Seco-steroids. Part III.[1] 5,6-Secoprogesterone

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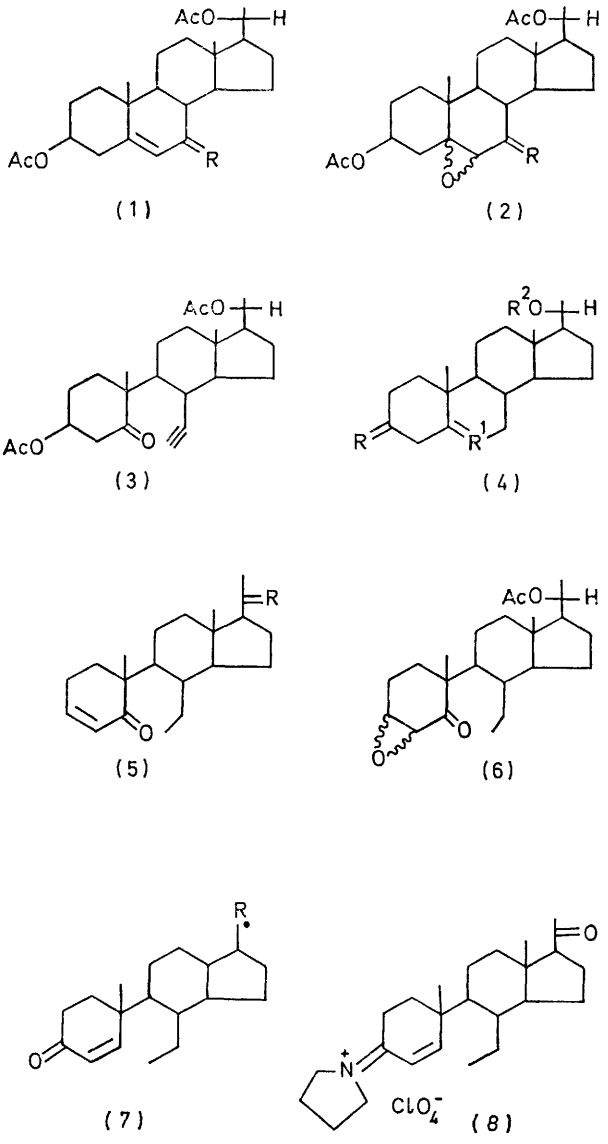
Fragmentation of the tosylhydrazone of a 5,6-epoxy-7-keto-steroid has been used as the key step in the synthesis of the title compound, from which the 5,6-seco-analogues of deoxycorticosterone acetate and testosterone acetate have been made.

In continuation of our study of the effect of specific bond cleavage on the endocrinological activity of steroids, we now describe the synthesis of 5,6-seco-analogues of progesterone, testosterone, and deoxycorticosterone. 5,6-Seco-steroids are of particular theoretical interest since they represent a half-way position between the stilboestrol analogues of testosterone,[2] and the fully condensed steroids themselves.

The well-documented [3] ozonolysis of readily available 5-dehydro-steroids is an obvious and direct route to the 5,6-seco-system. However, the subsequent removal of oxygen atoms at C-5 and C-6, together with the introduction of the 4,5-double bond, presents difficulties. In principle these could be overcome by using instead the fragmentation of a 5,6-epoxy-7-tosylhydrazone to give a 5-keto-6,7-acetylene, which could be transformed more easily into compounds with the required substituents.

We were unable to epoxidise the known [4] unsaturated 7-ketone (1; R = O) with alkaline hydrogen peroxide. However, the corresponding alcohol (1; R = H,OH) gave a mixture of epoxides (2; R = H,OH) on treatment with *m*-chloroperbenzoic acid, and oxidation then gave approximately equal amounts of the epoxy-ketones (2; R = O). Several methods [5,6] have been described for effecting fragmentation of epoxy-ketones *via* hydrazone derivatives. The simplest of these involves treatment of the epoxy-ketone with *p*-tolylsulphonylhydrazine in acetic acid.[5] Under these conditions the epoxide isomers (2; R = O) gave a mixture of products from which crude samples of the acetylenic ketone (3) were obtained by chromatography. Few of these samples could be hydrogenated satisfactorily. However, when the tosylhydrazone (2; R = N·NHTs) was isolated and treated with potassium carbonate, fragmentation occurred in high yield. The chromatographically pure but non-crystalline acetylenic ketone (3) made in this way could be hydrogenated readily, giving the crystalline saturated ketone (4; R = H,β-OAc, R^1 = O, R^2 = Ac). The structure of these ketones was confirmed by their n.m.r. spectra. In both cases the signal for the C-3 hydrogen atom was consistent with it being equatorial (half band-width 9 Hz), suggesting that a change in the conformation of ring A had occurred on cleavage of ring B.

On passing the saturated ketone (4; R = H,β-OAc, R^1 = O, R^2 = Ac) through an alumina column, elimination of acetic acid occurred, giving the unsaturated ketone (5; R = H,β-OAc), which on treatment with alkaline hydrogen peroxide gave a mixture of epoxy-ketones (6). It was expected that these isomers would



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undergo the Wharton rearrangement [7] on treatment with hydrazine to give a 3-hydroxy-4-dehydro-compound, but this failed to take place and no unsaturated products were obtained under a variety of conditions. Although neither the starting material nor the corresponding 20-hydroxy-compound could be recovered from these reactions it seems likely that steric hindrance at the C-5 carbonyl group prevented formation of a hydrazone.

In an attempt to make use of this hindrance, selective oxidation of the 3β,5,20β-trihydroxy-compounds (4; R = H,β-OH, R^1 = H,α- and β-OH, R^2 = H) was examined. This mixture of triols was made by reduction of the saturated ketone (4; R = H,β-OAc, R^1 = O, R^2 = Ac) with sodium dihydrobis-(2-methoxyethoxy)-aluminate.[8] The C-3 alcohol was selectively oxidised with silver carbonate on Celite,[9] giving a mixture of keto-diols (4; R = O, R^1 = H,α- and β-OH, R^2 = H) which was dehydrated with methanolic potassium hydroxide and oxidised at C-20 to give 5,6-secoprogesterone (7; R = Ac). By carrying out the last three stages without isolation of the intermediates a 35% yield of 5,6-secoprogesterone was obtained.

If selective oxidation had occurred at C-5 and not at C-3 the product would have been the isomeric αβ-unsaturated ketone (5; R = O). This compound was made by hydrolysis and oxidation at C-20 of the acetoxy-ketone (5; R = H,β-OAc), and shown to be different from 5,6-secoprogesterone.

It is known that the presence of additional double bonds can markedly alter the biological properties of steroids. With this in mind we have made 1,2-dehydro- and 6,7-dehydro-5,6-secoprogesterone. The 1,2-dehydro-compound was made directly by dehydrogenation of 5,6-secoprogesterone with 2,3-dichloro-5,6-dicyano-benzoquinone.[10] 6,7-Dehydro-5,6-secoprogesterone was made from the acetylene (3) by first partially hydrogenating the triple bond (Pd–$CaCO_3$–pyridine) to give the 6,7-dehydro-derivative of the diacetoxy-ketone (4; R = H,β-OAc, R^1 = O, R^2 = Ac). Reduction with sodium dihydrobis-(2-methoxyethoxy)aluminate then gave a mixture of unsaturated triols (C-5 epimers) which were converted into the progesterone analogue by the method described for the saturated triols (4; R = H,β-OH, R^1 = H,α- and β-OH, R^2 = H).

5,6-Secoprogesterone has been used to make the 5,6-seco-analogues of two other physiologically active steroids, deoxycorticosterone and testosterone. The method used was that of Gadsby and Leeming,[11] in which the 3-keto-4-dehydro-system was selectively protected by formation of the eniminium salt (8) and then treated with lead tetra-acetate to give, after hydrolysis of the protecting group, the 21-acetoxy-derivative (7; R = $CO{\cdot}CH_2{\cdot}OAc$). Treatment of the eniminium salt (8) with peroxy-acid and hydrolysis of the protecting group gave 5,6-secotestosterone acetate (7; R = OAc).

When dosed subcutaneously to rats, 1 mg./kg. of 5,6-secotestosterone acetate showed similar androgenic and anabolic activity to 0·025 mg./kg. of testosterone propionate. None of the other compounds described here showed any biological activity.*

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were determined for solutions in deuteriochloroform with a Varian HA100 spectrometer, with tetramethylsilane as internal standard. Optical rotations refer to solutions in chloroform. Light petroleum had b.p. 60—80°.

3β,20β-*Diacetoxy*-5,6-*epoxypregnan*-7-*one* (2; R = O).—A solution of 3β,20β-diacetoxypregn-5-en-7-one (1; R = O) (25·0 g.) in dioxan (200 c.c.) and methanol (200 c.c) was cooled to 15° and stirred during the addition of sodium borohydride (9·5 g.) in small portions over 30 min. After a further 30 min. water (500 c.c.) was added and the mixture was extracted with chloroform (3 × 200 c.c.). Evaporation of the combined extracts gave a crude oil which was redissolved in chloroform (300 c.c.). *m*-Chloroperbenzoic acid (15·8 g.) was added and the mixture was kept at room temperature for 18 hr. Calcium hydroxide (7·0 g.) was added and after 2 hr. stirring the solid material was filtered off; the filtrate was evaporated leaving a pale yellow oil. A solution of this oil in acetone (300 c.c.) was cooled to 15° and stirred during the dropwise addition of 8N-chromic acid (20 c.c.). Stirring was continued for 5 min. and the excess of reagent was then destroyed with propan-2-ol. Water was added and a crude oil (23·5 g.) was isolated with chloroform. Trituration with light petroleum–ether (3 : 1) gave a white solid (17·9 g.), which was shown by mass spectroscopy (M^+ 432. Calc. for $C_{25}H_{36}O_6$: *M*, 432) and n.m.r. [δ 3·02 (0·5H, s) and 3·16 p.p.m. (0·5H, s)] to be the mixture of epoxides (2; R = O).

3β,20β-*Diacetoxy*-5,6-*secopregn*-6-*yn*-5-*one* (3).—*p*-Tolylsulphonyl hydrazine (9·3 g.) was added to a solution of the epoxides (2; R = O) (17·3 g.) in ethanol (240 c.c.) and chloroform (120 c.c.), and the mixture was refluxed under nitrogen for 5 hr. Some of the solvent (100 c.c.) was distilled off and the residue was kept at 4° for 48 hr. A solid (8·3 g.), m.p. 190—195°, δ 3·72 (1H, s), 4·75 (2H, m), 7·24 (2H, m), and 7·78 p.p.m. (2H, m), was collected and used without further purification. The n.m.r. spectrum indicates that it is the tosylhydrazone (2; R = N·NHTs) of only one of the epoxide isomers (2; R = O).

A solution of the tosylhydrazone (2; R = N·NHTs) (8·3 g.) in methylene chloride (83 c.c.) and ethanol (210 c.c.) was stirred at room temperature during the dropwise addition over 5 min. of a solution of potassium carbonate (1·9 g.) in water (28 c.c.). Stirring was continued for 30 min. and then a crude yellow oil (7·0 g.) was isolated with chloroform. Filtration of a solution of this oil in ether through a column of Florisil gave a chromatographically homogeneous oil (5·3 g.), which was used without further purification. It was shown to be the acetylenic ketone (3) by its i.r. [$\nu_{max.}$

* We thank Dr. A. L. Walpole for these results.

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($CHCl_3$) 2100 and 3300 cm.$^{-1}$] and n.m.r. spectra [δ 0·64 (3H, s), 1·10 (3H, s), 4·85 (1H, m), and 5·40 p.p.m. (1H, m).

3β,20β-*Diacetoxy*-5,6-*secopregnan*-5-*one* (4; R = H,β-OAc, R^1 = O, R^2 = Ac).—A solution of the acetylenic ketone (3) (5·5 g.) in ethyl acetate (70 c.c.) was shaken with hydrogen in the presence of platinum oxide (0·5 g.) until the uptake of hydrogen ceased. The crude product was purified by filtration of a solution in ether through Florisil to give the *saturated ketone* (4; R = H,β-OAc, R^1 = O, R^2 = Ac) (5·0 g.) as a chromatographically homogeneous oil, δ 0·62 (3H, s), 0·62 (3H, t), 1·02 (3H, s), 1·14 (3H, d), 2·00 (6H, s), 4·82 (1H, m), and 5·38 p.p.m. (1H, m).

A sample of this oil which had been stored for several months crystallised, m.p. 89—94°. An analytical sample had m.p. 103—105° (from light petroleum), $[\alpha]_D^{25}$ +82° (c 1·0) (Found: C, 71·1; H, 9·7. $C_{25}H_{40}O_5$ requires C, 71·4; H, 9·6%).

3β,5,20β-*Trihydroxy*-5,6-*secopregnane* (4; R = H,β-OH, R^1 = H,α- and β-OH, R^1 = H).—A solution of the saturated ketone (4; R = H,β-OAc, R^1 = O, R^1 = Ac) (2·6 g.) in benzene (75 c.c.) was added to a stirred solution of sodium dihydrobis-(2-methoxyethoxy)aluminate in benzene (17·5% w/v; 36 c.c.), and the mixture was refluxed for 18 hr. It was then cooled in an ice-bath and saturated brine solution (25 c.c.) was added, followed by 2N-hydrochloric acid (50 c.c.) and more brine solution (100 c.c.). The mixture was extracted with ethyl acetate (3 × 50 c.c.) and the combined extracts were washed with water, dried, and evaporated to give a white solid (1·9 g.) which showed no i.r. carbonyl absorption and which was used without further purification. It was shown to be the mixture of triols (4; R = H,β-OH, R^1 = H,α- and β-OH, R^2 = H) by t.l.c. (two spots on silica gel eluted with ethyl acetate) and n.m.r. [δ 3·75 p.p.m. (3H, m)].

5,6-*Secopregn*-4-*ene*-3,20-*dione* (7; R = Ac).—Silver carbonate on Celite (57 g. containing *ca.* 28 g. of silver carbonate) was added to a solution of the triol mixture (4; R = H,β-OH, R^1 = H,α- and β-OH, R^2 = H) (3·3 g.) in toluene (195 c.c.), and the mixture was stirred and refluxed under nitrogen for 2 hr. A black solid was filtered from the hot solution and the filtrate was evaporated to give a yellow oil ($\nu_{max.}$ 1700 cm.$^{-1}$).

A solution of this oil in methanol (80 c.c.) was added to a solution of potassium hydroxide in methanol (50 c.c.) and the mixture was kept at room temperature under nitrogen for 30 min. Isolation with ether gave a brown oil ($\nu_{max.}$ 1675 cm.$^{-1}$) which was dissolved in acetone (300 c.c.) and oxidised with 8N-chromic acid. The crude oil (3·0 g.) obtained was chromatographed on Florisil (100 g.) and the white solid eluted with light petroleum–ethyl acetate (20 : 1) was crystallised from ether–light petroleum to give the *diketone* (7; R = Ac) (1·1 g.), m.p. 92—94°. An analytical sample had m.p. 94—96°, $[\alpha]_D^{25}$ +51° (*c* 1·0) (Found: C, 79·9; H, 10·0%; M^+, 316. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%; *M*, 316), δ 0·6 (3H, s), 0·76 (3H, t), 1·18 (3H, s), 2·06 (3H, s), 5·72 (1H, d), and 6·84 p.p.m. (1H, d), $\nu_{max.}$ ($CHCl_3$) 1670 and 1695 cm.$^{-1}$.

Reaction of 5,6-*Secopregn*-4-*ene*-3,20-*dione* (7; R = Ac) *with Pyrrolidine Perchlorate*.—A mixture of 5,6-secopregn-4-ene-3,20-dione (7; R = Ac) (1·09 g.), pyrrolidine perchlorate (631 mg.), pyrrolidine (1 drop), and ethanol (5 c.c.) was kept at room temperature for 2 days and then at 0° for 18 hr. The eniminium perchlorate (8) separated as a white solid (1·18 g., 73%), m.p. 170—174°, and was used without further purification. A satisfactory elemental analysis could not be obtained for a sample of m.p. 180—181° (from ethyl acetate–methanol), δ 0·78 (3H, t), 2·06 (3H, s), 6·38 (1H, d), and 7·28 p.p.m. (1H, d), $\nu_{max.}$ ($CHCl_3$) 1625 and 1695 cm.$^{-1}$.

21-*Acetoxy*-5,6-*secopregn*-4-*ene*-3,20-*dione* (7; R = CO·CH_2·OAc).—Boron trifluoride–ether complex (1·25 c.c.) was added to a stirred solution of the eniminium perchlorate (8) (315 mg.) and lead tetra-acetate (330 mg.) in benzene (9·5 c.c.) and methanol (0·55 c.c.). After 5 hr. at room temperature ethylene glycol (4 drops) was added, followed after 5 min. by water (20 c.c.). The mixture was extracted with ethyl acetate (3 × 10 c.c.), and the combined extracts were washed with saturated sodium hydrogen carbonate solution, dried, and evaporated, leaving a yellow oil (297 mg.).

After hydrolysis of the eniminium group at room temperature with potassium carbonate (250 mg.) in water (5 c.c.) and ethanol (20 c.c.), a crude oil (180 mg.) was isolated with ether and then acetylated by treatment at room temperature with acetic anhydride (1 c.c.) and pyridine (5 c.c.) for 2 days. Preparative layer chromatography gave a white solid which crystallised from ether to give the 21-*acetoxy-compound* (7; R = CO·CH_2·OAc) (80 mg.), m.p. 116—120°, $[\alpha]_D^{25}$ +64° (*c* 0·5) (Found: C, 73·9; H, 9·1%; M^+, 374. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·15%; *M*, 374), δ 0·66 (3H, s), 1·20 (3H, s), 2·14 (3H, s), 4·68 (2H, m), 5·78 (1H, d), and 6·90 p.p.m. (1H, d).

17β-*Acetoxy*-5,6-*secoandrost*-4-*en*-3-*one* (7; R = OAc).—A mixture of the eniminium perchlorate (8) (235 mg.) and *m*-chloroperbenzoic acid (100 mg.) in chloroform (4 c.c.) was kept at room temperature in the dark for 7 days. Ethanol (10 c.c.) and water (3 c.c.) were added, followed by potassium carbonate (200 mg.), and this mixture was stirred at room temperature for 1 hr. After dilution with water a crude yellow oil (156 mg.) was isolated with chloroform and purified by preparative layer chromatography. The chromatographically homogeneous oil (100 mg.) obtained was identified as the 17-*acetoxy-compound* (7; R = OAc) by its mass spectrum (M^+, 332. Calc. for $C_{21}H_{32}O_3$: *M*, 332) and n.m.r. spectrum [δ 0·79 (3H, t), 0·80 (3H, s), 1·22 (3H, s), 2·04 (3H, s), 4·58 (1H, t), 5·78 (1H, d), and 6·90 p.p.m. (1H, d).

5,6-*Secopregna*-1,4-*diene*-3,20-*dione*.—A mixture of 5,6-secopregn-4-ene-3,20-dione (7; R = Ac) (360 mg.), 2,3-dichloro-5,6-dicyanobenzoquinone (298 mg.), and toluene-*p*-sulphonic acid (30 mg.) in dioxan (15 c.c.) was stirred and refluxed under nitrogen for 1 hr., then cooled. A solid was filtered off and washed well with chloroform. The filtrate was evaporated and the residue, dissolved in a mixture of ethyl acetate and ether (1 : 1), was filtered through a column of alumina (Woelm neutral, grade I) to give a crude product. Crystallisation from ether–methylene chloride gave the *dienone* (98 mg.), m.p. 131—135°. An analytical sample had m.p. 135—136°, $[\alpha]_D$ +52° (*c* 1·0) (Found: C, 79·8; H, 9·5%; M^+, 314. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%; *M*, 314), δ 0·62 (3H, s), 0·70 (3H, t), 1·22 (3H, s), and 2·10 p.p.m. (3H, s).

3β,20β-*Diacetoxy*-5,6-*secopregn*-6-*en*-5-*one*.—A solution of the acetylenic ketone (3) (5·0 g.) in pyridine (60 c.c.) was shaken with hydrogen in the presence of 5% palladium–carbon (2·0 g.) until 1 equiv. of hydrogen had been taken up (4 hr.). After removal of the catalyst the solvent was evaporated off and the residue was chromatographed on Florisil. An oil (2·9 g.) was eluted with ether and identified as 3β,20β-diacetoxy-5,6-secopregn-6-en-5-one by its n.m.r.

spectrum [δ 0·64 (3H, s), 1·06 (3H, s), 1·13 (3H, d), and 4·50—5·50 p.p.m. (5H, m).

3β,5,20β-*Trihydroxy*-5,6-*secopregn*-6-*ene*.—Reduction of 3β,20β-diacetoxy-5,6-secopregn-6-en-5-one with sodium dihydrobis-(2-methoxyethoxy)aluminate in benzene as described for the saturated ketone (4; R = H,β-OAc, R^1 = O, R^2 = Ac) gave 3β,5,20β-trihydroxy-5,6-secopregn-6-ene as a mixture of 5α- and 5β-isomers in 92% yield, m.p. 94—99°. T.l.c. showed two spots (silica gel in ethyl acetate); δ 0·66 (3H, s), 1·00 (3H, s), 1·10 (3H, d), 4·80 (2H, m), and 5·50 p.p.m. (1H, m).

5,6-*Secopregna*-4,6-*diene*-3,20-*dione*.—Selective oxidation of 3β,5,20β-trihydroxy-5,6-secopregn-6-ene with silver carbonate on Celite followed by treatment with potassium hydroxide in methanol and then oxidation with 8N-chromic acid as described for the saturated triols (4; R = H,β-OH, R^1 = H,α- and β-OH, R^2 = H) gave 5,6-secopregna-4,6-diene-3,20-dione as a chromatographically homogeneous oil (M^+, 314. Calc. for $C_{21}H_{30}O_2$: M, 314), $\nu_{max.}$ ($CHCl_3$) 1675 and 1710 $cm.^{-1}$, δ 0·68 (3H, s), 1·18 (3H, s), 2·10 (3H, s), 4·80—5·60 (3H, m), 5·75 (1H, d), and 6·94 p.p.m. (1H, d).

20β-*Acetoxy*-5,6-*secopregn*-3-*en*-5-*one* (5; R = H,β-OAc).—A solution of the saturated ketone (4; R = H,β-OAc, R^1 = O, R^2 = Ac) (1·60 g.) in ether (20 c.c.) was adsorbed onto a column of basic alumina (50 g.). Elution with ether (200 c.c.) gave the unsaturated ketone (5; R = H,β-OAc) (1·20 g.) as a chromatographically homogeneous oil (M^+, 360. Calc. for $C_{23}H_{36}O_3$: M, 360), $\nu_{max.}$ 1675 and 1720 $cm.^{-1}$, δ 0·60 (3H, t), 0·64 (3H, s), 1·08 (3H, s), 1·14 (3H, d), 1·98 (3H, s), 4·80 (1H, m), 5·90 (1H, d), and 6·70 p.p.m. (1H, m).

20β-*Acetoxy*-3,4-*epoxy*-5,6-*secopregnan*-5-*one* (6).—A mixture of the unsaturated ketone (5; R = H,β-OAc) (200 mg.), aqueous 25% sodium hydroxide (1 c.c.) and methanol (16 c.c.) was cooled below 5° and stirred during the dropwise addition of aqueous 30% hydrogen peroxide (4 c.c.). The mixture was kept at room temperature for 30 min. and a crude product (176 mg.), m.p. 115—121°, was isolated with ether. It was shown by n.m.r. spectroscopy to be a mixture of α- and β-epoxides. Crystallisation from aqueous methanol gave a pure isomer of unknown stereochemistry, m.p. 135—137°, $[\alpha]_D^{25}$ +111° (*c* 1·0) (Found: C, 73·3; H, 9·6. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%), δ 0·62 (3H, s), 0·80 (3H, t), 1·12 (3H, s), 1·12 (3H, d), 1·94 (3H, s), 3·18 (1H, d), 3·55 (1H, m), and 4·80 p.p.m. (1H, m).

5,6-*Secopregn*-3-*ene*-5,20-*dione* (5; R = O).—The unsaturated ketone (5; R = H,β-OAc) (1·10 g.) was added to a solution of sodium hydroxide (8·0 g.) in ethanol (70 c.c.) and water (10 c.c.) and the mixture was refluxed for 30 min. After evaporation of the solvents a crude product (1·00 g.), $\nu_{max.}$ ($CHCl_3$) 1675 $cm.^{-1}$, was isolated with ethyl acetate and oxidised in acetone solution (50 c.c.) with 8N-chromic acid. Isolation with chloroform then gave a yellow oil (790 mg.) which was filtered through Florisil in ether and crystallised from acetone–hexane to give the diketone (5; R = O) (370 mg.), m.p. 145—150°. An analytical sample had m.p. 152—155°, $[\alpha]_D^{25}$ +170° (*c* 1·0) (Found: C, 79·7; H, 10·0. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%), δ 0·58 (3H, s), 0·60 (3H, t), 1·07 (3H, s), 2·06 (3H, s), 5·90 (1H, d), and 6·72 p.p.m. (1H, m).

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