finally allowed to evaporate to dryness. The residual brown solid was washed with ether, suspended in 200 ml. of warm water, enough conc. hydrochloric acid added to dissolve the product, decolorized with Norit, and the filtrate adjusted to *p*H 8 with 10% sodium hydroxide. The white product was filtered with suction, washed well with water, and dried *in vacuo* at 50°, yield 7.0 g. (75%), m.p. >350°. Further purification was achieved by precipitation of the product by neutralization of a solution in aqueous hydrochloric acid.

Anal. Calcd. for $C_5H_6N_6$: C, 40.00; H, 4.03; N, 55.97. Found: C, 40.13; H, 3.92; N, 56.29.

The *monohydrochloride* was prepared by dissolving the free base in aqueous hydrochloric acid, evaporating to dryness *in vacuo*, and recrystallizing the residual colorless solid from aqueous ethanol to obtain colorless leaflets, m.p. >350°.

Anal. Calcd. for $C_5H_7ClN_6$: C, 32.18; H, 3.78; Cl, 18.99; N, 45.05. Found: C, 32.62; H, 4.03; Cl, 18.92; N, 45.59.

6-Benzyl-5-benzylaminoimidazo[4,5-d]triazolo[4,3-b]pyridazine (XIII, R = $CH_2C_6H_5$). One gram (0.0035 mole) of 6-benzyl-5-chloroimidazo[4,5-d]triazolo[4,3-*b*]pyridazine (IX) was mixed with 15 ml. of ethanol and 2 ml. of benzylamine and refluxed for 3 hr. The clear solution was cooled, and the almost colorless product which separated was isolated by suction filtration. Recrystallization from *N,N*-dimethylformamide-water or methyl cellosolve-water gave colorless prisms, m.p. 238–239°, yield 0.80 g. (64.5%).

Anal. Calcd. for $C_{20}H_{17}N_7$: C, 67.59; H, 4.82; N, 27.59. Found: C, 67.66; H, 5.04; N, 27.33.

6-Benzyl-5-hydrazinoimidazo[4,5-d]triazolo[4,3-b]pyridazine (XIII, R = NH_2). One gram (0.0035 mole) of 6-benzyl-5-chloroimidazo[4,5-*d*]triazolo[4,3-*b*]pyridazine (IX), 25 ml. of ethanol, and 0.50 g. (0.010 mole) of hydrazine hydrate was mixed and refluxed for 2.5 hr. The precipitate of yellow needles which separated on cooling was filtered with suction and recrystallized from *N,N*-dimethylformamide containing a little ethanol to obtain yellow needles, m.p. 268–269° dec., yield 0.60 g. (61%). This material was extremely insoluble in the common organic solvents with the exception of hot *N,N*-dimethylformamide or hot nitrobenzene. It could be dissolved in aqueous hydrochloric acid but was apparently destroyed, as neutralization only precipitated an oil which could not be crystallized.

Anal. Calcd. for $C_{13}H_{12}N_8$: C, 55.70; H, 4.32; N, 39.98. Found: C, 56.02; H, 4.53; N, 40.07.

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NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

dl-18-nor-D-Homosteroids

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Several 17a-ethynyl and alkyl derivatives of *dl*-18-nor-D-homosteroids were prepared. None of the 17a-alkyl compounds was significantly active as an anabolic agent.

The enhanced anabolic activity of the 17-alkyl-19-nortestosterones compared with the analogous compounds in the natural series is well known.[2] W. S. Johnson and co-workers[3] have prepared and described the properties of several 18-nor-D-homosteroids bearing a carbonyl or hydroxyl group in the 17a-position. As a result of a cooperative effort with Professor Johnson, we became interested in 17a-alkyl-18-nor-D-homotestosterones and several closely related compounds.

Following the directions of Johnson *et al.*,[3c] 1-methoxy-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysene (I) was converted to the 3-ketal and reduced stepwise to produce *dl*-3-ethylenedioxy-18-nor-D-homoandrost-5-en-17a-one (II) along with a lesser amount of the C:D-*cis* isomer(III) which has not been previously reported. The latter was readily isomerized to the *trans* isomer (II) by treatment with base. In our hands the overall yield of pure II from the aromatic ketal was about 5% compared with 17% reported. In view of the critical nature of the Birch reduction, such variations in yields are not unexpected. Our yield of about 25% in the two step reduction of I to the saturated ketone (IV) compares more favorably with that obtained by Johnson's group.

Treatment of the saturated ketone (IV) with ethylmagnesium bromide afforded a good yield of a single product (VIII) which has been designated as a 17a α alcohol. This configuration assignment is based upon the work of Ruzicka and co-workers,[4] who have shown that the addition of methylmagnesium bromide to D-homoandrosterone gave the 17aβ-methyl isomer exclusively. Examination of molecular models (II and IV) indicates that the absence of an angular methyl group at C-13 favors frontside approach by a bulky molecule such as a

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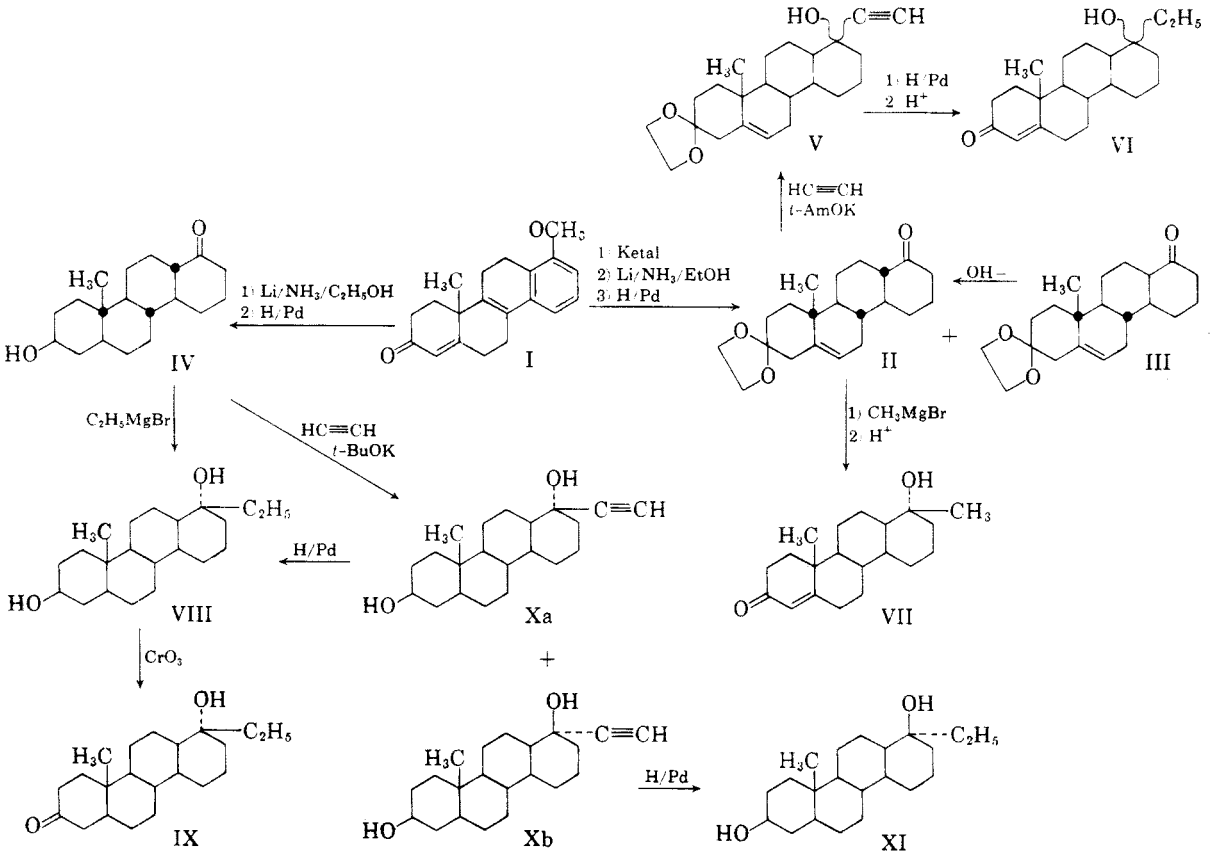
(2) (a) C. Djerassi, L. Miramontes, G. Rosenkrantz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954). (b) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957).

(3) (a) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **77**, 817 (1955). (b) W. S. Johnson, B. Bannister and R. Pappo, *J. Am. Chem. Soc.*, **78**, 6331 (1956). (c) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Am. Chem. Soc.*, **78**, 6354 (1956).

(4) L. Ruzicka, N. Wahba, P. Th. Herzig, and H. Heusser, *Ber.*, **85**, 491 (1952).

Grignard reagent to an even greater extent than that observed by Ruzicka.

Ethynylation of IV by Stavely's[5] method yielded two 17a-epimers (Xa and Xb) whose configurations were established by hydrogenation of X to form the Grignard adduct (VIII). Again referring to the models, we believe that the more compact potassium acetylide molecule can attack the ketone in a random manner, giving rise to both α- and β-isomers.



Similar treatment of the ketone (II) gave a crude product (V), undoubtedly a mixture of 17a-epimers, which upon catalytic hydrogenation and hydrolysis produced the alkyl nortestosterone (VI). The low yield and difficulty in isolation of the latter strongly indicates the formation of a 17a-isomer. Lack of material precluded the study necessary for configuration assignment in this instance.

Biology. The biological studies on compounds VI, VII, VIII, IX, Xb and XI were conducted by Dr. Francis Saunders and associates of these laboratories. The Hershberger[6] modification of the levator ani method of Eisenberg and Gordon was employed for the determination of the anabolic activities. The androgenic effects were measured by the increase in weight of the prostate and seminal vesicles. In both tests male rats castrated at thirty days of age were employed as subjects, and testosterone propionate was the reference standard. None of the test compounds exhibited androgenic or anabolic activities greater than 5% of that of the standard.

(5) H. Stavely, *J. Am. Chem. Soc.*, **61**, 79 (1939).

(6) L. G. Hershberger, Elva Shipley, and Roland Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

EXPERIMENTAL

C:D-cis Isomer of dl-ethylenedioxy-18-nor-D-homoandrost-5-en-16a-one (III). Twenty-five grams of the ketal of I were reduced with lithium and alcohol in ammonia.[3c] After hydrolysis of the enol ether and rearrangement, the crude unsaturated ketone was hydrogenated over palladium-on-carbon, and the product was chromatographed over Florisil. From the eluates just preceding the saturated ketone (II), there was obtained 400 mg. of a solid which, upon crystallization from isopropyl ether, weighed 260 mg. and melted at 205–207°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.36; H, 9.15. Found: C, 76.20; H, 9.25.

Isomerization was effected by treating a solution of 93 mg. of the *cis* compound (III) in 20 ml. of alcohol with a solution of 30 mg. of potassium hydroxide in 0.35 ml. of water. After 2.5 hr. at room temperature the solvent was vacuum distilled and the residual oil was taken up in ether. The ether solution was washed with water, dried and evaporated, yielding 94 mg. of product, m.p. 131–144°. Crystallization from isopropyl ether gave 62 mg. of the *trans* epimer (II) which melted at 141–144° and was shown to be identical with an authentic sample of II by infrared spectra and mixed melting point.

The identity of III was further established by hydrolysis with 80% acetic acid to form the known *dl*-18-nor-D-homoandrost-4-ene-3,17a-dione.[3c]

dl-18-nor-D-homo-17aβ-methyltestosterone (VII). To a solution of 570 mg. of the ketal (II) in 40 ml. of ether was added

10 ml. of a 4*M* solution of methylmagnesium bromide in ether. The resulting mixture was refluxed for 2.0 hr. and then cautiously hydrolyzed with 35 ml. of 70% acetic acid. After evaporation of the ether, the acidic solution was heated on a steam bath for 0.5 hr. to hydrolyze the ketal group. After the cooled solution was made alkaline with dilute sodium hydroxide, it was extracted well with ether and the extract was washed with water. Drying and removal of the solvent gave 555 mg. of crude product, which, after two crystallizations from isopropyl ether, weighed 226 mg. and melted at 198–200°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.56; H, 9.98.

Careful workup of the mother liquors yielded an additional 100 mg. of VII, m.p. 194–199°. There was no evidence of an isomeric product.

*dl-18-nor-*D*-homo-17a-ethyltestosterone* (VI). A solution of 0.5 g. of potassium in 60 ml. of dry *t*-amyl alcohol was saturated with acetylene at 0°. To this cold solution was added 0.5 g. of the ketone (II) in 40 ml. of dry toluene during a 0.3 hr. period, after which the mixture was treated with acetylene for 4.5 hr. at 0° with vigorous stirring. The stoppered flask was then stored in the refrigerator overnight. The mixture was treated with 100 ml. of water, the solvent layer was separated and the aqueous layer was extracted with ether. The combined solutions were washed free of alkali, dried, and evaporated to give 590 mg. of crude product (V), m.p. 145–168°. Infrared spectrum showed the absence of the carbonyl group.

The crude acetylenic alcohol was hydrogenated at atmospheric pressure in 80 ml. of absolute alcohol over 150 mg. of 5% palladium-on-carbon. The partially crystalline product (505 mg.) was dissolved in 15 ml. of 80% acetic acid and heated on a steam bath for 0.5 hr. to hydrolyze the ketal. The cooled solution was diluted with 20 ml. of water, neutralized with sodium bicarbonate, and extracted thoroughly with ether. The extract was washed, dried, and evaporated to yield 421 mg. of a partially crystalline oil which was chromatographed on silica. Crystallization of the solid fractions (170 mg.) afforded 80 mg. of VI as colorless needles, m.p. 160–161°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.88; H, 10.12.

Re-working the mother liquors gave 30 mg. of less pure product, m.p. 147–155°.

*dl-18-nor-*D*-homo-17aβ-ethylandrostane-3β,17aα-diol* (VIII). Grignard reagent was prepared in ether from 10.9 g. of ethyl bromide and 2.43 g. of magnesium. One hundred milliliters of dry benzene was added, and then the solvent was distilled until the vapor temperature reached 70°. To this solution was added during 5 min. with good stirring a solution of 1 g. of dl-18-nor-D-homoepiandrosterone (IV) in 50 ml. of dry benzene. The mixture was refluxed for 1 hr. and then stirred overnight at room temperature. After hydrolysis with 600 ml. of ice cold 1*M* hydrochloric acid, the benzene layer was separated, and the aqueous layer was extracted with three 100-ml. portions of chloroform. The combined solvent solutions were washed twice with water, dried, and then evaporated to give 1.08 g. of a pale yellow crystalline solid. Recrystallization from 30 ml. of ethyl acetate produced 700 mg. of tiny white needles, m.p. 188°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.70; H, 11.47.

*dl-18-nor-*D*-homo-17aβ-ethylandrostane-17aα-ol-3-one* (IX). A solution of 500 mg. of the diol (VIII) in 5 ml. of pyridine was added with swirling to an ice cooled mixture of 500 mg. of chromic acid in 5 ml. of pyridine. After 0.25 hr. the dark mixture was removed from the ice bath and stored overnight at room temperature. After dilution with 300 ml. of ethyl acetate, the mixture was filtered and the insoluble sludge was rinsed with 50 ml. of ethyl acetate. The filtrate and washings were combined and washed with two 100-ml. portions of 0.2*N* hydrochloric acid. The acid washings were back extracted with ethyl acetate and the combined extracts were washed with brine. Removal of solvent in vacuum gave 458 mg. of crude ketone (IX) which, upon crystallization from 20 ml. of ethyl acetate (Darco), weighed 365 mg. and melted at 197–198°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.02; H, 10.73.

*dl-18-nor-*D*-homo-17aβ-ethynylandrostane-3β,17aα-diol* (Xa) *and dl-18-nor-*D*-homo-17aα-ethynylandrostane-3β,17aβ-diol* (Xb). Eight-tenths of a gram of potassium was dissolved in 50 ml. of anhydrous *t*-butyl alcohol under nitrogen atmosphere. After the addition of 10 ml. of dry toluene the solution was chilled in an ice bath and saturated with acetylene. A solution of 0.2 g. of the saturated ketone (IV) in 40 ml. of dry toluene was then added during a 5 min. period while maintaining a moderate stream of acetylene. The resulting pale yellow solution was stirred for 4.5 hr. longer in an ice bath under a slow stream of acetylene and then stored in the refrigerator overnight. Following the addition of 250 ml. of water the solution was extracted with three 50-ml. portions of chloroform. The combined extracts were washed with water and dried over sodium sulfate. Removal of the solvent yielded 0.199 g. of a pale yellow solid which was very insoluble in common solvents and melted at 210–240°. Infrared showed no carbonyl absorption.

Eight-tenths of a gram of the above epimeric mixture was triturated with 8 ml. of ethyl acetate at room temperature. The insoluble portion was collected on a filter (400 mg.) and then extracted with 40 ml. of boiling isopropyl ether. The insoluble fraction was again separated (280 mg.) and crystallized from 16 ml. of absolute alcohol to give 180 mg. of white needles, m.p. 254–256° (Xb). A second crop of 50 mg., m.p. 253–256°, was obtained by concentration of the alcoholic mother liquor.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found C, 79.78; H, 10.22.

The ethyl acetate and isopropyl ether filtrates from the above procedure were combined and evaporated to dryness at room temperature (150 mg.). Successive crystallizations from ethyl acetate and absolute alcohol yielded 50 mg. of needles melting at 220–221° (Xa).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.71; H, 10.42.

*Hydrogenation of dl-18-nor-*D*-homo-17aβ-ethynylandrostane-3β,17aα-diol* (Xa). A solution of 30 mg. of Xa in 15 ml. of absolute alcohol was hydrogenated at atmospheric pressure over 10 mg. of 5% palladium-on-carbon catalyst. Crystallization of the crude product from 0.9 ml. of ethyl acetate gave 20 mg. of needles, m.p. 184–186°, which was identical (mixed melting point and infrared spectra) with the Grignard adduct (VIII).

*Hydrogenation of dl-18-nor-*D*-homo-17aα-ethynylandrostane-3β,17aβ-diol* (Xb). A solution of 123 mg. of the acetylenic alcohol (Xb) in 25 ml. of absolute alcohol was hydrogenated at atmospheric pressure over 20 mg. of 5% palladium-on-carbon catalyst. Crystallization of the crude product (m.p. *ca.* 225°) from 10 ml. of butanone yielded 105 mg. of the 17aα-ethyl compound (XI) m.p. 229–231°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 78.56; H, 11.26.

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