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ACID CATALYZED REARRANGEMENT OF β-IONONE EPOXIDE

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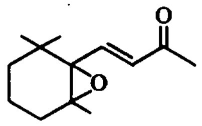
Abstract—Rearrangement of β-ionone epoxide with aqueous formic acid gave 1,2-dihydro-1,1,6-trimethylnaphthalene (**2**), 1-(1,2,2-trimethylcyclopent-1-yl)-2-penten-1,4-dione (**3**), 4-(5,5-dimethyl-2-acetyl-1-cyclopenten-1-yl)-2-butanone (**5**), 4-(1,3,3-trimethyl-2-cyclohexanon-1-yl)-3-buten-2-one (**6**), 4-(2,3,6-trimethylphenyl)-2-butanone (**7**) and 6,6-dimethyl-2,5-10-undecatrione (**8**). NMR assignments are made for each compound while a computer assisted analysis of the A_2B_2 portion of **7** has been completed. Possible mechanistic pathways leading to these compounds are discussed.

Terpenoids in tobacco and tobacco smoke condensate influence the aroma and flavor of tobacco smoke,[1] as well as being partially responsible for the presence of polynuclear aromatic hydrocarbons and other health-related compounds in the smoke.[2] The occurrence of a number of C_{13} "terpenoids" in the steam distillate of cured tobacco[3] prompted an examination of the action of aqueous formic acid on β-ionone epoxide (**1**), a known constituent of cured tobacco.[3] This type of reaction often provides information about the origin of certain plant products and may provide a synthetic route to the tobacco terpenoids.



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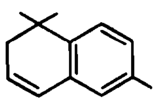
RESULTS AND DISCUSSION

Treatment of the epoxide (**1**) with refluxing 50% aqueous formic acid for 0·5 hr gave a mixture of compounds (Fig. 1). Initial separation of the components by distillation through a spinning band column at reduced pressure was followed by column and/or gas chromatography to provide final separation.

Peak A was purified by gas chromatography from an initial distillate and has been shown to have structure **2**.



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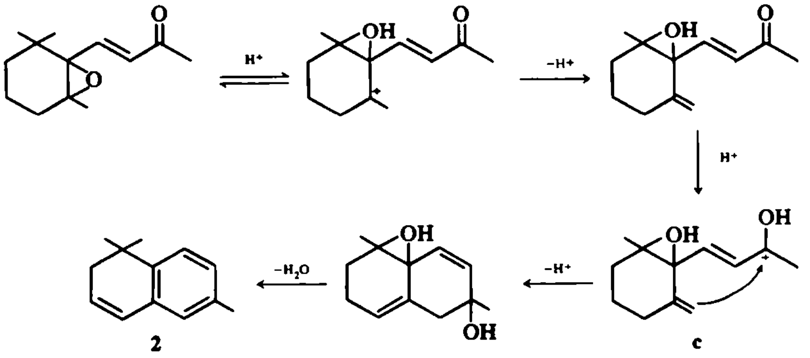
The NMR spectrum showed a typical ABC pattern characteristic of a 1,2,4-trisubstituted aromatic system with resonances between δ6·80 and δ7·24. The Me groups appeared at δ2·29 (3H, s, aromatic Me) and δ1·25 (6H, s, *gem* dimethyl). A two proton double-doublet (δ2·21; J = 4·5 Hz, 2·0 Hz) may be ascribed to the allyl protons, which are coupled to the vinyl protons occurring at δ6·31 (1 H, dt, J = 9·0 Hz, 2·0 Hz) and δ5·90 (1 H, dt, J = 9·0 Hz, 4·5 Hz). The IR and mass spectra of **2** correspond quite well with those reported for 1,2-dihydro-1,1,6-trimethylnaphthalene isolated from peaches[4] and strawberry oil.[5] In addition, this compound has been isolated from the volatile constituents of Greek tobacco.[6] The formation of this compound from β-ionone epoxide may be considered formally as a double dehydration with concomitant cyclization as envisioned below.



Peak B has been shown to have the cyclopentane structure **3** ($C_{13}H_{20}O_2$). The compound was non-hydroxylated and showed an IR CO band at 1680 cm^{-1} (conjugated) and a weaker band at 1620 cm^{-1} ($>$C=C$<$). The 100 MHz NMR spectrum showed *trans* vinyl protons

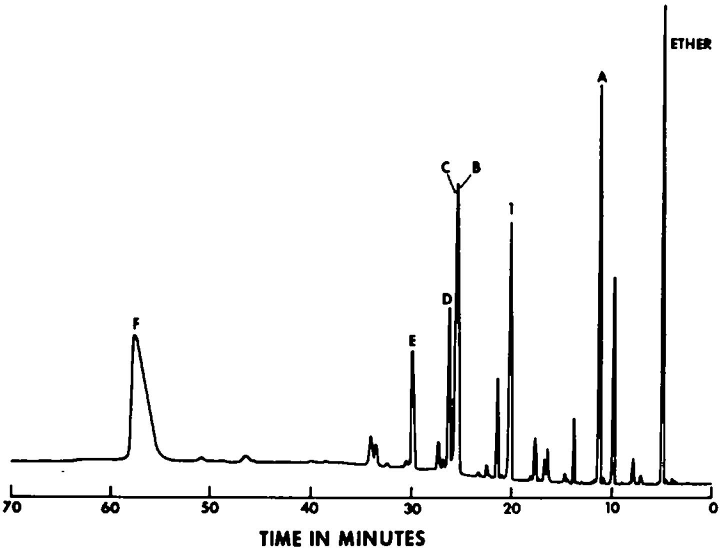
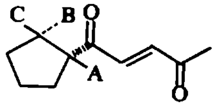


Fig. 1. Gas chromatogram of reaction mixture; 75′ × 0·01″ Igepal column, initial temp. 100°, programmed at 2°/min to 150°.



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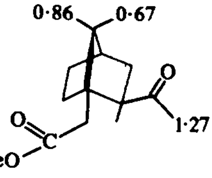

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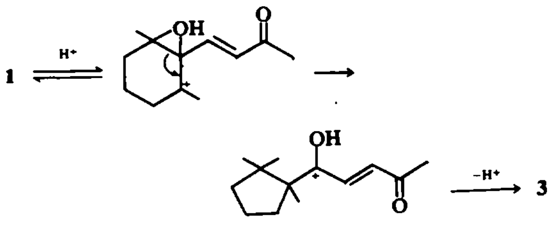
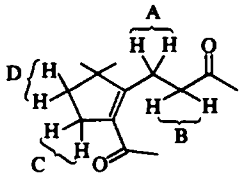
(d, δ6·88, δ7·26, J = 16·0 Hz) whose low field chemical shift suggested adjacency to the CO groups. The NMR spectrum further showed an acyl Me group (s, δ2·37) and three alkyl Me groups (s, δ0·86, 1·10, 1·20). Consideration of a model of 3 shows the Me group (B) in the diamagnetic region of the CO group; hence, one would expect an upfield shift (−0·24 ppm) of this magnitude from the "normal" position.[6] A close analogy[7] is found in compound 4 in which the Me group is within the shielding region of the CO group and is shifted approximately 0·19 ppm upfield. The remaining 6 protons of 3 occurred as a multiplet between δ1·35 and 1·95 and were not shifted significantly upon formation of a mono-2,4-dinitrophenylhydrazone derivative.

The formation of 3 may arise from the following scheme:





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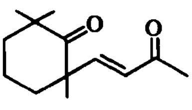
Peak C was isolated as an oil and has been shown to possess structure 5. High resolution mass spectral analysis gave $C_{13}H_{20}O_2$ as the molecular formula. Its IR spectrum showed the presence of a >C=C< stretching band at 1610 cm^{-1} and non-conjugated (1720 cm^{-1}) and conjugated (1675 cm^{-1}) CO groups, thus accounting for both oxygen functions in the molecule. The NMR spectrum of 5 showed a 6 H singlet at δ1·05 (*gem* dimethyl group) and a 6 H singlet at δ2·19 (acyl Me groups). A 6 H multiplet at δ2·50–2·65 and a 2 H triplet at δ1·71 (J = 7·0 Hz) accounted for the remainder of the spectrum; no vinyl protons were present. The 6 H multiplet is within the region one would expect for methylene groups adjacent to >C=O and/or >C=C<. An isolated methylene adjacent to another methylene group may be ascribed to the triplet at δ 1·71. The spectrum was considerably simplified by the addition of an equimolar amount of europium shift reagent. Two low field triplets (2 H ea., J = 7·0 Hz) coupled to each other appeared at δ6·91 and δ7·35. These may be assigned to the four methylene protons designated by A and D. Another pair of triplets 2 H ea., J = 7·0 Hz) occurred at δ3·82 and δ2·57 and may be ascribed to protons C and D, respectively. The acyl Me singlets shifted to δ5·11 and δ4·39. The *gem* dimethyl group remained a singlet at δ1·98.

Peak D has been shown to be **6** ($C_{13}H_{20}O_2$) with a >C=C< absorption at 1620 cm^{-1} in addition to non-conjugated (1705 cm^{-1}) and conjugated (1650 cm^{-1}) CO absorptions, thereby accounting for both O atoms. A pair of doublets appeared at δ6·10 (J = 16·0 Hz) and δ6·92 (J = 16·0 Hz) in the NMR spectrum and is typical of a 3-buten-2-one system, e.g. β-ionone epoxide.

The NMR spectrum showed an acyl Me group at δ2·27 and three other Me singlets at $\delta 1{\cdot}25$, $\delta 1{\cdot}14$ and $\delta 1{\cdot}08$. A 6 H multiplet occurred between $\delta 1{\cdot}55$ and $\delta 1{\cdot}90$, which accounted for the remaining hydrogens. Of the two possible structures, **6** and **6a**, the latter can be eliminated



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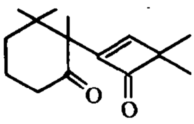
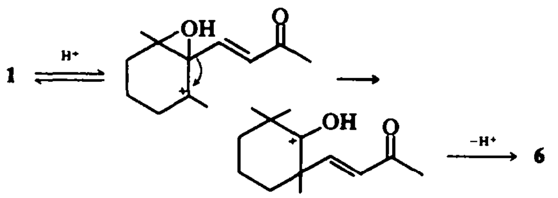
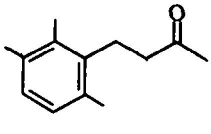


6a

because no methylene absorptions in the region of $\delta 2{\cdot}2$–$\delta 2{\cdot}6$ were observed. The formation of **6** may be rationalized as a Wagner Meerwein rearrangement;[8] i.e.:



Peak E was identified as compound 7 ($C_{13}H_{18}O$), which has also been independently synthesized by the action of



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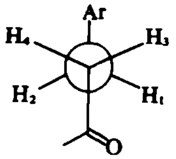


7

dehydrating agents on β-ionone.[9] The general structure was confirmed by its IR spectrum ($1720\,cm^{-1}$, nonconjugated CO) and its NMR spectrum, which showed $\delta 6{\cdot}92$ (2H, s, aromatic protons) and four Me singlets at $\delta 2{\cdot}17$, $2{\cdot}20$, $2{\cdot}25$, and $2{\cdot}27$. Upon the addition of europium shift reagent, one of the Me groups shifted downfield to $\delta 3{\cdot}80$, thus confirming the presence of one acyl Me group. Two multiplets at $\delta 2{\cdot}92$ (2 H) and $\delta 2{\cdot}56$ (2 H) are shown in Fig. 2. Deuteration of 7 with NaOD-D_2O caused the Me group at $\delta 2{\cdot}17$ and the multiplet at $\delta 2{\cdot}56$ to disappear. Thus we may assign the multiplet at $\delta 2{\cdot}56$ to H_3 and H_4 of 7.

Since the multiplicity of the spectrum precluded the possibility of a first order analysis, procedures similar to those employed for the analysis of 1-indanone[10] were followed. Line assignments (Fig. 2) satisfy all the identity and consistency tests as outlined in the reviews of Günther[11] and Garbisch.[12] The "g" line is weak and not observed while the "j" line is assigned a negative value since it is on the opposite side of $\nu 0$. These line assignments are somewhat different from those proposed by Forsen[10] on 1-indanone, yet give the ratio $K/N < 0$ which is necessary if the geminal coupling constants are to be negative. Alternate line assignments failed either the identity or consistency tests. NMR parameters are given in Table 1 using line assignments and peak positions as shown in Fig. 2.

A computer calculated iterative, least squares fit to a theoretical AA'BB' spectrum of twenty-one assigned transitions out of a possible twenty-four using LAOCN3[13] gave parameters with a root mean square deviation of 0·034 (Table 1). The computer generated spectrum is shown in Fig. 2. Additional confirmation of these peak assignments and consequently of the NMR parameters was found in the agreement between the experimental and theoretical spectra at 60 MHz. The B_2 portion is shown in Fig. 3.

The multiplet at $\delta 2{\cdot}56$ (Fig. 2) shows additional line broadening, which may be caused by long-range effects of the two adjacent Me groups on the aromatic ring. Although double resonance with irradiation in the region of $\delta 2{\cdot}20$–$\delta 2{\cdot}27$ showed considerable sharpening of these peaks, we were unable to ascribe it to NOE or long-range coupling.

The major product (peak F) of the reaction was the triketone **8**, which was isolated by distillation from the mixture. IR spectral analysis showed a strong CO absorption at $1712\,cm^{-1}$ indicative of a saturated system. In addition, the "fingerprint" region showed rather diffuse, weak bands, which is often characteristic of molecules devoid of rigid structural features and capable of assuming numerous noncharacteristic conformations.[14] High

Table 1. NMR parameters of A_2B_2 portion of 7

	ν_{34}	ν_{12}	$\delta\nu$	K*	$\lvert L \rvert$	$\lvert M \rvert$	N*	$J_{14(13)}$	$J_{13(14)}$	$J_{12(34)}$	$J_{34(12)}$
2nd ORDER ANALYSIS [8,9,10]			35.99	−31.26	7.11	3.06	16.62	4.76	11.87	−14.10	−17.16
COMPUTER CALCULATED BEST FIT	256.120	292.315	36.20	−31.41	6.96	3.19	16.68	4.859	11.822	−14.112	−17.302

$$\delta\nu = +\sqrt{4ab}$$

$$= +\sqrt{2(ce + df)}$$

$$N = a - b$$

$$K = 2b + k - h - j - l$$

$$K = b + i + k - a - j - l$$

$$L = +\sqrt{(c-e)^2 - M^2}$$

$$= +\sqrt{(d-f)^2 - M^2}$$

$$M = (ce - df)/\delta\nu$$

$$N = J_{13} + J_{14}$$

$$L = J_{13} - J_{14}$$

$$M = J_{12} - J_{34}$$

$$K = J_{12} + J_{34}$$

*Only the relative sign of K and N can be determined.[10] Since vicinal couplings are known to be positive and geminal couplings, negative, we assign K negative and N positive. L and M are assumed to be positive.

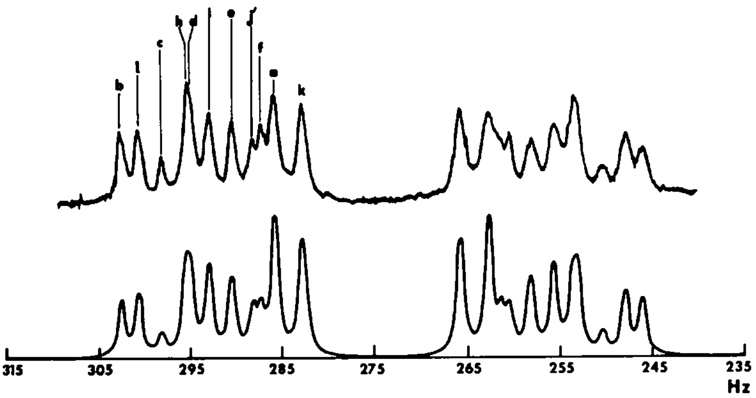


Fig. 2. NMR spectrum of A_2B_2 multiplet of compound 7. Upper, experimental; lower, theoretical, with $\nu_{12} = 292{\cdot}315$; $\nu_{34} = 256{\cdot}120$; $J_{12} = -17{\cdot}302$; $J_{13} = 4{\cdot}86$; $J_{14} = 11{\cdot}82$; $J_{23} = 11{\cdot}82$; $J_{24} = 4{\cdot}86$; $J_{34} = -14{\cdot}11$.

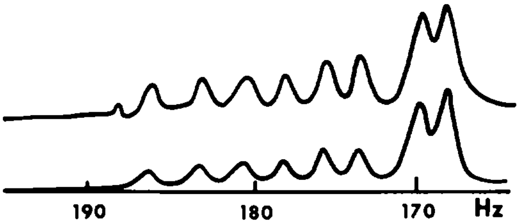
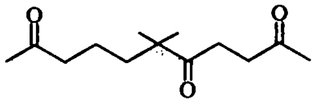


Fig. 3. Experimental (upper) and theoretical (lower) spectra of B_2 portion of 7 at 60 MHz.

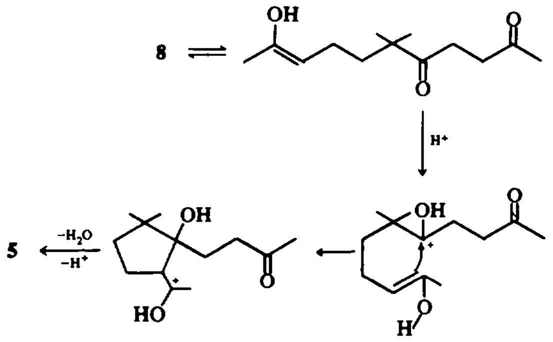


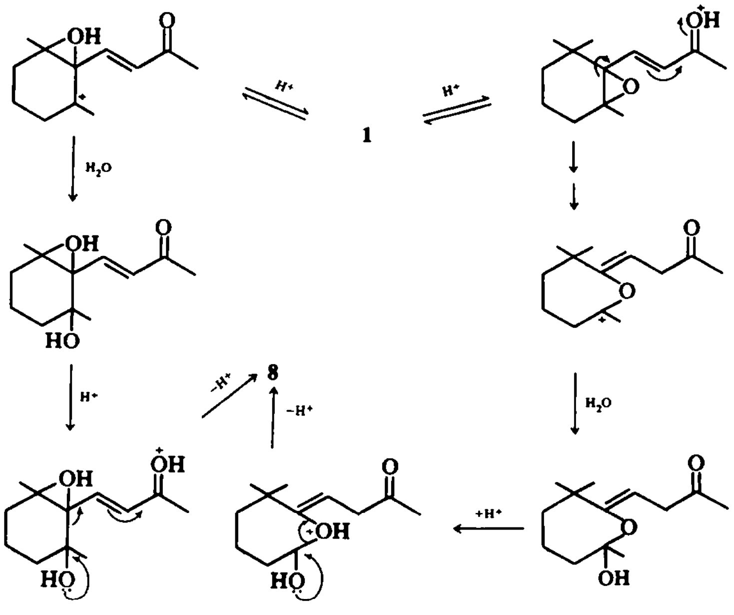
8

resolution mass spectral analysis gave the molecular formula as $C_{13}H_{22}O_3$. The compound formed an oxime (m.p. 152°) which by NMR was a *tris* oxime, thus accounting for all of the oxygen functions, and a di-2,4-dinitrophenylhydrazone (m.p. 165°). The NMR spectrum of 8 showed *gem* dimethyl groups at $\delta 1{\cdot}16$ (s, 6 H), two acyl Me groups at $\delta 2{\cdot}13$, and $\delta 2{\cdot}19$, a multiplet of 4 H at $\delta 1{\cdot}34$–$\delta 1{\cdot}70$, a 2 H triplet at $\delta 2{\cdot}44$ (acyl methylene), and a 4 H multiplet at $\delta 2{\cdot}58$–$2{\cdot}70$ (two acyl methylenes). In addition, the mass spectrum shows a prominent fragment at *m/e* 142 which arises *via* a McLafferty rearrangement involving the center CO to give the fragment $[C_8H_{14}O_2]^{+\cdot}$. These data uniquely establish the structure of peak F as **8**.

Two plausible reaction sequences for the formation of **8** are shown below.

A direct mechanistic route leading to the formation of **5** from **1** is not obvious; yet one may propose a route





starting from compound **8**. Refluxing compound **8** for 2 hr with 50% aqueous formic acid gave a small amount of **5**. This does not confirm the pathway suggested above, but shows it to be plausible.

EXPERIMENTAL

NMR spectra were run in CDCl$_3$ solns with either a Varian HR-100 or A-60 spectrometers. IR spectra were run neat on a Perkin-Elmer 237 spectrometer. High resolution mass spectra were obtained on a CEC model 110 spectrometer at 70 eV.

Rearrangement of β-ionone epoxide (**1**). β-Ionone epoxide, 20 g. (prepared *via* β-ionone and *m*-chloroperbenzoic acid) was refluxed for 0·5 hr under N_2 with 500 ml of 50% aqueous formic acid. After cooling, the mixture was diluted with 300 ml water and extracted with ether. The ethereal extract was washed with water, NaHCO$_3$aq, water, dried over MgSO$_4$, and the ether removed, leaving an oil which was distilled on a 1 ft spinning band column.

1,1,6-*Trimethyl*-1,2-*dihydronaphthalene* (**2**). The fraction boiling at 80–100° (10 mm) was further purified by chromatography on a 10′ × $\frac{1}{4}$″ Carbowax column at 160° and 20 psi pressure. See text for NMR and IR details. M.S.: *m*/*e* (relative abundance) 157(100), 142(66), 141(45), 128(35), 115(51), 77(36), 51(36), 43(47), 37(67), 27(74).

1-(1,2,2 - *Trimethylcyclopent* - 1 - *yl*) - 2 - *pentene* - 1,4 - *dione* (**3**). A distillation fraction boiling between 125 and 140° (10 mm) was chromatographed on a 1″ × 18″ column packed with silica gel, eluted with ether/Skelly F (10:90 v/v). The first peak to emerge was further purified by gas chromatography on a 10′ × $\frac{1}{4}$″ Carbowax column at 190° using 20 psi helium pressure. The first component to emerge was **3** which gave a mono-2,4-dinitrophenylhydrazone, m.p. 153–154°. See text for NMR and IR data. M.S.: *m*/*e* (relative abundance) 111(61), 109(14), 98(92), 97(32), 70(16), 69(100), 55(60), 43(60), 41(29), 28(11). Calc. for $C_{13}H_{20}O_2$, 208·1463; Found, 208·1465.

4 - (5,5 - *Dimethyl* - 2 - *acetyl* - 1 - *cyclopenten* - 1 - *yl*) - 2 - *butanone* (**5**). A third component eluted from the previous silica gel column gave compound **5**, which formed a mono-2,4-dinitrophenylhydrazone, m.p. 91–92° (EtOH). See text for NMR and IR data. M.S.: *m*/*e* (relative abundance) 208(13), 165(24), 109(68), 107(11), 95(11), 93(13), 91(13), 43(100), 41(10), 28(20). Calc. for $C_{13}H_{20}O_2$, 208·1463; Found, 208·1465.

4 - (1,3,3 - *Trimethyl* - 2 - *cyclohexanon* - 1 - *yl*) - 3 - *buten* - 2 - *one* (**6**). The second component eluted from the previous silica gel column gave the title compound, whose mono-2,4-dinitrophenylhydrazone gave m.p. 161–164° (EtOH). See text for NMR and IR data. M.S.: *m*/*e* (relative abundance) 122(28), 111(100), 109(43), 95(41), 81(54), 69(33), 55(26), 43(74), 41(35), 28(24). Calc. for $C_{13}H_{20}O_2$, 208·1463; Found, 208·1472.

4 - (2,3,6 - *Trimethylphenyl*) - 2 - *butanone* (**7**). The second component to emerge from the gas chromatograph during the purification of **3** was the title compound **7**. Its 2,4-dinitrophenylhydrazone gave m.p. 166–167° (EtOH) whereas the semicarbazone gave m.p. 174–177° (MeOH) (Lit.[9] 174°). M.S.: *m*/*e* (relative abundance) 172(55), 157(53), 147(22), 133(75), 132(100), 119(21), 117(23), 91(20), 43(43), 28(80).

6,6-*Dimethyl*-2,5,10-*undecatrione* (**8**). The title compound was isolated by distillation of the crude mixture (b.p. 125–140°/5 mm). Its di-2,4-dinitrophenylhydrazone gave m.p. 163–165° (EtOH) and trioxime gave m.p. 151–152° (EtOH). For NMR and IR data, see text. M.S.: *m*/*e* (relative abundance) 142(9), 127(18), 109(46), 99(100), 71(17), 69(45), 43(80), 41(17), 32(10), 28(56). Calc. for $C_{13}H_{22}O_3$, 226·1569; Found, 226, 1574.

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