## 202. *Modified Steroid Hormones. Part XXVII.* * *A New Route to 4-Methyl-3-oxo-Δ⁴-steroids.*

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3-Oxo-Δ⁴-steroids (I; R = H) of diverse types condense with form-aldehyde and organic thiols in the presence of tertiary amines as catalysts to give the corresponding 4-organothiomethyl derivatives (I; R = CH₂·SR′). The latter are converted by Raney nickel in acetone into 4-methyl-3-oxo-Δ⁴-steroids.[1]
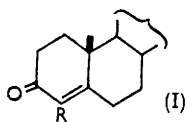
The limitations of this new reaction and the chemistry of the intermediate 4-organothiomethyl derivative are discussed.

(I)

OUR interest in 4-methylated hormones started from the concept that structures formally related to biogenetic precursors may be worthy of biological study. The prepar-ation of 4,4-dimethylcalciferol [2] and of some 4,4-dimethyl-3-oxo-derivatives of androstane and pregnane [3] was undertaken, but no satisfactory method existed for the preparation of 4-methyl-substituted hormone types. Sondheimer and Mazur [4] had used Turner's route [5] to 4-methyl-testosterone and -progesterone, and Atwater [6] had shown that cautious methylation of testosterone gave a mixture which yielded the 4-monomethyl derivative by chromatography on alumina. However, as these routes were awkward in practice we sought a convenient alternative.

We report a simple two-stage method for converting 3-oxo-Δ⁴-steroids into 4-methyl derivatives in overall yields of up to 80% in favourable cases. The new method, which involves the desulphurisation of a 4-organothiomethyl intermediate, is applicable to many types, thus making 4-methylated steroid hormones for the first time readily accessible.

We have found that treatment of a 3-oxo-Δ⁴-steroid (I; R = H) in ethanolic solution under reflux with an organic thiol (R′SH) and formaldehyde, in the presence of a tertiary aliphatic amine as catalyst, results in the formation of the 4-organomethyl derivative (I; R = CH₂·SR′) in generally excellent yield. The reaction resembles the Mannich condensation as modified by Poppelsdorf and Holt [7] for the thiomethylation of 2-naphthol. It seems to be highly specific for the 3-oxo-Δ⁴-system, no evidence for substitution else-where in the molecule being obtained in any of the compounds studied. For preparative purposes benzene- and *p*-toluene-thiol were generally convenient and gave somewhat higher yields than the heterocyclic thiols and the more obnoxious alkanethiols (see Table 1a).

" Formalin " (40% aqueous solution) or paraformaldehyde was used as sources of formaldehyde. Triethylamine was the preferred basic catalyst, although trimethylamine, tri-n-propylamine and *N*-methylpiperidine all gave satisfactory yields. The reaction usually required 30 to 50 hr. for completion under these conditions. By using triethanol-amine, which served as both basic catalyst and solvent, a temperature of 110—120° could be achieved, thereby reducing the reaction time to 8—12 hr.

The 4-organothiomethyl derivatives (I; R = CH₂·SR′) were generally obtained crystalline and in all cases were characterised from spectral data. Those derived from alkanethiols had $\lambda_{max.}$ *ca.* 246 mμ (ε 13,500—14,300), whilst derivatives from aromatic

* Part XXVI, *J.*, 1962, 29.

[1] Preliminary communication, Kirk and Petrow, *Proc. Chem. Soc.*, 1961, 114.
[2] Cooley, Ellis, and Petrow, *J.*, 1955, 2998.
[3] Adams, Patel, Petrow, Stuart-Webb, and Sturgeon, *J.*, 1956, 4490.
[4] Sondheimer and Mazur, *J. Amer. Chem. Soc.*, 1957, **79**, 2906.
[5] Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579.
[6] Atwater, *J. Amer. Chem. Soc.*, 1957, **79**, 5315.
[7] Poppelsdorf and Holt, *J.*, 1954, 1124.

thiols had λ_{max}. *ca.* 250—253 mμ (ε 16,000—21,000). All the derivatives had ν_{max}. (in CCl$_4$) at 1678—1671 and 1602—1598 cm.$^{-1}$.

Desulphurisation of the 4-organothiomethyl intermediates (I; R = CH$_2$·SR') with Raney nickel caused difficulty because, in solvents such as ethanol or dioxan, concomitant reduction (either partial or complete) of the 3-oxo-Δ^4-system occurred. It was ultimately found that by preheating the metallic catalyst with acetone [8] under reflux its activity could be reduced so that desulphurisation alone occurred with formation of the 4-methylated derivative (I; R = Me) in yields of up to 95%.

The experimental conditions required for both thiomethylation and desulphurisation limit the number of structural types suitable for 4-methylation by our method. 17α-Hydroxypregnan-20-ones, which undergo easy D-homoannulation under alkaline conditions, must clearly be protected by 17-acetylation before 4-thiomethylation. A similar difficulty in the case of the cortical side chain can be overcome by using the 17,20:20,21-bismethylenedioxy-derivative.[9] Both primary and secondary alcoholic groups undergo partial oxidation during the treatment with Raney nickel in acetone, but may be preserved by acetylation. The highly labile 16α,17α-dihydroxypregnan-20-one system is best converted into the isopropylidene derivative [10] and subsequently regenerated. 17α-Ethynyl and 17α-vinyl steroidal ketones undergo normal 4-thiomethylation, but suffer hydrogenation during the Raney nickel treatment. Pregn-16-en-20-ones represent a special case in that they readily add thiols to form 16β-organothiol derivatives.[11] Reduction of such products, or their 4-organothiomethyl derivatives, leads to the formation of the corresponding pregnan-20-ones. 16α,17α-Epoxypregnan-20-ones react readily with thiols to give products of unknown constitution. In spite of these few limitations the range of structures that can be 4-methylated by our method is comprehensive (see Table 1b and 2).

A limited study has been made of the hitherto unreported 4-organothiomethyl-3-oxo-Δ^4-system. In contrast to Mannich bases derived from the oxymethylene moiety, the 4-organothiomethyl system was resistant to certain replacement reactions. 4-Phenyl-thiomethyltestosterone acetate was unaffected by boiling with acetic anhydride or with pyridine. Alkaline reagents enforced partial conversion into acidic products of unknown structure. Reduction with zinc in acetic acid or with chromous chloride was unsuccessful, while catalytic hydrogenation over palladised charcoal was prevented by poisoning of the catalyst.

Oxidation of the 4-phenylthiomethyl group with hydrogen peroxide–acetic acid converted it successively into the sulphoxide (I; R = CH$_2$·SOPh) and into the sulphone (I; R = CH$_2$·SO$_2$Ph). The last compound resisted desulphurisation by Raney nickel, but catalytic hydrogenation of 4-phenylsulphonylmethyltestosterone acetate over palladised charcoal selectively reduced the Δ^4-unsaturated linkage to give a 4,5-dihydro-derivative. Attempts to eliminate benzenesulphinic acid from the last compound by treatment with lithium chloride–lithium carbonate–dimethylformamide failed to give the expected 4-methylene derivative. Similar treatment of 4-phenylsulphonylmethyl-progesterone led to the formation of a dimeric product possibly derived from the 4-methylene-Δ^5-structure. Analogous autocondensations of other α-methylene-ketonic systems have been recorded elsewhere.[12]

Several new routes to 4-methyl-steroids have been reported since the above work was initiated. Direct 4-monomethylation of cholest-7-en-3-one has been described by Mazur and Sondheimer.[13] Camerino *et al.*[14] have developed a multistage process involving

[8] Spero, McIntosh, and Levin, *J. Amer. Chem. Soc.*, 1948, **70**, 1907.
[9] Beyler, Moriarty, Hoffmann, and Sarett, *J. Amer. Chem. Soc.*, 1958, **80**, 1517.
[10] Cooley, Ellis, Hartley, and Petrow, *J.*, 1955, 4373.
[11] U.S.P. 2,702,297.
[12] Mauli, Ringold, and Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 5494; Romann, Frey, Stadler, and Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1900.
[13] Mazur and Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 6296.
[14] Camerino, Cattapan, Valcavi, and Patelli, *Gazzetta*, 1959, **89**, 674.

TABLE 1a.

4-Organothiomethyltestosterones.

R	M. p.	$[\alpha]_D$ [a]	$\lambda_{max.}$ (mμ) (ε) [b]	$\nu_{max.}$ (cm.⁻¹) [c]	Formula	Found C	Found H	Found S	Reqd. C	Reqd. H	Reqd. S
Ph	140—144°	+100°	251 (18,100)	1676, 1601	$C_{26}H_{34}O_2S$	76·0	8·3	8·1	76·05	8·3	7·8
Ph (17-Acetate)	115—117	+102	251·5 (18,960)	1737, 1673, 1598	$C_{28}H_{36}O_3S$	74·3	7·9	6·9	74·3		7·1
C₄H₄Me-p	106—121	+87	251 (16,900)	1673, 1597	$C_{27}H_{36}O_2S$	76·0	8·5	7·2	76·4	8·55	7·5
Et	89—94	+93	246·5 (13,200)	1673, 1601	$C_{22}H_{34}O_2S$	73·2	9·5	8·6	72·9	9·45	8·8
Bu	109—110	+108	246·5 (14,200)	1674, 1599	$C_{24}H_{38}O_2S$	74·2	9·5	7·8	73·8	9·8	8·2
C₆H₁₁	138—141	+91	240—250 (13,890)	1673, 1600	$C_{26}H_{40}O_2S$	74·5	9·4	8·1	75·0	9·7	7·8
CH₂CH₂OH	109—111	+86	249 (13,580)	1671, 1602	$C_{24}H_{36}O_3S$	69·7	9·1	8·7	69·8	9·1	8·5
[CH₂]₃CO₂Me	96—97	+79	248·5 (11,780)		$C_{27}H_{36}O_4S$	68·5	8·6	7·7	68·5	8·6	7·6
CH₂Ph	113—116	+98	245 (15,200)	1678, 1601	$C_{27}H_{36}O_2S$	76·8	8·8	7·3	76·4	8·5	7·55
Furfuryl	67—69	+92	226 (13,930) 246·5 (13,225)	1672, 1600	$C_{25}H_{34}O_3S$			7·4			7·7

TABLE 1b.

4-Phenylthiomethyl-3-oxo-Δ⁴-steroids.

Parent compound	M. P.	$[\alpha]_D$ [a]	$\lambda_{max.}$ (mμ), (ε) [b]	$\nu_{max.}$ (cm.⁻¹) [e]	Formula	Found C	Found H	Found S	Reqd. C	Reqd. H	Reqd. S
Androstanes											
Androst-4-ene-3,17-dione	136—138°	+150°	251 (17,650)	—	$C_{26}H_{32}O_2S$	76·0	7·4	8·3	76·4	7·1	7·85
2α-Methyltestosterone	118—120	+108	251 (21,060)	1675, 1605	$C_{27}H_{36}O_2S$	76·1	8·5	7·0	76·4	8·55	7·5
2α-Methyltestosterone " " acetate	143—146	+107	251 (16,250)	1739, 1675, 1605	$C_{29}H_{38}O_3S$	74·5	7·8	6·5	74·65	8·2	6·9
17α-Methyltestosterone	136—138	+102	252 (18,000)	1673, 1603	$C_{27}H_{36}O_2S$	76·4	8·6	7·8	76·4	8·55	7·5
6-Dehydrotestosterone	146—150	+108	291 (19,250)	1655, 1611, 1584 (CH₂Cl₂)	$C_{26}H_{32}O_2S$	76·3	7·7	7·9	76·4	7·9	8·2
17α-Vinyltestosterone	92—94	+62	251·5 (17,070)	1673 (CCl₄), 1001, 918 (CH₂Cl₂)	$C_{28}H_{36}O_2S$	77·0	8·4	7·3	77·0	8·3	7·3
11α-Hydroxytestosterone	210—211	+74	263 (17,875)	1666, 1598 (CH₂Cl₂)	$C_{26}H_{34}O_3S$	72·85	7·7	7·7	73·2	8·0	7·5
9α-Fluoro-11β-dihydroxy-17α-methyltesto-sterone	224—225	+107	250·5 (12,880)	1665, 1602 (CH₂Cl₂)	$C_{27}H_{35}O_3FS$	70·55	7·9	6·8	70·6	7·7	7·0
19-Nortestosterone	141—143	+87	251 (19,080)	1674, 1607	$C_{25}H_{32}O_2S$	75·4	8·2	8·75	75·7	8·1	8·4
Pregnanes											
Progesterone	98—100	+175	252 (18,960)	1707, 1674, 1600	$C_{28}H_{36}O_2S$	77·0	8·2	7·5	77·0	8·3	7·3
11α-Hydroxyprogesterone	137—139	+129	252·5 (18,000)	1708, 1676	$C_{28}H_{36}O_3S$	74·1	8·2	6·8	74·3	8·0	7·1
17α-Acetoxyprogesterone	187—190	+78	251 (18,000)	1739, 1717, 1874 (CS₂)	$C_{30}H_{38}O_4S$	73·2	7·6	6·45	72·8	7·7	6·5
Bismethylenedioxycortisone	183—185	+61	251·5 (20,150)	1706, 1673, 1601	$C_{30}H_{38}O_6S$	68·4	7·0	5·95	68·7	6·9	6·1
Ethyl 3-oxopregna-4,17(20)-dien-21-oate	127—128	+115	220·5 (25,850) 248·5 (19,770)	1701, 1663, 1656, 1598 (CH₂Cl₂)	$C_{30}H_{39}O_3S$	75·0	7·8	6·3	75·3	8·0	6·7
25D-Spirost-4-en-3-one	152—154	+4	252·5 (17,600)	1674, 1599	$C_{34}H_{46}O_3S$	76·0	9·0	5·85	76·35	8·7	6·0
4-(p-Tolylthiomethyl)-3-oxo-Δ⁴-steroids											
17↑-Methyltestosterone [d]	143—144	+87	227 (13,450) 253 (16,820)	1674, 1600	$C_{28}H_{38}O_2S$	76·6	8·7	7·6	76·9	8·7	7·3
25D-Spirost-4-en-3-one	164—166	+9	228 (11,750) 254 (15,860)	1673, 1598	$C_{35}H_{48}O_3S$	76·6	8·6	6·2	76·6	8·5	5·3

[a] At 22—26° in *ca.* 1% in chloroform. [b] In ethanol. [e] In carbon tetrachloride unless otherwise stated. [d] With G. O. Weston, B.Sc.

The 4-phenylthiomethyl derivatives of the following compounds were obtained in an amorphous state, and were characterised from the ultraviolet absorption maxima at 250—252 mμ: 11β-Hydroxytestosterone, androst-4-ene-3,11,17-trione, 16α-methylprogesterone, 17α-hexanoyloxyprogesterone, 9(11)-dehydroprogesterone, pregn-4-ene-3,11,20-trione, 16α,17α-isopropylidenedioxyprogesterone, hydrocortisone bismethylenedioxy-derivative, cholest-4-en-3-one, methyl-3-oxochol-4-en-24-oate.

TABLE 2.

4-Methyl-3-oxo-Δ⁴-steroids.

Parent compound	M. p.	[α]D [a]	λmax. (mμ) (ε) [a]	νmax. (cm⁻¹) [b]	Formula	Found		Required or Calculated	
						C	H	C	H
Androstanes									
Testosterone acetate [c]	168—170°	+112°	249 (15,190)	1670, 1604	$C_{22}H_{32}O_3$	76.55	9.5	76.70	9.4
2α-Methyltestosterone	156—158	+122	248.5 (14,400)	1670, 1613	$C_{21}H_{32}O_2$	79.5	10.3	79.6	10.2
2α-Methyltestosterone acetate	188—190	+117	248 (14,480)	1736, 1669, 1612	$C_{23}H_{34}O_3$	76.7	9.5	77.0	9.6
17α-Methyltestosterone	139—142	+96	249.5 (13,220)	1672, 1604	$C_{21}H_{32}O_2$	79.4	10.3	79.6	10.2
17α-Ethyltestosterone	154—156	+89	249.5 (15,340)	1670, 1604	$C_{22}H_{34}O_2$	79.8	10.4	79.95	10.4
19-Nortestosterone acetate [d]	127—129	+51	248 (16,230)	1740, 1672, 1611	$C_{21}H_{30}O_3$	75.9	9.0	76.3	9.15
19-Nortestosterone [e]	156—157	+52	248 (14,820)	1667, 1609	$C_{18}H_{26}O_2$	78.9	9.9	79.1	9.8
Androst-4-ene-3,17-dione	138—140	+207	248.5 (15,320)	1745, 1673, 1607	$C_{20}H_{28}O_2$	80.0	9.2	79.95	9.4
11α-Hydroxytestosterone [f]	179—180.5	+72	252 (14,200)	1658, 1602 (CH_2Cl_2)	$C_{20}H_{30}O_3$	75.3	9.5	75.4	9.5
11β-Hydroxytestosterone	256—261	+135	251 (13,500)	1656, 1601 (CH_2Cl_2)	$C_{20}H_{30}O_3$	75.4	9.7	75.4	9.5
Androst-4-ene-3,11,17-trione [f]	166—168	+311	247 (13,645)	1749, 1714, 1673, 1610	$C_{20}H_{26}O_3$	76.0	8.4	76.4	8.4
6-Dehydrotestosterone acetate [f]	154—155	+87	289 (29,180)		$C_{23}H_{30}O_3$	76.8	8.85	77.15	8.8
9α-Fluoro-11β-hydroxy-17α-methyltestosterone	217—220	+112	249 (16,440)	1659, 1607	$C_{21}H_{29}FO_3$	72.0	9.0	71.9	8.9
Pregnanes									
Progesterone [g]	164—166	+212	249 (15,320)	1709, 1671, 1606	$C_{22}H_{32}O_2$	80.6	10.0	80.4	9.8
16α-Methylprogesterone	152—154	+173	249 (16,270)	1705, 1668, 1606	$C_{23}H_{34}O_2$	80.4	9.6	80.65	10.0
11α-Hydroxyprogesterone	168—171	+146	250.5 (12,050)	1708, 1668	$C_{22}H_{32}O_3$	76.45	9.6	76.7	9.4
Pregn-4-ene-3,11,20-trione	179—181	+277	248 (13,835)	1700, 1669, 1601	$C_{22}H_{30}O_3$	76.8	8.5	77.15	8.8
9(11)-Dehydroprogesterone	146—149	+154	249 (14,800)	1668, 1606	$C_{22}H_{30}O_2$	81.1	9.4	80.9	9.3
17α-Acetoxyprogesterone [h]	142—144 or 176—180	+80	248.5 (13,720)	1736, 1722, 1673, 1608	$C_{24}H_{34}O_4$	74.6	8.8	74.6	8.9
17α-Hexanoyloxyprogesterone	122—124	+71	248.5 (14,740)	1734, 1719, 1669, 1610	$C_{28}H_{42}O_4$	76.4	9.5	76.0	9.6
16α,17α-Isopropylidenedioxyprogesterone	217—226	+131	248 (16,000)	1713, 1669, 1613	$C_{25}H_{36}O_4$	74.6	9.1	75.0	9.1
Bismethylenedioxycortisone [i]	279—284	+87	248 (13,700)	1708, 1672, 1609	$C_{25}H_{34}O_6$	68.8	7.6	69.2	7.7
Cortisone acetate	236—239	+231	248 (14,530)	3424, 1749, 1726, 1702, 1633, 1595	$C_{24}H_{32}O_6$	69.0	8.0	69.2	7.7
Bismethylenedioxyhydrocortisone	203—207	+24	250.5 (10,300)	3623, 1668, 1610	$C_{24}H_{32}O_6$	68.1	8.1	68.9	8.2
17α,20:20,21-Bismethylenedioxypregna-4,9(11)-dien-3-one	219—222	−46	247—248 (14,130)	1667, 1607	$C_{25}H_{32}O_5$	71.75	8.3	72.0	8.05
Ethyl 3-oxopregna-4,17(20)-dien-21-oate	131—132	+109	225 (18,670) 240 (infl.) (17,822)	1708, 1665, 1604	$C_{24}H_{34}O_3$	77.5	9.3	77.8	9.25
Miscellaneous									
Cholest-4-en-3-one [j]	101—103	+107	249.5 (15,480)		$C_{28}H_{46}O$	84.1	11.5	84.35	11.6
25D-Spirost-4-en-3-one	210—212	±0	249.5 (15,380)		$C_{28}H_{42}O_3$	78.7	10.0	78.8	9.9
Methyl 3-oxochol-4-en-24-oate	100—103	8	250 (13,980)	1738, 1668, 1606	$C_{26}H_{40}O_3$	77.8	9.3	77.95	10.1

[a] Optical rotation at 22—26°, in *ca.* 1% solutions in chloroform; ultraviolet spectra were measured in ethanol. [b] Infrared spectra in carbon tetrachloride except where otherwise indicated. [c] Lit.:[4] m. p. 158—160°, [α]D +122°. [d] Lit.:[4] m. p. 168—170·5°, [α]D +5°, [α]D +137°. [e] Lit.:[4] m. p. 128—129°, [α]D +42°. [f] Lit.:[5] m. p. 158—159°, [α]D +52°. [f] Cf. Kirk, Petrow, and Williamson, *J.*, 1960, 3872. [g] Lit.: m. p. 155—157°, [α] +251° (U.S.P. 2,891,075); m. p. 155—157°, [α] +235°. [h] m. p. 160—166°, [α]D +173°. [i] Lit.: m. p. 170—174°;[14] m. p. 175—180°, [α]D +86°. [j] Lit.: m. p. 272—280° (Steinberg, Hirschmann, and Chemerda, *Chem. and Ind.*, 1958, 975). [i] Lit.: m. p. 102—105°, [α]D +108° (Meakins and Rodig, *J.*, 1956, 4679); m. p. 102—103°, [α]D +110°.

conversion of a 3-oxo-Δ⁴-steroid into a 3,4-dione, followed by protection of the 3-oxo-function and Grignard reaction at $C_{(4)}$. The Syntex group have reported a process involving conversion of a 5β-dihydro-3-ketone into a 4-formyl derivative, followed by methylation at $C_{(4)}$, deformylation, and introduction of the Δ⁴-linkage by bromination. Melting points are conspicuously lacking in the examples so that their scientific value is difficult to assess. The Upjohn Company [16] describe the direct methylation of the enamine derived from 17α-acetoxyprogesterone to give the 4-methyl derivative in a yield of *ca.* 8%. This result is of particular interest in view of an earlier failure [17] to achieve this type of reaction.

<div align="center">EXPERIMENTAL</div>

Rotations were determined in a 1 dm. tube for chloroform solutions. Ultraviolet (in ethanol solution) and infrared absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc.

General Procedures for the Preparation of 4-Organothiomethyl-3-oxo-Δ⁴-steroids.—*Method A.* A mixture of the 3-oxo-Δ⁴-steroid (5 parts), thiol (4 parts), 40% aqueous formaldehyde (3 parts), triethylamine (3 parts), and ethanol (10—30 parts, depending upon the solubility of the steroid) was heated under reflux for 30—50 hr. In a few cases the 4-organothiomethyl derivative crystallised when the mixture cooled, and was collected and purified from a suitable solvent. When the derivative failed to crystallise directly, the solution was poured into aqueous sodium hydroxide, and the product isolated with ether or benzene. The steroidal material thus obtained was always contaminated with condensation products derived from the thiol and formaldehyde. These could often be removed by trituration with light petroleum. The residue was usually sufficiently pure for desulphurisation to give the 4-methyl derivative (see below), but could be purified by direct crystallisation or by chromatography on alumina if required.

Method B. The 3-oxo-Δ⁴-steroid (5 parts), thiol (4 parts), 40% aqueous formaldehyde (5 parts), and triethanolamine (10 parts) were heated under reflux (solution temperature 110—115°) for 8—16 hr., then the mixture was poured into water, and the product isolated with benzene or ether. The subsequent purification was similar to that in Method A.

Methods A and B could be modified by the use of paraformaldehyde instead of 40% aqueous formaldehyde. Method A could also be modified by the use of such other tertiary amines as trimethylamine, tri-n-propylamine, or N-methylpiperidine. Amines of low volatility were removed during the isolation of the product by washing the ethereal solution with dilute aqueous acids.

4-Phenylthiomethyltestosterone was acetylated by treatment with acetic anhydride–pyridine (1 : 1) at room temperature overnight or on the steam-bath for ½ hr. After precipitation into ice–water the 17-*acetate* (see Table 1a) was purified from methanol.

Other 4-organothiomethyltestosterones (see Table 1a and 1b) were acetylated in the same way before desulphurisation, but the acetates were usually amorphous and were used without purification.

Desulphurisation of 4-Organothiomethyl-3-oxo-Δ⁴-steroids.—*General procedure.* Raney nickel (10 ml. of settled sludge per 1 g. of steroid) was washed with acetone (25 ml. per 10 ml. of sludge) three times by decantation, and was finally suspended in acetone (50 ml.) and heated under reflux while being stirred for ½ hr. The 4-organothiomethyl-steroid (1 g.), dissolved in the minimum volume of acetone, was added and the mixture was heated under reflux while stirring for 4—5 hr. The hot solution was filtered and the nickel was washed with boiling ethanol and water. The filtrate was concentrated under reduced pressure, and the 4-methyl-3-oxo-Δ⁴-steroidal product separated out, usually crystalline, and was purified from a suitable solvent. When the product separated from the concentrated filtrate as an oil, it was isolated by extraction with ether or chloroform before crystallisation.

4-*Phenylsulphinylmethyltestosterone* (I; R = CH₂·SOPh).—4-Phenylthiomethyltestosterone (5 g.) in 80% aqueous acetic acid (100 ml.) was treated with 30% hydrogen peroxide (1·5 ml., *ca.* 1·1 mol.) for 18 hr. at room temperature, then the solution was poured into water, and the precipitate was purified from aqueous methanol, giving 4-*phenylsulphinylmethyltestosterone* as

[15] B.P. 851,998; 853,850.
[16] B.P. 851,679.
[17] Stork, Terrell, and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1954, **76**, 2029.

prisms, m. p. 190—194°, $[\alpha]_D^{26}$ +206°, λ_{max} 247 mμ (ε 13,225), ν_{max} (in carbon tetrachloride) 3618 (OH), 1674 (3-CO); Nujol mull 1665, 1601 (Δ^4-3-CO), 1334, 1320, 1167 cm.$^{-1}$ (sulphoxide) (Found: C, 72·7; H, 7·7; S, 7·1. $C_{26}H_{34}O_3S$ requires C, 73·2; H, 8·0; S, 7·5%).

4-Phenylsulphonylmethyltestosterone (I; R = CH$_2$·SO$_2$Ph).—4-Phenylthiomethyltestosterone (10 g.) in acetic acid (100 ml.) was treated with 30% hydrogen peroxide (10 ml.) for 5 hr. at room temperature. Gradual dilution with water caused separation of the crystalline *sulphone* which formed needles (from aqueous methanol), m. p. 182—184°, $[\alpha]_D^{26}$ +46° (c 0·94), λ_{max} 218 (ε 12,540) and 250 mμ (ε 14,880), ν_{max} (in carbon disulphide) 3548 (OH), 1654 (3-CO), 1324, 1311, and 1135 cm.$^{-1}$ (sulphone) (Found: C, 70·3; H, 7·6; S, 7·3. $C_{26}H_{34}O_4S$ requires C, 70·55; H, 7·7; S, 7·2%).

4-Phenylsulphonylprogesterone, prepared similarly, separated from methanol as prisms, m. p. 192—200°, $[\alpha]_D^{24}$ +106° (c 0·31), λ_{max} 218 (ε 11,920) and 250 mμ (ε 15,170), ν_{max} (in carbon disulphide), 1708 (20-CO), 1677 (3-CO), 1320, 1310, and 1137 cm.$^{-1}$ (sulphone) (Found: C, 71·8; H, 7·8; S, 6·55. $C_{28}H_{36}O_4S$ requires C, 71·8; H, 7·7; S, 6·8%).

Hydrogenation of 4-Phenylsulphonylmethyltestosterone.—The sulphone (2·5 g.) in methanol (250 ml.) was hydrogenated over 5% palladium–barium carbonate (2 g.); 1 mol. of hydrogen was absorbed. The product was purified from aqueous methanol giving *17β-hydroxy-4ζ-phenylsulphonylmethylandrostan-3-one* as needles, m. p. 160—164°, $[\alpha]_D^{26}$ +28° (c 1·30), ν_{max} (in carbon disulphide) 1720 (3-CO).

Elimination of the Elements of Benzenesulphinic Acid from 4-Phenylsulphonylmethylpro-gesterone.—The sulphone (1 g.), lithium chloride (2 g.), lithium carbonate (4 g.), and dimethyl-formamide (30 ml.) were heated under reflux for 3 hr., and the mixture was cooled, diluted with water, and extracted with ether. The extract was washed, the ether evaporated, and the product purified from chloroform–ethanol, giving *4-methylenepregn-5-ene-3,20-dione dimer* as flakes, m. p. 268—272°, $[\alpha]_D^{24}$ +92° (c 0·92), λ_{max} 255 mμ (ε 11,920), ν_{max} (in carbon tetrachloride) 1708, 1667 cm.$^{-1}$ [Found: C, 80·6; H, 9·3; M (Rast), 602. $C_{44}H_{60}O_4$ requires C, 80·9; H, 9·3%; M, 652].

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