and the catalyst (3 g.) then was washed by decantation with water 20–30 times, then three times with absolute methanol, and stored under absolute methanol in the ice-box for not longer than two weeks.

CHEMICAL LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA

Long-Acting Androgens[1]

SEYMOUR L. SHAPIRO, KURT WEINBERG, AND LOUIS FREEDMAN

Received June 7, 1956

Esterification of the hydroxyl groups has yielded derivatives of steroid hormones of desirable clinical utility which require less frequent administration for replacement therapy in hormone deficiency states. More important than the convenience and economy of such therapeutic measures is the release of the required replacement steroid at a physiological rate that does not invoke the potential dangers of overdosage and side reactions associated with derivatives which are absorbed rapidly and administered frequently.

Recent work with esters of testosterone[2–8] has yielded a variety of long-acting androgens far surpassing testosterone propionate (TP). Although the mode of action of these esters is still unsettled, it is believed that esterified steroids achieve their longer action because of slower absorption from the injection site.[7] Free testosterone,[9,10] however, appears to be required for the androgenic response.

If the sterol is varied, and the same acylating agent such as the hindered pivalic acid is used, then prolonged activity[11–13] or loss of activity[14] may result.

Our investigation of esters of testosterone and androstan-17-β-ol-on (Table I) involved relatively bulky acyl groups[2–8] and sterically hindered acyl groups[11–14] in an attempted conciliation of the factors of absorption and saponification to yield the free androgen at a rate compatible with physiological requirements.

The failure to obtain any androgenic response with the *tert*-butyl acetates and α,α-dibenzylacetates could be interpreted as due to resistance of such sterically hindered esters to saponification.[15–20]

With β-halopropionates, prolonged activity far superior to testosterone propionate or α-bromopropionate[21] was noted. The response with halogen in the *beta* position suggested that these structures might suffer metabolic dehydrohalogenation to yield testosterone acrylate. Synthesis and androgenic evaluation of testosterone acrylate showed activity considerably inferior to TP.

Testosterone β-chlorocrotonate was only mildly androgenic, paralleling observations[21] with the crotonate. The low androgenic potency of the α,β-unsaturated esters may be due to rapidity of their hydrolysis.[22]

An alternative possibility where the β-halopropionate yields acrylate which spontaneously polymerized *in vivo* was explored by polymerizing testosterone acrylate. The resultant polymer was so insoluble that it showed only slight androgenic activity.

Synthesis and evaluation of the group of testosterone esters such as the β-N-morpholinopropionate, β-N-pyrrolidinopropionate, hemisuccinate, and methyl ester of the hemisuccinate, indicated these

(1) Presented in part at the Meeting-in-Miniature, New York Section, American Chemical Society, New York, N. Y., March 16, 1956.

(2) Ott, Kuizenga, Lyster, and Johnson, *J. Clin. Endocrinol. and Metabolism*, **12**, 15 (1952), β-Cycloalkylpropionates.

(3) Dekanski and Chapman, *Brit. J. Pharmacol.*, **8**, 271 (1953), β-Phenylpropionate.

(4) Hamburger, Birket-Smith, and Kaae, *Acta Endocrinol.*, **9**, 79 (1952), Isobutyrate and valerate.

(5) Voss, *Arzneimittel-Forsch.*, **4**, 208 (1955), Long-chain β-keto acid esters.

(6) Gould, Finckenor, Hershberg, Perlman, Cassidy, Margolin, and Spoerlin, *Chemistry & Industry*, 1424 (1955), Aryloxyalkanoates.

(7) Kupperman, *et al.*, *Acta Endocrinol.*, **16**, 101 (1954), Phenylacetate.

(8) Feyel-Cabanes, *Compt. rend.*, **148**, 1196 (1954), Hexahydrobenzoate.

(9) Meyers, Simons, and Simons, *Biochem. J. (London)*, **55**, I (1954).

(10) Dirscherl and Dardenne, *Biochem. Z.*, **325**, 195 (1954).

(11) Gaunt, Leathem, Howell, and Antonchak, *Endocrinology*, **50**, 521 (1952), Desoxycorticosterone.

(12) Ciba Ltd., British Patent 694,462 (July 22, 1953); *Chem. Abstr.*, **48**, 10792 (1954), 20,21-Ketols of the pregnane series.

(13) Desaulles and Meier, *Schweiz. med. Wochschr.*, **84**, 741 (1954); *Chem. Abstr.*, **48**, 11641 (1954), Cortisone.

(14) Noland, *Arch. Biochem. and Biophys.*, **48**, 370 (1953), Cholesterol.

(15) Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950).

(16) Loening, Garrett, and Newman, *J. Am. Chem. Soc.*, **74**, 3929 (1952).

(17) Hammond and Hogle, *J. Am. Chem. Soc.*, **77**, 338 (1955).

(18) Cason, *et al.*, *J. Org. Chem.*, **18**, 1129 (1953).

(19) A 36-fold rate factor exists between propionic acid, and *tert*-butylacetic acid in acid-catalyzed esterifications.[16] It would appear that comparable rate differences in saponification would obtain.

(20) Schenck and Junkmann, *Nauyn-Schmiedebergs Arch. exptl. Pathol. Pharmakol.*, **227**, 210 (1955). Evaluation of androgen response and speed of saponification of esters did not show a clearcut relationship.

(21) Miescher, *et al.*, *Biochem. Z.*, **294**, 39 (1937).

(22) Meyers, Collett, and Lazell, *J. Phys. Chem.*, **56**, 461 (1952) report that an unsaturated carbon-to-carbon linkage near the carbonyl carbon in carboxylic esters always speeds the rate of hydrolysis compared to that of the saturated ester.

TABLE I

ESTERS OF TESTOSTERONE (17-OH)

Acylating Group	M.P., °C.[a]	Yield,[g] %	Formula	Carbon[b] Calc'd	Carbon[b] Found	Hydrogen Calc'd	Hydrogen Found	Activity[c,h]
$ClCH_2CH_2CO$	154–155	65	$C_{22}H_{31}ClO_3$	69.7	69.2	8.2	8.2	3+
$BrCH_2CH_2CO$	157	67	$C_{22}H_{31}BrO_3$	62.4	62.3	7.3	7.2	3+
$I—CH_2CH_2CO$	140[d]	75	$C_{22}H_{31}IO_3$	56.2	57.4	6.6	6.7	3+
$CH_2=CHCO$	159–160	48	$C_{22}H_{30}O_3$	77.2	76.8	8.8	8.8	1+
$(CH_2=CHCO)_n$	188–195	100	$C_{22}H_{30}O_3$[e]	77.2	75.5	8.8	8.8	1+
$(CH_3)_3CCH_2CO$	136.5–138	21	$C_{25}H_{38}O_3$	77.7	78.0	9.9	9.9	0
$(\Phi—CH_2)_2CHCO$	119–121	82	$C_{35}H_{42}O_3$	82.3	82.2	8.3	8.6	0
N-Piperidino-CH_2CH_2CO	86–89	20[ga]	$C_{27}H_{41}NO_3$	75.9	76.0	9.6	9.8	0
N-Morpholino-CH_2CH_2CO	105–107.5	32[ga]	$C_{26}H_{39}NO_4$	72.8	73.1	9.1	9.3	0
$CH_3CCl=CHCO—$	149–150	10[gb]	$C_{23}H_{31}ClO_3$	70.7	70.5	7.9	7.9	1+
$HOOCCH_2CH_2CO$[f]	184–194							0
$CH_3OOCCH_2CH_2CO$	154–157	48	$C_{24}H_{34}O_5$	71.6	71.3	8.5	8.4	0
$CH_3COCH_2CO—$	100	71	$C_{23}H_{32}O_4$	74.2	73.8	8.6	8.8	1+
ESTERS OF ANDROSTAN-17β-OL-3-ONE								
$ClCH_2CH_2CO$	102–104	60	$C_{22}H_{33}ClO_3$	69.4	69.4	8.7	8.7	3+
$BrCH_2CH_2CO$	83.5–84.5	40[ga]	$C_{22}H_{33}BrO_3$	62.1	62.1	7.8	7.8	3+
ICH_2CH_2CO	84–85.5	48	$C_{22}H_{33}IO_3$	55.9	56.4	7.0	6.8	3+
$(CH_3)_3CCH_2CO$	149–152	50[gb]	$C_{25}H_{40}O_3$	77.3	77.3	10.4	10.5	0
$(\Phi\text{-}CH_2)_2CHCO$	119–120	55	$C_{35}H_{44}O_3$	82.0	82.0	8.7	8.5	0

[a] All melting points are uncorrected. [b] Analyses by Drs. Weiler and Strauss, Oxford, England. [c] The pharmacological work followed established methods and was done using castrate young male rats of the Wistar strain; weights of seminal vesicles and prostates were noted at specific intervals post-injection. All compounds were evaluated using a single dose of the androgen dissolved in corn oil at the initiation of the experiment. A more detailed pharmacological report will be published elsewhere. In this report, the compounds have been graded in relation to their comparative molar activity (Table I) with testosterone propionate as a standard where 3+ signifies activity superior to the standard, 2+ equal to the standard, and 1+ less than the standard, while O denotes insignificant or no activity. [d] The compound could not be obtained analytically pure since it apparently suffered dehydrohalogenation on treatment. [e] The insolubility of this polymeric product did not permit adequate purification. [f] Reported m.p. (Ref. 25) dimorphic 182–184° and 191–193°. [g] Unless otherwise indicated the recrystallizing solvent was heptane; [ga] = hexane; [gb] = ethanol-water. [h] Shapiro, Freedman, and Kobrin, to be published, a detailed description of biological activity of β-halopropionates.

compounds to be inactive with a possible alternative route of absorption due to the polar groups.

The acetoacetate of testosterone was only feebly androgenic, in contrast to the good activity noted with larger keto-substituted acylating agents.[5]

The specific experimental findings for some of the more active androgens and a comparison with standard androgens are given in Tables II and III

TABLE II

EVALUATION OF ANDROGENS[a–d]; WEIGHT OF RAT SEMINAL VESICLES (SV) AND PROSTATE (P) IN MG./KG. *vs.* DAYS POST-INJECTION

Compound	11 Days SV	11 Days P	15 Days SV	15 Days P	19 Days SV	19 Days P
ESTERS OF TESTOSTERONE						
Propionate	1631	898	1154	1102	637	599
β-Chloropropionate	3280	1292	1522	1520	596	468
β-Bromopropionate	3708	1013	2966	1624	2245	1125
β-Iodopropionate	3371	1178	2742	1282	1961	1427
β-Bromopropionate[e]	2801	1212	2663	1779	1952	1490

[a] Compound injected s.c. in corn oil in quantity equivalent to 7.5 mg. of testosterone. [b] Uncastrated normal controls—2270 mg./kg. SV; 1176 mg./kg. P. [c] Castrated controls—304 mg./kg. SV; 135 mg./kg. P. [d] Rats—mature, average weight 250 g. [e] β-Bromopropionate of androstan-17-β-ol-3-one.

following established procedures[2,3] using castrated rats.

The esters were prepared by conventional procedures, using an acid chloride and testosterone, or androstan-17-β-ol-3-one. The *beta*-substituted amino derivatives were prepared from the β-halopropionates, as were the iodopropionates. Testosterone acrylate was prepared from acrylyl chloride, and also by dehydrohalogenating testosterone β-bromopropionate using phenylbiguanide as a dehydrohalogenating agent.[23] Testosterone acetoacetate was

TABLE III

EVALUATION OF LONG-ACTING ANDROGENS[a–c]; WEIGHT OF RAT SEMINAL VESICLES (SV) AND PROSTATE (P) IN MG./KG. *vs.* DAYS POST-INJECTION

Compound	12 Days SV	12 Days P	20 Days SV	20 Days P	33 Days SV	33 Days P
ESTER OF ANDROSTAN-17-β-OL-3-ONE (I)						
I	237	412	161	87	96	39
β-Chloropropionate	1534	728	925	1008	765	685
β-Bromopropionate	756	696	1480	1095	584	965
β-Iodopropionate	1540	960	1185	1140	757	815

[a] Compound injected s.c. in corn oil in quantity equivalent to 5.0 mg. of testosterone. [b] Castrated controls—50 mg./kg. SV; 40 mg./kg. P. [c] Growing rats—average weight 100 g.

(23) Shapiro and Overberger, *J. Am. Chem. Soc.*, **76**, 97 (1954).

prepared by a transesterification procedure.[24] Mono-testosterone succinate has been previously described[25] and the free carboxyl group was esterified by metathesis of the silver salt of the acid with methyl iodide.

EXPERIMENTAL[26]

The acid chlorides which were not commercially available were synthesized according to methods described in the literature: acrylyl chloride,[27] β-chlorocrotonyl chloride,[28] *tert*-butylacetyl chloride.[29] The acid chloride of α,α-dibenzylacetic acid was prepared using thionyl chloride (75%), b.p. 130–132° (1 mm.).

Testosterone β-chloropropionate. A solution of 24 g. of testosterone in 200 ml. of pyridine and 800 ml. of toluene was added dropwise with stirring and continued cooling at −10° to a solution of 70 ml. of β-chloropropionyl chloride in 600 ml. of toluene. After stirring at room temperature for 24 hours, 350 ml. of water was added. The toluene layer was separated and processed by successively washing with water, dilute hydrochloric acid, dilute bicarbonate, and water; it was dried with magnesium sulfate, filtered, and the filtrate was concentrated *in vacuo*. The solid residue of the product was dried *in vacuo* at 80°.

Androstan-17-β-ol-3-one-β-iodopropionate. One gram of androstan-17-β-ol-3-one-β-bromopropionate was dissolved in 5 ml. of acetone and 50 ml. of a 15% acetone solution of sodium iodide was added. After 2 days the sodium bromide formed was filtered off, and 100 ml. of water was added. Upon standing, crystals of the product formed which were separated and dried *in vacuo*.

Testosterone acrylate. (By dehydrohalogenation of testosterone β-bromopropionate). A solution of 1 g. (2.36 mmoles) of testosterone β-bromopropionate and 0.42 g. (2.36 mmoles) of phenylbiguanide in 135 ml. of hot ethanol was concentrated on the steam-bath to the initiation of crystallization, and cooled. Filtration afforded 0.8 g. of a crystalline mixture which was extracted with two successive 40-ml. portions of boiling heptane. The cooled heptane extract yielded 0.39 g. (48%) of testosterone acrylate which melted at 158–160° and which did not depress the melting point of the product obtained from testosterone and acrylyl chloride. The residue from the heptane extraction was identified as phenylbiguanide hydrobromide.[23]

Testosterone acrylate polymer. A solution of 1 g. of testosterone acrylate in 5 ml. of boiling propanol was treated with three successive 1-ml. portions of 20% hydrogen peroxide at 0, 5, and 15 minutes and refluxed for 2 hours. After cooling, the oily insoluble mass of product separated and was solidified by trituration with ether. The product was insoluble in a wide variety of typical solvents except chloroform, but could not be purified.

We could not polymerize testosterone acrylate by ultraviolet light, nor through the use of benzoyl peroxide.[30]

Testosterone acetoacetate. A solution of 2 g. of testosterone and 6.12 g. of ethyl acetoacetate was maintained at 100° and 200 mm. for 10 hours. The excess of the reactant then was removed by distillation leaving a viscous residue which crystallized on treatment with methanol-water.

Methyl ester of monotestosterone succinate. The silver salt of monotestosterone succinate was prepared from an equivalent amount of the sodium salt of the acid and silver nitrate in water in 82.3% yield. The reaction mixture of 0.8 g. of the silver salt and 1 ml. of methyl iodide in 48 ml. of methanol after standing 48 hours in the dark, was separated from the formed silver iodide by filtration. Evaporation of the filtrate yielded an oil which crystallized on standing.

Testosterone β-(N-piperidino)propionate. A solution of 4 g. of testosterone β-chloropropionate in 100 ml. of xylene was treated with 5 ml. of piperidine and refluxed for 2 hours. On cooling, 1.15 g. (90%) of piperidine hydrochloride was separated and the filtrate was concentrated to a syrupy residue. Crystallization was induced by trituration with ether.

Acknowledgment. We are grateful to S. Kobrin for evaluation of the androgenic response of the compounds reported in this series, and to A. Lawrence for his technical assistance in the preparation of the compounds.

RESEARCH LABORATORIES
U. S. VITAMIN CORPORATION
YONKERS 1, NEW YORK

(24) Bader, Cummings, and Vogel, *J. Am. Chem. Soc.*, **73**, 4195 (1951).

(25) Soc. pour l'ind. chem. a Bale, Swiss Patent 195,775 (May 16, 1938); *Chem. Abstr.*, **32**, 7217 (1938).

(26) Purification, yields, and melting points of the compounds described in this section are indicated in Table I.

(27) Stempel, Gross, and Mariella, *J. Am. Chem. Soc.*, **72**, 2299 (1950).

(28) Shriner and Keyser, *J. Am. Chem. Soc.*, **60**, 287 (1938).

(29) Homeyer, Whitmore, and Wallingford, *J. Am. Chem. Soc.*, **55**, 4211 (1933).

(30) Marvel, Weil, Wakefield, and Fairbanks, *J. Am. Chem. Soc.*, **75**, 2326 (1953).

Stereochemistry of Reduction of 2-Methylcyclopentanone

JEAN B. UMLAND AND BETTYE W. WILLIAMS[1]

Received June 8, 1956

The reduction of unsymmetrical ketones to secondary alcohols produces an asymmetric carbon atom and when the ketone already contains an asymmetric center, the problem arises as to which epimer will be formed in larger amounts. Generalizations concerning the steric course followed in the reduction of ketones by the common methods have been made by Barton.[2] Unfortunately some of these generalizations appear to be based on experiments in which it was assumed that the more soluble epimer was obtained in pure form by fractional crystallization. The purpose of the present research was to compare in a quantitative manner the stereochemistry of the common methods of reduction using a single simple model compound. 2-Methylcyclopentanone, which is reduced to a mixture of *cis*- and *trans*-2-methylcyclopentanol, was selected as this model compound since the preparation and proof of configuration of these alcohols, as well as a quantitative procedure for analyzing the mixtures, have recently been described.[3] The results of these reductions are summarized in Table I.

(1) Abstracted from a thesis submitted by Bettye W. Williams in partial fulfillment of the requirements for the degree of Master of Arts, 1956.

(2) Barton, *J. Chem. Soc.*, 1027 (1953).

(3) Umland and Jefraim, *J. Am. Chem. Soc.*, **78**, 2788 (1956).