegant procedures developed by Teutsch et al.[1,4] Birch-type reduction of 3a,b proceeded as a formal 1,4-hydrogenation leading to compounds 4a,b.[5] To our surprise, we

did not succeed in isomerizing the 5(10)-double bond of 4a,b to form the conjugated enones 5a,b, a process which is easily performed in the 11-unsubstituted series by short treatment with dilute mineral acids.



Molecular models indicate that steric interaction between the 10ß-hydrogen of 5 and an ortho hydrogen of the aromatic ring might be a plausible explanation of the experimental result.[6)]

We, consequently, replaced the aryl substituents of 3a,b by a benzyl group and performed the same sequence of reactions.[7,8)]



Acid treatment of 7, indeed, produced 8 although this process still needed more drastic conditions than the parent transformation in the 11-unsubstituted series.

Pharmacological and biochemical investigations undertaken with compounds of type 4 showed them to be devoid of anti-progestational activity. It may, therefore, be concluded that a conversion of 4 to 5 is neither chemically nor enzymatically possible.

The fixation of a double bond by a relatively remote substituent in a position which, at first sight, would not be considered to be thermodynamically stable, is not only a curious result, but demonstrates that some potentially interesting compounds such as 2 and its analogues in the androstane series will not be easily accessible.

References and notes:

1. A. Bélanger, D. Philibert and G. Teutsch, Steroids 37, 2742 (1981).
2. E.E. Baulieu et W. Herrmann, Médecine et Hygiène 40, 2087 (1982).
3. D. Philibert, T. Ojasoo and J.P. Raynaud, Endocrinology 10, 1850 (1977).
4. G. Teutsch and A. Bélanger, Tetrahedron Lett. 1979, 2051.
5. The yield of 4b was relatively low due to concomitant reductive attack upon the 11ß-aryl substituent.
6. The molecular model also shows that the 11ß-aryl substituent cannot avoid this interaction by rotation due to the angular C-13 methyl group. The large upfield shift observed for the signal of the C-13 methyl protons confirms a fixed conformation. Interestingly, this upfield shift is even more pronounced for compounds 4a,b compared to their precursors 3a,b.
7. a. Birch reduction (typical procedure)

   A solution of 11ß-benzyl-17ß-hydroxy-4,9-estradien-3-one 6 (4.6 g, 12.7 mmol) in 62 ml of absolute tetrahydrofuran and 6.2 ml of t-butanol is slowly added to 160 ml of liquid NH_3 at -60°C. Lithium (585 mg, 84.3 mmol) is added portionwise within a period of 10 min and stirring is continued for another 15 min. Solid ammonium chloride is added until the blue colour of the reaction solution has disappeared. After evaporation of ammonia the residue is taken up in 100 ml of water and extracted with ethyl acetate. Column chromatography on silica gel with hexane/ethyl acetate and crystallization of the main fraction from ethyl acetate yields 3.2 g (69.2 %) of 11ß-benzyl-17ß-hydroxy-5(10)-estren-3-one 7, m.p. 154-155°C. ^{1}Hnmr ($CDCl_3$): δ = 0.99 ppm (s, 3 H, H-18), 3.61 (m, 1 H, H-17), 7.17 (m, 5 H, arom. H).

   Analogous Birch reductions of 11ß-(4-dimethylaminophenyl)-17ß-hydroxy-4,9--estradien-3-one 3a and 17ß-hydroxy-11ß-(4-methoxyphenyl)-4,9-estradien--3-one 3b result in the formation of 4a (64 %) and 4b (37 %), respectively. 4a: ^{1}Hnmr ($CDCl_3$): δ = 0.35 ppm (s, 3 H, H-18), 2.91 (s, 6 H, N-CH_3), 3.45 (m, 1 H, H-11), 3.64 (m, 1 H, H-17), 6.56 and 7.17 (AA'BB', 4 H, arom. H). 4b: ^{1}Hnmr ($CDCl_3$): δ = 0.33 ppm (s, 3 H, H-18), 3.37-3.82 (m, 2 H, H-11 and H-17), 3.77 (s, 3 H, OCH_3), 6.73 and 7.26 (AA'BB', 4 H, arom. H).

b. acid-catalyzed isomerization

A solution of 11ß-benzyl-17ß-hydroxy-5(10)-estren-3-one 7 (500 mg, 1.37 mmol) and 400 mg of p-toluene sulfonic acid (monohydrate, 2.1 mmol) in 15 ml of ethanol and 2 ml of water is refluxed for 5 hours. After cooling the reaction mixture is diluted with water and extracted with methylene chloride. The crude product is chromatographied on silica gel with hexane/ethyl acetate to give, after crystallization of the main fraction from ethyl acetate/diisopropyl ether, 310 mg (62 %) of 11ß-benzyl-17ß-hydroxy-4-estren-3-one 8, m.p. 194-195°C. ^{1}Hnmr ($CDCl_3$): δ = 0.98 ppm (s, 3 H, H-18), 3.59 (m, 1 H, H-17), 5.84 (s, 1 H, H-4), 7.22 (m, 5 H, arom. H).

8. An alternative synthetic pathway was shortly investigated: Compound 3a as its 17ß-acetate was aromatized (Pd/C, ethanol), methylated (NaH, CH_3I, THF) and reduced (Li, NH_3, t-BuOH, THF) to give 4a after acid hydrolysis.

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