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Cycloaddition Route to 14-Hydroxymethyl-19-norprogesterone

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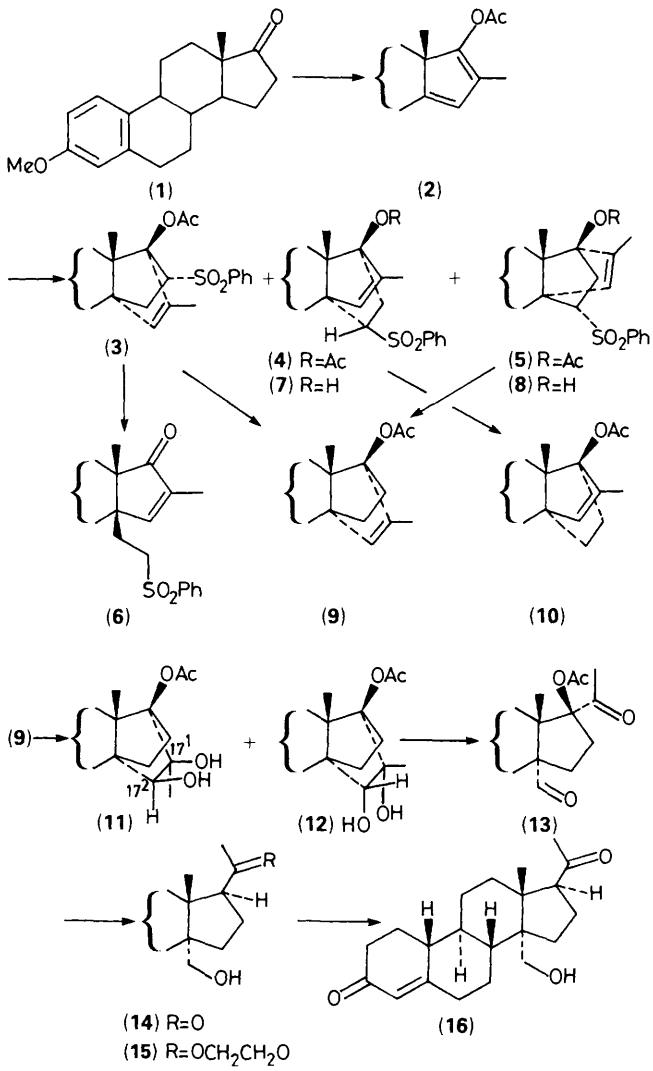
Diels–Alder reaction of 3-methoxy-16-methylestra-1,3,5(10),14,16-pentaen-17-yl acetate with phenyl vinyl sulphone affords three 14,17-cycloadducts, two of which are efficiently converted into 14-hydroxymethyl-19-norprogesterone.

An extension of the previously reported[1] cycloaddition approach to the synthesis of 14α-functionalised 19-norsteroids entails [4 + 2] cycloaddition of an ethylene equivalent to a 16-methyl-14,16-dien-17-yl acetate. It was expected that oxidative cleavage of the residual alkenic bond in such a cycloadduct would generate a 17-acetyl side chain, and thereby provide access to 14α-functionalised alkyl compounds in the 19-norpregnane series.

In pursuance of the objective, estrone 3-methyl ether (**1**) was converted into the desired starting material (**2**), through sequential α-methylenation, catalytic hydrogenation, bromination, dehydrobromination and enol acetylation.[2] Treatment of (**2**) in xylene with phenyl vinyl sulphone in a sealed tube at 140 °C for 120 h produced a three-component mixture (*ca.* 2.5 : 1 : 2.5, t.l.c.), from which the minor, relatively insoluble cycloadduct (**4**) (14%) of intermediate R_F was recovered directly as a crystalline product, m.p. 260–262 °C; $[\alpha]_D$ +103° (*c* 0.9, $CHCl_3$).† Chromatography of the mother liquor residue furnished the two remaining products (**3**) (*ca.* 38%), amorph.; $[\alpha]_D$ +60° (*c* 1.0, $CHCl_3$) and (**5**) (*ca.* 38%), amorph.; $[\alpha]_D$ +37°d (*c* 0.9, $CHCl_3$).

The n.m.r. spectroscopic properties of the cycloadducts demonstrated their gross structural similarity and the expected *endo*-orientation of the phenylsulphonyl group in each case, but failed to distinguish between the three of four possible isomers. However, one cycloadduct (**3**) underwent alkali-mediated cleavage to give the 14β-(2-phenylsulphonylethyl)-Δ^{15}-17-one (**6**), whereas (**4**) and (**5**) suffered only hydrolysis at the bridgehead under similar conditions, to give the respective alcohols (**7**) and (**8**). Furthermore, treatment of both (**3**) and (**5**) with sodium amalgam in tetrahydrofuran–methanol, at 0 °C for 4 h and 25 °C for 16 h, followed by reacetylation of the bridgehead hydroxy group, afforded the same product, 14,17α-etheno-3-methoxy-17[1]-methylestra-1,3,5(10)-trien-17β-yl acetate (**9**), m.p. 117—119 °C (from dichloromethane–methanol); $[\alpha]_D$ +87° (*c* 0.9, $CHCl_3$).



† All new compounds have been fully characterised and gave satisfactory microanalyses.

However, desulphonylation of (**4**) under similar conditions gave a complex mixture, which was chromatographically inseparable and showed n.m.r. spectral signals compatible with the presence of the 14β,17β-etheno compound (**10**) as a major component. Since subsequent transformations of (**9**) confirmed the assigned configuration of the etheno bridge, the regio- and stereo-chemistry of the three primary cycloadducts (**3**)—(**5**) was thus established.

This cycloaddition represents the first example of depressed regio- and stereo-selectivity in Diels–Alder reactions on steroidal 14,16-dienes.[1,3—5] It is evident that the 16-methyl group plays a decisive role in influencing the orbital coefficients of the substrate (**2**), and that the consequential *meta* regioselectivity is attended by a significant loss of β-face stereoselectivity. Nevertheless, the purpose in hand was well served by an overall conversion of the diene (**2**) into the desired 14α,17α-etheno compound (**9**) in *ca.* 60% yield.

Osmylation of compound (**9**), followed by reductive work-up gave a separable mixture (*ca.* 12 : 1) of the $17^1S,17^2S$- and $17^1R,17^2R$- diols (**11**) and (**12**) which were distinguished by distinctive n.m.r. spectroscopic properties. Thus the 17^2-proton of (**11**) appeared at δ 4.23 as a doublet (*J* 2.1 Hz, after D_2O exchange), owing to four-bond coupling with the favourably orientated 15β-proton (planar W-configuration), whereas the corresponding signal in (**12**) appeared as a singlet at δ 3.65. Furthermore, the proximity of the 17^2-*exo*-hydroxy group in (**12**) to the 9α-proton resulted in pronounced deshielding (δ 3.53) of that signal, in comparison with the analogous signal (δ 2.8) in (**11**).

Cleavage of the respective diols (**11**) and (**12**) with sodium periodate in aqueous ethanol gave 17β-acetoxy-3-methoxy-20-oxo-19-nor-17α-pregna-13,5(10)-triene-14-carbaldehyde (**13**) (95%), m.p. 212—223 °C (from ethyl acetate); $[\alpha]_D$ +3.5° (*c* 0.9, $CHCl_3$); δ 1.24 (3H, s, 18-H_3), 2.05 and 2.1 (each 3H, s, 17-OAc and 21-H_3), and 9.87 (1H, br.s, CHO), reduction of which with calcium in liquid ammonia–tetrahydrofuran resulted in 17-deacetoxylation and concomitant reduction of the 14-formyl group to give 14-hydroxymethyl-3-methoxy-19-norpregna-1,3,5(10)-triene-20-one (**14**), m.p. 155—156 °C (from ethyl acetate–hexane); $[\alpha]_D$ +158° (*c* 0.9, $CHCl_3$). The expected inversion at C(17) was verified by a circular dichroism (c.d.) spectrum, which displayed a Cotton effect ($\Delta\varepsilon_{max}$ +3.25 at 289 nm, in methanol) typical of 17β-acetyl steroids.[6]

Treatment of (**14**) with ethylene glycol and a catalytic amount of toluene-*p*-sulphonic acid in refluxing benzene for 8 h, with removal of water, afforded the labile 20,20-ethylenedioxy derivative (**15**), which was subjected to Birch reduction (lithium in liquid ammonia–tetrahydrofuran–t-butyl alcohol at −35 °C for 2.5 h), followed by hydrolysis and isomerisation in the presence of methanolic hydrochloric acid, to give 14-hydroxymethyl-19-norpregn-4-ene-3,20-dione (**16**) m.p. 198—200 °C (from chloroform–ethyl acetate); $[\alpha]_D$ +140° (*c* 0.5, $CHCl_3$); ν_{max} 3634(OH), 1700(20–CO), 1662(3–CO), and 1620(C=C) cm^{-1}. The chiroptical properties of (**16**) [$\Delta\varepsilon_{max}$ −1.69 (321 nm) and +3.14 (283 nm)] were comparable with those of 19-norprogesterone.

The method outlined here is clearly applicable in general to the synthesis of pregnane and 19-norpregnane analogues bearing 14α-hydroxymethyl functionality and, the unusual cycloaddition outcome notwithstanding, provides an efficient and simple route to this hitherto unknown series of compounds.

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