log ϵ 4.65; $\lambda_{max}^{CHCl_3}$ 5.83, 6.09 and 6.21 (shoulder) μ. The substance gave a red color with ferric chloride.

Anal. Calcd. for $C_{29}H_{42}O_3$: C, 79.40; H, 9.65; O, 10.94. Found: C, 78.97; H, 9.27; O, 11.10.

(b) **From the Trityl Ether VIIb.**—When 1.0 g. of the trityl ether VIIb was heated under reflux for 8 hr. with 50 cc. of ethanol and 0.5 cc. of sulfuric acid and then cooled, there separated approximately 50 mg. of crystals. These were filtered and recrystallized from methanol whereupon they exhibited m.p. 248–251°, undepressed upon admixture with a sample prepared according to (a). The ultraviolet absorption spectrum and the red color with ferric chloride supported the identification of this substance.

Anal. Calcd. for $C_{29}H_{42}O_3$: C, 79.40; H, 9.65. Found: C, 79.41; H, 9.53.

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[CONTRIBUTION FROM THE LABORATORIES OF THE SCHERING CORPORATION]

Long-acting Testosterone Esters. Some Considerations on their Biological Utilization[1]

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A series of testosterone 17-esters was prepared to find those with the best activity and duration. Several potent derivatives were found, including the entire family of aryloxyalkanoates. Injections of these esters in rodents are shown to be efficient and enduring sources of testosterone.

Since testosterone was established as the true androgenic hormone,[2] attempts have been made to potentiate its effect and prevent its rapid metabolic destruction.[3] The program reported here was carried out with this aim, and led to many esters considerably more valuable in potentiating the androgenic effect than testosterone propionate,[4] as well as a group of esters which are outstanding in the assays used with respect to intensity and duration of androgenic action. The results are given in Tables I-IV.

The acids corresponding to the esters, if they were not available commercially, were prepared by methods reported in the literature, mainly from "Beilstein: Handbuch der Organischen Chemie." The acid chlorides were made using thionyl chloride and generally isolated by vacuum distillation, though the residues were used when distillation caused decomposition. Although some of the acid chlorides had not been known previously, they are not reported here, since they were not characterized and analyzed. All of the esters were made according to the standard procedure given below, in which chilling was found to be essential for the ready preparation of pure products. In the case of oily esters, chromatography gave materials with the correct analyses.

The intensity and duration of androgenic action were tested in mice and rats, giving results which are shown qualitatively in the tables according to their relation to the action of testosterone propionate (TP). The effects were measured by weighing the seminal vesicles of castrated animals at various times after subcutaneous injection of the ester. We have considered that compounds effecting a maximum seminal vesicle weight less than $1/2$ of that due to TP are not of interest and such are rated "0." Conversely, compounds with maxima several times that of TP generally last correspondingly longer before falling below our cut-off point.

The original hypothesis on which this study was based stemmed from the maximal activity of the lowest melting members of the straight chain acid series of esters, *e.g.*, heptanoate and nonanoate.[4,5] This suggested that the more oil-soluble esters are most useful; therefore, a group of esters of branched chain acids was prepared (see Table I). The results show that, while none surpasses the heptanoate and nonanoate, several esters containing four to eleven carbons approached them in activity. The variation of the activity from good to poor of intermediate-length esters, all of them low melting solids or oils readily soluble in hydrocarbon solvents, shows the invalidity of the hypothesis. For example, the decreased activity of the 3,3-dimethylpentanoate compared to the 3-methylpentanoate is in disagreement.

It is, however, possible to make some generalizations. (1) All of the esters with dialkyl-substituted chains have poor activity. (2) The 2-alkyl-substituted esters (except isobutyrate) have a low order of activity. These statements suggest that steric hindrance plays an important role in decreasing the activity. Thus, fatty acids, such as trimethylacetic and diethylacetic, which are known to esterify at less than one-tenth the rate of acetic, and, therefore, also to hydrolyze with difficulty, due to hindrance caused by branching,[6] form testosterone esters whose intensity is so reduced that they are therapeutically useless.

Since no trend or advance in activity is observable in the fatty acid series, other types were prepared (Tables II-IV), especially a group of substituted cyclohexane-carboxylic acid esters (Table

(1) Presented in part before the Medicinal and Biological Chemistry Section of the Delaware Valley Regional Meeting of the American Chemical Society, Philadelphia, February 16, 1956.

(2) K. David, E. Dingemanse, J. Freud and R. Laqueur, *Z. physiol. Chem.*, **233**, 281 (1935); A. Butenandt and G. Hanisch, *Ber.*, **68**, 1859 (1935); L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1264 (1935).

(3) *Inter alia*, T. F. Gallagher, D. K. Fukushima, M. C. Barry and K. Dobriner, in: "Recent Progress in Hormone Research," Vol. VI, Academic Press, New York, N. Y., 1951, p. 131; L. T. Samuels and C. D. West, in: "Vitamins and Hormones," Vol. X, Academic Press, New York, N. Y., 1952, p. 251.

(4) K. Miescher, A. Wettstein and E. Tschopp, *Biochem. J.*, **30**, 1977 (1936); K. Miescher, H. Kägi, C. Scholz, A. Wettstein and E. Tschopp, *Biochem. Z.*, **294**, 39 (1937); L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **19**, 1141 (1936).

(5) K. Junkmann, *Arch. exper. Path. Pharmakol.*, **215**, 85 (1952).

(6) K. L. Loening, A. B. Garrett and M. S. Newman, THIS JOURNAL, **74**, 3929 (1952).

TABLE I

BRANCHED FATTY ACID ESTERS OF TESTOSTERONE

Ester				Analyses, % Calcd.		Found				
Stem	Substituent	M.p., °C.	$[\alpha]^{25}D$[g]	C	H	C	H	Duration[f]	Method[f]	Intensity[f]
Propionic	2-Methyl[a]	133–135	+71.0°	(Lit.[b] m.p. 134–136°)				2,3,2	A,B,C	2,3,3
Propionic	2,2-Dimethyl[a]	156–158	77.3	(Lit.[c] m.p. 157–158°) [α]D 88 (Chlf.)				0,0	A,C	0,0
Butyric	2-Methyl	135–137	74.8	77.37	9.74	77.21	9.49	2,2,3	A,B,C	1,1/2,3
Butyric	3-Methyl[a]	136–138	80.9	(Lit.[b] m.p. 138–140°)				2	A	2
Butyric	2-Ethyl	129–130	78.3	77.67	9.91	77.50	10.10	2,0	A,C	1,0
Butyric	2-Isopropyl	121–123	79.1	77.95	10.07	78.04	9.96	1,0	A,C	1/2,0
Pentanoic	2-Methyl	81–84	80.1	77.67	9.91	77.91	10.14	3	A	1
Pentanoic	3-Methyl	70–71.5	82.7	77.67	9.91	77.35	9.87	3,2,2	A,B,C	3,2,2
Pentanoic	4-Methyl	82–84.5	82.3	77.67	9.91	77.81	9.63	4	A	3
Pentanoic	3,3-Dimethyl	Oil	72.4	77.95	10.07	78.20	9.71	1	A	1/2
Pentanoic	3-Isopropyl-4-methyl	Oil	70.3	78.45	10.35	78.55	10.15	2	A	1
Hexanoic	3-Methyl	45–46.8	79.2	77.95	10.07	77.79	10.25	3	A	3
Hexanoic	5-Methyl	57–59	79.6	77.95	10.07	77.84	10.05	3	A	3
Hexanoic	2-Ethyl	89–90	75.0	78.21	10.21	78.38	10.18	3	A	1/2
Hexanoic	2-Isopropyl	Oil	66.7	78.45	10.35	78.12	10.71	0,0	A,B	0,0
Hexanoic	3,5,5-Trimethyl	57–60	70.9	78.45	10.35	78.20	10.58	0	A	0
Heptanoic[a]		Oil	75.3	(Lit.[d] m.p. 36–37.5°) [α] 78 (diox.)				3,3	A,B	3,3
Heptanoic[a]	6-Methyl	Oil	66.9	78.21	10.21	78.21	10.23	3[e]	A	3
Octanoic[a]		44–45.2	73.9	(Lit.[d] m.p. 47–48°) [α]D +76				2[e]	A	1/2
Octanoic[a]	2-Methyl	Oil	63.5	78.45	10.35	78.22	10.53	3	A	1
Nonanoic		49–51	75.5	78.45	10.35	78.35	10.59	3,3	A,B	3,3
Nonanoic	3-Methyl	Oil	67.8	78.68	10.48	78.33	10.57	2,2	A,B	1/2,3
Decanoic[a]		54–56	70.7	(Lit.[b] m.p. 55–57°)				2	A	1
Undecenoic		61–62.5	71.8	78.90	10.59	79.31	10.75	2,4,3	A,B,C	1/2,3,2
10-Undecenoic		52–54	72.3	79.24	10.20	79.03	10.02	4,4	A,B	2
Hexadecanoic[a]		72–73	72.4	(Lit.[b] m.p. 72–74°)				0	A	0

[a] Included for comparison. Analyses satisfactory. [b] L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, 19, 1141 (1936). [c] P. Wieland, J. Heer, J. Schmidlin and K. Miescher, *ibid.*, **34**, 354 (1950). [d] Footnote 5. [e] Extrapolated value. [f] The different procedures were: A, 2.5 mg. of ester in oil in mice; B, 7.5 mg. of ester in oil in rats; C, 7.5 mg. of ester in aqueous suspension in rats. Duration of effect is rated as follows: 0 = no effect. (Seminal vesicle weighs less than 1/2 of the TP maximum); 1 = *ca.* that of TP (2–2.5 weeks in mice; 3–4 weeks in rats). 2 = 1–2 × TP; 3 = 2–4 × TP; 4 = 4–6 × TP. Intensity is rated on seminal vesicle weights as follows: 0 = <1/2 TP maximum; 1/2 = 1/2–1 × TP; 1 = TP (55–75 mg. in mice; 200–250 mg. in rats); 2 = 1–1 1/2 × TP; 3 = 1 1/2–2 × TP; 4 = >2 × TP. [g] Rotations in dioxane.

TABLE II

SUBSTITUTED CYCLOHEXANECARBOXYLATES OF TESTOSTERONE

Ester	M.p., °C.	$[\alpha]^{25}D$[a]	Analyses, % Calcd. C	H	Found C	H	Duration[c]	Method[c]	Intensity[c]
Cyclohexanecarboxylate	125.4–127.2	+86.1°	(Lit.[b] m.p. 126–127°; [α]D +88 (Chlf.)				3,3,3	A,B,C	1,2,1
2-Methylcyclohexanecarboxylate	134–136	80.5	78.59	9.77	78.60	9.67	3,0,2	A,B,C	1/2,0,1
3-Methylcyclohexanecarboxylate	120–124	80.5	78.59	9.77	78.31	10.05	3,3,3	A,B,C	3,2,2
4-Methylcyclohexanecarboxylate	163–165.1	78.4	78.59	9.77	78.64	9.94	4,3,3	A,B,C	3,3,3
4-Ethylcyclohexanecarboxylate	138.4–140.5	77.3	78.82	9.92	78.72	9.78	3	A	3
4-Propylcyclohexanecarboxylate	139.5–141.6	75.7	79.04	10.06	78.76	10.11	3	A	2
4-Isopropylcyclohexanecarboxylate	141.5–142.5	81.8	79.04	10.06	78.89	10.20	3	A	2
3,3,5-Trimethylcyclohexanecarboxylate	135–136	78.7	79.04	10.06	79.14	10.14	2,0	A,C	1/2,0

[a] Rotations in dioxane. [b] G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950). [c] See footnote *f*, Table I.

II). Although these acids may be considered as disubstituted acetic acids, the ring ties the alkyl groups back so that hindrance is lessened, except in the case of the 2-methyl and trimethyl derivatives. The 3- and 4-alkylcyclohexane carboxylates generally have intensity about equal to the best fatty acid esters, but the peak activity is maintained better so that the duration of effective action is longer. Extension of the chain to the methylcyclohexylacetates decreases the potency and duration (Table IV). Further extension of the chain to phenyl or cycloalkyl propionates, butyrates, etc., gives esters of varying intensity and with duration similar to the heptanoate, with the exception of the 4-cyclohexylhexanoate whose activity curve climbs only slowly but is maintained high for an exceptionally long period of 14–18 weeks in rats (Table IV). The phenylacetate, 3-phenylpropionate and 3-cyclopentylpropionate which are given here for comparison have intensity and duration in oil similar to the heptanoate. Inexplicably, the 3-cyclopentylpropionate is, as an aqueous suspen-

TABLE III

17-ARYLOXYALKANOATES OF TESTOSTERONE

Ester	M.p., °C.	$[\alpha]^{25}D$[a]	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration[b]	Method[b]	Intensity[b]
Phenoxyacetic	173–174.8	+81.8°	76.74	8.11	76.60	8.33	3,3,3	A,B,C	3,3,4
2-Chlorophenoxyacetic	165–165.9	78.9	70.96 (Cl, 7.72)	7.28	70.70 (Cl, 7.22)	7.15	3[d],4	A,C	2,3
4-Chlorophenoxyacetic	178–180.2	75.3	70.96 (Cl, 7.72)	7.28	71.22 (Cl, 6.95)	7.48	4,3	A,C	4,2
4-Bromophenoxyacetic	174–175	66.8	64.67 (Br, 15.94)	6.63	64.84 (Br, 16.08)	6.93	3,4	A,C	3,3
2,4-Dichlorophenoxyacetic	118–120	74.7	65.98 (Cl, 14.43)	6.56	66.24 (Cl, 14.62)	6.77	3,3,3	A,B,C	3,3,4
2,4,5-Trichlorophenoxyacetic	157–158.4	59.7	61.66 (Cl, 20.23)	5.94	61.44 (Cl, 20.43)	6.10	4,3,3	A,B,C	3,3,3
2,4,6-Triiodophenoxyacetic	251–254	54.0	40.52 (I, 47.58)	3.90	40.77 (I, 48.36)	4.00	..	....	..
4-Methoxyphenoxyacetic	176–178	71.9	74.30	8.02	74.02	8.28	3,3	A,C	3,4
4-Methylphenoxyacetic	183.5–187	73.4	77.03	8.31	76.82	8.42	3	A	3
4-*t*-Butylphenoxyacetic	156.8–158.2	69.4	77.78	8.85	77.76	9.03	4,4,4	A,B,C	3,3,4
(−)-2-Phenoxypropionic[c]	164.5–166	49.4	77.03	8.31	76.83	8.41	3[d],2[d]	A,C	2,2
(+)-2-Phenoxypropionic[c]	126.4–129.8	90.7	77.03	8.31	76.88	8.55	3[d],3	A,C	2,3

[a] Rotations in dioxane. [b] See footnote *f*, Table I. [c] Resolved by crystallization of the mixed esters of the racemic acid. [d] Extrapolated value.

TABLE IV

MISCELLANEOUS ESTERS OF TESTOSTERONE

Ester	M.p., °C.	$[\alpha]^{25}D$[i]	Analyses, % Calcd. C	Calcd. H	Found C	Found H	Duration[h]	Method[h]	Intensity[h]
3-Ethoxypropionate[a]	51–52	+75.7°	(Lit.[b] m.p. 53–55°) [α]^{23}D 74.7 (EtOH)				1	A	1
3-(*n*-Butoxy)-butyrate	Oil	65.5	75.31	9.83	75.24	9.83	3,2	A,B	2,1
2-Furoate[a,d]	227–230	149.5	(Lit.[b] m.p. 221°) [α]^{27}D 170.5 (Chlf.)				3[e]	A	2
2-Chlorobenzoate	213–214.9	114.5	73.13	7.32	73.04	7.23	0	A	0
4-Chlorobenzoate	257–261	117.9	73.13 (Cl, 8.30)	7.32	73.31 (Cl, 8.35)	7.33	0	A	0
4-Ethoxybenzoate	163.2–164.2	148.2	77.03	8.31	77.21	8.45	3,2	A,C	2,2
3,4-Dimethoxybenzoate	147.5–149.0	155.0	74.30	8.02	74.23	8.19	1	A	½
p-Toluate	219–221.1	144.2	79.76	8.43	79.66	8.25	2	A	1
Phenylacetate[a,d]	126.5–127.5	89.0	(Lit.[f] m.p. 129–131°)				3,3	A,C	2,3
Cyclohexylacetate[a,d]	86.5–88.5	78.6	78.59	9.77	78.42	9.79	3	A	1
3-Methylcyclohexylacetate	Oil	68.7	78.82	9.92	78.69	10.05	2[e]	A	1
4-Methylcyclohexylacetate	Oil	68.6	78.82	9.92	78.85	10.11	2[e]	A	1
3-Cyclopentylpropionate[a]	104–105	78.2	(Lit.[d] m.p. 101–102°) [α]D 87, 76.4[g] (Chlf.)				3,3,1	A,B,C	3,3,1
3-Cyclohexylpropionate[a,d]	74.5–76	74.9	78.82	9.92	78.75	10.26	3	A	3
3-Phenylpropionate[a]	113–114.5	86.8	(Lit.[f] m.p. 114.5–115.5°) [α]D 85 to 91°				3[e],3	A,B	3,3
trans-Cinnamate	238.5–239.5	156.8	80.34	8.19	80.63	8.36	2	A	2
2-Phenylbutyrate	133–134	66.7	80.14	8.81	80.34	9.04	0	A	0
4-Phenylbutyrate	Oil	68.0	80.14	8.81	79.99	8.77	3,2	A,B	3,2
4-Cyclohexylhexanoate	Oil	68.1	79.44	10.32	79.66	10.57	3,4	A,B	3,4
1-Naphthylacetate	170–172	68.9	81.54	7.95	81.68	8.16	1	A	1
Diphenylacetate[a,d]	128.5–129.5	86.4	82.12	7.94	81.92	7.87	0	A	0

[a] Included for comparison. Analyses satisfactory. [b] A. Mooradian, C. Cavallito, A. Bergman, E. Lawson and C. Suter, THIS JOURNAL, **71**, 3372 (1949). [c] See Note 4. [d] A. C. Ott, M. H. Kuizenga, S. C. Lyster and B. A. Johnson, *J. Clin. Endoc. and Metabol.*, **12**, 15 (1952). [e] Extrapolated value. [f] Data from Dr. Eugene Shapiro, Organon Laboratories. [g] A. C. Ott, U. S. Patent 2,566,358. [h] See footnote *f*, Table I. [i] Rotations in dioxane.

sion, only equal to testosterone propionate in intensity and duration. Variation between activity of preparations in aqueous and oily vehicles and between mice and rats are observed in a few other cases, but generally only small differences exist and agreement is relatively good between the alternate procedures used here.

Further study beyond the series of alkylcyclohexane-carboxylates led to a new family of esters, the phenoxyalkanoates, having surprisingly enhanced intensity and duration[7] (Table III). The

(7) A preliminary announcement by D. Gould, L. Finckenor, P. Perlman, J. Cassidy, S. Margolin, M. T. Spoerlein and E. B. Hershberg appeared in *Chemistry & Industry*, 1424 (1955).

4-chlorophenoxyacetate (in oil in mice) has given a maximum peak of over twice that of the propionate, which has not been observed with any other ester, and has, along with the 4-*t*-butylphenoxyacetate, lasted 16 weeks while the previously outstanding esters drop off at 8 weeks. In rats in aqueous suspension, the phenoxyacetate and the 4-*t*-butylphenoxyacetate have given maxima as high as three times that of the propionate and twice that of previously known esters, and the 4-*t*-butylphenoxyacetate has shown a useful level of activity for over 120 days.[8] Variations in substituents do not have the severe effects on activity seen in other families of esters. For example, even when the molecular weight is increased as in the 2,4,5-trichlorophenoxyacetate, activity is not lost. It is also of interest that the isomeric pair of 2-phenoxypropionates did not differ greatly, the observed variation probably being related to the solubilities.

In view of the consistently useful esters in this family, a more fundamental basis than solubility or hydrolytic rate might be suspected. The thought occurs that the phenoxyalkanoic acids are plant growth regulators[9] as are phenylacetic, phenylpropionic, and other unsaturated ring-substituted fatty acids. The anabolic activity of testosterone and the superior effect of these particular esters suggests the intriguing possibility that there may be a basic similarity in the biochemical mechanisms of control of growth in plants and animals.[1,7,10]

The potentiation of androgenic activity of these esters is seen more clearly in comparison with normal effects from endogenous testosterone. While no experiments have been designed for the purpose of determining these values for mice and rats, it is possible to obtain useful estimates of minima. Castrated rats are stated to be maintained properly on: 3×1 mg. TP/wk.,[11] 0.5–1.4 mg. T/day,[12] 1–2 mg. of androsterone/day[13] (equivalent to 0.1–0.2 mg. T/day),[14] 2×0.3 mg. T/day,[15] and 0.1–0.5 mg. TP/day.[16] Castrated mice are reported to be maintained by 65 γ TP/day.[17] Urinary ketosteroids in rats are stated to be: 0.15 mg./day[11]; 0.2–0.5 mg./day[14,18]; in mice, 0.5–1.9 mg./month.[19] Since steroidal metabolites in rodents are only found to the extent of $^1/_4$–$^1/_8$ of the injected testosterone,[20] the endogenous production of C-19 steroids may be calculated to be at least 8 mg./wk. in rats and 4 mg./month in mice. Although the ratio of testicular to adrenal orgin is not known for rodents, it is probably high,[21] and it is not unreasonable to assume from these figures and the maintenance doses that minimal figures for the endogenous production of testosterone at 1 mg./wk. in rats and 1 mg./mo. in mice. The latter figure is supported by Chai's estimate of 1.95 mg./mo. in mice.[17]

Using these figures, maintenance with endogenous testosterone in mice requires 4 mg. in 16 weeks while only 2.5 mg. of testosterone 4-chlorophenoxyacetate lasted for that period; and in rats, maintenance was observed with 7.5 mg. of the 4-*t*-butylphenoxyacetate for 17 weeks, a period requiring 17 mg. of endogenous testosterone. The high efficacy of these derivatives implies that they protect the testosterone from metabolism until it reaches the site of action. In any case, it would appear that these esters supply the hormone in a manner at least as efficient and perhaps more so than the intact testis.

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Experimental[22]

Preparation of Acid Chlorides.—In a dry system, 100 g. of the acid was dissolved in 400 cc. of benzene and some benzene was distilled off to remove water. To this was slowly added 300 cc. of thionyl chloride, and the mixture was refluxed 12–16 hr.

The benzene and excess thionyl chloride were distilled off at atmospheric pressure in a dry system. If it was necessary to remove the last traces of thionyl chloride, another 100 cc. of benzene was distilled off. Finally, the pressure was reduced to 5–20 mm. and the acid chloride was distilled. Some high boiling acid chlorides were used without distillation.

General Procedure for Preparation of Testosterone Esters.—Five g. of testosterone was dissolved in 50 ml. of dry distilled pyridine. The solution was chilled to 0–10° in an ice-bath and 5 g. (or 1.25 equiv.) of acid chloride was added dropwise with good stirring. Stirring was continued for 12–15 hr. at room temperatures.

The mixture was poured with good stirring into a mixture of 400 g. of ice and 100 ml. of concd. sulfuric acid. If a precipitate was obtained, the product was filtered off, washed with 10% sodium carbonate and water (until neutral) and air-dried. The crude was then crystallized from methanol or methanol–benzene.

If the product did not solidify in the ice mixture, it was extracted several times with benzene and the benzene solution was washed with 10% sodium carbonate to remove the excess acid, with water until neutral, and dried over magnesium sulfate. The solution was evaporated, and the residue crystallized from methanol. If crystallization was not possible, the residue was chromatographed from hexane on alumina, removing oily impurities in the hexane eluates. Elution was continued with 1:1 hexane–benzene and with benzene to obtain the last of the ester. Ether eluted any unchanged testosterone. On standing or trituration with methanol, the benzene-containing fractions usually solidified. In any case, these fractions analyzed correctly, after sufficient drying *in vacuo*.

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(8) The last measurement still showed seminal vesicle weights greater than the TP maximum. It can be presumed that effective activity could be observed for a considerably longer duration.

(9) *Inter alia, cf.*, Å. Jönsson, *Acta Chem. Scand.*, **7**, 596 (1953).

(10) *Cf.*, I. A. Mirsky, D. Diengott and G. Perisutti, *Endocrinology*, **59**, 715 (1956).

(11) Unpublished data, these laboratories.

(12) V. Korenchevsky, M. Dennison and J. Brovsin, *Biochem. J.*, **30**, 558 (1936).

(13) C. R. Moore and D. Price, *ibid.*, **31**, 313 (1937).

(14) R. I. Dorfman and R. A. Shipley, in: "Androgens," John Wiley and Sons, Inc., New York, N. Y., 1956.

(15) J. S. Davis, R. K. Meyer and W. H. McShan, *Endocrinology*, **44**, 1 (1949).

(16) M. E. Simpson and H. M. Evans, *ibid.*, **38**, 281 (1946).

(17) C. K. Chai, *Am. J. Physiology*, **186**, 463 (1956).

(18) P. Koets, *J. Clin. Endocrinology*, **9**, 278 (1950).

(19) D. A. Karnofsky, I. T. Nathanson and J. C. Aub, *Cancer Research*, **4**, 772 (1944).

(20) M. C. Barry, M. L. Eidinoff, K. Dobriner and T. F. Gallagher, *Endocrinology*, **50**, 587 (1952).

(21) 1:1 or greater in man, *cf.* D. K. Fukushima, K. Dobriner and T. F. Gallagher, *J. Biol. Chem.*, **206**, 845, 863 (1954).

(22) All m.p.'s are corrected. Analyses and rotations were obtained by the Microanalytical Department of these laboratories.