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MODIFIED STEROID HORMONES—XXXVI

STEROIDAL 6-AMINOMETHYL-3-ALKOXY-3,5-DIENES AND THEIR REACTIONS

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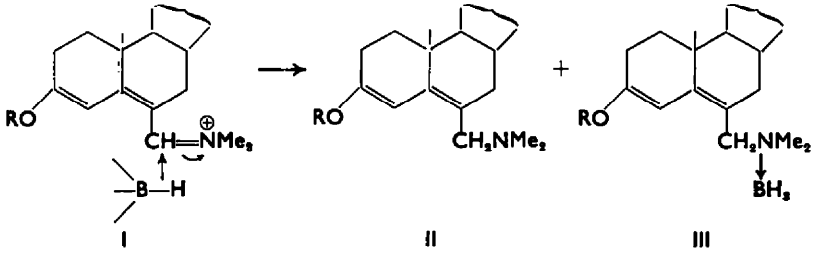
Abstract—Steroidal 3-alkoxy-3,5-dienes have been converted into 6-aminomethyl- and 6-methyl-derivatives by novel extensions of the Vilsmeier process.

IN PART XXXIII[1] we described the application of the Vilsmeier process[2] to steroidal 3-alkoxy-3,5-dienes when the 6-formyl derivatives were obtained in excellent yields. Subsequent transformations of these intermediates afforded 6-methylene and 6α-methyl-4-en-3-ones. We now describe an extension of this process to the preparation of the biologically important 6-methyl-3-alkoxy-3,5-dienes via their 6-aminomethyl analogues.

Initial experiments indicated that hydrogenolysis of the oxygen function present in 6-formyl- and 6-hydroxymethyl-3-alkoxy-3,5-dienes, without concomitant hydrolysis of the enol ether system, could not be achieved. We therefore turned our attention to the catalytic hydrogenation of the Vilsmeier iminium intermediate (cf. I). These intermediates have not been isolated in the present work, and attempts to effect their hydrogenation in situ were unsuccessful, due presumably to catalyst poisoning.[3]

On theoretical grounds, it seemed likely that the positive charge on the nitrogen atom present in the iminium intermediate (cf. I) would facilitate reduction by a simple

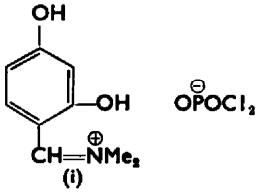


I II III

[1] D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow and D. M. Williamson, *Tetrahedron* **20**, 597 (1964).

[2] H. H. Bosshard and HcH. Zollinger, *Helv. Chim. Acta* **42**, 1659 (1959) and Refs there cited.

[3] Mangoni [*Ann. di Chim.* **48**, 930 (1958)] has described the isolation of the crystalline iminium salt (i) and its subsequent hydrogenation over Pd–C in acetic acid to the corresponding amine.

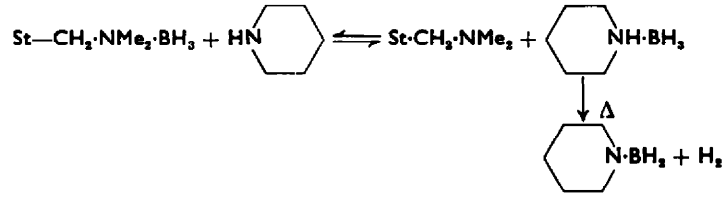


(i)

hydride ion transfer from, for example, a borohydride. When an excess of an anhydrous solution of sodium borohydride in pyridine or, more conveniently, lithium borohydride in tetrahydrofuran, was added to the deep red Vilsmeier reaction mixture, the colour was rapidly discharged to pale yellow. Two products could be isolated from the resulting solution. One of these was basic and proved to be the expected amine (cf. II), while the major, neutral product was the amine-borane adduct (cf. III). A convenient separation of these two substances consisted in extraction of the amine from an ether solution of the mixture with aqueous succinic acid. This acid gave stable, water-soluble salts but did not hydrolyse the enol ether system. The ratio of the two products formed depended upon the amount of borohydride used, although it was not possible to convert all the amine into its borane adduct even in the presence of a very large excess of reducing agent. It was also found that diborane gas, or the pyridine-borane complex,[4] was effective in the reduction of the iminium salt to the amine. In these cases however, little or no amine-borane adduct was formed. Presumably diborane, unlike the borohydrides, is too weakly acidic to displace hydrogen ion from the initially formed amine hydrochloride.

In addition to the 6-dimethylaminomethyl-3-alkoxy-3,5-dienes, the corresponding 6-piperidinomethyl- and 6-N-methyl-N-phenylaminomethyl derivatives were prepared using Vilsmeier reagents derived from N-formylpiperidine and N-methylformanilide respectively. As expected, the weakly basic N-methyl-N-phenylaminomethyl derivative did not form an amine-borane adduct, even in the presence of excess borohydride.

The amine-borane adducts were converted into the free amines in high yield by heating with a strongly basic secondary amine such as piperidine. A tertiary amine such as triethylamine was not effective, so that a possible mechanism would involve



the establishment of the equilibrium followed by decomposition of the secondary borane.[5]

The amine borane adducts proved to be extremely stable compounds. In contrast to the free amines, they are sparingly soluble and generally crystallized well. They are characterized by an UV maximum at 254–256 mμ, and by IR maxima at about 2370, 2320 and 2270 cm^{-1} due to the borane group.[6] The free amines, prepared by the use of a restricted quantity of reducing agent,[7] or from the amine-borane adducts, have λ_{max} ca. 250 mμ and normal enol ether C=C bands in the IR.

[4] M. D. Taylor, L. R. Grant and C. A. Sands, *J. Amer. Chem. Soc.* **77**, 1506 (1955).

[5] See, for example, F. G. A. Stone, *Quart. Rev.* **9**, 174 (1955).

[6] H. J. Hrostowski and G. C. Pimental, *J. Amer. Chem. Soc.* **76**, 998 (1954).

[7] The amount of borohydride required for the reduction of the iminium salt depends upon the amount of phosgene (or phosphoryl chloride) used to prepare the Vilsmeier reagent, as the borohydride will react with both the iminium intermediate and with any excess reagent that may be present. Optimum yields of free amines were found to be produced when a molar ratio of phosgene to borohydride of 1:0·6 was employed.

The preparation of the amines and their borane adducts was readily achieved with iminium salts lacking other readily reducible substituents. When such groups were present, they took part in competitive reduction to the extent of 15–20%, even when insufficient reducing agent was used. This was particularly true of carbonyl groups at C17 and C20 (when not subject to steric hindrance). This competition could be minimized to a large extent by the addition of a strong base such as triethylamine (or preferably phenazone) to the Vilsmeier reaction solution *before* the addition of the reducing agent. Presumably the hydrochloric acid produced during the Vilsmeier reaction is neutralized, thereby avoiding loss of borohydride ion, and generation of diborane. It is also possible that the borohydride ion exerts a more selective reducing action by virtue of solvation with the added amine. This type of effect has been employed before in selective reductions.[8] It has naturally not been possible to prepare in good yield the amine-borane adducts of compounds containing readily reducible carbonyl groups since the use of a large excess of reducing agent is automatically precluded for such compounds.

The 6-dialkylaminomethyl enol ethers are freely soluble in aqueous solutions of all but the weakest acids. Their salts (cf. IV), which are usually hygroscopic, may be obtained by allowing the amine and acid to react in ether solution.

Aqueous solutions of the amine and not more than 1 equivalent of acid are apparently quite stable, but in the presence of an excess of strong acid hydrolysis of the enol ether occurs with the formation of the corresponding salts of 6α-dimethylaminomethyl-4-en-3-ones (cf. V). There is no tendency towards elimination of the basic group, presumably due to its reluctance to accept an electron pair. In contrast, treatment of the weakly basic 6-N-methyl-N-phenylaminomethyl enol ether with acid effects hydrolysis of the enol ether and elimination of amine to give a 6-methylene-4-en-3-one in high yield.

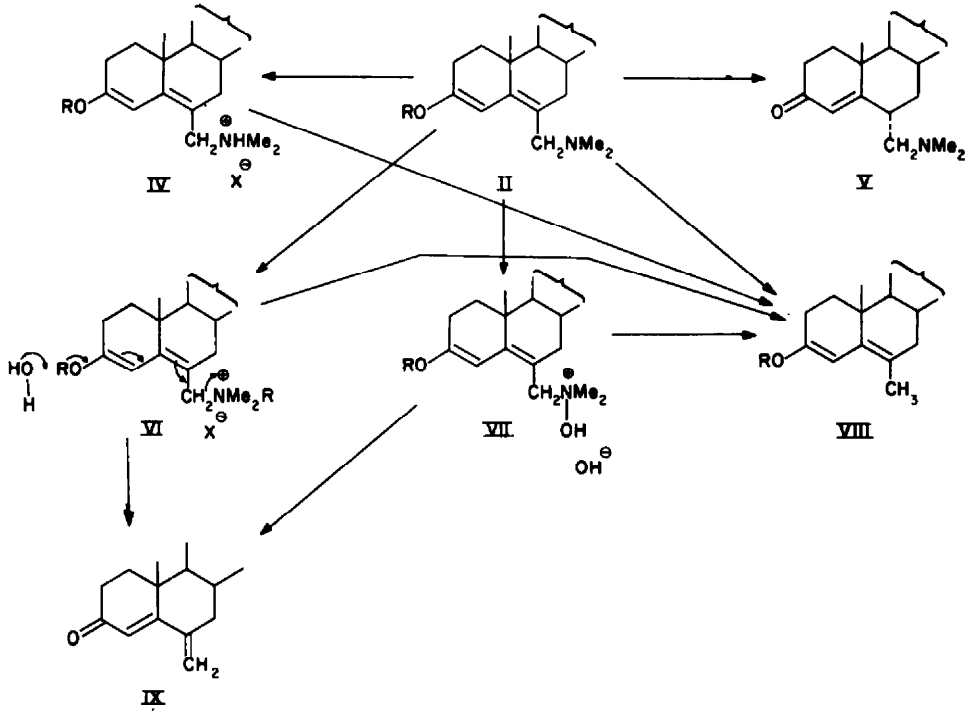
The 6-aminomethyl enol ethers (other than the N-phenyl-amines) react readily with lower alkyl halides, and with dimethyl sulphate, in non-polar solvents to give the corresponding quaternary salts in high yield (cf. VI). These salts, which are usually non-crystalline, are insoluble in non-polar solvents and give unstable solutions in water and the lower alcohols. The 6-aminomethyl enol ethers react slowly with hydrogen peroxide in methanol to give the corresponding N-oxides. These oxides are appreciably soluble in water and sparingly soluble in non-polar solvents, and melt with effervescence. Their IR spectra indicate the presence of an hydroxyl group, and the UV maximum (257–258mμ) is very similar to that of the quaternary salts (λ_{max} 257 mμ). These facts suggest that the N-oxides exist as hydrates (cf VII).

In agreement with this conclusion, both the quaternary salts and the N-oxides (but not the amine-borane adducts which have a semi-polar structure) undergo ready elimination of base on warming in aqueous solvents to afford the 6-methylene-4-en-3-ones (cf IX) in high yield. The presence of water has been shown to be essential for the success of this reaction. Thus, if the quaternary salt is prepared under strictly anhydrous conditions and heated in an aprotic solvent, no 6-methylene-4-en-3-one is obtained, although some ill-defined decomposition does occur. A possible mechanism for this transformation, involving water, is shown on the chart.

The 6-dialkylaminomethyl enol ethers resemble benzylamine in undergoing ready

[8] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1286 (1953).

C—N hydrogenolysis. This observation forms the basis of a new and efficient procedure for the preparation of steroidal 6-methyl-3-alkoxy-3,5-dienes (cf VIII), including the biologically significant corticoidal types.



The amines, their quaternary salts and their borane adducts are converted into 6-methyl enol ethers on simply heating under reflux with Raney nickel in methanol or ethanol. The amine-borane adducts are reduced more rapidly and in higher yield than the free amines and their quaternary salts. In addition, the quaternary salts under these conditions undergo decomposition, to a significant extent, to the 6-methylene-4-en-3-ones. Application of this procedure to corticoid 21-acetates results in rapid hydrolysis of the acetate group by residual alkali absorbed on the Raney nickel.[9] The resulting 17α,21-diol-20-one is then readily converted into the 17α,20,21-triol. The addition of sodium acetate to the reaction mixture gave considerably improved yields (up to 75%). Even more satisfactory results were obtained by maintaining the pH of the mixture at 7·0 to 7·5[10] by additions of acetic acid. In this way, the enol methyl ether of cortisone acetate may be converted without difficulty into its 6-methyl derivative in 75% overall yield.

Catalytic hydrogenation of the 6-dimethylaminomethyl enol ethers and their derivatives to the 6-methyl derivatives was also examined using a 5% Pd-C catalyst in methanol solution. Hydrogenation of the free amines was not selective for the C—N link, and further reduction of the 3,5-diene system occurred. Compounds containing

[9] This residual alkali is not removed by even prolonged washing with water. It is probable however that this complication could be avoided by using Raney Ni prepared under neutral conditions.

[10] The pH of the reaction mixture was periodically tested with a narrow-range indicator paper, pH 7·0–8·5.

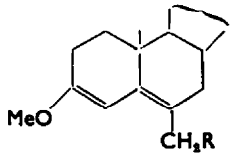
a quaternary nitrogen atom however gave more encouraging results. Thus the amine oxide and quaternary salts rapidly absorb 1 mole of hydrogen, and termination of the reaction at this point affords the 6-methyl enol ethers in satisfactory yield. Rapid reduction is essential however as the quaternary salts undergo slow decomposition. For this reason it is desirable to use fairly large amounts of catalyst; the addition of ca. 1 mole of sodium acetate to the hydrogenation medium appears to suppress this decomposition with a resulting improvement in yield. In contrast, the amine-borane adducts are not well suited to this hydrogenation procedure as the decomposition of diborane with evolution of hydrogen makes it difficult to determine the end-point of the hydrogenation.

The final and most satisfactory method investigated was the transfer hydrogenation using, for example, cyclohexene as hydrogen donor in the presence of a Pd-C catalyst. This method has the distinct advantage of specificity for hydrogenolysis of the C—N bond, and no attack upon the enol ether system, or indeed any other functional groups, was observed, even on prolonged reaction. The amine-borane adducts are particularly suitable for this procedure owing to their stability in hot ethanol; they give especially high yields of 6-methyl enol ethers. The quaternary salts and N-oxides, in contrast, cannot be used as they undergo rapid conversion into the 6-methylene-4-en-3-one under these experimental conditions.

Extension of this reductive procedure to the free amines proved unsatisfactory. Lengthy reaction times were required and the yields of (very impure) products were correspondingly low. The hydrogenolysis appears to require a non-basic medium, and the addition of ca. 1 equiv. of, for example, benzoic acid to the reaction mixture gave acceptable yields. (It was necessary, of course, to select acids that did not hydrolyse the resulting 6-methyl enol ethers). When crude amines (for example, a mixture of an amine and its borane adduct resulting from borohydride reduction of the iminium intermediate) were employed, the procedure was simplified by adding ca. 1 ml of acetic acid and 2–3 g of sodium acetate per 1 g of steroid when a suitably buffered medium was obtained.

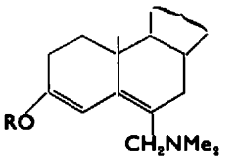
The UV absorption maxima of a series of 6-substituted-3-alkoxy-3,5-dienes are presented below. The bathochromic shift $\Delta\lambda$ of the absortpion maxima increases in magnitude in the order of the negative inductive effect of the substituent.

Variation in λ_{max}^{EtOH} for the system



R	λ_{max}(mμ)	$\Delta\lambda$ (mμ)
H	246	0
OH	248	2
NMe_2	249	3
$NMe_2 \cdot BH_3$	254·5	8·5
$\overset{\oplus}{N}HMe_2$	257	11
$\overset{\oplus}{N}Me_3$	261·5	15·5

TABLE 1

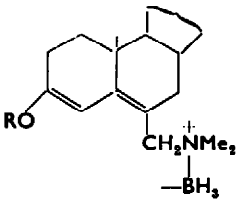


Parent compound	R	m.p.	$[\alpha]_D$ Solvent	λ_m ε	Molecular formula	Analyses Found C	Found H	Found N	Required C	Required H	Required N
Testosterone Acetate	Me	108–110°	−135 Di	250 20,020	$C_{25}H_{39}NO_3$	74·6	9·9	3·2	74·8	9·8	3·5
Testosterone Acetate	Et	92–94	−136 Di	250–251 20,370	$C_{26}H_{41}NO_3$	75·3	10·0	3·0	75·1	9·9	3·4
Androst-4-ene-3,17-dione	Et	94–96	-78 Di	249 21,400	$C_{24}H_{37}NO_2$	76·85	9·8	3·7	77·6	10·0	3·8
Androst-4-ene-3,17-dione	$C_6H_5{\cdot}CH_2$	141–146	−77·5 Di	250·5 21,250	$C_{30}H_{39}NO_2$	80·0	9·2	2·9	80·3	9·1	3·2
Oestra-4-ene-3,17-dione*	Me	115–116	−109 Di	250 20,335	$C_{23}H_{33}NO_2$	77·3	9·8	3·8	76·9	9·7	4·1
17α-Acetoxyprogesterone	Me	139·5–143	−146 Di	250–251 20,275	$C_{27}H_{41}NO_4$	72·7	9·4	3·3	73·1	9·3	3·2
17α-Acetoxyprogesterone	Et	124–127 or 150–151	−145 Di	250·5 20,590	$C_{28}H_{43}NO_4$	73·4	9·4	3·0	73·5	9·5	3·1
16α,17α-Epoxyprogesterone	Me	169–172	−76 Di	250 20,060	$C_{25}H_{37}NO_3$	74·9	9·1	3·7	75·15	9·3	3·5

Cortisone Acetate	Me	162–164	−5 Di	249·5 19,470	$C_{27}H_{38}NO_6$	68·1	8·1	2·9	68·5	8·3	3·0
Cortisone Acetate	Et	amorph.	+22 Di	250 16,540	$C_{28}H_{41}NO_6$						
Cortisone Acetate	n–Pr	amorph.	—	251 16,570	$C_{29}H_{43}NO_6$						
Cortisone 17α,21-acetonide	Me	141–143	−44 Di	249·5 19,855	$C_{28}H_{41}NO_6$	71·1	8·55	2·8	71·3	8·75	2·95
17α-Acetoxy-16-methyleneprogesterone	Me	152–154	−226 Cf	249·5 20,800	$C_{25}H_{41}NO_4$	73·5	8·8	3·2	73·8	9·05	3·05
21-Acetoxy-17α-hydroxypregna-4,9(11)-diene-3,20-dione	Me	144–147	−90 Di	250·5 19,720	$C_{27}H_{38}NO_5$	71·05	8·9	3·0	70·9	8·6	3·1
Testosterone	Me	144	−134·7 Cf	249 20,300	$C_{23}H_{37}NO_2$	76·4	10·15	4·05	76·85	10·35	3·9
Acetonide of 16α,17α-dihydroxyprogesterone	Et	158–161	−62 Di	251 18,630	$C_{29}H_{45}NO_4$	74·1	9·5	2·85	73·85	9·6	2·95
Cortisone bismethylene dioxy derivative	Et	184–187	−140 Di	249–50 19,550	$C_{28}H_{41}NO_6$	69·3	8·45	3·0	68·95	8·5	2·85
Androst-4-ene-3,17-dione	Me	146–148	−79·4 Di	250 19,200	$C_{23}H_{35}NO_2$	77·4	9·8	3·65	77·25	9·85	3·9

* Prepared from 3-methoxyoestra-2,5(10)-dien-17-one[1]

TABLE 2



Parent compound	R	m.p.	$[\alpha]_D$ Solvent	λ_m ε	Molecular formula	Analyses Found C	Found H	Found N	Required C	Required H	Required N
Testosterone acetate	Me	140–144	−135 Cf	254–255 19,310	$C_{25}H_{42}BNO_3$	73·6	9·3	3·2	73·8	9·5	3·4
Testosterone acetate	Et	176–180	−131 Cf	255 21,340	$C_{26}H_{44}BNO_3$	73·0	10·1	3·2	72·7	10·3	3·3
Androst-4-ene-3,17-dione	Et	192–195	−82 Cf	256–257 20,890	$C_{24}H_{40}BNO_2$	74·5	10·2	3·6	74·8	10·5	3·7
19-Nortestosterone acetate	Et	187–187·5	160·4 Cf	255–256 20,400	$C_{25}H_{42}BNO_3$	72·25	10·2	3·75	72·3	10·2	3·35
17α-Methyltestosterone propionate	Me	150–153	−119·7 Cf	255·5 20,800	$C_{27}H_{46}BNO_3$	72·9	10·4	3·35	73·1	10·45	3·15
Acetonide of 16α,17α-dihydroxyprogesterone	Et	197–201	−69 Di	256 20,680	$C_{29}H_{48}BNO_4$	71·7	9·7	3·0	71·75	9·95	2·9
Ethyl 3-oxopregna-4,17(20)-dien-21-oate	Et	141–143·5	−140 Cf	223–225 20,590 254·5–256 22,180	$C_{28}H_{46}BNO_3$	73·55	10·1	2·85	73·85	10·2	3·1
17α-Acetoxyprogesterone	Me	190–191	−132 Cf	256 19,080	$C_{27}H_{44}BNO_4$	71·2	9·5	2·9	70·9	9·65	3·05
17α-Acetoxyprogesterone	Et	173–176	−132 Cf	255–256 22,180	$C_{28}H_{46}BNO_4$	71·1	9·55	2·85	71·3	9·8	2·9

EXPERIMENTAL

Optical rotations were determined on ca. 1% solutions in $CHCl_3$ at room temp unless otherwise stated. UV spectra were determined in ethanol.

The 3-enol ethers of steroidal 4-en-3-ones were prepared by the general procedures described in Part XXXIII[1] of this series.

Preparation of 6-Aminomethyl Enol Ethers and their Borane Adducts

Method A (Suitable for compounds having no readily reducible carbonyl groups)

(i) *Amine borane adducts.* The Vilsmeier reaction was carried out using preferably phosgene, as described in Part XXXIII. To the resulting red solution containing the iminium salt was slowly added, with stirring, a 2–3% solution of $LiBH_4$ in anhydrous tetrahydrofuran until the colour faded to pale yellow. A small excess of reducing agent was added and the mixture was poured into water (the reduction process is virtually instantaneous). Sufficient ether was added to render the organic phase less dense than water, and the ether solution was washed with water. Evaporation of the dried extract left a residue consisting essentially of the amine-borane adduct which could be purified by conventional techniques. The residues contained small quantities of the free amine.

(ii) *Free amines.* A solution of $LiBH_4$ (10 g) in dry tetrahydrofuran (300 ml) was prepared and kept for 24 hr. The clear supernatent liquor was standardized by adding aliquots to stirred dil. HCl aq and measuring the volume of evolved H_2 (1 ml H_2 at 25° and 760 mm ≡ 0·000225 g $LiBH_4$). The Vilsmeier reaction was carried out as described above and a measured quantity of the $LiBH_4$ solution was slowly added to the stirred mixture (optimum yields were obtained using 0·6 mole $LiBH_4$ per 1 mole phosgene). The (still red) mixture was poured into Na_2CO_3 aq and extracted with ether. The ether extract was washed with water until no further colour was removed, and then with several portions of 5% succinic acid aq. (A small quantity of amine borane can be recovered from this ether extract.) The combined succinic acid washes were basified with ammonia or Na_2CO_3 aq and the precipitated amine was isolated with ether and purified in the usual way.

Other reducing agents which may be used

(i) $NaBH_4$ in pyridine [the anhydrous solution may be prepared by stirring pyridine (200 ml) with NaH (2–5 g) and $NaBH_4$ (10 g) for 4 hr and allowing the suspended matter to settle overnight. The clear supernatant solution may be standardized as before].

(ii) Pyridine-borane adduct, as a 5% ethereal solution and using ca. 2 moles per mole of steroid.

(iii) Diborane gas—bubbled through the Vilsmeier reaction mixture until the colour had faded. No amine borane is produced under these experimental conditions.

In cases where the amine could not be obtained crystalline, a convenient procedure involved its direct conversion into a quaternary salt. Thus the crude amine, in dry benzene, was treated with, e.g. methyl bromide or iodide or with dimethyl sulphate overnight at room temp. The quaternary salt usually precipitated in crystalline form and was generally used for further transformations without purification.

Method B (Suitable for compounds having readily reducible carbonyl groups, e.g. 17-one, 20-one)

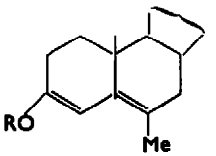
Procedure A(ii) was followed, with the addition of 1 molar proportion of solid phenazone immediately prior to the addition of the reducing reagent. The latter is preferably added very slowly with efficient stirring.

It has not been possible to prepare the amine-borane adducts of such steroids efficiently since the use of excess reducing agent is precluded by the presence of the carbonyl groups.

17*β*-*Acetoxy*-3-*ethoxy*-6-(N-*methyl*-N-*phenylaminomethyl*)*androsta*-3,5-diene

To a stirred and cooled (ice-bath) solution of N-methyl-formanilide (6 ml) in ethylene dichloride (25 ml) was added, dropwise, a solution of phosgene (2·2 g) in ethylene dichloride (20 ml) and the mixture was stirred at 0° for 10 min. 17*β*-Acetoxy-3-ethoxyandrosta-3,5-diene (7 g) in ethylene dichloride (30 ml) was added and the mixture was stirred and allowed to warm to room temp for ½ hr. A 5% solution of $NaBH_4$ in pyridine was then added dropwise until the red colour changed to pale yellow and the mixture was diluted with a large volume of ether. The ethereal solution was washed with several portions of dil H_2SO_4 (no amine was obtained on subsequent basification of the

TABLE 3



Parent compound	R	m.p.	$[\alpha]_D$ Solvent	λ_m ε	Molecular formula	Analyses Found C	Found H	Required C	Required H
Testosterone acetate	Me	137–139·5	−181·5 Di	246·5 19,360	$C_{21}H_{34}O_3$	76·8	9·3	77·05	9·6
Testosterone acetate	Et	140–141	−164 Cf	247·5 18,770	$C_{24}H_{36}O_3$	77·6	9·6	77·4	9·7
Androst-4-ene-3,17-dione	Me	152–154	−114 Di	246·5 19,650	$C_{21}H_{30}O_2$	80·4	9·3	80·2	9·6
Androst-4-ene-3,17-dione	Et	135–138	−113 Di	248 20,830	$C_{22}H_{32}O_2$	80·5	9·4	80·4	9·8
Oestr-4-ene-3,17-dione	Me	153–155	−145 Di	247 19,470	$C_{20}H_{28}O_2$	79·6	9·6	79·95	9·4
17β-Acetoxyoestr-4-en-3-one	Me	104–107	−155 Di	246 16,740	$C_{22}H_{32}O_3$	76·55	9·25	76·7	9·35
2α-Methyl testosterone acetate*	Et	156–157	−129 Di	249 20,100	$C_{25}H_{38}O_3$	77·25	9·6	77·65	9·9
17α-Acetoxy progesterone	Me	217–222	−167 Cf	247 19,300	$C_{23}H_{32}O_4$	74·95	9·05	74·8	8·95

17α-Acetoxy progesterone	Et	167–169	−160 Di	247·5 19,940	$C_{26}H_{36}O_4$	74·9	9·0	75·3	9·2
16α,17α-Epoxy progesterone	Me	167–170	−114 Di	247 19,720	$C_{22}H_{32}O_3$	77·0	8·8	77·5	9·05
17α-Acetoxy-16-methyleneprogesterone	Me	202–205	−255 Cf	246 19,890	$C_{26}H_{36}O_4$	75·4	8·65	75·7	8·8
17α-Acetoxy-16α-methylprogesterone*	Me	191–193	−130 Cf	246–247 18,200	$C_{26}H_{38}O_4$	75·0	9·05	75·3	9·2
Acetonide of 16α,17α-dihydroxyprogesterone*	Me	191–194	−108 Di	247 19,490	$C_{26}H_{38}O_4$	75·25	9·2	75·3	9·2
Acetonide of 16α,17α-dihydroxyprogesterone*	Et	194–199	−105 Di	247–248 19,600	$C_{27}H_{40}O_4$	75·3	9·35	75·65	9·4
Ethyl 3-oxopregna-4,17(20)-dien-21-oate	Et	117·5–122	−188 Di	230–233 22,660	$C_{26}H_{38}O_3$	78·2	9·5	78·3	9·6
17α,21-dihydroxy progesterone bis methylenedioxy derivative	Et	178–182	−137·5 Di	—	$C_{26}H_{36}O_6$	70·55	8·6	70·25	8·15
Cortisone acetate	Me	178–180	−12·5 Di	246 17,650	$C_{25}H_{34}O_6$	69·65	7·65	69·7	8·0
Cortisone acetate	Et	108–110 or 120–130	−11 Di	246·5 18,250	$C_{26}H_{36}O_6$	68·8	8·3	70·2	8·2
Cortisone acetate	n-Pr	172–175	−14 Di	247·5 20,180	$C_{27}H_{38}O_6$	70·3	8·6	70·7	8·35
Cortisone 17α,21-Acetonide	Me	157–163	−55 Di	244·5 18,170	$C_{26}H_{36}O_5$	72·4	8·6	72·9	8·5

* Prepared by reduction of crude amine–amine-borane product with Pd-C–cyclohexene in buffered medium.

acid washes), then with Na_2CO_3 aq and water, dried (Na_2SO_4) and evaporated to dryness, finally under high vacuum. The solid residue was crystallized from methanol containing a trace of pyridine to give the *amine* as needles, m.p. 152–154°, $[\alpha]_D$ −129·2°, λ_{max} 255 mμ (ε 31,530). (Found: C, 78·05; H, 8·9; N, 2·85. $C_{31}H_{43}NO_3$ requires: 77·95; H, 9·05; N, 2·95%).

17β-Acetoxy-3-methoxy-6-piperidinomethylandrosta-3,5-diene

A mixture of 17β-acetoxy-3-methoxyandrosta-3,5-diene (5 g), N-formylpiperidine (10 ml) and methylene chloride (30 ml) was stirred at 0° and treated dropwise during ½ hr with a solution of phosgene (5 g) in methylene chloride (50 ml). After a further 45 min at 0°, the red solution was treated dropwise with a 2% solution of $LiBH_4$ in tetrahydrofuran until the colour was discharged. The mixture was poured into aqueous sodium carbonate and isolated with ether. Evaporation of the water-washed and dried extract left a gum which crystallized from methanol to give the *amine* as prisms, m.p. 125–127°, $[\alpha]_D$ −138°, λ_{max} 250 mμ (ε 19,520). (Found: C, 75·9; H, 9·8; N, 3·2. $C_{28}H_{43}NO_3$ requires: C, 76·15; H, 9·8; N, 3·2%). No amine-borane was isolated.

Preparation of 17β-acetoxy-6-dimethylaminomethyl-3-methoxyandrosta-3,5-diene from its borane adduct

A solution of the amine-borane (1 g) in piperidine (10 ml) was refluxed for 4 hr. The piperidine was evaporated under red. press. and the semi-solid residue was triturated with ether. Evaporation of the ether left a gum which crystallized from methanol aq to give the amine, m.p. 92–94°, not depressed on admixture with an authentic sample, m.p. 92–94°.

17α-Acetoxy-6-dimethylaminomethyl-3-methoxypregna-3,5-dien-20-one citrate

A solution of citric acid monohydrate (0·1 g) in dry ether (20 ml) was added dropwise to a stirred solution of the amine (0·25 g) in dry ether (20 ml) and the precipitated *citrate* was collected. It was hygroscopic, and after drying at 60° *in vacuo* over P_2O_5 had m.p. 128–132°, $[\alpha]_D$ −99° (dioxan), λ_{max} 255·5 mμ; satisfactory analytical data could not be obtained.

21-Acetoxy-6-dimethylaminomethyl-3-ethoxy-17α-hydroxypregna-3,5-diene-11,20-dione hydrochloride

The Vilsmeier process (in ethylene dichloride), followed by reduction with $LiBH_4$ in tetrahydrofuran, was carried out on cortisone acetate 3-enol ethyl ether as described in the general procedure. During the reduction, the amine hydrochloride separated as a gel and was isolated by dilution of the mixture with ether and filtration. Crystallization from ethanol–ether gave the *hydrochloride* as a solvated, hygroscopic solid which, after drying *in vacuo* at 50°, had m.p. 164–170° dec, $[\alpha]_D$ −5°, λ_{max} 258·5 mμ (ε 19,100); satisfactory analytical data could not be obtained.

17β-Acetoxy-6-dimethylaminomethyl-3-ethoxyandrosta-3,5-diene methobromide

(a) The amine (5 g) in dry ether (50 ml) was treated with methyl bromide (5 ml) in a stoppered flask at room temp for 24 hr. Precipitation was completed with hexane, and the solid was collected and dried at 45°. The *hydrated methobromide* was an amorphous, cream solid m.p. 160–190° dec. It had ν_{max}^{Nujol} 3395 (OH), 1733 (acetate), 1631 and 1602 cm^{-1} (enol ether).

(b) A solution of the amine (0·5 g) in toluene (50 ml) was freed from water by distilling ca. 25 ml and anhydrous methyl bromide (1 ml, freshly distilled from P_2O_5) was added. The flask was stoppered and kept at room temp for 24 hr. The anhydrous methobromide separated as plates lacking hydroxyl absorption in the IR, which rapidly absorbed water and lost their crystalline form on exposure to air.

17α-Acetoxy-6-dimethylaminomethyl-3-ethoxypregna-3,5-dien-20-one methiodide

The amine (2 g) in benzene (20 ml) was treated with methyl iodide (2 ml) at room temp for 6 hr. Precipitation was completed by the addition of hexane and the solid was crystallized from acetone–hexane to give the *solvated methiodide* as needles, m.p. 170–178° dec, ν_{max}^{Nujol} 3470 (OH), 1730 (acetate), 1711 (20-one) and 1621 cm^{-1} (enol ether). (Found: C, 56·4; H, 7·6; N, 2·1; I, 19·0. $C_{30}H_{46}NO_4I \cdot H_2O$ requires; C, 56·5; H, 7·8; N, 2·3; I, 20·6%).

21-Acetoxy-6-dimethylaminomethyl-3-ethoxy-17α-hydroxypregna-3,5-diene-11,20-dione methiodide

The total crude gummy amine produced from cortisone acetate enol ethyl ether (5 g) in benzene (50 ml) was treated with methyl iodide (10 ml) for 24 hr at room temp in a stoppered flask. Precipitation was completed by the addition of ether and the solid was purified by *rapid* crystallization from

methanol containing a trace of pyridine to give the *solvated methiodide* as needles, m.p. 188–196° dec, ν_{max}^{Nujol} 3350 (OH), 1748 (OAc), 1728 (20-one), 1695 (11-one), 1631, 1602 cm^{-1} (enol ether). (Found: C, 53·3; H, 7·15; N, 2·0; I, 19·05. $C_{29}H_{44}NO_6I \cdot H_2O$ requires: C, 53·7; H, 6·85; N, 2·2; I, 19·6%).

17α-Acetoxy-6-dimethylaminomethyl-3-methoxypregna-3,5-dien-20-one N-oxide

A solution of the amine (5 g) in methanol (100 ml) was treated with 30% H_2O_2 (20 ml) for 4 days at room temp. Water (500 ml) was added and the mixture was extracted with methylene chloride (6 × 25 ml). The extract was washed once with a small volume of water, dried and evaporated at room temp under red. press. The residue crystallized from acetone–hexane to give the N-*oxide hydrate* as prisms, m.p. 117–120° dec, $[\alpha]_D$ −121°, λ_{max} 257–258 mμ (ε 18,900), ν_{max}^{Nujol} 3681, 3362 (H_2O, OH), 1732 (OAc), 1694 (20-one), 1640 and 1612 cm^{-1} (enol ether); satisfactory analytical data could not be obtained due to progressive loss of solvent of crystallization.

17β-Acetoxy-6α-dimethylaminomethylandrost-4-en-3-one

17β-Acetoxy-6-dimethylaminomethyl-3-ethoxyandrosta-3,5-diene (10 g) was suspended in acetic acid (20 ml) and treated with conc. HCl (3 ml, 1·3 equiv.) when the amine rapidly dissolved. The mixture was poured into water and the resulting, slightly turbid, solution was extracted once with ether (ether rejected). The clear aqueous solution was made alkaline with 0·880 ammonia, the precipitated solid was collected and crystallized from methanol aq to give the *amine* as needles, m.p. 178–180°, $[\alpha]_D$ +62·5°, λ_{max} 239 mμ (ε 14,140), ν_{max} (CCl_4) 2769, 2715 (t-amine), 1739 (OAc), 1680 and 1607 cm^{-1} (Δ⁴-3-one). (Found: C, 74·5; H, 9·7; N, 3·2. $C_{24}H_{37}NO_3$ requires: C, 74·4; H, 9·6; N, 3·6%).

17α-Acetoxy-6α-dimethylaminomethylpregn-4-ene-3,20-dione

17α-Acetoxy-6-dimethylaminomethylpregna-3,5-dien-20-one (0·5 g) was dissolved in conc. HCl (5 ml) and water (10 ml) and kept at room temp for 15 min. The solid obtained on pouring the solution into dil Na_2CO_3 aq was crystallized from acetone–hexane to give the *amine* as prisms, m.p. 190–192°, $[\alpha]_D$ +37°, λ_{max} 239·5 mμ (ε 14,220), ν_{max}^{CCl4} 2804, 2755 (t-amine), 1738 (OAc), 1719 (20-one), 1678 and 1608 cm^{-1} (Δ⁴-3-one). (Found: C, 73·05; H, 9·3; N, 3·0. $C_{26}H_{39}NO_4$ requires: C, 72·7; H, 9·15; N, 3·3%).

17β-Acetoxy-6α-piperidinomethylandrost-4-en-3-one

17β-Acetoxy-3-methoxy-6-piperidinomethylandrosta-3,5-diene (0·5 g) was treated with HCl–HOAc as described above. The product crystallized from methanol aq to give the *amine* as flakes, m.p. 152–154°, $[\alpha]_D$ +70°, λ_{max} 239·5 (ε 14,500). (Found: C, 75·7; H, 9·45; N, 3·1. $C_{27}H_{41}NO_3$ requires: C, 75·85; H, 9·65; N, 3·3%).

Elimination of nitrogen from 6-disubstituted aminomethyl enol ethers and their derivatives

(1)17α,20:20,21-Bismethylenedioxy-6-dimethylaminomethyl-3-ethoxypregna-3,5-dien-11-one methiodide (0·6 g) [prepared from the free base (0·5 g) and methyl iodide in benzene] was suspended in water containing ca. 10% of ethanol and heated to 100° for 1 hr. The solid slowly dissolved and a new substance separated. The was collected and crystallized from methanol to give 17α,20:20,21-bismethylenedioxy-6-methylenepregn-4-ene-3,11-dione, m.p. 197–200° alone or admixed with an authentic specimen.[1]

(2) 17β-Acetoxy-6-(N-methyl-N-phenylaminomethyl)-3-ethoxy-androsta-3,5-diene was (a)treated in methanol with slightly less than 1 molar equivalent of 2 N HCl and (b) dissolved in excess acetic acid. In each case, after 15 min at room temp, the sole product obtained was 17β-acetoxy-6-methyleneandrost-4-en-3-one, m.p. 137–140° alone or admixed with an authentic specimen.[1]

(3) A mixture of 17β-acetoxy-6-dimethylaminomethyl-3-ethoxy-androsta-3,5-diene (0·5 g), methyl iodide (5 ml), methanol (10 ml) and water (5 ml) was warmed to ca. 40° for 30 min, and then heated so that methanol was lost. The solid which separated was identified as 17β-acetoxy-6-methyleneandrost-4-en-3-one, m.p. 138–140°.

(4) The foregoing procedure was repeated with 30% H_2O_2 in place of methyl iodide; 17β-acetoxy-6-methyleneandrost-4-en-3-one was produced.

General Procedures for the Preparation of 6-methyl Enol Ethers

(1) *Using Raney nickel*

(a) Raney Ni sludge (ca. 6 ml per 1 g of steroid) was washed by decantation with methanol, the steroid (free amine or its borane adduct), suspended or dissolved in methanol, was added and the mixture was stirred under reflux for 2–5 hr. The free amines generally required somewhat longer reaction times than the amine borane adducts. The Raney Ni was removed by filtration and washed thoroughly with hot methanol. Evaporation of the solvent usually yielded the 6-methyl enol ether in crystalline form; when a gummy product resulted it was isolated with ether.

(b) When a quaternary salt was used, the addition of sodium acetate (1 g per 1 g of steroid) minimized the (slow) decomposition of the salt to the 6-methylen-4-en-3-one. The Raney Ni should preferably be a fairly active sample to avoid undue prolongation of the reaction time.

(c) When an amine or amine derivative containing a group sensitive to alkali (e.g. 21-acetoxy-20-ketone) was used, some form of pH control gave improved yields of the corresponding 6-methyl enol ether. Thus, for example, the Raney Ni could be washed with methanol containing methyl acetate overnight to neutralize much of the absorbed alkali. The amine (or amine derivative) and methanol were then added and the mixture was refluxed, the pH being tested periodically with Narrow Range indicator paper (pH 7·0–8·5) with addition of acetic acid to maintain the pH in the region of 7–7·2.

(2) *Catalytic hydrogenation*

(a) Catalytic reduction of free amines and their borane adducts was not satisfactory.

(b) The amine quaternary salt or N-oxide (10 parts) in methanol (ca. 100 parts) may be hydrogenated over pre-reduced 5% Pd-C (1 part); addition of sodium acetate (10 parts) minimizes decomposition to a 6-methylen-4-en-3-one. The catalyst is removed and the solution concentrated under red. press. and diluted with water. The 6-methyl enol ether may be isolated by filtration or extraction

(c) In cases where the quaternary methiodide or methobromide was sparingly soluble in methanol or ethanol, it was first converted into the methacetate. The methobromide or methiodide (10 parts) was added to a stirred solution of sodium acetate (10 parts) and silver acetate (5 parts) and stirred for 20 min. The precipitated silver halide was filtered off and the filtrate was immediately hydrogenated as in (b) above.

(3) *Transfer hydrogenation*

(a) Hydrogenation of the free amines, their quaternary salts and N-oxides was not satisfactory.

(b) A mixture of the amine borane (1 part), 5% Pd-C (0·25 part), cyclohexene (2 parts) and ethanol (15 parts) was stirred and heated under reflux for 4 hr, when dimethylamine was rapidly evolved. The catalyst was removed and the solution concentrated under red. press. After dilution with water the product was collected by filtration or was extracted with ether.

(c) A mixture of the amine (1 part), benzoic acid (0·8 to 1·0 molar proportions, based on amine), 5% Pd-C (0·25 part), cyclohexene (2 parts) and ethanol (15 parts) was stirred and heated under reflux for 2 hr and the product was isolated as in (b) above.

(d) A mixture of the amine (or the crude total mixture of amine and its borane adduct resulting from a Vilsmeier reduction preparation) (1 part), acetic acid (1 part), sodium acetate (3 parts), 5% Pd-C (0·25 part), cyclohexene (2 parts) and ethanol (15 parts) was stirred and heated under reflux for 2–4 hr, and the product was isolated as in (b) above.