Total Synthesis of 3-Methoxy-7-oxaoestra-1,3,5(10),8,14-pentaen-17-one

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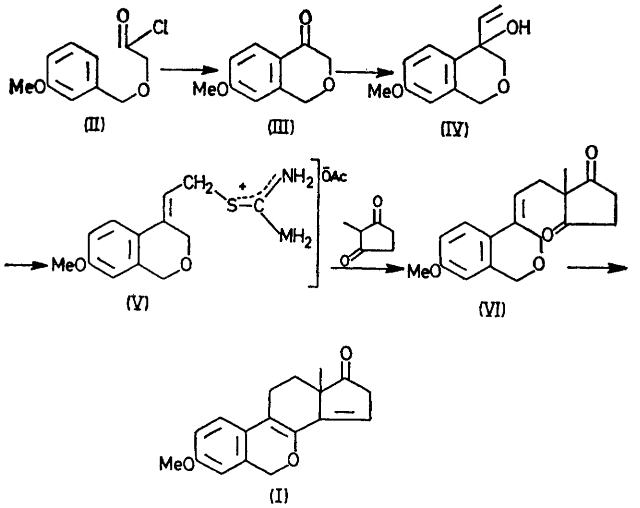
Summary The total synthesis of the title compound from 7-methoxyisochroman-4-one is described.

Recent reviews on oxasteroids[1] and on total syntheses of heterocyclic steroidal systems[2] mention that there has been no report on the total synthesis of 7-oxaestrone. This prompted us to report here a total synthesis of the title compound (I) (Scheme) starting from 7-methoxyisochroman-4-one (III).



Scheme

The sodio-derivative of *m*-methoxybenzyl alcohol[3] on treatment with ethyl bromoacetate in refluxing benzene gave ethyl *m*-methoxybenzyloxyacetate (40%). Alkaline hydrolysis of the acetate afforded *m*-methoxybenzyloxyacetic acid (68%). Attempts to cyclise this acid using Lewis acids were unsuccessful.[4] However, the acid chloride (II), on treatment with anhydrous $SnCl_4$ in benzene at 8—10°, gave the anticipated methoxyisochromanone (III) as pale yellow needles, m.p. 78—80° (30%). Treatment of the methoxyisochromanone (III) with vinylmagnesium bromide[5] gave the expected isochroman (IV) (90%) as a thick gum. Colonge and co-workers[6] have reported, in contrast, that 7-methylisochroman-4-one on treatment with methylmagnesium halide gave 2-(2-ethyl-4-methylphenyl)propane-1,2-diol (90%) instead of the normal Grignard product. Such a product was ruled out here where mass and n.m.r. spectra indicated the allyl alcohol (IV).

The allyl alcohol (IV) on treatment with thiourea in glacial acetic acid gave the desired isothiuronium acetate (V) as a white amorphous solid, m.p. 137—138° (60%). Treatment of the isothiuronium acetate (V) with 2-methylcyclopentane-1,3-dione gave compound (VI) as white crystals, m.p. 86—87° (73%). Cyclodehydration of the seco-oxasteroid (VI) with methanolic hydrochloric acid gave the title compound (I) as a light yellow solid, m.p.

143—144° (70%) M^+ 282 (100%); λ_{max} (MeOH) 320 nm (ϵ 13,170) and 221 nm (ϵ 12,330), $\nu_{C=O}$ ($CHCl_3$) 1730 cm^{-1}, δ ($CDCl_3$) 1·13 (s, 3H, CH_3), 1·49—1·96 (m, 2H, CH_2), 2·5—3·3 [m, 4H, CH_2 at C(11) and C(16)], 3·75 (s, 3H, OCH_3), 5·0 (s, 2H, benzylic CH_2), 6·07 (t, 1H, olefinic), and 6·58—7·3 (m, 3H, aromatic).

All new compounds mentioned above gave satisfactory u.v., i.r., n.m.r., mass spectral, and analytical results.

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