A Silyl Ether as a Protecting Group in the Synthesis of an Isomer of Ecdysone, 20*R*-Hydroxy-22-deoxyecdysone

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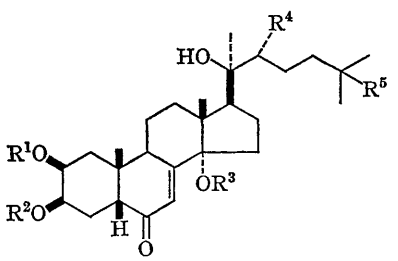
SYNTHESES of arthropod hormones and related compounds have so far been accomplished by the introduction of oxygen functions into less polar sterols.[1,2] However, the availability in quantity of compounds such as ponasterone A (I)[3] and crustecdysone (II)[4] from plants now permits syntheses by elimination of oxygen functions or structural modifications. This approach is exemplified by the synthesis of 2β,3β,14α,20*R*,25-pentahydroxy-5β-cholest-7-en-6-one (III, 20*R*-hydroxy-22-deoxyecdysone). The synthesis incorporates the novel and potentially useful application of a trimethylsilyl ether as a protecting group for sterically hindered hydroxy-groups.



(I) $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OH$
(II) $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = OH$
(III) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OH$
(IV) $R^1 = Ac$, $R^2 = R^3 = H$, $R^4 = R^5 = OH$
(V) R^1, $R^3 = >CMe_2$, $R^2 = SiMe_3$, $R^4 = H$, R^5 = *O*-tetrahydropyranyl

Crustecdysone 2-acetate (IV), m.p. 223—224°, prepared by selective acetylation of crustecdysone, was oxidized with periodic acid to 2β-acetoxy-3β,14α-dihydroxy-5β-pregn-7-ene-6,20-dione (VI) m.p. 247—248°. Mild hydrolysis of this acetate with potassium carbonate (0·05N) in aqueous methanol afforded the known ketone (VII)[5] in good yield. The corresponding acetonide (VIII), m.p. 183·5—184°, prepared with acetone and catalytic amounts of phosphomolybdic acid[6] was treated with bistrimethylsilylacetamide in dimethylformamide solution at 78° to give the silyl ether (IX).[7] This was treated, in tetrahydrofuran at 0°, with the Grignard reagent prepared from 5-chloro-2-methylpentan-2-ol tetrahydropyranyl ether (b.p. 127°/13 mm., n_D^{20} 1.4607),[8] and a small amount of ethylene dibromide.[9,10] The reaction product was treated with 0·1N-hydrochloric acid in 10% aqueous tetrahydrofuran at room temperature to remove the protecting groups. The silyl-ether group was hydrolysed at the slowest rate. Column chromatography of the product afforded 2β,3β,14α,20*R*,25-pentahydroxy-5β-cholest-7-en-6-one (III) in 25% yield [the yield was only 0—1% when (VIII) was alkylated without protection of the 14-hydroxy-group]. The analytical sample had m.p. 131—134° [λ_{max} (ethanol) 242 mμ log ε 4·17, ν_{max} (KBr) 1660 cm.$^{-1}$, R_F 0·17 in thin-layer chromatography using silica gel with chloroform–96% ethanol (80 : 20) as solvent, and grey-green spot with the vanillin–sulphuric acid spray reagent [11]].

As expected,[10,12] only one C-20 isomer was found and may be assigned the 20*R*-configuration from Cram's rule.[13] The structure of the product (III) follows from its mode of synthesis and is confirmed by spectral evidence. In its mass spectrum (III) has a molecular ion at *m/e* 464 and prominent ions at *m/e* 446, 428, and 410 indicating the loss of one to three molecules of water respectively, as in the case of ecdysone.[14] Fragmentation of the C-20–C-22 bond as in crustecdysone is indicated by the presence of ions at *m/e* 363 ($M-101$) and 345 ($M-101-18$).[15] However, the intensities of the peaks indicate that in the absence of a C-22 hydroxy-group, this process is less favoured. As expected from a study of the mass spectra of simple 20-hydroxy-steroids, side-chain cleavage at the C-17–C-20 bond, not observed in the spectrum of crustecdysone, is more favoured. Strong ions at *m/e* 145, 127, and 109 correspond to the side-chain fragment and fragments with further loss of one or two molecules of water, respectively. Ions at *m/e* 320 and 302 correspond to the tetracycle and this fragment with the further loss of one molecule of water respectively, the fragmentation being accompanied by hydrogen transfer, as in the case of the side-chain fragmentation of ecdysone.[14]

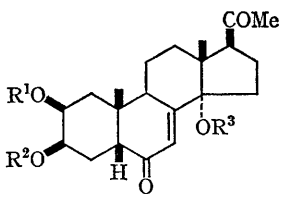
TABLE

Chemical shifts of methyl resonances (δ)

Compound	Solvent	C-18	C-19	C-21	C-26/27
20*R*-Hydroxy-22-deoxyecdysone (III)	C_5D_5N	1·14	1·06	1·54	1·35
Crustecdysone (II)	C_5D_5N	1·20	1·07	1·58	1·38
20*R*-Hydroxy-22-deoxyecdysone	CD_3OD	0·86	0·96	1·26	1·19
Crustecdysone	CD_3OD	0·88	0·95	1·19	1·19

The chemical shifts of the methyl resonances of 20*R*-hydroxy-22-deoxyecdysone (III) and crustecdysone (II) for deuteriopyridine and deuteriomethanol solutions are compared in the Table. From spectra obtained with mixtures of these solvents, it is evident that the relative positions of the signals given by the C-18 and C-19 methyl groups are interchanged when the spectra are measured in deuteriomethanol instead of deuteriopyridine.[16]

The biological activity of 20*R*-hydroxy-22-deoxyecdysone in the *Calliphora* test is only about one-fiftieth that of crustecdysone. The 22*R*-hydroxy-group is thus important for high biological activity, and more important than the 20*R*-hydroxy-group.



(VI) R^1 = Ac, R^2 = R^3 = H
(VII) R^1 = R^2 = R^3 = H
(VIII) R^1, R^2 = $>CMe_2$, R^3 = H
(IX) $R^1{}_5R$ = $>CMe_2$, R^3 = $SiMe_3$

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[16] In an earlier communication (M. N. Galbraith, D. H. S. Horn, E. J. Middleton, and R. J. Hackney, *Chem. Comm.*, 1968, 83), the C-18 and C-19 methyl resonances of deoxycrustecdysone and crustecdysone measured with deuteriomethanol solutions were incorrectly assigned.