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MODIFIED STEROID HORMONES—XXXVIII[1]

SOME TRANSFORMATIONS OF STEROIDAL 3-ALKOXY-6-FORMYL-3,5-DIENES AND RELATED COMPOUNDS

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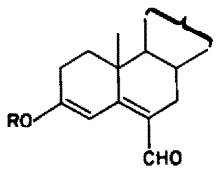
Abstract—An improved route to 6-methylated steroidal 4-en-and 4,6-dien-3-ones is described.

IN PART XXXIII[2] the reaction of steroidal 3-alkoxy-3,5-dienes with the Vilsmeier reagent to yield the corresponding 3-alkoxy-6-formyl-3,5-dienes (I) was described. These derivatives were converted, *via* the 3-alkoxy-6-hydroxymethyl-3,5-dienes (II), into 6-methylen-4-en-3-ones (III). We now describe the conversion of these intermediates into 6-methyl-4-en- (IV and VI) and 6-methyl-4,6-dien-3-ones (V).



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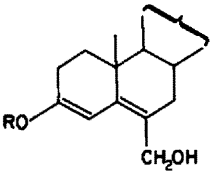

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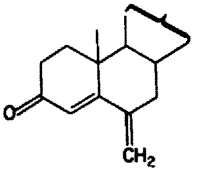

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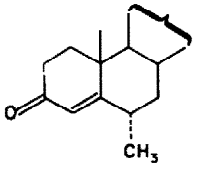

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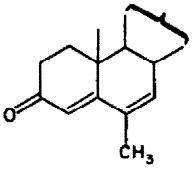

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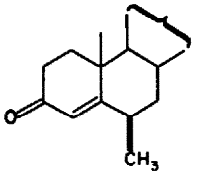

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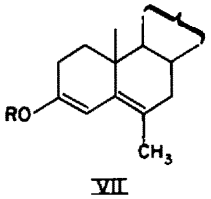


VII

[1] Part XXXVII, C. Burgess, D. Burn, P. Feather, M. Howarth and V. Petrow, *Tetrahedron* **21**, 1197 (1965).

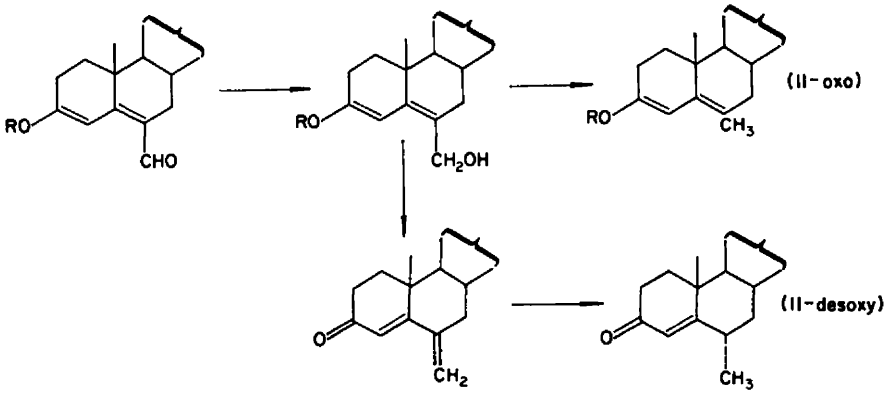
[2] D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow and D. M. Williamson, *Tetrahedron* **20**, 597 (1964).

Initial experiments on the catalytic reduction of 6-methylen-4-en-ones were unpromising. In spite of variations in catalyst, solvent and additives (e.g. pyridine), the reduction was not selective for the 6-methylene group and the products were mixtures containing considerable amounts of saturated 3-ketones. More encouraging results, however, were obtained by transfer hydrogenation.[3] When a solution of a 6-methylen-4-en-3-one (III) was refluxed in ethanol containing cyclohexene as hydrogen donor and in the presence of a 5% Pd–C catalyst, an excellent yield of the corresponding 6α-methyl-4-en-3-one (IV) was obtained. The reaction was conveniently followed by examination of the UV spectra of samples, and was usually complete within 3 hr. Further reduction to saturated ketones was very slow, reaching only ca 50% after 12 hr. The major product appeared to be the 6α-methyl isomer; presumably some of the 6β-epimer (VI) was also formed, as a purer product could be obtained by brief treatment of the reaction mixture with acid or alkali prior to crystallization.

Application of the transfer hydrogenation technique to (11-desoxy)-3-alkoxy-6-formyl-3,5-dienes (I) again resulted in the formation of 6α-methyl-4-en-3-ones. Surprisingly, a different pattern of behaviour was observed with 3-alkoxy-6-formyl-3,5-dienes containing an 11-oxo function. Under the above experimental conditions a 3-alkoxy-6-methyl-11-oxo-3,5-diene (VII) was obtained in high yield, in place of the expected 6α-methyl-4-ene-3,11-dione. The latter compounds were, however, obtained when e.g. acetic acid was added to the reaction mixture (Experimental). It seemed likely from these observations that it might be possible to convert the 3-alkoxy-6-formyl-3,5-dienes of the 11-desoxy series into their 6-methyl enol ethers by suitable control of pH. However, all attempts to adjust the acidity, for example by the addition of small quantities of sodium hydroxide, sodium acetate or pyridine, were unsuccessful, the starting material being recovered in every case. It was subsequently found that reduction of the 6-formyl group occurs only under faintly acidic conditions, which presumably arise through the use of this particular catalyst (5% Pd–C). Thus palladium on "basic" supports such as barium sulphate and calcium carbonate proved ineffective unless acid was added to the reaction medium.

The foregoing results may be rationalized in the following way (Chart 1). It seems certain that the first step is the reduction of the formyl group to hydroxymethyl

Chart 1



[3] E. A. Braude, R. P. Linstead and P. W. D. Mitchell, *J. Chem. Soc.* 3578 (1954).

and requires an "acidic" medium. In the absence of an 11-oxo group, the unstable 6-hydroxymethyl enol ether readily undergoes hydrolysis and dehydration as rapidly as it is formed to give a 6-methylen-4-en-3-one[2] which is subsequently reduced to a 6α-methyl-4-en-3-one as described before.

In the 11-oxo series, the 6-hydroxymethyl enol ether is presumed to be more stable and survives for a sufficient time to undergo hydrogenolysis—being structurally analogous to a benzyl alcohol—to a 6-methyl enol ether. Some support for this scheme was provided by a study of the transfer hydrogenation of a (pre-formed) 3-alkoxy-6-hydroxymethyl-3,5-diene. Under the standard (i.e. acidic) conditions, a 6α-methyl-4-en-3-one was rapidly formed in accordance with expectations. If, however, a small quantity of sodium acetate was added to the reaction mixture, the hydrolysis–dehydration of the 6-hydroxymethyl enol ether system was almost completely suppressed, and a slow reduction to the 6-methyl enol ether was observed.*

During the course of early catalytic hydrogenation studies on the 3-alkoxy-6-formyl-3,5-diene system, the unique behaviour of a 5% Pt–C catalyst, leading to the corresponding 3-alkoxy-6-hydroxymethyl-3,5-diene, was observed. In marked contrast to the non-selective reductions effected by e.g. Pd–C and PtO_2, no attack upon the diene system was detected. The technique is of particular value for the preparation of the 3-alkoxy-6-hydroxymethyl-3,5-diene derivatives of steroids containing other readily reducible (by, e.g. borohydrides) carbonyl groups.

We next attempted the isomerization of the 6-methylen-4-en-3-one system to the biologically important 6-methyl-4,6-dien-3-one. Rather unexpectedly, the 6-methylene group proved to be completely resistant to a variety of acid and base treatments. A clue to a possible method of isomerization was provided by a study of the reduction of either the 6-methylen-4-en-3-one or the 3-alkoxy-6-formyl-3,5-diene systems. Examination of the UV spectra of samples taken in the early stages of these reductions revealed the transient formation of some 6-methyl-4,6-dien-3-one as characterized by the spectral changes λ_{max} 260 mμ → 285 mμ + 240 mμ → 240 mμ and λ_{max} 320 mμ → 285 mμ + 240 mμ → 240 mμ respectively. Clearly part, at least, of the 6-methylen-4-en-3-one was being reduced by a process involving prior isomerization to the corresponding 6-methyl-4,6-dien-3-one. Initial attempts to effect this isomerization by heating a 6-methylen-4-en-3-one in ethanol with 5% Pd–C, with or without added base or acid, but in the absence of a hydrogen donor, were unsuccessful. However, if the catalyst was pre-treated with hydrogen, either by shaking in a hydrogen atmosphere or by refluxing with a small quantity of cyclohexene, isomerization occurred to give the desired 6-methyl-4,6-dien-3-one in reasonable yield. Unfortunately, it proved difficult to standardize this procedure. A preferred technique consisted in the slow addition of a ca 1% solution of cyclohexene in ethanol to a refluxing solution of the steroid in ethanol containing 5% Pd–C. The small amount of reduction (to a 6-methyl-4-en-3-one) occurring under these conditions was virtually eliminated by the addition of an excess of sodium acetate which appears to suppress reduction with no effect on isomerization. In this way, yields of 6-methyl-4,6-dien-3-ones approaching 90% may be obtained in favourable cases. It was subsequently

* Rather surprisingly, considering the presence of an excess of cyclohexene, the major product observed in early experiments was the 6-formyl enol ether. The 6-hydroxymethyl group clearly undergoes extremely facile catalytic oxidation which was suppressed, in later experiments, by working under oxygen-free nitrogen.

found that the ethanol used as solvent could act as the hydrogen donor, although it was clearly inefficient in comparison with cyclohexene and reaction times of the order of 16–24 hr were required for complete conversion.

Selective reduction of 6-methyl-4,6-dien-3-ones occurred readily under transfer-hydrogenation conditions to give mixtures of 6-methyl-4-en-3-ones rich in the 6β-methyl isomer. Thus, from the reduction of 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione, it was possible to isolate 17α-acetoxy-6β-methylpregn-4-ene-3,20-dione in ca 50% yield. The reduction is equally selective in the absence of a 6-methyl group, and provides an effective method for the conversion of a 4,6-dien-3-one into the corresponding 4-en-3-one.

EXPERIMENTAL

Optical rotations were determined on ca 1% solutions in $CHCl_3$ at room temp by Mr. M. T. Davies, B.Sc., F.R.I.C., of our Physical Chemistry Department.

A *Reduction of 6-methylen-4-en-3-ones*

17α-Acetoxy-6α-methylpregn-4-ene-3,20-dione. A solution of 17α-acetoxy-6-methylenepregn-4-ene-3,20-dione[3] (1 g) and cyclohexene (3 ml) in EtOH (50 ml) was heated under reflux and stirred with 5% Pd–C (0·2 g) for 3 hr. The catalyst was removed by filtration. Conc. HCl (0·1 ml) was added to the filtrate, which was then concentrated under red. press. and diluted with water. Crystallization of the product from aqueous MeOH gave 17α-acetoxy-6α-methylpregn-4-ene-3,20-dione, m.p. 204–207°, $[\alpha]_D$ +53° (lit.[4] m.p. 205–208°, $[\alpha]_D$ +51°).

21-Acetoxy-6α-methylpregn-4-ene-3,20-dione. A solution of 21-acetoxy-6-methylenepregn-4-ene-3,20-dione[3] (3·75 g) and cyclohexene (15 ml) in EtOH (100 ml) was refluxed and stirred with 5% Pd-C (1 g) for 2½ hr. The product, isolated as above, was crystallized from aqueous MeOH to give 21-acetoxy-6α-methylpregn-4-ene-3,20-dione as needles, m.p. 128–130°, $[\alpha]_D$ +163·5°, λ_{max} 240 mμ (ε 15,850) [lit.[5] m.p. 126–128°, $[\alpha]_D$ +165°, λ_{max} 241 mμ (ε 15,150)].

6α-Methylandrost-4-ene-3,17-dione. A solution of 6-methyleneandrost-4-ene-3,17-dione (1 g) and cyclohexene (2 ml) in EtOH (50 ml) was refluxed and stirred with 5% Pd-C (0·2 g) for 2 hr. The product, isolated as above, crystallized from acetone–hexane to give 6α-methylandrost-4-ene-3,17-dione as needles, m.p. 166–168°, $[\alpha]_D$ +170°, (lit.[6] m.p. 167–168°, $[\alpha]_D$ +172°).

B *Reduction of 3-alkoxy-6-formyl-3,5-dienes*

17α-Acetoxy-6α-methylpregn-4-ene-3,20-dione. A solution of 17α-acetoxy-6-formyl-3-methoxypregna-3,5-dien-20-one[2] (1 g) and cyclohexene (2 ml) in EtOH (20 ml) was heated under reflux and stirred with 5% Pd–C (0·3 g); ca. 2 ml samples were withdrawn at 15 min intervals, filtered, evaporated to dryness and UV spectra determined on EtOH solutions of the residues. Figure 1 shows the approx. composition of the reaction mixture as a function of time, as determined from the UV spectra: A similar reaction, worked up after 2½ hr, followed by crystallization of the product from aqueous MeOH containing ca. 1% HCl, gave 17α-acetoxy-6α-methylpregn-4-ene-3,20-dione (0·7 g), m.p. 202–206°. Similar sampling techniques indicated that

(a) little or no reaction occurred in benzene, tetrahydrofuran, acetone or ethyl acetate.

(b) Pd–$CaCO_3$, Pd–$BaSO_4$, Ru–C and Pt–C were not effective catalysts. Very slow conversion occurred with Rh–C (50–60% in 6 hr) and with Pd–$BaSO_4$ in EtOH–acetate acid (1:1); inferior quality products were recovered from both these experiments.

(c) the addition of NaI (1%), pyridine (10%), NaOH aq (1%) to reactions carried out with Pd–C EtOH completely inhibited reduction.

21-Acetoxy-6α-methylpregn-4-ene-3,20-dione. A solution of 21-acetoxy-6-formyl-3-methoxypregna-3,5-dien-20-one[2] (5 g) and cyclohexene (15 ml) in EtOH (150 ml) was heated under reflux and stirred with 5% Pd–C (1 g). Sampling technique indicated that reaction was complete after 5 hr (considerable variation in catalyst activity from batch to batch has frequently been observed in the

[4] S. P. Barton, B. Ellis and V. Petrow, *J. Chem. Soc.* 478 (1959).
[5] C. Gandolfi and D. Chiaramonti, *Ann. di. Chim.* **51**, 912 (1961).
[6] M. Ackroyd, J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.* 4099 (1957).

course of this study) and the product, isolated as above and briefly warmed with acetic acid (25 ml) and conc. HCl acid (0·1 ml), was crystallized from aqueous MeOH to give 21-acetoxy-6α-methylpregn-4-ene-3,20-dione (3·5 g) as flakes, m.p. 128–130°.

6α-Methylcortisone acetate and its 3-methyl enol ether. A solution of 21-acetoxy-6-formyl-17α-hydroxy-3-methoxypregna-3,5-diene-11,20-dione (2·5 g) and cyclohexene (5 ml) in EtOH (25 ml) and varying amounts of acetic acid (Table) was heated under reflux and stirred with 5% Pd–C (0·75 g) for

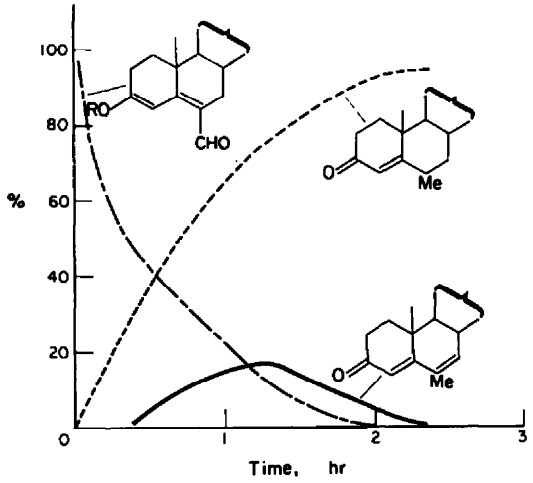


FIG. 1

1½ hr. The catalyst was filtered off, the filtrate was diluted with water and extracted with methylene chloride. Evaporation of the dried (Na_2SO_4) extract afforded a residue which was crystallized twice from ether to yield essentially pure 6α-methylcortisone acetate, m.p. 220–225° (lit.[7] m.p. 225–227°). Fractionation of material contained in the mother-liquors yielded 6-methylcortisone acetate 3-enol methyl ether, m.p. 175–178°, $[\alpha]_D$ −10°, λ_{max} 245·5 mμ (ε, 17,100) [lit.[8] m.p. 178–180°, $[\alpha]_D$ −12·5°, λ_{max} 246 mμ (ε, 17,650)].

HOAc in Ethanol	Yield of 6α-Me-Δ^4-3-one
0%	28%
2·5%	53%
20%	64%
50%	80%

6α-Methyltestosterone acetate. A solution of 17β-acetoxy-6-hydroxymethyl-3-methoxyandrosta-3,5-diene[8] (0·5 g) and cyclohexene (2 ml) in EtOH (10 ml) was heated under reflux and stirred with 5% Pd–C (0·15 g). After 2½ hr a sample had λ_{max} 240 mμ, and isolation of the product as above gave 6α-methyltestosterone acetate (needles from acetone-hexane), m.p. 138–140°, $[\alpha]_D$ +78°, (lit.[8] m.p. 140°, $[\alpha]_D$ +84°).

Repetition of the foregoing experiment employing 17α-acetoxy-6-hydroxymethyl-3-methoxypregna-3,5-dien-20-one (0·5 g) under oxygen-free N_2, and with the addition of sodium acetate (0·05 g) gave a mixture of products from which 17α-acetoxy-3-methoxy-6-methylpregna-3,5-dien-20-one[9], (0·1 g), m.p. 217–221° was isolated by chromatography on alumina.

[7] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1951).

[8] D. Burn, G. Cooley, M. T. Davies, A. K. Hiscock, D. N. Kirk, V. Petrow and D. M. Williamson, *Tetrahedron* **21**, 569 (1965).

[9] D. Burn, B. Ellis, P. Feather, D. N. Kirk and V. Petrow, *Chem. & Ind.* 1907 (1962).

C *Isomerization of 6-methylen-4-en-3-ones to 6-methyl-4,6-dien-3-ones*

17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione. (i) 5% Pd–C (0·5 g) was stirred and heated under reflux in EtOH (40 ml) and cyclohexene (1 ml) for 1 hr. A solution of 17α-acetoxy-6-methylenepregn-4-ene-3,20-dione (2 g) in EtOH (10 ml) was added and heating under reflux and stirring was continued for a further 4 hr, by which time the UV spectrum of a sample showed λ_{max} 288 mμ only. The catalyst was removed, and the product obtained on dilution with water was crystallized from dichloromethane–MeOH to give 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione (1 g) as needles, m.p. 213–215°, λ_{max}^{EtOH} 288 mμ (ε, 24,500), (lit.[10] m.p. 214–216°, λ_{max} 287·5 mμ (ε, 25,120).

(ii) 5% Pd–C (0·5 g) in EtOH (40 ml) was shaken in H_2 for 1 hr. The H_2 supply was disconnected, the 6-methylene compound (2 g) in EtOH (10 ml) was added and the mixture was stirred under reflux for 2 hr. The UV spectrum of a sample indicated ca. 50% conversion to the 4,6-dien-3-one, which was not increased on prolonged heating. 17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (0·7 g), m.p. 210–214°, was isolated as above.

(iii) A mixture of 17α-acetoxy-6-methylenepregn-4-ene-3,20-dione (2 g), sodium acetate (1 g), EtOH (40 ml) and 5% Pd–C (0·1 g) was stirred under reflux while a 1% solution of cyclohexene in EtOH was added slowly by means of a micro-pump (ca. 5 ml per hr). The UV spectrum of samples indicated ca. 95% reaction in 1 hr, and very little reduction to Δ^4-3-one after 2½ hr. 17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (1·75 g), m.p. 214–216°, was isolated as above. Omission of the sodium acetate gave a mixture of products containing significant quantities of the 6-methyl-4-en-3-one.

(iv) A mixture of 17α-acetoxy-6-methylenepregn-4-ene-3,20-dione (10 g), sodium acetate (5 g), 5% Pd–C (1·5 g) and EtOH (150 ml) was stirred under reflux until isomerization was complete as judged by UV spectra (ca. 18–24 hr). 17α-Acetoxy-6-methylpregna-4,6-diene-3,20-dione (8 g), m.p. 214–216°, was isolated as above.

17β-Acetoxy-6-methylandrosta-4,6-dien-3-one. A solution of 17β-acetoxy-6-methyleneandrost-4-en-3-one (10 g) and sodium acetate (5 g) in EtOH (100 ml) was stirred and heated under reflux with 5% Pd–C (1 g) for 18 hr. Removal of the catalyst, concentration of the filtrate and dilution with water gave 17β-acetoxy-6-methylandrosta-4,6-dien-3-one (7·5 g), m.p. 171–174° (from aqueous MeOH (lit.[10] m.p. 173–174°)).

21-Acetoxy-6-methylpregna-4,6-diene-3,20-dione. A solution of 21-acetoxy-6-methylenepregn-4-ene-3,20-dione (1·1 g) and sodium acetate (0·25 g) in EtOH (50 ml) was stirred and heated under reflux with 5% Pd–C (0·25 g) for 10 hr. The product, isolated as above, was crystallized from MeOH to give 21-acetoxy-6-methylpregna-4,6-diene-3,20-dione as rods, m.p. 126–128°, $[\alpha]_D$ +168·8°, λ_{max}^{EtOH} 288 mμ (ε 25,260) [lit.[5] m.p. 126–128°, $[\alpha]_D$ +165°, λ_{max} 287 mμ (ε 23,600)].

17α-Acetoxy-6β-methylpregn-4-ene-3,20-dione. A solution of 17α-acetoxy-6-methylpregna-4,6-diene-3,20-dione (1 g) and cyclohexene (5 ml) in EtOH (25 ml) was stirred and heated under reflux with 5% Pd–C (0·25 g) for 2 hr, by which time the UV spectrum showed the presence of ca. 5% 4,6-dien-3-one. Removal of the catalyst and dilution with water gave a crude product (m.p. 225–245°) which crystallized from dichloromethane–MeOH to give *17α-acetoxy-6β-methylpregn-4-ene-3,20-dione* (0·45 g) as laths, m.p. 255–258°, $[\alpha]_D$ +33·2°, λ_{max}^{EtOH} 241 mμ (ε 15,770). (Found: C, 74·15; H, 8·6. $C_{24}H_{36}O_4$ requires: C, 74·55; H, 8·85%.) This substance does not appear to have been described in the literature although its biological properties have been investigated.[11]

To the mother liquors of the crystallizations were added a few drops of conc. HCl, the mixture was boiled for 15 min and diluted with water. 17α-Acetoxy-6α-methylpregn-4-ene-3,20-dione (0·4 g), m.p. 200–203° was obtained.

Reduction of 17β-acetoxyandrosta-4,6-dien-3-one. A solution of the dienone (0·5 g) and cyclohexene (2 ml) in EtOH (10 ml) was stirred and heated under reflux with 5% Pd–C (0·5 g). Reduction was complete after ca. 1 hr as judged from IR and UV spectra. Removal of the catalyst and dilution of the filtrate with water gave testosterone acetate (0·4 g), m.p. 137–139°, not depressed on admixture with an authentic specimen, m.p. 140°.

Reduction of 21-acetoxy-17α-hydroxypregna-4,6-diene-3,11,20-trione. A solution of the dienone (0·5 g) and cyclohexene (2 ml) in EtOH (20 ml) was stirred and heated under reflux with 5% Pd–C (0·5 g) for 1½ hr, by which time a sample showed λ_{max} 237 mμ only. The product (0·4 g) isolated as before, had m.p. 238–242°, not depressed on admixture with cortisone acetate (m.p. 243–244°).

[10] B. Ellis, D. N. Kirk, V. Petrow, B. Waterhouse and D. M. Williamson, *J. Chem. Soc.* 2828 (1960).
[11] R. L. Elton, R. A. Edgren and D. W. Calhoun, *Proc. Soc. Exp. Biol. Med.* **103**, 175 (1960).