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THE ADAMANTYL CARBONIUM ION AS A DEHYDROGENATING AGENT, ITS REACTIONS WITH ESTRONE

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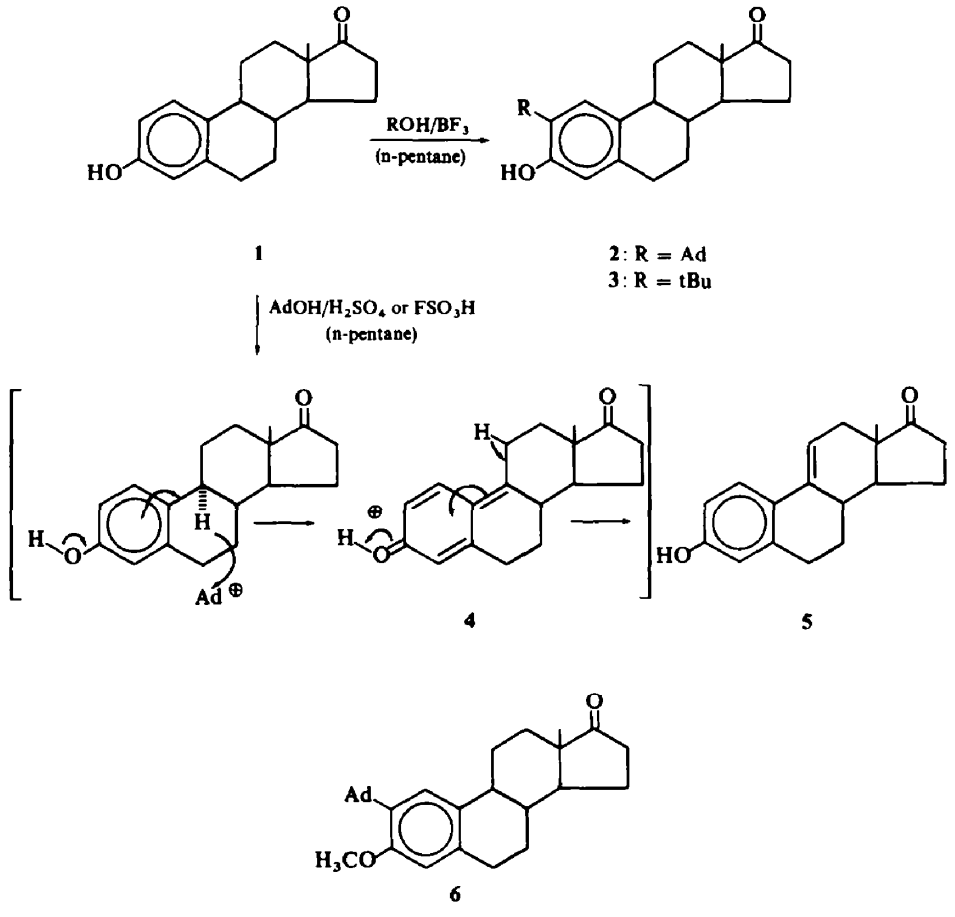
Abstract—An unusual and useful dehydrogenation of estrone to $\Delta^{9(11)}$-estrone has been observed on its reaction with the adamantyl carbonium ion. With modified conditions both t-butyl and adamantyl carbonium ion sources gave 2-substituted estrone derivatives in this reaction.

IN THE course of a continuing investigation of the pharmacological properties of adamantane compounds; and particularly following the finding that 19-nortestosterone adamantoate is a useful anabolic agent;[1] the synthesis of various adamantylestrone derivatives was undertaken. The adamantyl carbonium ion can be visualized as reacting with estrone to form the ether or the 2-substituted Friedel–Craft product. Thus estrone (**1**) was treated with adamantanol and boron trifluoride in n-pentane, a method known to give rise to the adamantyl carbonium ion.[2] This gave 2-[adamantyl-(1)]estrone (**2**) in a yield of 16%, which was doubled when BF_3–etherate was used. Using similar conditions, excellent yields of 2-t-butylestrone (**3**) were obtained when t-butyl alcohol was the cation source.

Both **2** and **3** are characterized by the absence from their NMR spectra of the signal at 3·45 τ present in that of estrone.[3] Furthermore, the doublet at 2·93 τ ($J \sim 9{\cdot}5$ c/s) in the spectrum of estrone, arising from the aromatic proton at C-1, is reduced to a singlet in the 2-alkylated products due to the absence of the adjacent proton. Also, whereas in the case of estrone the UV absorption maximum at 280 mμ suffers a bathochromic shift to 298 mμ when alkali is added; no such change is evident with all the 2-alkylated products described.

Previous workers have found that treatment of estrone with isobutene in methylene chloride–sulphuric acid gave rise to the tertiary butyl ether.[4] The difference between these results, arising via what must be the intermediacy of the tertiary butyl carbonium ion and the present work, is not readily understood. However, it may be reasonable to assume that the carbonium ion would be better solvated in sulphuric acid than with the medium containing BF_3, and perhaps the latter acid provides an ion sterically more favored for attack at the 2-position.

Having witnessed the dependence of product on the conditions, estrone was treated with adamantanol with sulphuric acid in n-pentane. Surprisingly, no alkylation product was obtained, rather dehydrogenation of the estrone occurred, $\Delta^{9(11)}$-estrone (**5**) being isolated in 28% yield. When fluosulfonic acid, an acid which should minimize ring sulfonation, was used, the yield was raised to 60%. Qualitative studies using TLC demonstrated that estrone and adamantanol with trifluoroacetic acid alone, or polyphosphoric acid and n-pentane, also produced $\Delta^{9(11)}$-estrone.



SCHEME 1

The stereoselectivity of this dehydrogenation is remarkable with no evidence for the formation of any of the Δ^8 product. Most frequently mixtures of double-bond isomers are expected in the steroid series under acid conditions. Recently the use of 2,3-dichloro-5,6-dicyanobenzoquinone was reported similarly to give good yields of $\Delta^{9(11)}$-estrone.[5] Because of the simplicity of the procedure, the purity of the product, and the relatively high yield, the use of the adamantyl carbonium ion procedure appears attractive.

Whereas carbonium ions are generally sp^2 hybridized, hence planar in character, the hybridization at the positive carbon of the adamantyl carbonium ion must involve considerable more p character by virtue of the pyrimidal shape enforced by the rest of the molecule. It has been suggested[6] that stabilization of this unusual hybridization state is achieved by 'intracage' overlap of part of the empty p orbital with the backsides of the three bridgehead C—H orbitals. The empty p orbital will be spatially less demanding in reactions than will sp^2 carbonium ions. This may well permit the abstraction of a hydride ion at C-9, which would be difficult in the case

of planar cations. In fact, we have found that even nitrosonium hexafluorophosphate,[7] usually a capable hydride ion abstractor at benzyl positions, failed to produce any detectable $\Delta^{9(11)}$ compound.

The oxidative process is doubtless assisted by the oxygen at the 3-position, removal of a proton from the quinonoid intermediate **4** providing the desired product. It is reasonable to assume that the proton lost will be axial, this providing for maximum overlap with the developing positive charge at C-9. This being the case, the stereoselectivity of the dehydrogenation is understandable. Dreiding models indicate that approach towards the 11β proton is hindered by the C-18 methyl group and the single hydrogen at C-8, whereas the path to the 8β proton has the same methyl group and three hydrogens (at C-6, 9, and 14) to contend with (Fig. 1).

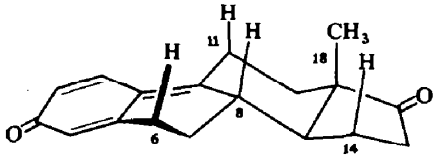


FIG. 1

In order to evaluate the importance of the presence of the phenol function, the methyl ether of estrone was used as the substrate for the two different types of reactions, the alkylation and the dehydrogenation. The corresponding 2-adamantyl product **6** was obtained in good yield in the former reaction, however, a mixture was obtained on attempted dehydrogenation.

EXPERIMENTAL*

2-[*Adamantyl-(1)*]-*estrone*, (**2**)

(a) *With* BF_3. Estrone (2·70 g), adamantanol (4·50 g, 3·0 mole equiv) and n-pentane were stirred gently while BF_3 was passed over the surface of the mixture for 1·5 hr during which time the mixture became brown. The whole was poured into ice water and then extracted with chloroform. The organic extract, after washing with dil $NaHCO_3$ aq and drying over $MgSO_4$, was evaporated to dryness and the solid residue chromatographed on Grace–Davison Silica gel (160 g). Benzene–EtOAc 98:2 eluted crystalline material (0·97 g), which was dissolved in chloroform, treated with charcoal, and crystallized to provide 2-(adamantyl-(1)]-estrone (0·65 g), m.p. 292–296°. An analytical sample melted at 295–296°. (Found: C, 82·80; H, 8·97. Calc. for $C_{29}H_{36}O_2$: C, 83·12; H, 8·97%).

(b) *With* BF_3–*etherate*. Estrone (5·40 g), adamantanol (3·30 g) and n-pentane (120 ml) were stirred in an ice bath while BF_3–etherate (8 ml) was added over a 10 min period; 15 min after the completion of the addition, the ice bath was removed and the mixture stirred at room temp for a further 45 min when it was poured onto cracked ice with agitation. On filtration, there was obtained a light-yellow product, which was washed with water and pentane, dried and crystallized from chloroform–isopropanol. This provided three crops of the 2-adamantyl compound (2·59 g), m.p. 294–295°; (1·31 g), m.p. 294–295 ; and (0·43 g), m.p. 292–294°.

2-*t-Butylestrone*, (**3**). Estrone (2·70 g), t-butanol (6 ml), and n-pentane (35 ml) were stirred gently under a slow stream of BF_3 for 0·5 hr at 5°, then 2 hr at room temp. Ice water was then added with stirring and the mixture was extracted with chloroform; the chloroform extract washed with $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated to dryness to give a slightly pink crystalline residue (4·8 g). Crystallization from chloroform provided two crops of 2-t-butylestrone (2·4 g), m.p. 243–245° and (0·5 g), m.p. 243–245°.

* M.ps are uncorrected and NMR data are reported for $CDCl_3$ solutions.

Analytically pure material melted at 244–245°. (Found: C, 80·83; H, 9·29. Calc. for $C_{22}H_{30}O_2$: C, 80·93; H, 9·26%).

Estra-1,3,5(10), 9(11)-*tetraene*-17-*one*, (**5**)

(a) *With sulphuric acid.* Estrone (13·5 g), conc H_2SO_4 (37·5 ml) and n-pentane (200 ml) were stirred gently under N_2 at −10° while adamantanol (8·25 g, 1·08 mole equiv) was added over a 5 min period and stirring was then continued for 10 min after the completion of the addition. The mixture was poured onto stirred cracked ice and then extracted with chloroform. The chloroform extract, after washing with dil $NaHCO_3$aq and drying over $MgSO_4$, was evaporated to dryness and the solid residue triturated with several volumes of warm pentane to remove the adamantane. Multiple fractional crystallization from acetone produced three crops of the $\Delta^{9,11}$ compound (2·10 g), m.p. 254–258°; (0·75 g), m.p. 254–258°; (0·30 g), m.p. 252–256°. This product and estrone travel similarly in TLC but can be differentiated by spraying with acidic cobaltous chloride and heating; the former gives rise to a green spot and the estrone a pink one.

(b) *With fluosulfonic acid.* Estrone (5 g) was placed in a flask equipped with stirrer and pentane (125 ml) was added. The mixture was stirred and cooled to −20°. Then under a N_2 atmosphere, there was added fluosulfonic acid (25 ml) and then adamantanol (5 g), in portions. The reaction was stirred for 10 min and the pentane layer was decanted. The remaining thick red oil was poured into ice water. The resulting mixture was washed several times with CH_2Cl_2; the latter combined soln was washed with sat $NaHCO_3$aq and dried. After evaporation to dryness the residue was recrystallized from acetone to give the $\Delta^{9,11}$ compound (3·1 g), m.p. 252–257°; λ_{max}^{EtOH} 263 mμ (ε 18,200).

2-[*Adamantyl*-(1)]-*esterone*-3-*methyl ether*, (**6**). A soln of estrone 3-methyl ether (0·5 g), adamantanol (0·3 g) and pentane (11 ml) was cooled and then BF_3-etherate (0·75 ml) was added. The mixture was stirred in the cold for 5 min and at room temp for 45 min and poured onto crushed ice. After filtration the ppt was washed with pentane and recrystallized from acetone to give colorless crystals (0·31 g), m.p. 248–250°. (Found: C, 83·33; H, 9·28. Calc. for $C_{29}H_{38}O_2$: C, 83·21; H, 9·15%).

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