Totally Synthetic Hormones. XVI.[1] The Conversion of Estr-4-en-17β-ol to Testosterone and the Total Synthesis of Some 18-Methylandrostane and 18-Methylpregnane Derivatives

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A novel reaction sequence has been developed for converting estr-4-en-17β-ol, by way of 17β-hydroxy-5α-androstan-4-one (VII) and 17β-acetoxy-4-hydroxyandrost-4-en-3-one (4-hydroxytestosterone-17-acetate, XI), to testosterone acetate (XIV). Application of an analogous sequence to the racemic 18-homolog Ia has given racemic 18-methyltestosterone acetate (XIVa) which has been converted to the corresponding 18-methylpregnane derivatives XXI–XXIII. Biological activities are reported for racemic 18-methyltestosterone (XV) and XXI–XXIII and compared with those of appropriate analogs in the androstane, 13β-ethylgonane, and estrane series.

Previous publications from these laboratories[3] have described the total synthesis of a wide variety of 13β-polycarbonalkylgonane derivatives which were required for biological evaluation. The interesting biological activities of these substances,[4-9] extending, for several 13β-ethylgonane members of the series, to pronounced clinical effectiveness,[10-12] necessitated the preparation of analogs having a 10β-methyl group. The total synthesis and biological properties of such 13β-ethyl-10β-methylgonanes (18-methylandrostanes and -pregnanes) will be reported in this and subsequent papers.

Because of the ready availability of 13β-ethylgonanes[4a,b] we proposed to synthesize the required compounds by the introduction of a single carbon substituent at the 10 position of the gonane nucleus. Another group,[13] apparently motivated by the previously mentioned biological properties of 13β-ethylgonanes, have chosen to make the 10β-methyl homologs by partial synthesis through 18-oxygenated pregnanes. Here we describe the synthesis of 10β-methylgon-4-en-3-ones through the Michael addition of the elements of hydrogen cyanide to gon-5(10)-en-4-ones. Our plan was to develop an effective method in the estrane series before applying it to the 13β-ethylgonane series. The novel estr-5(10)-en-4-one III required as starting material was readily made from the acetate I[14] by conversion with N-bromosuccinimide in acidic aqueous dioxane to a bromohydrin, followed by Jones oxidation,[15] and dehydrobromination of the resulting bromo ketone II in refluxing pyridine. In accord with its assigned structure, III had λ_{max} 251 mμ (ε 13,000) characteristic of an α,β,β-trisubstituted α,β-unsaturated ketone, and showed no vinylic proton signal in its pmr spectrum. The addition of the elements of HCN to III in the presence of diethylaluminum bromide[16a] gave a 73% yield of the cyano ketone IV shown to be a 10β-cyanoestrane[16b] by its subsequent conversion to an androstane derivative. The cyano group in IV was converted to a methyl group by ketalization, reduction of the ketal V to the imine VI with lithium aluminum hydride in tetrahydrofuran, Wolff–Kishner reduction, and acidic hydrolysis. Reaction sequences of this type were originally developed by Nagata, *et al.*,[17] for transforming angular cyano to angular methyl groups in steroids and related structures. Notably, the Wolff–Kishner reduction proceeded efficiently with the imine VI, thereby saving one step. The resulting ketone VII was identical with an authentic specimen prepared from testosterone.[18] The 5α configuration in VII was confirmed by the ORD and proton nmr spectra. The ORD spectrum, determined for a dioxane solution, displayed a negative Cotton effect of amplitude −76°, which is to be compared with amplitudes of −94°[19] and −91°[20] given for typical 10β-methyl-4-oxo 5α-steroids, and that of +8°[20] given for a typical 10β-methyl-4-oxo 5β-steroid. The −94° value was obtained for a methanolic solution; the solvent in the other two cases was not disclosed. The pmr spec-

(1) Part XV: G. C. Buzby, Jr., G. H. Douglas, C. R. Walk, and H. Smith, Second International Congress on Hormonal Steroids, Excerpta Medica Foundation, New York, N. Y., 1966, in the press.

(2) Postal address: P. O. Box 8299, Philadelphia, Pa 19101.

(3) G. C. Buzby, Jr., C. R. Walk, and H. Smith, *J. Med. Chem.*, **9**, 782 (1966), and earlier papers.

(4) (a) H. Smith, *et al.*, *Experientia*, **19**, 394 (1963); (b) *J. Chem. Soc.*, 4472 (1964); (c) G. H. Douglas, G. C. Buzby, Jr., C. R. Walk, and H. Smith, *Tetrahedron*, **22**, 1019 (1966).

(5) R. A. Edgren, H. Smith, D. L. Peterson, and D. L. Carter, *Steroids*, **2**, 319 (1963).

(6) R. A. Edgren, H. Smith, G. A. Hughes, L. L. Smith, and G. Greenspan, *ibid.*, **2**, 731 (1963).

(7) R. M. Tomarelli and F. W. Bernhart, *ibid.*, **4**, 451 (1964).

(8) R. A. Edgren and H. Smith, "Hormonal Steroids, Biochemistry, Pharmacology, and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids," Volume 2, Academic Press, Inc., New York, N. Y., 1965, p 161.

(9) R. A. Edgren, D. L. Peterson, R. C. Jones, C. L. Nagra, H. Smith, and G. A. Hughes, *Recent Progr. Hormone Res.*, in the press.

(10) R. B. Greenblatt, E. C. Jungck, and G. C. King, *Am. J. Med. Sci.*, **248**, 317 (1964).

(11) M. Roland, M. J. Clyman, A. Decker, and W. B. Ober, *Obstet. Gynecol.*, **27**, 222 (1966).

(12) R. B. Greenblatt, E. C. Jungck, R. A. Puebla, and M. C. Ward, *Clin. Pharmacol. Therap.*, **7**, 490 (1966).

(13) C. Baddeley, H. Carpio, and J. A. Edwards, *J. Org. Chem.*, **31**, 1026 (1966).

(14) M. S. deWinter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959), have described the corresponding alcohol.

(15) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(16)(a) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, 461 (1962), have described the diethylaluminum chloride mediated addition of HCN to steroids containing α,β-unsaturated carbonyl groups, but not including the novel estr-5(10)-en-4-one system. (b) After the completion of our work, J. Fishman and H. Guzik, *ibid.*, 1483 (1966), disclosed the conversion with KCN in boiling ethylene glycol of two estr-5(10)-en-6-ones, obtained through the degradation of androstane derivatives, to corresponding 10β-cyanoestran-6-ones, and the transformation of the latter substances to intermediates which had previously been converted to androst-4-en-3-ones.

(17) *E.g.*, W. Nagata, *Tetrahedron*, **13**, 287 (1961); W. Nagata and I. Kikkawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 289 (1963); W. Nagata, T. Terasawa, and T. Aoki, *ibid.*, **11**, 819 (1963).

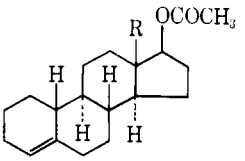
(18) K. Hensler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1963).

(19) W. Klyne, *Experientia*, **20**, 349 (1964).

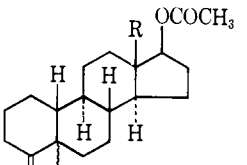
(20) N. D. Hartshorn and D. Kirk, *Tetrahedron Letters*, 89 (1965).

trum showed a C_{19}-methyl singlet at δ 0.73 in excellent agreement with the chemical shift of 0.76, calculated for 5α-androstan-4-one using previously summarized data,[21] and quite distinct from that of 1.125 similarly calculated for 5β-androstan-4-one.

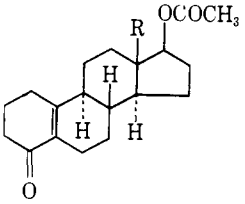
The next phase in the synthesis called for the preparation of 4-hydroxytestosterone 17-acetate XI from the acetate VIII *via* the oxime X. Direct oximination of VIII with amyl nitrite and sodium methoxide failed, but X was satisfactorily prepared from VIII by Claisen condensation with ethyl formate and treatment of the resulting 3-hydroxymethylene steroid IX with nitrous acid.[22] Hydrolysis of X with a mixture of acetic and pyruvic acids gave 4-hydroxytestosterone 17-acetate XI, identical with an authentic sample prepared by a known method from testosterone.[23] This substance is formulated as such, rather than the alternate 2-en-3-ol-4-one, from its pmr spectrum which shows no vinylic proton signal. Oxidation of VIII with selenium dioxide in aqueous ethanol gave an intractable product from which no XI could be obtained. For conversion to testosterone acetate, XI was converted to its mesylate formulated as XII rather than as a derivative of the alternate enol, from its pmr spectrum which showed no vinylic proton signal. Hydrogenation of XII in acidified ethyl acetate at atmospheric pressure over palladized charcoal until 1.4 moles of gas had been absorbed resulted in saturation of the double bond and partial reduction of the carbonyl group. Oxidation of the product with the Jones' reagent[15] then gave a single isomer of structure XIII which was converted by refluxing with lithium chloride and lithium carbonate in dimethylformamide to testosterone acetate XIV, identical with an authentic sample. Hydrogenation of XIII under similar conditions over Adam's catalyst until hydrogen uptake ceased gave a complex mixture from which 17β-acetoxy-5α-androstan-3-one was isolated in 17% yield.



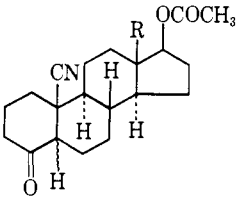
I, R = CH_3
Ia, R = C_2H_5



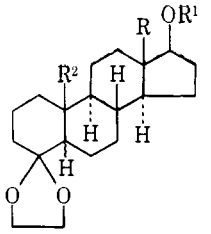
II, R = CH_3
IIa, R = C_2H_5



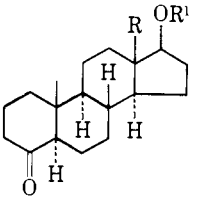
III, R = CH_3
IIIa, R = C_2H_5



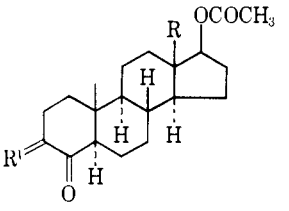
IV, R = CH_3
IVa, R = C_2H_5



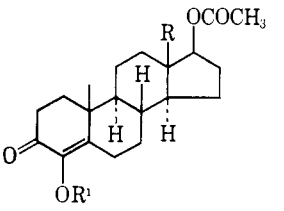
	R	R^1	R^2
V,	CH_3	$COCH_3$	CN
Va,	C_2H_5	$COCH_3$	CN
VI,	CH_3	H	CH=NH
VIa,	C_2H_5	H	CH=NH



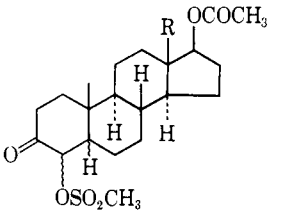
	R	R^1
VII,	CH_3	H
VIIa,	C_2H_5	H
VIII,	CH_3	$COCH_3$
VIIIa,	C_2H_5	$COCH_3$



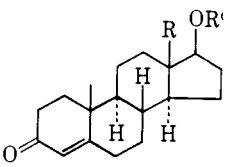
IX, R = CH_3; R' = CHOH
IXa, R = C_2H_5; R' = CHOH
X, R = CH_3; R' = NOH
Xa, R = C_2H_5; R^1 = NOH



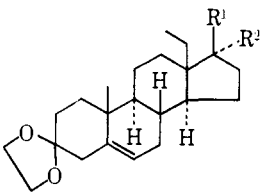
XI, R = CH_3; R' = H
XIa, R = C_2H_5; R' = H
XII, R = CH_3;
R' = SO_2CH_3
XIIa, R = C_2H_5;
R' = SO_2CH_3



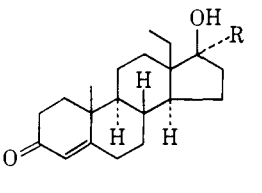
XIII, R = CH_3
XIIIa, R = C_2H_5



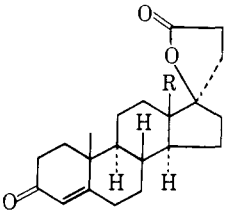
XIV, R = CH_3; R' = $COCH_3$
XIVa, R = C_2H_5; R' = $COCH_3$
XV, R = C_2H_5; R' = H



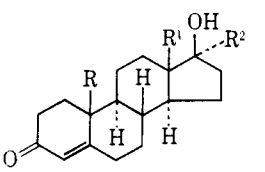
XVI, R' = OH; R^2 = H
XVII, R' + R^2 = O
XVIII, R' = OH; R^2 = C≡CH
XIX, R^1 = OH; R^2 = C_2H_5
XX, R^1 = OH; R^2 = C≡CCO_2H



XXI, R = C≡CH
XXII, R = C_2H_5



XXIII, R = C_2H_5
XXIV, R = CH_3



XXV

In an analogous fashion the racemic acetate Ia,[24] derived from the corresponding alcohol,[4b] was converted to *dl*-18-methyltestosterone acetate XIVa through the respective intermediates IIa–XIIIa. The

(21) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry, Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, pp 19–22.

(22) Merck and Co., Inc., Netherlands Patent Application 6,407,322 (1963); *Chem. Abstr.*, **62**, 16338 (1965).

(23) B. Camerino, B. Patelli, and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3540 (1956).

(24) This and other racemic substances described in this paper are depicted by the enantiomorphs having the 13-alkyl group in the β configuration. Where appropriate such enantiomorphs are given the prefix *d*, and racemic steroids the prefix *dl*.

TABLE I: ESTRANE, ANDROSTANE, *dl*-18-METHYLANDROSTANE, AND *dl*-18-METHYLPREGNANE DERIVATIVES

Compd	Yield, %[a]	Cryst[b] solvent	Mp, °C[c]	[α]D, deg	Formula	Calcd, % C	Calcd, % H	Calcd, % Br	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % Br	Found, % N	Found, % S	λmax, mμ (ε × 10⁻³)	Pmr data[d]
I	77	A	81–82		$C_{20}H_{30}O_2$	79.42	10.00				79.21	9.70					
dl-Ia	74	B	93–94		$C_{21}H_{32}O_2$	79.70	10.19				79.69	10.31					
II	38	B + C	151–153		$C_{20}H_{29}BrO_3$	60.45	7.36	20.11			60.61	7.25	19.90				
dl-IIa	28	B	137–138		$C_{21}H_{31}BrO_3$	61.31	7.60	19.42			61.45	7.37	19.00				
III	56	B + C	140.5–142		$C_{20}H_{28}O_3$	75.91	8.92				76.18	8.94				251 (13.0)	0.83 s (3, 18H), 2.07 s (3, acetate CH_3), 4.72 t (1, 7, 17H)
dl-IIIa	66	B + C	143–144		$C_{21}H_{30}O_3$	76.32	9.15				76.08	9.01				251 (13.6)	0.95 t (3, 7, 18aH), 2.07 s (3, acetate CH_3), 4.84 t (1, 7, 17H)
IV	73	B	201–203		$C_{21}H_{29}NO_3$	73.43	8.51		4.08		73.32	8.71		3.99			
dl-IVa	75	B + C	183–185		$C_{22}H_{31}NO_3$	73.91	8.74		3.92		74.08	8.42		3.88			
VII[e]	59	B + D	128–129	+14.4	$C_{19}H_{30}O_2$	87.57	10.41				78.59	10.57					0.73 s (6, 18, and 19H), 3.48 t (1, 8 17H)
dl-VIIa	50	B + D	182–184		$C_{20}H_{32}O_2$	78.89	10.59				78.75	10.47					0.75 s (3, 19H), 0.98 t (3, 6, 18aH), 3.75 t (1, 7, 17H)
XI[f]	23	B + C	187–189	+82.4	$C_{21}H_{30}O_4$	72.80	8.73				73.28	8.37				281 (12.0) 332 (7.4)[h]	0.83 s (3, 18H), 1.19 s (3, 19H), 2.05 s (3, acetate CH_3), 4.63 t (1, 8, 17H)
dl-XIa	20	C	184–186		$C_{22}H_{32}O_4$	73.30	8.95				73.22	8.89				275 (12.6) 328 (7.7)[h]	0.96 t (3, 6, 18aH), 1.16 s (3, 19H), 2.03 s (3, acetate CH_3), 4.70 t (1, 8, 17H)
XII	69	B + C	185–187		$C_{22}H_{32}O_5S$	62.24	7.60			7.55	62.53	7.47			7.70	248 (14.9)	0.83 s (3, 18H), 1.26 s (3, 19H), 2.03 s (3, acetate CH_3), 3.36 s (sulfonate CH_3), 4.65 t (1, 8, 17H)
dl-XIIa	67	C	211–213		$C_{23}H_{34}O_6S$	62.98	7.81			7.31	63.01	7.88			7.20	243 (14.4)	1.26 s (3, 19H), 2.03 s (3, acetate CH_3), 3.36 s (3, sulfonate CH_3), 4.67 t (1, 8, 17H)
XIII	55	B + C	174–175		$C_{22}H_{34}O_5S$	61.94	8.03			7.52	61.99	7.99			7.80		0.83 s (3, 18H), 1.14 s (3, 19H), 2.05 s (3, acetate CH_3), 3.23 s (3, sulfonate CH_3)
dl-XIIIa	50	C	187–188		$C_{23}H_{36}O_6S$	62.70	8.24			7.28	62.82	8.27			7.30		0.94 t (3, 6, 18aH), 1.11 s (3, 19H), 2.01 s (3, acetate CH_3), 3.20 s (3, sulfonate CH_3)
XIV[g]	38	B + C	157–159		$C_{21}H_{30}O_3$	76.3	9.15				76.2	9.2				241 (16.0)	0.85 s (3, 18H), 1.20 s (3, 19H), 2.05 s (3, acetate CH_3), 4.65 t (1, 8, 17H), 5.76 s (1, 4H)
dl-XIVa	69	B + C	159–160		$C_{22}H_{32}O_3$	76.70	9.36				76.75	9.08				238 (15.7)	1.18 s (3, 19H), 2.02 s (3, acetate CH_3), 4.67 t (1, 8, 17H), 5.71 s (1, 4H)
dl-XV	54	C	198–200		$C_{20}H_{30}O_2$	79.42	10.00				79.23	9.93				240 (15.6)	1.03 t (3, 6, 18aH), 1.20 s (3, 19H), 3.75 t (1, 8, 17H), 5.71 s (1, 4H)
dl-XXI	21	B + C	205–207		$C_{20}H_{30}O_2$	80.93	9.26				80.94	9.11				240 (16.0)	1.02 t (3, 7, 18aH), 1.18 s (3, 19H), 2.58 s (1, 21H), 5.71 s (1, 4H)
dl-XXII	43	B + C	132–133		$C_{20}H_{34}O_2$	79.95	10.37				79.67	10.14				241 (16.0)	1.20 s (3, 19H), 5.71 s (1, 4H)
dl-XXIII	14	B + C	217–219		$C_{21}H_{32}O_2$	77.49	9.05				77.53	9.08				240 (16.2)	0.97 t (3, 7, 18aH), 1.19 s (3, 19H), 5.72 s (1, 4H)

[a] Unless noted otherwise yields refer to crystalline substance sufficiently pure for further chemical reaction. [b] A = methanol, B = hexane, C = acetone, D = ether. [c] Refers to samples of analytical purity. [d] Chemical shift and multiplicity are given for each signal; s = singlet, t = triplet. Data in parentheses refer consecutively to strength of signal in protons, coupling constant *J* (where appropriate), and location of protons giving rise to the signal. [e] Identical in melting point, [α]D, and infrared and pmr spectra with a sample prepared as described by Heusler, *et al.*,[18] who give mp 125–126°, [α]^{25}D +16° ($CHCl_3$). [f] A sample made as described by B. Camerino, *et al.*,[23] had [α]^{25}D + 83°, mp 191–193° and 188–190° on admixture with XI. Both samples had identical ultraviolet, infrared, and pmr spectra. [g] Identical in melting point and ultraviolet, infrared, and pmr spectra with an authentic sample, mp 139–140°. [h] In solution containing NaOH.

TABLE II

BIOLOGICAL ACTIVITIES OF *dl*-18-METHYLANDROSTANE, *dl*-18-METHYLPREGNANE DERIVATIVES, AND ANALOGOUS ANDROSTANE, *dl*-13β-ETHYLGONANE, AND ESTRANE DERIVATIVES

Compd	R	R^1	R^2	Anab[a]	And.[b]	Anab/And.	Prog[c]	Antiestr[d]
dl-XV				20	21	0.95	0	30
d-XXV[e]	CH_3	CH_3	H	10	15	0.67	?[f]	100
dl-XXV[g]	H	C_2H_5	H	54	27	2	3	1100
d-XXV[h]	H	CH_3	H	60	4	15	?[f]	200
dl-XXI				7	0.7	10	71	100
d-XXV[i]	CH_3	CH_3	C≡CH	0	1	0	0	100
dl-XXV[j]	H	C_2H_5	C≡CH	50	6	8.3	915	7300
d-XXV[k]	H	CH_3	C≡CH	20	2	10	8.5	730
dl-XXII				5	5.4	0.93	0	0
d-XXV[l]	CH_3	CH_3	C_2H_5	5	2.8	1.79	0	0
dl-XXV[m]	H	C_2H_5	C_2H_5	340	17	20	500	2600
d-XXV[n]	H	CH_3	C_2H_5	80	12	7	750	1900

[a] Anabolic potency expressed in terms of testosterone propionate (= 100). [b] Androgenic potency expressed in terms of testosterone propionate (= 100). [c] Progestational potency expressed in terms of progesterone (= 100). [d] Antiestrogenic potency expressed in terms of progesterone (= 100). [e] Testosterone. [f] Active but with proliferation of endometrial glands different from that observed with progesterone. [g] References 4a,b, 5, 6, 8, 9. [h] 19-Nortestosterone [A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953)] obtained from Syntex, S. A. [i] Ethisterone [L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); H. H. Inhoffen, W. Logemann, W. Holweg, and A. Seriui, *Chem. Ber.*, **71**, 1024 (1938)] supplied by Steraloids Inc. [j] Norgestrel.[4a,b,5,6,8,9] [k] Norethisterone [H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 2477 (1956)] kindly supplied by Ortho Corp. [l] L. Ruzicka, K. Hofmann, and F. Meldahl, *Helv. Chim. Acta*, **21**, 597 (1938); prepared by catalytic hydrogenation of XXV (R = R' = CH_3; R^2 = C≡CH) in benzene over 2% Pd-$CaCO_3$. [m] Norbolethone.[4a,b,5,6,8,9] [n] Norethandrolone [F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957)] supplied by G. D. Searle and Co.

stereo structure assigned to each member of this series follows by analogy with that demonstrated for its 13-methyl analog. Analytical and other data for both series are given in Table I.

The preparation of the *dl*-18-methylpregnane analogs XXI and XXII proceeded through the alcohol XV which on ketalization and Oppenauer oxidation gave the oxo ketal XVII. Interaction of XVII with the lithium acetylide–ethylenediamine complex[4b,25] afforded the alcohol XVIII, which was converted by acid hydrolysis to XXI, and, by catalytic hydrogenation followed by acid hydrolysis, to XXII. The intermediate XVIII was also transformed to the spirolactone XXIII by carbonation of the bromomagnesium derivative, catalytic hydrogenation of the resulting XX, and acidic hydrolysis. The lower homolog XXIV has been recognized as an inhibitor of the mineralocorticoid activity of deoxycorticosterone acetate in laboratory animals.[26]

Biological Activities.—We deemed it of interest to compare the biological activities of the series XV, XXI, and XXII in anabolic, androgenic, progestational, and antiestrogenic tests with those of their analogs in the androstane, 13β-ethylgonane, and estrane series. The anabolic and androgenic activities were determined in the Hershberger test,[27] the progestational activities in the Clauberg test,[28] and the antiestrogenic activity in a vaginal cornification inhibitory test.[29] The results are assembled in Table II. Since it has been established[4a,6,9] that various biological activities of the racemates XXV (R = H; R^1 = C_2H_5; R^2 = H, C≡CH, C_2H_5) are confined to the enantiomorphs corresponding in absolute configuration to the naturally occurring steroids, such enantiomorphs in XV, XXI, and XXII presumably have twice the potencies recorded. Baddeley, *et al.*,[13] have described the preparation of the corresponding enantiomorphic steroids without disclosing their biological activities. The data show clearly that the compounds of the estrane and 13β-ethylgonane series are superior to those of the androstane and 18-methylandrostane series as anabolic, progestational, and antiestrogenic agents, and that XXV (R = H; R^1 = C_2H_5; R^2 = C≡CH) is the most potent progestational and antiestrogenic agent, and XXV (R = H; R^1 = R^2 = C_2H_5), the most potent anabolic agent, in the group. In a deoxycorticosterone antagonist test[30] in the rat, a 4-mg dose of XXIII administered subcutaneously produced a 33% inhibition of the mineralocorticoid excreting effects of a 10-μg dose of deocycorticosterone acetate. In a similar test a 0.22-mg dose of the lower homolog XXIV is reported to produce a 50% inhibition of the effects of a 12-μg dose of deoxycorticosterone acetate.[26c]

Experimental Section

All evaporations were under reduced pressure. All hydrogenations were at atmospheric pressure. Melting points were determined in capillary tubes (Thomas–Hoover apparatus) and are uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol solutions. Optical rotations were determined on 0.5–1% solutions in $CHCl_3$ at 25° using the Zeiss 0.005° photoelectric polarimeter. Pmr spectra were measured on the Varian A-60 spectrometer using 5–10% solutions in $CDCl_3$ containing $(CH_3)_4Si$ as internal reference standard. Shifts are expressed in δ units measured downfield from the reference, and coupling constants, *J*, in cps. The former should be accurate to ±0.1 ppm, the latter to ±0.5 cps. All substances had infrared absorption spectra in accord with the assigned structures.

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dl-**13β-Ethylgon-4-en-17β-ol.**—3,3-Ethylenedithio-13β-ethylgon-4-en-17β-ol[45b] was reduced with sodium in liquid ammonia as previously described,[46] and the product was recrystallized from hexane to give the alcohol, mp 124–125°.

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.17; H, 10.98.

17β-Acetoxyestr-4-ene (I).—Estr-4-en-17β-ol[47] (21.5 g) was kept on the steam bath for 1 hr in pyridine–acetic anhydride (100:30 ml). The product in hexane was filtered through neutral alumina and recrystallized twice from methanol to give the acetate (19.2 g).

17β-Acetoxy-5ξ-bromoestran-4-one (II).—N-Bromosuccinimide (2.1 g) and 12% $HClO_4$ (3.6 ml) were added to I (3 g) in dioxane–water (60:15 ml) and the mixture was kept at room temperature for 2 hr. After neutralization ($NaHCO_3$), the mixture was diluted with water and extracted with ether. Chromic acid[48] (8 *N*, 4 ml) was added to the product in acetone (6.5 ml) and the mixture was stirred at room temperature for 15 min. 2-Propanol was added to discharge the red color and the mixture was extracted with ether. Two recrystallizations of the product from hexane–acetone gave the ketone (1.5 g).

17β-Acetoxy-5(10)-en-4-one (III).—II (10.8 g) was refluxed in pyridine (100 ml) for 1 hr. The solvent was evaporated, water was added to the residue, and the mixture was extracted with ether. Evaporation of the washed and dried extracts gave a residue which was percolated in benzene through neutral alumina. Three recrystallizations of the product from acetone–hexane gave the ketone (4.8 g).

17β-Acetoxy-10β-cyano-5ξ-estran-4-one (IV).—Hydrogen cyanide (1.6 ml) in tetrahydrofuran (THF) (40 ml) was added slowly with stirring under nitrogen to 25% diethylaluminum bromide in heptane[49]–THF (48:50 ml) at 0°. III (4.8 g) in THF (60 ml) was added and the mixture was lightly stoppered and kept for 5 hr at room temperature with occasional unstoppering during the first hour to release increased pressure. The mixture was added with stirring to ice-cold 5% aqueous NaOH and extracted with chloroform. The product in benzene was percolated through neutral alumina and recrystallized from hexane–acetone to give the ketone (3.8 g).

17β-Hydroxy-5α-androstan-4-one (VII).—IV (1 g) was refluxed in benzene (100 ml) containing ethylene glycol (10 ml) and *p*-toluenesulfonic acid (0.1 g) for 9 hr (Dean–Stark water separator). The benzene was evaporated, water was added to the residue, and the mixture was extracted with $CHCl_3$. The product V in THF (50 ml) was added over 15 min with stirring to $LiAlH_4$ (1.1 g) in THF (80 ml) at 0° under N_2, the mixture was refluxed for 18 hr, 0.86 *M* aqueous potassium sodium tartrate–0.5 *M* tartaric acid (20:5 ml) was cautiously added, and the mixture was diluted with water and extracted with $CHCl_3$. The product VI (1 g), λ_{max} 6.15 μ, was kept for 2 hr at 140–150° in diethylene-glycol–hydrazine hydrate (70:5 ml) containing KOH (5 g). The mixture was distilled until the boiling point reached 210° and refluxed for 6 hr. The product (1 g) was refluxed for 10 min in acetone–10 *N* HCl (50:2 ml) and the solution was evaporated, diluted with water, and extracted with $CHCl_3$. The product was chromatographed on neutral alumina, elution with benzene–ether (20:1) giving the 5α-androstanone (0.5 g); ORD (*c* 0.097, dioxane): $[\phi]_{329}$ −1200°, $[\phi]_{312}$ −3390°, $[\phi]_{300}$ −2190°, $[\phi]_{296}$ −2520°, $[\phi]_{271}$ +4190°, $[\phi]_{229}$ +2940°.

17β-Acetoxy-4-hydroxyandrost-4-en-3-one (XI).—VII (0.97 g) was kept on the steam bath for 1 hr in pyridine–acetic anhydride (15:5 ml). The product (VIII, 1.1 g) was kept at room temperature for 2 days with sodium methoxide (2 g) in ether–ethyl formate (50:10 ml). The mixture was diluted with water, washed with ether, acidified with HCl, and extracted with $CHCl_3$. The solid product IX (0.96 g), λ_{max} 279 mμ in CH_2Cl_2–acetic acid–water (12:60:3 ml), was treated at 0° with $NaNO_2$ (0.36 g) in water (5 ml). The mixture was stirred at 0° for 45 min, diluted with CH_2Cl_2, washed with water until neutral, dried, and evaporated to give the solid product X (0.9 g), λ_{max} 240 mμ, which was refluxed for 10 hr in acetic acid–water–pyruvic acid (35:15:5 ml). The mixture was concentrated to a slurry, diluted with $CHCl_3$, washed with 5% aqueous $KHCO_3$ and water, dried, and evaporated to a red oil which was chromatographed on silica gel. Elution with benzene–ether (9:1) gave the hydroxyandrostenone (0.268 g).

17β-Acetoxy-4-methanesulfonyloxyandrost-4-en-3-one (XII).—XI (5 g) was kept at 0° for 16 hr in pyridine–methanesulfonyl chloride (100:5 ml). The mixture was added to ice water (1 l.), and the precipitate was filtered off and refluxed in acetone (charcoal). Two recrystallizations of the product from acetone–hexane gave the methanesulfonate (4.2 g).

17β-Acetoxy-4ξ-methanesulfonyloxy-5ξ-androstan-3-one (XIII).—XII (4 g) was shaken with H_2 in ethyl acetate–H_2SO_4 (40:1 ml) containing 10% Pd–C (0.2 g) until 1.4 moles of H_2 had been absorbed (35 min). The mixture was filtered and the filtrate was washed with 5% aqueous $KHCO_3$ and water, dried, and evaporated. Chromic acid[48] (8 *N*) was added to the product in acetone (60 ml) until a red color persisted, and the mixture was stirred at room temperature for 30 min. The red color was discharged with 2-propanol, and the mixture was concentrated to 15 ml, diluted with water, and extracted with $CHCl_3$. Recrystallization from acetone–hexane gave the ketone (0.55 g).

Testosterone Acetate (XIV).—XIII (0.54 g) was stirred under nitrogen at 140° for 4 hr in DMF (75 ml) containing LiCl (2 g) and lithium carbonate (1.2 g). The solvent was evaporated and the residue was dissolved in ether and washed with water. Evaporation of the dried extract gave a residue which was percolated in benzene through neutral alumina. The product was recrystallized from acetone–hexane, refluxed in acetone (charcoal), and recrystallized from acetone–hexane to give testosterone acetate (0.16 g), mp 137–139°.

***dl*-18-Methyltestosterone (XV).**—XIVa (2.1 g) was refluxed for 1 hr under N_2 with KOH (2 g) in methanol–water (100:10 ml). The mixture was concentrated to a slurry and dissolved in $CHCl_3$, and the solution was washed with water and dried. Three recrystallizations of the product from acetone gave the methyltestosterone (1 g).

***dl*-17β-Hydroxy-18-methyl-17α-pregn-20-yn-4-en-3-one (XXI).**—XV (0.35 g) was refluxed for 18 hr in benzene–ethylene glycol (40:4 ml) containing *p*-toluenesulfonic acid (20 mg) (Dean–Stark water separator). The solid product XVI was refluxed for 4 hr under N_2 with aluminum isopropoxide (0.5 g) in benzene–methyl ethyl ketone (80:25 ml). The cooled mixture was diluted with ether, washed with water, dried, and evaporated. The residue was chromatographed on neutral alumina, elution with benzene giving XVII (0.26 g), mp 162–166°, λ_{max}^{KBr} 5.75 μ. Lithium acetylide–ethylenediamine complex[46,25] (0.7 g) was added to XVII (1 g) in dimethylacetamide (35 ml, previously saturated at room temperature with acetylene), and acetylene was passed with stirring through the mixture for 2.5 hr. The solution was added to ice water and the mixture was extracted with ether. The product XVIII (1 g), having no infrared absorption in the 5.75-μ region, was kept at room temperature for 2 hr in THF–3 *M* $HClO_4$ (30:6 ml). The mixture was basified with 5% aqueous $KHCO_3$, concentrated, diluted with water, and extracted with $CHCl_3$. The product was chromatographed on neutral alumina, elution with benzene–ether (19:1) giving a product which was recrystallized twice from acetone–hexane to give the alcohol (0.31 g).

***dl*-17β-Hydroxy-18-methyl-17α-pregn-4-en-3-one (XXII).**—XVIII (1.2 g) was shaken with hydrogen in ethyl acetate–benzene (70:45 ml) containing 2% $SrCO_3$–Pd until 2.2 moles of gas had been absorbed (2.5 hr). The product XIX was kept at room temperature for 2 hr in THF–3 *M* $HClO_4$ (40:9 ml). It was chromatographed on neutral alumina, elution with benzene giving a product which was recrystallized twice from acetone–hexane to give the methylpregnene (0.47 g).

***dl*-17β-Hydroxy-18-methyl-17α-pregn-4-en-3-one-21-carboxylic Acid Lactone (XXIII).**—Ethereal methylmagnesium bromide (3 *M*, 25 ml) was added under N_2 to XVIII (1.3 g) in THF (60 ml) and the mixture was refluxed for 1 hr. CO_2 was bubbled through the cooled solution for 1 hr, and the mixture was added to ice–water and extracted with ether. The ether solution was extracted with 5% aqueous $KHCO_3$ and the aqueous extracts were acidified with tartaric acid and extracted with ether. Evaporation of the washed and dried extracts gave XX (0.5 g). The neutral fraction (0.8 g) was recycled to obtain further XX (0.3 g). The combined product was shaken with hydrogen in ethyl acetate–benzene (50:20 ml) containing 2% $CaCO_3$–Pd (0.6 g) until 2 moles of gas had been absorbed (2.5 hr). The mixture was filtered, and the filtrate was heated on the steam bath for 10 min with 11 *N* HCl (5 ml). The product was chromatographed on neutral alumina, elution with benzene giving a product which was recrystallized from acetone–hexane to give the lactone (0.175 g).

(31) Supplied by Orgmel, Hampstead, N. H.

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8-Aza Steroids. IV.[1] 8-Aza-19-norprogestogens

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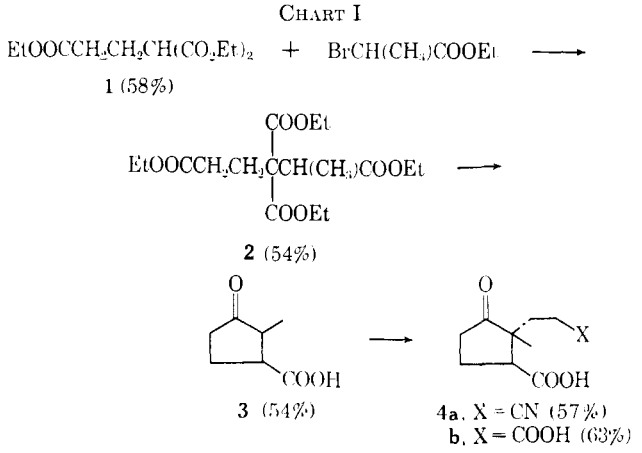
The synthesis of 8-aza-19-norprogesterone, 17α-hydroxy-8-aza-19-norprogesterone, and several isomeric products has been accomplished by application of the previously described sequence. Spectral data are described on the basis of which the stereochemical assignments are made. The products were essentially inactive as progestogens.

Previous papers[2] in this series have described the synthetic route to the 8-aza steroid nucleus developed in these laboratories, and application of the method to the synthesis of 8-azaestrogens and 8-aza-19-norandrogens. The present communication deals with the preparation of the 8-aza analog of 19-norprogesterone and related products. Subsequent publications will be concerned with applications of the method to the preparation of the 8-aza analogs of other 19-nor steroid hormones.

Preparation of the known[3] 2-methyl-2-β-carboxyethylcyclopentanone-3-carboxylic acid (**4b**) was carried out by modifications of published procedures as summarized in Chart I. Triethyl 2-carboxyglutarate[4] (**1**)

Chart I



was prepared by adaptation of the method of Floyd and Miller.[5] This was alkylated with ethyl α-bromopropionate to give the known[6] **2**, which was converted to acid **3**[6,7] by the procedure of Shimyakin, *et al.*[6]

Michael addition of **3** to ethyl acrylate failed under a variety of conditions. Addition of acrylonitrile, however, did take place exothermally under strongly basic conditions and led to adduct **4a**. That addition to the cyanoethyl group occurred at the more substituted carbon atom, as desired, was established by the unsplit methyl nmr signal at 1.02 ppm. Hydrolysis to the required ketodicarboxylic acid **4b** was accomplished with HCl.[3] On the basis of thermodynamic considerations, the methyl and secondary carboxyl groups in this product were assumed in previous work[3] to have a *cis* relationship to each other. Some additional evidence relative to the configuration of **4b** was obtained in the present work (see ref 8).

Condensation of **4b** with *m*-methoxyphenethylamine[2b] was carried out by both of the previously described[1,2] procedures. Direct condensation in refluxing xylene afforded the unsaturated lactam **5** in 77% yield. Catalytic reduction of **5** proceeded stereospecifically to afford a single saturated lactam **7** (Chart II[9]). This was also obtained as the sole product of reductive condensation of the amine and **4b**. Proof of the *trans* fusion of the pyrindone rings in **7** was obtained in later work (see ref 10).

Lactams **5** and **7** were treated in succession with $POCl_3$, ethanol, and dilute base to give the unsaturated esters **6** and **8**, respectively, in high yields, the reactions

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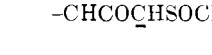
(8) Some additional evidence on the configuration of **4b** may now be derived in the following way. In **12a**, the acetyl group is β and therefore *cis* to the angular methyl. Since no change in configuration during acid-catalyzed hydrolysis would be expected, ketone **10a** (as obtained by the Corey procedure) must also have the acetyl group *cis* to the methyl. Likewise, the Corey procedure probably proceeds without change in configuration (the stable anion



presumably preventing abstraction of the proton at C-17), leading to the conclusion that the COOR group in **9** is also *cis* to the CH3. The same must then be true in the precursor **4b**.

(9) All compounds described in this paper were obtained as *dl* pairs. For convenience, the structures depict only one of the optical antipodes.

(10) The C–D *trans* ring junction in the saturated lactam **7** was established in the following way. When sulfoxide **10b** was treated with acetic acid followed by Raney Ni, a minor product isolated from the reaction was identified as hydroxy ketone **15c**. Since the ring junction of **15c** was established unequivocally as *trans* by its preparation from keto lactam **13a** of known *trans* ring junction, it follows that sulfoxide **10b**, its precursors **7–9**, and its transformation products **11** and **12** must also have the C–D *trans* ring junction. This work will be discussed in detail in a subsequent publication.