Optical Rotatory Dispersion and Circular Dichroism. Part LXXX.[1] Circular Dichroism of the Ethylidenecyclohexane system

By **David N. Kirk** * and **Richard J. Mullins**, Chemistry Department, Westfield College, London NW3 7ST

The isomeric (*Z*)- and (*E*)-3-ethylidene-5α-cholestanes have been synthesized, and their c.d. curves determined. The chiral unit of structure represented by a conformationally rigid ethylidenecyclohexane unit (XIVa or b) makes a major contribution to the c.d. of these and some other olefinic steroids.

No satisfactory general interpretation of the c.d. of chiral mono-olefins has yet been achieved, although a number of groups of workers have reported c.d. data covering a wide variety of olefinic compounds, and have suggested different empirical interpretations. The main developments during the last few years are reviewed

[1] Part LXXIX, D. R. Dunstan, W. P. Mose, and P. M. Scopes, *J.C.S. Perkin I*, 1973, 2749.

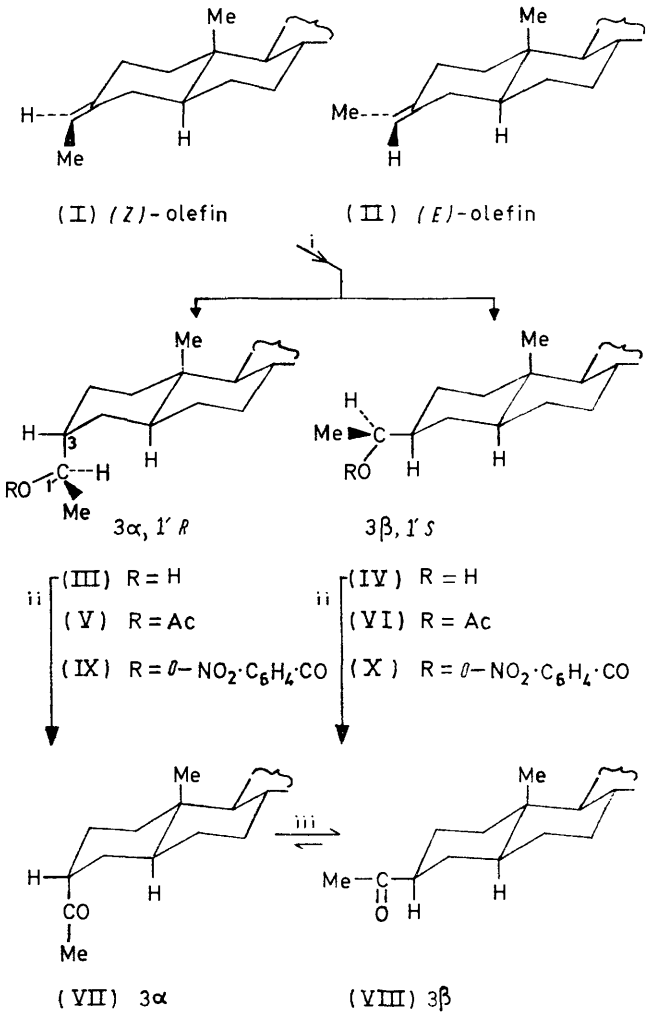
elsewhere.[2] Most recently, Mason has suggested,[3] from a study of the c.d. of pin-2-ene, that a low energy c.d. band which appears at various wavelengths, depending upon the conditions of measurement, is due to the Rydberg $\pi \longrightarrow 3s$ transition; its sign is opposite to that of the main (probably $\pi_x \longrightarrow \pi_x^*$) low energy c.d. band.

As part of a wider investigation into the structural features influencing the c.d. of olefins,[4] we have determined the c.d. curves for (*Z*)- and (*E*)-3-ethylidene-5α-cholestanes (I) and (II), prepared from 5α-cholestan-3-one by the Wittig method.

The reaction product appeared to be homogeneous when examined either by t.l.c. (on silica gel–$AgNO_3$)[5] or by g.l.c. (on SE30, QF1, or Carbowax columns), but was seen to comprise two components (overlapping peaks, ratio 3 : 2) when cholesteryl *p*-phenylbenzoate[6] was used as the stationary phase for g.l.c. Column chromatography either on alumina or on silica gel–$AgNO_3$ gave no evidence of any separation of isomers, but the (*Z*)-isomer, the lesser component, was slightly the more mobile on a column of activated charcoal. This permitted the isolation of a small sample in apparently pure condition. A sample of the (*E*)-isomer of constant m.p. and Δε was obtained by fractional crystallisation of the mixture of olefins.

The olefin configurations were established by the reaction sequence outlined in the Scheme. Hydroboration–oxidation of the pure (*Z*)-olefin (I), which was available in larger quantity despite being the minor product, afforded a mixture of the isomeric 1′-alcohols (III) and (IV). The alcohols could not readily be separated, but their ratio was estimated as *ca.* 2 : 1, respectively, by g.l.c. analysis as trimethylsilyl derivatives, which afforded overlapping peaks. The derived acetates (V) and (VI) were separated by preparative layer chromatography (p.l.c.), followed by crystallisation, and the alcohols (III) and (IV) were obtained from the acetates by treatment with lithium aluminium hydride. The configurations at C-3 in the two alcohols were determined by oxidising a sample of each to give 3α-acetyl- (VII) and 3β-acetyl-5α-cholestane (VIII), respectively. The 3α- (axial) isomer (VII) was readily epimerised with acid to give the 3β- (equatorial) acetyl derivative (VIII); equilibration of either product gave the same mixture, which contained *ca.* 90% of the stable 3β-isomer (g.l.c.).

The configurations of the side-chain alcohol systems (C-1′) were determined by two chiroptical methods, which gave concordant results. The c.d. curves of the acetates (Table) showed Cotton effects of opposite signs due to the acetate $n \longrightarrow \pi^*$ transition (214 nm). By analogy with the acetates of steroidal and other aliphatic secondary alcohols which we have studied,[7] the 1′-acetate giving a positive Cotton effect has the 1′*R*-configuration, and that giving a negative Cotton effect the 1′*S*-configuration. The same conclusion followed from the long-wavelength (330 nm) Cotton effects of the *o*-nitrobenzoates (IX) and (X) of the alcohols (III) and



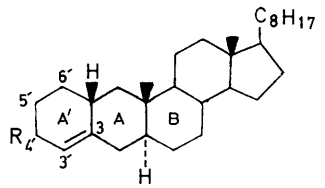
SCHEME Transformations which establish the configuration of (*Z*)-ethylidene-5α-cholestane (I)
Reagents: i, B_2H_6, then $NaOH–H_2O_2$; ii, Jones chromic acid–acetone; iii, H^+–acetone

(IV), respectively; in this case a negative sign can be correlated with the 1′*R*-configuration, and a positive sign with the 1′*S*-configuration.[8] The alcohols (III) and (IV) are therefore the 3α,1′*R*- and 3β,1′*S*-isomers, respectively.

Inspection of models of these alcohols shows that both must have arisen from the (*Z*)-ethylidene compound (I), for the hydroboration–oxidation steps are known to introduce H and OH groups stereospecifically in the *cis*

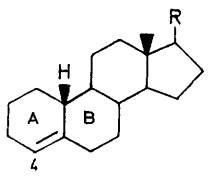
[2] 'Terpenoids and Steroids,' ed. K. H. Overton, Specialist Periodical Reports, The Chemical Society, 1971, vol. 1, p. 274; 1972, vol. 2, p. 232; 1973, vol. 3, p. 290.
[3] A. F. Drake and S. F. Mason, *J.C.S. Chem. Comm.*, 1973, 253.
[4] J. Hudec, D. N. Kirk, and R. J. Mullins, in preparation.
[5] D. R. Idler and L. M. Safe, *Steroids*, 1972, **19**, 315.
[6] D. N. Kirk and P. M. Shaw, *J. Chem. Soc.* (*C*), 1971, 3979.
[7] L. Bartlett, D. N. Kirk, and P. M. Scopes, in preparation.
[8] U. Nagai and H. Iga, *Tetrahedron*, 1970, **26**, 725.

sense.[9] The observed preponderance of the 3α,1′*R*-isomer (III) is reasonable, implying that diborane reacts preferentially at the β-face of the ethylidene group, which is the less hindered, owing to the sense in which ring A is folded.



(XI) R = H_2

(XII) R = O



(XIII)

The 3,3′-unsaturated pentacyclic steroid analogue (XI), which corresponds approximately in olefin geometry to (*E*)-3-ethylidene-5α-cholestane (II), but has two additional methylene groups completing ring A′, was obtained from the pentacyclic enone (XII)[10] by a well known reaction sequence [(i) reduction with borohydride to the allylic alcohol; (ii) acetylation; (iii) deoxygenation with lithium–ethylamine].[11]

C.d. Results and Discussion.—The Table gives c.d.

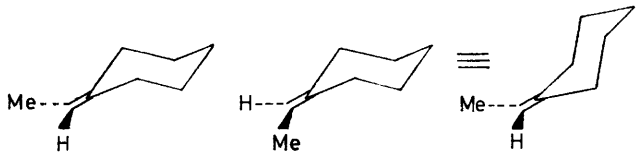
C.d. data for olefinic compounds and esters

	Lowest-energy band		Higher-energy band	
Olefins (in hexane)	Δε	$\lambda_{max.}$/nm	Δε	$\lambda_{max.}$/nm
(*Z*)-3-Ethylidene-5α-cholestane (I)	−6·0	212	+11·2	194
(*E*)-3-Ethylidene-5α-cholestane (II)	+8·6	208	−8·0 [a]	185 [a]
Pentacyclic steroidal olefin (XI)	+5·7	212	−5·0 [a]	185 [a]
Oestr-4-en-17β-ol (XIII)	+4·8	211	−7·6	190
Esters of 1′-alcohols (in methanol)				
	3α,1′*R*		3β,1′*S*	
	Δε	$\lambda_{max.}$/nm	Δε	$\lambda_{max.}$/nm
Acetates (V) and (VI)	+0·57	214	−0·37	214
o-Nitrobenzoates (IX) and (X)	−1·23	331	+0·52	330

[a] Value at lowest wavelength measured; not a maximum.

data for the (*Z*)- and (*E*)-ethylidene compounds, the pentacyclic olefin (XI), and a typical oestr-4-ene (XIII).

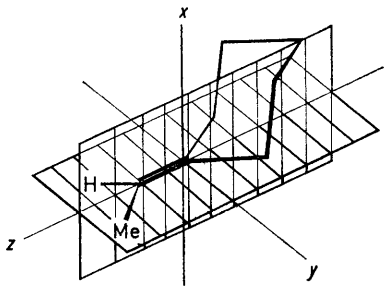
The most significant feature is the close resemblance between the profiles of the c.d. curves for the (*E*)-ethylidene compound (II), the pentacyclic olefin (XI), and the oestr-4-ene (XIII). In each of these compounds the olefinic bond is trisubstituted, and has a similar geometrical relationship to the adjoining saturated ring. The simplest structural feature common to all three compounds corresponds to an ethylidenecyclohexane fragment, locked in the conformation (XIVa). In contrast, the (*Z*)-ethylidene compound (I) contains the enantiomeric form (XIVb) of ethylidenecyclohexane, and gives a c.d. curve of a type enantiomeric to those for the other three compounds. We therefore attribute the major role in determining the



(XIVa) (XIVb)

sign and magnitude of the c.d. curve to the ethylidenecyclohexane component, which is held in a rigid conformation, either (XIVa) or (XIVb), by its mode of attachment to the rest of the molecule.

Ethylidenecyclohexane itself is an unusual molecule in that chirality arises only from the preference of the cyclohexane ring for one of two favourable chair conformations. The two forms (XIVa and b) of the monocyclic structure, though enantiomeric, would be interconverted too readily to offer any prospect of resolution. Any single substituent, however, and most of the possible patterns of disubstitution in the cyclohexane ring, would be expected to disturb the conformational equilibrium and lead to observable optical activity. The conformationally rigid ethylidenecyclohexane can be regarded either as having a chiral axis (collinear with the C=C bond),[12,13] or, preferably, as possessing two chiral planes (Figure).[13]



The three compounds (II), (XI), and (XIII), of type (XIVa), exhibit only relatively small *differences* between their Δε values. The slight variations probably reflect subtle changes in the geometry and electronic perturbation of the olefinic groups, consequent upon the differences in gross molecular structure. The third ring (ring B) in the pentacyclic olefin, for example, appears to make a very small positive contribution to the low-energy c.d. band (δΔε +0·9), in comparison with the data for oestr-4-ene. A similar comparison of Δε values for the (*E*)-ethylidene and pentacyclic compounds suggests that a relatively small negative increment (δΔε −2·9) is associated with the closure of ring A′ in the latter compound. It is not possible, at present, to place reliable interpretations on these additional effects,

[9] H. C. Brown, 'Hydroboration,' Benjamin, New York, 1962.
[10] J.-C. Bloch and G. Ourisson, *Bull. Soc. chim. France*, 1964, 3011.
[11] A. J. Birch and H. Smith, *Quart. Rev.*, 1958, **12**, 17.
[12] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 311.
[13] R. S. Cahn, Sir Christopher Ingold, and V. Prelog, *Angew. Chem. Internat. Edn.*, 1966, **5**, 385.

which are small in comparison with the magnitude of the c.d. contribution ($\Delta\varepsilon$ −6 or +8·6 at the lowest energy band) evidently associated with the rigid ethylidenecyclohexane system. Similar considerations apply to the second c.d. band, of opposite sign.

A $\Delta^{1(9)}$-octalin unit, corresponding to rings A and B of oestr-4-ene (XIII), or rings A′ and A of the pentacyclic olefin (XI), is a feature common to many steroidal and related olefins [*e.g.* steroidal 4-, 5-, 7-, and 9(11)-enes]. Each of these classes of trisubstituted olefinic compounds (except those containing an angular methyl group in the allylic position [4,14]), exhibits a low-energy c.d. band of the sign expected from its conformational and steric similarity to one or other of the ethylidenecyclohexanes (XIVa) and (XIVb). Moreover the magnitudes of $\Delta\varepsilon$ are such as to suggest that additional structural features make only relatively modest contributions, if any. Typical $\Delta\varepsilon$ values, apart from those cited in the Table, are: [4,14] oestr-5-enes, $\Delta\varepsilon$ −5 to −6; steroidal 7-enes, $\Delta\varepsilon$ −7 and −9; 9(11)-enes, $\Delta\varepsilon$ +8 to +10. (The 10β-methyl group in ordinary steroids reverses the signs of $\Delta\varepsilon$ for 4-enes and 5-enes,[4,14] but this is a separate effect, not directly related to the present findings.)

The observation of large Cotton effects for the rigid ethylidenecyclohexane fragment can be rationalised tentatively on the basis of recent findings reported by Yogev and his co-workers.[15] These authors showed that the lowest-energy transition for trisubstituted ethylene derivatives like cholest-4-ene and -5-ene, is polarised at an angle which deviates appreciably from the C=C axis of the olefinic bond.

In our ethylidene compounds, the olefinic methyl substituent lies in the nodal plane of the π-orbitals, and should itself make no contribution to the dichroism. By disturbing the symmetry of the olefinic bond and its surroundings about the *xz* plane (Figure), however, the methyl group would deflect the direction of polarisation of the electronic transition away from the C=C bond axis; this would result in dissymmetry of the cyclohexane ring with respect to the direction of polarisation. Perturbations of the transition by the ' left-hand ' and ' right-hand ' halves of the cyclohexane ring would therefore be unequal, leading to dichroic absorption. The nature of the transition and its perturbation are insufficiently understood to permit prediction of the sign of the Cotton effect.

EXPERIMENTAL

I.r. spectra were taken for KBr discs, n.m.r. spectra for solutions in $CDCl_3$ at 60 MHz, and $[\alpha]_D$ values for 0·5—1% solutions in $CHCl_3$ at room temperature. Charcoal for chromatography was May and Baker, ' Decolourising '. Preparative layer chromatography was carried out on Merck Kieselgel $PF_{254+366}$. Light petroleum refers to the fraction of b.p. 60—80°.

3-Ethylidene-5α-cholestanes.—(*a*) Sodium hydride (50% dispersion in oil; 3 g) was washed with light petroleum, then dissolved by stirring under N_2 with anhydrous dimethyl sulphoxide (25 ml) at 70° for 1 h. The solution was cooled to room temperature, and treated with dried ethyltriphenylphosphonium iodide (14 g) in dimethyl sulphoxide (50 ml). 5α-Cholestan-3-one (0·5 g) in dry benzene (5 ml) was added to the red phosphorane solution, and the mixture was kept at 50° for 3 h. Addition of water and extraction with ether gave a crude product which was passed through a short column of silica gel in hexane solution to remove polar by-products. Evaporation of the eluate left the mixed 3-ethylidene-5α-cholestanes (0·3 g), m.p. 35—45°.

(*b*) A similar reaction was carried out, but with use of anhydrous potassium t-butoxide (4 g) instead of sodium hydride. The result was essentially the same as under (*a*).

G.l.c. analysis (cholesteryl *p*-phenylbenzoate column; [6] 200°) of the mixed olefins gave two overlapping peaks with areas indicating *ca.* 60% of the (*E*)-isomer (t_R 2·52) and *ca.* 40% of the (*Z*)-isomer (t_R 2·36) (retention times, t_R, relative to 5α-cholestane).

Slow crystallisation of the mixture from evaporating acetone at 0° gave a mixture of hard granular crystals, m.p. 45—55°, and long blades, m.p. 67—70°. The latter were separated by hand and recrystallised eight times from acetone at 0°, to give (E)-3-*ethylidene-5α-cholestane* (II) as blades, m.p. 70·5—71·5°, $\nu_{max.}$ 1678 and 817 cm^{-1}, $[\alpha]_D$ +4°; for c.d. see Table; τ 9·37 (s, 13-Me), 9·20 and 9·12 (cholestane side chain), 9·17 (s, 10-Me), 8·47 (d, *J* 7·5 Hz, CH_3–CH=), and 4·93 (d, *J* 6·5 Hz, MeC*H*=) (Found: C, 87·5; H, 12·5. $C_{29}H_{50}$ requires C, 87·4; H, 12·6%). The granular crystals were a mixture of (*Z*)- and (*E*)-isomers (g.l.c.).

The mixture of olefins (1 g), in hexane, was chromatographed on a column of charcoal (25 g). The eluate (hexane) was collected in 125 ml portions. The first ten portions gave no steroid, but the eleventh contained (Z)-3-*ethylidene-5α-cholestane* (I) (32 mg), m.p. 75—81° (from acetone), $[\alpha]_D$ +35°; i.r. and n.m.r. spectra indistinguishable from those of the (*E*)-isomer.

Hydroboration of (Z)-3-*Ethylidene-5α-cholestane* (I).—(*Z*)-3-Ethylidene-5α-cholestane (60 mg) in bis-(2-methoxyethyl) ether (2 ml) was added with stirring at −5° to a suspension of sodium borohydride (100 mg) in the same solvent (1 ml), under nitrogen. Boron trifluoride–ether complex (0·38 ml) in the same solvent (3 ml) was then added during 30 min, and the mixture was left overnight at −5°. It was then treated with 30% sodium hydroxide (2·5 ml) and 30% hydrogen peroxide (2·5 ml) and stirred for 1 h. Extraction with ether gave the mixed 3-(1′-hydroxymethyl)-5α-cholestanes [(III) + (IV)].

The mixed alcohols were acetylated with acetic anhydride–pyridine. The acetates crystallised from ethanol as a mixture, m.p. 76—81°; $\Delta\varepsilon$ −0·007 (*ca.* 220 nm; broad minimum) (Found: C, 81·0; H, 12·0. $C_{31}H_{54}O_2$ requires C, 81·2; H, 11·9%).

A separation, probably imperfect, was achieved by preparative t.l.c. The main components of the fractions were (i) the *acetate* (VI) on the 3β,1′*S*-alcohol (IV) (10 mg; the more polar component), m.p. 90—92° (from methanol), $[\alpha]_D$ +17°; $\nu_{max.}$ 1740 and 1242 cm^{-1}; and (ii) the *acetate* (V) of the 3α,1′*R*-alcohol (III) (16 mg; the less polar component), m.p. 87—88° (from methanol), $[\alpha]_D$ −7°; $\nu_{max.}$ 1730 and 1248 cm^{-1}. Since each acetate was probably contaminated with a little of the other isomer, only the *signs* of chiroptical data ($[\alpha]_D$ and $\Delta\varepsilon$; see Table) are regarded as significant.

[14] A. I. Scott and A. D. Wrixon, *Tetrahedron*, 1970, **26**, 3695.
[15] A. Yogev, J. Sagiv, and Y. Mazur, *J. Amer. Chem. Soc.*, 1972, **94**, 5123; *J.C.S. Chem. Comm.*, 1972, 411.

Each acetate (*ca.* 10 mg) was treated separately with lithium aluminium hydride (0·2 g) in ether under reflux for 1 h, to give the corresponding alcohol.

o-*Nitrobenzoates of the* 1′-*Alcohols*.—Samples of the alcohols were converted, without purification, into their *o*-nitrobenzoates in the usual way (*o*-nitrobenzoyl chloride–pyridine). The 3α,1′R-o-*nitrobenzoate* had m.p. 185—190°, $\nu_{max.}$ 1721, 1522, and 1300 cm^{-1}; M^+ 565 (required 565); the 3β,1′S-o-*nitrobenzoate* had $\nu_{max.}$ 1721, 1522, and 1300 cm^{-1}; M^+ 565.

Oxidation of the 3α,1′R- *and* 3β,1′S-*Alcohols* (III) *and* (IV).—Each 1′-alcohol (*ca.* 0·5 mg) in acetone was oxidised with Jones reagent to give the corresponding 3-acetyl compound. G.l.c. of these ketones (QF-1; 230°) showed each isomer to be contaminated with only a trace of the other. Retention times were in the ratio 6 : 5 (3β : 3α). Equilibration of either ketone with dilute hydrochloric acid in refluxing acetone for 30 min gave a mixture containing *ca.* 90% of the 3β-isomer.

Larger quantities of the 3-acetyl compounds were prepared from the mixed 3-ethylidene-5α-cholestanes by hydroboration-oxidation essentially as already described, followed by Jones oxidation (8N-chromic acid) of the mixture of 1′-alcohols in acetone. The resulting mixture of 3α- and 3β-acetyl compounds (ratio *ca.* 3 : 1) was separated by preparative t.l.c., followed by crystallisation of each isomer from aqueous acetone.

3β-*Acetyl-5α-cholestane* formed leaflets, m.p. 107—109°, $[\alpha]_D$ +33°, c.d. (hexane) Δε +0·14sh (312 nm), +0·30 (302), +0·38m (294), +0·36sh (285), +0·21m (193), and −0·7! (185); $\nu_{max.}$ 1715 and 1352 cm^{-1} (COMe); τ 9·37 (13-Me), 9·23 (10-Me), 9·18 and 9·12 (side chain), 7·99 (Ac), and 7·76 (m, *W ca.* 25 Hz, 3α-H) (Found: C, 84·3; H, 11·9. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%).

3α-*Acetyl-5α-cholestane* formed leaflets, m.p. 94—95°, $[\alpha]_D$ +32°, c.d. (hexane) Δε −0·05sh (316 nm), −0·10 (304), −0·12m (297), and +1·23! (185); $\nu_{max.}$ 1714 and 1350 cm^{-1} (COMe); τ 9·37 (13-Me), 9·23 (10-Me), 9·17 and 9·11 (side chain), 7·95 (Ac), and 7·55 (m, *W* 13 Hz, 3β-H) (Found: C, 83·7; H, 12·0. $C_{29}H_{50}O$ requires C, 84·0; H, 12·15%).

1′β,4′,5′,6′-*Tetrahydrobenzo*[2,3]-5α-*cholestane* (XI).—5′,6′-Dihydrobenzo[2,3]-5α-cholestan-4′(2β*H*)-one (XII) (100 mg) in ethanol (5 ml) was heated under reflux for 4 h with sodium borohydride (25 mg) and sodium hydroxide (25 mg) in water (0·25 ml). After extraction with ether, the crude product ($\nu_{max.}$ 3310 and 1660 cm^{-1}; no carbonyl absorption) was acetylated (acetic anhydride–pyridine; 30 min on a steam-bath), and the crude acetates (*ca.* 100 mg) were treated at 0° in ethylamine (10 ml) and tetrahydrofuran (5 ml) with small pieces of lithium, with stirring until the blue-black colour of unchanged lithium persisted (6 h). Ethanol was added carefully to discharge the colour, then the products were isolated with ether (oil; 72 mg).

The whole product, in light petroleum (b.p. 60—80°), was chromatographed on alumina (2 g). Elution with light petroleum gave the required *olefin* (38 mg), m.p. 115·5—116·5° (from acetone), $\nu_{max.}$ 3040, 1669, and 802 cm^{-1}, τ 4·82 (*J* 8 Hz, 3′-H), 9·13 and 9·20 (side chain Me groups), 9·18 (10-Me), and 9·37 (13-Me) (Found: C, 87·9; H, 12·4. $C_{31}H_{52}$ requires C, 87·7; H, 12·3%).

We thank the S.R.C. for a research grant (to Professor W. Klyne).

[3/1566 *Received*, 25*th July*, 1973]