

SYNTHESIS OF 1- α -VINYL-1- β -HYDROXY- β -OXO-7 α -METHYL-2, 3, 5, 6, 7, 7 α -HEXAHYDROINDENE

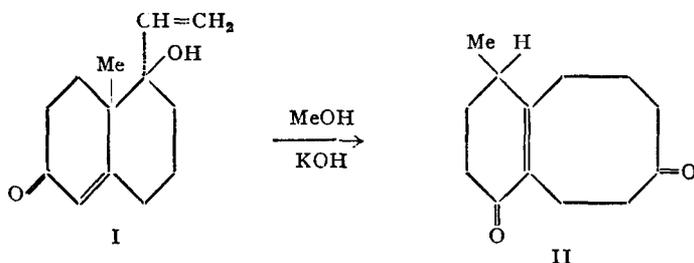
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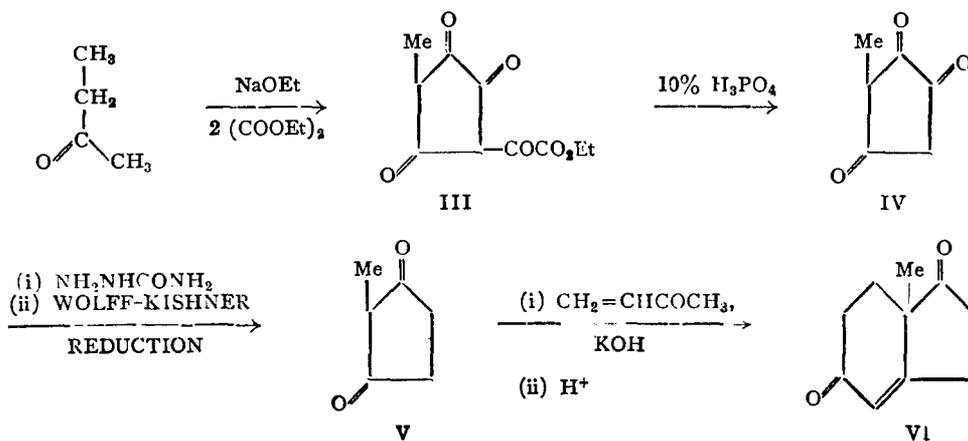
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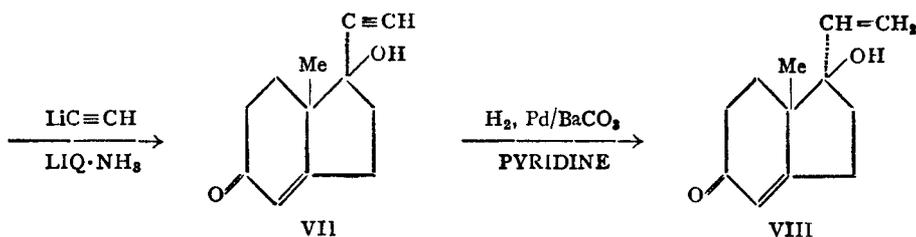
THE title compound (VIII) was required in connection with further studies of the ring enlargement recently reported by us¹ whereby the analogous compound I is smoothly rearranged to II in the presence of base.



Furthermore, compound VIII and its ethynyl precursor VII are useful intermediates for the synthesis of bicyclic analogs of steroid hormones lacking rings A and B.

Compound VIII has been synthesised as follows:





Boyce and Whitehurst² have reported an excellent method of preparation of VI made possible by improvements effected by them for the preparation of V which until then could be prepared by either poor or erratic methods.³⁻⁵ During the course of the present study, further improvements have been effected particularly in (a) the conversion of III to IV and (b) of IV to V. The use of 10% phosphoric acid for the cleavage of the ethoxalyl moiety in III and thorough extraction with ether of the residue rejected earlier³ as oxalic acid have increased the yield of IV to 85% (reported earlier³ as 59%). For the success of the conversion of IV to V, the conditions of formation of the mono-semicarbazone of IV are found to be critical, as was pointed out by Boyce and Whitehurst.² But the conditions worked out by them, though constituting an improvement on the earlier procedure,⁴ proved somewhat unsatisfactory since samples of "semicarbazone" thus prepared, quite often afforded us poor yields or none at all of the product V, after the Wolff-Kishner reduction. However, by adjusting the pH of the trione solution to about 5.4 before mixing with the semicarbazide reagent, the authentic semicarbazone of IV was obtained and could be invariably reduced to V without any difficulty. The need for adjusting the pH arises because the trione solution itself is acidic (pH 2.3) and under conditions of such acidity the trione, probably, forms with semicarbazide a salt along with or in place of the true semicarbazone. In the reduction step also, an improvement was made by the addition of one mole of water per mole of semicarbazone whereby yields varying between 65 and 75% of V were obtained (Reported² yield 51%).

The conversion of V to VI was carried out as described earlier² but without isolation of any intermediate. The reaction of VI, without protection of the 5-oxo group, with lithium acetylide in liquid ammonia at -70° afforded VII in 55% yield. There was no evidence of formation of the epimeric β -ethynyl alcohol in these experiments. The assignment of the β -hydroxy structure VII to our product is based on analogy to the addition of metal acetylides to 17-keto steroids⁶ and also to 1, 6-diketo-8 α -methyl-1, 2, 3, 4, 6, 7, 8, 8 α -octahydronaphthalene.⁷

Catalytic reduction of VII in pyridine solution in the presence of palladium on barium carbonate furnished VIII. The action of base on VIII is under study.

EXPERIMENTAL

2-Methylcyclopentane-1, 3, 4, trione (IV).—A solution of 2-methyl-5-ethoxalyl-cyclopentane-1, 3, 4-trione³ (III, 140 g.) in a mixture of water (630 ml.) and 85% phosphoric acid (70 ml.) was refluxed for 4 hours, cooled to -5° and filtered. The precipitate thus obtained was dried and extracted with ether. The ether extract when concentrated and cooled furnished 34 gm. of crude IV, m.p. $72-76^{\circ}$. An additional 55 g. of product was obtained by continuous ether extraction of the aqueous filtrate. Recrystallization of the combined material from water (110 ml.) gave 75 g. (83%) of the trione monohydrate, m.p. $75-76^{\circ}$.

The overall yield of IV from butanone-2 is only 31% if pure III is used in the above experiment. Since there is appreciable loss during crystallization of III from ethyl acetate, it is preferable to use crude III obtained in the condensation of diethyl oxalate with butanone-2. The overall yield of IV is then raised from 39 to 44%.

2-Methyl-1, 3-cyclopentanedione (V).—To a solution of IV (75 g.) in ethanol (500 ml.) and water (250 ml.) was added sodium acetate (75 g.) to raise the pH to about 5.4. Some insoluble precipitate (15 g.) which was formed was rejected by filtration. To the well-stirred filtrate was added at 30° during one hour a solution of semicarbazide hydrochloride (56 g.) and sodium acetate (75 g.) in water (125 ml.). After stirring for a further one hour, the cream-yellow semicarbazone was collected, washed with aqueous ethanol and dried *in vacuo* (yield 75 g.). To a stirred solution of potassium hydroxide (115 g.) in ethylene glycol (1150 ml.) at 130° was added water (12 ml.) followed by the semicarbazone (115 gm.) in portions over half an hour. The solution was then heated at 150° for half an hour and at $180-190^{\circ}$ for two hours. The solvent was removed *in vacuo* (1–2 mm.), the residue dissolved in 300 ml. of water and then acidified with concentrated hydrochloric acid. The crude brown precipitate was collected and crystallized from a mixture of ethanol (150 ml.) and water (250 ml.) after charcoal treatment to give two crops amounting to 53 g. (75% yield), m.p. $207-09^{\circ}$. The yields varied from 65 to 75% in different runs.

1- α -Ethynyl-1- β -hydroxy-5-oxo-7 α -methyl-2, 3, 5, 6, 7, 7 α -hexahydroindene (VII).—A solution of VI (5 g.) in dry ether (100 ml.) was added over 5 minutes to a stirred solution of lithium acetylide (prepared from 0.35 g. of lithium) in liquid ammonia (200 ml.) kept cooled in a dry ice-acetone bath

1- α -Vinyl-1- β -hydroxy-5-oxo-7 α -methyl-2, 3, 5, 6, 7, 7 a-hexahydroindene 47

while maintaining a slow stream of acetylene through the reaction mixture. Stirring was continued for another 20 minutes and the reaction mixture then decomposed with saturated ammonium chloride solution. The ether layer was separated and mixed with a further chloroform extract of the aqueous solution. The combined extracts were neutralized with dry ice, washed with a little water and dried (MgSO_4). The solvent was removed and the crude product crystallized from ethyl acetate to furnish colourless crystals of VII (3.2 g., 55% yield), m.p. 129.5–130.5° $\lambda_{\text{max}}^{\text{EtOH}}$ 241 m μ , $\log_{10}E$, 4.16. I.R. absorption (CHCl_3) at 2.95 μ , 4.7 μ and 6.0 μ . Calculated for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.8; H, 7.4. Found: C, 75.9; H, 7.1.

1- α -Vinyl-1- β -hydroxy-5-oxo-7 α -methyl-2, 3, 5, 6, 7, 7 a-hexahydroindene (VIII).—Compound VII (1 g.) was hydrogenated at 50 p.s.i. with Pd-BaCO_3 in pyridine (20 ml.) solution for half-an-hour. The catalyst was filtered off and pyridine removed *in vacuo*. The residue was dissolved in ether, treated with charcoal and filtered. The filtrate was concentrated, diluted with petroleum ether (30–60°) and chilled to furnish colourless crystals of VIII (0.7 g.), m.p. 104.5–105° C. Calculated for $\text{C}_{12}\text{H}_{16}\text{O}_2$: C, 75.0; H, 8.3. Found: C, 74.9; H, 8.0 $\lambda_{\text{max}}^{\text{EtOH}}$ 243 m μ , $\log_{10}E$, 4.13. I.R. Absorption (CHCl_3) at 2.9 μ , 6.03 μ and 10.8 μ .

SUMMARY

The synthesis of the title compound (VIII) by selective ethynylation of 1, 5-Dioxo-7 α -methyl-2, 3, 5, 6, 7, 7 a-hexahydroindene (VI) followed by reduction is described.

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