Aromatization of Some Steroidal Enediols

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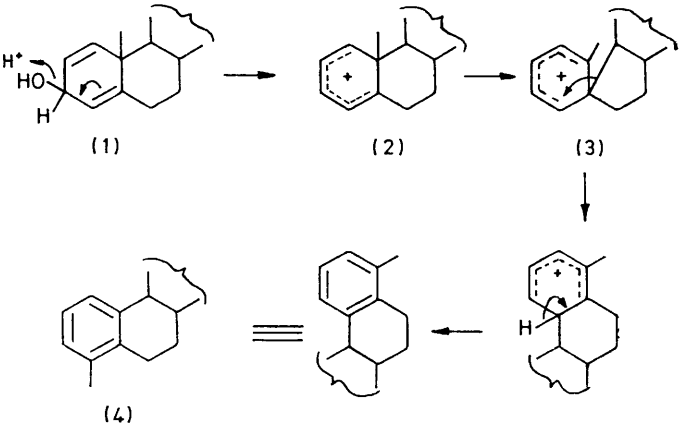
17β-Acetoxy-4β,5α-dihydroxyandrost-2-ene, 5α,6α- and 5α,6β-dihydroxyandrost-2-en-17-one, 4β-acetoxy-3β-hydroxyandrost-5-en-17-one, and 3β,6β,17β-triacetoxyandrost-4-ene rearrange in hydrogen bromide–glacial acetic acid to form 4-methylestratrienes. Similar treatment of 6β,17β-diacetoxy-3β-hydroxyandrost-4-ene gives both 17β-acetoxy-4-methylestra-1,3,5(10)-triene and testosterone acetate. 3β,17β-Diacetoxy-6β-hydroxyandrost-4-ene gives 17β-acetoxyandrost-4-en-6-one.

A NUMBER of reactions are possible when a carbonium ion is generated at C-5 in a steroid which also contains in the vicinity two further double bond equivalents. These include methyl migrations, backbone rearrangements, and the aromatization of either ring A or ring B.[1] The dienol–benzene rearrangement (Scheme 1), which proceeds through a C-5 spirocyclic cation (3),[2] belongs to a general class of aromatization reactions.[3] In this paper[4] we describe the reactions of some steroidal enediols under the conditions of the dienol–benzene rearrangement that lead to aromatic products.

The carbonium ion (2) that may precede a spirocyclic intermediate (3) could be formed by successive dehydrations of 17β-acetoxy-4β,5α-dihydroxyandrost-2-ene (7). Treatment of steroid (7) with hydrobromic acid in glacial acetic acid gave 17β-acetoxy-4-methylestra-1,3,5-(10)-triene (8). Steroid (7) was prepared by oxidation[5] of 17β-acetoxy-5α-hydroxyandrost-2-ene (5) with 8N-chromium trioxide to afford the C-4 ketone (6), reduction of which with sodium borohydride gave the C-4 alcohol (7). The axial (β) stereochemistry was assigned to alcohol (7) by analogy with the reduction of 5α-hydroxy-



SCHEME 1

cholestan-4-one to the 4β,5α-diol with lithium aluminium hydride[6] and from its n.m.r. spectrum. Comparison of

[1] For recent reviews see D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, London, 1968; D. N. Kirk in 'Terpenoids and Steroids,' Specialist Periodical Reports, The Chemical Society, London, vol. 1, 1971, p. 376; vol. 2, 1972, p. 309.

[2] E. Caspi, D. M. Piatak, and P. K. Grover, *J. Chem. Soc.* (*C*), 1966, 1034.

[3] J. Libman and Y. Mazur, *Chem. Comm.*, 1971, 729.

[4] Preliminary communication, J. R. Hanson, *Tetrahedron Letters*, 1972, 4501.

[5] J. R. Hanson and A. G. Ogilvie, *J.C.S. Perkin I*, 1972, 590.

[6] D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 1955, 2876.

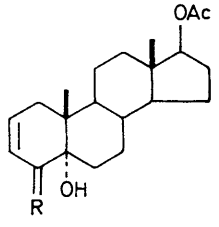
the spectra of compounds (5) and (7) revealed a shift in the 19-H resonances (τ 9·07 to 8·90) in accord with an additional diaxial interaction; this shift was amplified by addition of the $Eu(fod)_3$ shift reagent [7] (see Table).

The effect of the $Eu(fod)_3$ shift reagent on the n.m.r. spectra of steroids (5) and (7)

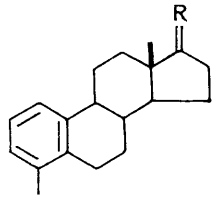
		C-18 (H)	C-19 (H)	C-17 (OAc)	C-17 (H)	C-2 and C-3 (H)	C-4 (H)
(5)	*a*	9·17	9·07	7·93	5·38	4·33	
	b	9·02	8·99	7·52	4·80	4·25	
	c	8·94	8·89	7·25	4·40	4·20	
(7)	*a*	9·18	8·90	7·95	5·36	4·13	6·30
	b	9·06	8·65	7·60	5·05	3·90	5·70
	c	8·98	8·46	7·43	4·80	3·76	5·30

Steroid (40 mg) (*a*) alone in $CDCl_3$; (*b*) +6·67 mg ml^{-1} $Eu(fod)_3$; (*c*) +10 mg ml^{-1} $Eu(fod)_3$

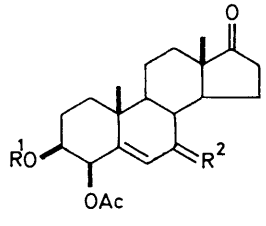
5α,6α- and 5α,6β-Dihydroxyandrost-2-en-17-one were prepared from the corresponding methanesulphonates by elimination with collidine,[5] and both gave 4-methylestra-1,3,5(10)-trien-17-one on treatment with hydrobromic acid in glacial acetic acid.



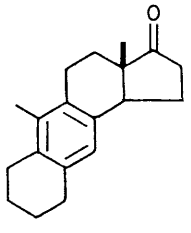
(5) R = H_2
(6) R = O
(7) R = H, β-OH



(8) R = H, β-OAc
(9) R = O



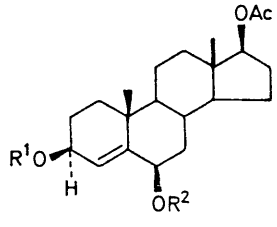
(10) R^1 = H, R^2 = H_2
(11) R^1 = Ac, R^2 = O



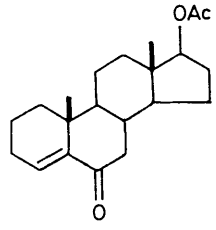
(12)

The carbonium ion (2) may also be formed from 3,4-dihydroxy-5-enes and the isomeric 3,6-dihydroxy-4-enes by successive dehydrations and double-bond migrations. Treatment of dehydroisoandrosterone with bromine and silver acetate gave 4β-acetoxy-3β-hydroxyandrost-5-en-17-one (10),[8] whose n.m.r. spectrum supported the presence of a 4β-acetoxy-substituent. Steroid (10) and the corresponding diacetate both underwent rearrangement with hydrobromic acid in glacial acetic acid to form 4-methylestra-1,3,5(10)-trien-17-one (9) and a small amount of the anthrasteroid (12). These reactions were accompanied by the development of a deep blue colour. Trichloroacetic acid has been reported [8] to give this colour when used as a spot-test reagent in this series, and we have isolated 4-methylestra-1,3,5(10)-trien-17-one (9) on treatment of steroid (10) and its diacetate with trichloroacetic acid. However the trienone (9) is not the chromogen, since on re-suspension in trichloroacetic acid it gives a pink colouration. Oxidation of 3β,4β-diacetoxyandrost-5-en-17-one with chromium trioxide in glacial acetic acid gave 3β,4β-diacetoxyandrost-5-ene-7,17-dione (11) in high yield, but this compound gave intractable products on treatment with hydrobromic acid in glacial acetic acid.

3β,17β-Diacetoxy-6β-hydroxyandrost-4-ene (13) was prepared by dehydration of 3β,17β-diacetoxy-5α-hydroxyandrost-6-one [9] with thionyl chloride, followed by reduction of the C-6 ketone with sodium borohydride.[10] Treatment of steroid (13) with hydrobromic acid–glacial acetic acid gave 17β-acetoxyandrost-4-en-6-one (16) (τ 4·80, t, *J* 4 Hz 4-H) [11] and only a trace (t.l.c.) of the aromatic steroid. On the other hand 3β,6β,17β-triacetoxyandrost-4-ene (14) gave a high yield of 17β-acetoxy-4-methylestra-1,3,5(10)-triene (8). 6β,17β-Diacetoxy-3β-hydroxyandrost-4-ene (15) gave a mixture of testosterone acetate and 17β-acetoxy-4-methylestra-1,3,5(10)-triene. Reduction of 17β-acetoxy-6β-bromoandrost-4-en-3-one [12] with sodium borohydride gave an unstable product which formed 17β-acetoxy-4-methylestra-1,3,5(10)-triene on treatment with hydrobromic acid in glacial acetic acid. Thus the formation of unsaturated ketones may occur instead of aromatization.



(13) R^1 = Ac, R^2 = H
(14) R^1 = R^2 = Ac
(15) R^1 = H, R^2 = Ac



(16)

In this connection testosterone acetate has been reported [13] to undergo aromatization when treated with trichloroacetic anhydride in the presence of toluene-*p*-sulphonic acid.

[7] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.
[8] V. Petrow, O. Rosenheim, and W. W. Starling, *J. Chem. Soc.*, 1943, 135.
[9] L. Knof, *Annalen*, 1961, **647**, 53.
[10] Y. Lefebvre, F.P. M3344/1965 (*Chem. Abs.*, 1965, **63***P*, 11670a).
[11] C. H. Robinson, O. Gnoj, and F. E. Carlon, *Tetrahedron*, 1965, **21**, 2509.
[12] J. W. Dean and R. G. Christiansen, *J. Org. Chem.*, 1963, **28**, 2110.
[13] R. Bixon, D. Amar, and Y. Mazur, *Chem. Comm.*, 1965, 138.

EXPERIMENTAL

General experimental details have been described previously.[14]

17β-*Acetoxy*-5α-*hydroxyandrost*-2-*en*-4-*one* (6).—17β-Acetoxy-5α-hydroxyandrost-2-ene [15] (1·70 g) in acetone (40 ml) was treated with 8N-chromic acid (3 ml) for 1 h. Methanol (5 ml) was added, the solution was concentrated *in vacuo* and then diluted with water (200 ml), and the product was recovered in ethyl acetate. 17β-*Acetoxy*-5α-*hydroxyandrost*-2-*en*-4-*one* (6) (940 mg) crystallized from acetone–light petroleum as prisms, m.p. 202—204°, $[\alpha]_D^{20}$ +12° (*c* 0·2) (Found: C, 73·1; H, 8·5. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), $\nu_{max.}$ 3530, 3430, 1725, 1690, and 1630 cm^{-1}, τ 9·20 (3H, s), 9·08 (3H, s), 7·96 (3H, s), 5·37 (1H, t, *J* 8 Hz), 4·03 (1H, d, *J* 11 Hz), and 3·18 (1H, m).

17β-*Acetoxy*-4β,5α-*dihydroxyandrost*-2-*ene* (7).—17β-Acetoxy-5α-hydroxyandrost-2-en-4-one (350 mg) in methanol (15 ml) was treated with sodium borohydride (200 mg) at 0° for 2 h. The solution was acidified and diluted with water, and the product was recovered in chloroform. 17β-*Acetoxy*-4β,5α-*dihydroxyandrost*-2-*ene* (7) (210 mg) crystallized from acetone–light petroleum as needles, m.p. 188—190°, $[\alpha]_D$ +73° (*c* 0·2) (Found: C, 72·1; H, 9·1. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·3%), $\nu_{max.}$ 3520br and 1720 cm^{-1}, τ 9·20 (3H, s), 8·93 (3H, s), 7·95 (3H, s), 6·30 (1H, m), 5·35 (1H, t, *J* 8 Hz), and 4·13 (2H, m). The *diacetate*, prepared with acetic anhydride in pyridine, crystallized from acetone–light petroleum as needles, m.p. 203—204°, $[\alpha]_D$ +151° (*c* 0·2) (Found: C, 70·3; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·3%), $\nu_{max.}$ 3520, 1735, and 1660 cm^{-1}, τ 9·20 (3H, s), 8·95 (3H, s), 7·94 (6H, s), 5·40 (1H, t, *J* 7 Hz), 5·05 (1H, d, *J* 4 Hz), 4·30 (1H, m), and 4·10 (1H, m). This diacetate was also prepared by reduction of 5α-hydroxyandrost-2-ene-4,17-dione [5] with sodium borohydride in methanol followed by acetylation with acetic anhydride in pyridine.

5α,6β-*Dihydroxyandrost*-2-*en*-17-*one*.—The 3β-methanesulphonate of 5α,6α-epoxy-3β-hydroxyandrostan-17-one [16] (2·7 g) in acetone (75 ml) was treated with periodic acid (3·2 g) in water (10 ml) for 4 h at room temperature. The solution was diluted with water and the product was filtered off. The 3β-*methanesulphonate* of 3β,5α-6β-trihydroxyandrostan-17-one crystallized from aqueous acetone as needles, m.p. 156—157° (decomp.) (Found: C, 56·9; H, 8·0. $C_{20}H_{32}O_6S,H_2O$ requires C, 57·4; H, 8·2%), $\nu_{max.}$ 3550br and 1750 cm^{-1}, τ 9·10 (3H, s), 8·80 (3H, s), and 6·90 (3H, s). The 6β-*acetate*, prepared with acetic anhydride in pyridine, crystallized from chloroform–light petroleum as needles, m.p. 187—188° (decomp.), $[\alpha]_D$ 0° (*c* 0·2) (Found: C, 60·0; H, 7·6. $C_{22}H_{34}O_7S$ requires C, 59·7; H, 7·75%), $\nu_{max.}$ 3580 and 1730br cm^{-1}, τ 9·08 (3H, s), 8·80 (3H, s), 7·85 (3H, s), 6·95 (3H, s), 5·18 (1H, m), and 4·95 (1H, m).

The 3β-methanesulphonate of 3β,5α,6β-trihydroxyandrostan-17-one [5] (1·5 g) in collidine (15 ml) was heated under reflux for 4 h. The solution was poured into dil. hydrochloric acid and the product was recovered in ether. 5α,6β-*Dihydroxyandrost*-2-*en*-17-*one* crystallized from chloroform–light petroleum as prisms, m.p. 193—194°, $[\alpha]_D$ +95° (*c* 0·2) (Found: C, 74·9; H, 9·0. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%), $\nu_{max.}$ 3500br and 1735 cm^{-1}, τ 9·08 (3H, s), 8·90 (3H, s), 6·28 (1H, m), and 4·30 (2H, m).

4β-*Acetoxy*-3β-*hydroxyandrost*-5-*en*-17-*one* (10).—This was prepared according to the method of Petrow *et al.*,[8] and had m.p. 192—193°, $[\alpha]_D$ −68° (*c* 0·2) (lit.,[8] m.p. 192—193°, $[\alpha]_D$ −60°), $\nu_{max.}$ 3430, 1740, 1705, and 1670 cm^{-1}, τ 9·15 (3H, s), 8·91 (3H, s), 7·96 (3H, s), 6·4br (1H), 4·66 (1H, d, *J* 3·5 Hz), and 4·19 (1H, m). The *diacetate*, prepared with acetic anhydride in pyridine, crystallized from light petroleum as needles, m.p. 162—164°, $[\alpha]_D$ −61° (*c* 0·2) (Found: C, 70·8; H, 8·5. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%), $\nu_{max.}$ 1745, 1735, and 1665 cm^{-1}, τ 9·11 (3H, s), 8·83 (3H, s), 8·00 (3H, s), 7·94 (3H, s), 5·28 (1H, m), 4·50 (1H, d, *J* 3·5 Hz), and 4·18 (1H, m).

3β,4β-*Diacetoxyandrost*-5-*ene*-7,17-*dione* (11).—Chromium trioxide (1·5 g) was added in portions over 0·5 h to a solution of 3β,4β-diacetoxyandrost-5-en-17-one (1·5 g) in glacial acetic acid (9 ml) containing sodium acetate (0·8 g). After a further 1 h, the solution was poured into water, and the product was filtered off and taken up in ethyl acetate. The solution was dried, concentrated, and passed through a plug of alumina. Evaporation of the solvent gave 3β,4β-*diacetoxyandrost*-5-*ene*-7,17-*dione* (11) (750 mg), which crystallized from methanol as needles, m.p. 157—159°, $[\alpha]_D$ −94° (*c* 0·2) (Found: C, 68·8; H, 7·5. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%), $\nu_{max.}$ 1750, 1735, and 1680 cm^{-1} τ 9·12 (3H, s), 8·65 (3H, s), 7·95 (3H, s), 7·87 (3H, s), 5·2 (1H, ddd, *J* 3·5, 5, and 11 Hz), 4·35 (1H, d, *J* 3·5 Hz), and 4·0 (1H, s), $\lambda_{max.}$ 237 (ε 9500).

3β,17β-*Diacetoxy*-6β-*hydroxyandrost*-4-*ene* (13).—3β,17β-Diacetoxyandrost-4-en-6-one [10] (400 mg) in methanol (40 ml) was treated with sodium borohydride (350 mg) at 0° for 2 h. The solution was acidified with dil. hydrochloric acid and diluted with water, and the product was recovered in chloroform. 3β,17β-*Diacetoxy*-6β-*hydroxyandrost*-4-*ene* (13) (210 mg) crystallized from acetone–light petroleum as prisms, m.p. 164—165°, $[\alpha]_D$ −5° (*c* 0·25) (Found: C, 70·5; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), $\nu_{max.}$ 3400, 1730, 1710, and 1665 cm^{-1}, τ 9·20 (3H, s), 8·93 (3H, s), 7·94 (6H, s), 5·85 (1H, m), 5·40 (1H, t, *J* 7 Hz), 4·70 (1H, m), and 4·35 (1H, m). The *triacetate*, prepared with acetic anhydride in pyridine, crystallized from light petroleum as needles, m.p. 136—137°, $[\alpha]_D$ +5° (*c* 0·25) (Found: C, 69·0; H, 8·3. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%), $\nu_{max.}$ 1735, 1730, and 1665 cm^{-1}, τ 9·19 (3H, s), 8·88 (3H, s), 7·96 (3H, s), 7·92 (3H, s), 7·89 (3H, s), 5·40 (1H, t, *J* 7 Hz), 4·70 (1H, m), and 4·52 (1H, s).

6β,17β-*Diacetoxy*-3β-*hydroxyandrost*-4-*ene* (15).—6β,17β-Diacetoxyandrost-4-en-3-one [17] (860 mg) in methanol (20 ml) was treated with sodium borohydride (600 mg) at 0° for 2 h. The solution was acidified and diluted with water, and the product was recovered in chloroform. Chromatography on alumina in 25% ethyl acetate–light petroleum gave 6β,17β-*diacetoxy*-3β-*hydroxyandrost*-4-*ene* (15) (520 mg), which crystallized from light petroleum as needles, m.p. 134—136°, $[\alpha]_D$ +38° (*c* 0·2) (Found: C, 70·4; H, 8·6. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), $\nu_{max.}$ 3400br, 1720, and 1660 cm^{-1}, τ 9·18 (3H, s), 8·80 (3H, s), 7·95 (6H, s), 5·84 (1H, m), 5·35 (1H, t, *J* 8 Hz), 4·70 (1H, t, *J* 2·5 Hz), and 4·25 (1H, m).

Aromatization Reactions.—(*a*) 4β-Acetoxy-3β-hydroxyandrost-5-en-17-one (10) (1·4 g) in glacial acetic acid (12 ml) and aqueous 48% hydrobromic acid (3 ml) was heated under reflux for 15 min. The solution was poured into

[14] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.
[15] P. D. Klimstra, U.S.P. 3,271,425/1966 (*Chem. Abs.*, 1967, **66**, 1094).
[16] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 2473.
[17] J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, 1954, **19**, 1509.

aqueous sodium hydrogen carbonate and the product was recovered in chloroform and chromatographed on alumina. Elution with 8% ether–light petroleum gave the *anthrasteroid* (12) (47 mg), which crystallized from light petroleum as needles, m.p. 133—135°, $[\alpha]_D$ +142° (*c* 0·2) (Found: C, 84·9; H, 8·9. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%), $\nu_{max.}$ 1730 cm^{-1}, τ 8·97 (3H, s), 7·96 (3H, s), and 3·40 (1H, s). Elution with 10% ether–light petroleum gave 4-methylestra-1,3,5(10)-trien-17-one (9) (364 mg), which crystallized from light petroleum as needles, m.p. 180—182°, $[\alpha]_D$ +150° (*c* 0·2) (lit.,[2] m.p. 180—181° $[\alpha]_D$ +150°), identified by comparison with an authentic sample.

(*b*) 4β-Acetoxy-3β-hydroxyandrost-5-en-17-one (10) (100 mg) was mixed with trichloroacetic acid (1 g) and heated at 100° for 1 h. The solution was poured into aqueous sodium hydrogen carbonate and the steroid was recovered in ethyl acetate. Chromatography on alumina gave 4-methylestra-1,3,5(10)-trien-17-one (9) (10 mg) as needles, m.p. 180—183°, identified by its i.r. spectrum.

(*c*) 3β,4β-Diacetoxyandrost-5-en-17-one (250 mg) was dissolved in glacial acetic acid (2 ml) and aqueous 48% hydrobromic acid (0·5 ml) and heated under reflux for 15 min. The solution was poured into aqueous sodium hydrogen carbonate, and the product was recovered in ethyl acetate and chromatographed on alumina. Elution with 8—10% ether–light petroleum gave 4-methylestra-1,3,5(10)-trien-17-on (9) (64 mg), which crystallized from light petroleum as needles, m.p. 180—182°, identified by its i.r. spectrum. T.l.c. indicated that traces of the anthrasteroid (12) were present in these fractions.

(*d*) 17β-Acetoxy-4-methylestra-1,3,5(10)-triene was obtained under similar conditions from the following steroids.

Steroid (mg)	17β-Acetoxy-4-methylestra-1,3,5(10)-triene/mg
17β-Acetoxy-4β,5α-dihydroxyandrost-2-ene (7) (170)	59
3β,6β,17β-Triacetoxyandrost-4-ene (14) (600)	150
6β,17β-Diacetoxy-3β-hydroxyandrost-4-ene (15) (250)	35 *
17β-Acetoxy-6β-bromo-3β-hydroxyandrost-4-ene (from 350 mg parent bromo-ketone)	54

* Together with testosterone acetate (30 mg).

(*e*) 4-Methylestra-1,3,5(10)-trien-17-one (9) was obtained under similar conditions from the following steroids.

Steroid (mg)	4-Methyloestra-1,3,5(10)-trien-17-one/mg
5α,6α-Dihydroxyandrost-2-en-17-one (400)	110
5α,6β-Dihydroxyandrost-2-en-17-one (120)	30

(*f*) 3β,17β-Diacetoxy-6β-hydroxyandrost-4-ene (13) (200 mg) in acetic acid (5 ml) and aqueous 48% hydrobromic acid (1 ml) was heated under reflux for 15 min. The solution was poured into aqueous sodium hydrogen carbonate. The product was recovered in chloroform and chromatographed on alumina. Elution with 15% ether–light petroleum gave 17β-acetoxyandrost-4-en-6-one (75 mg), which crystallized from light petroleum as prisms, m.p. 159—160°, $[\alpha]_D$ +20° (*c* 0·25) (lit.,[11] m.p. 159—164°, $[\alpha]_D$ +26°), $\nu_{max.}$ 1738, 1680, and 1620 cm^{-1}, τ 9·17 (3H, s), 9·01 (3H, s), 7·95 (3H, s), 5·36 (1H, t, *J* 7 Hz), and 3·59 (1H, t, *J* 3·5 Hz).

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