Labeling of Steroids in the 4-Position[1]

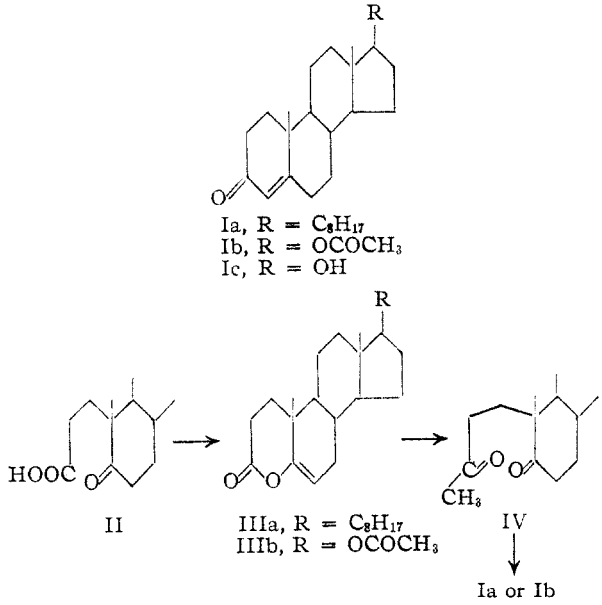
BY GEORGE I. FUJIMOTO

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.



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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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).

The reducing action of *t*-butylmagnesium chloride[3] on di-(*p*-chlorophenyl)-acetyl chloride did give the ethanol as a colorless crystalline solid, m.p. 98.5–99.5°, in 27% yield

$$(p\text{-}ClC_6H_4)_2CH\text{—}COCl + 2t\text{-}C_4H_9MgCl \longrightarrow (p\text{-}ClC_6H_4)_2CH\text{—}CH_2OMgCl + 2i\text{-}C_4H_8 + MgCl_2$$

Acid-catalyzed dehydration of the ethanol was accompanied by rearrangement and the product was *p,p'*-dichlorostilbene. Both DMC and the new isomer (*i*-DMC) have an ultraviolet absorption maximum at 226 mμ; the primary alcohol absorbs more strongly (Table I).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF DMC AND *i*-DMC[a]

Wave length (mμ)	Specific extinction DMC	Specific extinction *i*-DMC
220	79.0	77.0
226	80.0	91.3
230	67.0	87.5
234	34.0	39.4
240	10.8	8.2
250	3.0	4.3
270	2.5	5.8

[a] Determined in isoöctane solution with a Beckman model DU ultraviolet spectrophotometer.

Insecticidal tests with red spiders, two spotted mites, house flies, German roaches, webbing clothes moths, pea aphids, milkweed bugs, Southern armyworms and Mexican bean beetle larvae showed low or no activity for the β,β-di-(*p*-chlorophenyl)-ethanol.[4] Therefore, a necessary structural feature for activity in the DMC type of compound is probably the oxidized tertiary carbon atom in the diarylalkylmethane: $Ar_2C(OH)R$.

Experimental

***p,p'*-Dichlorobenzhydrylmagnesium Chloride Plus Formaldehyde.**—A solution of 27.0 g. (0.1 mole) of di-(*p*-chlorophenyl)-chloromethane[5] in 150 ml. of ether was added to 2.4 g. (0.1 atom) of magnesium and 40 ml. of ether in the usual three-necked flask apparatus during one hour while a stream of formaldehyde was led to the surface of the Grignard reagent. Formaldehyde was generated from 15 g. (0.5 mole formaldehyde) of trioxane (du Pont) and 0.75 g. of anhydrous zinc chloride by heating the mixture at 80–85° in a stream of dry nitrogen. After the addition of the chloride and formaldehyde the mixture was stirred for one hour and then hydrolyzed with 25 g. of ammonium chloride in 150 ml. of ice and water. Collecting the precipitate and washing with water gave 10 g. (40% yield) of *sym*-tetra-(*p*-chlorophenyl)-ethane, which decomposed at 300–325° with the formation of a red color.[5] The ether layer from the hydrolysis gave some unreacted chloride and *p,p'*-dichlorobenzhydrol, but no *i*-DMC could be isolated.

β,β-Di-(*p*-chlorophenyl)-ethanol.—*i*-Butylmagnesium chloride in ethyl ether (2.3 molar) was made in 77% yield.[6] This was diluted with ether to give 150 ml. containing 0.23 mole, placed in the usual three-necked flask apparatus, and 14.6 g. (0.049 mole) of di-(*p*-chlorophenyl)-acetyl chloride[7] in 75 ml. of ether was added during 2.5 hours while the reaction mixture was gently refluxed. After 0.5 hour additional refluxing the ether solution was hydrolyzed with 13.5 g. of ammonium chloride in 150 ml. of ice and water. The ether layer yielded 11.5 g. of waxy solid which on crystallization from benzene gave 5.1 g. (39%) of crude ethanol melting 93–95°. Several crystallizations from benzene–Skellysolve B and finally from alcohol–water raised the melting point to 98.5–99.5°.

Anal. Calcd. for $C_{14}H_{12}Cl_2O$: Cl, 26.6; OH, 6.35. Found: Cl, 26.4; OH, 6.18.[8]

Di-(*p*-chlorophenyl)-acetyl chloride was previously reported as an oil which did not crystallize at 0° and which decomposed on vacuum distillation at 3–4 mm.[7] The material used here melted 34.5–35.0° as the result of purifying by high vacuum distillation (140–150° at 0.1 mm.) from a short path pot still and washing the partially solidified distillate with Skellysolve A. Crystallization from the filtrate gave additional solid. The total recovery of purified acid chloride from the crude was about two-thirds which melted above 28°.[9]

Anal. Calcd. for $C_{14}H_9Cl_3O$: Cl, 35.4. Found: Cl, 35.0.

The 3,5-dinitrobenzoate derivative of *i*-DMC was made in pyridine from 3,5-dinitrobenzoyl chloride in the usual way[10]; m.p. 149–150°.

Anal. Calcd. for $C_{21}H_{14}Cl_2N_2O_6$: N, 6.08. Found: N, 5.82.

***p,p'*-Dichlorostilbene from β,β-Di-(*p*-chlorophenyl)-ethanol.**—A mixture of 50 mg. of the ethanol and 50 mg. of sodium bisulfate was heated in a microsublimation apparatus for 10 hours at 110–130°. When a vacuum of 1 mm. was applied, 20 mg. of crude product sublimed. Crystallization from ethanol gave 10 mg. (20%) melting 173–174°. A mixed melting point with authentic *p,p'*-dichlorostilbene gave 170–173°.

Refluxing a solution of 0.1 g. of ethanol and 0.5 g. of phosphorus pentoxide in 5 ml. of benzene for one hour, washing with water and evaporating the benzene failed to effect dehydration.[11]

The authentic stilbene was made by the thermal decomposition of di-(*p*-chlorophenyl)-fumarate at 250–255°. After 18 hours heating carbon dioxide was no longer given off. Crystallization from ethanol gave a product melting 172–173°.[12]

Di-(*p*-chlorophenyl)-fumarate, m.p. 174–176°, was made from *p*-chlorophenol and fumaryl chloride.[13]

(3) F. C. Whitmore, *et al.*, THIS JOURNAL, **63**, 643 (1941).

(4) George S. Kido, unpublished results, Wisconsin Alumni Research Foundation, Madison, Wisconsin.

(5) P. J. Montagne, *Rec. trav. chim.*, **25**, 379 (1906).

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(7) O. Grummitt and D. Marsh, *ibid.*, **71**, 4156 (1949).

(8) M. Freed and A. M. Wynne, *Ind. Eng. Chem., Anal. Ed.*, **8**, 278 (1936).

(9) D. Marsh of this Laboratory carried out the purification.

(10) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 165.

(11) M. S. Kharasch and H. G. Clapp, *J. Org. Chem.*, **3**, 355 (1938).

(12) R. Kade, *J. prakt. Chem.*, [2] **19**, 461 (1879).

(13) R. Anschutz, *Ber.*, **60**, 1320 (1927).

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Preparation of Some Aromatic Sulfonyl Fluorides

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The method reported by Ferm and VanderWerf[1] for the synthesis of aromatic sulfonyl fluorides[2] by addition of sodium nitrite to a solution of the corresponding sulfonamide in anhydrous hydrogen fluoride has been extended by the preparation of the following compounds in the yields indicated: benzenesulfonyl fluoride (53%), *m*-nitrobenzenesulfonyl fluoride (64%) and *o*-toluenesulfonyl fluoride (78%).

Attempted preparation of acyl fluorides by the same method was unsuccessful, only starting amide

(1) R. L. Ferm and C. A. VanderWerf, THIS JOURNAL, **72**, 4809 (1950).

(2) These compounds, as well as acyl fluorides, are usually prepared by treatment of the corresponding chlorides with fluorosulfonic acid or with aqueous solutions of inorganic fluorides. See W. Steinkopf, German Patent 497,242, Feb. 22, 1927 [*C. A.*, **24**, 3516 (1930)]; W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931); A. I. Mashentsev, *J. Applied Chem. (U. S. S. R.)*, **20**, 854 (1947).