Tobacco Smoke Chemistry. 1. A Chemical and Mass Spectrometric Study of Tobacco Smoke Alkyl 2-Hydroxy-2-cyclopentenones

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Arnarp, J., Enzell, C., Petersson, K. and Pettersson, T., 1986. Tobacco Smoke Chemistry. 1. A Chemical and Mass Spectrometric Study of Tobacco Smoke Alkyl 2-Hydroxy-2-cyclopentenones. – Acta Chem. Scand. B 40: 839–854.

A series of alkyl 2-hydroxy-2-cyclopentenones, which comprise biologically and organoleptically active compounds, have been synthesized and subjected to high resolution mass spectrometric studies to clarify structurally significant fragmentation pathways. On the basis of these results, 26 alkyl 2-hydroxy-2-cyclopentenones were identified in the weakly acidic fraction of smoke condensate from American blend type cigarettes, eighteen of which had not been detected in tobacco smoke previously. The utility for identification purposes of the corresponding quinoxaline derivatives, obtained through condensation with *o*-phenylenediamine, is discussed.

The occurrence of alkyl 2-hydroxy-2-cyclopentenones in tobacco smoke was first demonstrated by Elmenhorst[1] in 1972. He showed 3-methyl- and 3-ethyl-2-hydroxy-2-cyclopentenone to be present both in cigarette smoke and in Latakia tobacco, a fire-cured tobacco, and found these compounds to possess flavour-enhancing properties modifying the impact of smoke phenols from a "phenolic" to a "smoky" character. Subsequent work by Hecht *et al.*[2] on the constituents of subfractions derived from the weakly acidic part of cigarette smoke condensate and exhibiting tumor-promoting and co-carcinogenic activity revealed the presence of 3-methyl-, 3-propyl-, 3,4-dimethyl-, 3,5-dimethyl-, 3,5-diethyl-, 5-ethyl-3-methyl and 3-ethyl-5-methyl-2-hydroxy-2-cyclopentenone in some of these. Later investigations[3,4] have confirmed much of this work, and quantitative studies by Hecht *et al.*[5] using ^{14}C-labelled reference material have shown 3-methyl-, 3-ethyl-, 3,5-dimethyl- and 3,4-dimethyl-2-hydroxy-2-cyclopentenone to be present in cigarette smoke on the μg/cigarette level, the major component being the 3-methyl derivative.

In an ongoing study of cigarette smoke condensate (CSC) we have recently come across a series of these compounds. Since most of them are present in low concentration, gas chromatography-mass spectrometry (GC-MS) constitutes the only convenient way to detect them. In order to improve the possibility of accessing the structural information contained in the mass spectra, we prepared a set of mono- and dialkylated 2-hydroxy-2-cyclopentenones, and corresponding quinoxaline derivatives obtained through condensation with *o*-phenylenediamine, and recorded their mass spectra. The outcome of these studies is discussed below.

Procedure and discussion

The 2-hydroxy-2-cyclopentenones were obtained from CSC by smoking 100000 commercial plain cigarettes of American blend type (23 mg tar, 11 mg CO, 1.8 mg nicotine) and collecting the condensate using procedures described previously.[6,7] Since only the semivolatile material was of interest, the CSC was distilled *in vacuo* using CO_2 as carrier gas[8] to give a volatile, a semivolatile and a nonvolatile fraction. Subsequent fractionation of the semivolatiles by liquid-liquid extraction us-

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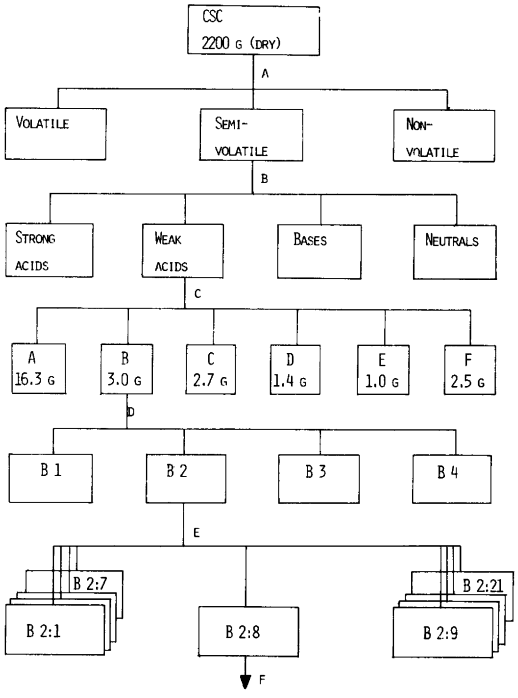
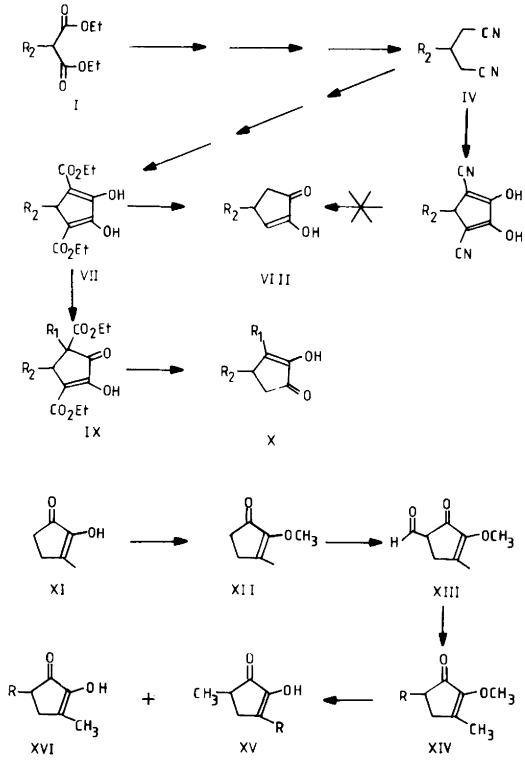
ing, consecutively, aqueous $NaHCO_3$, NaOH and HCl, furnished four dichloromethane-soluble fractions, see Scheme 1. Of these, the NaOH-extractable weak acids were subjected to flash chromatography[9] on silica gel using a stepwise gradient to give six main subfractions, which were examined by GC-MS. It followed from these studies that the third fraction (C) contained 3-methyl-2-hydroxy-2-cyclopentenone as the major component and that most of the more heavily substituted compounds of this type occurred in the second fraction (B). Since the resolution of the latter fraction was inadequate, mainly due to the presence of other major components, it was separated further into four subfractions, two of which, B2 and B3, contained the major part of the alkyl 2-hydroxy-2-cyclopentenones. Most of these were unknown, and the compounds described in the following section were therefore synthesized to allow comparison.

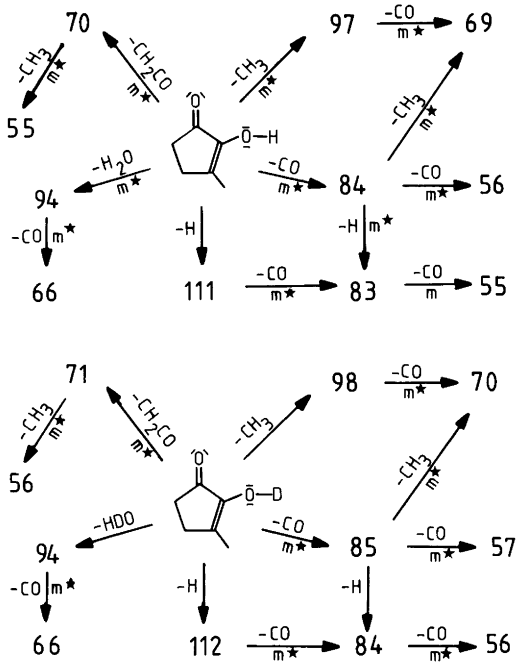


Scheme 1. A) Distillation, B) Liquid-liquid extraction, C) Silica gel chromatography, D) Silica gel chromatography, E) HPLC CN column, F) HPLC C_{18} column.



Scheme 2.

Synthesis of reference compounds. Only two of the compounds required were commercially available; the rest were therefore synthesized. Since the major purpose of these syntheses was to obtain reference substances for identification of CSC constituents by GC and GC-MS, conventional synthetic steps were used throughout and no attempts were made to optimize the yields. Of the many synthetic routes which have been published, and recently reviewed by Strunz,[10] most furnish poor yields. While this is also true for those selected here (outlined in Scheme 2), they have the advantage of being quite general. The initial steps involved the conversion of the appropriately substituted malonic esters (I) to the corresponding glutaronitriles (IV), accomplished by LAH reduction followed by esterification of the alcohols (II) obtained and subsequent treatment of the resulting tosylates (III) with sodium cyanide. While attempts to condense the nitriles



Scheme 3.

(IV) with diethyl oxalate were successful, efforts to hydrolyse/decarboxylate the condensation product failed. The nitriles (IV) were therefore hydrolysed and the resulting glutaric acids (V) converted into the corresponding ethyl esters (VI). These were condensed with diethyl oxalate using sodium ethoxide in ether or sodium hydride in toluene. The products (VII) obtained were either hydrolysed/decarboxylated to yield the desired 4-alkyl-2-hydroxy-2-cyclopentenones and 2-hydroxy-2-cyclopentenone (VIII) or alkylated to give the corresponding, more substituted compounds (IX). The latter were transformed into the 3-alkyl- and 3,4-dialkyl-2-hydroxy-2-cyclopentenones (X) using the same hydrolysis/decarboxylation procedure as in the previous case.

The required 3,5-dialkyl-2-hydroxy-2-cyclopentenones were prepared from 2-hydroxy-3-methyl-2-cyclopentenone (XI) by conversion to the enol ether (XII) and subsequently to the formyl derivative (XIII), which was alkylated to give the 3,5-dialkyl derivatives (XIV) furnishing the desired products on demethylation.[11] Although XV and XVI are tautomeric forms of the same compound, they can be separated by GC, as previously shown (for R = ethyl) by Hecht *et al.*,[2] and they give rise to different mass- and ^{1}H NMR spectra.

Mass spectrometric results. Examination of the fractions of interest by capillary GC-MS revealed the presence of some 20 compounds assumed to be 2-hydroxy-2-cyclopentenones. Since earlier studies[2] had provided only mass spectra of the corresponding 3-methyl-, 3-ethyl- and 3-propyl derivatives and a mechanistic proposal for the elimination of ethylene from the molecular ion of the last compound, further information was required to settle the structures not only of the compounds identical to those synthesized but also of the remainder. High resolution spectra were therefore recorded under GC-MS conditions for all of the synthetic compounds, and B/E spectra obtained for unlabelled and deuterium-labelled XI to clarify the metastable transitions (see Scheme 3), the aim being to elucidate fragmentation reactions typical of alkyl-substituted 2-hydroxy-2-cyclopentenones and useful for structural elucidation purposes. On the basis of the results obtained, it was possible to propose the fragmentation pathways outlined in Schemes 4–8.

Routes given in eqns. 4.1 and 4.2 dominate in the case of unsubstituted and monomethyl-substituted compounds, but decrease rapidly in importance with disubstitution and introduction of heavier substituents. The relative importance of the other pathways invoked is discussed below for the various substitution patterns.

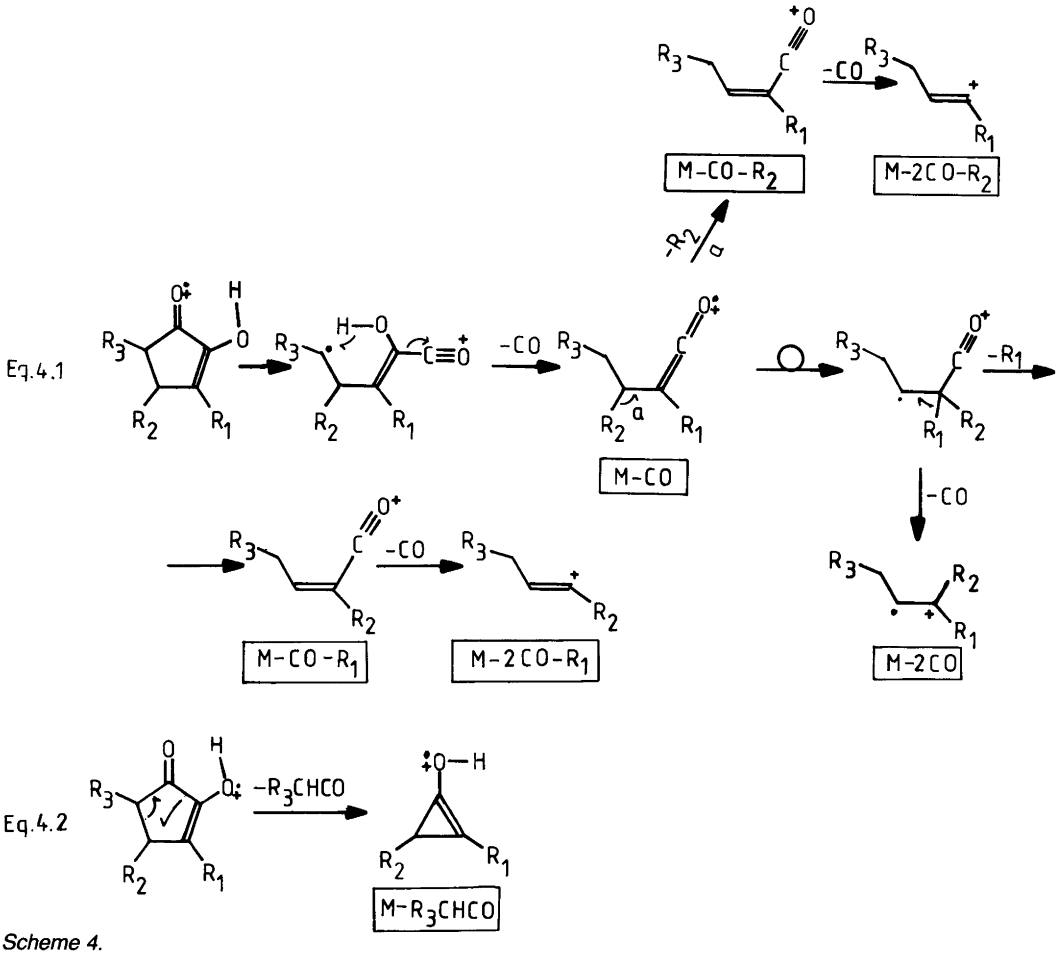
Some of the high resolution results obtained for 2-hydroxy-2-cyclopentenone and corresponding 3-alkyl derivatives are detailed in Table 1. In agreement with expectation, the intensities of the molecular peaks, expressed as a percentage of the total ion current (% TIC), decrease in a regular manner with increasing length of the alkyl chain.

It follows from Table 1 that the abundance of the $(M\text{-}R_{12})^+$ ion is about the same as that of the $(M\text{-}R_{11})^+$ ion in the spectrum of the *n*-alkyl derivatives, despite the fact that the latter is an allylically stabilised ion; a plausible reason for this is that the elimination of the R_{12} radical is assisted by cyclisation (see Scheme 5, eqns. 5.1 and 5.2).

Another important reaction, which distinguishes the 3-propyl derivative from the 3-ethyl-

and 3-methyl derivatives of the present series is, as already pointed out by Hecht *et al.*,[2] the favoured loss of ethylene from the molecular ion. Although of less significance, we prefer a six-membered ring mechanism with hydrogen transfer to C-2 (eqn. 5.3) to that invoked by Hecht *et al.*,[2] which involves a five-membered ring transition state with hydrogen transfer to C-3. A further consequence of this favoured reaction is that the $(M-28)^{+\cdot}$ peak is due exclusively to the loss of ethylene in the case of the 3-propyl derivative but mainly to the loss of CO in the case of the 3-methyl- and 3-ethyl derivatives of Table 1. This result also implies that the enol form dominates over the keto form in the 3-alkyl compounds, since the losses of fragments R_1-H from the molecular ions of the derivatives having $R_1 \geq$ Et are not favoured reactions.

It has previously been shown by NMR[12] that the enol form of 2-hydroxy-3-methyl-2-cyclopentenone predominates in solution, and according to present ^{1}H NMR results this is true for all the synthetic compounds discussed here, including the 4-monoalkylated derivatives. Worthy of mention also are two reactions in the fragmentation of the 3-alkyl derivatives which compete with the aforementioned (eqns. 5.1–5.3). One is of importance when R_1 is short (Me, Et, *i*-Pr) and corresponds to the formation of $(M-CH_2CO)^{+\cdot}$ fragments by eqn. 4.2, while the other is significant when R_1 contains three or more consecutive carbons (Pr, Bu, *sec*-Bu, Pentyl) and corresponds to



Scheme 4.

Table 1. Selected ions from the electron-impact spectra (70 eV) of 3-alkyl-2-hydroxy-2-cyclopentenones. See Schemes 4 and 5 for designation of ions. Intensities are given as a percentage of the total ion current, $\sum_{n=40}^{M+1} I_n$, and were obtained from low-resolution mass spectra using the high-resolution results to determine the ratios between ions of the same nominal mass. No attempts were made to distinguish between different routes leading to the same fragment ions. Intensities less than 1 % of base peak are set to 0.

Substituents	H	Me	Et	Pr	Bu	Pentyl	*i*-Pr	*sec*-Bu
M	98 (23)	112 (16)	126 (6.2)	140 (3.8)	154 (2.8)	168 (2.9)	140 (7.5)	154 (9.6)
M-CO	70 (3.2)	84 (5.4)	98 (1.0)	112 (0)	126 (0)	140 (0)	112 (0.7)	126 (0.4)
M-CO-H	69 (7.1)	83 (5.9)	97 (1.1)	111 (0)	125 (0)	139 (0)	111 (0.6)	125 (0)
M-2CO	42 (7.3)	56 (3.9)	70 (0.6)	84 (0)	98 (0)	112 (0)	84 (0.1)	98 (0)
M-2CO-H	41 (6.8)	55 (5.5)	69 (1.6)	83 (0)	97 (0)	111 (0)	83 (1.0)	97 (0)
M-CH_2CO	56 (1.4)	70 (1.0)	84 (2.8)	98 (0.5)	112 (0)	126 (0)	98 (2.7)	112 (0)
M-CO-R_1	69 (7.1)	69 (10.8)	69 (3.3)	69 (1.2)	69 (1.2)	69 (0.8)	69 (3.0)	69 (2.5)
M-R_{11}	–	111 (0.9)	111 (1.3)	111 (4.0)	111 (5.6)	111 (5.1)	125 (11)	125 (22)
M-R_{11}-CO	–	83 (5.9)	83 (6.1)	83 (4.1)	83 (3.7)	83 (2.8)	97 (6.3)	97 (3.0)
M-R_{12}	–	–	125 (0.7)	125 (3.9)	125 (7.9)	125 (8.8)	139 (0)	139 (4.5)
M-R_{12}-CO	–	–	97 (1.1)	97 (1.0)	97 (1.2)	97 (0.7)	111 (0.6)	111 (1.8)
M-CH_2CHR_{13}	–	–	–	112 (3.7)	112 (21)	112 (23)	–	126 (2.4)
M-CH_2CHCHR_{13}	–	–	–	99 (1.5)	99 (6.3)	99 (8.6)	–	99 (3.2)

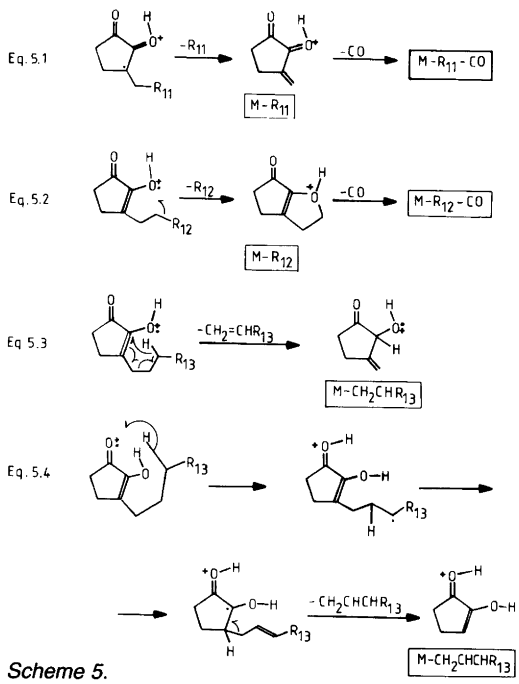
a "McLafferty +1" reaction leading to the generation of $(M\text{-}R_1 + 2H)^+$ ions. A plausible mechanism for the latter reactions is outlined in eqn. 5.4.

The 4-alkyl-2-hydroxy-2-cyclopentenones (Table 2) exhibit molecular peaks whose intensities also decrease with increasing molecular weight. The formation of the $(M\text{-}R_2)^+$ ions is a dominant reaction (eqn. 6.1), which makes the 4-alkyl derivatives readily distinguishable from the corresponding 3-alkyl compounds. The intensity (I) for the $(M\text{-}R_2)^+$ ions increases in a regular manner with increasing chain length in the *n*-alkyl series, while the intensities for the $(M\text{-}CH_2CHR_{22})^{+\cdot}$ and $(M\text{-}CH_2CHR_{22}\text{-}H_2O)^{+\cdot}$ ions increase with the bulkiness of the substituent, i.e. $I_{isopropyl} > I_{propyl} > I_{ethyl}$. It therefore seems that both steric effects and activation energy differences influence this rearrangement reaction (eqn. 6.2). The ^1H NMR spectra of the 4-isopropyl derivative and of 2-hydroxy-3-methyl-4-isopropyl-2-cyclopentenone show that the two nonallylic methyl groups are non-equivalent and, especially in the latter compound, one of them has an abnormal shift (0.64 ppm) probably due to anisotropic shielding by a nearby π-electron system.

The 3,4-disubstituted 2-hydroxy-2-cyclopentenones (Table 3) give mass spectra that indicate a close relationship with the 4-monoalkylated compounds (eqns. 6.1 and 6.2). The only major difference is the $(M\text{-}R_1)^+$ ion of high relative intensity in the spectrum of 3-ethyl-2-hydroxy-4-methyl-2-cyclopentenone. One explanation is a rearrangement reaction such as that outlined in eqn. 7.1, which gives a prominent $(M\text{-}R_1)^+$ when the substituent in the 3 position (R_1) can form a more stable radical than the substituent in the 4 position (R_2). In all other cases, the fragment ions arising by this route are the same as those produced according to eqn. 6.1.

As mentioned above, the 3,5-disubstituted 2-hydroxy-2-cyclopentenones (Table 4) can exist in two different tautomeric forms when the alkyl substituents in the 3- and 5 positions are different. The equilibration at room temperature seems to be slow since at least the 3-methyl-5-propyl- and 5-methyl-3-propyl-substituted compounds can be separated by HPLC. On the 60 m Supelcowax 10 GC column used to measure the relative retention times, however, they elute as one broad peak and clearly equilibrate. On a 30 m OV351 fused silica GC column, the equilibration rate was sufficiently low to give good separation and thereby adequate mass spectra of the individual compounds.

When the 5-substituent is methyl, the 3,5-disubstituted compounds seem to give almost the same fragmentation pattern as the 3-monoalkylated compounds (i.e. Scheme 5). The only major difference seems to be an additional pos-



Scheme 5.

sibility for losing a methyl group (eqn. 8.1), which explains the high intensity of the $(M-15)^+$ ion in the spectrum of the 3,5-dimethyl-substituted compound relative to that of the corresponding ion in the spectrum of the 3-methyl-substituted compound (cyclotene). If the substituent in the 5 position is heavier than methyl, the McLafferty rearrangement (eqn. 8.2) gives the dominating fragment ions, even if simple loss of the alkyl group (eqn. 8.1) is still important.

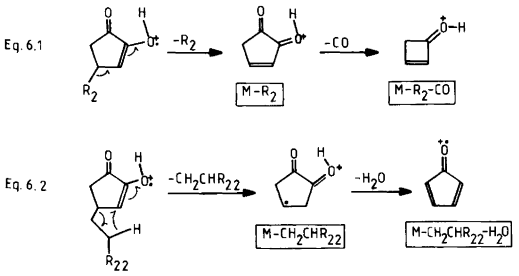
In order to illustrate the actual spectral appearance and the influence of the substituents, the spectra of three compounds containing the propyl substituent are reproduced in Fig. 1, i.e. those of 3-propyl-, 4-propyl-, and 3-methyl-5-propyl-substituted 2-hydroxy-2-cyclopentenone. Indicated in the spectra for the most prominent peaks are the routes by which the major part of the corresponding ions arise.

Quinoxaline derivatives. In order to circumvent difficulties such as poor stability[13] and tautomeric effects, attempts were made to develop a general and simple method for making quinoxaline derivatives. We found, however, that the rate of reaction of alkylated 2-hydroxy-2-cyclopentenones with *o*-phenylenediamine is affected considerably by both size and position of the substituents. In view of this and their apparent lability under acidic conditions, it was necessary to treat each compound individually.

The structural information that can be obtained from the mass spectra of these derivatives was evaluated by examining all *o*-phenylenediamine condensation products derived from the synthetic mono- and dialkyl-2-hydroxy-2-cyclopentenones having a molecular weight of 140 or less. It follows from the results summarized in Table 5, which details mass numbers and intensities of relevant peaks, that rather little information can be obtained about the substitution pattern in addition to that already available from the

Table 2. Selected ions from EI spectra (70 eV) of 4-alkyl-2-hydroxy-2-cyclopentenones. See Schemes 4 and 6 for designation of ions. Data obtained as for the 3-alkyl compounds, cf. Table 1.

Substituents in 4 position	Me	Et	Pr	*i*-Pr
M	112 (9.3)	126 (7.5)	140 (4.9)	140 (4.0)
M-CO	84 (5.9)	98 (2.0)	112 (1.6)	112 (0.4)
M-CO-H	83 (4.0)	97 (0)	111 (0)	111 (0.5)
M-2CO	56 (8.0)	70 (1.0)	84 (0)	84 (0.2)
M-2CO-H	55 (2.7)	69 (1.0)	83 (0)	83 (0.2)
$M-CH_2CO$	70 (0.2)	84 (1.0)	98 (0)	98 (2.8)
$M-R_2$	97 (9.1)	97 (25)	97 (28)	97 (11)
$M-R_2-CO$	69 (13)	69 (15)	69 (11)	69 (7.0)
$M-CH_2CHR_{22}$	–	98 (0.3)	98 (2.2)	98 (11)
$M-CH_2CHR_{22}-H_2O$	–	80 (0.4)	80 (3.1)	80 (16)



Scheme 6.

spectra of corresponding underivatised compounds. It may be concluded, however, that when R_1 and R_3 = H or Me and R_2 = H or C_nH_{2n+1} (Scheme 9), the molecular ion furnishes the base peak or the second largest peak. The remainder of the major fragment ions are due to loss of H, R_{1-3} or part of R_{1-3}, as shown schematically in eqn. 9.1. When R_1 (or R_3) $\geq C_2H_5$ and R_2 = H, a rearrangement reaction (eqn. 9.2) furnishes the most abundant ion, while when R_2 = alkyl, it gives the second most abundant ion which extrudes R_2 to produce the most abundant ion. The presence of this typical ion of even mass reveals both the size of R_1 and the presence or absence of any other alkyl substituents.

The ions arising by initial fragmentation of the alkyl substituent can give an indication of any branching in the substituent, e.g. the M-29 peak, which is the second largest when R_2 is propyl, is absent when R_2 is isopropyl.

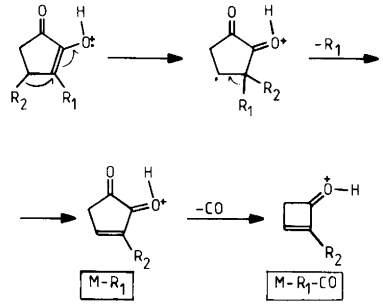
Alkyl-2-hydroxy-2-cyclopentenones found in CSC. Using the MS results obtained for the synthetic substances, 26 different alkyl-2-hydroxy-2-cyclopentenones (disregarding tautomeric forms) were identified in CSC (Table 6). This was achieved mainly by GC-MS, and required further separation of the CSC fractions (see Scheme 1). Chromatography of fraction B2 on a CN-HPLC column (cyclohexane : dichloromethane : methanol, 89:10:1) eliminated most of the major components already identified which interfered with the separation, e.g. the 3-ethyl-, 3,4-dimethyl-, 3,5-dimethyl-, 3-ethyl-5-methyl-, 5-ethyl-3-methyl- and 3-propyl derivatives of 2-hydroxy-2-cyclopentenone. Good spectral results could then be obtained for the less abundant components. One of the subfractions, B2:8, which contained many of the most heavily substituted compounds, was fractionated further on a C_{18} HPLC column using methanol/water (1:1) as eluent. Although the amount of material was very small, it was possible to isolate a few of the new compounds in a fairly pure state (>90 %). ^{1}H NMR studies of these demonstrated the presence of terminal branching in the 3-isobutyl- and the 3-isopentyl derivatives, thus confirming the structures assigned on the basis of the MS results.

Additional proof of the structures of these compounds and of the 3,4,5-trimethyl- and 4-methyl-3-propyl derivatives was obtained by derivatisation of the corresponding fractions using *o*-phenylenediamine followed by GC-MS exam-

Table 3. Selected ions from EI spectra (70 eV) of 3,4-dialkyl-2-hydroxy-2-cyclopentenones. See Schemes 4, 6 and 7 for designation of ions. Data obtained as for the 3-alkyl compounds, cf. Table 1.

Substituents in 3 (R_1) and 4 (R_2) positions	R_1:Me R_2:Me	R_1:Me R_2:Et	R_1:Me R_2:*i*-Pr	R_1:Et R_2:Me
M	126 (21)	140 (5.4)	154 (8.4)	140 (6.0)
M-CO	98 (2.9)	112 (0.8)	126 (0.5)	112 (1.4)
M-CO-H	97 (2.8)	111 (0)	125 (0)	111 (0)
M-2CO	70 (0.6)	84 (0)	98 (0)	84 (0)
M-2CO-H	69 (0)	83 (0)	97 (0)	83 (1.1)
M-CH_2CO	84 (0.5)	98 (0)	112 (0)	98 (1.1)
M-CO-R_1	83 (5.8)	97 (1.1)	111 (0.3)	83 (2.3)
M-R_2	111 (9.3)	111 (17)	111 (16)	125 (3.6)
M-R_2-CO	83 (5.8)	83 (10)	83 (8.6)	97 (4.4)
M-CH_2CHR_{22}	–	112 (0.8)	112 (9.9)	–
M-CH_2CHR_{22}-H_2O	–	94 (0.2)	94 (12)	–
M-R_1	111 (9.3)	125 (0)	139 (0.2)	111 (7.4)

Eq.7.1



Scheme 7.

ination of the products. The mass spectrometric results obtained for these quinoxaline derivatives were in good agreement with those expected based on the findings for the corresponding derivatives of the synthetic compounds discussed above.

All data for the alkyl- 2-hydroxy-2-cyclopentenones found in CSC are given in Table 6, along with the criteria of identification. Only some of the most abundant representatives in the total weak acid fraction were detectable by GC and the amounts of these were in decreasing order: 3-methyl-, 3-ethyl-, 3,5-dimethyl-, 5-ethyl-3-methyl-, 3-ethyl-5-methyl-, 3,4-dimethyl-, 3-propyl-, and 3,5-diethyl-2-hydroxy-2-cyclopentenone.

Experimental

General methods. The ^1H NMR spectra were recorded in $CDCl_3$ at 200 or 300 MHz on a Varian XL-200 or XL-300 instrument using TMS as internal standard. Mass spectra (70 eV) were measured on a Kratos MS 50 mass spectrometer; intensities are given as a percentage of the base peak, unless otherwise stated. Melting points, uncorrected, were measured on a Leitz Wetzlar Heizstativ apparatus. Molecular weight determinations were made by high resolution MS.

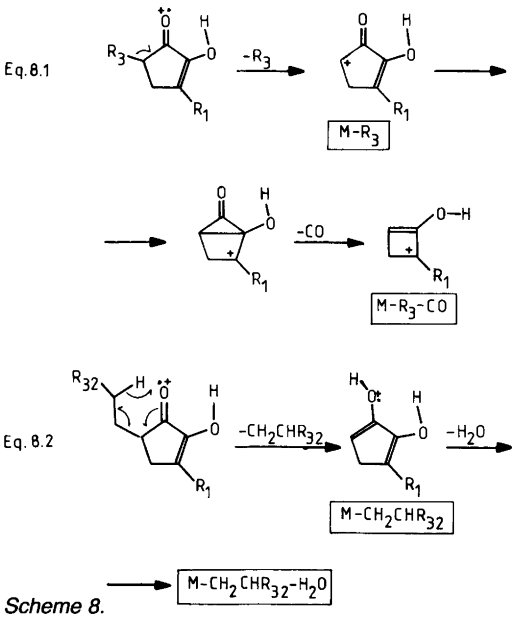
Gas chromatography was performed on a Hewlett-Packard model 5880 A instrument equipped with a flame-ionisation detector. The relative retention times were measured on a Supelcowax 10 fused silica column (0.32 mm i.d., 60 m) programmed from 60 to 250 °C at 2 °C min^{-1} using helium as carrier gas. Merck Kieselgel 60 (230–400 mesh) was used for column chromatography. HPLC was performed on a Varian 5000 instrument, equipped with a Waters R401 differential refractometer and a Pharmacia UV-2 Dual Path Monitor (254 nm).

Preparation of cigarette smoke condensate fractions. The CSC was prepared from 100000 plain cigarettes of American blend type (23 mg tar, 11 mg CO and 1.8 mg nicotine). The cigarettes were smoked according to a standard procedure[6] using a Borgwaldt automatic smoking machine (Type R 09.012, Heinr. Borgwaldt, Hamburg, FRG). The CSC was condensed in an Elmenhorst trap cooled in a CO_2(s)/ethanol mixture.[7] The CSC was distilled *in vacuo* with CO_2 as carrier gas[8] giving 3 fractions:[14] volatiles, semivolatiles and nonvolatiles. The semivolatiles were separated into 4 dichloromethane-soluble fractions: acids, weak acids, bases and neutrals, utilising an extraction procedure described earlier.[15]

Portions (8–9 g) of the weak acids were subjected to flash chromatography[9] on silica gel. The column was eluted with 1300 ml batches of 6 different mixtures of cyclohexane, ethyl acetate and methanol (6:1:0, 3:1:0, 1:1:0, 1:3:0, 0:3:1 and 0:0:1). The eluate was collected in 25 ml tubes and, after TLC evaluation, combined into 6 fractions, A–F. Fraction A contained most of the

Eq.8.1

Eq.8.2



Scheme 8.

Table 4. Selected ions from EI spectra (70 eV) of 3,5-dialkyl-2-hydroxy-2-cyclopentenones. See Schemes 4, 5 and 8 for designation of ions. Data obtained as for the 3-alkyl compounds, cf. Table 1.

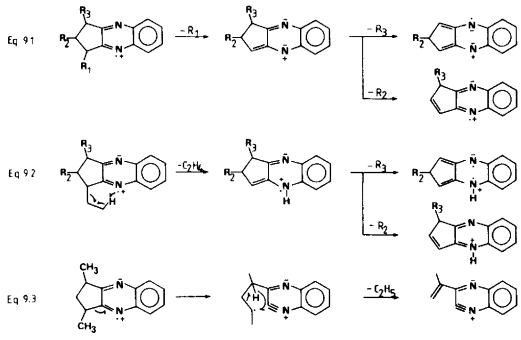
Substituents in 3 (R_1) and 5 (R_3) positions	R_1:Me R_3:Me	R_1:Et R_3:Me	R_1:Pr R_3:Me	R_1:Me R_3:Et	R_1:Me R_3:Pr
M	126 (6.1)	140 (6.9)	154 (8.4)	140 (2.5)	154 (3.4)
M-CO	98 (3.8)	112 (0)	126 (0)	112 (0)	126 (0)
M-CO-H	97 (1.9)	111 (0)	125 (0)	111 (0)	125 (0)
M-2CO	70 (2.3)	84 (0)	98 (0)	84 (0)	98 (0)
M-2CO-H	69 (1.7)	83 (0)	97 (0)	83 (0)	97 (0)
M-CHR_3CO	70 (0.4)	84 (1.6)	98 (0.7)	70 (1.9)	70 (0.8)
M-R_{11}	125 (0.2)	125 (4.0)	125 (3.9)	139 (0)	153 (0)
M-R_{12}	–	139 (0.1)	139 (8.0)	–	–
M-CH_2CHR_{13}	–	–	126 (4.6)	–	–
M-CH_2CHCHR_{13}	–	–	113 (1.4)	–	–
M-R_3	111 (6.9)	125 (4.0)	139 (8.0)	111 (1.5)	111 (1.8)
M-CH_2CHR_{32}	–	–	–	112 (6.1)	112 (20.0)
M-CH_2CHR_{32}-H_2O	–	–	–	94 (8.6)	94 (20.0)

phenols and fraction C most of the 2-hydroxy-3-methyl-2-cyclopentenone (cyclotene). Fraction B was then further fractionated as shown in Scheme 1 and the subfractions combined according to results obtained by TLC and GC.

General methods for the synthesis of alkyl-2-hydroxy-2-cyclopentenones. Since the same reaction sequence was used for the preparation of all 3-monoalkylated, 4-monoalkylated and 3,4-dialkylated compounds, only a general description of the steps involved is given here. The 3,5-dialkylated compounds are presented in the same way; the Roman numbers refer to Scheme 2. Relevant spectroscopic data for each alkylated 2-hydroxy-2-cyclopentenone and, when available, its

Table 5. Selected ions from the electron-impact spectra (70 eV) of the quinoxaline derivatives. See Scheme 9. Intensities are given as a percentage of base peak. Zero values indicate that intensities are not among the 20 largest in the spectrum.

Substituents			M	M-1	M-15	M-16	M-28	M-29	M-30	M-42	M-43	M-44
R_1	R_2	R_3										
H	H	H	100	56	0	0	13	0	0	0	0	0
Me	H	H	64	29	100	10	0	5	0	0	0	0
Et	H	H	4	0	4	0	100	72	16	0	0	0
i-Pr	H	H	6	0	3	0	0	0	0	100	68	16
Pr	H	H	3	0	0	0	4	17	0	100	60	36
H	Me	H	100	60	48	8	0	0	0	7	0	0
H	Et	H	100	24	56	7	0	32	13	7	0	0
H	*i*-Pr	H	100	10	52	0	5	12	7	9	40	16
H	Pr	H	100	11	36	0	10	56	10	7	52	12
Me	Me	H	76	22	100	11	0	19	14	0	0	0
Me	H	Me	88	40	100	21	0	25	32	0	0	0
Me	Et	H	100	13	84	0	9	56	19	9	32	19
Et	Me	H	7	0	5	0	72	21	7	17	100	17
Et	H	Me	9	0	3	0	100	88	6	4	28	15



Scheme 9.

corresponding quinoxaline derivative are given in the subsequent part.

2-Alkylpropan-1,3-diol (II).[16] The malonic ester I was reduced with lithium aluminium hydride in ether. After addition of water, hydrochloric acid (pH 1) and sodium chloride, the aqueous phase was separated and extracted continuously with ether under reflux for 3 d. The combined ether extracts were dried and concentrated to give 80–90 % yields of the diol II, used further without purification.

2-Alkylpropan-1,3-diol ditosylate (III) was prepared using *p*-toluenesulfonyl chloride and pyridine. After work-up and recrystallisation from ethanol, III was obtained in 65–70 % yield.

3-Alkyl-1,5-pentanedinitrile (IV). The tosyl ester III was dissolved in absolute ethanol and a slight excess (2.2 mol per mol of ditosylate) of sodium cyanide added. The mixture was heated under reflux for 6 h. Evaporation of the ethanol to near dryness, followed by dilution with water and extraction with ether gave, after drying and evaporation, the substituted glutaronitrile IV in 65–70 % yield.

3-Alkylpentanedioic acid (V).[17] The nitrile was hydrolysed under reflux for 4 h in concd. hydrochloric acid. After evaporation of the hydrochloric acid, the residue was dissolved in ether, washed with water, dried and concd. to give the 3-alkylpentanedioic acid in 65–70 % yield.

3-Alkylpentanedioic acid diethyl ester (VI). The acid V was heated under reflux for 4 h in ethanol to which a catalytic amount of *p*-toluenesulfonic acid had been added. The water formed was removed by hourly additions of cyclohexane, which was distilled off. Evaporation, dissolution in ether, washing with satd. aq. $NaHCO_3$, drying and evaporation gave the ester VI in 65–70 % yield.

4-Alkyl-3,5-bis(ethoxycarbonyl)-2,5-cyclopentadiene-1,2-diol (VII). The properly substituted glutaric ester VI was condensed with diethyl oxalate in 45 % yield using sodium ethoxide in ether.[18] The condensation was, however, more conveniently effected with sodium hydride in toluene: 10 mmol of the diethyl glutarate VI, 11 mmol of diethyl oxalate and 22 mmol of sodium

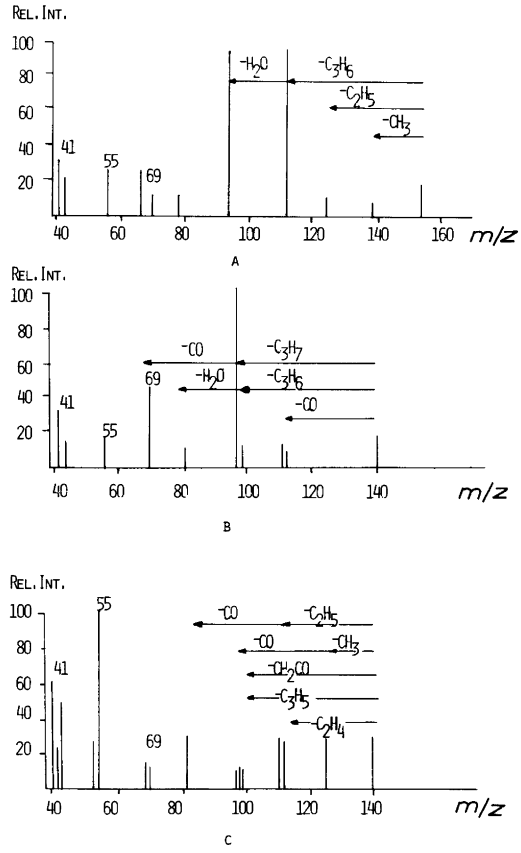


Fig. 1. Mass spectra (EI, 70 eV) of: A) 2-hydroxy-3-methyl-5-propyl-2-cyclopentenone; B) 2-hydroxy-4-propyl-2-cyclopentenone; C) 2-hydroxy-3-propyl-2- -cyclopentenone.

Table 6. Alkylated 2-hydroxy-2-cyclopentenones found in CSC.

Substituent(s) on 2-hydroxy-2-cyclopentenone	MW	Rel. RT[a]	Fraction[b]	Mass spectrum *m/z* (%)
None[c]	98	0.872	D	[h]
3-methyl[d]	112	0.923	C	112 (100), 84 (34), 83 (37), 69 (67), 56 (31), 55 (48), 53 (15), 43 (51), 42 (16), 41 (72)
4-methyl[c,e]	112	0.863	B3	[h]
3-ethyl[d]	126	0.981	B2	126 (48), 84 (22), 83 (48), 69 (39), 56 (22), 55 (100), 53 (22), 43 (72), 42 (32), 41 (56)
4-ethyl[c,e]	126	0.966	B2:13	[h]
3,4-dimethyl[c]	126	0.934	B2	[h]
3,5-dimethyl[c]	126	0.892	B2	[h]
3-propyl[c]	140	1.053	B2	[h]
3-isopropyl[c,e]	140	0.995	B2	[h]
3-ethyl-4-methyl[c,e]	140	0.977	B2	[h]
3-ethyl-5-methyl[c]	140	(0.97)[g]	B2	[h]
5-ethyl-3-methyl[c]	140	(0.97)[g]	B2	[h]
4-ethyl-3-methyl[c,e]	140	1.025	B2	[h]
3,4,5-trimethyl[e,f]	140	0.899	B2:8	140 (82), 125 (100), 112 (18), 97 (78), 83 (29), 69 (24), 56 (22), 55 (70), 43 (71), 41 (50)
3-butyl[c,e]	154	1.141	B2:8	[h]
3-isobutyl[e,f]	154	1.074	B2:8	154 (25), 139 (12), 112 (100), 111 (23), 99 (17), 83 (7), 66 (8), 55 (20), 43 (45), 41 (19)
3-(2-butyl)[c,e]	154	1.063	B2:8	[h]
3-methyl-5-propyl[c,e]	154	(1.05)[g]	A	[h]
4-methyl-3-propyl[e,f]	154	1.039	B2:8	154 (70), 139 (58), 126 (40), 111 (100), 97 (29), 83 (32), 69 (32), 55 (95), 43 (80), 41 (64)
3-methyl-4-propyl[e]	154	1.1039	B2:8	154 (24), 112 (9), 111 (100), 94 (8), 83 (44), 71 (13), 69 (9), 55 (32), 43 (63), 41 (26)
4-isopropyl-3-methyl[c,e]	154	1.070	B2:9	[h]
3,4-diethyl[e]	154	1.057	B2:8	154 (27), 126 (12), 125 (100), 97 (30), 79 (10), 69 (14), 67 (10), 55 (33), 43 (40), 41 (41)
3,5-diethyl	154	1.015	A	154 (82), 139 (27), 126 (100), 125 (36), 111 (36), 108 (51), 97 (27), 55 (59), 43 (32), 41 (39)
3,5-dimethyl-4-ethyl[e]	154	1.013	B2:8	154 (15), 126 (21), 125 (100), 111 (17), 97 (32), 69 (18), 67 (14), 55 (43), 43 (80), 41 (49)
3-pentyl[c,e]	168	1.225	B2:8	[h]
3-isopentyl[e,f]	168	1.185	B2:8	125 (22), 112 (100), 111 (25), 99 (48), 83 (10), 70 (11), 57 (17), 55 (28), 43 (23), 41 (29)
3-(2-methylbutyl)[e]	168	1.176	B2:8	168 (7), 139 (6), 113 (8), 112 (100), 111 (11), 99 (8), 57 (30), 55 (19), 43 (22), 41 (31)

[a]Relative GC retention time to 2,6-dimethylphenol on Supelcowax 10 fused silica GC column. [b]Refers to Scheme 1. [c]Identified by comparison with a synthesized reference. [d]Identified by comparison with a commercially available reference. [e]Presence in CSC not previously demonstrated. [f]Isolated and *o*-phenylenediamine derivative prepared. [g]Equilibrates with its tautomeric form, elutes as a broad peak. [h]Mass spectrum identical to that of the synthesized reference, see Experimental.

hydride (added as a 50 % dispersion in mineral oil) in 50 ml of toluene were heated under reflux for 2 h. The mixture was poured into ice-water, the phases separated and the aqueous phase washed with ether. Acidification and extraction with dichloromethane, drying and evaporation gave the desired compound in 60–70 % yield.

Alkylation of 4-alkyl-3,5-bis(ethoxycarbonyl)-2,5-cyclopentadiene-1,2-diol (VII). The alkylating agent, i.e. methyl iodide, ethyl iodide, propyl iodide, isopropyl bromide, butyl iodide, pentyl iodide or *sec*-butyl iodide (1.1 mmol), and the substrate VII (1 mmol) were dissolved in 5 ml of dichloromethane. Tetrabutylammonium hydrogen sulfate (1 g) in 1M sodium hydroxide (5 ml) and the dichloromethane solution were shaken vigourously for 20 min in a separating funnel. The dichloromethane phase was removed and the aqueous phase acidified and extracted twice with dichloromethane. The combined dichloromethane phases were dried and the solvent evaporated to give the alkylated product together with ammonium salts. The solid mixture was triturated with ether and the ether washed with dilute acid and water. Drying and evaporation gave the product IX, which was not purified; yields were estimated from GC to be in excess of 80 %.

4-Alkyl-2-hydroxy-2-cyclopentenone (VIII) and 3,4-dialkyl-2-hydroxy-2-cyclopentenone (X). Treatment of compounds VII and IX with 20 % sulfuric acid at 140 °C for 2–8 h effected the desired hydrolysis/decarboxylation reaction.[19] Yields were commonly 15–30 % on decarboxylation of compound IX, but reached 70 % in the case of compound VII.

5-Formyl-2-methoxy-3-methyl-2-cyclopentenone (XIII). The compound 2-hydroxy-3-methyl-2-cyclopentenone, XI, was converted to the enol ether XII by treatment with methanol acidified by addition of acetyl chloride.[1] The enol ether XII (10 mmol) and ethyl formate (20 mmol) were dissolved in anhydrous ether and the solution, after addition of sodium hydride (20 mmol; suspension in paraffin oil), heated under reflux overnight. Addition of water, separation and washing of the aqueous phase with ether to remove the paraffin oil, acidification and extraction with ether, and finally drying and evaporation followed by recrystallisation from a mixture of isopropyl acetate and petroleum ether (b.p. 80–110 °C) gave pure XIII; yield 45 %, m.p. 100–102 °C (lit.[11] 101–102 °C).

5-Alkyl-2-methoxy-3-methyl-2-cyclopentenone (XIV). Compound XIII was alkylated with methyl iodide, ethyl iodide or propyl iodide as described above for VII to give XIV in 40–65 % yield; the formyl group was eliminated under the conditions used.

Hydrolysis of methyl ether (XIV).[11] The methyl ether XIV was heated for 1 h with aqueous hydroiodic acid (1:1) under reflux. Dilution with water, extraction with ether, drying and evaporation gave the target compounds XV and XVI in 60–70 % yield.

Preparation of o*-phenylenediamine derivatives.*[20] The compound to be derivatised, VIII, (10 mg) was heated under reflux in toluene with an equimolar amount of *o*-phenylenediamine and a catalytic amount of *p*-toluenesulfonic acid. Water, formed in the reaction, was removed by a Dean-Starke trap containing molecular sieves. The reaction was monitored by GC. The reaction time varied from 4 to 48 h depending on the substrate. After the reaction was complete, the mixture was dissolved in ether, washed with IM sodium hydroxide and water, dried and evaporated to give the quinoxaline derivative in about 70 % yield.

2-Hydroxy-2-cyclopentenone (1). Commercial diethyl glutarate, VI:R_2 = H, was condensed with diethyl oxalate to give VII:R_2 = H in 40 % yield, which had m.p. 117–119 °C (lit.[21] 118 °C). Hydrolysis/decarboxylation gave a 70 % yield of *1* having m.p. 54–56 °C (lit.[21] 56 °C); HRMS: M^{+} 98.0375 ($C_5H_6O_2$ requires 98.0367); ^{1}H NMR (200 MHz): δ 6.58 (t, J = 3, 1H), 5.75 (broad s, 1H), 2.5 (m, 4H); MS *m/z* (%): 98 (100), 70 (14), 69 (31), 56 (6), 55 (63), 44 (5), 43 (24), 42 (55), 41 (34), 40 (11).

*2,3-Dihydro-*1H*-cyclopenta(b)quinoxaline* (2) was obtained in 56 % yield from *1*; ^{1}H NMR (200 MHz): δ 8.02 (m, 2H), 7.68 (m, 2H), 3.22 (t, J = 7.5, 4H), 2.31 (quint., J = 7.5, 2H); MS *m/z* (%): 170 (100), 169 (56), 76 (18), 102 (18), 50 (16), 142 (13), 75 (12), 171 (12), 39 (11), 77 (10).

2-Hydroxy-4-methyl-2-cyclopentenone (3). Com-

pound VI:$R_2 = CH_3$ was prepared in 95% yield from commercial 3-methylglutaric anhydride. Condensation with diethyl oxalate gave a 45% yield of VII:$R_2 = CH_3$, m.p. 110–112°C (lit.[18] 108°C). Hydrolysis/decarboxylation furnished *3* in 67% yield, m.p. 59–61°C (lit.[11] 60–62°C); HMRS: M^{+} 112.0509 ($C_6H_8O_2$ requires 112.0523); ^{1}H NMR (200 MHz): δ 6.46 (d, $J = 4$, 1H), 5.6 (broad s, 1H), 2.9 (m, 1H), 2.69 and 1.99 (ABX-pattern, $J_{AB} = 18$, further split by $J_{AX} = 6$ and $J_{BX} = 3$, 2H), 1.17 (d, $J = 8$, 3H). MS *m/z* (%): 112 (51), 97 (50), 84 (35), 83 (22), 69 (71), 56 (44), 55 (29), 43 (42), 42 (34), 41 (100).

*2,3-Dihydro-*1H*-2-methylcyclopenta(b)quinoxaline* (4) was obtained from *3* in 80% yield; ^{1}H NMR (200 MHz): δ 8.01 (m, 2H), 7.67 (m, 2H), 3.4 (m, 2H), 2.8 (m, 3H), 1.29 (d, $J = 6.5$, 3H); MS *m/z* (%): 184 (100), 183 (60), 169 (48), 102 (15), 76 (13), 182 (13), 50 (12), 77 (12), 185 (12), 39 (11).

4-Ethyl-2-hydroxy-2-cyclopentenone (5). Compound VII:$R_2 = C_2H_5$ was prepared in 9.4% yield from diethyl ethylmalonate by the general procedure outlined in Scheme 2 and described above. Hydrolysis/decarboxylation gave *5* in 60% yield, which had HMRS:M^{+} 126.0722 ($C_7H_{10}O_2$ requires 126.0680); ^{1}H NMR (200 MHz): δ 6.54 (d, $J = 3$, 1H), 5.65 (broad s, 1H), 2.7 (m, 1H), 2.63 and 2.08 (ABX-pattern, $J_{AB} = 19$, further split by $J_{AX} = 6$ and $J_{BX} = 1$, 2H), 1.5 (m, 2H), 0.98 (t, $J = 8$, 1H); MS *m/z* (%): 126 (30), 98 (13), 97 (100), 83 (9), 70 (8), 69 (64), 55 (29), 43 (19), 42 (17), 41 (42).

*2,3-Dihydro-2-ethyl-*1H*-cyclopenta(b)quinoxaline* (6) was obtained in 62% yield from *5*; ^{1}H NMR (200 MHz): δ 8.02 (m, 2H), 7.68 (m, 2H), 3.33 and 2.87 (ABX-pattern, $J_{AB} = 18$, further split by $J_{AX} = 8$ and $J_{BX} = 8$, 4H), 2.56 (sept., $J = 8$, 1H), 1.66 (quint., $J = 8$, 1H), 1.05 (t, $J = 8$, 1H); MS *m/z* (%): 198 (100), 183 (56), 169 (32), 197 (24), 76 (15), 102 (14), 199 (14), 39 (13), 168 (13), 77 (12).

2-Hydroxy-4-isopropyl-2-cyclopentenone (7). Compound VII:R_2 = isopropyl was obtained in 11% yield from diethyl isopropylmalonate. Hydrolysis/decarboxylation gave *7* in 67% yield. The compound was sublimed and recrystallised from ethanol, m.p. 78–80°C. HMRS: M^{+} 140.0894 ($C_8H_{12}O_2$ requires 140.0836); ^{1}H NMR (200 MHz): δ 6.53 (d, $J = 3$, 1H), 5.4 (broad s, 1H), 2.63 (m, 1H), 2.51 and 2.14 (ABX-pattern, $J_{AB} = 19$ further split by $J_{AX} = 6$ and $J_{BX} = 1.5$, 2H), 1.70 (m, 1H), 0.95 (d, $J = 6.5$, 3H), 0.93 (d, $J = 6.5$, 3H). MS *m/z* (%): 140 (26), 98 (89), 97 (69), 80 (100), 69 (57), 55 (13), 52 (20), 43 (63), 42 (12), 41 (70).

*2,3-Dihydro-*1H*-2-isopropylcyclopenta(b)quinoxaline* (8) was obtained in 64% yield from *7*; ^{1}H NMR (200 MHz): δ 8.02 (m, 2H), 7.68 (m, 2H), 3.29 and 2.91 (ABX-pattern, $J_{AB} = 18$, further split by $J_{AX} = 8$ and $J_{BX} = 9.5$, 4H), 2.36 (m, 1H), 1.80 (m, 1H), 1.05 (d, $J = 6.5$, 6H); MS *m/z* (%): 212 (100), 197 (52), 169 (40), 168 (16), 213 (15), 41 (13), 183 (12), 211 (10), 170 (9), 77 (8).

2-Hydroxy-4-propyl-2-cyclopentenone (9). Compound VII:$R_2 = C_3H_7$ was prepared in 14% yield from diethyl propylmalonate; *9*, obtained in 60% yield, had HMRS:M^{+} 140.0881 ($C_8H_{12}O_2$ requires 140.0836); ^{1}H NMR (200 MHz): δ 6.52 (d, $J = 3$, 1H), 5.35 (broad s, 1H), 2.78 (m, 1H), 2.65 and 2.05 (ABX-pattern, $J_{AB} = 19$, further split by $J_{AX} = 6$ and $J_{BX} = 1.5$, 2H), 1.60 (m, 2H), 1.42 (m, 2H), 0.95 (t, $J = 7$, 3H); MS *m/z* (%): 140 (18), 98 (12), 97 (100), 80 (11), 69 (43), 56 (9), 55 (16), 43 (15), 42 (9), 41 (32).

*2,3-Dihydro-*1H*-2-propylcyclopenta(b)quinoxaline* (10). Compound *10* was obtained in 75% yield from *9*; ^{1}H NMR (200 MHz): δ 8.02 (m, 2H), 7.68 (m, 2H), 3.33 and 2.88 (ABX-pattern, $J_{AB} = 18$, further split by $J_{AX} = 8$ and $J_{BX} = 8.5$, 4H), 2.64 (m, 1H), 1.5 (m, 4H), 0.98 (t, $J = 7$, 3H); MS *m/z* (%): 212 (100), 183 (56), 169 (52), 197 (36), 41 (20), 102 (15), 39 (13), 213 (13), 168 (12), 44 (11).

*2,3-Dihydro-*1H*-1-methylcyclopenta(b)quinoxaline* (11). Compound *11* was prepared from commercially available XI in 70% yield and had m.p. 71–73°C (lit.[20] 70–74°C); ^{1}H NMR (200 MHz): δ 8.05 (m, 2H), 7.70 (m, 2H), 3.44–3.0 (two groups of lines, 3H), 2.56 (m, 1H), 1.85 (m, 1H), 1.48 (d, $J = 8$, 3H). MS *m/z* (%): 169 (100), 184 (64), 183 (29), 170 (13), 168 (10), 76 (9), 102 (9), 185 (9), 50 (8), 77 (7).

*2,3-Dihydro-1-ethyl-*1H*-cyclopenta(b)quinoxaline* (12). From the commercially available 3-

ethyl-2-hydroxy-2-cyclopentenone, *12* was obtained in 74 % yield; ^{1}H NMR (200 MHz): δ 8.05 (m, 2H), 7.70 (m, 2H), 3.3–3.1 (m, 3H), 2.6–1.5 (four groups of multiplets, 4H), 1.12 (t, $J = 8$, 3H). MS *m/z* (%): 170 (100), 169 (72), 168 (16), 171 (12), 41 (10), 76 (8), 102 (8), 39 (7), 77 (7), 104 (7).

2-Hydroxy-3-isopropyl-2-cyclopentenone (13). Compound VII:R_2 = H (see *1*) was alkylated and decarboxylated in 20 % yield. The product had HMRS:M^+ 140.0837 ($C_8H_{12}O_2$ requires 140.0836); ^{1}H NMR (200 MHz): δ 5.35 (broad s, 1H), 3.02 (sept., $J = 7$, 1H), 2.44 (m, 4H), 1.17 (d, $J = 7$, 6H). MS *m/z* (%): 140 (68), 125 (98), 98 (23), 97 (61), 83 (31), 69 (81), 56 (42), 55 (48), 43 (86), 41 (100).

2,3-Dihydro-1H-*1-isopropylcyclopenta(b)quinoxaline* (14). Obtained from *13* in 65 % yield, *14* showed ^{1}H NMR (200 MHz): δ 8.05 (m, 2H), 7.70 (m, 2H), 3.4–3.0 (m, 3H), 2.6–1.8 (m, 3H), 1.16 (d, $J = 8$, 3H), 0.88 (d, $J = 8$, 3H). MS *m/z* (%): 170 (100), 169 (68), 168 (16), 41 (13), 171 (13), 39 (7), 77 (7), 76 (6), 102 (6), 212 (6).

2-Hydroxy-3-propyl-2-cyclopentenone (15). Compound VII:R_2 = H (see *1*) was alkylated and decarboxylated in 29 % yield to give *15* which had m.p. 53–55 °C (lit.[13] 54–56 °C); HMRS: M^+ 140.0847 ($C_8H_{12}O_2$ requires 140.0836); ^{1}H NMR (200 MHz): δ 5.7 (broad s, 1H), 2.45 (m, 6H), 1.59 (sext., $J = 7.5$, 2H), 0.96 (t, $J = 7.5$, 3H). MS *m/z* (%): 140 (29), 125 (29), 112 (28), 111 (30), 83 (31), 55 (100), 53 (26), 43 (50), 42 (23), 41 (62).

2,3-Dihydro-1H-*1-propylcyclopenta(b)quinoxaline* (16). Obtained from *15* in 70 % yield, *16* had ^{1}H NMR (200 MHz): δ 8.05 (m, 2H), 7.70 (m, 2H), 3.4–3.0 (m, 3H), 2.7–1.4 (four groups of lines, 6H), 1.04 (t, $J = 7$, 3H). MS *m/z* (%): 170 (100), 169 (60), 168 (36), 183 (17), 171 (13), 41 (10), 39 (6), 77 (6), 102 (6), 76 (5).

3-(2-Butyl)-2-hydroxy-2-cyclopentenone (17). Alkylation of VII:R_2 = H (see *1*) followed by decarboxylation gave *17* in very low yield. A sample had the following characteristics: HRMS: M^+ 154.1016 ($C_9H_{14}O_2$ requires 154.0994); ^{1}H NMR (300 MHz): δ 2.79 (sext., $J = 7.0$, 1H), 2.41 (broad s, 4H), 1.54 (dq, $J = 7.0$ and 7.5, 2H), 1.14 (d, $J = 7.0$, 3H), 0.89 (t, $J = 7.5$, 3H). MS *m/z* (%): 154 (43), 139 (20), 126 (12), 125 (100), 99 (14), 97 (13), 69 (15), 55 (23), 43 (27), 41 (25).

3-Butyl-2-hydroxy-2-cyclopentenone (18). Alkylation of VII:R_2 = H (see *1*) followed by decarboxylation gave *18* in very low yield. A sample had the following characteristics: HRMS: M^+ 154.0990 ($C_9H_{14}O_2$ requires 154.0994); ^{1}H NMR (300 MHz): δ 5.55 (broad s, 1H), 2.42 (m, 6H), 1.53 (m, 2H), 1.37 (m, 2H), 0.94 (t, $J = 7.5$, 3H). MS *m/z* (%): 154 (13), 125 (37), 112 (100), 111 (33), 99 (30), 83 (18), 70 (9), 55 (43), 43 (26), 41 (26).

2-Hydroxy-3-pentyl-2-cyclopentenone (19). Alkylation of VII:R_2 = H (see *1*) followed by decarboxylation gave *19* in very low yield. A sample had the following properties: HRMS: M^+ 168.1144 ($C_{10}H_{16}O_2$ requires 168.1150); ^{1}H NMR (300 MHz) showed three badly resolved groups of lines centered at 2.4, 1.6 and 1.4, and a triplet at 0.9 ppm. MS *m/z* (%): 168 (13), 125 (39), 112 (100), 111 (27), 99 (38), 83 (12), 57 (9), 55 (34), 43 (17), 41 (25).

3,4-Dimethyl-2-hydroxy-2-cyclopentenone (20). Compound VII:R_2 = CH_3 (see *3*) was alkylated and decarboxylated in 20 % yield and had m.p. 70–72 °C (lit.[11] 71–72 °C). HRMS: M^+ 126.0716 ($C_7H_{10}O_2$ requires 126.0680); ^{1}H NMR (200 MHz): δ 5.6 (broad s, 1H), 2.67 and 2.01 (ABX-pattern, $J_{AB} = 16.5$, further split into multiplets, 2H), 2.7 (m, 1H), 1.97 (s, 3H), 1.18 (d, $J = 7$, 3H). MS *m/z* (%): 126 (100), 111 (44), 98 (14), 97 (13), 83 (28), 69 (37), 56 (23), 55 (24), 43 (16), 41 (23).

2,3-Dihydro-1,2-dimethyl-1H-*cyclopenta(b)quinoxaline* (21). Obtained from *20* in 70 % yield, *21* showed ^{1}H NMR (200 MHz): δ 8.01 (m, 2H), 7.64 (m, 2H), 3.27 and 2.76 (ABX-pattern, $J_{AB} = 17.5$, further split by $J_{AX} = 8$ and $J_{BX} = 10$, 2H), 2.86 (m, 1H), 2.16 (m, 1H), 1.50 (d, $J = 6.5$, 3H), 1.35 (d, $J = 6.5$, 3H). MS *m/z* (%): 183 (100), 198 (76), 197 (22), 169 (19), 184 (15), 168 (14), 91 (12), 102 (12), 76 (11), 181 (11).

3-Ethyl-2-hydroxy-4-methyl-2-cyclopentenone (22). Compound VII:R_2 = CH_3 (see *3*) was al-

kylated and decarboxylated to give *22* in 25 % yield as an oil[19] which had HRMS: $M^{\cdot+}$ 140.0848 ($C_8H_{12}O_2$ requires 140.0836); ^1H NMR (200 MHz): δ 5.45 (broad s, 1H), 2.8 (m, 1H), 2.65 and 1.98 (ABM-pattern, $J_{AB} = 19$, further split by $J_{AM} = 6$ and $J_{BM} = 1.5$, 2H), 2.54 and 2.26 (ABX_3-pattern, $J_{AB} = 15$, further split by $J_{AX} = J_{BX} = 7.5$, 2H), 1.17 (d, $J = 7$, 3H), 1.15 (t, $J = 7.5$, 3H). MS *m/z* (%): 140 (57), 125 (35), 111 (71), 97 (43), 83 (33), 69 (67), 55 (56), 53 (30), 43 (74), 41 (100).

*2,3-Dihydro-1-ethyl-*1H*-2-methylcyclopenta(b)-quinoxaline* (23). Obtained from *22* in 61 % yield, *23* showed ^1H NMR (300 MHz): δ 8.02 (m, 2H), 7.65 (m, 2H), 3.35 and 2.77 (ABX-pattern, $J_{AB} = 18$, further split by $J_{AX} = J_{BX} = 6$, 2H), 2.82 (q, $J = 6$, 1H), 2.44 (quint., $J = 6$, 1H), 1.92 (m, 2H), 1.31 (d, $J = 6$, 3H), 1.12 (t, $J = 6$, 3H). MS *m/z* (%): 169 (100), 184 (72), 183 (21), 168 (17), 170 (17), 77 (10), 102 (10), 181 (10), 185 (9), 39 (8).

4-Ethyl-2-hydroxy-3-methyl-2-cyclopentenone (24). Compound VII:$R_2 = C_2H_5$ (see *5*) was alkylated and decarboxylated in 32 % yield to give *24* which had HRMS: $M^{\cdot+}$ 140.0847 ($C_8H_{12}O_2$ requires 140.0836); ^1H NMR (200 MHz): δ 5.53 (broad s, 1H), 2.62 (m, 1H), 2.52 (m, 1H), 2.07 (m, 1H), 1.96 (d, $J = 2$, 3H), 1.8 (m, 1H), 1.3 (m, 1H), 0.89 (t, $J = 7.5$, 3H). MS *m/z* (%): 140 (32), 112 (11), 111 (100), 83 (61), 69 (10), 65 (11), 55 (41), 53 (17), 43 (96), 41 (36).

*2,3-Dihydro-2-ethyl-*1H*-1-methylcyclopenta(b)-quinoxaline* (25). Obtained from *24* in 60 % yield, *25* showed ^1H NMR (300 MHz): δ 8.06 (m, 2H), 7.70 (m, 2H), 3.32 and 2.79 (ABX-pattern, $J_{AB} = 17.5$, further split by $J_{AX} = 8$ and $J_{BX} = 9.5$, 2H), 2.98 (dq, $J = 8.5$ and 7, 1H), 2.06 (m, 1H), 1.88 and 1.56 (AB-pattern, $J_{AB} = 13.5$, further split into multiplets, 2H), 1.51 (d, $J = 7$, 3H), 1.08 (t, $J = 7.5$, 3H). MS *m/z* (%): 212 (100), 197 (84), 183 (56), 169 (32), 168 (19), 182 (19), 181 (18), 213 (15), 211 (13), 77 (12).

2-Hydroxy-3-methyl-4-isopropyl-2-cyclopentenone (26). Alkylation and decarboxylation of VII:R_2 = isopropyl (see *7*) gave *26* in 15 % yield which had HRMS: $M^{\cdot+}$ 154.1010 ($C_9H_{14}O_2$ requires 154.0994); ^1H NMR (300 MHz): δ 2.7 (m, 1H), 2.13 (m, 1H), 2.31 and 2.14 (ABX-pattern, $J_{AB} = 19$, further split by $J_{AX} = 6$ and $J_{BX} = 2$, 2H), 1.95 (d, $J = 1.5$, 3H), 0.99 (d, $J = 7.0$, 3H), 0.64 (d, $J = 7.5$, 3H). MS *m/z* (%): 154 (51), 112 (61), 111 (100), 94 (76), 83 (52), 66 (26), 55 (23), 53 (10), 43 (70), 41 (25).

2-Hydroxy-3,5-dimethyl-2-cyclopentenone (27). Cyclotene (XI) was alkylated as shown in Scheme 2 in 11 % overall yield; *27* had m.p. 90–92 °C (lit.[11] 91–92 °C). HRMS: $M^{\cdot+}$ 126.0693 ($C_7H_{10}O_2$ requires 126.0680); ^1H NMR (200 MHz): δ 5.7 (broad s, 1H), 2.67 and 2.04 (ABX-pattern, $J_{AB} = 18$, further split into multiplets, 2H), 2.44 (m, 1H), 2.00 (s, 3H), 1.19 (d, $J = 7.5$, 3H). MS *m/z* (%): 126 (46), 111 (52), 98 (29), 83 (60), 70 (20), 69 (24), 55 (100), 53 (25), 43 (90), 41 (49).

*2,3-Dihydro-1,3-dimethyl-*1H*-cyclopenta(b)quinoxaline* (28). This compound was prepared from *27* in 65 % yield. That both the *cis* and *trans* isomers were obtained was obvious from the NMR spectrum; ^1H NMR (200 MHz): δ 8.04 (m), 7.66 (m), 3.53–3.13 (m), 2.84–2.65 (m), 2.14 (t, $J = 7$), 1.52 (d), 1.46 (d); MS *m/z* (%): 183 (100), 198 (88), 197 (40), 168 (32), 184 (32), 181 (28), 102 (25), 169 (25), 199 (24), 77 (23).

3-Ethyl-2-hydroxy-5-methyl-2-cyclopentenone (29) *and 5-ethyl-2-hydroxy-3-methyl-2-cyclopentenone* (30). These are tautomeric forms of the same compound, prepared, as described above, from cyclotene as a mixture in 16 % yield. The mixture did not separate in HPLC, even though both straight- and reversed phase columns were tested. GC (OV 351, fused silica, 30 m) showed two peaks in a ratio of 1:3. The ^1H NMR spectrum of the mixture was complicated but with two-dimensional technique, an interpretation was possible.

Compound *29* showed HRMS: $M^{\cdot+}$ 140.0901 ($C_8H_{12}O_2$ requires 140.0836); ^1H NMR (200 MHz): δ 5.65 (broad s, 1H), 2.46 (q, $J = 8$, 2H), 2.44 (quint., $J = 8$, 1H), 2.72 and 2.06 (ABX-pattern, $J_{AB} = 16$, further split by $J_{AX} = 8$ and $J_{BX} = 1$, 2H), 1.20 (d, $J = 8$, 3H), 1.16 (t, $J = 8$, 3H). MS *m/z* (%): 140 (76), 125 (44), 111 (32), 97 (57), 83 (42), 69 (41), 57 (48), 55 (100), 43 (59), 41 (79).

Compound *30* showed HRMS: $M^{\cdot+}$ 140.0812 ($C_8H_{12}O_2$ requires 140.0836); ^1H NMR (200 MHz): δ 5.65 (broad s, 1H), 2.36 (m, 1H), 2.61

and 2.13 (ABX-pattern, $J_{AB} = 16$, further split by $J_{AX} = 6$ and $J_{BX} = 2$, 2H), 2.02 (s, 3H), 1.8 (m, 1H), 1.45 (m, 1H), 0.96 (t, $J = 8$, 3H). MS *m/z* (%): 140 (21), 112 (51), 94 (73), 69 (25), 66 (33), 55 (67), 53 (26), 43 (70), 42 (20), 41 (100).

*1-Ethyl-2,3-dihydro-*1H*-3-methylcyclopenta(b)-quinoxaline* (31). Obtained from the tautomeric mixture of *29* and *30* in 53 % yield, *31* had ^{1}H NMR (200 MHz): δ 8.04 (m, 2H), 7.66 (m, 2H), 3.44 (m, 1H), 3.24 (m, 1H), 2.26 (m, 1H), 2.06 (m, 1H), 1.58 (m, 2H), 1.46 (d, $J = 8$, 3H), 1.10 (t, $J = 7$, 3H). MS *m/z* (%): 184 (100), 183 (88), 169 (28), 155 (25), 168 (15), 185 (14), 102 (10), 212 (9), 77 (9), 76 (8).

2-Hydroxy-3-methyl-5-propyl-2-cyclopentenone (32) *and 2-hydroxy-5-methyl-3-propyl-2-cyclopentenone* (33). An 1:1 mixture of *32* and *33* was obtained from XI in 30 % yield. The mixture was separated by repeated HPLC fractionation (silica gel column, 12 % *tert*-butyl methylether in cyclohexane), samples of both isomers being obtained.

Compound *32* showed HRMS: $M^{\cdot+}$ 154.0980 ($C_9H_{14}O_2$ requires 154.0994); ^{1}H NMR (300 MHz): δ 5.15 (broad s, 1H), 2.38 (m, 1H), 2.60 and 2.10 (ABX-pattern, $J_{AB} = 17.5$; further split by $J_{AX} = 6$ and $J_{BX} = 1.5$, both further coupled, $J_{\text{long range}} = 1.5$, to a methyl group, 2H), 2.0 (t, $J = 1.5$, 3H), 1.76 (m, 1H), 1.37 (m, 3H), 0.93 (t, $J = 7$, 3H). MS *m/z* (%): 154 (17), 125 (13), 112 (100), 95 (12), 94 (99), 69 (13), 66 (20), 55 (24), 43 (20), 41 (29).

Compound *33* showed HRMS: $M^{\cdot+}$ 154.0973 ($C_9H_{14}O_2$ requires 154.0994); ^{1}H NMR (300 MHz): δ 5.15 (broad s, 1H), 2.67 and 2.0 (ABX-pattern, $J_{AB} = 18$, further split by $J_{AX} = 6$ and $J_{BX} = 1$; both further coupled, $J_{\text{long range}} = 1$, to a methylene group, 2H), 2.35 (m, 3H), 1.55 (m, 2H), 1.15 (d, $J = 7.5$, 3H), 0.95 (t, $J = 7.5$, 3H). MS *m/z* (%): 154 (100), 139 (94), 126 (55), 112 (57), 97 (51), 94 (53), 69 (49), 55 (73), 43 (56), 41 (78).

Acknowledgement. We are grateful to Drs. J. Bielawski, O. Dahlman and Petra Ossowski-Larsson for recording the mass spectra, and to Dr. T. Nishida for recording the NMR spectra.

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Received July 4, 1986.