

## Chromium Trichloride Tetrahydrofuranate<sup>1</sup>

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The reaction of anhydrous chromium trichloride and phenylmagnesium bromide in ether<sup>2</sup> or in tetrahydrofuran<sup>3</sup> is necessarily a heterogeneous one owing to the extreme insolubility of this metallic halide in organic solvents. Inorganic salts of chromium are in fact generally insoluble in all non-hydroxylic solvents; and this property presents difficulties in promoting their reactions in organic solvents with organic reagents. We have now found that the trichloride may be made soluble by complexing it with tetrahydrofuran and that its reactions with Grignard reagents proceed rapidly, quantitatively, and homogeneously in this form.

The conversion of anhydrous chromium trichloride into its tetrahydrofuranate is achieved by the continuous extraction with anhydrous tetrahydrofuran of its solid form admixed with catalytic amounts of zinc dust. In this manner the halide is quantitatively extracted by the solvent from which the violet tetrahydrofuranate is crystallized. The zinc metal which is recovered unchanged is considered to behave as a reducing agent, solubilizing chromium in its divalent form, followed by subsequent reduction itself and concurrent formation of  $\text{CrCl}_2(\text{THF})_3$ .<sup>4</sup> The coordinating tetrahydrofuran molecules are very tightly bound in the complex, for they are not lost even upon heating of the complex to 100° at 20 mm., and the tetrahydrofuranate may be kept in the open air several hours without appreciable hydrolysis, since the crystals are only slightly hygroscopic and deliquesce quite slowly to a green hydrate. Consequently, as a reagent it may be stored indefinitely without decomposition so long as it is kept dry.

### EXPERIMENTAL

**Chromium trichloride tri-tetrahydrofuranate.** The tetrahydrofuran (Mathieson, Coleman and Bell, b.p. 64–66°) used in this preparation was purified and dried by refluxing over sodium ribbon with fresh ribbon being added until new ribbon maintained a clean surface after 5 hr. of refluxing. Just prior to use the THF was distilled, treated with fresh sodium ribbon and with lithium aluminum hydride, and then redis-

(1) Paper VI, " $\pi$ -Complexes of the Transition Metals"; Paper V, H. H. Zeiss and W. Herwig, *J. Am. Chem. Soc.*, **80**, 2913 (1958).

(2) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, **79**, 3062 (1957).

(3) W. Herwig and H. H. Zeiss, *J. Am. Chem. Soc.*, **79**, 5959 (1957).

(4) This phenomenon has been observed previously in that chromous chloride will cause the trichloride to dissolve in ether: N. V. Sidgwick, *The Chemical Elements and Their Compounds*, Oxford Univ. Press, New York, N. Y., 1950, p. 1012.

tilled in a stream of dry, oxygen-free nitrogen (GE lamp grade is suitable for this purpose without further drying and/or purification).

Anhydrous chromium trichloride (Fisher), 12.21 g., mixed with 0.15 g. of zinc dust, is placed in the thimble of a Soxhlet extraction apparatus and then extracted overnight with 140 ml. of boiling THF or until no further color is observable in the cycling liquid (10–15 hr.). After complete extraction only zinc dust remains in the extraction thimble, while the pot flask contains the solution of the tetrahydrofuranate (2.8 g./100 ml. of hot THF) together with the crystalline chromium trichloride tri-tetrahydrofuranate which has crystallized during extraction. Concentration, cooling, and filtration are employed to isolate the crystalline form in essentially quantitative yield.

*Anal.* Calcd. for  $\text{CrCl}_3(\text{C}_4\text{H}_8\text{O})_3$ : Cr, 13.88; Cl, 28.39. Found: Cr, 13.42; Cl, 28.57, 28.19.

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## Preparation of a New Class of Steroids with Unnatural Configuration. The 19-Nor-5 $\alpha$ ,10 $\alpha$ Series

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There are four possible steric arrangements of the A/B rings of the 19-nordihydrosteroid nucleus (the *trans-syn-trans* conformation requires a boat form for ring B), all other centers of asymmetry being kept constant. The allo configurational series (5 $\alpha$ ,10 $\beta$ ) was reported by Bowers, Ringold, and Dorfman<sup>1</sup> while the normal series (5 $\beta$ ,10 $\beta$ ) was described recently from this Laboratory.<sup>2</sup>

This communication reports the synthesis of a third and hitherto unknown series of 19-norsteroids, and evidence is presented which permits assignment of structure and classification as 19-nor-5 $\alpha$ ,10 $\alpha$ -dihydrosteroids.

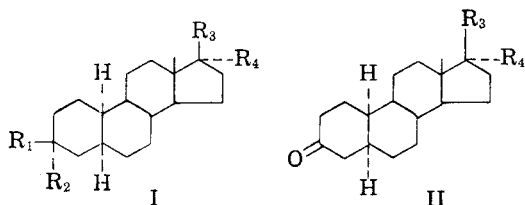
Hydrogenation of 17 $\alpha$  - ethinyl - or 17 $\alpha$  - ethyl-17 $\beta$  - estradiol with ruthenium dioxide catalyst at elevated pressures afforded a crystalline product, 17 $\alpha$ -ethyl-5 $\alpha$ ,10 $\alpha$ -estrane-3 $\beta$ ,17 $\beta$ -diol (Ia) (m.p. 143–145°;  $[\alpha]_D^{25}$  –20.9° (CHCl<sub>3</sub>). Found for C<sub>20</sub>H<sub>34</sub>O<sub>2</sub> · C, 78.11; H, 11.27) in excellent yield. Oxidation of this diol with chromic anhydride - pyridine gave 17 $\alpha$ -ethyl-5 $\alpha$ ,10 $\alpha$ -estrane-17 $\beta$ -ol-3-one (IIa) (m.p. 205–207°;  $[\alpha]_D^{25}$  –66.4°. Found for C<sub>20</sub>H<sub>32</sub>O<sub>2</sub>: C, 78.67; H, 10.99).<sup>3</sup> Sodium and pro-

(1) A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, **79**, 4556 (1957).

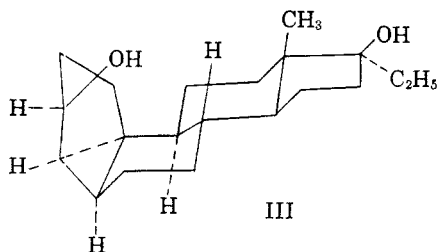
(2) R. T. Rapala and E. Farkas, *J. Am. Chem. Soc.*, **80**, 1008 (1958).

(3) All melting points are uncorrected. We gratefully acknowledge valuable technical assistance by Messrs. W. Scanlon, hydrogenation experiments; Messrs. G. M. Maciak, W. L. Brown, and H. L. Hunter, elemental analysis. All rotations are done in methanol unless otherwise specified.

panol reduction of this ketone furnished 17 $\alpha$ -ethyl-5 $\alpha$ ,10 $\alpha$ -estrane-3 $\alpha$ ,17 $\beta$ -diol (Ic) (m.p. 221–223°. Found for C<sub>20</sub>H<sub>34</sub>O<sub>2</sub>: C, 77.93; H, 11.50) (3-monoacetate, m.p. 146–147°;  $[\alpha]_D^{25}$  –30.1°. Found for C<sub>22</sub>H<sub>36</sub>O<sub>3</sub>: C, 75.59; H, 10.23) while reduction with sodium borohydride gave the original diol (Ia) (3-monoacetate, m.p. 126–127°. Found for C<sub>22</sub>H<sub>36</sub>O<sub>3</sub>: C, 75.48; H, 10.34).



- (a) R<sub>1</sub> = R<sub>3</sub> = OH, R<sub>2</sub> = H  
R<sub>4</sub> = C<sub>2</sub>H<sub>5</sub>  
(b) R<sub>1</sub> = R<sub>3</sub> = OH,  
R<sub>2</sub> = R<sub>4</sub> = H  
(c) R<sub>2</sub> = R<sub>3</sub> = OH, R<sub>1</sub> = H  
R<sub>4</sub> = C<sub>2</sub>H<sub>5</sub>  
(a) R<sub>3</sub> = OH, R<sub>4</sub> = C<sub>2</sub>H<sub>5</sub>  
(b) R<sub>3</sub>, R<sub>4</sub> = O  
(c) R<sub>3</sub> = COCH<sub>3</sub>, R<sub>4</sub> = H  
(d) R<sub>3</sub> = OH, R<sub>4</sub> = H



These assignments are supported by the following considerations: (a) Assuming a single period of adsorption, catalytic hydrogenation of the benzenoid ring<sup>4</sup> would allow for only two stereochemical products, 5 $\beta$ ,10 $\beta$  and 5 $\alpha$ ,10 $\alpha$ . (b) Reduction of ketone IIa with sodium - alcohol gave the more stable 3 $\alpha$ -alcohol with the equatorial configuration. This is borne out by the fact that the 3 - monoacetate of this diol shows the simple infrared band in the 8 $\mu$  region typical of equatorial acetoxy steroids.<sup>5</sup> (c) Furthermore, the 3 - monoacetate derived from the borohydride reduced ketone and the original diol (Ia) shows a complex band indicative of axial orientation. (d) The rotatory dispersion curve of ketone IIa is distinctive and quite different from the curves of the 3-keto allo-

and the normal estrane series.<sup>2</sup> Using an all chair conformation these results are consistent only with structure III involving an unnatural configuration at C<sub>10</sub><sup>6</sup> for the diol Ia.

High yields of 5 $\alpha$ ,10 $\alpha$ -estrane-3 $\beta$ ,17 $\beta$ -diol (Ib) (m.p. 179–181°. Found for C<sub>18</sub>H<sub>30</sub>O<sub>2</sub>: C, 77.95; H, 11.09) were obtained from similar hydrogenations (RuO<sub>2</sub>) of estrone,  $\beta$ -estradiol or  $\Delta^{5:10}$ -estrane - 17 $\beta$  - ol - 3 - one. Oxidation with *N*-bromoacetamide gave the corresponding dione, 5 $\alpha$ ,10 $\alpha$ -estrane-3,17-dione (IIb) (m.p. 163–165°;  $[\alpha]_D^{25}$  +27.5° (dioxane). Found for C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>: C, 78.66; H, 9.78).

Reduction of 3-hydroxy-17 $\beta$ -acetyl-1,3,5-estratriene gave a diol which upon oxidation yielded the related 5 $\alpha$ ,10 $\alpha$ -dione (IIc) (m.p. 140–142°;  $[\alpha]_D^{25}$  –1.0° (CHCl<sub>3</sub>). Found for C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>: C, 79.22; H, 10.19).

Selective ketalization<sup>7</sup> of diones IIb and IIc followed by reduction and then hydrolysis gave 5 $\alpha$ ,10 $\alpha$ -estrane-17 $\beta$ -ol-3-one (IIId) (m.p. 192–194°;  $[\alpha]_D^{25}$  –31.1°. Found for C<sub>18</sub>H<sub>28</sub>O<sub>2</sub>: C, 77.95; H, 10.28) and 5 $\alpha$ ,10 $\alpha$ -19-norpregnan-20 $\beta$ -ol-3-one (m.p. 152–154°). Found for C<sub>20</sub>H<sub>32</sub>O<sub>2</sub>: C, 79.02; H, 10.88.

The rotatory dispersion curves<sup>8</sup> of the 3-mono-ketone derivatives are essentially identical. They differ, however, from the curves of the 3-keto, *cis* A/B (5 $\beta$ ,10 $\beta$ ) and the *trans* A/B (5 $\alpha$ ,10 $\beta$ ) steroids as well as from the curves of lumistanone A, B, and C.<sup>9</sup>

The results of hydrogenations of 11-oxygenated 1,3,5-estratrienes, equilenin and ring B aromatic steroids to complete the series of 5 $\alpha$ ,10 $\alpha$  analogs of the major classes of natural steroids will be reported shortly.

*Added in proof.* Careful R. D. determinations of these 3-keto-5 $\alpha$ ,10 $\alpha$ -steroids in methanol, 2-propanol and dioxane confirmed the absence of any Cotton-effect while infrared analysis in methanol showed intense carbonyl absorption. Thus, this is the first example of a monoketosteroid containing the usual asymmetric centers which lacks the Cotton-effect commonly occurring in rotatory dispersion studies.

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(7) E. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6114 (1954).

(8) Kindly performed by M. Marsh and J. Carson of these Laboratories. Duplicate curves were obtained from two samples submitted for comparison to Wayne State University through the courtesy of Dr. E. J. Eisenbraun.

(9) We are indebted to Drs. E. R. H. Jones, G. Meakins, and C. Djerassi for making the curves available to us prior to publication.

(4) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

(5) D. H. R. Barton, *J. Chem. Soc.*, 1036 (1953).

(6) The only reported unnatural configurations at C<sub>10</sub> are the C<sub>10</sub>—CH<sub>3</sub> isomers, lumisterol and pyrocalciferol, and their reduced products. For leading references, see I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J. Chem. Soc.*, 869 (1938); J. Castells, E. R. H. Jones, R. W. J. Williams, and G. Meakins, *Proc. Chem. Soc.*, 7 (1958).