which is badly contaminated. Presumably this contamination is due to the decomposition of the unreacted *N*-aryl hydroxylamine to complex products.

In general, the preparations are trouble-free when pyridine is replaced by aqueous suspensions of sodium bicarbonate. For comparison of yield and purity several hydroxamic acids reported previously (*3*) were prepared by the modified procedure. Use of aqueous suspensions of sodium bicarbonate gave white crystalline products instead of the light brown sticky products obtained before when pyridine was employed. Even ortho- and meta- substituted derivatives, which readily turned into oily forms when prepared by the previous method, were obtained in crystalline form and satisfactory yield.

At first glance, the use of aqueous suspensions of sodium bicarbonate may appear objectionable on ground of hydrolysis of acid chlorides. However, under the experimental conditions employed, the rate of hydrolysis of acid chlorides is extremely slow because diethyl ether which constitutes the reaction medium, is immiscible with water and is maintained at low temperature. Even aliphatic acid chlorides, which generally, hydrolyze much more readily than aromatic types, give satisfactory products.

The hydroxamic acids prepared in this study are summarized in Table I.

## EXPERIMENTAL

**Materials and Apparatus.** The materials and apparatus have been described (*3*). All melting points were taken by the capillary method and are uncorrected. Ultraviolet absorption spectra of the hydroxamic acids were scanned on a Beckman Model DK-2 ratio recording spectrophotometer using two 10-mm. matched silica cells. The absorption measurements, made at constant wavelength for the calculation of molar absorptivity, $\epsilon$, were performed on a Unicam SP 500 spectrophotometer. Molar absorptivity is expressed in units of liters per mole cm. All samples were dissolved in spectroscopic grade of 95% ethyl alcohol.

**Procedure for Synthesis.** One-tenth mole of freshly crystallized *N*-aryl hydroxylamine, dissolved in 150 ml. of diethyl ether, and a fine powder of 0.15 to 0.2 mole of sodium bicarbonate in 25 ml. of water, were mixed together and stirred mechanically with external cooling to bring the temperature to 0 ° C. or lower. A solution of 0.1 mole of appropriate acid chloride in 100 to 150 ml. of diethyl ether was added from a dropping funnel during the course of about an hour. Usually a granular, white precipitate was obtained, but in a few cases no solid product separated. The ethereal layer was separated and the ether removed under vacuum. Any solid matter thus obtained was combined with the bulk of the product, which was thoroughly triturated in a porcelain mortar with an excess of saturated solution of sodium bicarbonate for about 15 minutes to remove the acidic impurities. The solution was filtered, and the solid was washed with water and dried. The products were generally crystallized from a mixture of benzene and petroleum ether—in a few cases, when restricted by the limitations of solubility, from a mixture of ethyl alcohol and water—without the use of charcoal. Heating for prolonged periods in the solvent mixture should be avoided since discoloration of the product usually occurs. The yields of the hydroxamic acids ranged from 50 to 90%.


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# 17$\alpha$-*n*-Propyl- and 17$\alpha$-Isopropylestra-1,3,5(10)-triene-3,17$\beta$-diol


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THE PREPARATION of 17$\alpha$-*n*-propyl- and 17$\alpha$-isopropylestra-1,3,5(10)-triene-3,17$\beta$-diol was carried out in connection with studies concerned with the physiological activities of various estrogenic hormones.

The first two members of the homologous series, 17$\alpha$-methylestra-1,3,5(10)-triene-3,17$\beta$-diol (*1*) and 17$\alpha$-ethylestra-1,3,5(10)-triene-3,17$\beta$-diol (*2*) have been reported previously in the chemical literature.

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## EXPERIMENTAL

Melting points were taken in a modified Hershberg apparatus and are uncorrected. The microanalyses were carried out by Huffman Microanalytical Laboratories, Wheatridge, Colo.

**17$\alpha$-*n*-Propylestra-1,3,5(10)-triene-3,17$\beta$-diol (I).** To 8.6 grams of Mg turnings suspended in 100 ml. of absolute ether was added at 1 ° C. with vigorous stirring 15 to 20 ml. of a solution of 38.8 grams of allyl bromide in 290 ml. of ether. The reaction started immediately, and the temperature rose to 21 ° C. After cooling to 3 ° C., the main amount of the reagent solution was added during 1 1/4 hours and the mixture stirred an additional 1 1/2 hours at 0 to 4 ° C. To this solution was added over 1 hour, 7.03 grams of 3-benzyloxyestra-

**The preparation of 17α-*n*-propylestra-1,3,5(10)-triene-3,17β-diol (I) and 17α-isopropylestra-1,3,5(10)-triene-3,17β-diol (II) is described. Treatment of 3-benzyloxyestra-1,3,5(10)-triene-17-one with allyl magnesium bromide gave a product which was not isolated, but subjected to hydrogenation, hydrogenolysis, and acetylation to give 17α-*n*-propylestra-1,3,5(10)-triene-3,17β-diacetate, m.p. 110–110.5° C. Treatment of the diacetate with lithium aluminum hydride yielded I, m.p. 162.5–163.5° C. The isopropyl compound (II, m.p. 177–178.5° C.) was prepared by the reaction of 3-benzyloxyestra-1,3,5(10)-triene-17-one with isopropyllithium in *n*-heptane.**

1,3,5(10)-triene-17-one (*3*) in 500 ml. of absolute ether. The resulting solution was stirred $5^1/_2$ hours at room temperature and then treated with saturated ammonium chloride solution. The ether phase was separated and evaporated to give 7.6 grams of a viscous yellow oil which was dissolved in ethanol and hydrogenated at 15 p.s.i.g. in the presence of 5% Pd/C catalyst. The filtered solution was evaporated and yielded 5.9 grams of crude product. This was suspended in 500 ml. of 1*N* KOH, warmed gently on the steam bath, filtered, and acidified with 6*N* $H_2SO_4$ to pH 2 to 3. After standing in the refrigerator overnight, the precipitate was filtered (3.40 grams, m.p. 104 to 109° C.) and recrystallized four times from aqueous methanol to give small plates of m.p. 161.5–162.5° C. which did not analyze correctly for carbon. For this reason, an aliquot of 1.19 grams was refluxed 4 hours with 75 ml. of acetic anhydride, the solution poured into 2 liters of ice-water, and the precipitate filtered and dried to give 1.45 grams of product of m.p. 64 to 70° C. Three recrystallizations from aqueous methanol afforded 900 mg. of 17α-*n*-propylestra-1,3,5(10)-triene-3,17β-diacetate, flat needles, m.p. 110–110.5° C. Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.08; H, 8.61.

A solution of 857 mg. of the above diacetate in 70 ml. of tetrahydrofuran was added under $N_2$ to 4 grams of $LiAlH_4$ in 150 ml. of tetrahydrofuran. The mixture was refluxed $1^1/_2$ hours, kept at room temperature overnight, and the excess $LiAlH_4$ decomposed with ethyl acetate. After addition of saturated $Na_2SO_4$ solution and decantation, the residue was taken up in 350 ml. of 6*N* HCl and extracted three times with 150 ml. of ether. The ether solutions were washed with $NaHCO_3$ solution and water and combined with the tetrahydrofuran–ethyl acetate solution. After drying over $Na_2SO_4$ and distillation in vacuo, 855 mg. of crude product was obtained which was recrystallized three times from acetone-hexane and once from aqueous methanol to give white plates of m.p. 162.5–163.5° C. Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.20; H, 9.60.

**17α-Isopropylestra-1,3,5(10)-triene-3,17β-diol (II).** To a refluxing solution of 3.1 grams of 3-benzyloxyestra-1,3,5(10)-triene-17-one in 300 ml. of olefin-free *n*-heptane was added under $N_2$ during 15 minutes, 50 ml. of a 2.4*M* solution of isopropyllithium in *n*-heptane. The slurry was stirred and refluxed 3 hours and kept at room temperature overnight. After addition of 100 ml. of saturated $NH_4Cl$ solution, the heptane phase was separated, washed with dilute HCl, water, $NaHCO_3$ solution, and water, dried, and evaporated in vacuo to give 3.35 grams of a yellow oil. In order to remove any 17β-ol formed by reduction, this oil was refluxed for 3 hours with 70 ml. of pyridine and 5.0 grams of succinic anhydride. After addition of 170 ml. of $H_2O$, refluxing was continued $^1/_2$ hour. The mixture was diluted with 1 liter of saturated NaCl solution and extracted four times with 250 ml. of ether. The ether extracts were washed with water, dilute HCl, water, $K_2CO_3$ solution, and water, dried, and evaporated to give 3.22 grams of dark brown oil. To remove unreacted ketone, this oil was dissolved in 120 ml. of *n*-propanol and 36 ml. of water and treated with 3.3 grams of (aminooxy)acetic acid hemihydrochloride and 3.8 grams of anhydrous potassium acetate. The solution was refluxed for 3 hours and extracted with 1 liter of ether which was washed with $NaHCO_3$ solution and water, dried, and evaporated. The 2.18 grams of yellow oil thus obtained was taken up in 500 ml. of ethanol and hydrogenated with 5% Pd/C catalyst at 22 p.s.i.g. After filtration and evaporation in vacuo, the residue was dissolved in 250 ml. of hot 1*N* KOH and the solution cooled, filtered, and acidified with 6*N* HCl to give 950 mg. of precipitate. Three recrystallizations from aqueous methanol yielded 383 mg. of flat white needles, m.p. 177–178.5° C. Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.50; H, 9.46.

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