Labeling of Steroids in the 4-Position[1]

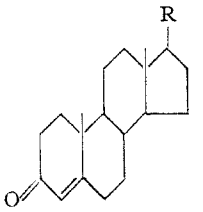
BY GEORGE I. FUJIMOTO

Turner's method[2] for the introduction of isotopic carbon into ring A of cholestenone and testosterone has made available steroids labeled in the nucleus by chemical synthesis. A modification of his method whereby the labeled carbon is introduced in the 4-position of these steroids through the use of methyl Grignard reagent is simpler and milder and gives higher yields.

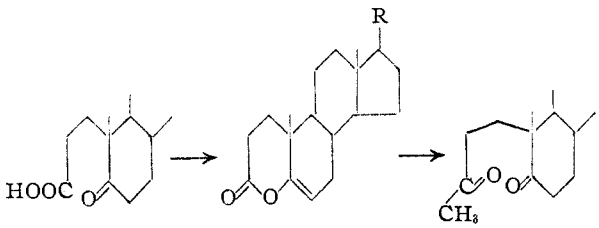
We have found that by adding methylmagnesium iodide to an equivalent amount of Turner's enol lactone (IIIa), the intermediate (possible structure IV) may be isolated in 45–65% yield. Alkali treatment of IV gave cholestenone (Ia). Over-all yield without isolation of the intermediate was 52–60%.

This modification was applied to testosterone. The methyl Grignard reagent was added to the enol lactone (IIIb) prepared from testosterone acetate (Ib) by methods identical with those developed by Turner for the synthesis of the enol lactone from testosterone benzoate.[2] The acetate was chosen because of greater solubility in ether. After cyclization in alkali, testosterone (Ic) was obtained in an over-all yield of 25–50%.

Work with other steroids and with C-14 methyl iodide using the above procedures is now in progress.



Ia, R = C_8H_{17}
Ib, R = $OCOCH_3$
Ic, R = OH



II IIIa, R = C_8H_{17} IIIb, R = $OCOCH_3$ IV

Ia or Ib

Experimental

Procedure for Cholestenone.—Methylmagnesium iodide prepared from 142 mg. (1 mmole) of methyl iodide was added slowly dropwise with stirring to a solution of 386 mg. (1 mmole) of the enol lactone (IIIa, recrystallized from Skellysolve B, m.p. 93.5–94.5°) in 3 ml. of ether under nitrogen and cooled to 0°. After the addition the solution was let stand in the cold for 20 hours, then decomposed with 3 ml. of saturated ammonium chloride solution. A crude mixture was obtained from the ether solution after washing with dilute sodium carbonate and water. The intermediate IV was isolated after repeated crystallization from acetone, colorless plates, m.p.[3] 174–178°, yield 45–65%. *Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.34; H, 11.66.

The crude mixture from the Grignard reaction was stirred in 30 ml. of methanol, 5 ml. of water, and 1 g. of sodium hydroxide and let stand 24 hours with occasional stirring. After removal of methanol and washing with alkali there was obtained the crude cholestenone. Purification by chromatography over alumina yielded two fractions, the first from petroleum ether–benzene, 9:1, with m.p. 80–82°, and the second from petroleum ether–benzene, 4:1, m.p. 86–88°. The melting point of either was not depressed when mixed with an authentic sample of cholestenone.[4] The infrared spectra of the three samples were identical. The yield of Ia without isolation of IV was 52–60% (based on IIIa or on methyl iodide).[5]

When a portion of the intermediate (IV) was treated with methanolic alkali, there was obtained cholestenone, m.p. 77–81°. There was no depression in melting point when mixed with an authentic sample.

Procedure for Testosterone.—The enol lactone from testosterone acetate was prepared by a procedure patterned after Turner.[2] On ozonization of testosterone acetate (Ib) the keto acid (II) was isolated in 76% yield, colorless needles from dilute acetone, m.p. 138.5–139.5°. *Anal.* Calcd. $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.77. Lactonization of II yielded the corresponding enol lactone (IIIb) (78%), m.p. 129–133°. *Anal.* Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.10; H, 8.33.

The Grignard reaction with 332 mg. (1 mmole) of the enol lactone by a procedure essentially identical to the one mentioned above was followed by cyclization in alkali to give testosterone (Ic) without isolation of the intermediate substance. The product was purified by chromatography on alumina and 145 mg. (50% based on IIIb and on methyl iodide, the isotopically labeled reagent) colorless plates from acetone, m.p. 150–154° was obtained. Recrystallization from acetone gave a sample melting at 154–155°. Mixed melting points with an authentic sample of testosterone showed no depression. Infrared absorption spectra were identical.

(1) This work was supported in part by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council, and by the National Cancer Institute of the National Institute of Health, U. S. Public Health Service.

(2) R. B. Turner, THIS JOURNAL, **72**, 579 (1950).

(3) All melting points were taken on a Kofler micro hot-stage and have been corrected.

(4) D. H. R. Barton and E. R. H. Jones, *J. Chem. Soc.*, 602 (1943).

(5) This procedure has been repeated by Dr. W. G. Dauben of the University of California who reported a 55% yield of cholestenone.

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RECEIVED JANUARY 29, 1951

β,β-Di-(*p*-chlorophenyl)-ethanol

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The miticidal activity of di-(*p*-chlorophenyl)-methylcarbinol (DMC)[1] suggests the synthesis of many related compounds in a study to correlate structure and activity. One of the most interesting is the isomeric primary alcohol, β,β-di-(*p*-chlorophenyl)-ethanol.

The first synthesis tried was the simultaneous formation of *p,p'*-dichlorobenzhydrylmagnesium chloride and the addition of formaldehyde to the mixture, along the line of previous work on benzhydrylmagnesium chloride which showed that the formation of the Grignard reagent *alone* gave the coupled product, *sym*-tetraphenylethane, but that simultaneous addition of a reactant for the reagent would give moderate yields of the expected product.[2] This failed to give the desired ethanol; the major product was *sym*-tetra-(*p*-chlorophenyl)-ethane.

(1) O. Grummitt, *Science*, **111**, 2884 (1950).

(2) H. Gilman and R. McCracken, THIS JOURNAL, **45**, 2462 (1923).