The Chemistry of Conjugated Polyenoic Acids in Sulphuric Acid: A Homologous Series of Retinoic Acid (Vitamin A Acid)

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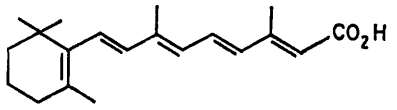
Homologues of retinoic acid are converted by acid-catalysed cyclization into hydrindene compounds bearing a non-conjugated (αβ-saturated) enoic acid (or lactone) side-chain. Explanations are given for the colour reaction including structural elucidation of the quenched products and their mechanism of formation.

A HIGHLY selective quantification method of retinoic acid (vitamin A acid) (1), currently one of the most interesting members of the retinoid family,[1-3] was proposed originally by Kawasaki *et al.* They estimated an absorbance at 454 nm in a 74% sulphuric acid solution,[4] and used this method for the assay of (1) in animal tissues.[5] They also examined the chemical structure of a quenched product and proposed that the 6-hydroxy-5,6-dihydro-derivative of (1) might be the single product in this reaction.[6] Since no other chemical approaches



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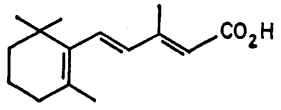

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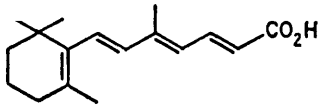


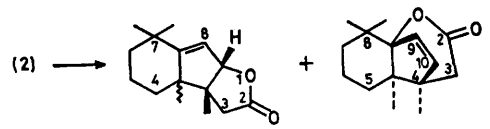
(3)

have been attempted on this colour reaction, it seemed desirable that the mechanism of the reaction should be better understood, so that the method may become a highly selective method of analysis. Furthermore, such an investigation is expected to afford a basic knowledge of the chemistry of conjugated polyenoic acids, little information currently being available on their behaviour towards strong acids. We present here a full account of a colour reaction of (1) in sulphuric acid and describe a survey on the chemistry of its homologues, including the trienoic acid (2) and the tetraenoic acid (3), towards the same strong acid.

RESULTS AND DISCUSSION

Unlike the case for steroids,[7-9] the poor solubility of (1) in aqueous sulphuric acid and the diffusion of the olefinic proton signals into a general background fail to give direct and unequivocal ^1H n.m.r. spectral evidence for evaluating the key intermediate in sulphuric acid even when the spectra are run at low temperatures or when Fourier-transform methods are used. Therefore, we decided to examine first the properties and structures of the quenched products derived from the protonated, conjugated polyenoic acid. Further, since formation of a complex mixture of at least four or five quenched products was suggested in a preliminary test on (1), we started the investigation from the lower member of the homologous series [(2), then (3), successively], hoping that the information so accumulated would facilitate the study on (1).

From the trienoic C_{15}-acid (2) were obtained two major



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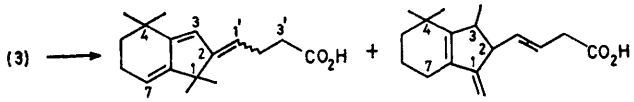
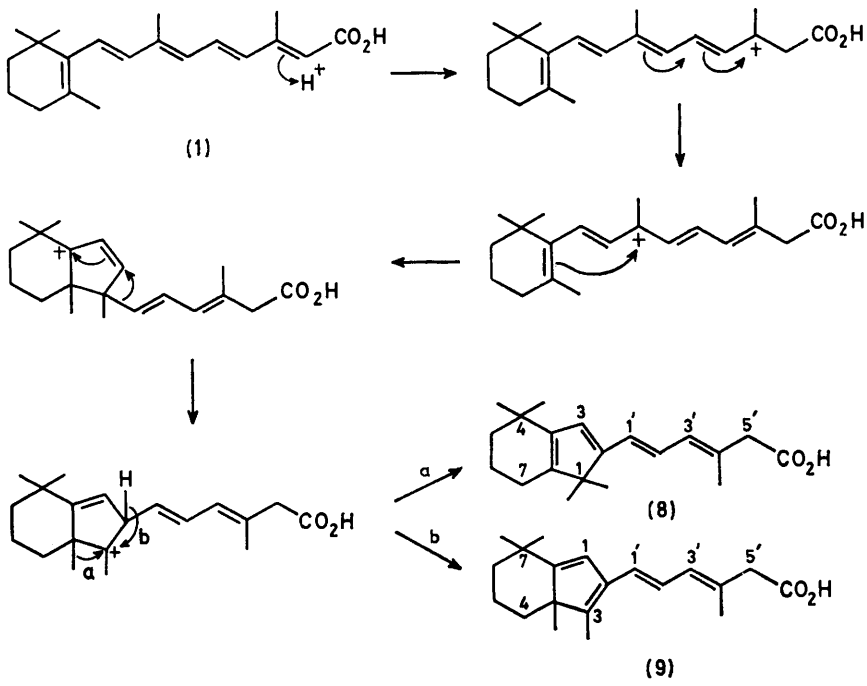


(6) (7)

quenched products [(4) and (5)], and the interconversion between these was also examined.[10] Their structures, determined on the basis of the spectral data, suggest that the acid (2) undergoes an acid-catalysed double-cyclization reaction in sulphuric acid, *i.e.* initial formation of the hydrindene ring, followed by lactonization *via* intermediate cations, to afford the hydrindene *non-conjugated* (*αβ-saturated*) γ- and δ-lactones almost exclusively. Since there had appeared only a few reports on the chemical behaviour of conjugated polyenoic acids toward sulphuric acid, and *conjugated* (*αβ-unsaturated*) γ- and δ-lactones were obtained in the reported conjugated dienoic acid system,[11,12] we believe that our finding offers a new insight into the chemistry of conjugated polyenoic acids.

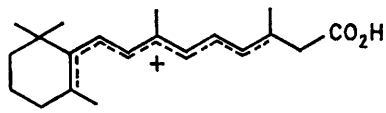
In the case of the higher member, the tetraenoic C_{17}-acid (3), quenched products were isolated by methylation of a reaction mixture, followed by preparative g.l.c.[13]

Two major products, the methyl esters of (6) and (7), were obtained pure, and their structures were determined on the basis of the spectral data. From the results for (3) together with those for (2), we have developed a reaction scheme involving the intermediacy of the cyclized, hydrindene cation (acid-catalysed cyclization), followed by competitive and successive rearrangements to afford the product (6) or (7). This competition seems to depend on the concentration of sulphuric acid used. Thus, it can be seen that the acid (3) affords the cyclized, and subsequently rearranged, *non-conjugated* (αβ-*saturated*) enoic acid isomers almost quantitatively, *via* the same type of key intermediate as in the case of (2) above. This information is useful for studying the title reaction of (1).

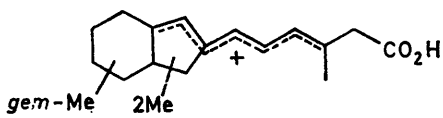


SCHEME

At an early stage in our study of (1), serious difficulties were encountered in complete separation of the methylated quenched products by conventional methods. Later, h.p.l.c. on a Zorbax SIL column finally afforded the predominant pure methylated quenched products. On the basis of the spectral data and by analogy with the results for (2) and (3) described above, the structures of some intact quenched products were determined as (8) (linear polyene type) and (9) (cross-conjugated polyene type). Furthermore, the formation of these hydrindene compounds bearing a *non-conjugated* (αβ-*saturated*) enoic acid side-chain can be accounted for most reasonably through the mechanism shown in the Scheme.[14] The striking red colour of (1) in 74% sulphuric acid can be regenerated from the methyl esters of (8) or (9) in the same concentrations of sulphuric acid. This acid-catalysed colouration is clearly due to an ionic species, for the regenerated red colour is also quite insoluble in as the main coloured species in 85 or 90% sulphuric acid, while certain cyclized trienylic cations could be expected in 74 or 80% sulphuric acid. Judging from all the experimental results, it seems most reasonable to propose



(10)



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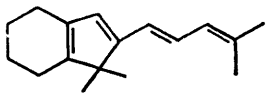

(12)

the formulae (10) and (11) as the respective coloured species. We have recently communicated [17] a direct proof of the chromophoric structure in the title reaction of (1) by synthesizing 4,5,6,7-tetrahydro-1,1-dimethyl-2-(4-methylpenta-1,3-dienyl)indene (12). Details of this will be published elsewhere.

In summary, we have clarified the properties and structures of the quenched products derived from a series of conjugated polyenoic acids (1)—(3) and have proposed their mechanisms of formation. It can be concluded that all the quenched products produced in the present reactions are hydrindene compounds bearing a *non-conjugated* (*αβ-saturated*) enoic acid moiety, and the formation of moderately stable polyenyl cyclized (hydrindene) cations now appears to be a general concept for the homologous series of (1) in sulphuric acid.

EXPERIMENTAL

The main u.v. absorption maxima are italicised. Mass spectra were obtained at 75 eV on a JEOL JMS-01SG double-focus high resolution spectrometer using electron-impact ionization (sample temp. *ca.* 50—100 °C, chamber temp. 110—180 °C). ^{1}H and ^{13}C N.m.r. spectra were recorded on a NEVA-NV 21 spectrometer at 90 and 22.6 MHz, respectively, with tetramethylsilane as internal standard. Unless otherwise stated, column chromatography was carried out on Merck alumina. Analytical and preparative g.l.c. were performed on a Shimadzu GC-4AP gas chromatograph equipped with a hydrogen flame-ionization detector or on a Varian Aerograph model 90–75 instrument, respectively (column, 1.5% OV-17). H.p.l.c. was conducted on a Shimadzu–DuPont 830 liquid chromatograph using a Zorbax SIL (0.79 × 25 cm) (silica) normal-phase column with 3% v/v ether–hexane as eluant under 35 kg cm^{-2} pressure, the component being detected by a UV-202 spectrometer at 275 or at 333 nm.

All-*trans*-retinoic acid (the pentaenoic C_{20}-acid) (1),[18,19] all-*trans*-β-ionylideneacetic acid (the trienoic C_{15}-acid) (2),[20,21] and all-*trans*-β-ionylidenecrotonic acid (the tetraenoic C_{17}-acid) (3) [21,22] were prepared by the reported methods. Satisfactory spectroscopic data (u.v., i.r., n.m.r., and mass spectra) were recorded for these compounds.

Reaction of the Polyenoic Acids with Sulphuric Acid.—(a) *Colour reaction.* The C_{20}-acid (1) showed $\lambda_{max.}$ 454 nm (*E* 2 160) [5] in 74% H_2SO_4, 550 and 452 nm (*E* ratio 1 : 3.6) in 80% H_2SO_4, 544 and 450 nm (1.4 : 1) in 85% H_2SO_4, and 540 and 445 nm (3 : 1) in 90% H_2SO_4; the C_{15}-acid (2) showed $\lambda_{max.}$ 272 nm in 74% H_2SO_4, and 305 nm in 85% H_2SO_4; the H_{17}-acid (3) showed $\lambda_{max.}$ 369 nm in 74% H_2SO_4, 364 nm in 85% H_2SO_4, and 360 and 462 nm (shift to 364 nm within a few min) in 90% H_2SO_4.

(b) *Isolation of the quenched products.* The quenched products (4) and (5) were obtained from the C_{15}-acid reaction (formation ratio : 6 : 1 in 74%, 3 : 8 in 80%, and 1 : 15 in 85% H_2SO_4), while (6) and (7) were obtained from the C_{17}-acid reaction (formation ratio : 7 : 2 in 80%, 2 : 1 in 85%, and 1 : 4 in 90% H_2SO_4), and (8) and (9) were obtained from the C_{20}-acid reaction (formation ratio: 1.8 : 1 in 74% H_2SO_4). The typical procedure, as applied for the C_{20}-acid (1), is as follows. To a solution of the acid (1) (110 mg in 30 ml) in chloroform was added 74% sulphuric acid (*d* 1.6574; 700 ml) in three portions. The mixture was shaken for a few min and then left for 1 h at room temperature. The acidic aqueous layer ($\lambda_{max.}$ 454 nm) was poured onto ice–water (*ca.* 2 l) and the mixture was extracted with ether (×3). The ether layer was washed, dried, and evaporated. The residue [$\lambda_{max.}$ (hexane) 349, *333*, and 318 nm; $\nu_{max.}$ ($CHCl_3$) 1 714 cm^{-1}] was methylated conventionally with diazomethane in absolute ether. After the reaction was complete the excess of the reagent was decomposed with acetic acid, and the ether layer was washed with aqueous $NaHCO_3$ and water, dried, and evaporated [*ca.* 90 mg of the residue, $\lambda_{max.}$ (ether) 349, *332*, and 316 nm; $\nu_{max.}$ ($CHCl_3$) 1 743 cm^{-1}]. Since complete separation of the methylated quenched products by preparative g.l.c. was not accomplished, the reaction mixture from one run was first divided into several fractions through a column of alumina (*ca.* 70 g; containing 5% H_2O) using ether–hexane (1 : 20 v/v) as eluant. Each fraction was then analysed by h.p.l.c. and the major products D and E were finally obtained by repeated h.p.l.c. of the appropriate fraction. Product A, R_t 16.7 min, showed $\lambda_{max.}$ (EtOH) 347, *331*, 317, and 236 nm; product B had R_t 17.3 min; product C, R_t 18.0, $\lambda_{max.}$ *307*, *257*, and 250 nm; product D, R_t 20.3 min, $\lambda_{max.}$ 348, *333*, 318, and 236 nm; and product E, R_t 22.3 min, $\lambda_{max.}$ *307*, *257*, and 250 nm. From a C_{15}-acid reaction mixture, the quenched products were easily separated by preparative g.l.c. (0.25 in × 5 ft column, injector 210 °C, column 190 °C, detector 250 °C, He 60 ml min^{-1}). Although an effective separation of quenched products from a C_{17}-acid reaction mixture was rather difficult, the methylated quenched products were finally separated by successive column chromatography and preparative g.l.c. (3/8 in × 10 ft column, injector 215 °C, column 170 °C, detector 235 °C, He 150 ml min^{-1}).

The Methylated Quenched Product D [(8)-*Methyl Ester*] [4,5,6,7-*Tetrahydro*-2-(5-*methoxycarbonyl*-4-*methylpenta*-1,3-*dienyl*)-1,1,4,4-*tetramethyl indene*].—The *methyl ester* was obtained as an oil; $\lambda_{max.}$ (EtOH) 348, *333*, 318 (sh), and 236 nm (*cf.* the standard $\lambda_{max.}$ for conjugated aliphatic pentaene and tetraene chromophores of 348 and 317 nm, respectively) $\lambda_{max.}$ (74% H_2SO_4) 454 nm; $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 150 (saturated aliphatic ester), 1 622 and 1 592 (C=C), and 958 cm^{-1} (*trans*-CH=CH); δ($CDCl_3$ 1.08 (12 H, s, 1-, 1-, 4-, and 4-Me), 1.92 (3 H, s, 4′-Me), 2.13 (2 H, t, *J* 5.5 Hz, 7-H_2), 3.13 [2 H, s, 5′-H_2 (α to CO_2Me)], 3.72 (3 H, s, CO_2Me), 6.05 (1 H, d of m, *J* 10.5 Hz, 3′-H), 6.31 (1 H, d, *J* 15.5 Hz, 1′-H), 6.44 (1 H, s, 3-H), and 6.61 (1 H, dd, *J* 10.5 and 15.5 Hz, 2′-H) [Eu(dpm)$_3$ paramagnetic shift in ^{1}H n.m.r., relative degree, 5′-H_2 ≃ OMe ≫ 4′-Me ≃ 3′-H] (Found: M^+, 314.226. $C_{21}H_{30}O_2$ requires *M*, 314.225); *m/e* 314 (M^+, 100%), 255 (M − CO_2Me, 15), 241 (M − CH_2CO_2Me, 5), and 175 (M − side-chain, 5). The free acid (8) had R_F (Woelm polyamide, $CHCl_3$) *ca.* 0.4 (blue fluorescence); $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (saturated aliphatic acid).

The Methylated Quenched Product E [(9)-*Methyl Ester*] [4,5,6,7-*Tetrahydro*-2-(5-*methoxycarbonyl*-4-*methylpenta*-1,3-*dienyl*)-3,3a,7,7-*tetramethyl*-3a*H*-*indene*].—The *methyl ester* was obtained as an oil; $\lambda_{max.}$ (EtOH) *307*, *257*, and 250 nm [*cf.* $\lambda_{max.}$ 259 nm for 4,5,6,7-tetrahydro-3,3a,7,7-tetramethyl-3a*H*-indene [23]); $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 146 (saturated aliphatic ester), 1 640, 1 585, and 953 cm^{-1}; δ($CDCl_3$) 1.12, 1.19, and 1.25 (9 H, each s, 3a-, 7-, and 7-Me), 1.83 (3 H, s, 3-Me), 1.91 (3 H, s, 4′-Me), 3.11 [2 H, s, 5′-H_2 (α to CO_2Me)], 3.69 (3 H, s, CO_2Me), 6.10 (1 H, d, *J* 10 Hz, 3′-H), 6.20 (1 H, s, 1-H), 6.44 (1 H, d, *J* 15 Hz, 1′-H), and 6.66 (1 H, dd, *J* 10 and 15 Hz, 2′-H) [Eu(dpm)$_3$ para-

magnetic shift in ^1H n.m.r., relative degree, 5′-H_2 ≃ OMe ≫ 4′-Me ≃ 3′-H]; (Found: M^+, 314.225. $C_{21}H_{30}O_2$ requires M, 314.225), m/e 314 (M^+, 100%), 255 (M − CO_2Me, 16), 241 (M − CH_2CO_2Me, 5.5), and 175 (M − side-chain, 4). The free acid (9b) showed $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (saturated aliphatic acid).

The Quenched Product (4a) (3,3a,3b,4,5,6,7,8a-*Octahydro*-3a,3b,7,7-*tetramethylindeno*[2,1-b]*furan*-2-*one*).—The *γ-lactone* (4) had m.p. 62—63 °C; g.l.c. [injector 180 °C, column (0.4 × 100 cm) 150 °C, detector 220 °C, N_2 60 ml min^{-1}] R_t 8.1 min; t.l.c. (Woelm polyamide, $CHCl_3$) R_F *ca.* 0.6; $\lambda_{max.}$ (EtOH) end-absorption; $\nu_{max.}$ (CCl_4) 1 780 (saturated *γ*-lactone), 1 626 (C=C), 1 168, and 998 cm^{-1}; δ(CCl_4) 1.14 (12 H, s, 4 × Me), 1.83 and 2.46 (2 H, ABq, J 16.0 Hz, 3-H_2; long-range coupling with 3a-Me), 4.87 (1 H, d, J 1.2 Hz, 8a-H), and 5.38 (1 H, d, J 1.2 Hz, 8-H) (no indication of a vinyl methyl group) (Found: M^+, 234.161. $C_{15}H_{22}O_2$ requires M, 234.162), m/e 234 (M^+), 219 (M − Me), and 178 (M − 56, 100%).

The Quenched Product (5) (3,4,4a,5,6,7,8,8a-*Octahydro*-4,4a,8,8-*tetramethyl*-4,8a-*ethenochromen*-2-*one*).—The δ-*lactone* (5) had m.p. 190 °C (subl.); g.l.c. and t.l.c. [conditions as for (4)] R_t 11.4 min, R_F *ca.* 0.5; $\lambda_{max.}$ (EtOH) end-absorption; $\nu_{max.}$ (CCl_4) 1 728 (saturated δ-lactone), 1 256, and 1 080 cm^{-1}; δ(CCl_4) 0.94, 1.00, 1.13 and 1.34 (12 H, each s, 4 × Me), 2.01 and 2.43 (2 H, ABq, J 18.0 Hz, 3-H), and 5.06 and 5.57 (2 H, ABq, J 9.8 Hz, 9- and 10-H), (no indication of a vinyl methyl group); m/e 234 (M^+), 219 (M − Me), and 178 (M − 56, 100%) (Found: C, 76.75; H, 9.7%; M^+, 234.162. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46% M, 234.162).

The Methylated Quenched Product (6)-*Methyl Ester* [1,2,5,6-*Tetrahydro*-2-(3-*methoxycarbonylpropylidene*)-1,1,4,4-*tetramethyl*-4H-*indene*].—The *methyl ester* had m.p. *ca.* 30 °C; g.l.c. [injector 170 °C, column (0.4 × 100 cm) 140 °C, detector 200 °C, N_2 60 ml min^{-1}] R_t 10.5 min; $\lambda_{max.}$ (ether) 295, *284*, and 273 nm, $\lambda_{max.}$ (EtOH) 284 nm, $\lambda_{max.}$ (80% H_2SO_4) 369 nm; $\nu_{max.}$ (CS_2) 1 739 and 1 165 (saturated aliphatic ester), 1 640 and 1 625 (C=C), and 812 (trisubstituted alkene) (no indication of a *trans*-CH=CH group); δ(CCl_4) 0.99 and 1.11 (12 H, each s, 4 × Me), 2.10—2.65 (6 H, m, 6-, 2′-, and 3′-H_2), 3.59 (3 H, s, CO_2Me), 4.90 (1 H, t, J 3.5 Hz, 1′-H), 5.37 (1 H, d of t, J 1.7 and 4.2 Hz, 7-H), and 6.22br (1 H, s, 3-H) (no indication of a vinyl methyl group) [Eu(dpm)$_3$ paramagnetic shift in ^1H n.m.r., relative degree, 3′-H and CO_2Me > 2′-H > 1′-H > 3-H > 7-H] (Found: M^+, 274.195. $C_{18}H_{26}O_2$ requires M, 274.193); m/e 274.195 (M^+, 100%), 259.170 ($C_{17}H_{23}O_2$, M − Me, 22), 201.161 ($C_{15}H_{21}$, M − CH_2CO_2Me, 72), and 185.133 ($C_{14}H_{17}$, M − 89, 12).

The Methylated Quenched Product (7)-*Methyl Ester* [2,3,4,5,6,7-*Hexahydro*-2-(3-*methoxycarbonylprop*-1-*enyl*)-1-*methylene*-3,4,4-*trimethylindene*].—The *methyl ester* was obtained as an oil; g.l.c. [conditions as for (6a)-methyl ester] R_t 12.5 min; $\lambda_{max.}$ (ether) 244 nm, $\lambda_{max.}$ (80% H_2SO_4) 361 nm; $\nu_{max.}$ (film) 1 744 and 1 165 (saturated aliphatic ester), 1 628 (C=C), 974 (*trans*- CH=CH), and 860 cm^{-1} (>C=CH_2); δ(CCl_4) 1.01 (6 H, s, *gem*-Me), 1.11 (3 H, d, J 8.5 Hz, 3-Me), 2.0—2.35 (4 H, m, 2- and 3-H and 7-H_2), 2.95 (2 H, m, 3′-H_2), 3.60 (3 H, s, CO_2Me), 4.43 and 4.60 (2 H, each s, 1-*exo*-CH_2), and 5.48 (2 H, m, 1′- and 2′-H) (no indication of a vinyl methyl group) [Eu(dpm)$_3$ paramagnetic shift in ^1H n.m.r., relative degree, 3′-H and CO_2Me > 2′-H > 1′-H] (Found: M^+, 274.193. $C_{18}H_{26}O_2$ requires M, 274.193), m/e 274.193 (M^+, 59%) 259.168 ($C_{17}H_{23}O_2$, M − Me, 100), 201.162 ($C_{15}H_{21}$, M − CH_2CO_2Me, 25), and 185.133 ($C_{14}H_{17}$, 29).

4,5,6,7-*Tetrahydro*-1,1-*dimethyl*-2-(4-*methylpenta*-1,3-*dienyl*)*indene* (12).—Isopropyltriphenylphosphonium bromide [24] (385 mg) and n-butyl-lithium (1 ml of 15% solution in hexane) in dry ether (3 ml) were stirred for *ca.* 10 h at room temperature in a pressure bottle under argon. To this alkylidene solution was added the trienal (4,5,6,7-tetrahydro-1,1-dimethyl-2-formylvinylindene, prepared from the corresponding 3-hydrindanone [17]) (50 mg) in a dry ether (1 ml) under argon. The bottle was sealed and stirred at room temperature for 1 h. The mixture was then filtered and the solid material was extracted with ether several times. The ether extracts were evaporated to give a gum which was purified by preparative t.l.c. (10% v/v ether–hexane, 0.5 mm silica gel) to yield the *tetraene* (12) (40 mg) as an unstable yellow oil; $\lambda_{max.}$ (EtOH) 347 (ε 18 100), 331 (21 300), 318 (sh), and 237 nm; δ($CDCl_3$) 1.09 (6 H, s, 1-*gem* Me), 1.81 (6 H, s, 5′-H_3 and 4′-Me), 5.92 (1 H, d, J 10 Hz, 3′-H), 6.19 (1 H, s, 3-H), 6.22 (1 H, d, J 16 Hz, 1′-H), and 6.60 (1 H, dd, J 10 and 16 Hz, 2′-H); (Found: M^+, 228.190. $C_{17}H_{24}$ requires M, 228.188).

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