Tetrahedron, 1960, Vol. 9, pp. 149 to 155. Pergamon Press Ltd. Printed in Northern Ireland

REACTION OF POLYHALOMETHANES WITH ENOLETHERS OF Δ^4-3-KETOSTEROIDS

A NEW PATHWAY TO 6α-METHYLSTEROIDS

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(*Received* 26 *January* 1960)

Abstract—Reaction of enol ethers of Δ^4-3-ketosteroids with tetrabromomethane affords via 6-tribromomethylsteroids the corresponding 6-dibromomethylene-Δ^4-3-ketosteroids. Upon catalytical hydrogenolysis over $Pd/SrCO_3$ these are smoothly transformed into 6-methyl-Δ^5-3-ketosteroids, which without isolation are rearranged to 6α-methyl-Δ^4-3-ketosteroids. Other polyhalomethanes react in a similar way with enol ethers of Δ^4-3-ketosteroids.

INTRODUCTION of a 6α-methyl group in certain Δ^4-3-ketosteroids causes a remarkable increase of their biological activities. Thus 6α-methylhydrocortisone and 6α-methylprednisolone, were found to be four times as active as hydrocortisone, and prednisolone respectively, in the glycogen deposition assay,[1] and 6α-methyl-17α-acetoxyprogesterone is one of the most active progestational agents yet known.[2]

The syntheses are generally [1–11]* based on the cleavage of a 3-hydroxy- or 3-cycloethylenedioxy-5α,6α-oxidosteroid with methylmagnesium halide to afford the 5α-hydroxy-6β-methyl system, from which the 6α-methyl-Δ^4-3-ketone may be formed readily by conversion of the 3-hydroxyl group or 3-ketal to the 3-ketone, dehydration of the 5-hydroxyl group, and inversion of the 6β-methyl group.

Since the existing methods involve a Grignard reaction, it is necessary to protect other carbonyl functions in the molecule. Consequently, the total yields are often relatively low, and a simplified synthesis seemed therefore desirable.

In a search for new ways to introduce the 6-methyl group, the well known addition of polyhalomethanes to olefines[12] seemed to constitute an attractive possibility. This type of reaction, which has been extensively investigated by Kharasch, Haszeldine and others, is catalysed by light and peroxides, and is therefore considered to proceed by a free-radical mechanism. The reaction has, however, as far as we are aware, never been used in the steroid series.

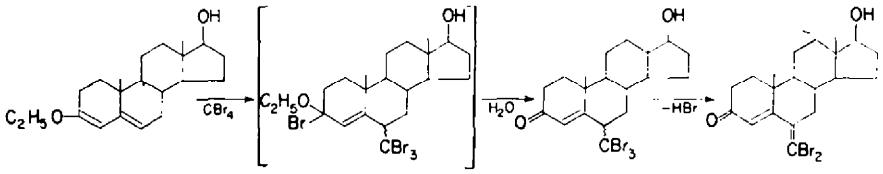
* See, however, references 6 and 8 where the authors describe alternative routes through a 6-keto-3,5-cyclosteroid or a 6-keto-5α-bromo-3β-acetate system.

[1] G. P. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).
[2] J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, *J. Amer. Chem. Soc.* **80**, 2904 (1958).
[3] H. J. Ringold, E. Batres and G. Rosencranz, *J. Org. Chem.* **22**, 99 (1957).
[4] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1958).
[5] J. A. Campbell, J. C. Babcock and J. A. Hogg, *J. Amer. Chem. Soc.* **80**, 4717 (1958).
[6] D. Burn, B. Ellis, V. Petrow, J. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4092 (1957).
[7] M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and J. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957).
[8] V. Greenville, D. K. Patel, V. Petrow, J. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.* 4105 (1957).
[9] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).
[10] S. P. Barton, B. Ellis and V. Petrow, *J. Chem. Soc.* 478 (1959).
[11] O. S. Madaeva, M. I. Ushakov and N. F. Kosheleva, *J. Gen. Chem. U.S.S.R.* **10**, 213 (1940).
[12] Ch. Walling, *Free Radicals in Solution* pp. 247–272. John Wiley, New York (1957).

As starting material for such additions a steroid derivative containing a Δ^5-double bond was necessary. Among easily obtainable derivatives of Δ^4-3-ketosteroids fulfilling this requirement cyclic ketales, enol ethers, enol acetates, and enamines came into question. Of these, the enol ethers were soon found best suited, and only additions to this type of compounds will be dealt with in the following.

It will be shown that several polyhalomethanes, viz. CBr_4, CCl_2Br_2, and CCl_3Br are able to react with enol ethers of Δ^4-3-ketosteroids; of these CBr_4, however, has been found specially suited in the new synthesis of 6α-methyl steroids presented in this paper and reactions with this substance will therefore be treated in greater detail.

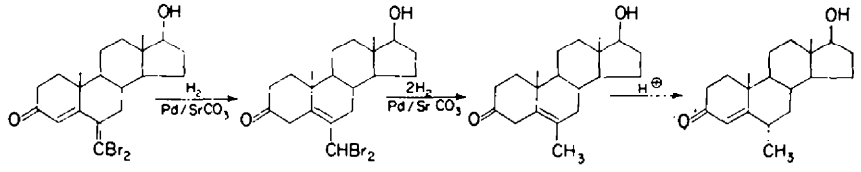
When a solution of testosterone 3-ethylenol ether (I) in collidine is treated with tetrabromomethane at room temperature, without any irradiation or addition of peroxides, a reaction takes place which, presumably through the intermediate II, leads to 6-tribromomethyltestosterone (III).



I II III IV

This compound readily eliminates hydrogen bromide with the formation of the crystalline, stable dibromomethylene compound IV.*

Upon catalytical hydrogenolysis over palladium on strontium carbonate in the presence of 2 moles of triethylamine, 3 moles of hydrogen are rapidly absorbed. The hydrogenolysis product contains no bromine and shows no selective absorption in the ultra-violet. In acid solution, however, it rearranges to a product, which in all respects is identical with authentic 6α-methyltestosterone (V), a result which is readily understood by assumption of the reaction sequence shown in formulae IV–V.



IV V

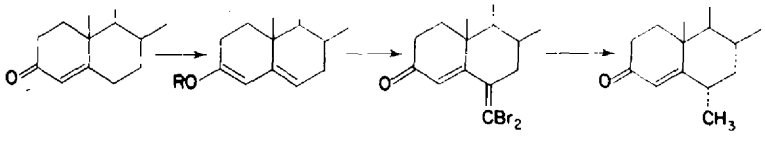
Besides testosterone the following Δ^4-3-ketosteroids were transformed into their respective 6-dibromomethylene derivatives by reaction of their 3-ethylenol ethers with tetrabromomethane: 17α-methyltestosterone, 19-nor-testosterone, progesterone,

* The assignment of IV to the elimination product is based mainly upon infra-red evidence: Besides bands at 1660 and 1607 cm^{-1} characteristic of the Δ^4-3-keto system, the infra-red spectrum possesses a band at 1578 cm^{-1}, which could be due to the extra conjugated double bond present in IV. The possibility that one of the hydrogen atoms at C_7 has participated in the elimination with the formation of a cyclopropane ring can, however, not be excluded.

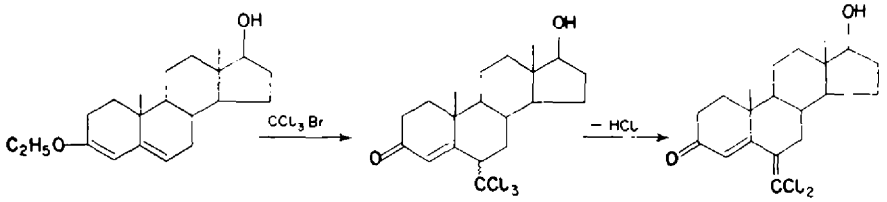
17α-hydroxyprogesterone, 11-desoxycorticosterone acetate, 17α-hydroxy-11-desoxy-corticosterone acetate, and cortisone acetate. In most cases the tribromo-methyl compounds were not isolated, but directly transferred into the corresponding dibromo-methylene compounds by heating the reaction mixtures. The yields varied from 30–80 per cent of the theoretical.

In contrast to 17α-hydroxyprogesterone, 6-dibromomethylene-17α-hydroxyprogesterone is acetylated at C-17 in nearly quantitative yield, a significant fact in the synthesis of the important progestational agent 6α-methyl-17α-hydroxyprogesterone.

All of the 6-dibromomethylene compounds, mentioned above, were readily converted into the corresponding 6α-methyl steroids by catalytical hydrogenolysis over $Pd/SrCO_3$,ollowed by an acid catalysed rearrangement. The hydrogenolyses were carried out in methyl cellosolve or dioxane in the presence of 2 moles of triethyl-amine, and the treatment with acid was performed directly on the hydrogenolysis mixtures after removal of the catalyst. The yields were mostly good, and the reaction sequence, shown below, therefore represents a convenient synthesis of 6α-methyl steroids.



It has already been mentioned that other polyhalomethanes react in a similar way as tetrabromomethane. Thus, treatment of testosterone 3-ethylenol ether (I) with CCl_3Br in dioxane containing pyridine affords 6-trichloromethyltestosterone (VI), which readily eliminates hydrogen chloride to give 6-dichloromethylenetestosterone (VII),* a product which also is obtained if CCl_3Br is replaced by CCl_2Br_2. In analogy with IV, VII upon catalytical hydrogenolysis followed by acid catalysed rearrangement smoothly affords 6α-methyltestosterone.



I VI VII

Since the completion of this work a new synthesis of 6α-methylsteroids, based upon hydroformylation of a starting material having a 5,6-double bond and no other reactive groups, is described.[13,14] The 6-formyl compounds formed during this reaction are reduced to the corresponding 6-hydroxymethyl compounds which via the tosylates are converted to 6α-methyl steroids.

* As regards the constitution of the elimination product the same considerations as stated for the corresponding dibromo compound are valid.

[13] A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman and J. Wender, *J. Amer. Chem. Soc.* **81**, 1228 (1959).

[14] P. F. Beal, M. A. Rebenstorf and J. E. Pike, *J. Amer. Chem. Soc.* **81**, 1231 (1959).

EXPERIMENTAL

All melting points are corrected. Optical rotations, unless otherwise stated, were measured in chloroform and ultra-violet spectra in 96% ethanol solution. The infra-red spectra were obtained with a Perkin–Elmer Model 21 spectrophotometer with a sodium chloride prism.

17α-Hydroxyprogesterone-3-ethylenol ether

17α-Hydroxyprogesterone (66 g) and *p*-toluenesulphonic acid (200 mg) were dissolved in dry benzene (1000 ml). Ethyl orthoformate (33 ml) and abs ethanol (30 ml) were added, and the solution refluxed for 3 hr. After cooling and addition of pyridine (25 ml) the solution was washed with water (2 × 250 ml), dried, and evaporated *in vacuo*. The residue was recrystallized from methanol containing 0·5% pyridine to give *17α-hydroxyprogesterone-3-ethylenol ether* (49·5 g) m.p. 172–175°, raised by further crystallizations to 175–178°. (Found: C, 75·58; H, 9·59. $C_{23}H_{34}O_3$, $\frac{1}{2}CH_3OH$ requires: C, 75·36; H, 9·69%).

From the mother liquors 17α-hydroxyprogesterone (12·5 g) m.p. 218–219° was recovered by concentration and acidification with conc hydrochloric acid.

In the same manner the following enol ethers were synthesized:

Testosterone-3-ethylenol ether: m.p. 123–126°. Serini and Köster[15] report m.p. 118–122°.

17α-Methyltestosterone-3-ethylenol ether: m.p. 85–90°. (Found: C, 79·83; H, 10·15. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·37%).

Progesterone-3-ethylenol ether: m.p. 103–105°. (Found: C, 80·56; H, 10·04. $C_{23}H_{34}O_2$ requires: C, 80·65; H, 10·01%).

The 3-ethylenol ethers of *cortisone acetate* and *17α-hydroxy-11-desoxycorticosterone acetate* (*Reichsteins compound S acetate*) were prepared as described by Julian *et al.*[16] In a similar way the 3-ethylenol ether of *11-desoxycorticosterone acetate* was prepared. m.p. 138–140°. (Found: C, 74·52; H, 9·22. $C_{25}H_{36}O_4$ requires: C, 74·96; H, 9·06%).

19-Nortestosterone-3-ethylenol ether

To a solution of 3-ethoxy-19-nor-$\Delta^{3,5}$-androstadien-17-one[17] (10 g) in ether (500 ml) was added a solution of $LiAlH_4$ (3 g) in ether (200 ml). The mixture was refluxed for 1 hr and, after cooling, washed with saturated aqueous ammonium chloride and dried. After removal of the solvent the residue was crystallized from methanol to afford *19-nortestosterone-3-ethylenol ether* (9·9 g) m.p. 111–113°, raised by crystallization from methanol to 112–113°. (Found: C, 79·89; H, 9·94. $C_{20}H_{30}O_2$ requires: C, 79·42; H, 10·00%).

6-Tribromomethyltestosterone (III)

A. Testosterone-3-ethylenol ether (31.6 g) was dissolved in freshly distilled 2,4,6-collidine (250 ml). Tetrabromomethane (66·4 g) was added, and, after standing for 48 hr at room temp, a precipitate consisting of collidine hydrobromide, CBr_4 was filtered off. With stirring, the filtrate was poured into chilled, dil hydrochloric acid, and the crystalline *tribromomethyltestosterone*, hereby precipitated, was collected on a filter, triturated with ether, followed by methanol and dried at room temp to give 45 g (83%) of material m.p. 215–216° (dec). U.V. λ_{max} 238 mμ (ε 12900); I.R. ($CHCl_3$): 1600 and 1672 cm^{-1}. (Found: C, 44·60; H, 5·19; Br, 44·32. $C_{20}H_{27}Br_3O_2$ requires: C, 44·55; H, 5·05; Br, 44·47%).

B. Testosterone-3-ethylenol ether (3·16 g) was dissolved in propylene oxide (25 ml). Tetrabromomethane (3·32 g) was added, and the resulting solution exposed to direct sunlight. Shortly afterwards crystals began to separate. The reaction mixture was allowed to stand at room temp for 5 hr, whereafter the crystals were collected and washed with ether to yield 1·9 g *6-tribromomethyltestosterone* (m.p. 213–216°) identical with that prepared by method *A* above.

6-Dibromomethylenetestosterone (IV)

6-Tribromomethyltestosterone (5·39 g) in pyridine (100 ml) was heated on the steam bath for 30 min. After cooling, water was added, and the crystalline precipitate collected, and recrystallized

[15] A. Serini and H. Köster, *Ber. Dtsch. Chem. Ges.* **71**, 1766 (1938).
[16] P. L. Julian, E. W. Meyer, W. J. Karpel and W. Cole, *J. Amer. Chem. Soc.* 73, 1982 (1951).
[17] C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **76**, 4092 (1954).

from ethanol to give 4·05 g of material, m.p. 230–231°. The analytical sample, obtained by further recrystallizations from ethanol, had m.p. 232–233°. $[\alpha]_D^{20}$ +210°. U.V. λ_{max} 250 mμ (ε 10400), $\lambda_{shoulder}$ 285 mμ (ε 6000); I.R. (KBr): 1578, 1607, 1660 cm^{-1}. (Found: C, 52·17; H, 5·72; Br, 34·88. $C_{20}H_{26}Br_2O_2$ requires: C, 52·42; H, 5·72; Br, 34·88%).

The acetate of IV was obtained directly from III as follows: To a solution of 6-tribromomethyltestosterone (5·7 g) in dry pyridine (65 ml) acetic anhydride (20 ml) was added. After standing overnight at room temp, the mixture was poured into water (500 ml). The precipitate was collected and recrystallized from ethanol to afford 6-*dibromomethylenetestosterone acetate* (5·1 g), m.p. 168–169°. $[\alpha]_D^{20}$ +180°. I.R. ($CHCl_3$): 1570, 1610, 1675, 1725 cm^{-1}. (Found: C, 52·99; H, 5·78; Br, 31·98. $C_{22}H_{28}Br_2O_3$ requires: C, 52·81; H, 5·64; Br, 31·95%).

The following 6-dibromomethylene compounds were obtained in analogy with 6-dibromomethylenetestosterone, method *A* being used for the preparation of the intermediate 6-tribromomethyl steroids, which without purification, were converted to the corresponding dibromo compounds by heating in pyridine as described above.

6-*Dibromomethylene*-17α-*methyltestosterone*: m.p. 194–195° (from ethanol). $[\alpha]_D^{20}$ +193°; yield, 55%; U.V. λ_{max} 251 mμ (ε 10600), $\lambda_{shoulder}$ 285 mμ (ε 5700). (Found: C, 53·48; H, 6·18; Br, 33·70. $C_{21}H_{28}Br_2O_2$ requires: C, 53·40; H, 5·97; Br, 33·85%).

6-*Dibromomethylene*-19-*nortestosterone acetate*: m.p. 146–147° (from methanol); yield, 35%; U.V. λ_{max} 250 mμ (ε 13900), $\lambda_{shoulder}$ 286 mμ (ε 4900); I.R. (KBr): 1565, 1610, 1683, 1735 cm^{-1}. (Found: C, 51·93; H, 5·38; Br, 32·79. $C_{21}H_{26}Br_2O_3$ requires: C, 51·87; H, 5·39; Br, 32·87%).

6-*Dibromomethylene*-11-*desoxycorticosterone acetate:* m.p. 176–177° (from methanol). $[\alpha]_D^{20}$ +222°; yield, 45%; U.V. λ_{max} 250 mμ (ε 11400), $\lambda_{shoulder}$ 282 mμ (ε 5000); I.R. (KBr): 1573, 1618, 1680, 1725, 1750 cm^{-1}. (Found: C, 52·91; H, 5·69; Br, 29·31. $C_{24}H_{30}Br_2O_4$ requires: C, 53·16; H, 5·57; Br, 29·47%).

The 6-dibromomethylene compounds of progesterone, 17α-hydroxyprogesterone, comp S acetate, and cortisone acetate were prepared by the following general procedure: The 3-ethylenol ether (0·1 mole) was dissolved in a mixture of dioxane (200 ml) and pyridine (16·1 ml ~ 0·2 mole). Tetrabromomethane (66·4 g ~ 0·2 mole) was added, and the resulting yellow solution was left standing at room temp for 24 hr. A crystalline precipitate, consisting of an addition compound of 1 mole pyridine hydrobromide and 1 mole tetrabromomethane was filtered off, and the filtrate heated on the steam bath for 3–4 hr. After cooling, a precipitate, mainly consisting of pyridine hydrobromide was removed; the filtrate was diluted with ether (500 ml), washed thoroughly with water, and dried; whereafter the solvent was removed *in vacuo*.

The residue crystallized with methanol, and the crude products, obtained in this way, were purified as follows:

6-*Dibromomethyleneprogesterone*. One recrystallization from methanol afforded 36% of material, m.p. 201–202°. The analytical sample had m.p. 202–203°. $[\alpha]_D^{22}$ +242°. U.V. λ_{max} 250 mμ (ε 9750), $\lambda_{shoulder}$ 285 mμ (ε 5600); I.R. ($CHCl_3$): 1570, 1622, 1678 and 1700 cm^{-1}. (Found: C, 54·48; H, 5·82; Br, 32·95. $C_{22}H_{28}Br_2O_2$ requires: C, 54·58; H, 5·83; Br, 33·01%).

6-*Dibromomethylene*-17α-*hydroxyprogesterone*. After one recrystallization from methyl cellosolve 64% of prisms, m.p. 243–244° were obtained. The analytical sample had m.p. 246–247°. $[\alpha]_D^{22}$ +169°. U.V. λ_{max} 252 mμ (ε 10250), $\lambda_{shoulder}$ 280–285 mμ (ε 5850). (Found: C, 52·93; H, 5·88; Br, 31·70. $C_{22}H_{28}Br_2O_3$ requires: C, 52·81; H, 5·62; Br, 31·95%).

6-*Dibromomethylene*-17α-*hydroxy*-11-*desoxycorticosterone acetate*. The crude product, which was contaminated with some comp S acetate, was dissolved in hot acetone. Upon cooling the impurity separated as needles. Addition of water to the filtrate precipitated the dibromo-compound, which was recrystallized from methanol to give a 30% yield of a product with m.p. 221–222°. The analytical sample, obtained from methyl cellosolve, had m.p. 228–229·5°. $[\alpha]_D^{20}$ +201°. U.V. λ_{max} 251 mμ (ε 9950), $\lambda_{shoulder}$ 280–285 mμ (ε 5800). (Found: C, 51·61; H, 5·49; Br, 28·70. $C_{24}H_{30}Br_2O_5$ requires: C, 51·63; H, 5·42; Br, 28·63%).

6-*Dibromomethylenecortisone acetate*. A contamination of cortisone acetate was removed in the same way as the comp S acetate mentioned above. Recrystallization from methyl cellosolve afforded pure material with m.p. 236–237° in 55% yield. $[\alpha]_D^{20}$ +256°. U.V. λ_{max} 252 mμ (ε 9650), $\lambda_{shoulder}$ 275–280 mμ (ε 5250); I.R. ($CHCl_3$): 1570, 1607, 1668, 1703, 1720 and 1735 cm^{-1}. (Found: C, 50·27; H, 5·12; Br, 27·96. $C_{24}H_{28}Br_2O_6$ requires: C, 50·37; H, 4·93; Br, 27·94%).

Acetylation of 6-dibromomethylene-17α-hydroxyprogesterone

6-Dibromomethylene-17α-hydroxyprogesterone (13·0 g) and *p*-toluene-sulphonic acid (13·0 g) were suspended in a mixture of glacial acetic acid (200 ml) and acetic anhydride (50 ml). The suspension was stirred until a clear solution resulted (about 1 hr) and then allowed to stand overnight at room temp. Water was added, and the amorphous precipitate collected on a filter, washed with water, and dried over P_2O_5. The dried product (14·2 g) was crystallized from benzene–hexane to give 14·6 g *6-dibromomethylene-17α-acetoxyprogesterone*, containing 1 mole of benzene: m.p. 111–115°.

For analytical purposes, a sample was recrystallized from benzene, m.p. 114·5–117°. $[\alpha]_D^{30}$ +143°. U.V. λ_{max} 249 mμ (ε 10200), $\lambda_{shoulder}$ 280–285 mμ (ε 6200). (Found: C, 58·14; H, 6·06; Br, 25·72. $C_{24}H_{30}Br_2O_4$, C_6H_6 requires: C, 58·08; H, 5·85; Br, 25·76%).

TABLE 1

Compound	M.p.	$[\alpha]_D$	Recrystallized from	Yield[c] %	Ref.
6α-Methyltestosterone[b]	158–159°	+90°	acetone-hexane	70	3, 5, 7
6α,17α-Dimethyltestosterone[b]	137–139°	+66°	ether-hexane	74	3, 5, 7, 8
6α-Methylnortestosterone acetate[b]	126–128°	+8°	ether-hexane	65	
6α-Methylprogesterone[a]	122–123·5°	+177°	hexane		3, 6, 14
6α-Methyl-17α-acetoxyprogesterone[a]	202–204°	+60·8°	isopropanol	86	2, 10
6β-Methyl-17α-acetoxyprogesterone	249–254°	−38·5°	methanol		
6α-Methyl-17α-hydroxy-11-desoxy-corticosterone acetate[a]	198·5–200°		acetone-hexane	75	
6α-Methylcortisone acetate[a]	240–241·5°	−219°	ethanol	80	4

[a] The hydrogenation was performed in methyl cellosolve
[b] The hydrogenation was performed in dioxane
[c] The yields are based upon the amounts of material obtained after one recrystallization of the crude products

6-Trichloromethyltestosterone (VI)

To a solution of testosterone 3-ethylenol ether (20 g) in dioxane (60 ml), pyridine (5 ml) and bromotrichloromethane (10 ml) were added, and the mixture was allowed to stand at room temp for 20 hr. After filtration the filtrate was poured into a large amount of water, whereby an oil separated which, after decanting, was triturated with ether to give 12·5 g of crystals with m.p. 212–215° (dec). U.V. λ_{max} 242 mμ (ε 12500). (Found: C, 59·87; H, 6·84; Cl, 26·90. $C_{20}H_{27}Cl_3O_2$ requires: C, 59·20; H, 6·71; Cl, 26·21%).

6-Dichloromethylenetestosterone (VII)

6-Trichloromethyltestosterone (VI, 10 g) was dissolved in pyridine (150 ml) and the solution heated on the steam bath for 30 min. After cooling, water was added, and on scratching the product crystallized. It was collected and recrystallized from ethanol to give 7·6 g of material, m.p. 208–210°. $[\alpha]_D^{30}$ +264°. U.V. λ_{max} 246 mμ (ε 10400), $\lambda_{shoulder}$ 275 mμ (ε 5800); I.R. (KBr): 1612, 1665 cm^{-1}. (Found: C, 65·15; H, 7·20; Cl, 19·23. $C_{20}H_{26}Cl_2O_2$ requires: C, 65·04; H, 7·10; Cl, 19·20%).

6α-Methyl-Δ⁴-3-ketosteroids

General procedure. The 6-dibromomethylenesteroid (0·03 mole) was dissolved in methyl cellosolve or dioxane. Triethylamine (8·4 ml, 0·06 mole) was added, and the mixture shaken under hydrogen in the presence of 20 g of pre-reduced 2% palladium–strontium carbonate catalyst.[18]

[18] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Amer. Chem. Soc.* 74, 4223 (1952).

In 30–60 min, 3 moles of hydrogen were absorbed, and the consumption of hydrogen ceased. The catalyst was removed, and the filtrate acidified with 10% of 1 N hydrochloric acid. After standing for 1 hr at room temp water was added, and on scratching the product crystallized. It was filtered, washed with dil methanol, and, after drying, recrystallized from an appropriate solvent. The data of the hydrogenation products, which all gave satisfactory microanalyses, are given in Table 1.

By the hydrogenation of 6-dibromomethylene-17α-acetoxyprogesterone a small amount of 6β-methyl-17α-acetoxyprogesterone could be isolated from the mother liquor of the main product 6α-methyl-17α-acetoxyprogesterone. It was readily epimerized at C-6 upon treatment with hydrogen chloride in chloroform according to Campbell *et al.*[5]

Acknowledgements—The authors wish to thank Dr. P. Mørch for I.R.- and U.V.-spectra and Mr. G. Cornali for the microanalyses.