ml. of concentrated hydrochloric acid was added and refluxed 1 hr.; after dilution with water the precipitate was filtered. Crystallization from acetone–ether furnished prisms (500 mg.), m.p. 165–168°. The analytical sample showed m.p. 171–173° (from acetone–ether), $[\alpha]^{23}D$ −70°, λ_{max} 242 mμ, log ε 4.25, ν_{max} 1680 cm.$^{-1}$ and free hydroxyl band. (Plattner and Schreck[15] report m.p. 168–169°, $[\alpha]D$ −65° in dioxane.)

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 80.44; H, 9.82. Found: C, 80.43; H, 9.38.

The acetate showed m.p. 191–193° (needles from chloroform–methanol), $[\alpha]^{23}D$ −65°, λ_{max} 242 mμ, log ε 4.22 (Plattner and Schreck[15] report m.p. 189–190°, $[\alpha]D$ −63°, λ_{max} 240 mμ, log ε 4.25).

21-Methyl-Δ^5-pregnen-3β-ol-21-one Acetate (IVc).—A solution of the acetate Ie (1 g.) in 125 ml. of ethyl acetate was hydrogenated with 100 mg. of 5% palladium-on-charcoal until 1 mole of hydrogen was absorbed. The catalyst was filtered and the solution evaporated. Crystallization from ethyl acetate–methanol afforded long needles (780 mg.), m.p. 156–158°, $[\alpha]^{23}D$ −50° (Plattner and Schreck[15] report m.p. 156–157°, $[\alpha]D$ −49° in dioxane).

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.49; H, 9.53.

Alkaline Treatment of the Ketone XVIIb.—To a solution of the ketone XVIIb (1 g.) in 50 ml. of methanol, 1 g. of potassium carbonate in 10 ml. of water was added and refluxed 1 hr. The solution was diluted with water and extracted with ether, the organic layer was washed with water and concentrated. On addition of hexane there crystallized 625 mg. of prisms, m.p. 147–148°. A second crop (200 mg.) was obtained, m.p. 143–145°, $[\alpha]^{23}D$ −3°, ν_{max} 1736 cm.$^{-1}$ and free hydroxyl band (this material proved to be identical with Δ^5-androstene-3β-ol-17-one by mixed m.p. determination and infrared comparison).

The acetate showed m.p. 169–171° (from ether–hexane), $[\alpha]^{23}D$ −1.3° (identical with Δ^5-androstene-3β-ol-17-one acetate by mixed m.p. and infrared comparison).

MEXICO, D.F.

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

17-Alkyl-19-nortestosterones

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A series of 17-alkyl-19-nortestosterone derivatives was prepared for evaluation as anabolic and androgenic agents. Of the compounds studied, 17-ethyl-19-nortestosterone appears to be of greatest interest from a biological point of view.

A concerted effort has been made in our laboratory directed toward finding a substance with an anabolic potency of the order of testosterone but with a lower androgenic activity. To this end, a series of 17-alkyl-19-nortestosterone (17α-alkyl-17-hydroxy-4-estren-3-one) derivatives was prepared and biologically evaluated.

19-Nortestosterone was first synthesized by Birch[1] and was reported[2] to possess about 20% of the androgenic activity of testosterone. Hershberger and co-workers recently reported[3] that the substance I was a potent anabolic agent having a very favorable anabolic to androgenic ratio. This work has since been confirmed by Stafford and co-workers[4] as well as in our laboratories.[5] Djerassi and co-workers[6] have prepared 17-methyl-19-nortestosterone and stated that this substance was at least as potent an androgen as 17-methyltestosterone in the chick comb test but only weakly active in rats in so far as the increase in seminal vesicle weight was concerned. No mention was made of its anabolic activity.

Recent publications[7] disclosed the preparation of several 11-oxygenated derivatives of 17-methyltestosterone possessing very marked activity as oral anabolic and androgenic agents. The most active compound in this series, 17-methyl-9α-fluoro-11-oxotestosterone, is reported to possess 22 and 8.5 times the oral anabolic and androgenic activity, respectively, of 17-methyltestosterone.

The 19-nortestosterone derivatives included in this study and their physical constants are recorded in Table I.

TABLE I

17-ALKYL-19-NORTESTOSTERONE DERIVATIVES

	M.p., °C.	$[\alpha]D$ ($CHCl_3$)
19-Nortestosterone	123–124	55°
17-Methyl-19-nortestosterone[6]	156–158	31
17-Ethyl-19-nortestosterone[8]	136–139	25
17-Propyl-19-nortestosterone[8]	122–123	21
17-Butyl-19-nortestosterone[8]	126–127	
17-Octyl-19-nortestosterone[8]	120–122	
17-Vinyl-19-nortestosterone[9]	169–171	25, 36 (C_2H_5OH)
17-Allyl-19-nortestosterone[8]	93–95	
17-Ethynyl-19-nortestosterone[6]	202–204	−22

The anabolic potency of the substances studied was determined by the levator ani method of Eisenberg and Gordan and the androgenic properties were ascertained by the increase in weight of the seminal vesicle and the ventral prostate.[10]

Of the compounds studied, 17-ethyl-19-nortestosterone (I)[8,11] appeared to be the most applicable for clinical use because of its high anabolic po-

(1) A. J. Birch, *J. Chem. Soc.*, 367 (1950); A. J. Birch and S. M. Mukherji, *Nature*, **163**, 766 (1949); *J. Chem. Soc.*, 253 (1949).

(2) A. J. Birch, *Annual Reports on the Progress of Chemistry for 1950*, The Chemical Society, London, 1951, p. 210.

(3) L. G. Hershberger, E. G. Shipley and L. K. Meyer, *Proc. Soc. Exp. Biol. and Med.*, **83**, 175 (1953).

(4) R. O. Stafford, B. J. Bowman and K. J. Olson, *ibid.*, **86**, 322 (1954).

(5) Private communication from our biology staff.

(6) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954).

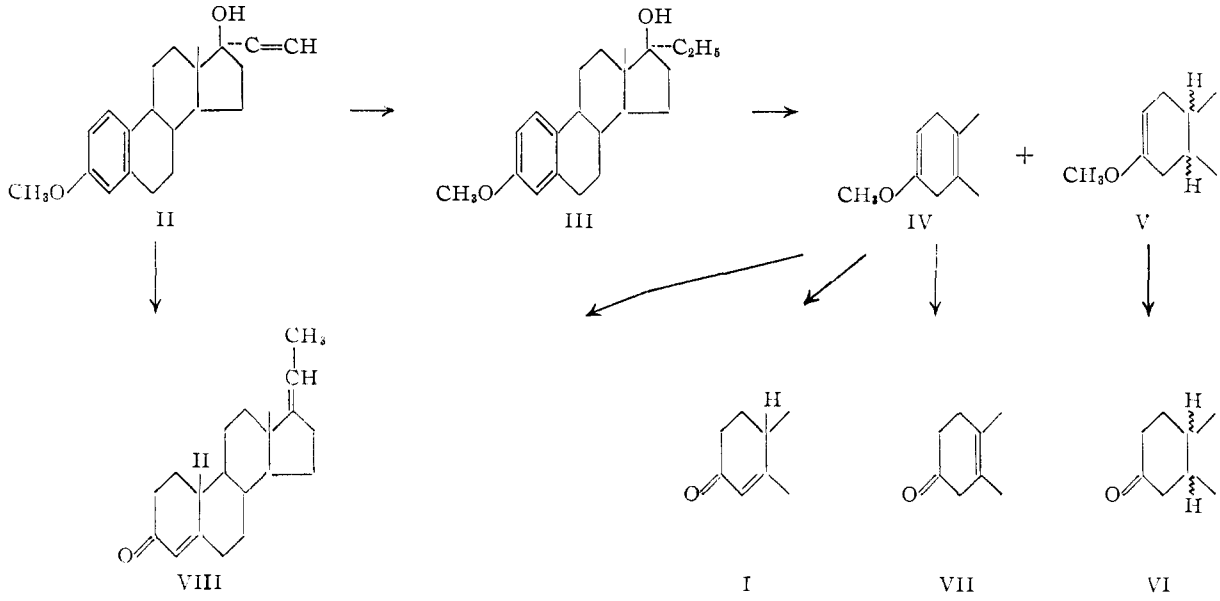
(7) M. E. Hesr, J. A. Hogg and R. H. Levin, *ibid.*, **78**, 500 (1956); S. C. Lyster, G. H. Lund and R. O. Stafford, *Endrocrinology*, **58**, 781 (1956).

(8) F. B. Colton, U. S. Patent 2,721,871 (1955).

(9) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 4117 (1953); F. B. Colton, U. S. Patents 2,655,518 (1953), 2,704,768 (1955).

(10) F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1956); (10a) V. A. Drill and F. J. Saunders, "Hormones and the Aging Process," Academic Press Inc., New York, N. Y., 1956, pp. 99–113.

(11) G. D. Searle and Co. has recently introduced this material under the trade name of Nilevar.



tency (comparable to testosterone propionate) and its low androgenic activity (about one-sixteenth that of testosterone propionate). When administered orally to rats this substance had at least five times the anabolic activity of 17-methyltestosterone or 19-nortestosterone. The pharmacological findings on this substance have been validated clinically in extensive studies in more than thirty medical centers in the United States and England.[12] It is of interest to note that 17-ethyltestosterone, in contrast to its 19-nor analog, is a very weak anabolic agent.

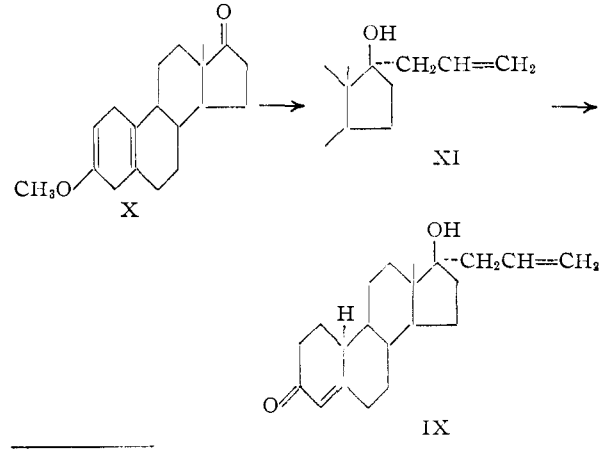
In addition to the biological properties discussed above many of the compounds mentioned possessed potent progestational activity.[13]

Two procedures were employed for the preparation of 17-ethyl-19-nortestosterone (I). The selective reduction of 17-ethynyl-19-nortestosterone[6] to I with hydrogen in the presence of palladium-on-charcoal catalyst proceeded in a yield of 73%.

In an alternate synthesis for the preparation of I the methyl ether of estrone was ethynylated in excellent yield to give the 3-methyl ether of 17-ethynylestradiol (II), and this was selectively reduced with hydrogen in the presence of palladium-on-charcoal catalyst to yield the 3-methyl ether of 17-ethylestradiol (III). A modified Birch reduction[14] of III gave predominantly the 3-methyl ether of 17-ethyl-1,4-dihydroestradiol (IV) together with a small amount of the 3-methyl ether of 17-ethyl-1,4,5,10-tetrahydroestradiol (V). The latter compound was not isolated, but its presence was inferred by the observation that 17-ethyl-19-nor-4,5-dihydrotestosterone (VI)[15] was one of the substances obtained by the acid cleavage and rearrangement of the crude reaction mixture from the Birch reduction of III.

The formation of V in the Birch reduction finds precedence in the report of Wilds and Nelson that a similar reduction of 1-methoxy-5,6,7,8-tetrahydronaphthalene yielded a small amount of the enol ether of α-decalone. The dihydro derivative IV could be cleaved and rearranged in excellent yield to I with dilute aqueous methanolic hydrochloric acid. The 5(10)-dehydro isomer VII was obtained in excellent yield from IV by a mild acid hydrolysis similar to that employed by Wilds and Nelson. Under more drastic conditions, however, removal of the 17-hydroxyl group occurred to give 19-norpregna-4,17(20)-dien-3-one (VIII). Compound VIII could also be obtained by the modified Birch reduction[16] of the 3-methyl ether of 17-ethynylestradiol (II), followed by cleavage and rearrangement. This is the expected product in view of the results of Birch[16] on the reduction of 1-ethynylcyclohexanol with sodium and ethyl alcohol in liquid ammonia.

17-Allyl-19-nortestosterone (IX) was prepared from the 3-methyl ether of 1,4-dihydroestrone (X) by reaction with allylmagnesium bromide followed



(12) The clinical results on this substance will be published elsewhere.

(13) We are indebted to V. A. Drill and F. J. Saunders of our biology staff for this private communication. Details of these findings will be published elsewhere.

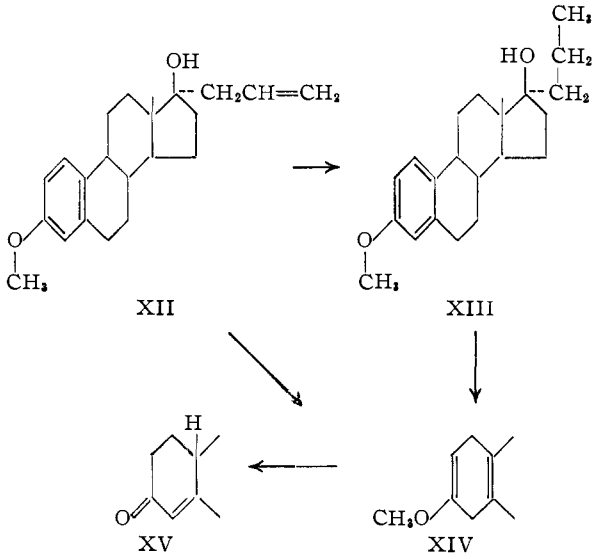
(14) A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5360, 5366 (1953).

(15) A study pertaining to the reduction of 19-nor compounds and to the stereochemistry of the 5-hydrogen atom is currently under way and will appear in a forthcoming publication.

(16) A. J. Birch, *J. Chem. Soc.*, 809 (1945).

by acid cleavage and rearrangement of the intermediate 1,4-dihydro derivative (XI).

The 3-methyl ether of 17-allylestradiol (XII) was prepared by the reaction of allylmagnesium bromide on estrone 3-methyl ether. Catalytic reduction of the 17-allyl group gave 17-propylestradiol 3-methyl ether (XIII). The modified Birch reduction of either XII or XIII gave the same 1,4-dihydro product XIV. For compound XII this represents an instance of the reduction of an isolated double bond under the Birch conditions. The acid-catalyzed cleavage and rearrangement of XIV resulted in the formation of 17-propyl-19-nortestosterone (XV).



The 17-butyl and 17-octyl derivatives of 19-nortestosterone were prepared by the acid cleavage and rearrangement of the Birch reduction products of the 3-methyl ethers of 17-butyl and 17-octylestradiol, respectively. 17-Butylestradiol 3-methyl ether was obtained by the reaction between estrone 3-methyl ether and *n*-butyllithium[17] whereas the octylestradiol derivative was obtained by the condensation of 1-octyne with estrone 3-methyl ether followed by the catalytic reduction of the side chain.

Experimental[18]

17-Ethyl-19-nortestosterone (I).—To a solution of 8.6 g. of 17-ethynyl-19-nortestosterone in 350 ml. of dry dioxane was added 1.1 g. of a 5% palladium-on-charcoal catalyst and the mixture was reduced until two moles of hydrogen were absorbed. The catalyst was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was chromatographed over 450 g. of silica gel. The product was eluted with 20–30% ethyl acetate in benzene and was crystallized from methanol–water to furnish 6.12 g. (73%) of product with m.p. 133–134° followed by resolidification and melting at 137–138°, $[\alpha]_D$ 25° (1% in $CHCl_3$); λ_{max} 240 mμ, log *E* 4.22. The infrared spectrum (KBr disk) shows bands at 2.84, 6.06, 6.23, 6.90, 7.38, 7.95, 9.09, 10.06 and 11.2 μ.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.44; H, 10.00. Found: C, 79.59; H, 9.99.

(17) For the reaction between 17-keto steroids and alkyl lithium compounds see C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(18) Melting points were determined on a Fisher–Johns block and are uncorrected. We are indebted to R. T. Dillon and his staff of our company for our analytical data.

17-Ethynylestradiol 3-Methyl Ether (II).—A slow stream of acetylene was passed over the surface of a stirred solution of potassium *t*-amylate (prepared from 5.0 g. of potassium) in *t*-amyl alcohol (100 ml.) and anhydrous ethyl ether (100 ml.) maintained at 0°. After saturation of the solution with acetylene gas, 5.0 g. of methyl estrone was added. The addition of acetylene gas was continued for 3–4 hours at 0° and then at room temperature for 18 hours. To the reaction mixture was added 100 ml. of a 10% ammonium chloride solution, and the *t*-amyl alcohol was removed by steam distilling. Filtration of the residue and crystallization from acetone gave a product, 5.1 g., melting at 150–151.5°.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.43; H, 8.30.

17-Ethylestradiol 3-Methyl Ether (III).—To a solution of 5.0 g. of 17-ethynylestradiol 3-methyl ether in 75 ml. of purified dioxane was added 0.5 g. of 5% palladium-on-charcoal catalyst and the mixture was shaken in an atmosphere of hydrogen until two moles were absorbed. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Upon crystallization from acetone–petroleum ether and drying *in vacuo* at 80°, 4.8 g. of product melting at 85–87° was obtained, λ_{max} 278 mμ, log *E* 3.35.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.21; H, 9.62. Found: C, 80.30; H, 9.51.

17-Ethyl-1,4-dihydroestradiol 3-Methyl Ether (IV).—To a stirred solution of 4.0 g. of 17-ethylestradiol 3-methyl ether in 100 ml. of dry ethyl ether and 300 ml. of liquid ammonia was added 4.0 g. of lithium wire cut into 1-cm. pieces. The mixture was stirred for 1 hour and then 30 g. of ethanol diluted with an equal volume of dry ethyl ether was added dropwise over a 90-minute period. An additional 100 ml. of dry ether was used to wash the sides of the flask during the ethanol addition. The reaction mixture was warmed gently until all the ammonia evaporated and then 100 ml. of cold water was carefully added. The product, 3.4 g. melting at 126–128°, was obtained by extraction and crystallization from ether–methanol. The infrared spectrum (KBr disk) shows bands at 2.85, 5.9, 6.0, 6.83, 6.91, 7.2, 7.28, 7.78, 8.0, 8.18 and 8.65 μ.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 79.69; H, 10.19. Found: C, 79.97; H, 10.22.

17α-Ethyl-17-hydroxy-5(10)estren-3-one (VII).—To a suspension of 1.25 g. of 17-ethyl-1,4-dihydroestradiol 3-methyl ether in 20 ml. of methanol was added 2.2 ml. of glacial acetic acid. The mixture was refluxed for 5 minutes and then 100 ml. of water was added. The product, 1.15 g. melting at 134–136°, was obtained by filtration and crystallization from acetone–petroleum ether.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.42; H, 10.00. Found: C, 79.52; H, 9.92.

17-Ethyl-19-nortestosterone (I) (Alternate Synthesis).—To a stirred solution of concentrated hydrochloric acid (2.4 ml.) and water (1.6 ml.) in methanol (36 ml.) was added 2.0 g. of 17-ethyl-1,4-dihydroestradiol 3-methyl ether. The solid dissolved rapidly and the resulting solution was allowed to stand at room temperature for 2 hours. Addition of water, filtration and crystallization from acetone–petroleum ether gave 1.7 g. of a product melting at 136–139°. The analytical data of this substance (ultraviolet, infrared and rotation) was the same as that obtained for the product described in the first experiment.

17-Octylestradiol 3-Methyl Ether.—To a solution of 3.0 g. of 17-octynylestradiol 3-methyl ether in 75 ml. of purified dioxane was added 0.5 g. of a 5% palladium-on-charcoal catalyst. The mixture was shaken in an atmosphere of hydrogen until 2 moles were absorbed. The catalyst was removed by filtration and the filtrate taken to dryness *in vacuo*. Upon trituration of the residue with methanol 1.9 g. of a product was obtained melting at 79–81°, $[\alpha]_D$ 40° (1.25% in $CHCl_3$). The infrared spectrum (KBr disk) shows bands at 2.85, 6.24, 6.68, 6.83, 7.6, 7.75, 8.08, 8.6 and 9.63 μ.

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.40; H, 10.62. Found: C, 81.37; H, 10.46.

17-Octyl-19-nortestosterone.—The Birch reduction (as previously described) on 1.5 g. of 17-octylestradiol 3-methyl ether gave a solvated crystalline substance (1.2 g.) which became amorphous on drying *in vacuo*. The amorphous material was cleaved and isomerized as previously described and the product, wt. 0.8 g., obtained by crystallization from

methanol–water, melted at 120–122°, λ_{max} 240 mμ, log *E*, 4.22.

Anal. Calcd. for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found: C, 80.75; H, 10.99.

3-Methoxy-19-norpregna-2,5(10),17(20)-triene.—Reduction of 4.0 g. of 17-ethynylestradiol 3-methyl ether by the procedure previously described for 17-ethylestradiol 3-methyl ether gave 3.1 g. of a product melting at 111–112°.

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.51; H, 10.13. Found: C, 84.74; H, 10.20.

19-Norpregna-4,17(20)-dien-3-one (VIII).—Cleavage and isomerization of 1.0 g. of 3-methoxy-19-norpregna-2,5(10),-17(20)-triene according to the procedure described for the 3-methyl ether of 1,4-dihydro-17-ethylestradiol (IV) gave 0.76 g. of product melting at 124–125°, λ_{max} 242 mμ, log *E* 4.22.

Anal. Calcd. for $C_{20}H_{26}O$: C, 84.45; H, 9.92. Found: C, 84.73; H, 10.06.

17-Allylestradiol 3-Methyl Ether (XII).—To 8.5 g. of magnesium turnings (activated with iodine) covered with 200 ml. of anhydrous ethyl ether was added dropwise 5.0 g. of allyl bromide in 20 ml. of dry ethyl ether. The reaction began rapidly. To the spontaneously refluxing reaction was added, over a 45-minute period, 20.0 g. of estrone methyl ether as a suspension in 95 g. of allyl bromide and 400 ml. of ethyl ether. After spontaneous refluxing ceased, the reaction was refluxed for an additional 2.5 hours. The reaction was then cooled in an ice-bath and 500 ml. of a 10% ammonium chloride solution was added. The ether layer was washed with additional portions of ice water, and then dried over sodium sulfate. The ether was removed *in vacuo* and the residue, upon crystallization from ether–petroleum ether, yielded 18.4 g. of a product melting at 91–91.5°, $[\alpha]_D$ 57.4° (1.02% in $CHCl_3$), λ_{max} 278 mμ, log *E* 3.32. The infrared spectrum (KBr disk) shows bands at 2.85, 5.9, 6.0, 6.82, 6.92, 7.2, 7.28, 8.0, 8.08, 8.65, 10.91 and 11.05 μ.

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.93; H, 9.44.

17-Propylestradiol 3-Methyl Ether (XIII).—To a solution of 11.5 g. of 17-allylestradiol 3-methyl ether in 200 ml. of ethanol was added 5 g. of a 5% palladium-on-charcoal catalyst and the mixture was shaken in an atmosphere of hydrogen until one mole was absorbed. The catalyst was removed by filtration and the filtrate taken to dryness *in vacuo*. Crystallization of the residue from ether–methanol yielded 10.1 g. of a product melting at 93–94°, $[\alpha]_D$ 47.7° (1.09% in $CHCl_3$), λ_{max} 278 mμ, log *E* 3.32. The infrared spectrum (KBr disk) shows bands at 2.83, 6.23, 6.35, 6.7, 6.82, 7.8, 7.95, 8.68, 9.6 and 9.96 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.60; H, 9.95.

17-Propyl-1,4-dihydroestradiol 3-Methyl Ether (XIV) from XIII.—The experimental conditions for this reduction were the same as those outlined for the reduction of the 17-ethyl derivative. From 6.0 g. of 17-propylestradiol 3-methyl ether (XIII), 4.7 g. of the corresponding 1,4-dihydro derivative, m.p. 150–152° was obtained, $[\alpha]_D$ 105° (1.16% in $CHCl_3$). The infrared spectrum (KBr disk) shows bands at 2.84, 5.9, 6.01, 6.82, 6.9, 7.2, 7.29, 7.78, 8.0, 8.16, 8.65, 9.0, 9.73 and 9.99 μ.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.96; H, 10.45.

17-Propyl-1,4-dihydroestradiol 3-Methyl Ether (XIV) from XII.—Reduction of 5.0 g. of 17-allylestradiol 3-methyl ether by the procedure previously described for 17-ethylestradiol 3-methyl ether gave a product, 4.0 g., melting at 149–151°. The infrared spectrum (KBr disk) and the rotation of this material was the same as that obtained in the preceding experiment.

17α-Propyl-17-hydroxy-5(10)-estren-3-one.—Treatment of 1.0 g. of 17-propyl-1,4-dihydroestradiol 3-methyl ether according to the conditions described for the preparation of 17α-ethyl-17-hydroxy-5(10)-estren-3-one gave 0.8 g. of a product melting at 90.0–91.5°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 80.01; H, 10.37.

17-Propyl-19-nortestosterone (XV).—Cleavage and isomerization of 1.8 g. of 17-propyl-1,4-dihydroestradiol 3-methyl ether using the conditions described for 17-ethyl-19-nortestosterone yielded 1.4 g. of a product melting at 122–123°, $[\alpha]_D$ 21° (0.98% in $CHCl_3$), λ_{max} 241 mμ, log *E* 4.21. The infrared spectrum (KBr disk) shows bands at 2.83, 6.03, 6.22, 7.22, 7.38, 7.92, 8.21, 9.06 and 9.91 μ.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.97; H, 10.27.

1,4-Dihydroestrone 3-Methyl Ether.[19]—The oxidation and the steam distillation were carried out in an atmosphere of nitrogen. To a solution of 25 g. of 1,4-dihydroestradiol 3-methyl ether in cyclohexane (242 ml.) and toluene (860 ml.) was added a solution of 25 g. of aluminum isopropoxide in 347 ml. of dry toluene, and the mixture was refluxed for two hours. Saturated Rochelle salt solution (169 ml.) was added, dropwise, over a 10-minute period, and the mixture was steam distilled. The product was separated from the aqueous residue by filtration, and was triturated with methanol (100 ml.). On cooling to 0°, 21.0 g. of product which melted at 142–144° was obtained; λ_{max} 278 mμ, E76.[20] For analysis this material was crystallized from methanol, m.p. 141–141.5°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.21, 79.25; H, 9.63, 9.51.

17-Allyl-19-nortestosterone (IX).—To 1.7 g. of magnesium turnings (activated with iodine) covered with 100 ml. of ethyl ether was added 9.0 g. of allyl bromide in 100 ml. of ethyl ether. After refluxing for 15 minutes there was added a solution of 2.0 g. of X in 100 ml. of ether. The reaction mixture was refluxed for 90 minutes and then 100 ml. of a 10% Rochelle salt solution was added slowly. The ether layer was washed with water, dried over sodium sulfate, and then concentrated *in vacuo*. The residue was dissolved in a solution of 40 ml. of methanol, 1.5 ml. of concentrated hydrochloric acid and 5 ml. of water and the resulting solution was allowed to stand at room temperature for two hours. The product was precipitated by the addition of 200 ml. of cold water and was purified by chromatographing over 150 g. of silica gel. Crystallization from acetone–petroleum ether of the material which was eluted with 25% ethyl acetate in benzene gave 1.1 g. of product melting at 93–95°, λ_{max} 240 mμ, log *E* 4.23. The infrared spectrum (KBr disk) shows bands at 2.91, 6.03, 6.9, 7.02, 7.25, 7.32, 7.49, 7.87, 8.22, 9.51, 10.12, 10.31 and 10.97 μ.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.20; H, 9.57.

17-Octynylestradiol 3-Methyl Ether.—To a stirred solution of potassium *t*-amylate (prepared from 7.8 g. of potassium) maintained at 0° was added 24 g. of 1-octyne in 125 ml. of dry ethyl ether. After stirring for 1 hour 5.7 g. of estrone methyl ether was added, the reaction mixture was allowed to warm to room temperature, and stirring was continued for an additional 24 hours. A 10% ammonium chloride solution (150 ml.) was added and the organic layer was washed with water, dried, and concentrated *in vacuo*. The residue was chromatographed on silica gel and the product (4.6 g.) was eluted as an oil with 0.5% chloroform in benzene. The infrared spectrum ($CHCl_3$) shows bands at 2.76, 6.22, 6.67, 6.82, 7.23, 7.75, 7.97 and 8.15 μ.

Anal. Calcd. for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 82.28; H, 9.81.

17-Butylestradiol 3-Methyl Ether.—A solution of butyllithium, prepared from 9.0 ml. of butyl bromide and 0.67 g. of lithium wire according to the procedure of Gilman,[21] in ether was added to a stirred suspension of estrone methyl ether (1.65 g.) in anhydrous ether (40 ml.). Upon stirring for one hour the mixture was decomposed with methanol and dilute sulfuric acid. Additional ether was added, and the organic phase was washed twice with a saturated solution of sodium chloride and dried over sodium sulfate. The solvent was removed on the steam-bath and the residue was chromatographed over alumina (100 g.). Elution with 20% Skellysolve-A in benzene followed by crystalliza-

(19) We are indebted to E. A. Brown for carrying out this experiment for us.

(20) It can be seen from the value of the extinction coefficient that very little aromatization occurred in the oxidation. Even if we were to ignore the contribution to this absorption of the 17-carbonyl, the extent of aromatization is only 4%. This value is in sharp contrast to that recently reported by H. J. Ringold, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 2479 (1956).

(21) H. Gilman, THIS JOURNAL, **71**, 1499 (1949).

tion from aqueous methanol gave a product (426 mg.) which melted at 52–55°, partially solidified, and then melted at 92–94°.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.67; H, 10.00. Found: C, 80.61; H, 10.07.

17-Butyl-19-nortestosterone.—The Birch reduction of 17-butylestradiol 3-methyl ether and the cleavage and rearrangement of the resulting 1,4-dihydro derivative was carried out by the procedure previously described for the 3-methyl ether of 17-ethylestradiol. The product from the reaction was purified by chromatography over silica gel (35 g.). Elution with 20% ethyl acetate in benzene followed by crystallization from aqueous methanol gave 118 mg. of 17-butyl-19-nortestosterone which melted at 126–127°, λ_{max} 240.5 mμ, log E 4.23. The infrared spectrum (KBr disk) shows bands at 2.82, 6.03, 6.22, 7.92, 8.21, 9.81, 10.39 and 11.31 μ.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.66; H, 10.53.

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[CONTRIBUTION OF THE RESEARCH LABORATORIES, THE UPJOHN CO.]

The Separation of Stigmasterol from Soybean Sterols[1]

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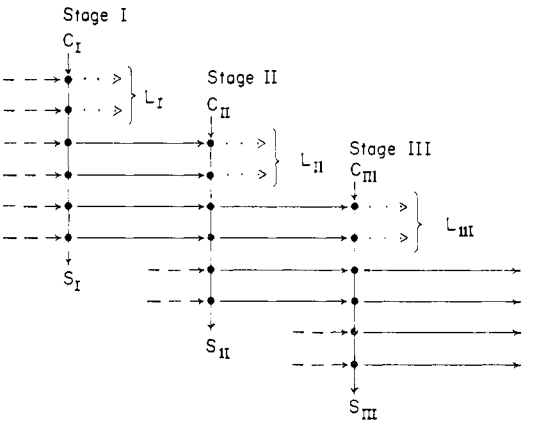
Several new esters of stigmasterol and a new process for the isolation of stigmasterol of about 88% or better purity from soybean sterols *via* the α-naphthylcarbamates are described.

Stigmasterol, one of the most abundant raw materials for the synthesis of steroid hormones,[2] was separated from soybean sterols[3] in 1911 by Matthes and Dahle.[5] The separation method was applied earlier by Windaus and Hauth[6] who isolated stigmasterol from the sterols of calabar beans. The Windaus–Hauth process has been the classical method for the isolation of stigmasterol and a method for its estimation. This process was shown to be inefficient by Neu and Ehrbächer[7] and by Johnson, Donia and Ott.[8] Analysis of given lots of soybean sterols by both radioactive isotope dilution[9] and infrared assays[10] showed that about twice as much stigmasterol was present as was indicated by the Windaus–Hauth separation. On these bases crude soybean sterols were believed to contain more stigmasterol than previously indicated. One objective of this study was to confirm by actual isolation the stigmasterol content indicated by the newer assay methods.

A study of several esters (Table I) of soybean sterols showed that stigmasterol α-naphthylcarbamate could be effectively separated from the other soybean steryl α-naphthylcarbamates. Other carbamate esters studied are less efficient and the carboxylic acid esters have little utility for the separation of stigmasterol.

The most efficient process for the separation of the soy steryl α-naphthylcarbamates was a discontinuous countercurrent leaching process described in Fig. 1. The important factors affecting the leaching were the volume of solvent per pass[11] and the number of passes required to dissolve the sitosteryl α-naphthylcarbamates. Other variables, particle size, temperature, rate and duration of stirring had little effect within reasonable limits.

Figure 1.
Discontinuous Countercurrent Leaching Process



Legend:
- • A pass
  path of solids is down
  path of liquors is left to right
- → fresh chlorobenzene
- → liquors reused
- C = charge of crude soy steryl α-naphthylcarbamates
- S = solid stigmasteryl α-naphthylcarbamate
- L = liquors containing sitosteryl α-naphthylcarbamates

Separations of the soy steryl α-naphthylcarbamates as described in Fig. 1 gave, after hydrolysis, stigmasterol of 88 to 93% purity by infrared analysis in 90 to 96% of the theoretical amount indicated by the infrared analysis of the starting sterols.[12] The yields and purities correspond to a recovery of about 85% of the stigmasterol. The product thus isolated was identical in m.p., optical

(1) Presented before the Division of Organic Chemistry at the 128th Meeting of the American Chemical Society, Minneapolis, Minn., September 11–16, 1955.

(2) F. W. Heyl and M. E. Herr, THIS JOURNAL, **72**, 2617 (1950).

(3) Soybean sterols as obtained from the unsaponifiable fraction of soybean oil generally contain 12–25% stigmasterol; the remainder is largely various sitosterols.[4]

(4) K. S. Markley, "Soybean and Soybean Products," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1951, p. 837.

(5) H. Matthes and A. Dahle, *Arch. Pharm.*, **249**, 436 (1911).

(6) A. Windaus and A. Hauth, *Ber.*, **39**, 4378 (1906).

(7) R. Neu and P. Ehrbächer, *Arch. Pharm.*, **283**, 227 (1950).

(8) B. A. Johnson, R. A. Donia and A. C. Ott, unpublished work from the Upjohn Co.

(9) R. A. Donia, N. A. Drake and A. C. Ott, *Anal. Chem.*, in press.

(10) J. L. Johnson and A. O. Jensen, *Anal. Chem.*, to be published.

(11) In these studies a leaching operation (or pass) consisted of stirring a mixture of the solid carbamate with a solvent and separating the phases by filtration. The stigmasteryl α-naphthylcarbamate remained in the undissolved portion.

(12) The soy sterols used in these studies contained 17 to 24% stigmasterol by infrared assay.