*Solution:* Solutions of vinyl azide in methanol (about 1 ml. in 3 ml.) containing *ca.* 3 mg. of azobisisobutyronitrile were heated for from 1 to 24 hr. at temperatures of from 50–75° in screw cap vials. The vials were cooled, opened, and the solution evaporated to dryness. The white flakes of polymer were soluble in methanol but insoluble in water. The yields of polymer were under 5%.

*Suspension:* Exploratory attempts to polymerize vinyl azide by suspension techniques in water by the usual techniques gave no polymer.

*Emulsion:* Emulsion polymerizations with a standard recipe[2b] of ammonium persulfate 0.5%, sodium lauryl sulfate 10%, and sodium bisulfite 0.2% in water acidified to *p*H 2 with acetic acid, gave only small yields of polymer at temperatures of from 50 to 75° and times of 1 to 24 hr. The amount of polymer in all cases was very small and did not seem to increase in quantity after the first few hours. The vinyl azide was never completely reacted.

*Bulk:* Bulk polymerizations were run using benzoyl peroxide or azobisisobutyronitrile as initiators in concentrations of 0.1 to 1%. At temperatures of 50–70° yields of less than 5% were obtained. Temperatures over 70° caused decomposition of the vinyl azide as evidenced by brown coloration. This decomposition was very rapid at 100°.

The polymer obtained in the polymerizations listed above was a white, flaky, apparently infusible solid. It burned furiously when held to a flame and decomposed violently when touched with a hot wire. Such combustibility makes carbon-hydrogen analysis impossible. Nitrogen analyses, which are notoriously untrustworthy for polymers, were also not attempted. As a result, no ultimate analytical data are available to characterize the polymer. It is to be noted that polymers obtained in such low yield may very well include fragments from the initiator as a significant portion of their composition.

In all polymerizations a large part of the vinyl azide was converted into higher boiling liquids which were always completely water soluble. No 1,2,3-triazole was ever detected although sensitive methods were used to detect it.

In polymerizations run at temperatures over about 70° ammonium azide crystals formed on the upper wall of the vials. This is a known decomposition product[3] of hydrazoic acid. If vinyl azide cleaves above 70° into hydrazoic acid, the other product would probably be acetylene but that has not been detected.

*Acknowledgment.* This research was completed under Contract DA-33-008 ord-734 between the Office of Ordnance Research and the University of Louisville. The authors gratefully acknowledge this support.

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[3] L. F. Audrieth, *Chem. Revs.*, **15**, 169 (1934).

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## Radioactive Estrogens[1a]

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*Received February 22, 1957*

The recent publication of Hartman *et al.*[1b] prompts us to report a very similar synthesis with radioactive carbon, as well as with tritium.

Ozonolysis of 19-nortestosterone 17-acetate[2] (III) followed by decomposition of the ozonide with hydrogen peroxide gave, in 50% yield, 17β-acetoxy-5-keto-3,5-seco-4-norestrane-3-oic acid.

Lactonization by treatment with acetic anhydride and sodium acetate furnished, in 54% yield, the desired 17β-acetoxy-5-hydroxy-3,5-seco-4-nor-5(10)-estrene-3-oic acid 3,5-lactone.

This enol lactone acetate was added to the equimolar amount of methyl magnesium iodide-C$^{14}$ in ether. The reaction mixture was decomposed with dilute hydrochloric acid and after being worked up as usual, the obtained crude product cyclized with hydrochloric acid in acetic acid.[3] The reaction product furnished after purification, in 47% yield, 19-nortestosterone acetate-4-C$^{14}$ (III).

Attempts to aromatize that compound directly by dehydrogenation[4] with selenium dioxide gave, consistently, a yield below 35%. Dehydrogenation of estra-3,5-diene-3,17β-diole diacetate (I)[2] with selenium dioxide gave however, in very good yield, the desired 17-dihydroequilenin-17β 3,17-diacetate-4-C$^{14}$ (IIb).

Bromination[5] of 19-nortestosterone 17-acetate-4-C$^{14}$ (III) in dry ether with bromine and a few drops of hydrogen bromide in acetic acid gave crude 2,6-dibromo-19-nortestosterone 17-acetate-4-C$^{14}$, which was dehydrobrominated[6] with lithium chloride in dimethylformamide, giving in 75% yield (calculated on 19-nortestosterone 17-acetate-4-C$^{14}$) the desired estra-1,3,5(10),6-tetraene-3,17β-diol 17-monoacetate-4-C$^{14}$ (IVa), m.p. 247–250°. This tetraene, obtained from a nonradioactive model run, was reacted with tritium and prereduced palladium-on-charcoal to give estradiol 17β-acetate-6,7-*t*.

Estra-1,3,5(10),6-tetraene-3,17β-diol 17-acetate-4-C$^{14}$ (IVa) gave, after reduction[5] with 30% palladium-on-charcoal in ethyl acetate under hydrogen for 3 hr., estradiol 17β-acetate-4-C$^{14}$ (V), in 95% yield. The specific radioactivity of this product and of its starting material (4-C$^{14}$-19-nortestosterone 17-acetate) was identical.

Estra-1,3,5(10),6-tetraene-3,17β-diol 17-acetate-4-C$^{14}$ (IVa) was acetylated[5] with acetic anhydride in pyridine and the resulting 3,17-diacetate (IVb) was dehydrogenated[5] with selenium

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[1a] Since this note was submitted S. Kushinsky, Abstracts of 131st Meeting, American Chemical Society, p. 36-O, reported a very similar synthesis.

(1) [b] J. A. Hartman, A. J. Tomasewski, and A. S. Dreiding, *J. Am. Chem. Soc.*, **78**, 5662 (1956).

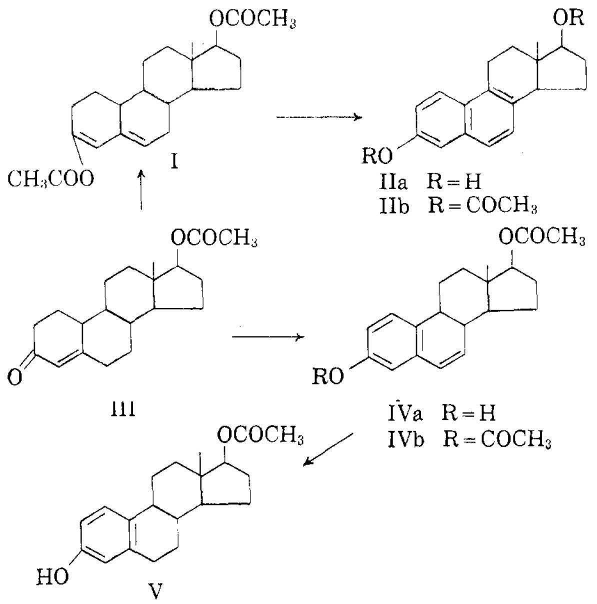
[2] J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955).

[3] Compare L. M. Thompson, C. H. Yates, and A. D. Odell, *J. Am. Chem. Soc.*, **76**, 1194 (1954).

[4] Compare H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Org. Chem.*, **21**, 239 (1956); C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

[5] Compare C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

[6] Compare R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).



dioxide in boiling acetic acid to give 17-dihydroequilenin-17$\beta$ 3,17-diacetate-4-$C^{14}$ (IIb). The crude diacetate afforded after alkaline saponification, followed by chromatography, 17-dihydroequilenin-17$\beta$-4-$C^{14}$ (IIa), in 35% yield. The specific activity was again identical with the activity of 19-nortestosterone acetate-4-$C^{14}$ (III).

## EXPERIMENTAL

Melting points were taken on a Kofler hot stage and are not corrected. The ultraviolet spectra were recorded on a methanol solution with a Cary spectrophotometer model 11 MS. All chromatographic separations, if not indicated otherwise, were made on Davison Silica Gel mesh 100–200. A Packard Tri-Carb liquid scintillation spectrometer was used for radioanalysis.

*19-Nortestosterone acetate-4-$C^{14}$* (III). To a solution of two mmoles of methyl magnesium iodide carbon-14 (4 mc.) in 15 ml. of ether and frozen to $-70°$ was added at once the solution of 637 mgs. (2 mmoles) of 17$\beta$-acetoxy-5-hydroxy-3,5-seco-4-nor-5-estrene-3-oic acid 3,5-lactone in 60 ml. of ether-benzene (1:1), care being taken to exclude all moisture. The mixture was allowed to warm up to 25° in the course of 6 hr.,[7] then decomposed with 2*N* hydrochloric acid and the product taken up in benzene. The benzene layer was washed with dilute sodium carbonate solution, then with water, dried, and evaporated to dryness. The residue was dissolved in 15 ml. of glacial acetic acid, 1.5 ml. of conc. hydrochloric acid added and kept for two days at room temperature in an atmosphere of nitrogen. After removal of the acids *in vacuo* the remaining sirup was dissolved in benzene, washed with sodium bicarbonate solution and with water. The benzene layer was dried, the benzene distilled off, leaving a partially crystalline residue which was chromatographed. The benzene-ether fractions gave after recrystallization from ether-pentane 298 mg. 19-nortestosterone acetate-4-$C^{14}$, m.p. 91–93°, $\lambda_{\max}^{\text{MeOH}}$ 240 m$\mu$, $\epsilon$ 17700. The specific activity was 2 mc/mM.

*3,17$\beta$-Diacetoxy-estra-3,5-diene-4-$C^{14}$* (I). A solution of 316 mg. (1 mmole containing 1 mc.) of 19-nortestosterone acetate-4-$C^{14}$ in 20 ml. of acetic anhydride-acetyl chloride 3:1 was refluxed under nitrogen for 3 hr. The solvents were evaporated off *in vacuo* and the residue was recrystallized from ethanol to give 300 mg. large plates, m.p. 153–156°,[8] $[\alpha]_D^{25}$ $-155°$ (chf.), $\lambda_{\max}^{\text{MeOH}}$ 234 m$\mu$, $\epsilon$ 20200, specific activity 1 mc/mM.

*17-Dihydroequilenin 3,17$\beta$-diacetate-4-$C^{14}$* (IIb) *and 17-dihydroequilenin-17$\beta$-4-$C^{14}$* (IIa). Dehydrogenation of 320 mg., 1 mc/mM, of the enol diacetate (I) in 20 ml. of glacial acetic acid with 200 mg. of freshly sublimed selenium dioxide under nitrogen for 15 min. gave 235 mg. impure 17-dihydroequilenin 3,17$\beta$-diacetate-4-$C^{14}$, m.p. 112–119°, which could not be obtained in pure form on repeated recrystallizations, by distillation or chromatography. Reductive hydrolysis with lithium aluminum hydride gave, after purifying on a Hyflow Super Cel column[9] 188 mg. 17-dihydroequilenin-17$\beta$-4-$C^{14}$ with m.p. 238–241°, $[\alpha]_D^{23}$ $+53°$ (dioxane), ultraviolet maxima at 230 m$\mu$ ($\epsilon$ 72000), 271 m$\mu$ ($\epsilon$ 6500), 283 m$\mu$ ($\epsilon$ 7500), 292 m$\mu$ ($\epsilon$ 5000), 328 m$\mu$ (shoulder, $\epsilon$ 2800), 341 m$\mu$ ($\epsilon$ 3900). Specific activity 1 mc/mM.

*Estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-$C^{14}$* (IVa). A solution of 316 mg. (1 mmole, containing 1 mc.) of 19-nortestosterone acetate-4-$C^{14}$ in dry ether was brominated exactly as described by Djerassi *et al.*[5] The crude dibromide gave after dehydrobromination as described by Holysz[6] 235 mg. estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-$C^{14}$, m.p. 247–250°, $[\alpha]_D^{25}$ $-201°$ (chlf.) ultraviolet maxima at 222 m$\mu$ ($\epsilon$ 28000), 262 m$\mu$ ($\epsilon$ 8310), 272 m$\mu$ (shoulder, $\epsilon$ 6300), 203 m$\mu$ ($\epsilon$ 2900).

*Estradiol 17$\beta$-acetate-4-$C^{14}$* (V). A solution of 156 mg. of estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-$C^{14}$, containing 1 mc/mM, was reduced with 20% palladium-on-charcoal.[5] The usual work up gave, after recrystallization from methanol, 132 mg. colorless prisms, m.p. 214–217°, $[\alpha]_D^{24}$ $+48°$ (chlf.), $\lambda_{\max}^{\text{MeOH}}$ 280 m$\mu$ ($\epsilon$ 2650), specific activity 1 mc/mM.

*Estradiol 17$\beta$-acetate-6,7-t* (V).[10,11] To a suspension of 50 mg. pre-reduced 30% palladium-on-charcoal in 38 ml. ethyl acetate, in which was dissolved 96 mg. of estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17$\beta$-acetate, 16 ml. hydrogen gas containing 1.6 c tritium were added at two atmospheres and the mixture allowed to stand overnight. After 2 hr. shaking 8.3 ml. residual gas was removed, the take-up amounting to 7.7 ml. The catalyst was filtered off, the solvent evaporated and the residue recrystallized from methanol which gave 81 mg. colorless prisms, m.p. 218–219°, $[\alpha]_D^{23}$ $+50°$ (chlf.), $\lambda_{\max}^{\text{MeOH}}$ 280 m$\mu$ ($\epsilon$ 2700), spec. activity calcd.: 8.0 mc/mg.; found: 7.35 mc/mg. The specific activity remained unchanged after 1 hr. equilibration (refluxed with 7% methanolic sodium hydroxide solution).

*17-Dihydroquilenin-17$\beta$-4-$C^{14}$* (IIa). Acetylation of 316 mgs. of estra-1,3,5(10),6-tetraene-3,17$\beta$-diol 17-acetate-4-$C^{14}$ (1 mmole containing 1 mc) produced the diacetate, m.p. 150–152°, $\lambda_{\max}^{\text{MeOH}}$ 263 m$\mu$ ($\epsilon$ 10200).

The selenium dioxide dehydrogenation was carried out exactly as described by Djerassi *et al.*,[5] but the reaction product could not be obtained in pure form by chromatography. Alkaline hydrolysis gave, after chromatography on a Hyflow Super Cel partition column[9] and recrystallization from methanol, 122 mg. 17-dihydroequilenin-17$\beta$-4-$C^{14}$ with m.p. 240–241°, $[\alpha]_D^{24}$ $+49°$ (dioxane), ultraviolet maxima

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[7] L. M. Thompson, C. H. Yates, and A. D. Odell, *J. Am. Chem. Soc.*, **76**, 1194 (1954), have already pointed out that the order of addition of Grignard reagent and enol lactone was of no apparent importance.

[8] J. A. Hartman and J. A. Hartman *et al.* (footnotes 1 and 2) give m.p. 170–174°, while the ultraviolet spectrum and the rotation data agree very well.

[9] E. O. Haenny, J. Carol, and D. Banes, *J. Am. Pharm. Assn.*, **42**, 167 (1953).

[10] W. H. Pearlman and M. R. J. Pearlman, *J. Am. Chem. Soc.*, **72**, 5781 (1950) have reported on estrone acetate-6,7-$d_2$.

[11] Thanks are due to New England Nuclear Corp., Boston 18, Mass., for carrying out this reduction.

at 230 mμ (ε 71400), 272 mμ (ε 6500), 283 mμ (ε 7480), 292 mμ (ε 5000), 329 mμ (shoulder, ε 2800), 341 mμ (ε 4000).

*Acknowledgment.* This investigation was assisted in part by grants from The U. S. Public Health Service (C-321) and The American Cancer Society (INSTR-63).

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## Attempted Oxygenolysis of Some Halide-LiAlH$_4$ and Nitrile-LiAlH$_4$ Reaction Products

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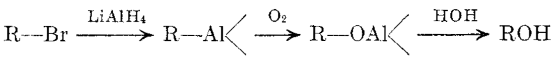
*Received March 1, 1957*

The literature contains several instances of the reaction of oxygen with hydride reduction complexes to yield hydroxylic products. Thus Hochstein and Brown[1] obtained 1-phenyl-1,3-propanediol (25%) from the reduction of cinnamyl alcohol, Soffer and Katz[2] isolated α-phenyl-β-aminoethanol (7%) from the reduction of phenylacetonitrile, and Cotman[3] reduced polyvinyl chloride to a polyethylene containing approximately one hydroxyl per 25 carbon atoms. In the first two instances these products were taken as evidence for a carbon-metal bond, probably carbon-aluminum. In the last, several alternate explanations were made, of which one assumed the presence of a carbon-lithium bond, and another, the oxidation of aluminohydride ion to an oxyaluminohydride ion which displaced chloride, thus leading to a product which on hydrolysis would yield a secondary hydroxyl group.

In addition, Badger and coworkers obtained the cyclic ether of 4,5-bishydroxymethylphenanthrene from the reduction of 4,5-bisbromomethylphenanthrene.[4] Although an ordinary basic hydrolysis of dibromide to diol cannot be definitely excluded, it seemed possible that the incorporation of oxygen might occur by the reaction of a carbon-metal species with atmospheric oxygen.



$$\mathrm{R{-}Br} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{R{-}Al}\langle \xrightarrow{\mathrm{O_2}} \mathrm{R{-}OAl}\langle \xrightarrow{\mathrm{HOH}} \mathrm{ROH}$$

The purpose of this study was to attempt the oxygenolysis of simple halides and nitriles under varying conditions and thus obtain additional information on the role of carbon-metal species in hydride reductions.

Assuming that a reaction of oxygen with a carbon-metal bond occurs, it could conceivably be influenced by many factors in the overall process, such as the nature of the substrate, the molar ratio of hydride and substrate, the manner in which the hydride reaction was performed (with reference to solvent, temperature, and whether by direct or reverse addition[2]), the manner in which oxygen was supplied (concurrent with the hydride-substrate reaction, or following it), as well as by the temperature and time of contact with oxygen. A number of experiments using some of the many possible reaction conditions are summarized in Table I. It can be seen that in no case, except the previously reported run 11, were hydroxylic materials isolated. The products obtained were normal for reductions without attempted oxygenolysis, but yields were considerably lower. The low recoveries were undoubtedly due to the difficulties experienced in extraction of the large quantities of gelatinous, post-hydrolysis reaction mixture.[5] The low yields of expected products can be explained likewise, and by the consumption of hydride by oxygen. Although it is regarded as unlikely that significant amounts of hydroxylic materials could have been present in the reaction mixture, the low recoveries preclude the definite conclusion that no hydroxylic products were formed.

Run 5 was made as a test of Cotman's hypothesis[3] that oxyaluminohydride ions are responsible for the displacement of halide with hydroxyl. Oxygen was passed into the hydride suspension solution at 65° for 4.5 hr., after which benzyl bromide was added and the mixture stirred at 65° for 17 hr. The isolation of toluene and benzyl bromide indicated that the reaction of hydride with oxygen had been incomplete and that little or no reaction occurred between benzyl bromide and the oxidized hydride. The failure to obtain any product other than a 10% yield of phenylacetaldehyde in run 9 can be attributed to the factors of low temperature and concurrent admission of oxygen.

Thus, under the conditions of our experiments, the attempted oxygenolysis of halide-hydride and aliphatic nitrile-hydride reduction complexes were unsuccessful, affording no evidence for a carbon-metal bond in such species. A single test of Cotman's "oxyaluminohydride hypothesis" for the production of hydroxyl during halide-hydride reductions failed to support the hypothesis.

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(1) F. A. Hochstein and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3484 (1948).

(2) L. M. Soffer and M. Katz, *J. Am. Chem. Soc.*, **78**, 1705 (1956).

(3) J. D. Cotman, Jr., *J. Am. Chem. Soc.*, **77**, 2790 (1955).

(4) G. M. Badger, J. E. Campbell, J. W. Cook, R. A. Raphael, and A. I. Scott, *J. Chem. Soc.*, 2326 (1950). The ether was obtained by sublimation of the actual reduction product which was undoubtedly 4,5-bishydroxymethylphenanthrene. The dehydration of the latter material to the ether was demonstrated by these workers to occur very readily.

(5) Extraction was particularly difficult in the runs where oxygen input was concurrent with the substrate-hydride reaction.